UWE WINDHORST

SENSOMOTION

SENSORY-MOTOR SYSTEMS

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REMARKS

Writing this book was a pastime. Much time has passed since early ideas many years ago. The book has survived many delays, interruptions, reorgnizations and deviations.

I am very grateful to Dr. Peter Lalley for meticulously editing this book, to Dr. Yiannis Laouris for publishing it, and to Dr. Payam Dibaj for helping with literatrure. My wife Sigrid deserves special thanks for her patience and support.

A technical note: Glossary entries list the chapters in which the keywords (in **bold letters**) occur. These are underlined for better identification. Horizontal arrows before the underlined notions indicate glossary entries giving definitions and providing more information.

Errare humanum... – no error, no progress.

Prosit!

Ciao

U.W.
Göttingen, Autumn 2021

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Abstract

• We cherish the power, efficiency, versatility, flexibility, swiftness and elegance of animal movements in continuous dynamic interaction with an ever changing environment. These properties tend to hide the underlying problems to be solved and the solutions invented, of which this introductory chapter gives a preliminary and cursory overview.

• Purposeful goal-oriented movements require target perception and evaluation, preparation and planning, predictions and selections, various transformations, adaptable motor and sensory functions, along with learning and memory.

• Movement necessitates control by sensory and other types of feedback from large, often complex arrays of sensory receptors and systems, each adapted to the properties of a special environmental niche.

• Movements can be categorized into reflexes, posture, rhythmic and voluntary movements that normally blend with each other.

• Multi-segmented skeletal structures provide multiple degrees of freedom, within various constraints.

• Movements occurring in space and time dimensions are organized and represented in multifold ways in the central nervous system (CNS).

• Organization of posture and movement by the CNS has both kinematic and kinetic aspects. Kinematics deals with the spatio-temporal paths or trajectories head, eyes, limbs etc. Kinetics deals with the forces and torques needed for movements.

1.1 Introduction

The diversity, swiftness, accuracy and elegance of animal and human movements create the superficial impression that they are generated easily and effortlessly. However, when mechanisms and processes underlying the organization of animal movements are studied in detail, they turn out to be much more complex. The elegance of animal movements can be fully appreciated only when due consideration is given to the tasks to be performed and the problems to be solved in the performances. This is borne out by comparison with the performance of sophisticated modern robots. Even when these are designed using up-to-date `high-tech´, they fall far behind any higher animal in terms of sensory-motor performance. To understand this difference, we must be aware of the nature of the underlying problems to be solved and conceive of possible solutions. Solutions come with a price, however. Their availability and efficacy are limited by various natural constraints, e.g., →energy costs, properties of the instruments available, etc. This implies that any solution selected may create new problems.

This chapter provides a general overview of the tasks to be mastered and the problems to be solved by organisms when purposefully moving in their environments. A number of important notions and concepts that are currently being used in the study of animal movements are presented together with principles and examples of motor control.

As a starting point, we consider the processes involved in reaching and grasping.

1.2 Processes in Reaching and Grasping

Several neural processes come into play when a subject reaches out and successfully grasps an object.

Target Perception. The object must be noticed and visually →perceived and →recognized in terms of its physical properties, such as size, shape, color, material constitution as well as its location and orientation Chapters 13, 14). Reach-related targets can also be pain (Chapters 4, 5), or touch (Chapters 6, 7) to the skin or →sound (Chapter 11, 12). The determination of object size, shape and location require the →central nervous system (CNS) to construct representations of space. There must also be at least one representation of body configuration (body schema). Movements of the eyes or head or body through space change the sensory flow, here the image motion of the external world across the retina (Hayhoe 2017). For accurate perception of and target-directed movements in space, it is essential that the external world appear as constant or stable (→spatial constancy or spatial stability). The CNS must therefore have mechanisms to distinguish between self-generated sensory changes (re-afference) and externally generated sensory changes (ex-afference) (Brooks and Cullen 2019; Medendorp 2011).

Evaluation. Once perceived, the object´s physical properties must be evaluated in relation to the subject's →attention, →emotion and drive, including needs, desires, e.g., thirst and hunger, →motivation to seek a goal considering the potential →reward vs. the efforts required, the potential costs and risks, and →memories of previous experiences with-present or similar objects (Hayhoe 2017; Mirabella 2014). An object´s potential edibility must be determined by taste (Chapter 2), smell (Chapter 3) and touch (Chapters 6, 7).

Decision Making. Once the object has been recognized as desirable and attainable, several →decisions must be taken. An early decision is whether to make a movement, considering the internal and external circumstances. The →intention to act involves deciding which goal or task to perform (task selection) and which movement to make or the means to use (action selection) depending on the circumstances. A late decision involves a final predictive check and a potential veto function if circumstances have changed (Haggard 2008; Hayhoe 2017; Mirabella 2014).

Preparation and Planning. If the decision is positive, the reaching/grasping movement must be prepared and planned (Chapter 24). In case the target is in immediate reach distance, things are relatively straightforward. If not, additional movements must be utilized, such as trunk or locomotor movements (Chapters 21-23). Preparation includes a number of predictions and selection processes; possibly an action sequence with sub-goals (Johansson and Flanagan 2009; Soechting 2009) and, as far as vision (Chapters 13, 14) is involved, coordination with eye movements (Hayhoe 2017) (Chapters 15, 16).

Predictions and Selections. Grasping an object for lift or manipulation requires a number of predictions and selections (Chapter 24). Since not all object properties may be known in advance, the motor act must be planned initially on the basis of reasonable estimates and previous experience with the same or similar objects (Hayhoe 2017; Johansson and Flanagan 2009). Then a number of specific selections must be made:

(i) *Choice of equivalent motor acts*. Target location and initial hand position must be determined. Since there are many ways of moving a hand to a target, one must be selected based on economic criteria. The decision must be made in the face of incomplete knowledge about the state of body and world, and despite →noise in sensory and motor signals. It thus requires probability estimates of body and environmental states based on their statistics. Also, the costs (e.g., energy expenditure) for a particular movement must be weighed against its potential rewards (Guigon et al. 2008; Franklin and Wolpert 2011; Körding and Wolpert 2006)

(ii) *Selection of movement sequence* (Soechting 2009).

(iii) *Selection of →anticipatory postural adjustments*. Contraction of an individual skeletal muscle →accelerates not only the segments that it originates from and inserts on, but also remote segments via dynamic inter-segmental interactions which, in addition, depend on joint angles and angular velocities. Thereby, movement of the arm and interactions with the object alter the equilibrium conditions of the entire body. This requires selection of adequate compensatory postural adjustments executed in anticipation of, and in parallel with, the arm and hand movement (Chapter 24).

(iv) *Selection of movement variables*. Reaching and grasping movements require anticipatory, initially tentative selection of kinematic variables (direction, extent, velocity, etc.) and kinetic variables (forces, →torques) of the arm, hand and fingers, which are based on internal representations of the object and on →internal models of the motor apparatus (McNamee and Wolpert 2019). When the targeted object moves relative to the subject, an appropriate point and time of interception must be calculated to allow enough time for both perception and action (Chapter 25). On the perceptual side, the future object location at interception time must be predicted based on current trajectory and speed. On the motor side, movement planning must select movement variables appropriate for attaining the goal in time.

(v) *Adjustments of finger and hand actions to object properties*. Efficient grasping requires pre-shaping of the hand during object approach, and selection of appropriate grasp sites and forces, depending on task and object properties (size, shape, →mass, mass distribution, surface frictional properties). If these properties are not known and not stored in →memory from previous experience, they need to be predicted (Hayhoe 2017). The initial adjustments depend heavily on vision. Before contact, the forces applied to the object, e.g., grip force, distribution of finger forces etc., must be selected tentatively, small enough so as not to squeeze the object and large enough so as not to drop it. After object contact, tactile information from cutaneous mechano-receptors plays an important role in adjusting action variables to the real circumstances (local shape, frictional properties, weight, etc.).

(vi) *Estimation of expected feedback signals*. Since sensory feedback is so important for the planning and execution of movements, the CNS must be able to distinguish self-generated sensory feedback from external sensory inputs. For this distinction, the CNS must predict the expected sensory feedback resulting from motor acts. Such predictions may be performed by the use of →forward internal models according to von Holst and Mittelstaedt´s (1950) re-afference principle (below).

Transformations. Reaching, grasping and manipulation require localization of the object and determination of the initial arm/hand position. The two may be signaled by different senses; object location predominantly by vision, and arm/hand position by vision, proprioception (Chapters 8, 9) and/or touch (Makin et al. 2008). Thus, the two criteria are potentially coded in different →frames of reference, which at some stage must be brought together by →multi-sensory integration. Furthermore, sensory representations must be transformed into motor actions by sensory-motor transformations, so that the sensory coordinate frame can be transformed into the motor frame.

Execution. If a late decision to make a hand movement is positive, the planned path needs to be transformed into appropriate muscle activation patterns by processes involving kinematic-to-kinetic transformations. These involve →inverse internal models that acquire information about →stiffness, →viscosity and →inertia of the arm/hand and about external loads such as →gravity. This general transformation is composed of many sub-processes involving essentially the entire CNS.

Sensory Updates. The progression of ongoing movement and attainment of sub-goals in the action sequence must be monitored by sensory feedback from proprioceptors, tactile cutaneous →mechano-receptors, auditory and visual receptors, so that the central selections can be updated. For instance, after object contact, tactile afferent nerve fibers contribute to estimate the material and surface properties of the object (Komatsu and Goda 2018) and to signal the friction between skin and object surface, the local shape of the contact site(s), and the timing, magnitude, direction and spatial distribution of fingertip forces. Material properties and contact events can also be signaled by proprioception, vision and audition, requiring multi-modal integration and alignment. Sensory update is used for several sub-functions (Flanagan et al. 2006; Johansson and Flanagan 2009): comparison of predicted and actual sensory feedback leads to the detection of →prediction errors, which can be used for fast error correction; triggering of successive steps in the movement sequence; revision and updating of the internal model of body and musculo-skeletal system; revision and updating of the internal model of object properties (e.g., object weight and inertia). Sensory feedback and →motor commands are subject to signal transfer delays, probably requiring predictive control (→predictive internal models) for a solution (Franklin and Wolpert 2011).

Learning and Memory. The role of →learning and memory systems in the above processes cannot be overestimated (Chapter 27). In addition to providing the basis for →motor learning, memory systems serve to retrieve pertinent object properties based on olfactory, →haptic or visual information, identification of task features and the initial state of the skeleto-motor system and of sensory events during task progress. In planning and executing movements, the CNS must deal with several dynamic problems, such as gravity, →Coriolis forces and arm dynamics.

Gravity. Except under special conditions (e.g., under water or in zero-gravity flight), gravity must be taken into account by the CNS in planning and executing movements. It has been argued that the CNS constructs an →internal model of gravity (Hubbard 2020). While gravity is ever-present and mostly constant, other forces arise and change during movement.

Coriolis Forces. When a subject´s trunk rotates, reaching movements exert velocity-dependent →Coriolis forces on the arm, whose magnitude and direction depend on angular velocity of the torso relative to external space, arm mass plus that of any carried object, and linear velocity of the arm relative to the torso. The Coriolis forces disrupt movement trajectory and end-point accuracy unless taken into account by the CNS.

Anisotropic Arm Dynamics. The arm´s configuration causes its inertia to vary in different directions of movement. This inertial anisotropy is reflected in the initial acceleration of the hand, which is smaller in directions of higher inertia. The CNS is able to account for these variations by properly scaling the forces applied to an object as a function of the inertia expected, which implies the existence of a predictive internal model (Flanagan and Lolley 2001; Davidson and Wolpert 2003).

From the above description, it might be surmised that reaching/grasping movements are essentially organized in a serial sequence of processes, starting with perception and ending with the actual mechanical event. However, many processes in the nervous system actually run in parallel, and many feedback operations invert the flow of information. Not surprisingly, an intricate network of neural structures carries out these actions.

1.3 Acquisition, Use and Creation of Information

An essential primary requirement in the above behavioral reaction is the capacity to acquire and handle proper information. More generally, this applies to all organismal activities, since there is no movement without sensation.

1.3.1 Information Environments

At the cellular level, information acquisition, transmission and processing must occur between its different parts, and with the environment at the cell surface. By contrast, in multi-cellular organisms (metazoa), the different functions are performed by specialized cell systems in a more or less complex nervous system. This division of labor redefines the environment. From the viewpoint of the CNS, there are two environments: its own body and the body´s external environment. There will therefore be reactions to changes in either part of the environment and coupled reactions to both.

1.3.2 Signal Carriers

Information is an abstract entity that needs to be encoded in a signal that can be transmitted and processed. Multi-cellular organisms use a variety of signals, adapted to different purposes. Signals are generated by a material substrate or carrier that may engage one or the other mechanism to produce them. For example, the signal may be the concentration of a chemical substance (e.g., a →hormone), or the frequency of occurrence of electrical impulses called →action potentials.

1.3.3 Skeletal Muscles

Muscles attached to skeletal structures are the executive elements of the sensory-motor system, which enable it to control its environment (Chapter 17, 18). They are parts of chains and loops of information exchange by acquiring, transmitting, processing, storing and retrieving information.

1.3.4 Sensory Functions

In a simultaneously nutritious and dangerous environment, an organism must be able to control its environment and body, to the extent required for survival, well-being and reproduction. But "you can only control what you sense" (McCloskey and Prochazka 1994).

Sensation starts with reception of signals of importance to the organism by means of specialized receptor cells Once external signals are converted into nerve-specific signals, they are processed in the CNS in a multitude of ways (Chapters 2-14). Part of these processes may lead to sensations that are perceived. Most of the sensory signals, however, do not lead up to perception, but are used in various ways for motor, regulatory and other functions.

To function efficiently, sensory systems require representation in several dimensions, selective focusing and segregation capability, the ability to discriminate between constant and variable sensory stimuli, and interplay between memory, attention, expectation and emotion.

1.3.4.1 Estimation of Stimuli from Sensory Signals

Any particular value of a stimulus variable when presented repeatedly to a sensory system will result in varying sensory signals. The task of the brain is to come up with a probabilistic estimate of the stimulus that may have caused a sensory input. This estimate must be as precise as possible, reliable and fast, imposing high demands on brain operations (Rieke et al. 1997). This task is made more difficult by the fact that the body and its central representation influence the interpretation of sensory information, such that body attributes like shape, size, proportion, posture and movement can affect the perception of the world and own body (Harris et al. 2015).

1.3.4.2 Specialization of Senses

To receive information about crucially important aspects of environment and bodily interior, metazoa have developed specialized receptor cells that are differentially →sensitive to specific variables. Receptor specialization is the basis of the law of specific sense energies propounded by Johannes Müller in 1926 (Müller 1833-40). It states that the →quality of a sensation is not due to the stimulus but to the special sensory organ stimulated. An overview of the diverse senses in terms of modalities and sub-modalities (qualities) is given in **Table 1**. Many organisms are capable of sensing stimuli beyond the human →spectrum, e.g., high-frequency or low-frequency sound waves (bats, plants); infrared electro-magnetic radiation (snakes); ultraviolet electro-magnetic radiation (bees, plants); electrical potentials (sharks); magnetic fields (from crustaceans over fish, birds to turtles).

Receptor specialization and sensitivity are particularly affected by location and by auxiliary receptor components.

Receptor Location. Different types of cutaneous mechano-receptors involved in tactile sensation lie in different regions of the skin (Chapter 5), and it is the different spatial relation and mechanical coupling to skeletal →muscle fibers that makes sensory endings of muscle spindles and Golgi tendon organs (Chapter 8) respond to different mechanical variables of muscle performance.

Auxiliary apparatus. Cutaneous mechano-receptors display specific sensitivity to particular temporal aspects of mechanical stimuli because they have special anatomical structures associated with their sensory endings. Also, in the auditory system, the complete mechanical apparatus from the tympanic membrane to the basilar membrane of the cochlea transforms and filters the frequency content of the mechanical stimulus before reaching the →hair cells in the inner ear (Chapter 11).

*Specialized →ion channels in the →*receptor membrane open preferentially in response to a specific class of stimuli. For example, ion channels in cutaneous mechano-receptors open to distortion of the receptor membrane; and those in photoreceptor cells in the retina open, via complex intermediate steps, to various ranges of light waves (Chapter 13).

Primary, secondary, and tertiary receptor systems. In primary receptor systems, the receptor cell has its own afferent →axon, hence performs →sensory transduction and encoding at different membrane sites. In secondary receptor systems, such as those in the inner ear, the receptor cell releases a →neurotransmitter, which →depolarizes the afferent axon to produce propagated action potentials (Chapters 10, 11). In tertiary sensory systems such as the retina, at least two →synapses are intercalated between receptor cell and afferent axon (Chapter 13).

1.3.5 Multi-sensory Integration

The perception of events and objects in an organism´s internal and external worlds as well as actions on them require sensory information. Myriads of →sensory receptors signal selected aspects, bits and pieces of these events and objects. Thus, events and objects are commonly sensed by an array of sensory receptors, generating multi-faceted, parceled representations (Driver and Noesselt 2008). For their identification and characterization, the CNS must integrate the →multi-sensory signals (Hidaka et al. 2015; Holmes et al. 2009; Murray et al. 2016). To →optimize this task, the CNS uses the sensory modalities at disposal at any time in a proper weighting.

Table 1: Sensory Modalities, Qualities, Receptors and Adequate Stimuli

Modality	Quality	Receptors	Stimuli
Vision	brightness green red blue	rods cones	electro-magnetic radiation 400-700 nm
Hearing	tone frequencies	hair cells	air pressure fluctuations ca. 20-20,000 Hz
Touch	touch	Meissner	mechanical
	pressure vibration	Merkel Pacini etc.	deformation
Sensual touch	stroking	free nerve endings	mechanical deformation
Statokinetic sense	equilibrium	hair cells	absolute head position and acceleration
Graviception		mechano-sensitive graviceptors in trunk	gravity
Proprioception*	body position	joint and ligament receptors	joint position and motion
Extremity motion		muscle spindles Golgi tendon organs skin mechano-receptors	muscle length muscle force

Table 1, continued

Temperature	cold hot (warm)	cold receptors warm receptors	electro-magnetic radiation 700-900 nm
Pain	fast (first) pain	nociceptors	injuries, inflammtion etc.
Taste	sweet salty sour bitter umami fat? water?	chemo-receptors	chemical substances and ions
Smell	odors	„	odorants
Internal mechano-reception	stomach extension lung extension blood pressure	extension receptors presso-receptors	extension and pull
Internal fluids, chemo-reception	osmotic pressure CO_2 pressure O_2 pressure	chemo-receptors	osmolarity of body pH and pCO_2 pO_2

In some animals: electro-magnetic senses

Proprioceptors monitor positions, movements and forces, and include all receptors that carry signals related to these variables, irrespective of whether the signals reach consciousness or contribute to movement control at subconscious levels (Prochazka 1996).

The existence of different modality- and quality-specific experiences implies parallel processing in separate neural pathways that convey signals from sets of peripheral receptors. The modality-specific organization confers certain advantages. Each individual sense provides information that is optimally tailored to particular aspects and certain circumstances (Stein and Stanford 2008). On the other hand, combining →redundant information from different modalities minimizes the uncertainty about the state of the body and world when the sensory signals are weighted according

to their reliability. Thus, human perception is almost optimal when integrating proprioceptive-visual or haptic-visual or auditory-visual or vestibular-visual information (Oostwoud Wijdenes and Medendorp 2017). But multi-sensory integration is also used at sub-conscious levels for motor control (e.g., Chapter 19).

Multi-sensory integration occurs at various levels of the CNS. Some peripheral sensory receptors, →polymodal receptors, are sensitive to stimuli of different modalities. In addition, different uni-modal afferent nerve fibers converge on CNS neurons. Poly-modal sensory integration and interactions between modality-specific areas are widespread at supraspinal stages of processing (Driver and Noesselt 2008). The relative weighting of different senses changes over lifetime. It also changes over shorter time spans through experience and learning (Murray et al. 2016; Ernst and Bülthoff 2004; Stein and Meredith 1993).

The selection of the aspects of an organism´s worlds and the sensitivity with which they are signalled by sensory receptors is co-determined by the CNS that controls and modulates most centro-petal sensory pathways at some stage via →top-down signals. The most conspicuous example of such a top-down control is the muscle spindle which receives partially separate motor innervation from so-called fusimotor neurons (Chapter 8).

1.3.6 Re-afference Principle

One great problem with sensory signals is that they may change as a result of external events or as a result of own-body movements, and these two situations must be distinguished for accurate perception and motor control.

For example, movements of the eyes or head or body through space change the sensory inflow to the CNS and could thus destabilize the representation of the surrounding space in relation to the body and consequently compromise accurate perception and target-directed movements in space. It is essential, however, that the representation of the external world remains constant or stable for perceptual and action purposes. The CNS must therefore be, and indeed is, able to distinguish between self-generated sensory changes (re-afference) and externally generated sensory changes (ex-afference) (Brooks and Cullen 2019; Medendorp 2011). One basic mechanism uses so-called →efference copies (Perrone and Krauzlis 2008; von Holst and Mittelstaedt 1950; called →corollary discharge by Sperry 1950). The concept of →efference copy comes in different versions, with early precursors dating back to von Helmholtz (1867), and has been applied to circuits in various animals (Crapse and Sommer 2008; Feldman 2016).

At first glimpse, the basic idea is simple. For example, during self-generated movements of the eyes or head or body through space, the externally generated sensory changes could be re-constructed by subtracting the self-generated sensory changes from the actual total sensory inflow. The self-generated sensory changes could be estimated and computed by a feedforward system deriving its input from a copy of the motor outflow and feeding back onto the systems processing sensory information. Simple as this idea appears, it requires that the copy system, to be precise, should take into account the possibly complex transformations from motor signals to sensory signals with possibly different →coordinate systems. The only way to establish such a precise model, if existent, appears to be by adaptability and learning (Schwartz 2016; below). Other objections have been raised against the re-afference principle based on efference copies, and an alternative has been suggested (Feldman 2016).

1.4 Classes of Movement

As a first attempt at order, movements can be broadly grouped into different classes: →Reflexes provide an appropriate response closely coupled to a sensory input of some sort. Motor activity is required to maintain posture, which is the necessary support for any dynamic movement. Rhythmic movements include over-ground locomotion, swimming, flying, scratching, mastition, breathing (Chapters 21-23). Voluntary are goal-oriented movements, such as reaching, grasping and object manipulation (Chapters 24-26). While stimulus-driven reflexes are at one end of a spectrum of movements, voluntary movements are at the other end (Haggard 2008). But such a classification must be taken with caution, as will become evident below.

1.4.1 Reflexes

A reflex has often been defined as a stereotypic motor response tightly coupled to a sensory stimulus. But although there are examples of such responses which have often been studied in isolation and under restricted conditions (below), "...a simple reflex is probably a purely abstract conception, because all parts of the nervous system are connected together and no part of it is probably ever capable of reaction without affecting and being affected by various other parts..." (Sherrington 1906). Hence, "... reflexes are not separate entities, but are in fact closely integrated into all movements that we perform..." (Nielsen 2016).

Stretch Reflex. An example of a `simple´ reflex involved in →closed-loop feedback control is the phasic →stretch reflex or →tendon reflex. When a reflex hammer strikes the Achilles tendon, the calf muscles contract a little later because the hammer indents the tendon and stretches the attached calf muscle fibers. Dispersed in parallel among the muscle fibers are muscle spindles, which are excited by the stretch. The excitation is conveyed by group Ia afferent fibers to the →spinal cord, where it activates →skeleto-motoneurons with large diameter, fast-conducting axons that innervate and activate muscle fibers, causing them to contract. The stretch stimulus is, at least partially, counteracted by the reflex contraction, which occurs initially with an onset time of about 40 ms. "The knee jerk itself is seen as a `physiological artefact´, resulting from a mode of stimulation that does not occur in life, with the normal function of its underlying circuitry still under debate" (Matthews 1990), but still neurologists use it for diagnostics. Stretch reflexes may consist of sequences of components at different latencies generated by different stretch receptors and different neural pathways. Overall, the reflex regulation of muscle length and force is fairly complicated (Chapter 19). Finally, even the gain of the monosynaptic tendon reflex underlies central regulation.

Vestibulo-ocular Reflex (VOR). One of the phylogenetically oldest and arguably simplest reflexes is the vestibulo-ocular reflex (VOR) (Chapter 16). When the head is passively rotated in the dark about a vertical axis, the VOR generates slow eye movements in opposite direction to keep the image of the external world on the retina stable. When the retinal image is perfectly stabilized, the VOR has a gain of 1, defined as eye velocity, Ė, divided by head velocity, Ḣ. The core neural element of this reflex is the so-called `three-neuron arc´, consisting of sensory hair cells in the semicircular canals and otolith organs of the vestibular system (Chapter 10), neurons in the →vestibular nuclei and oculomotor motoneurons (Chapter 15). This reflex is an open-loop reflex because the output (eye movement) does not have a feedback effect on the input (head movement). Like the gain of the spinal monosynaptic

reflex, the VOR´s gain can be adapted to changing circumstances, which are examples of sensory-motor adaptation and learning (Thompson and Wolpaw 2014), as well as →habituation and →sensitization (Funahashi 2009; Grau 2014).

Withdrawal Reflex. Another example of an open-loop reflex, again phylogenetically old, is the withdrawal reflex (Schouenborg 2002; Sandrini et al. 2005). Open-loop reflex responses must often be rapid to escape →noxious stimuli and tissue insult. For example, when a human subject sitting in a comfortable armchair is stung by a wasp in the foot, he/she will withdraw the leg (→flexion reflex) without severely jeopardizing posture. In a standing subject, though, withdrawal of the affected foot would have to be →balanced. Extensor muscles of the contralateral leg are activated (crossed extension reflex) and body mass is shifted to the contralateral side to maintain upright stance (Chapters 19, 20). In general, reflex responses depend on initial and contextual conditions, in that their magnitude and at times their sign (excitatory or inhibitory) are modulated, for example as a function of the phase of the locomotor cycle.

Wiping Reflex. The wiping reflex in frogs is an example of fairly complex reaction. When a frog is placed on a platform with three legs fixed and the right hind leg free to move, paper soaked with a noxious acid placed on the right forearm causes the right hindleg to perform a withdrawal sequence of movements to remove the noxious stimulus (Chapters 4, 5). First, the toes of the free hind leg are placed close to the stimulus (the postural component), the paper is whisked away (extension movement), and another flexion movement brings the toes back close to the stimulus. The latter two phases may be repeated in a rhythmic fashion, depending on the success of the first whisking phase. This movement pattern can be adjusted to varying external circumstances such as the position of the stimulus, and the frog´s body configuration (Fukson et al. 1980).

Complexity of Reflexes. As exemplified above, reflexes are variably complex because of composition, modifiability and flexibility, and sensory-motor transformations.

Reflex Composition. The withdrawal reflex and the frog´s wiping reflex are anything but simple stereotypic reflexes. The withdrawal reflex is a whole-body reaction that recruits several systems depending on the initial posture. The wiping reflex of the frog, as well as the scratch reflex of cats, dogs and turtles, are composed of sequences of postural, goal-oriented and rhythmic components triggered by sensory input, which are set up by different neural sub-systems (see Windhorst 2009). Because reflexes may be intricate behaviors, the term reflex has lost its original connotation of simplicity and stereotypy.

Reflex Modulation. Reflexes are flexible and modifiable. The magnitude and sign of reflexes depend on the task and the contextual circumstances, and often vary throughout a movement, e.g., during locomotion.

Sensory-motor Transformations. Reflex transformations are of two basic types: *spatial transformations and kinematic-to-kinetic transformations.* Vectors of spatially distributed sensory signals are converted into vectors of muscle actions by spatial transformations. For example, in the scratch or wiping reflex, the two-dimensional (2D) array of cutaneous receptors is transformed into three-dimensional (3D) limb movement. In addition, because many sensory inputs are related to movement (kinematic variables), while muscles primarily produce forces (kinetic or dynamic variables), kinematic-to-kinetic transformations are essential (Poppele and Bosco 2003).

1.4.2 Posture and Equilibrium

Most movements involve aspects of more than one class. All movements in some way require posture as a basis to work on. In terrestrial vertebrates, whose bodies are maintained above the ground by legs, posture depends on some basic excitatory →muscle tone from muscle groups that counteract gravity, as well as on reflexes (Chapter 19). In addition, rhythmic and goal-oriented movements make use of reflexes. Conversely, reflexes may incorporate rhythmic components.

Postural orientation and equilibrium are mutually interactive, whether standing in place or during locomotion, and mutually modulated by the CNS.

Postural Orientation includes positioning of body segments relative to each other and to the environment. Of outstanding importance is the orientation of the body to gravity. Trunk orientation is an important variable to be controlled because it determines the orientation of the limbs relative to objects to be interacted with. Trunk and head position together determine the head´s position in space, which is essential for interpreting sensory data from head-based (vestibular, auditory and visual) receptors. During many complex tasks, many animals stabilize their heads in space in order to keep the retina and →vestibular apparatus in a relatively constant position relative to the environment, at least temporarily. Nonetheless, body orientation and posture influence and modulate the perception of the world (Dakin and Rosenberg 2018; Harris et al. 2015; Lacquaniti et al. 2015).

Postural Equilibrium (or →balance) is defined by the state in which all the forces acting on the body are in equilibrium. This state can be static or dynamic. In static postural equilibrium, the body stays in the desired position and orientation, while in dynamic postural equilibrium, it moves in a controlled way.

1.4.2.1 Reference Values

Posture and equilibrium need references existing in the outside world, as well as own-body references.

Outside-world References are used for orientation and ordered movement in the world. One important reference is up and down, where gravity supplies a convenient signal. Gravity is used by the CNS as a reference for space and time perception and the organization of movement (Lacquaniti et al. 2015; Pozzo et al. 1998). Some animals may use other fields as reference, such as electro-magnetic fields. For many sea and terrestrial animals, the proper alignment of one of their body axes with the up-down axis is essential for organizing movement. This is particularly evident for terrestrial animals standing and moving on legs with the trunk suspended above the ground.

Own-body References are needed to define a framework, within which one body part (e.g., a limb) moves with respect to the rest of the body. Such a framework is usually called a body schema. Body schemata take several forms (Sect 1.7.2).

1.4.2.2 Anticipatory Adjustments

Dynamic movements pose a critical challenge related to Newtonian mechanics, namely acceleration. When, for instance, a limb is accelerated, a reaction force that affects the rest of the body counterbalances the generating force. Neuromuscular mechanisms account for these effects in order to prevent disturbances of equilibrium.

For example, when a subject is asked to maintain the right forearm in a horizontal position against a load of 1 kg, and the load is removed either by an experimenter or by the subject himself with the left hand, the change in forearm position is relatively minimal during voluntary unloading. The →electromyographic (EMG) activity in the right elbow flexor muscles is reduced in parallel with an increase in left biceps brachii muscle activity before unloading began, attesting to the anticipatory nature of the brachio-radialis brachii muscle activity (Viallet al. 1992).

Another example of anticipatory adjustment is voluntary abduction of the left leg during stance, which requires an anticipatory shift of the body´s →center of mass (COM) above the support surface of the right foot to maintain equilibrium (Chapter 19). Usually, this is accompanied by a leftward flexion of the head in order to keep it vertical as reference for visual perception (postural adjustment). These anticipatory adjustments are open-loop, as shown in a case report of a patient who suffered from selective loss of touch, pressure and kinesthetic sensation (Chapter 9). The patient was still able to produce the correct postural adjustments, independent of peripheral sensory feedback (Forget and Lamarre 1990). Anticipatory adjustments are mostly learned from experience, many of them in early childhood.

1.4.3 Rhythmic Movements

Even unicellular organisms such as Paramecium easily move by rhythmically beating flagellae (Brette 2021). In multi-cellular organisms, the actual movement pattern is co-determined by the mechanics of the body components and the environment, but the driving and organizing control signals are delivered by neuronal networks, so-called central pattern generators (CPGs) at spinal and →brainstem levels, whicht are capable of generating the basic rhythmic and patterned muscle activities (Chapter 22).

For terrestrial locomotion, the CNS must make context-dependent choices and produce adequate activities: initiate and stop locomotion, select the direction and the appropriate speed and associated gait pattern. During the locomotor phase, the CNS must generate basic patterns of rhythmic muscle activities, coordinate different limb activities, maintain balance and equilibrium during the dynamic movements, and adjust the basic locomotor pattern to changing contexts and behavioral goals. In quadrupedal animals, the hindlimbs produce the bulk of forward thrust, and the forelimbs support the head and are used for propping and steering (Yamaguchi 2004). Different gaits require different coordination patterns for leg and back kinematics, and for forward walking and backward walking. Consequently, different patterns and →synergies of muscle activations are necessary.

1.4.3.1 Central Pattern Generators

Conceptually, CPGs can be divided into rhythm-generating networks and pattern-generating networks (Chapter 22).

Rhythm-generating Networks (Clocks) establish the fundamental frequency of locomotor rhythm, which must be variable to accommodate different gaits. Locomotor CPGs in several vertebrate species are composed of and divided into sub-components. Each utilizes genetically and molecularly diverse →interneuron sub-populations with different →ontogenetic developments, which play different roles within networks and are subject to neurotransmitter modulation (Chapter 22).

Pattern-formation Networks orchestrate precise spatial and temporal activation patterns in different →motoneuron pools that are necessary to generate coordinated muscle contractions of the musculo-skeletal periphery required for a particular movement, such as the human walking pattern. The spatio-temporal muscle activation patterns need to be tailored to the peripheral →biomechanics of the limb and the muscles acting on it. This requirement is satisfied, in part, by sensory feedback (Chapter 22).

1.4.3.2 Role of Sensory Inputs in Rhythmic Movements

Sensory inputs have diverse roles in locomotion. Proprioceptive feedback reinforces ongoing motor output, shapes muscle activities and contributes to timing the transitions between the different locomotor step phases. It also plays an important role in adjusting the basic locomotor rhythm to environmental conditions and in compensating for unexpected perturbations. Various sources of sensory feedback change throughout the gait cycle, and all known spinal reflex pathways are modulated during locomotion. Sensory information most appropriate for the particular step phase is selected by the CPGs (Büschges 2005; Duysens and Forner-Cordero 2018; Hultborn and Nielsen 2007; McCrea 2001; Pearson 1993, 2008; Rossignol et al. 2006; Windhorst 2007) (Chapter 22).

1.4.3.3 Supraspinal Controls

For behavioral flexibility, the CPGs must be controlled by various other inputs:

General Activating Systems →arouse the animal to new and unexpected stimuli and initiate appropriate actions. For example, sudden attack by a predator must →alert the subject to make an immediate decision about →fight or flight or play dead, in all cases implicating changes in posture and locomotion.

Motivation Systems. Most often, locomotion is goal-directed by motivational brain systems, such as the →limbic system (Morgane et al. 2005; Morgane and Mokler 2006; Zahm and Heimer 2009) (Chapter 23).

Supraspinal Locomotor Drive Systems provide energizing sources for posture and for mobilizing the CPGs (Chapter 23).

Adaptive Fine-tuning Systems provide, in particular, anticipatory adaptations to upcoming events, whose detection and processing require higher-level sensory systems (Chapter 23).

Navigation. Obtaining food and water, finding mates, avoiding predators or chasing prey require goal-oriented locomotion and navigation, which in turn require →cognitive spatial abilities (Chapter 23).

1.4.4 Voluntary Movements

Voluntary movements enable the brain to communicate with the external world (Schwartz 2016). They appear more versatile and less restricted than reflexes and locomotion and typically include reaching, grasping and object manipulation (Chapters 24-26). They may make use of reflexes and CPGs as subsidiary devices. They also require postural adjustments. →Skilled movements may have their evolutionary precursors in food-handling behavior, dating back to early tetrapods (Iwaniuk and Whishaw 2000), and are expressed in precision walking on complex ground, where accurate foot placement is of essence, and in arboreal locomotion in non-human →primates, which requires precise reaching for, and grasping of, tree branches (Grillner and Wallín 2004). They usually require excellent visuo-motor coordination at cerebro-cortical level. The term *coordination* is here used in two ways: as an ability to perform motor tasks in an efficient way (→dexterity, skill), and as a purposeful pattern of actions by a set of effectors (Latash 2009).

1.5 Freedom and its Limitations

Freedom to move is not unbounded. Generation and control of movements introduces a number of requirements and constraints that have evolved by specialization to meet the particular demands of particular organisms. While specialization opens certain options, it also generates constraints. For example, peripheral instruments or tools that a subject uses to move not only enable movement, but also limit its extent, speed etc., by their specific properties. These properties must be taken into account by the nervous system when controlling and using these tools.

1.5.1 External and Internal Challenges and Constraints

External constraints are imposed in part by Newtonian mechanics, which define the movements of bodies in space under the influence of gravity and inertia. Movements also encounter different resistances and dynamics in air, liquid or solid media, and need to be adequately adjusted and controlled. Internal constraints are imposed by skeletal structure, joints, cartilages, capsules, ligaments, tendons and muscles, which introduce non-linearities in locomotion and fatigue in skeletal muscles. The nervous system must take into account the properties of its peripheral instruments and those of the external world. Proprioception appears well suited to contribute to the solution of challenges resulting from the mechanics of the musculo-skeletal system. There is compelling evidence (Hasan and Stuart 1988; Stuart 1999; Windhorst 2007) suggesting that proprioception corrects to some extent for non-linear muscle properties and partially compensates for →muscle fatigue, muscle´s lever-arm variations at joints and for inter-segmental interaction effects (Chapters 17, 19).

1.5.2 Degrees of Freedom

Many animals possess multi-segmented skeletons made up of hundreds of bones linked at joints. For example, the human skeleto-muscular system has over 200 joints operated by some 600 muscles (Franklin and Wolpert 2011). This construction principle provides for a multitude of options for moving the segments relative to each other and through space. The options are commonly referred to as →degrees of freedom (DOFs). DOFs are the number of variables needed to describe a body´s motion in space (Shrive and Frank 1994; Zajac and Gordon 1989). The DOFs can change during a motor act, as easily seen when a human being lands from a jump. In the sagittal plane, the number of DOFs decreases by 2 when the toes make contact with the ground and by 1 more when the sole is flat on the ground. In vertical jumping, this sequence is reversed, with the number of DOFs increasing (Zajac and Gordon 1989).

1.5.3 Bernstein´s Problem

The construction principle of multi-segmented skeletons poses a problem referred to as →Bernstein´s problem (Bernstein 1967).

Depending on the type of joint, the distal segment can be moved in up to three DOFs with respect to the proximal one. For example, in a ball-and-socket joint, such as the human shoulder joint, there are two dimensions for extension-flexion and abduction-adduction, and one for rotation. This allows the humerus to be aimed at any point in almost half a sphere. Assembling bones into limbs with several joints increases the number of DOFs. The consequence is that a desired position of the index finger in external 3D space could be realized by an infinite number of different combinations of joint angles. This problem arises whenever the combined number of directions, into which joints of multi-joint limbs can move, exceeds the three-dimensionality of external space. This redundancy of possibilities holds for many postures and movements. Theoretically, there are an infinite number of possible movement trajectories to reach the same target, leaving the CNS with a selection challenge (Franklin and Wolpert 2011). In addition, there are often more muscles spanning and influencing a joint than the joint´s number of DOFs. Redundancy also results from other circumstances: Thus, a particular joint torque can be generated by many muscle activation patterns, and a particular muscle activation can be generated by many neural activation patterns (Karniel 2011; Latash 2012).

1.5.4 Exploiting Freedom

Redundancy in DOFs also has advantages. It allows for flexibility, stability and accuracy. Taking the example of fingertip localization, arm orientation at the shoulder joint is usually less precise than fingertip location, such that more distal joints can compensate for errors committed by more proximal joints (Darling and Miller 1993). Therefore, redundancy can also be considered a virtue to be exploited rather than a problem to be solved. This has recently been emphasized by a hypothetical `principle of abundance´, stating that no DOF is ever eliminated or frozen, but instead all DOFs always participate in all the tasks, thereby assuring both flexibility and stability of performance (Scholz and Schöner 1999; Latash 2012).

1.5.5 Constraining Freedom

Practically all movements are reigned in by various mechanisms. A rough distinction can be made between mechanical constraints of the musculo-skeletal system itself and the nervous system dealing with the peripheral system.

The cat hindlimb with its hip, knee and ankle joints is an example of mechanical mechanisms that can constrain movement and contribute to reduced DOFs. If each of these joints were assumed to be a hinge joint with one DOF, then the hindlimb would be a 3-DOF linkage of segments that allows 2D movement in a parasagittal plane, i.e., a reduction in DOF. One possible way to bring this about is to constrain the independence of movements in the different joints, i.e., to tightly couple changes in the three joint angles of the hindlimb. This coupling indeed occurs during both passive and active limb movements. The relationship among the three joint angles shows a planar or 2D co-variation over a large range of limb positions (Lacquaniti et al. 2012; Poppele and Bosco 2003). Both biomechanics and neural factors account for the co-variation.

Biomechanics. In a passive limb, bi-articular muscles spanning two joints as well as passive structures such as ligaments are involved in coupling. During limb movement, inter-segmental →interaction forces may contribute to couple the movements of limb segments (Bosco and Poppele 2001). Moreover, several biomechanical mechanisms related to joint shapes, joint capsules and ligaments reign in freedom of movement.

Neural Factors. It has been hypothesized that so-called →synergies could help reduce redundancy (Bruton and O'Dwyer 2018; Latash 2020). The neural systems involved in organizing synergies are complex and manifold and are spread throughout the entire →neuraxis (Santello et al. 2013; Windhorst 2007). It appears that synergies in part utilize inborn neuronal networks, and in part are acquired by learning (Lacquaniti et al. 2012).

1.6 Kinetics

Posture and movement require forces to initiate and/or maintain them against →visco-elastic and inertial properties of the body and its parts suspended in a gravitational field. This is the kinetic or dynamic aspect of movement organization.

1.6.1 Muscles and Inter-segmental Interactions

The kinetic characteristic of movement plays a significant role in interactions between the different body segments. Because body segments are coupled at joints, motion of a segment acts on those of other segments, such that the contraction of an individual muscle accelerates movement not only in the segments that it originates from and inserts on, but also in remote segments via inter-segmental interactions that also depend on the joint angles and angular velocities (Hasan and Stuart 1988). In any case, inter-segmental mechanics clearly contribute to dynamic motor acts, which must be taken into account by the nervous system in organizing the coordinated muscle activations.

In summary, the kinetics of body movements involves complex interactions between internal and external forces and torques. Mathematical concepts have proven useful to evaluate the forces involved in such a complex system and how the nervous system acts on them. Calculation of internal forces based on movements and external forces is termed inverse dynamics. Computation of movements and external reaction forces based on known internal forces is called forward dynamics (Otten 2003).

1.6.2 Forward and Inverse Dynamics

Forward Dynamics. The sequence of events in the musculo-skeletal periphery, referred to as forward (direct) dynamics (Otten 2003; Zajac and Gordon 1989) is as follows. Muscle excitations by motoneurons are the inputs and body motions are the outputs. If there are *m* muscles, their inputs are reflected in the electromyographic (EMG) signals, $EMG^1 ... EMG^m$. The activations are transformed into the set of muscle forces, $F^1 ... F^m$. These are converted, depending on musculo-tendon dynamics and moment arms *R(F's)*, into a set of →muscle torques at *n* joints, $T_1^{mus} ... T_n^{mus}$. These torques finally are transformed into sets of joint angles $\Phi_1 ... \Phi_n$, their velocities and accelerations, which ultimately result in the motion of the limb end-point. There are some feedback loops because, for example, joint angles determine muscle lengths and these in turn co-determine muscle forces (Chapter 18). On the whole, however, this is a feedforward scheme, and indicates that the input signals should be precisely tuned to achieve the correct output.

Inverse Dynamics. It has been suggested that the CNS plans reaching/grasping movements in terms of extrinsic coordinates of hand position and/or trajectory in peri-personal space. Although other suggestions have been put forward, it is instructive to consider the consequences of the kinematic model. Conceptually, the desired trajectory would have to be transformed into the appropriate muscle activation patterns as follows:

Desired trajectory → joint angles → joint torques → muscle forces → muscle activation patterns.

If the CNS used this approach, it would have to take into account the dynamics by inverting them. That is, in order to achieve the desired movement trajectory, the planned trajectory must be implemented by a process compensating for the forward dynamics described above. Thus, body positions would be the inputs, and the flow of events is inverted. From the desired end-point movement in extrinsic coordinates, intrinsic joint angles (muscle lengths) can be derived from an inverse-dynamics calculation, which would successively yield joint velocities and joint accelerations, the net muscle torques needed to achieve them, the muscle forces needed to generate the torques, and then the excitations needed to generate the forces. An inverse internal model would perform such computations.

Computation of inverse dynamics is complex and often requires non-unique transformations. For example, individual muscle forces are not uniquely determined by net muscle torques because the latter can be achieved with many combinations of muscle forces. Also, the musculo-skeletal periphery has complex non-linear properties. Furthermore, the different segments in multi-joint limbs influence each other via inter-segmental interactions. These complexities result in myriads of equations of motion, all of which would be task-dependent. In order to solve the problems, the CNS would have to

somehow represent these equations as well as precise estimates of the initial and boundary conditions and parameters involved, such as the segment masses, locations of the centers of mass (COMs), principal axes of inertia, and moments of inertia (Hasan 1991). Moreover, the computation itself would have to be very accurate because even small errors, or small mis-estimates of initial and boundary conditions, could lead to large movement errors.

The above considerations are based on the presumption that the inverse-dynamics calculations would be performed in a feedforward fashion, i.e., without the CNS receiving feedback to correct for errors. Sensory feedback would alleviate some problems, but create others. First, considerable delays for visual or proprioceptive processing would occur. Therefore, fast (ballistic) movements would initially be uncontrolled by sensory feedback. Second, the gains in →feedback systems are usually low because high gains with long delays run the risk of instability. Two mechanisms may mitigate this risk. The gain of sensory (proprioceptive) feedback may be regulated and kept reasonably low by →presynaptic inhibition, exerted by specialized interneurons in the spinal cord (Chapter 19). Furthermore, rather than waiting for the actual feedback to arrive, estimating and predicting the expected sensory feedback by mechanisms located within the CNS could much reduce delays (Azim et al. 2014). This appears to be accomplished by predictive internal models.

1.7 Orientation and Movement in Space

Senses explore and movements pass through various sub-spaces that are of different importance to the organism and are neurally represented in multiple and different ways. Space representations in the nervous system in general vary widely, being constructed from multi-modal interactions between tactile senses, proprioception, audition and vision (Cléry and Ben Hamed 2018; Di Pellegrino and Làdavas 2015).

1.7.1 Functional Divisions of Space

Body Space and Extra-corporeal Space. The most immediate and obvious distinction of organism-related spaces is between space occupied by the body and extra-corporeal space beyond the bodily confines. While extra-corporeal space is usually perceived as unitary, the CNS has distinctive representations of far space and near space (Cléry and Ben Hamed 2018; Martel et al. 2016).

Far and Near Space. Far space is beyond arm´s reach and cannot be immediately acted upon. Near space or peri-personal space is here referred to as the space within arm´s, leg´s or mouth´s reach, where objects can be grasped and manipulated or where defensive and avoidance movements occur against threatening objects. These two functional spaces evidently require different neural organizations (Martel et al. 2016; de Vignemont and Iannetti 2015). Both far and peri-personal spaces must be sensed and represented centrally in order to be able to relate external objects to each other and to the body and its parts and to interact with them. Far space is sensed predominantly by vision and audition, while peri-personal space involves primarily the tactile, auditory and visual senses, both representations requiring multi-sensory integration (Cardinali et al. 2009; Serino 2019; van der Stoep et al. 2015). Peri-personal space representation is modifiable and extensible, for example by the inclusion of tools, such that part of distant space is remapped as `within reach´ (Arbib et al. 2009;

Cléry and Ben Hamed 2018; Di Pellegrino and Làdavas 2015; Holmes and Spence 2004; Macaluso and Maravita 2010; Makin et al. 2008; Martel et al. 2016; Serino 2019). The space representations may be used for the guidance of gaze in far space or hand-arm movements in peri-personal space.

Visual and Memory Space. Since orientation and actions are possible in the absence of vision, there must be an `egocentric memory´ of space. This representation is more panoramic than the visual space representation. Both need to be updated during movements of hands and arms, eyes, head and body as well as during locomotion, and must be re-aligned to each other (Land 2012).

Proprioceptive Maps. For reaching/pointing movements, the CNS needs a map representing hand and arm location with respect to other body parts. This proprioceptive map receives its input from all sensory sources that provide proprioceptive information, such as muscle spindles, Golgi tendon organs, joint receptors and cutaneous mechano-receptors. It thus differs from visuo-motor maps, but depends on visual input for calibrating and putting in register limb and target locations (Jeannerod 1991).

1.7.2 Body Schemata

There must also be a neural representation of the body itself. For perception and action, the nervous system must relate the positions and movements of the body parts to each other and to a representation of the external world (Chapter 9). Based on neurological findings linked to brain lesions, Head and Holmes (1911) distinguished body representations into a →body image and a body schema, the latter divided into a postural schema based on proprioceptive signals and a superficial schema based on cutaneous mechano-reception (Medina and Coslett 2010). Considerable research has been invested in defining, classifying and unraveling the neural implementations of CNS body representations, but there are still much confusion and debate (Berlucchi and Aglioti 2010; Di Vita et al. 2016; Harris et al. 2015; Martel et al. 2016). If the notion of body schema is to be retained, it seems necessary to be aware of three points. First, the body schema should be recognized as multiple, task-dependent, flexible and adaptable. Second, the body schema´s sensory basis, cutaneous mechano-reception and proprioception should be expanded to include inputs from small-fiber sensory afferents which convey →nociception, →itch, →thermoreception and pleasant touch, and which can contribute to actions directed toward the body (Berlucchi and Aglioti 2010). Third, →chronic pain can distort the mental representation of the afflicted body part´s size and posture or even neglect it completely (Tsay et al. 2015).

The postural body schema represents both the relative positions of body parts in space and the biomechanical properties of the body for motor action. It is also involved in keeping the body upright. It incorporates a representation of verticality, requiring sensory information on the earth vertical with respect to which the body can be aligned (Chapter 19). Probably, there is a locomotor body schema that is used in navigation to estimate step length and walking distance (Ivanenko et al. 2011).

While some body schemata require brain functions represented in the →frontal cortex (lobe) and →posterior parietal cortex (PPC) (Martel et al. 2016), some schemata appear to be implemented by lower CNS structures. The frog's wiping reflex was executed without a brain, so a schema in the isolated spinal cord allowed it to localize the stimulus on its body surface and to direct its right hind foot to the stimulus.

1.8 Frames of Reference

In order for spatial relations between sensory and/or motor events to be properly assessed and organized, reference frames, or coordinate systems, are needed. The sensory representations of position, orientation and motion of external objects and those of an animal´s body parts are based on sensory signals in different modalities, which are coded in different reference frames (Makin et al. 2008). The motor output system is represented by non-orthogonal intrinsic muscle space, defined by the directions in which muscle fibers contract or exert force. The directions are independent of extrinsic coordinates, and are determined only by the relations of body segments (Soechting and Flanders 1992).

To enable a reach for a target, the CNS must represent the locations of both the target and the initial hand position relative to the body, i.e., in an →egocentric frame of reference.

1.8.1 Target Position Reference Frames

Determination of target position involves several reference frames (Schwartz 2016). Generally, the reach target is first projected onto the peripheral retina and localized in a two-dimensional (2D) →retino-centric or →eye-centered reference frame. This representation is not invariant to eye-in-head position, so the CNS transforms the retino-centric target position into a 3D →head-centered reference frame, taking account of the action of the eye muscles and using →extra-retinal (proprioceptive) and/or motor efference copy signals (Sect 1.9). Since the head can move on the trunk, another transformation of target position into a →shoulder-centered reference frame follows, using neck proprioceptor signals. A final transformation yields a →hand-centered reference frame using body and arm proprioceptive signals (Schwartz 2016). A shoulder-centered reference frame could also underlie the organization of the muscle contractions needed to move arm and hand.

1.8.2 Hand Position Reference Frames

The position and movement of the hand can be described and assessed relative to at least two coordinate systems. Suppose the right arm to be held in a horizontal plane and viewed from above (direction of the *z*-axis). The hand position can be given in terms of an extrinsic, rectangular Cartesian coordinate system, where the *x*-axis is in a parafrontal and the *y*-axis in a parasagittal plane through the right shoulder. Alternatively, it can be described in polar coordinates as the direction and distance of the hand from the shoulder.

Another way of determining hand position with respect to the shoulder is by segment length l_1 of the upper arm and its joint angle a_1 with respect to the parafrontal plane through the shoulder, as well as by segment length l_2 and joint angle a_2 of the lower arm with respect to the direction of the upper arm, establishing an intrinsic coordinate system based on body geometry (Lacquaniti 1989; Soechting and Flanders 1992). It is clear that, if the CNS were to use both representations, it would have to rely on different sensory systems. Hand position in an extrinsic coordinate system could be determined by vision, while its determination in an intrinsic system would require the measurement of segment lengths and joint angles by proprioceptive receptors.

1.8.3 Coordinate Transformations

The existence of different reference frames or coordinate systems requires the CNS to transform the positions of limbs and their trajectories during movements from one system into the other, or else the representation in some common coordinate system. If the descriptions in different reference frames are to be compatible and exchangeable, they must be transformable. As an example, consider the transformation from joint angles to Cartesian coordinates, which is given by trigonometric relations in which l_1 and l_2 are segment lengths.

$$x = l_1.cos(a_1) + l_2.cos(a_1 + a_2) \quad (1a)$$
$$y = l_1.sin(a_1) + l_2.sin(a_1 + a_2). \quad (1b)$$

From equations 1a and 1b, it can be assumed that a neuronal network that would implement this transformation would have to receive convergent input signals from the independent variables. This requirement may be one of the reasons for the widespread *convergence* of many inputs onto many central neurons. Conversely, the inputs may affect more than one output, which in neural terms accounts for *divergence* of neuronal signals. In general, →coordinate transformations are much more complex than in this particular example.

1.9 Movement in Time

Perception and movements occur in space and time. In addition to spatial representations, the CNS must have ways of measuring, estimating and representing time, which is of crucial importance particularly in skilled movements such as goal-directed reaching, grasping, manipulation, tool use, music playing and speech. Timing goes beyond organizating the correct order of sequential elements of movement; it involves the precise timing of these elements relative to an external or internal reference point, e.g., a stimulus or joint state, respectively (Kornysheva 2016).

It might be assumed that to measure time would simply require a clock. Amazingly, although the CNS has clocks of different periodicity at almost all levels of organization, from individual neurons to neuronal networks, there is no single universal clock but a number of distributed structures and mechanisms involved in timing (Ashe and Bushara 2014; Kornysheva 2016; Merchant et al. 2015). In addition to rhythms, the CNS must be able to estimate durations and time intervals, but the precise mechanisms used to do so are still being studied and discussed (Bareš et al. 2018).

1.10 Sensory-motor Learning

The sheer complexity of the body and its environment and their diverse interrelations require that movements be adapted, learned or optimized for new conditions (Chapter 27). Motor learning ranges from low-level calibration of movements to high-level decisions about how to act in novel situations (Krakauer et al. 2019) and requires various forms of attention (Song 2019). The processes can be classified into two broad categories. One type, →motor adaptation, refers to the fast return of motor behavior to baseline performance level after perturbation. Examples are adaptation of the vestibulo-ocular reflex (VOR), adaptation of movements to altered visuo-motor associations; and adaptation of movements to altered dynamics.

Another type, →motor-skill learning, involves practice-related and experience-dependent improvements in motor performance (Shmuelof and Krakauer 2011). In everyday life, such processes are important for activities that require smooth coordination of finger movements, regular multi-joint movement synergies during reaching and grasping of small objects, or smooth coordination of eye-body actions. Improving motor performance often entails reducing the variability of successive actions, for instance in learning to play tennis or the piano to some perfection or learning movement sequences. Many learning processes involve use of internal models to adapt to new circumstances (Karniel 2011; Shadmehr et al. 2010) (Chapter 27).

In order to learn and adapt to changing circumstances, nervous system structures need to be →plastic. Many processes and mechanisms contribute to plasticity in structures all along the neuraxis. The establishment of the proper neuronal connections and →topographic maps at some critical stage of ontogenetic development in part relies on such processes, as does the change in such maps in adult life. Many of the basic events underlying learning, information storage and retrieval are thought to take place at a molecular level, in particular at synapses. →Synaptic transmission is vastly flexible or plastic, at time scales ranging from the order of milliseconds to life-long, but also structural changes also occur (Butz et al. 2009) (Chapter 27).

Even the most peripheral executors of movement, skeletal muscles, are plastic. They grow and strengthen during ontogenetic development and during exercise, and waste and weaken during aging and immobility and disease (Chapter 18).

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2

Taste

CONTENTS

Abstract

• The primary function of taste is to guard the chemical well-being of the body through the acquisition of nutrients and the rejection of toxins.

• The quality of potential food is assessed by other sensory properties: smell, temperature, touch, proprioception, audition and vision, requiring multi-sensory integration of signals from several senses.

• The quality of food is judged by various types of sensory receptor cells, including taste receptor cells located in taste buds. Taste buds include: fungiform, foliate, circumvallate and filiform papillae.

• Different receptor cells are specialized for salty, sour, sweet, bitter and umami substances, and perhaps fat.

• Central connections of afferent gustatory nerve fibers in the brainstem are involved in reflexes and emesis. Further projections to higher neural structures including the cerebral cortex are involved in the detection and recognition of tastes and the generation of emotions and reward.

• The neural coding of gustatory signals is complex, in particular because signals from various senses converge onto central neurons.

• For survival, animals must be able to discriminate between safe and edible or toxic food. Animals must therefore have mechanisms to remember the consequences of eating certain foods, that is, a taste memory.

2.1 Introduction

The primary function of taste is to guide ingestion and metabolism while guarding the chemical well-being, health and survival of the body through the acquisition of nutrients and the rejection of potentially harmful substances including toxins (Breslin 2013; Schier and Spector 2019; Vincis and Fontanini 2019). Oral taste receptor cells start processes for absorbing nutrients and adjusting metabolism (Roper and Chaudhari 2017). These processes are continued by extra-oral taste receptors from the brain to the gut, which sense nutrients and noxious substances after ingestion, and the nutritional state feeds back on the taste system (Behrens and Meyerhof 2019). The inputs from taste receptors elicit →reflexes (e.g., salivation upon biting into an acidic lemon), evoke the →perception of taste quality and →intensity, as well as positive and negative →emotions and →affects (e.g., pleasure, displeasure) (Olofsson and Freiherr 2019). The responses to different classes of chemicals (e.g., sweet or bitter substances) can be temporarily or permanently modified under certain conditions (e.g., nutritional deficiency) or through experience (Schier and Spector 2019). Taste is not just a passive assessment of a chemical stimulus, but an active prediction of effects that a chemical would have if swallowed (Scott and Giza 2000).

The →decision to ingest an item of food depends on other sensory properties, i.e., the →flavor which is synthesized from the taste, smell, texture and temperature of a food (Carleton et al. 2010; Schier and Spector 2019; Verhagen and Engelen 2006). Smell (olfaction), whose receptor cells are located in the nasal airways (and elsewhere), identifies biologically important environmental chemicals and, via the retro-nasal pathway, contributes to construct the complex flavor. Temperature co-determines potential food hazards. Touch contributes to evaluate the consistency and texture of food. Proprioception aids in the identification of food properties by active oral exploration including mastication and tongue movements. Audition analyses the →sounds of chewing or biting food. Visual appearance is provided by the far-sense of vision. Thus, the full-range evaluation of food requires →multi-sensory integration of signals from several senses, which occurs at various stages of neural processing (Braud and Boucher 2020; Spence 2015; Verhagen and Engelen 2006). Human taste and food preferences have a long evolutionary history (Breslin 2013) and change throughout life (Podzimek et al. 2018). Eating and drinking behaviors are influenced by →attention (Spence 2019).

2.2 Functional Anatomy of the Gustatory System

The classically defined sense of taste, originating from taste receptor cells in taste buds (Sugita 2009), occurs only in vertebrates and is always associated with feeding (Finger 1997; Kotrschal 2000). Most often, the taste bud network coexists with the more caudally distributed chemo-sensitive cells of the respiratory and digestive tracts (Roper and Chaudhari 2017; Sbarbati et al. 2010) as well as, in some species, cells on the outer body surface (Northcutt 2004).

2.2.1 Taste Buds and Receptors

The quality of food is judged by various →sensory receptor cells including taste receptor cells located in taste buds (Roper and Chaudhari 2017; Liman et al. 2014; Sugita 2009). With the exception of hagfishes, all vertebrates have taste buds (Northcutt 2004). In mammals, taste buds are located primarily in the tung epithelium, but also throughout the oral cavity, in the pharynx, larynx, epiglottis and at the entrance of the oesophagus. There are 2000-5000 taste buds in man, with a large variation.

Taste buds in mammals are aggregates of 30-100 individual elongated neuro-epithelial cells that are often embedded in specializations of surrounding epithelium, termed papillae. Taste buds on the dorsal lingual surface are contained within four major classes of papillae: Fungiform papillae are located on the anterior two-thirds of the tongue, each containing on average 3 taste buds (range 0-21). Foliate papillae, located on the postero-lateral sides, contain 600 taste buds on each side and are predominantly →sensitive to sour tastes. Circumvallate papillae, 8-12 in man with a trough separating them from the surrounding wall, confer a sour/bitter sensitivity to the posterior 2/3 of the tongue. Filiform papillae are mechanical and non-gustatory. While all tastes can be sensed across the whole tongue and other regions of the mouth with taste buds (epiglottis, soft palate), some areas are more responsive to certain tastes than others, and their central processing stages thus show some degrees of specificity and pattern of expression (chemotopy; Montmayeur and Matsunami 2002; Spector and Travers 2005; Yamamoto 2006).

On grounds of ultrastructure, gene expression and functions, taste bud cells have been classified into three main types. The most abundant type I cells (ca. 50%) appear to exert →glia-like functions. Type II cells (roughly a third) are chemo-sensitive to sugars, certain amino acids (umami) and/or bitter substances and express →G-protein-coupled receptors (below). Type III cells (2-20%) detect sour tastants (Behrens and Meyerhof 2019; Roper and Chaudhari 2017). At the apex of the taste bud, →microvillar processes of taste bud cells protrude through a small opening, the taste pore, into the oral milieu. Just below the taste bud apex, taste cells are joined by tight junctional complexes (Chandrashekar et al. 2006; Simon et al. 2006).

Normal taste cells function for only about eight to ten days and are then replaced by daughter cells of dividing epithelial cells that surround the taste bud (basal cells). The taste nerve endings, which innervate the taste cells, also continuously move and innervate new taste cells.

The taste receptors for bitter, sweet, and umami are expressed in many organs, including the upper and lower airways, cardiovascular system, gastrointestinal tract, genito-urinary system, reproductive systems, →immune system, and brain. Neither the roles of the extra-oral receptors nor those of their endogenous ligands that activate them are completely known as yet (Behrens and Meyerhof 2019; Dalesio et al. 2018; Freund and Lee 2018; Patel et al. 2018; Schier and Spector 2019)

2.2.2 Taste Receptor Innervation

Taste receptor cells receive →synaptic terminals from small →myelinated afferent sensory nerve fibers conducting at 1-5 m/s. The afferent nerve fibers innervate the taste bud at its base and ramify extensively, each fiber typically synapsing with multiple receptor cells.

The receptor mechanism involves an initial →depolarization at the apical receptor site, which generates local →action potentials in the receptor cell. These then cause synaptic activation by chemical transmission to the afferent sensory neurons. This peripheral arrangement thus classifies as a secondary receptor system.

2.2.3 Central Connections

Taste processing serves at least three purposes: sensory-discriminative identification of the stimulus as to its quality and intensity; ingestive →motivation which elicits or reinforces certain behavioral responses that facilitate or curtail ingestion (e.g., gagging, retching and emesis); and digestive preparation. These functions are executed by different neural systems (Schier and Spector 2019; Vincis and Fontanini 2019).

A sub-population of gustatory neurons in the rostral nucleus tractus solitarii (rNTS) project locally to →medullary motor nuclei, which are involved in oromotor, salivatory, and digestive reflexes, while a separate population of gustatory neurons originating in the rNTS terminate in the →parabrachial nucleus (PBN), primarily the medial PBN (mPBN). From there, two →forebrain-projecting gustatory pathways take origin. Some neurons in the mPBN project to the ventro-postero-medial parvicellular →thalamus (VPMpc) and thence to the gustatory cortex (GC). The second pathway from the mPBN targets various ventral forebrain structures, with strong inputs to the central →amygdala (CeA) and the lateral hypothalamus (LH) (Schier and Spector 2019).

Physiological, metabolic, →inflammatory and toxin-related blood-borne signals are sensed in circumventricular organs (*CVOs*) of the →hindbrain and forebrain (e.g., →area postrema, median eminence, subfornical organ, and the vascular organ of lamina terminalis) (Schier and Spector 2019)..

Reflexes and Emesis are organized at the →brainstem level. Signals from →cranial nerves VII, IX and X that contain information on the chemical properties of tastants are conveyed to the nucleus tractus solitarii (NTS) of the →medulla oblongata, the principal visceral-sensory nucleus of the brainstem. This is the level where somatic →reflex responses for acceptance or rejection of food (licking, swallowing, chewing, mastication, gagging), and →autonomic reflexes related to digestive processes are organized (Simon et al. 2006; Small 2006; Spector and Glendinning 2009). The area postrema with strong inputs to the NTS is located on each side of the fourth ventricle, rostral to the obex. Stimulation of an emetic chemotaxic center in the area postrema triggers vomiting.

Detection, Recognition and Evaluation of Tastes depend on higher neural structures. Ascending connections from the NTS differ in rats and →primates. Rats have an important intermediate station, the parabrachial nucleus (PBN) of the pons. From here, a first pathway projects to the ventro-posterior medial nucleus, parvocellular part (VPMpc), of the thalamus, the →taste thalamus. The PBN also sends projections to the central nucleus of the amygdala, lateral →hypothalamus, bed nucleus of the stria terminalis (BNST), and to a lesser extent the diagonal band of Broca and the lateral preoptic areas (Vincis and Fontanini 2019). In primates, second-order NTS fibers bypass the PBN and project directly to the VPMpc. VPMpc projects to the anterior →insula/→operculum hosting the primary taste cortex. Less dense VPMpc projections end in the taste region of →primary somatosensory cortex (area 3, area 1, area 2), which primarily receives mechano-sensitive signals from the tongue and oral cavity, so that taste and touch processing are related in this area (Kaas 2005; Small 2006). The primary taste cortex in insula/operculum projects to various →sub-cortical and cortical regions, including the amygdala, →midbrain →dopaminergic regions (indirectly via the amygdala), lateral hypothalamus, medio-dorsal thalamus, →nucleus accumbens, piriform nucleus (which integrates gustatory and olfactory information), →anterior cingulate cortex (ACC) (the `tertiary´ taste area), and the →orbito-frontal cortex (OFC), hosting the secondary taste cortex. Taste neurons in the OFC receive inputs from the primary olfactory cortex, which could contribute to flavor perception, and from the lateral hypothalamus, whereby OFC taste responses can be modutated by satiety. Cortical taste areas also send efferents to the rostral NTS and PBN, enabling →top-down modulation of gustatory processing in the brainstem (Bermúdez-Rattoni 2004; Hallock and Di Lorenzo 2006; Scott and Plata-Salamán 1999; Simon et al. 2006; Small 2006; Vincis and Fontanini 2019; Yamamoto 2006).

Reward and Emotion. The orbito-frontal cortex (OFC) contributes to the conscious perception of tastes and is strongly involved in evaluating the →reward value of tastes and other stimuli. The OFC also contains the secondary olfactory cortex and tertiary olfactory cortex, in which the identity and reward value of odors are represented (Rolls 2015). OFC receives further inputs from somatosensory, auditory and visual areas, thus allowing for associations between different aspects of food (Barbas 2007; Rolls 2015; Wallis 2007). The OFC has reciprocal connections with the amygdala, whose neurons are also involved in evaluating the reward and →hedonic value and the palatability or aversive nature of tastes (Schier and Spector 2019). The OFC and amygdala project to the lateral hypothalamus which is also involved in reward signals from taste, smell and vision. In addition, the OFC and amygdala project to the →striatum of the →basal ganglia, which contains neurons responding to taste, flavor or the sight of food and may be involved in the formation of →habits (Rolls 2015; Vincis and Fontanini 2019).

Human Brain Imaging. Meta-analyses of many studies yielded a functional taste map including bilateral anterior insula and overlying frontal operculum, bilateral mid-dorsal insula and overlying operculum, bilateral posterior →insula/→parietal operculum/postcentral gyrus, left lateral orbito-frontal cortex (OFC), right medial OFC, pre-genual anterior →cingulate cortex (prACC) and right medio-dorsal thalamus

(Veldhuizen et al. 2011), as well as →hippocampus and →caudate nucleus (Olofsson and Freiherr 2019). A later study presented three different meta-analyses regarding the taste dimensions quality, intensity and affective value, showing differential activation clusters in response to different gustatory dimensions. The quality and intensity of liquid tastants activated only the insula. Quality was processed in the right middle insula, whereas intensity was processed in the right antero-middle insula. The affective value was reflected in four clusters of activation (two in each hemisphere) bilaterally in the anterior to middle insula and eight clusters of activation outside the insula covering the middle and →posterior cingulate cortex, pre- and post-central gyri, caudate nucleus and thalamus. The right middle-dorsal insula was responsible for processing both the affective value and quality of taste (Yeung et al. 2018).

2.3 Processing of Gustatory Signals

Tastants are discriminated with respect to quality, intensity and affective value (pleasantness/unpleasantness). These dimensions are not independent because, for instance, the affective value may influence perceived intensity and vice versa, and these interactions depend on quality (Small 2006). The quality of one tastant may also depend on, and change with, the presence of other tastants. Furthermore, there are cross-modal interactions between taste and other senses, such as smell, irritation, temperature, touch, vision, which contribute to the construction of flavor (Spence 2015; Verhagen and Engelen 2006).

2.3.1 Taste Quality

Taste quality is organized along the dimension of physiological welfare, bounded by nutrients at one end and toxins at the other. To span this dimension, many types of taste receptors possessing several distinct →sensory transduction mechanisms and →ion channels have evolved, which serve distinct physiological needs (Liman et al. 2014; Roper and Chaudhari 2017; Scott and Giza 2000; Schier and Spector 2019) such as →energy balance (sugars, amino acids), electrolyte balance (salt), acid-base balance (pH) (acids, bases), and avoidance of toxins (→alkaloids and others).

Via the taste system, nutrients activate reflexes of consumption, release of dopamine in the ventral forebrain, and they induce positive reactions concerned with pleasure (→hedonics) (Spence 2015; Verhagen and Engelen 2006). At the other extreme, toxins →arouse rejection reflexes and negative taste hedonics. Rats reject chemicals in direct proportion to toxicity. Many toxins are bitter, hence bitterness is usually associated with rejection. Many animals (e.g., mammals such as rats and primates) have a taste system that permits an accurate assessment of toxicity across a broad range of chemicals of diverse physical characteristics (Scott and Giza 2000).

Taste sensitivity varies widely between individual humans. Part of the variation is due to genetic differences (Bachmanov and Beauchamp 2007; Drayna 2005; Reed et al. 2006; Roper and Chaudhari 2017). In general, several different primary taste qualities (sub-modalities) can be distinguished in the →cerebral cortex: salty, sour, sweet, bitter and umami (Lindemann 2001;

Montmayeur and Matsunami 2002; Rolls 2015; Spector and Travers 2005). Additional taste qualities have been suggested: calcium (Ca^{2+}) taste, metallic taste, fatty taste, starchy taste, and kokumi (mouthfullness, heartiness). Sensations that are mainly mediated by →trigeminal nerve (→cranial nerve V) fibers include irritation, pungency or spiciness, astringency, cooling, warmth, prickling or burning, caused by spices and herbs and the co-activations of tastants and mediating information on the food's texture, weight, and temperature (Olofsson and Freiherr 2019; Rhyu et al. 2021).

2.3.2 Excitation of Taste Receptor Cells

The ways that tastants act on the different types of receptors differ with respect to receptor location, binding selectivity and ion channel effects. In general, sweet, umami and bitter tastants are detected by type II receptor cells via G-protein-coupled receptors T1R and T2R; sour tastants are detected by type III cells expressing sour receptors OTOP1, an ion channel selectively permeable to protons (H^+) (Liman and Kinnamon 2021); and salty tastants by unidentified cells, both using ion channels in the →receptor membrane (Breslin and Huang 2006; Carleton et al. 2010; Chandrashekar et al. 2006; Dalton and Lomvardas 2015; Liman et al. 2014; Lindemann 2001; Roper and Chaudhari 2017; Schier and Spector 2019; Simon et al. 2006).

Sweet Taste is mediated by taste receptor type 1 (T1R) members 2 (T1R2) and 3 (T1R3) belonging to the G-protein-coupled receptor family and binding glucose, sucrose, fructose, and other carbohydrates as well as some D-amino acids. Binding to T1R receptors causes release of Ca^{2+} from internal Ca^{2+} stores. Elevated intracellular Ca^{2+} concentration leads to the opening of →transient receptor potential (TRP) channel subfamily M member 5 (TRPM5), which causes depolarization and firing of primary afferent nerve fibers. There appear to be T1R3-independent pathways for sweet stimuli via glucose transporter type 4 (GLUT4) and sodium/glucose cotransporter 1 (SGLT1), which transport glucose into the cell and transiently elevate →adenosine triphosphate (ATP) and thereby block ATP-inhibited potassium (K^+) channels leading to depolarization. T1R3-independent pathways may trigger physiological reflexes independently of taste perception, e.g., a small elevation of plasma →insulin concentration. Insulin is also increased by →glucagon-like peptide-1 (GLP-1) (or incretin) which is secreted by sweet-tasting receptor cells (Roper and Chaudhari 2017).

Umami Taste. Umami designates a savoury taste produced by some amino acids such as →glutamate and →aspartate. Umami stimuli act through several receptors. Monosodium glutamate appears to bind to T1R1-T1R3 receptors and to two →metabotropic →glutamate receptors, mGluR1 and mGluR4 (Roper and Chaudhari 2017). Binding to T1R receptors causes release of Ca^{2+} from internal Ca^{2+} stores. Elevated intracellular Ca^{2+} concentration leads to the opening of transient receptor potential (TRP) channel subfamily M member 5 (TRPM5), which causes depolarization and firing of primary afferent nerve fibers. mGluR4 activates a G-protein-mediated elevation of intracellular Ca^{2+} and primary afferent discharge. Monosodium glutamate may also stimulate →ionotropic glutamate receptors. Calcium (Ca^{2+}) enters, causing →neurotransmitter release and increased firing in primary afferent nerve fibers. Monosodium glutamate and arginine also activate →N-methyl-D-aspartate (NMDA) receptors, leading to influx of Na^+ and Ca^{2+} ions and activation of taste receptor cells.

Bitter Taste is elicited by an enormous variety of substances, from simple salts to large complex molecules. Bitter substances, often poisonous, bind to T2R receptors, causing release of Ca^{2+} from internal Ca^{2+} stores. Elevated intracellular Ca^{2+} concentration leads to the opening of transient receptor potential (TRP) channel subfamily M member 5 (TRPM5), which causes depolarization and firing of primary afferent nerve fibers. T2R receptors may respond to one or very few bitter compounds or to a broad array (Roper and Chaudhari 2017).

Sour Taste is mediated by intracellular acidification effected by extracellular acids. Weak organic acids, such as citric acid or acetic acid are more effective than strong acids such as HCl, probably because of greater membrane permeability. Protons (H^+) permeate the receptor cell membrane through proton →conductances, this influx causing a small depolarization, acidify the cell interior and block leak K^+ channels, resulting in further membrane depolarization (Roper and Chaudhari 2017). Acid-sensing taste receptor cells also mediate taste responses to external water, these responses being dependent on the internal state of the animal (Zocchi et al. 2017).

Salt Taste. It is still not clear exactly which taste cell and what →transduction mechanism underlie salt taste (Roper and Chaudhari 2017). One mechanism might be that, in rodents but not humans, sodium (Na^+) ions enter the salt-receptor cell through amiloride-sensitive epithelial $Na^{\pm}$ channels (ENaC), i.e., Na^+ channels that are characterized primarily by their high affinity for the diuretic blocker amiloride (Garty 1994). The entry of Na^+ causes a depolarization, calcium (Ca^{2+}) enters through voltage-gated Ca^{2+} channels initiating neurotransmitter release, which in turn results in increased firing in the primary afferent nerve fibers.

Taste for Fat? Most animals crave for fats. Sensitivity for dietary lipids, e.g., long-chain fatty acids, could also be a sixth gustatory modality based on lipid receptors in taste buds (Besnard et al. 2016; Roper and Chaudhari 2017). It is also increasingly recognized that many animals use their gustatory systems to detect other compounds, such as Ca^{2+}, CO_2, and water (Liman et al. 2014).

TRP channels are also found in somatosensory endings of nerve fibers travelling in the trigeminal (cranial nerve V), glossopharyngeal (cranial nerve IX) and vagus (cranial nerve X) nerves. Such endings often surround taste buds and mediate signals about mechanical, thermal and →nociceptive stimuli (Gerhold and Bautista 2009; Simon and Gutierrez 2017; Viana 2013).

2.3.3 Synaptic Transmission in Taste Buds

Several neurotransmitters are involved in →synaptic transmission within taste buds (Roper and Chaudhari 2017).

Sweet, umami and bitter tastants excite type II taste receptor cells via G-protein-coupled receptors. Type II cells release adenosine triphosphate (ATP) that activates postsynaptic sensory afferents via →purinergic receptors (purinoceptors) P2X. The released ATP and its decay products retrogradely reinforce ATP release from type II cells by actions on P2X and P2Y receptors. In addition, the released ATP excites type III receptor cells via P2Y receptors and induces them to secrete →serotonin (5-HT) and →γ-amino-butyric acid (GABA), which in turn

inhibit ATP release from type II cells. These also release →acetylcholine (ACh) which appears to increase ATP release from type II cells (Roper and Chaudhari 2017).

Type III taste receptor cells are activated by sour tastants, but also indirectly by sweet, umami and bitter tastants (above). Type III cells release serotonin (5-HT) in response to sour tastants in a depolarization- and Ca^{2+}-dependent way. Type III cells also release GABA which acts on →$GABA_A$ and →$GABA_B$ receptors in type II cells where it inhibits ATP release. $GABA_A$ receptors are also expressed by gustatory sensory afferents. Type III cells also contain →noradrenaline, the function being unclear (Roper and Chaudhari 2017).

2.3.4 Neuromodulation of Processing in Taste Buds

The responsiveness of the peripheral gustatory apparatus can be modified by a number of endogenous and exogenous chemical modulators. Thus, a multitude of peptide →hormones and the corresponding receptors are located in taste buds to coordinate taste perception with nutritional needs (Behrens and Meyerhof 2019). For instance, taste receptor cells contain receptors for the peptide →leptin that is released from fat cells following eating. Leptin selectively reduces the responses of chorda tympani afferents to sweet tastants, while such responses are increased by →endocannabinoids such as anandamide. →Cannabinoids modulate subsets of TRP channels (Muller et al. 2019). Modulatory influences are also exerted by →neuropeptides such as neuropeptide Y (NPY), →cholecystokinin (CCK), →galanin and glucagon-like peptide-1 (GLP-1), →capsaicin (active agent of chili), →menthol, →tannic acid, fatty acids and circulating hormones (Carleton et al. 2010; Gerhold and Bautista 2009; Loper et al. 2015; Simon et al. 2006). In addition, taste responses are influenced by temperature.

2.3.5 Neural Coding of Taste

In view of the complex interactions between taste cells enabling feedback and feedforward effects, the question arises as to how specific tastes are encoded in neural activity. Three hypotheses are being discussed: the →labeled-line code hypothesis, the →across-neuron pattern code, and the temporal coding hypothesis (Carleton et al. 2010; Chandrashekar et al. 2006; Hallock and Di Lorenzo 2006; Lemon and Katz 2007; Ohla et al. 2019; Roper and Chaudhari 2017; Simon et al. 2006; Spector and Travers 2005).

Labeled-Line Hypothesis. The labeled-line hypothesis is a fairly simple scheme of encoding sensory stimuli and, for taste coding, contends that there is a small number of basic tastes, each of which is signaled by an independent neural transmission line from the specialized taste cell to the highest processing levels.

Across-Fiber Pattern Hypothesis. This theory proposes that the quality of taste is signaled by the overall pattern of activity in a neuronal population (ensemble). Individual taste neurons are broadly tuned to stimuli representing different qualities as well as to stimulus intensity. Stimuli with similar tastes produce similar patterns of activity. The intensity of taste is represented by the total number of action potentials arriving at a given time from the population of fibers. Hence, individual gustatory neurons would contribute to the coding of more than one stimulus

parameter, which in turn implies that no single cell alone signals the quality, intensity and context of a taste.

Experimental testing of the hypotheses suggests that both may hold true at different levels. For example, at the level of taste receptor cells, T2Rs that detect bitter stimuli, do not exist in cells expressing T1Rs that detect sweet and umami tastes, and cells detecting sour tastes differ from T1R- and T2R-expressing taste cells. Even at this level, however, taste receptor cells are differently tuned to tastes, based in part by their interactions (above). At the level of primary sensory afferents, there are fibers that respond fairly specifically to an individual taste quality, while others have a wider reponse profile (below), implying that taste distinction would have to use ensemble coding (Roper and Chaudhari 2017). By and large, the peripheral sensory neurons appear more narrowly tuned than central gustatory neurons (Carleton et al. 2010).

Temporal Coding Hypothesis. Both the labeled-line and across-neuron pattern hypotheses have been criticized for not taking into account the temporal structure of neuron responses, such as systematic changes of firing rate over time, adaptation, rhythmic →bursting, timing of spikes during a response, sequence of interspike intervals, cooperative activity between synchronously firing neuron ensembles. Thus, during prolonged firing of central gustatory neurons, early response portions may convey information about taste quality, while later portions are related to palatability, which requires convergence of signals from various sources, in part mediated by feedback signals from higher processing stages. There is some experimental evidence to suggest that temporal codes are behaviorally important (Hallock and Di Lorenzo 2006; Lemon and Katz 2007).

Multi-sensory Integration. In addition to gustatory signals, taste-processing neurons also process non-gustatory information about food and eating, including texture, temperature and odor, as well as visceral signals concerning the post-ingestive effects of food and →homeostatic signals conveying the metabolic state. Gustatory neurons are also modulated by psychological, affective and →cognitive states associated with the present and past experience of eating (Vincis and Fontanini 2019).

2.3.6 Discharge Patterns of Primary Taste Afferents

Primary sensory afferents often convey mixed signals. Taste buds contain presynaptic cells, which, since they receive signals from differently tuned receptor cells, are more broadly tuned to different tastants including salty and sour. The presynaptic cells in turn transfer their signals, together with receptor cells, to primary sensory nerve fibers, so that these are generally more broadly tuned than receptor cells (Tomchik et al. 2007).

Single afferent fibers usually respond to combinations of basic tastes, albeit with different relative sensitivities (e.g., Ogawa et al. 1968). Afferents in the chorda tympani of the facial nerve (VII) that originate from the taste buds in the front of the tongue respond best to sweet and salty stimuli, moderately to sour tastants and less to bitter compounds, while fibers in the glossopharyngeal nerve (IX) respond best to bitter and somewhat less well to sweet and savory tastants (Small 2006). Hence, each individual fiber is unable to signal any pure taste quality. The broadness of tuning also depends on species. Chimpanzees exhibit a greater taste-fiber

specificity than any other mammalian species so far studied (Hellekant et al. 1997), and there is some degree of →topographical segregation (chemotopy) of the respective sub-populations of neurons (Simon et al. 2006; Small 2006).

2.3.7 Gustatory Activity from Brainstem to Sub-Cortex

Further taste processing occurs in complex networks according to three principles: First, taste responses of central neurons are more broadly tuned to different tastents than are peripheral neurons; second, neurons integrate →multi-sensory inputs and, third, are modulated by inputs from various other brain regions (Carleton et al. 2010; Vincis and Fontanini 2019).

NTS and PBN. The NTS receives, besides gustatory inputs, convergent olfactory, somatosensory (e.g., touch, texture of food and temperature) and lick-related signals and signals related to food quality conveyed in the trigeminal nerve from →thermo-receptors, →nociceptors and →mechanoreceptors located on the lips and in the oral cavity and lower down in the alimentary tract. In addition, the NTS receives vagal visceral afferent inputs signaling distension of the gut (Carleton et al. 2010; Simon et al. 2006; Vincis and Fontanini 2019). Similarly, the PBN also receives inputs conveying oro-sensory tactile information and various autonomic visceral signals related to nociception, respiration, blood flow, blood pressure and gastro-intestinal function (Vincis and Fontanini 2019).

Solitary-nucleus cell (NTS) activity can be modulated by a number of factors, such as intravenous concentrations of hormones (e.g., insulin and →glucagon), glucose, temperature, visceral inputs, and by →conditioned taste aversion (Schier and Spector 2019; Yamamoto 2009). The activity of NTS and PBN taste cells is modulated by inputs descending from various forebrain regions, in particular the central nucleus of the amygdala (CeA), the lateral hypothalamus (LH) and the gustatory cortex (Simon et al. 2006; Vincis and Fontanini 2019). In rats, the activity of gustatory afferents or NTS neurons is influenced by satiety, taste-related experiences and need states (Scott and Plata-Salamán 1999).

VPMpc. The VPMpc receives strong excitatory inputs from the gustatory cortex. Neuron discharge in the taste thalamus resembles that in NTS, in responding to gustatory, tactile and thermal stimuli. VPMpc neuron discharge also reflects the hedonic value of taste and the expectation of anticipated tastes (Vincis and Fontanini 2019)..

Lateral Hypothalamus. The lateral hypothalamus receives projections from the primary taste cortex, frontal cortices including the olfactory cortex, and from the amygdala and the PBN. It is involved in regulating feeding behavior and controlling energy balance. Neuronal activity is modulated by hunger and satiety, responds to palatable and aversive stimuli and rewards as well as to the hedonic value and expectations depending on the energy requirements (Vincis and Fontanini 2019).

Amygdala. Cells in the amygdala, receiving gustatory inputs from the brainstem, VPMpc and taste cortex, are broadly tuned and respond to multiple tastants as well as multiple modalities, e.g., taste and oro-sensory stimuli or taste as well as auditory and visual stimuli, but mainly encode the palatability and aversiveness as well as reward and hedonic values of tastes (Schier and Spector 2019; Vincis and Fontanini 2019).

2.3.8 Taste Processing in the Cerebral Cortex

In humans, taste stimuli activate the anterior insula/frontal operculum (primary taste cortex), orbito-frontal cortex (secondary taste cortex) and anterior cingulate cortex (ACC) (Rolls 2015).

Primary Taste Cortex. The primary taste cortex lies in the insular-opercular region. In rodents, it receives fibers from the PBN, the VPMpc, from →limbic structures, such as the amygdala, lateral hypothalamus, →prefrontal cortices, olfactory areas and from →neuromodulatory nuclei (→locus coeruleus and the nucleus basalis of Meynert). Neurons in the anterior insular cortex may carry nociceptive information, while neurons in the posterior insula relay visceral, somatosensory, and auditory signals (Vincis and Fontanini 2019). Thus the primary taste cortex is multi-sensory, with cells responding to tastants as well as mechanical, nociceptive, thermal and visceral stimuli (Carleton et al. 2010; Rolls 2015).

In rats, gustatory neurons are broadly tuned, the majority being modulated by more than one tastant, suggesting an across-fiber code. The responses to tastants show rich temporal structures. The taste cortex integrates information from various sources as indicated by the fact that gustatory neurons can respond to olfactory, somatosensory, auditory, visual and visceral stimuli. Gustatory neuron discharge also reflects the affective value of taste (hedonic value), expectations, and other cognitive states (Vincis and Fontanini 2019).

In awake monkeys, some individual cortical neurons may respond specifically to various taste and other stimuli, e.g., →viscosity, fat texture, temperature and capsaicin, but most cells are broadly tuned to tastants and may respond to gustatory, olfactory and somatosensory (temperature, oral movements) stimuli (Rolls 2015; Simon et al. 2006). In the insular-opercular cortex of cynomolgus macaques there are four differently sized, independent cell groups responsive to the main stimulants glucose, NaCl, HCl and quinine. The coding of taste quality is similar to that in humans. Most cells respond to several tastants, but to different degrees. Moreover, the response strength scales with the concentration of the tastants (Scott and Plata-Salamán 1999).

In summary, the insular-opercular cortex represents the identity and intensity of food by integrating information from smell, taste, touch, and visceral sensations. This integration is required to give food its flavor. Flavor is processed by a network of sensory and associative areas and the taste cortex appears to be one of the neural hubs. Taste cortex neurons also encode specific expectations and differentially respond to cues that predict different gustatory outcomes (i.e., sucrose and quinine), and they encode the valence of taste, i.e., whether a tastant is palatable or aversive. Gustatory activity is also strongly influenced by motor activity such as licking which results in rhythmic (6-12 Hz) activity. Whether this activity results entirely from movement-induced somatosensory stimulation of the mouth and tongue or also reflects motor components, is not yet well known (Vincis and Fontanini 2019).

Orbito-frontal Cortex (OFC) and Anterior Cingulate Cortex (ACC). OFC and ACC have been considered as higher-order gustatory cortices. The OFC contains the secondary taste cortex (Rolls 2015), with major inputs from the primary taste cortex, amygdala, and medio-dorsal thalamus, the latter also being the main source of olfactory information. The ACC is connected to the primary taste cortex, medio-dorsal thalamus and lateral hypothalamus. Neurons in both the OFC and ACC are broadly tuned to different taste qualities and can also respond to other

sensory qualities. OFC and ACC represent the sensory identity of rewarding and aversive stimuli and process rewards and expectations (Vincis and Fontanini 2019).

The posterior region of the OFC receives olfactory, somatosensory, auditory and visual inputs (Barbas 2007), which provides the basis for multi-sensory integration. In humans, partly overlapping and partly distinct areas of the OFC are activated by pleasantly sweet and unpleasantly salty tastes. Just thinking about tastes without actual gustatory stimulation (gustatory imagery) elicits activation of the frontal gyri, which may be due to retrieval of long-term taste memories (Jones et al. 2006).

Many of the OFC neurons in monkeys are unimodal in responding to odors or tastes, although some cells respond to combinations of stimuli. Neurons responding to both odors and tastes represent flavor which is learned by odor-and-taste associations (Rolls 2015; Thomas-Danguin 2009). Neurons may also respond to stimuli such as the temperature, viscosity of food and texture of fat in the mouth, and to visual objects or faces and/or their expression, in particular in association with their reward value. Associations between responses to visual and taste stimuli enable predictions of the taste associated with what is seen and contribute to the visual selection of foods (Rolls 2015).

2.4 Affective Value of Taste

In order to serve its biological function, a taste must be labeled with an affective value, i.e., be capable of arousing feelings or emotions. The affective value is influenced by factors such as quality, intensity, physiological significance, and by individual preference, internal state and experience. Although affective values associated with different taste qualities are innate, they can be modulated by dietary history or rewards (Olofsson and Freiherr 2019). The variety of these factors implies that extensive neuronal networks are involved, in particular the orbito-frontal cortex (OFC), anterior insula, →cingulate cortex, amygdala, hippocampus, striatum of the basal ganglia, and midbrain. Taste-related activity in the OFC is not scaled with intensity, but depends on hunger and satiety (Rolls 2004). Animals prefer sweet and fatty food and eat often more of it than necessary. Food palatability thus plays an important role in the regulation of ingestion, in which the hypothalamus is intricately involved (Yamamoto 2006). The ventral striatum and midbrain are more easily activated in anticipation rather than receipt of a pleasant taste, whereas the dorsal striatum and anterior cingulate cortex (ACC) are more easily recruited while tasting a pleasant food. The amygdala may play a role in combining affective value, intensity and novelty. While genetic factors may influence taste preferences, these are not immutable, but can change in the course of →learning (Rolls 2004; Schier and Spector 2019; Small 2006).

In humans, the identification of a chemical appears to be independent of its hedonic appreciation. In macaques, satiety induced by consumption of glucose leaves unaffected the activity of taste-related neurons in solitary nucleus and primary taste cortex. By contrast, cell responses in the secondary taste cortex, central nucleus of the amygdala and the lateral hypothalamus can be depressed by satiety, in a way specific to the food used to feed to satiety (Rolls 2004; Scott and Plata-Salamán 1999). Furthermore, internally generated attentional states and expectations influence taste processing, in which the →prefrontal cortex (PFC) plays an important part (Jones et al. 2006; Rolls 2015).

2.5 Taste Memory

It is of utmost importance for the survival of animals to be able to discriminate between safe and edible or toxic food. The choice of accepting or rejecting a novel tastant requires a capacity to classify tastes on a continuum from familiar-safe, most preferred and associated with pleasure, to new, aversive, arousing rejection and least preferred (Bermúdez-Rattoni 2004; Yamamoto 2006). This distinction must in part be learned and stored in taste memory (Yiannakas and Rosenblum 2017).

The first guard against poisoning is caution: When an animal encounters a new taste, it needs to be careful (taste neophobia). In case of no subsequent negative consequences, the new taste may be accepted and consumption increased (attenuation of neophobia). Otherwise, with malaise following, the new taste should be rejected (conditioned taste aversion) (Chambers 2018; Gallo 2009; Yamamoto 2009; Yiannakas and Rosenblum 2017).

Animals thus need to have mechanisms to remember the consequences of eating certain foods. These mechanisms must associate particular tastes and odors with post-ingestive well-being or malaise that may occur minutes to hours later. This is a paradigm of associative learning (Yiannakas and Rosenblum 2017). Signals that enable the association between a taste and gastro-intestinal consequences arise from specialized sensory cells in the gut and visceral sensory afferents, particularly in the vagus (X) nerve, which project centrally in parallel with gustatory ones, and blood-borne signals reaching the area postrema (with a reduced blood-brain barrier) (Gallo 2009; Gutierrez and Simon 2011). It requires about 2-4 hours for animals to ascertain that a new taste is neutral and safe.

A distributed system is involved in the formation of taste memory traces (TMTs). Taste and visceral pathways converge in several brain areas. The →insular cortex plays an important role, because lesioning disrupts →memory trace formation, and other areas including the amygdala and medial prefrontal cortex (PFC) are also involved (Yiannakas and Rosenblum 2017). Since memory trace seems to consist of at least two dissociable components, namely safe and aversive, somewhat different structures and molecular mechanisms are involved in its formation. Neuromodulatory systems, such as the →cholinergic, dopaminergic and glutamatergic systems, also play important roles in memory formation and consolidation. For example, the `safe TMT´ appears to depend on cortical cholinergic (→muscarinic) activity, while `aversive TMT´ at least partially depends on NMDA receptor activity (Bermúdez-Rattoni 2004; Ramírez-Lugo et al. 2007; Yamamoto 2006). The amygdala, which plays an important role in →fear conditioning, does not appear to be involved in forming the stimulus-consequence association in conditioned taste aversion but rather in generating the neophobia or fear of negative consequences of consuming novel foods (Gallo 2009; Reilly and Bornovalova 2005; Yamamoto 2009; Yiannakas and Rosenblum 2017).

2.6 Taste and Behavior

Food is able to generate conditioned preferences and response habits that depend on the brain dopamine system, which also plays important roles in →reinforcement and energizing food-seeking behaviors and feeding (Graybiel 2008; Martin-Soelch et al. 2001; Wise 2006). Cannabinoids, via CB1 receptors, increase appetite and stimulate feeding, while blockade of CB1 receptors suppresses hunger and induces hypophagia (Tarragon and Moreno 2019).

In human infants, different tastes evoke innate stereotyped facial expressions and movements. A sweet or slightly salty stimulus evokes a relaxed expression, mild rhythmic smacking, and protrusions of the tongue. By contrast, a bitter, sour or strongly salty taste elicits a grimace, gape or gagging movements, turning away, and pushing out the stimulus (Steiner 1979). Prefrontal cortex influences the brainstem circuits generating the licking behavior in response to palatable food; prefrontal inactivation changes the temporal structure of licking and its magnitude (Jones et al. 2006).

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3

Smell

CONTENTS

Abstract

• Olfaction or smell is the far-sense of chemoreception. It enables the sensing of extra-corporeal chemicals that may be of vital significance for life. It powerfully and often stereotypically influences behavior.

• Odorants are volatile molecules capable of stimulating the sense of smell. Odor, or scent, is the property of a substance that activates the sense of smell. Odors are typically complex mixtures of many odorants. Humans may distinguish several thousand different smells.

• Pheromones are a group of often chemically unrelated substances present in body fluids for the purpose of social and reproductive behaviors.

• The two main neural systems involved in the reception and processing of odorants and pheromones are the main olfactory system (MOS) and the accessory olfactory system (AOS).

• Olfaction starts with olfactory and vomeronasal receptor neurons located in the main olfactory epithelium and vomeronasal organ of Jacobson in the nasal cavity, and progresses through the main olfactory bulb and accessory olfactory bulb, respectively, towards various brainstem and cerebro-cortical structures.

• The main olfactory bulb contains an intricate network of neurons that perform the initial analysis of odors. There is a gross rhinotopic map of connections from the main olfactory epithelium to the main olfactory bulb.

• The primary and secondary olfactory cortices are concerned with odor identification and recognition, intensity and familiarity coding, stimulus localization and hedonics, olfactory attention, learning and memory, habituation, cross-modal associations and gating functions shaped by previous experience with familiar odors.

• The orbito-frontal cortex is involved in passive smelling, odor detection, associative learning, odor recognition memory and hedonics.

3.1 Introduction

Almost all organisms, from single-cell organisms to mammals, are able to sense volatile organic compounds (Genva et al. 2019). Olfaction, the form of chemoreception that establishes the sense of smell, enables the sensing of extra-corporeal chemicals that may be of vital significance to survival, and it powerfully and often stereotypically influences behavior (Stowers and Kuo 2015).

The mammalian olfactory system consists of several sub-systems, of which the main and accessory olfactory systems are most important (Breer et al. 2006; Ma 2007). The olfactory system participates in a large variety of inter-related functions, from finding food, locating prey, tracking of odor trails or odor plumes, olfactory-guided navigation, avoiding danger, recognizing con-specifics, searching for a mate, building newborn-mother bonds, assigning →hedonic values to odors, eliciting species-specific appetitive and defensive behaviors, cross-modal processing of the faces of others, causing →autonomic, →emotional and empathic reactivity, →learning and →memory formation related to odors and odorants (Ache and Young 2005; Baum and Kelliher 2009; Bigiani et al. 2005; Brennan 2009; Chamero et al. 2012; Genva et al. 2019; Gottfried 2006; Jacobs 2012; Kermen et al. 2021; Li and Liberles 2015; Marin et al. 2021; Munger et al. 2009; Nevo and Heymann 2015; Soria-Gomez et al. 2014; Stevenson 2010). Scents play an immense role in human social life, creating ambient and atmospheric cues related to certain moods and triggering memories and nostalgia etc. (Spence 2021). Olfaction decays at older age, particularly in various forms of dementia (Brai et al. 2020; Mobley et al. 2014). In humans, olfactory processing depends on the state of →attention, which might occur at an early stage (Gelperin 2009; Krauel et al. 1998).

Like other sensory systems, olfaction functions in four dimensions: quality, →intensity, space and time (Ache et al. 2016), but the mechanisms of encoding olfactory information are quite different (Brann and Datta 2020; Blazing and Franks 2020).

The structures and mechanisms of olfaction are remarkably conserved across many species and evolutionary stages (Ache and Young 2005; Brennan and Keverne 2015; Jacobs 2012; Leon and Johnson 2009). Nonethelesss, odor perception variations depend on sex, age, health status, cultural origin and individual differences (Genva et al. 2019). In individual species, there is considerable variability in terms of odor detection →threshold, intensity perception and the attractiveness of specific odors, which in the latter case, varies in association with differences in olfactory receptor genes (Logan 2014; Bear et al. 2016).

3.2 Olfactory Stimuli and Functions

3.2.1 Odors and Odorants

Odors are usually generated by complex mixtures of many monomolecular odorants that can act as agonists, antagonists, and partial agonists, and define characteristic odoriferous objects (Brann and Datta 2020; Thomas-Danguin et al. 2014; but see Barwich 2019). Odor stimuli are complex as to their physical properties, including concentration variations and time-varying spatio-temporal distributions in odor plumes (Pannunzi and Nowotny 2019; Young et al. 2020).

Odors need to be detected and →recognized despite changing intensity and background. Humans may distinguish several thousand different odors.

Odorants are volatile molecules capable of stimulating the sense of smell. They are usually small, organic, lipophilic molecules of less than 400 Da, and exhibit large variations in size, shape, functional groups and electric charge. They may be aliphatic acids, alcohols, aldehydes, ketones, and esters. Small variations in molecular structure and in concentration result in differences in their perceived odor, and perception varies among subjects (Buck 1996; Genva et al. 2019; Lledo et al. 2005; Malnic et al. 1999; Touhara and Vosshall 2009; Wilson et al. 2006; Wilson and Mainen 2006). While individual odorants may elicit physiological and behavioral responses, full-fledged biological activity often requires stimulation with complex odors (Ache and Young 2005).

3.2.2 Pheromones

Pheromones are a group of often chemically unrelated substances present in body fluids for the purpose of innate social and reproductive behaviors and involved in →hormone modulation (Liberles 2014). Pheromones can be functionally sorted into various classes. *Releaser pheromones* initiate immediate behavioral responses upon reception. *Primer pheromones* cause longer-term physiological changes in animals that ultimately result in a behavioral response. *Signaler (recognition) pheromones* provide information about an animal´s individuality, social status, social group, physiological state, type of food consumed. *Aggregation pheromones* mediate feeding, sex and aggression. *Dispersion pheromones* ensure individual spacing and minimize predation. *Reproductive pheromones* trigger courtship displays and postures. *Modulator pheromones* change another individual´s mood and →affect. Chemical substances used for interspecies communication (predation and defense purposes) are often called `allomones´ (Ache and Young 2005; Bigiani et al. 2005; Dulac and Wagner 2006; Schaal 2009; Tirindelli 2021; Tirindelli et al. 2009; Touhara and Vosshall 2009; Witt and Hummel 2006).

3.3 Functional Anatomy of the Olfactory System

Multiple chemosensory sub-systems are involved in the reception and perception of smell (Chamero et al. 2012; Hayden and Teeling 2014; Liberles 2014; Lledo et al. 2005; Munger et al. 2009; Tirindelli et al. 2009). Two of the olfactory nervous networks are discussed here: the main olfactory system (MOS) and the accessory olfactory system (AOS). (For →ontogenetic development of specific neuronal wiring in the olfactory system, see Komiyama and Luo 2006).

3.3.1 Main Olfactory Epithelium and Receptors

The anatomy of the nose has an important role in differentiating odorants. For example, rodents and other long-snouted animals have their intranasal space organized into distinct channels that enable laminar airflow during sniffs, which may permit different odorants to be differentially absorbed in different areas of the MOS (Hornung 2009; Schaefer and Margrie 2007; Schoenfeld and Cleland 2005; Yeshurun and Sobel 2010). This allows the volatility and solubility of

odorants to influence the odor representations which, in turn, are influenced by the dynamic regulation of sniffing (Schoenfeld and Cleland 2005; Wilson and Mainen 2006; Yeshurun and Sobel 2010), under the control of →brainstem pattern generators that are subject to →forebrain control and can be reconfigured depending on behavioral requirements.

Volatile odorants are detected by specialized olfactory receptor neurons (ORNs) located in the olfactory epithelium, which is covered by mucus (Ache and Young 2005; Elsaesser and Paysan 2007; Kurian et al. 2021; Munger et al. 2009). The receptor cells are bipolar neurons capable of regeneration (Choi and Goldstein 2018). Their apical tip protrudes into the mucus and carries non-motile cilia or →microvilli (Elsaesser and Paysan 2007) with membrane-borne odorant receptors (ORs). The human epithelium contains about 10-12 million olfactory receptor cells, and the rat epithelium contains ca. 50 million. The different receptor cell populations specialized for different odorants are distributed non-uniformly along the inspiratory axis. In humans, olfactory receptors are also expressed in other tissues including skin, testis, intestine, lung, heart, thyroid gland and blood, and are involved in other than olfactory functions, such as cell-cell →recognition, apoptotic cycle, exocytosis, cell migration and proliferation (Dalesio et al. 2018; Maßberg and Hatt 2018; Weidinger et al. 2021). The receptor cells´ basal →axons project in the olfactory nerve to the olfactory bulb (OB). 10-100 non-myelinated axons are grouped in bundles, which may lead to →ephaptic transmission (coupling of adjacent nerve fibers caused by the exchange of ions between the cells or as a result of local electric fields) and synchronization of →action potentials with sub-millisecond precision (Lledo et al. 2005). These axons penetrate the cribriform plate and form →synaptic glomeruli in the main olfactory bulb (MOB), one on each side.

3.3.2 Main Olfactory Bulb

Across vertebrates, the size of the olfactory bulb as well as that of the entire olfactory →limbic system (including the →hippocampus and →amygdala) does not scale predictably with whole brain size as compared with other brain regions. This difference has been explained by the hypothesis of a primacy of olfaction in spatial navigation, even in visual specialists (Jacobs 2012; Sect 3.4.7).

In mammals, the main olfactory bulb (MOB) (Kay 2009) normally translates olfactory information into a language intelligible to the brain (Spors et al. 2012; Wilson and Mainen 2006). Miraculously, in a low percentage of left-handed women, the MOB is apparently missing without compromising olfactory performance (Weiss et al. 2020). It has been argued that the MOB has structures and functions similar to the →thalamus (Kay and Sherman 2006) or to the retina and primary visual cortex (Cleland 2010).

The olfactory receptor cell axons end in the glomeruli, roughly spherical bundles of →dendritic processes, 50-200 µm in diameter. In a glomerulus, receptor cell axons make synaptic contacts with mitral cell and periglomerular cell (PG) →dendrites, M/T cells, short-axon cells and granule cells.

Mitral cells are →glutamatergic principal neurons, amounting to ca. 50,000 cells in the adult human. About 20-25 of them send primary dendrites to a single glomerulus, where glutamate release activates →N-methyl-D-aspartate (NMDA) and →α-Amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA) receptors (Buck 1996; Mori et al. 1999; Wilson and Mainen 2006). Tufted cells send a single dendrite to a single glomerulus. They are often combined with mitral cells as mitral/tufted (M/T) cells. Within a glomerulus, M/T cells are coupled electrically and via glutamatergic →synapses (Lledo et al. 2005; Wilson and Mainen 2006). M/T cell axons combine to form the lateral olfactory tract.

Periglomerular (PG) cells are inhibitory neurons that release →γ-amino-butyric acid (GABA) and →dopamine. They receive excitatory glutamatergic inputs from receptor cells and →presynaptically inhibit transmitter release from receptor cell axons, thus preventing overloading of the glomerulus by glutamate during strong odor stimuli.

Periglomerular (PG) cells also form reciprocal dendro-dendritic synapses with M/T cells, producing local →recurrent inhibition or lateral inhibition up to a short distance away (<5 glomerular diameters). Lateral inhibition may be involved in boosting the →signal-to-noise ratio of odor signals by silencing the basal firing rate of surrounding non-activated neurons, while recurrent inhibition might serve to regulate network tone and modulate the propagation and extent of mitral cell neural activity. Periglomerular cells within a glomerulus also inhibit each other (mutual inhibition) and mediate mutual inhibition between M/T cells, even in neighboring glomeruli. In short, PG cells seem to keep the output dynamic range limited in face of wide variations of inputs from olfactory receptor neurons, thereby improving →contrast between neighboring glomeruli (Lledo et al. 2005; Wilson and Mainen 2006). Short-axon cells are glutamatergic. They exert fairly long-range excitation (>15 glomerular diameters) on PG cells and may shape spatio-temporal discharge patterns in response to odors (Lledo et al. 2005; Wilson and Mainen 2006).

Granule cells, the most numerous cells in the olfactory bulb, are GABAergic inhibitory →interneurons with dendrites but no axons. In the external plexiform layer, they form reciprocal dendro-dendritic synapses with secondary dendrites of M/T cells. In this arrangement, they receive excitatory synaptic input from M/T cells and provide feedback inhibition to the latter. The circuit produces self-inhibition of M/T cells and mutual inhibition between pairs of M/T cells. Its spatial extent is quite large, since M/T basal dendrites spread across 10-12 glomerular diameters. These interactions have been proposed to control the gain of output from the olfactory bulb, selectively decrease the response of particular M/T cells to some odors, and orchestrate temporal synchrony between M/T cells (below) (Lledo et al. 2005; Wilson and Mainen 2006). There are many other GABAergic interneurons (Burton 2017).

Zone-to-Zone Projection Pattern. The projection patterns of receptor cell axons to the main olfactory bulb (MOB) follow a zone-to-zone pattern. The olfactory epithelium in mice is divided into four zones that are defined by the expression of odorant receptors. Olfactory sensory neurons in a given zone project to glomeruli in a corresponding zone of the MOB, establishing a rough rhinotopic map that reflects the spatial organization of olfactory receptor surfaces and odorant passageways within the nasal cavity (Buck 1996; Mori et al. 1999, 2006;

Mouret 2009). Along with differential absorption of different odorants in different parts of the intranasal cavity, rhinotopy enhances discrimination among odorants.

Glomerular Convergence and Divergence. There is a large convergence of olfactory receptor neurons onto glomeruli, but very limited divergence. While much detailed information from individual receptors is lost due to convergence, averaging activity from many receptors could amplify the signals, increase the signal-to-noise ratio or extend the dynamic range of each glomerulus (Lledo et al. 2005; Wilson and Mainen 2006).

Constraining divergence may have the advantage of conserving the association of glomeruli with particular odorants, i.e., preserving a →labeled line with specific behavioral significance. There are sparse connections between glomeruli, in part extending over long distances (Spors et al. 2012).

3.3.3 Central Connections of the Main Olfactory Bulb

Axons of M/T cells project to multiple central structures of the brain, many of which, in turn, send axons back into the MOB and/or to one another (Cleland and Linster 2019). These central structures include locations within the limbic system concerned with →motivation, emotion, certain kinds of memory, autonomic →reflexes and →hormonal regulation; to regions of the paleo-cortex, concerned with stimulus and circumstance →recognition; and to the thalamus, →hypothalamus, →striatum of the →basal ganglia and brainstem. There are parallel connections to some brain structures, including the anterior olfactory nucleus (AON), →piriform cortex (PC), postero-lateral cortical amygdala (LA), lateral →entorhinal cortex (EC), and olfactory tubercle (OT). These areas, except for the OT, are interconnected via recurrent connections (for more detailed information, see: Albrecht and Wiesmann 2009; Barbas 2007; Brann and Datta 2020; Cleland and Linster 2019; Dulac and Wagner 2006; Gottfried 2006; Lledo et al. 2005; Martínez-Marcos 2009; Wilson et al. 2006; Wilson and Mainen 2006; Zahm and Heimer 2009).

All cortical regions receiving direct inputs from M/T cells have traditionally been defined as `primary olfactory cortex´ (Royet and Plailly 2004). Since this is such a diverse assembly, there has been a growing tendency to designate the piriform cortex (PC) (Yeshurun and Sobel 2010), which is the largest cortical region receiving direct synaptic input from the olfactory bulb (Bekkers and Suzuki 2013; Giessel and Datta 2014), as the primary olfactory cortex.

Individual neurons in the piriform cortex (PC) receive input from M/T cells scattered throughout the MOB, and the axons of individual M/T cells branch extensively throughout PC. Thus, PC neurons receive convergent inputs from a population of odorant receptors (ORs) and might function as hubs that integrate activity from diverse molecularly defined olfactory sensory neurons. Via the entorhinal cortex, mitral cells are also coupled to the hippocampus (Gire et al. 2013).

3.3.4 Accessory Olfactory System

An accessory olfactory system (AOS) is present in many vertebrates, but vestigial in Old World →primates, apes and humans (Brennan and Keverne 2015; Chamero et al. 2012; Holy 2018; Liberles 2014). It processes chemical signals that may be unaccessible to →cognitive processes. The subject, although exhibiting behavioral or physiological responses, may be unaware of the olfactory stimulus (Bigiani et al. 2005; Brennan and Kendrick 2006; Dulac and Wagner 2006; Lledo et al. 2005; Martínez-Marcos 2009; Tirindelli et al. 2009; Witt and Hummel 2006). The AOS consists of two structures: The vomeronasal organ (VNO) and the accessory olfactory bulb (AOB) (Mohrhardt et al. 2018).

Vomeronasal Organ (VNO) of Jacobson consists of a pair of tiny, tubular sacs located just behind the nostrils in the nose´s septum. The lumen is filled with mucus rich in lipocalins, which appear to serve as pheromone carriers (Bigiani et al. 2005). Access of these complexes to the sensory neurons appears to require an active pumping process regulated by centrifugal, autonomic and nerve fibers containing vasoactive intestinal protein (VIP) acting on blood vessels (Dulac and Wagner 2006). *Vomeronasal receptor neurons* are located in a sensory epithelium that resembles the main olfactory epithelium (Tirindelli 2021).

Accessory Olfactory Bulb (AOB) resembles the main olfactory bulb in cytological respects, but shows some organizational and numerical differences (Bigiani et al. 2005; Brennan and Keverne 2015; Dulac and Wagner 2006). Centripetal axons of M/T cells bypass cortical structures and project to four nuclei of the limbic system, from where projections target hypothalamic nuclei (Dulac and Wagner 2006; Keverne 2004)**.**

3.4 Functional Processing of Odors

Olfaction usually has a low temporal and often low spatial resolution (Laurent et al. 2001), but exhibits superb →sensitivity to very small concentrations of a vast variety of odorous molecules of different shapes and sizes. Humans can distinguish more than 400,000 different substances (Gottfried 2009), and trained humans can distinguish between 5,000-10,000 different smells, with large inter-individual variations. Olfactory abilities depend on many factors, including species, sex, age, menstrual state, sensory context, past experience and cognitive factors (Brand and Millot 2001; Gottfried 2006). For example, the color of a liquid modifies the perception of its odor (Elsaesser and Paysan 2007; Yeshurun and Sobel 2010).

The main olfactory system also mediates pheromone-like effects (Baum and Kelliher 2009; Swaney and Keverne 2009; Stowers and Kuo 2015; Tirindelli et al. 2009). For example, during the breeding season, anestrous ewes do not undergo ovarian cycles, but exposure to odors of sexually active males or their fleece elicits secretion of luteinizing hormone (LH), leading to ovulation (`male effect´) (Gelez and Fabre-Nys 2004). The effect is mediated by the main and accessory olfactory systems. Male-female attraction in hamsters and pigs requires the functioning of the main olfactory system to trigger mating behavior, while the accessory olfactory system is required for sex discrimination (Dulac and Wagner 2006).

Olfaction often involves specific →odor-sampling behaviors such as nuzzling, sniffing, appendage flicking and casting behaviors that differentiate odors according to specific patterns, onset latencies and spatial distributions. These behaviors enable the animal to sample spatial regions of interest, regulate stimulus intensity and protect olfactory receptor neurons from damage from excess exposure to toxic stimuli, and extract stimulus features of interest (Keverne 2004; Laurent et al. 2001; Marin et al. 2021; Schaefer and Margrie 2007; Wachowiak 2010).

3.4.1 Olfactory Receptor Mechanisms

While there are significant differences between olfactory receptor proteins and their encoding genes within animals of the same evolutionary phylum, olfactory nervous tissues nonetheless share some anatomical and physiological features: similar odorant and receptor proteins, similar →transduction mechanisms, and the capability to adapt rapidly to particular odors (Ache and Young 2005; Dalton and Lomvardas 2015; Hayden and Teeling 2014; Liberles 2014; Lledo et al. 2005).

Odorant Binding Proteins (OBPs). In the olfactory mucus, odorants bind to olfactory binding proteins (OBPs), which may aid the diffusion of the odorants through the aqueous/lipid environment. Additionally, OBPs may enhance detection by concentrating odorants in mucus, present odorants to their receptors, act as terminators by removing used odorants, and allow additional molecules to interact with the receptor (Buck 1996).

Odorant Receptor Proteins belong to the large family of →G-protein-coupled-seven transmembrane proteins from the rhodopsin-related superfamily (Ache and Young 2005; Munger et al. 2009; Touhara and Vosshall 2009). In rodents, there are more than 1,000 unique odorant receptors (ORs) (Brann and Datta 2020), each receptor neuron carrying only one receptor protein coded by one gene. In humans, more than half of the genes are apparently non-functional, leaving only about 350 functional genes (Brennan and Keverne 2015; Buck 1996; Dulac and Wagner 2006; Lledo et al. 2005; Munger et al. 2009; Wilson and Mainen 2006). Most monomolecular odorants expose multiple chemical features that can be detected by different ORs, so that an odorant is recognized by various types of OR. Conversely, individual ORs generally exhibit broad tuning properties reflecting responses to many oderant molecules, so that each odorant receptor recognizes multiple chemical compounds. It has therefore been suggested that in the periphery odors are uniquely represented by the specific combination of activated ORs. But there are exceptions (Brann and Datta 2020; Breer et al. 2006). By comparison, mice and rats have 170-300 vomeronasal class 1 receptors (V1Rs) and 220-280 vomeronasal class 2 receptors (V2Rs), while in Old World primates and apes including humans, the vomeronasal receptors are virtually all non-coding pseudogenes (Brennan and Keverne 2015). (For the evolution of odorant receptor genes in vertebrates see Bargmann 2006; Kambere and Lane 2007; Niimura and Nei 2006).

In mice and rats, the neurons expressing the same receptor proteins are broadly distributed spatially, but only in certain regions of the epithelium, such that there are four overlapping zones (Buck 1996; Mori et al. 1999). A limited sub-population of olfactory neurons and M/T cells is involved in pheromone reception (Dulac and Wagner 2006; Munger et al. 2009; Tirindelli et al. 2009).

Traditionally it has been assumed that almost all individual receptor cells respond to several odorants. There are exceptions, however. Some receptor cells are specific for certain chemical ligands, not only in the accessory olfactory system, but also in the main olfactory and gustatory systems. For example, there is a human odorant receptor specialized for →androstenone and →androstadienone derived from steroid hormones in urine and sweat that is able to change hormone levels in human subjects. Specialized receptors may therefore have evolved to ascertain high detection sensitivity and discrimination acuity for substances with special behavioral relevance (Katz et al. 2008).

Interestingly, low environmental oxygen concentrations that endanger survival directly activate a sub-population of sensory neurons in the main olfactory epithelium (Bleymehl et al. 2016). The mouse olfactory system comprises a variety of sub-systems, including sensory neurons referred to as type B cells in the main olfactory epithelium that detect a wide diversity of molecular cues in the external environment. Low oxygen induces calcium (Ca^{2+}) influx in type B neurons. Low environmental oxygen also induces conditioned place aversion, enabling mice to rapidly assess the oxygen level in the external environment well before arterial blood becomes →hypoxic and survival is compromised. This peripheral oxygen-sensing system may influence certain social behaviors as well, such as nest building and other parenting behaviors, because newborns are particularly liable to suffer from hypoxia.

Transduction Mechanisms. Binding of odorants to receptor proteins is followed by transduction into electrical signals (Breer and Strotmann 2009). There are multiple transduction mechanisms. Once odorants bind to olfactory receptors, a parallel-serial cascade of responses is elicited. Calcium (Ca^{2+}) ions flow through →cyclic nucleotide-gated channels into cilia, where they elicit two effects: activation of an excitatory chloride (Cl^-) →conductance associated with →depolarizing outward chloride (Cl^-) current across the cell membrane, and →negative feedback at various stages of the transduction mechanism (Matthews and Reisert 2003). The first eventually leads to →receptor potentials that elicit action potentials in the axons to the bulb. Intracellular signaling involves →cyclic adenosine monophosphate (cAMP), →cyclic guanosine monophosphate (cGMP), →inositol-1,4,5-trisphosphate (IP_3), carbon monoxide (CO), →nitric oxide (NO), and several ion conductances (Na^+, K^+, Ca^{2+}, Cl^-) modulated by odorants (Buck 1996; Hayden and Teeling 2014; Lledo et al. 2005; Munger et al. 2009; Schild and Restrepo 1998; Touhara and Vosshall 2009).

Adaptation. The olfactory system is able to →adapt rapidly, as evidenced by the well-known failure to continue smelling a foul odor for prolonged periods. But the system also recovers quickly. This is important for sensing changing concentrations of an odorant, which in turn is significant, e.g., for tracking a prey (Pellegrino et al. 2017). The mechanisms of adaptation may include receptor de→sensitization, reduction of open-channel probability by accumulated Ca^{2+}, and reduction of →second-messenger activity by kinases (Buck 1996).

3.4.2 Neural Processing in the Olfactory Bulb

Axons from olfactory sensory neurons (OSNs) make excitatory glutamatergic synaptic connections on bulbar M/T and periglomerular cells via AMPA and NMDA receptors (Lledo et al. 2005). The pattern of convergence has as consequence that odors are represented in the OB by odorant-specific spatio-temporal maps (Kermen et al. 2021).

Further synaptic interactions are vital components of neural processing in the olfactory bulb, which determines the specificity and coding of odors. For example, periglomerular interneurons mediate inter-glomerular interactions, thereby enhancing olfactory contrast and input de-correlation. Feedback loops between output neurons and granule cells have been said to be involved in olfactory discrimination and memory (Kermen et al. 2021).

Specificity of Cell Responses to Odors. According to the "one glomerulus-one receptor hypothesis", axons from olfactory receptor cells expressing the same receptor molecules converge onto the same glomeruli in the main olfactory bulb (Mori et al. 1999). This imposes a modular specificity on glomeruli and generates a rough chemotopic map such that odors are represented by characteristic spatial patterns of activated glomeruli (Dulac and Wagner 2006; Johnson and Leon 2007; Mori et al. 2006; Mori and Sakano 2011; Murthy 2011; Spors et al. 2012; Wilson and Mainen 2006). The glomerular specificity is transferred to M/T cells by glutamatergic →synaptic transmission because each of the cells extends a single dendrite into a glomerulus (Buck 1996; Mori et al. 1999), although there are exceptions (Laurent et al. 2001). In general, most odorants activate many olfactory receptors, although they may bind to different receptors with different affinities. A recent estimate presumes that, in the mouse, 40-90 different receptor neurons may respond to a given odor (Ma and Shepherd 2000).

Conversely, most olfactory receptors are activated by multiple ligands, although some receptors are more specifically activated by ligands sharing particular molecular features (Lledo et al. 2005; Wilson and Mainen 2006). The set of all odorants exciting an olfactory neuron has been called the `molecular receptive range´ (MRR), which can vary considerably among receptor neurons and M/T cells. Nonetheless, even cells with a broad MRR can be relatively specific by responding strongly to one or a few odorants and less to others (Wilson and Mainen 2006). An individual odorant molecule may then activate a characteristic combination of M/T cells, distributed over the bulb with a particular spatial pattern.

More generally, a particular odorous object that releases many odorant molecules would activate a characteristic combination of glomeruli and associated M/T cells. However, a minority of first- and second-order olfactory neurons (e.g., in the posterior bulb) exhibits a specific chemical sensitivity related to specialized functions (Wilson and Mainen 2006). For example, the number of glomeruli and M/T cells activated by natural scents is not as large as might be expected. Such narrow tuning is lost at the next station, the anterior olfactory nucleus (AON), where cell responses are broader, indicating that synaptic integration of inputs from several functionally distinct M/T cells takes place (Lei et al. 2006).

Topography of Innate Odorant Hedonics. The hedonic values of odors appear to be differentially represented in the OB. Thus, the ventral OB domain may be specialized in detecting appetitive and social odors. For example, in mice M/T cells located in the ventral OB are activated by urine opposite-sex of the opposite sex, and the rat ventral OB is preferentially activated by floral, woody, fruity and herbaceous odorants. By contrast, the dorsal OB, despite responding to numerous odorants with neutral hedonic value, is important for processing odorants signaling danger such as spoiled food and predator odorants. Optogenetic activation of a postero-dorsal glomerulus responding to a component of fox odor induces →freezing. The OB sends topographically organized projections to downstream areas. Thus in mice, M/T cells at different OB locations differentially target the olfactory tubercle known to code odor hedonic value. The cortical amygdala primarily receives dorsal OB input, while the anterior olfactory nucleus (AON) receives topographically organized projections from the dorso-ventral axis of the OB (Kermen et al. 2021).

Neuromodulation of Processing in the Olfactory Bulb. Olfactory processing in the OB can be modulated intrinsically as well as extrinsically from many structures in the →central nervous system (CNS), from which the OB receives massive inputs that even outweigh the sensory input from the nose. OB operation is also influenced by substances carried by the bloodstream, such as hormones (grhelin, →insulin, leptine, adiponectine) and nutrients (glucose, amino acids, lipids) related to hunger and satiety states and involved in food intake control (Brunert and Rothermel 2021; Julliard et al. 2017; Soria-Gomez et al. 2014). In awake animals, MOB neuron discharge is determined not only by the stimulus, but also by the behavioral state, attention, expectations, context, learning and →working memory.

The olfactory bulb receives inputs from regions that have been implicated in olfactory learning: the ipsi- and contralateral anterior olfactory nuclei (AON), piriform cortex (PC), lateral entorhinal cortex, the ipsilateral horizontal limb of the diagonal band of Broca, the →basal forebrain, hypothalamus, and →trigeminal →ganglion and from diffuse neuromodulatory systems, including the →locus coeruleus (LC), and the dorsal and median →raphé nuclei, which emit →cholinergic, →noradrenergic and →serotonergic projections (D´Souza and Vijayaraghavan 2014; Gaudry 2018; Jacob and Nienborg 2018; Linster 2018; Linster and Cleland 2016; Lizbinski and Dacks 2018; Wilson and Mainen 2006). The state-dependent release of acetylcholine, noradrenaline, serotonin (5-HT), and other neuromodulators alters physiological parameters in neurons and synapses that modify the computations performed on sensory signals. These modifications affect the specificity, detectability, discriminability, and other properties of odor representations and thereby govern perceptual performance (Linster and Cleland 2016). Neuromodulation is also exerted by the →endocannabinoid system and the dopaminergic system (Harvey and Heinbockel 2018; Terral et al. 2020). →Vasopressin neurons occur in the MOB, AOB, AON and piriform cortex; their function has to be established (Wacker and Ludwig 2018). Widespread effects on neurotransmission and neuromodulation are exerted by →purinergic receptors (purinoceptors). P2X, P2Y and →adenosine receptors are involved in adult neurogenesis in the olfactory epithelium, link neuronal activity to vascular responses in the olfactory bulb and modulate synaptic transmission in the olfactory bulb as well as in the olfactory cortex, the precise roles in olfactory perception and behavior remaining to be established (Rotermund et al. 2019).

Mitral cells in the MOB receive direct centrifugal feedback from piriform cortex (PC) or anterior olfactory nucleus (AON). Optogenetic stimulation of the PC and AON suppresses odor-evoked excitation of mitral cells through disynaptic inhibition via inhibitory interneurons, the periglomerular and granule cells. Thus, cortical feedback could contribute to the well-known changes in →steady state firing in M/T cells during olfactory learning, as well as precisely timed synchrony between M/T cells (Gire et al. 2018).

Summary. The OB is not simply a relay. 1) Lateral inhibition and local inter-glomerular processing normalize odor processing. 2) Centrifugal projections from PC to the OB appear to recruit local inhibition to decorrelate peripheral odor representations. 3) Centrifugal projections amplify the earliest signals from the OB while filtering slower signals that reflect odor concentration and are therefore essential for building concentration-invariant representations of odorants. 4) Centrifugal projections provide neuromodulation which modifies odor representations in the mitral/tufted cell (M/TC) neurons in a state-dependent and experience-dependent manner; for example, acetylcholine is necessary for olfactory learning (Brann and Datta 2020). The olfactory bulb is also part of the system that represents hedonic value, i.e., pleasantness or unpleasantness, of an odor, this value assignment being innate or learned. Hedonic value representations have been found at all levels of the olfactory system, including the olfactory epithelium, the olfactory bulb (OB), the piriform cortex, →orbito-frontal cortex (OFC), →insula and amygdala (Kermen et al. 2021; below).

3.4.3 Neural Processing in Higher-order Areas

Human brain imaging shows that odors activate a number of →sub-cortical areas and cerebro-cortical regions, including the piriform, →entorhinal, orbito-frontal, cingulate cortices and anterior insula, temporal and occipital regions and the →cerebellum (Savic 2002). Odors also promulgate complex interactions in brain regions beyond olfactory regions. Even when they are not perceived consciously, odors affect a variety of complex brain functions. For example, odor can negatively influence an individual´s understanding and interpretation of the face, as processed by the visual system, while subconscious odor processing can enhance memory formation in other senses (Walla 2008).

Olfactory Cortex. The functions of primary and secondary olfactory cortices, in general, are concerned with odor localization, identification, recognition and learning (Giessel and Datta 2014; Wilson and Linster 2008). Some functions are localized to particular regions or even lateralized to one or the other hemisphere (Dalal et al. 2020; Royet and Plailly 2004; Wilson et al. 2006; Yeshurun and Sobel 2010). While odor perception and behavior have been said to be the consequence of the coordinated action of the entire network, there are signs of some specialization. For example, the piriform cortex (PC) has been suggested to have a primary role in learning, the olfactory tubercle (OT) to be primarily involved in linking odors to outcomes after →reward-based learning, the cortical amygdala (LA) to mediate innate odor-triggered behaviors, and the anterior olfactory nucleus (AON) to be involved in →orienting toward salient odor sources (Brann and Datta 2020).

Each OB glomerulus distributes signals in a diffuse and overlapping way across the entire piriform cortex (PC). Conversely, individual PC neurons sample inputs from many OB glomeruli. Thus, odors activate distributed populations of PC neurons without any apparent topography (Blazing and Franks 2020; Brann and Datta 2020; Gire et al. 2018). Odor identity and intensity are represented by complementary coding strategies (Blazing and Franks 2020). This system plays a role in recognizing complex combinations of odorant features.

The anterior piriform cortex maintains close links to the outside world, encodes odor identity, and is activated by pleasant and unpleasant odors. The posterior piriform cortex encodes odor quality and is activated by odors without regard to their hedonic value. The piriform and orbito-frontal cortices (medial and posterior gyri) can also be activated by sniffing (Bekkers and Suzuki 2013; Sobel et al. 1998a).

Posterior piriform and orbito-frontal cortical neurons are more selective to odorants than cells in the anterior piriform cortex. Odorant-evoked responses in cortical pyramidal neurons show fast, odorant-specific adaptation. In the piriform cortex, cells are often in phase with respiration. →Arousal, attention, behavioral state and experience also modulate odor responses (Gelperin 2009; Spors et al. 2012).

Pyramidal cells receive afferent bulbar inputs in apical dendrites and, at more proximal dendritic sites, associative inputs from other pyramidal cells via axon collaterals. Several types of inhibitory interneurons mediate feedforward and feedback inhibition between pyramidal neurons. Furthermore, signals from brainstem and basal forebrain mediate noradrenergic, serotonergic and cholinergic neuromodulation of signal processing, and of →synaptic plasticity and memory formation (D´Souza and Vijayaraghavan 2014; Giessel and Datta 2014; Wilson et al. 2006).

Orbito-frontal Cortex (OFC). Neuroimaging in humans suggests that the caudal orbito-frontal cortex (OFC) is involved in passive smelling and odor detection and the rostral regions in associative learning, working memory, and odor recognition memory. Pleasant odors evoke activity medially and unpleasant odors laterally, thus establishing a hedonic map (Gottfried 2006; Rolls 2015). Activity in the OFC is depressed by satiety (Rolls 2015) and is subject to cognitive influences, such as intensity, familiarity and hedonicity judgments (Gottfried 2006).

Lesions in macaques impair learning about which stimuli are rewarding or not, and in altering behavior when reward contingencies change, and also produce emotional changes such as decreased aggressiveness to humans and snakes and a reduced tendency to reject food (Gottfried 2006; Rolls 2004; Wallis 2007).

Amygdala. Neuroimaging in humans implicates the amygdala in hedonic or emotional processing of olfactory stimuli, in associative learning, and in the evocation of emotional odor memories (Gottfried 2006).

Cerebellum. In humans, odorants like vanillin and propionic acid activate the posterior lateral hemispheres of the cerebellum, while sniffing non-odorized air activates the anterior cerebellum. This involvement of the cerebellum might establish a feedback mechanism whereby sniff volume is regulated in relation to odor concentration (Sobel et al. 1998b).

3.4.4 Odor Quality Coding

While some first- and second-order neurons are probably specialized and give rise to a →labeled-line code (Dulac and Wagner 2006; Wilson and Mainen 2006), many other cells are generalized in responding to several odorants (Lledo et al. 2005; Wilson and Mainen 2006). A more general hypothesis is that the *quality* of an odor is encoded by a *combinatorial code* composed of the set of olfactory receptor neurons and glomeruli activated by each odor (also called spatial code or identity code). Moreover diverse, possibly overlapping combinations of receptors recognize different odorants (Buck 1996; Fauré 2009; Kurian et al. 2021; Ma and Shepherd 2000; Malnic et al. 1999; Perl et al. 2020; Spors et al. 2012). By using only 1,000 receptors, this combinatorial code could easily encode more than 10,000 odors. At the level of the olfactory bulb, the combination of receptor activations would be recoded into a stimulus-specific two-dimensional spatial pattern of glomerulus and associated M/T cell activations, with the capability to predict odor-guided behavior (Leon and Johnson 2009; Lledo et al. 2005).

3.4.4.1 Role of Neuronal Activity Patterns

The olfactory system utilizes spatio-temporal patterns of neuronal discharge activity in distributed populations of neurons, in order to modulate various behaviors involved with odor detection and assessment of odor quality and concentration. One hypothesis is that odors are encoded by a combinatorial code composed of the set of glomeruli activated by each odor. This code was termed the spatial code or identity code (Perl et al. 2020). In addition, odor information might be signalled by various patterns of oscillatory discharge activity, by slow temporal firing patterns, or by the relative timing of discharge activity in the OB, which could be decoded by neural circuits in the piriform cortex (Manabe and Mori 2013; Uchida et al. 2014). be represented (Manabe and Mori 2013; Perl et al. 2020; Uchida et al. 2014).

Oscillations. In terrestrial mammals, rhythmic respiration induces rhythmic fluctuations of spontaneous M/T activity. During inhalation of odors, many M/T cells respond to odor input by transiently phase-locking their spiking to the ongoing respiratory rhythm without increasing their action-potential rate averaged over the respiratory cycle. Dense phase locking of M/T cells to respiration in awake rodents is sensitive to the identity of the odor (Gire et al. 2018). More generally, odor inhalation evokes various kinds of oscillatory synchronization in the olfactory bulb: *theta rhythms* (frequency range 3-12 Hz), *beta rhythms* (15-40 Hz), and *gamma rhythms* (30-80 Hz). Whereas the first is phase-locked to respiration, the latter two are induced by odors and never co-exist but alternate (Fontanini and Bower 2006; Giurfa 2009; Kay 2009; Kay et al. 2009; Lledo et al. 2005; Ravel et al. 2009). Such oscillations become more conspicuous in →local field potentials (LFPs). In rabbits, neighboring M/T cells with different but overlapping response profiles to odor molecules show synchronized oscillatory firing in response to an odor that excites both. Similar oscillations have been recorded across and between olfactory areas, including piriform and entorhinal →cortical areas (Bekkers and Suzuki 2013; Laurent et al. 2001; Kay 2009; Lledo et al. 2005). These oscillations could help fine-tune discrimination between odorants that use overlapping spatial representations in the olfactory bulb (Lledo et al. 2005). Desynchronization of projection neurons by the →$GABA_A$ receptor/Cl^- channel →antagonist →picrotoxin leads higher-order cells to lose response selectivity to odors, implying

that they are sensitive to input synchronization and use it to fine-tune sensory properties (Laurent et al. 2001).

Synchronizations might have other functions. They might, for example, coordinate signals from different odorant receptors (ORs), thus contributing to perception of an odor object (Lledo et al. 2005; Wilson and Mainen 2006; but see Barwich 2019). In addition, synchronization might contribute to the formation of olfactory and pheromone memory mediated by lateral interactions between M/T cells of the olfactory bulb (Mori et al. 1998).

Slow Temporal Response Profiles. Brief odor stimuli produce odor-specific temporal action-potential patterns that develop over seconds (Leon and Johnson 2009, Wilson and Mainen 2006). Representation of odor by activity patterns across the M/T cell population changes continuously throughout a stimulus in an odor-specific manner (Friedmann and Laurent 2001). The differential sensitivity of a mitral cell to a set of odors changes over response time. It does not simply become sharper, i.e. more specific. Instead, odor representation by the distributed ensemble of cells is progressively reduced.

Functional reorganization of activity patterns within the main olfactory bulb makes the representation of each odor more specific, differentiating and less redundant over time. Since this type of →optimization is only seen in mitral cell ensembles but not among olfactory receptor cell afferents, it is bound to result from the dynamics of neuronal circuits in the main olfactory bulb. Time can therefore gradually optimize stimulus representations in a sensory network. Initially, the mitral cell population responses are similar and may thus help classify odors (e.g., as `aromatic´). Later, optimization favors fine discrimination within classes (Friedrich and Laurent 2001; Friedrich 2006).

3.4.4.2 Construction of Odor Objects

Most natural scents emanating from objects are composed of tens to hundreds of odorants. For, example, chocolate contains over 600 compounds and is still perceived, recognized and learned as a unitary olfactory whole, or odor object (but see Barwich 2019). Since the olfactory system initially detects the composite odorants, it must integrate them into odor objects. It does so in face of changing intensity and background chemical `→noise´, which may arise from the direction and speed of wind, fluctuations of temperature and humidity, and dietary factors. Despite these variations, which may degrade the fidelity of the signals reaching the olfactory epithelium, the olfactory system manages fairly well to reconstruct the signal and to maintain →perceptual constancy in the recognition of odor objects. How it does so remains enigmatic but involves, at the very least, odor perception, odor categorization and →multi-sensory integration (Brennan 2009; Gottfried 2009; Thomas-Danguin et al. 2014; Wilson et al. 2006; Wilson and Mainen 2006).

Perceptual Constancy, despite varying odor concentrations, is maintained by a mechanism in the olfactory glomeruli in which projection neurons are subject to increasing inhibition with increasing stimulus intensity, thus preventing spread of excitation. Perceptual constancy is also aided by mechanisms of *pattern completion* at the cortical level. For example, neuron ensemble

activity in the rat piriform cortex fills in missing information on a complex odor mixture when one odorant is missing. On the other hand, perceptual discrimination remains insured because neural ensembles generate different activity patterns when an odorant replaces another (Gottfried 2009).

Odor Categorization may be a way of dealing with the enormous numbers of possible odorant combinations. Human brain imaging suggests that the posterior piriform cortex plays a role in categorizing odors because different odor categories evoke spatially overlapping, yet distinct, activations that support discrimination (Howard et al. 2009). Odor discrimination is reinforced by learning mechanisms (Gottfried 2009).

Multi-sensory Integration is required to generate a full-fledged odor object. Assembling various odorant features is thought to involve the olfactory bulb, anterior olfactory nucleus and anterior piriform cortex. However, the construction of odor objects involves other senses than smell. Thus, the insular and orbito-frontal cortices play an important role in incorporating smell, taste and touch into the →flavor of food (Verhagen and Engelen 2006). The perception of a predator combines its smell, →sound and sight which appears to happen in the posterior piriform cortex (Brennan 2009). Furthermore, there are cross-modal interactions between smell, taste, temperature, touch, tactile irritation and vision (Aglioti and Pazzaglia 2011; Verhagen and Engelen 2006). Color, for example, profoundly influences the perception of odors (Osterbauer et al. 2005). The multi-sensory processing of olfactory, acoustic and visual information may raise the sense of danger and urge to act, e.g., when smelling smoke, hearing a fire alarm or seeing flames. Multi-modal processing is even more important for social perception of the actions of other individuals (Aglioti and Pazzaglia 2011).

Odor and Motor Systems. The grasping of small or large objects with characteristic odors is influenced by the presentation of the same or of different smells. For example, when participants smelled an odorant and then grasped an object presented in central vision, the time and amplitude of maximum hand aperture were later and greater, respectively, when the odor evoked a larger object (e.g., an orange) than when the odor evoked an object of a similar size as the target or no odor was presented. Conversely, the time and amplitude of maximum hand aperture were earlier and reduced, respectively, when the target was large (e.g., a peach) and the odor evoked a smaller sized object (e.g., an almond) than when the odor evoked an object of a similar size as the target or no odor was presented (Castiello et al. 2006). Similar effects were seen in reach-to-grasp movements. Subjects reached towards and grasped a small or a large visual target with a →precision grip or a →power grip, respectively, in the absence or in the presence of an odor evoking either a small or a large object. When the type of grasp evoked by the odor did not match that for the visual target, interference effects were evident on the kinematics of hand shaping and the level of synergies among fingers decreased. When the visual target and the object evoked by the odor required the same type of grasp, facilitation emerged and the intrinsic relations among individual fingers were maintained (Tubaldi et al. 2008). Odors have other effects on the motor system. For example, mere perception of smelling food objects induces a facilitation of the →cortico-spinal tract and neural activity in the `action observation network´ [AON: inferior frontal gyrus (IFG) and →inferior parietal lobule (IPL)] (Aglioti and Pazzaglia 2011). Brain imaging in humans showed that, when individuals observed a hand grasping a

smelled object, temporal, parietal and frontal cortical areas were activated. Superadditive activity occurred when the target object was both seen and smelled (Tubaldi et al. 2010).

3.4.5 Odor Intensity Coding

Some challenges arise from the need to code the intensity of an odor in relation to its concentration. For example, a large amount of indole imparts a putrid odor, while a small trace smells flowery. Two possible mechanisms appear to enable encoding of odor intensity. First, up to a certain level, responses of an olfactory receptor neuron (ORN) and an M/T cell increase with odor concentration (→rate coding). Second, the number of ORNs and glomeruli recruited increases with stimulus concentration (recruitment coding), leading to an increase in dynamic range (Lledo et al. 2005; Wilson and Mainen 2006). Apparently, these quantitative changes sometimes lead to qualitative changes, e.g., in the case of indole.

3.4.6 Time Coding

While specific neuronal discharge patterns including oscillations and synchronizations contribute to signal processing and characterization of odors, additional mechanisms are needed to accurately detect temporal features of odor objects.

Odors emitted by a source into air or water are usually distributed by turbulent flows, thus yielding a complex spatio-temporal pattern of changing odor concentrations (Marin et al. 2021). This problem could be alleviated in part by additionally judging turbulence using →mechano-sensitive receptors (Jacobs 2012). To detect the temporal structure of arriving odor waves, the olfactory system needs mechanisms to measure intervals. In crustaceans and mammals, one such mechanism is provided by small ensembles of →bursting olfactory receptor neurons (ORNs). Unlike canonical ORNs, whose tonic discharge reflects the odor concentration or its rate of change, bursting ORNs fire rhythmically, each at its own frequency. The probability that a bursting ORN responds to an odor wave increases with the time elapsed from the last burst. The burst rhythm can thus be entrained by odor rhythms and thereby encode the time intervals between past odor encounters at intervals ranging from hundreds of milliseconds to tens of seconds. The ability to determine time intervals could also help in navigation towards an odor source (Ache et al. 2016; Jacobs 2012; Park et al. 2016).

In the MOB, precise sub-millisecond synchrony between M/T cells conveys information related to the reward contingency associated with a given odor. Synchronized spikes can possibly discriminate between a rewarded and unrewarded odor. This synchrony can occur between widely separated M/T cells, which enables arbitrary combinations of M/Ts to become synchronized and signal arbitrary combinations of odors associated with behaviorally relevant events. Such synchrony on fast timescales (<1 ms) is well suited to transmit information from the MOB to the piriform cortex, where a feedforward inhibition mechanism operating on this timescale provides for temporal filtering. It uses a succession of early excitation and delayed inhibition. While excitatory inputs from M/T fibers target the dendrites of piriform pyramidal cells, di- and polysynaptic inhibitory pathways do so via inhibitory piriform interneurons. Thus,

M/T cells will most effectively drive pyramidal cells, if they are synchronized on a very short timescale of <2 ms. Otherwise, polysynaptic inhibition functions to limit the window for temporal integration in pyramidal cells to 5-10 ms, suggesting that individual pyramidal cells act primarily as →coincidence detectors (Gire et al. 2018).

3.4.7 Space Coding

Many animals rely on olfaction to localize or track an odor source (Baker et al. 2018; Marin et al. 2021). This type of odor-guided navigation appears to be based on detection and analysis of gradients of mean odor concentration, which requires taking successive samples at successive loci. Two spatially separated nostrils make this possible. Humans and various animals are able to localize an odor by differences in concentration at the two nostrils, and to guess the direction of an expanding odor by differences in the arrival times at the two nostrils. This mechanism presupposes fairly smooth odor fields. In turbulent fields, it appears more efficient to detect, at each nostril, the time interval since the last arrival of an odor wave and then steer towards the shorter time interval (Ache et al. 2016; Park et al. 2016). Olfactory stimuli also contribute to make a choice between directions of locomotor behavior, in which choice the →superior colliculus (SC) plays an important role (Felsen and Mainen 2008).

In space coding, the olfactory system has been associated early on with the hippocampus. As with olfactory space, the hippocampus carries specialized maps of spatial relations. The map is based on the integration of multi-sensory (chemo-sensory, mechano-sensory, auditory, visual) inputs (Jacobs 2012). In early vertebrates, the memory of smells and sights, of their spatial layout and of the order and timing in which they are encountered during navigation is laid down in a map enabling animals to navigate toward locations associated with resources or safety. These specialized representations also enable the learning and executions of tasks involving serial order, relations, sequences of events and behavioral contexts (Murray et al. 2018).

3.4.8 Olfactory Learning and Memory

Olfactory learning and memory of odors are critical for the survival of animals. Certain odors can trigger the evocation of vivid emotional experiences, which might be sustained by the direct connections between the olfactory bulb (OB) and piriform/olfactory cortex with the amygdala and hippocampus. Learning and memory involve complex networks of brain areas and occur on several time scales.

Animals are usually exposed to odors intermittently due to relative movements of animals and environment, and to turbulent air or water flows (Ache and Young 2005). Keeping track of odors and tracking odors therefore require very →short-term memory (Brennan and Keverne 2015). Animals can rapidly, within tens of trials, learn to select a rewarded odor and neglect unrewarded odors, during which short-term memory comes into play. Discrimination of odors can be learned within a few trials and, once learned, can be made within a few hundred milliseconds or within a sniff. Rats have short-term memory of odors lasting for roughly 60 s (Brennan 2009). →Aversive conditioning results in avoidance of a conditioned odor (Ross and Fletcher 2019). Food aversion, for example, is found across a large range of species and has a

strong olfactory component (Ache and Young 2005). Even one episode of exposure to certain tastes or smells associated with nausea-inducing substances can establish robust aversion to stimuli.

Olfactory learning and the underlying neural changes occur at the level of the olfactory bulb (OB) (Kermen et al. 2021; Tong et al. 2014), but are also prominent at cortical levels (Wilson and Stevenson 2003; Wu et al. 2020). In the OB, local inhibitory interneurons are regenerated throughout life in the process of adult neurogenesis, and this process can be modulated by associative learning based on sensory stimuli presented with reward or punishment (Lledo and Valley 2016). Adult neurogenesis is associated with the acquisition and/or memory of associative appetitive learning and →fear conditioning (Kermen et al. 2021). Odor-evoked mitral cell activity changes after learning a new odor-reward association, probably resulting, at least partially, from changes in the gains of lateral and recurrent inhibition. In the mouse, training to discriminate very similar odorants enhances the ability of M/T cells to do so; and local inhibitory GABAergic cells contribute to this separation (Makino et al. 2016). In the ventral striatum of awake, behaving rats, few neurons are selective when first exposed to odors, but many acquire a differential sensitivity after associating odors with either appetitive (sucrose) or aversive (quinine) outcomes (Setlow et al. 2003). Conditioned fear responses depend on the amygdala (Brennan 2009). Aversive conditioning can enhance the perceptual and neural discrimination of initially indiscriminable olfactory stimuli, with the underlying plasticity in humans residing in the posterior piriform cortex. In mice, aversive conditioning enhances the expression of →brain-derived neurotrophic factor (BDNF) (→neurotrophic factors (neurotrophins, NTs) in the posterior piriform cortex and the basolateral amygdala. In postnatal rat pups as well, the posterior piriform cortex is activated during aversive odor learning (Gottfried 2009).

Recognition Learning. Responses to odors are much less innate than those to tastes and to some extent they are learned prenatally. An especially important type of olfactory learning (Wilson et al. 2009) establishes mother-offspring bonds, which usually occurs in sheep during a sensitive period after parturition (Brennan and Keverne 2015; Lévy et al. 2004). The ewe learns to distinguish her lamb from others by odor within 2-4 hours after birth, but only after vagino-cervical stimulation during parturition. Conditioning mechanical stimulation releases noradrenaline from locus coeruleus (LC) fibers projecting to the main olfactory bulb, which induces a number of plastic processes and facilitates learning. In particular, responses of MOB mitral cells to lamb odors are dramatically changed (Brennan 2009; Brennan andKeverne 2015). Initial memory formation and its short-term retention involve the olfactory bulb, piriform and entorhinal cortices, and hippocampus, while after memory consolidation (after several hours) only the olfactory bulb and piriform cortex appear important for memory →recall (Sánchez-Andrade et al. 2005).

Smell and Memory are closely linked. In fact, memory is essential for olfactory perception (Slotnick and Weiler 2009). Smells evoke memories and, conversely, memories of certain situations may recall associated smells. In this respect, smell is more effective than other sensory cues (Chu and Downes 2000a,b). Due to the intimate connection of the olfactory with the limbic system (Yeshurun and Sobel 2010), odors are easily associated with experiences, so that a smell alone can recall the experience, complete with all associated emotions. This occurs unconsciously and cannot be prompted →voluntarily. The strength and precision of odor

memories are modified during →sleep (Barnes and Wilson 2014).

Olfactory Imagery. Humans are good at mentally imagining visual scenes in the absence of sensory stimuli, and motor actions without actually moving. The ability to evoke odors from memory depends on experience. Naïve subjects have difficulty doing it, while odor experts, e.g. perfumers, can easily and voluntarily produce vivid mental odor perceptions (Royet et al. 2013).

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4

Pain and Nociceptive Processing

CONTENTS

Abstract

• Pain is a subjective experience. It serves as a warning signal of actual or potential tissue damage. It can be acute or chronic, originate in different body locations, have different causes (nociception, inflammation, neuropathy), and be affected by cognitive (sensory discriminative), affective and motivational aspects. Pain elicits stress, and stress modulates the perception of pain.

• Acute pain is adaptive and protective in that it enables undisturbed healing and repair. Chronic pain is defined as pain lasting for more than three months or beyond the time expected for healing and is maladaptive.

• Pain is usually elicited by the stimulation of free nerve endings and associated nociceptive sensory afferents in myelinated group III (Aδ) or unmyelinated group IV (C). The endings can be excited by mechanical, chemical or thermal stimuli.

• Nociceptive afferents from the facial region project to the trigeminal nucleus. Afferents from the rest of the body project to the spinal cord. The dorsal horn is the first central stage in the spinal cord where afferent signals from body parts are processed.

• The complex networks in the spinal cord produce phenomena such as touch-induced analgesia, referred pain and nociceptive motor actions (e.g., withdrawal reflexes) .

• From the dorsal horn, several ascending tracts target supraspinal regions including various brainstem, thalamic and cerebro-cortical areas.

4.1 Introduction

A general definition of pain is endorsed by the *International Association for the Study of Pain (IASP)*: "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Loeser and Treede 2008, p. 475). However, especially persistent pain cannot be understood merely by a reductionist approach focussing on underlying mechanisms (Brodal 2017).

Pain as a subjective experience must be distinguished from →nociception defined as "the neural processes of encoding and processing an actual or potential tissue-damaging event" (Loeser and Treede 2008, p. 475). Although nociception is the physiological basis of many painful states, it is not necessary nor sufficient for experiencing pain (Brodal 2017; Tracy et al. 2015).

Pain →perception is a highly subjective, conscious, mostly aversive experience described as pricking, burning, aching, stinging or soreness. It differs from other senses in having multiple dimensions: sensory-discriminative, →affective and →motivational, and →cognitive (Caputi et al. 2019; Kuner and Kuner 2021). The neutral discriminative aspect relates to the →intensity and location of a →noxious stimulus. The →hedonic aspect refers to the pleasure or dislike of the sensation. The motivational aspect elicits behaviors.

Pain perception is influenced by many factors, including genetic constitution, sex, →emotional state, mood, →attention, expectations, meaning given to it, →memory, →stress, and pathological circumstances (Brodal 2017; Bushnell et al. 2013; Butler and Finn 2009; Hollins 2010; Kuner and Kuner 2021; Mogil 2020; Neugebauer et al. 2009; Price and Ray 2019; Queme and Jankowski 2019; Sandkühler 2009; Tracey 2011; Tracey and Mantyh 2007; Tracy et al. 2015; Villemure and Schweinhardt 2010; Vincent and Tracey 2010). Pain is also modulated by pleasure in that it is decreased by pleasant food and odors, music, images, and sexual behavior (Leknes and Tracey 2008; Sandri et al. 2021).

There is a large inter-individual variability in pain →sensitivity, to the extent that some humans are insensitive to physical pain, partially due to mutations in the voltage-gated sodium channel $Na_v1.7$ (Benke 2021;Goodwin and McMahon 2021; Kuner and Kuner 2021; Mogil et al. 2000; Nahorski et al. 2015; Tracey and Mantyh 2007). Hereditary loss of nociception can result in repeated injury, self-mutilation (Costigan et al. 2009) and complete indifference to pain without other cognitive or motor deficits (Dib-Hajj and Waxman 2019).

The motivational aspect of pain elicits willingness to move towards a goal or away from a threat in order to avoid impending harm (Bushnell et al. 2013). This involves an array of behavioral responses on different time scales, from immediate nocifensive responses such as withdrawal reflexes to →learned behaviors that allow an animal to mitigate, avoid, or escape from, predictable future harm and include innate behavioral reactions such as freeze or →fight-or-flight. It has been argued hat such learned behaviors are acquired by →reinforcement learning. In parallel, nociception induces other effects, including facial expressions, →vocalization, →autonomic nervous and →hormonal responses (Seymour 2019).

4.2 Classification of Pain

There are many ways to classify pain. Some categorize types of pain based on detailed cellular and molecular mechanisms while others are more generalized and differentiate pain on properties such as genesis and site of origin or on time course (Basbaum et al. 2009).

Genesis and Site of Origin. Somatic pain can originate at the body surface as cutaneous pain or in the body interior as deep pain. These loci may indicate different causes of pain and therefore evoke different reactions.

Cutaneous pain is usually described as brief pricking (first pain), which may be followed in quick succession by a longer-lasting burning sensation (second pain).

Pain from deep tissues is commonly described as aching (Willis 1996). Central pain may occur after lesions of sensory pathways in the →spinal cord or brain, such as in →spinal cord injury, →inflammation or neoplasm of brain and spinal tissue, →multiple sclerosis, →stroke, →Parkinson´s disease or →epilepsy (Borsook 2012; Jensen and Finnerup 2009; Saab et al. 2008). Psychogenic pain arises without any demonstrable somatic tissue damage.

Time Course. Pain classified by time course, i.e., distinguished as acute pain and chronic, is arbitrary and subjective. Most experts agree that its use should be replaced by distinctions based on the underlying mechanisms (Reichling and Levine 2009).

Acute pain in response to a physical or chemical stimulus can be precisely localized in →somatotopy and described in modality and →intensity (Kuner and Kuner 2021). It.occurs with soft-tissue damage or inflammation. It is adaptive and protective in that it enables undisturbed healing and repair by making the injured/inflamed tissue hypersensitive (tender) to contact, so that movement is discouraged. Hypersensitivity occurs within minutes through peripheral sensitization and later through →central sensitization.

→Chronic pain is defined as pain lasting for more than three months or beyond the time expected for healing (Tsay et al. 2015). Different chronic pain states may result from long-term inflammatory tissue damage or nerve damage via trauma (→neuropathic pain), metabolic dysfunction, pathogenic infections, or cancer growth. Chronic pain manifests itself in various ways, e.g., spontaneous pain, enhanced sensitivity to painful stimuli (→hyperalgesia), pain in response to normally innocuous stimuli, e.g. gentle brushing of skin (mechanical allodynia) or mild cool temperatures (cold allodynia), and aberrant referral of pain to unaffected body parts (Kuner and Kuner 2021). Chronic, have different pathophysiological, neurochemical and clinical characteristics, as expressed, for example, in the different susceptibility to →analgesics (Apkarian et al. 2009; Costigan et al. 2009; Hunt and Mantyh 2001; Kuner and Flor 2017). For the suffering from chronic pain, motivational and emotional influences appear to be of particular importance, with an inability to extinguish the associated pain memory trace (Mansour et al. 2014).

4.2.1 Causes of Pain

Nociceptive or Physiological Pain can be elicited by chemical and by excessive thermal or mechanical stimuli that excite →nociceptors. This type of pain has a high →threshold and limited duration. It is a warning sensation that indicates impending or actual tissue damage. It protects against a potentially hostile external environment or internal tissue damage by initiating behavioral and →reflex avoidance strategies.

Inflammatory Pain is a response to transient inflammation evoked by tissue damage of various origins, and characterized by redness, heat, swelling and pain. Inflammatory pain aids healing and tissue repair by promoting immobility and rest (Costigan et al. 2009).

Neuropathic Pain is often the result of complete or partial severance or other damage to peripheral nerves [(e.g., nerve trauma, amputation, tumor invasion, infection and inflammation (e.g., →herpes zoster), →trigeminal neuralgia], or toxic or metabolic neuropathies (e.g., chemotherapy, →diabetic neuropathy, and can be accompanied by neuropathic itch, e.g. in post-herpetic states or small-fiber neuropathy (Cevikbas and Lerner 2020). It may also result from lesions or disease in the →central nervous system (CNS), such as spinal cord injury, stroke, or multiple sclerosis (Borsook 2012; Cao and DeLeo 2009; Finnerup et al. 2021; Saab et al. 2008). It is characterized by spontaneous burning, bursts of `pins and needles´, excruciating pain when clothes touch the skin, or searing pain after spinal cord injury. Post-traumatic neural damage may also lead to more extensive →complex regional pain syndromes characterized by sensory disturbances, skeletal motor and autonomic nervous dysfunctions. Neuropathic pain is often associated with affective aspects, depression, anxiety and insomnia (Baron 2006; Borsook 2012; Jänig 2009; Ji et al. 2019; Wasner et al. 2003). Neuropathic pain reflects a mal-adaptive →plasticity that causes spontaneous or exaggerated pain, with no protective or reparative consequence (Baron 2006; Costigan et al. 2009; Saadé and Jabbur 2008; Scholz and Woolf 2002).

4.2.2 Pain and Stress

Pain powerfully activates systems involved in emotional stress responses, such as anxiety, fear and frustration; and those that affect metabolic and cardiovascular →homeostasis (Holsboer and Ising 2010; Carrasco and Van de Kar 2003; Davidson and McEwen 2013; Kvetnansky et al. 2009):

Chronic pain can indirectly contribute to all categories of stress. Conversely, stress may influence the generation, maintenance and perception of pain. There are significant differences between *acute* and *chronic* states of pain and stress. While the acute states are frequently beneficial in ensuring survival, chronic pain and stress are generally detrimental and may have adverse effects on health, depending on various factors including genetic predisposition, early life experience and other factors (de Kloet et al. 2005; Gunnar and Quevedo 2007).

4.3 Anatomical Overview

4.3.1 Nociceptive Pathways

Nociceptive pathways from the periphery to the →cerebral cortex are complex.

4.3.2 Nociceptors

All animals have nociceptors (Sneddon 2018). In higher mammals, nociceptors are a heterogeneous group of neurons. Nociceptive afferents from the facial region project to the trigeminal nucleus and those from the rest of the body to the spinal cord. The latter´s cell bodies are located in →dorsal-root ganglia (DRG), their processes extending into peripheral tissues and centrally into the →dorsal horn of the spinal cord.

The peripheral free nerve endings →transduce noxious stimuli into →receptor potentials which are then transformed into →action potential sequences (Dubin and Patapoutian 2010). Nociceptors and their afferent nerve fibers fall into broad classes of sensory nerve fibers that signal the physiological state of body tissues in response to a variety of →stressors such as mechanical stress, cell damage and various disturbances of temperature, acid-base balance, tissue oxygenation, osmolarity, glucose regulation and hormonal activity. Nociceptors also interact bidirectionally with the →immune system by recognizing cytokines or pathogens and by producing various immune factors that act like →endocrine or →paracrine signals (Maruyama 2021).

The different variables are assessed by partially specialized nociceptors, →thermo-receptors, ergoreceptors, metaboreceptors and osmoreceptors, whose messages are conveyed through partially segregated processing pathways. However, many afferent, thalamic and cortical neurons in the thermal system show →multi-modal responses (mostly to touch and temperature). Thus, the different processing pathways also converge onto common central substrates (Basbaum et al. 2009; Bokiniec et al. 2018; Craig 2002, 2003). Thus, the processing pathways also converge onto common CNS substrates (Basbaum et al. 2009; Craig 2002, 2003).

Types of Nociceptors. Nociceptors are free nerve endings that are located in skin, deep tissues such as →skeletal muscles (Arendt-Nielsen and Graven-Nielsen 2009), joints (Schaible 2009), bones (Nencini and Ivanusic 2016), and internal organs (Bielefeldt 2009). Most afferents from thermo- and nociceptive free nerve endings are either un-myelinated (group IV or C) or thinly →myelinated (group III or Aδ) afferents, which also in part originate in paciniform corpuscles (Laurin et al. 2015), although there are also nociceptive fibers in the group II (Aß) range, that are found in different proportions in different mammalian species (Djouhri and Lawson 2004; Koch et al. 2018).

First and Second Pain. Since group III (Aδ) and group IV (C) fibers have different conduction velocities (6–25 and about 1.0 m/s, respectively), they are considered the first elements in distinct pathways underlying the fast first pain and the slow second pain responses to injury (Julius and Basbaum 2001). In response to brief noxious stimuli to the skin, first pain is brief, sharp, pricking and well localized and occurs at a latency of 400-500 ms, while second

pain lasts longer, is perceived as burning, diffuse and less well localized and occurs at a longer latency of about 1,000 ms (Ploner et al. 2002). This is in line with the finding that electrical stimulation of cutaneous group III fibers in humans evokes pricking pain, stimulation of group IV fibers elicits burning pain and stimulation of muscle nociceptive afferents evokes aching pain (Willis 1996). First and second pain sensations likely have different functions. First pain signals threat and provides precise sensory information for an immediate withdrawal, whereas second pain attracts longer-lasting attention and motivates behavioral responses to limit further injury and →optimize recovery (Ploner et al. 2002).

4.3.3 Spinal Dorsal Horn

In addition to the brainstem, the spinal cord is the first stage in the CNS where somatosensory signals from body parts are processed in a sophisticated manner. Spinal nociceptive processing is distributed both rostro-caudally and dorso-ventrally. In the rostro-caudal direction, processing is spread by the extensive arborization of primary nociceptive afferents as well as by wide-ranging propriospinal interconnections that also extend contralaterally. In the dorso-ventral direction, processing is distributed across multiple spinal laminae of the dorsal and →ventral horns. Thus, →nociceptive neurons with ascending projections (→projection neurons) are located in the superficial dorsal horn (lamina I), deep dorsal horn (laminae V, VI), ventral horn (lamina VII) of primates, and central gray (lamina X) of other species. Even the isolated spinal cord can encode noxious stimulus intensity, stimulus location, and can generate dynamic withdrawal responses to widespread, spatially complex noxious stimuli (Coghill 2020).

In the dorsal horn, small-diameter afferents (group III or Aδ and group IV or C) contact a large variety of excitatory and inhibitory →interneurons that provide for complex signal processing at spinal levels, and also connect with a minority of projection neurons that send →axons rostrally (Cordero-Erausquin et al. 2016; Häring et al. 2018; Koch et al. 2018; Wercberger and Basbaum 2019; Wu et al. 2010). Projection neurons also produce axon collaterals that are widely distributed within and between spinal segments, whose functions are hardly known, however (Browne et al. 2020).

Many projection neurons in lamina 1 are nociceptive-specific, with inputs from nociceptive afferents only. Lamina V contains wide-dynamic-range neurons (WDR) neurons with inputs from nociceptive and non-nociceptive sensory afferents and appear to be able to encode noxious stimulus intensity (Braz et al. 2014). The seeming contradiction between individual WDR neurons responding to non-noxious stimuli and yet encoding the intensity of noxious stimuli could be overcome by population coding (Coghill 2020).

Dorsal-horn neurons also receive modulating inputs from higher centers.

4.3.4 Supraspinal Projections

Nociceptive signals are conveyed to supraspinal structures via several distributed ascending tracts (Coghill 2020; Kuner and Kuner 2021). The main spinally ascending pathway is the spino-thalamic tract (STT), which projects to the posterior, medial and lateral →thalamus,

different nuclei of which project on to different →cortical areas. The →primary somatosensory cortex (S1, SI) mediates the sensory-discriminative aspect of nociception ("when, where, how strong"). The →secondary somatosensory cortex (S2, SII) contributes to sensory-discriminative functions, but likely also to higher-order cognitive functions. Motor areas of the →cingulate cortex, but also anterior parts of the cingulate and the →prefrontal cortex (PFC) mediate motor aspects, attentional →orienting, and the emotional component of the pain percept (Kuner and Kuner 2021). Parallel projections reach several other targets, including the →reticular formation (RF), →parabrachial nucleus (PBN), →locus coeruleus (LC), →midbrain →peri-aqueductal gray (PAG), →superior colliculus (SC), →globus pallidus, central nucleus of the →amygdala and →hypothalamus. There is also a projection via the postsynaptic dorsal-column (Almeida et al. 2004; Braz et al. 2014; Brodal 1981; Coghill 2020). The ascending pathways transmit nociceptive information across bilateral routes. That is, the spino-thalamic projections may arise from deep dorsal-horn and ventral-horn neurons with bilateral and/or whole-body →receptive fields (RFs). The projections of other spino-thalamic neurons travel ipsilaterally instead of contralaterally to the cell body (Coghill 2020).

A diverse array of supraspinal structures react to painful experience. A meta-analysis of many human neuroimaging studies shows a core of areas exhibiting a largely bilateral pattern of pain-related activation in the thalamus, secondary somatosensory cortex (S2, SII), →insula (insular cortex), and mid-cingulate cortex. These regions are activated regardless of stimulation technique, location of induction, and participant sex (Xu et al. 2020). Individual studies show more diverse patterns. For example, noxious cold exposure activates the thalamus, →putamen and right anterior →insular cortex (insula), while innocuous cold exposure activates the posterior insular cortex, middle/orbital cortex and →posterior parietal cortex (PPC) (King and Carnahan 2019). Heat-evoked acute pain activates both somatic-specific areas such as the ventro-lateral thalamus, the secondary somatosensory cortex (S2, SII) and the dorsal posterior insula, as well as regions related to affect and mood, such as the anterior insula, the dorsal →anterior cingulate cortex (ACC) and the medial thalamus (Kuner and Kuner 2021). Signals associated with the pain experience also reach the CNS via the blood stream, by →inflammatory mediators that ultimately cause the sickness response of fever, general muscle and joint ache, anorexia and lethargy (Bartfai 2001; Sandkühler 2009).

Lamina I Pathways. Lamina I nociceptive projection neurons project to the posterior ventro-lateral →thalamus, which projects on to the primary somatosensory cortex (S1, SI) and mainly contributes to sensory-discriminative qualities of pain sensation, including the localization and discrimination of pain intensity (Caputi et al. 2019). In humans, the primary somatosensory cortex (S1, SII) carries a fine-grained somatotopic map of nociceptive inputs from the fingers, aligned with maps from tactile inputs (Mancini et al. 2012). Lamina V neurons project to the ventral posterior (VP) and ventral posterior inferior (VPI) thalamic nuclei, the ventral lateral nucleus (motor thalamus) and to →intralaminar nuclei with further projections to the →basal ganglia and motor and →parietal cortices. Nociceptive signals also reach the →cerebellum (Moulton et al. 2010; Saab and Willis 2003).

Projections from lamina I neurons also give rise to a medial, more extensive system which projects from the medial thalamic nuclei to the anterior cingulate cortex (ACC), insular

cortex and other regions, where ACC appears to be particularly involved in the emotional and affective qualities of pain (Caputi et al. 2019; Gracely and Harte 2009; Neugebauer et al.2009), as well as organizing autonomic responses (Craig 2002, 2003; Gracely and Harte 2009). Lamina I neurons project to CNS regions involved in homeostatic regulation: spinal →sympathetic →preganglionic neurons in the intermediate lateral cell column that mediate spinal somato-autonomic reflexes (Burton et al. 2016); →brainstem regions that receive vagal and glossopharyngeal nerve afferents via the nucleus tractus solitarii (NTS), including putamen →catecholaminergic cell groups (A1-A2, A5-A7); peri-aqueductal gray (PAG); dorsal reticular nucleus (DRT); and lateral →parabrachial nuclei (PBN) in the rostral →pons. PBN neurons project on to the ventro-medial hypothalamus and amygdala, where affective dimensions of pain and control of autonomic activity are modulated. These structures in turn project back to the PAG, which is crucially involved in the fight-or-flight response and stress-induced analgesia (Behbehani 1995; Butler and Finn 2009; Chiang et al. 2019; Craig 2002, 2003; Caputi et al. 2019; Hunt and Mantyh 2001; Koutsikou et al. 2017; Neugebauer et al. 2009; Tracey and Mantyh 2007; Wu et al. 2010).

Laminae III-V Pathways. In cats and primates, WDR neurons occur in the deep dorsal horn (lamina V). Laminae III–IV contain neurons projecting via the spino-cervical tract. Postsynaptic dorsal column neurons, many of which respond to noxious visceral stimulation, originate in laminae III/IV and X, send axons through the →dorsal columns and terminate in the →dorsal column nuclei. Their long, dorsally directed →dendrites can extend to lamina I and thus receive inputs from primary afferents that terminate throughout the superficial dorsal horn, including a significant low-→threshold Aβ input. Many spinal and medullary projection neurons in laminae III-V respond robustly to pruritogens. Some WDR neurons in laminae III-V are somatotopically organized, which would provide a substrate for stimulus localization and intensity coding (Wercberger and Basbaum 2019).

Laminae VII-VIII Pathways. The spino-reticulo-thalamic tract take origin in cells that are distributed throughout laminae VII and VIII. Most of these cells send ipsilateral or bilateral projections that either terminate in the medial brainstem reticular formation or emit collaterals as they course to the medial thalamus, thus exerting diverse influences in pain processing. Some of these cells are nociceptive-specific and respond to both cutaneous and visceral inputs while others have WDR properties. Many have very large, bilateral RFs, with complex excitatory and inhibitory inputs (Wercberger and Basbaum 2019).

Itch Pathways. Itch is a unique sensation that urges organisms to scratch away external threats, and scratching in turn induces an immune response that can enhance itchiness (Lay and Dong 2020). The central pathways and circuits processing itch and pain overlap anatomically, but some neurons transmit itch signals independently of other modalities (Lay and Dong 2020). After spinal processing, itch signals are transferred via projection neurons which connect to the STT. The next supraspinal itch-processing station is the parabrachial nucleus (PBN), which projects to different brain regions including the amygdala. As shown for pain, the amygdala links anxiety and stress to chronic itch. Functional MRI in humans implicates cortical regions including the primary somatosensory cortex (S1, SI) and secondary_somatosensory cortex (S2, SII), the cingulate cortex and prefrontal cortex (PFC) (Cevikbas and Lerner 2020).

4.4 Nociceptive Substances, Receptors and Functions

Painful experiences and reactions are initiated by mechanical, chemical, thermal or microbial stimuli that activate nociceptors at multiple locations in the body, and by assorted, generally intricate mechanisms. For example, nociceptive primary afferents, despite their morphologically simple appearance, are quite complex. They contain numerous ligands (e.g., →substance P, →growth factors, →hormones such as →somatostatin, and →neurotransmitters (e.g., →glutamate, →adenosine, →adenosine triphosphate (ATP). They express dozens of receptors, along with →voltage-gated and →ligand-gated ion channels that contribute to the detection of mechanical, chemical, thermal and/or microbial stimuli, resulting in action potential generation, regulation of discharge patterns, and release of ligand/neurotransmitters that mediate complex interactions between nociceptors (Bourinet et al. 2014; Carlton 2014; Devesa and Ferrer-Montiel 2014; Dubin and Patapoutian 2010; Sexton et al. 2014; Woolf and Ma 2007).

While various data support the existence of modality-specific nociceptors that respond to either mechanical or chemical or thermal stimuli, many nociceptors are polymodal in that they respond to combinations of stimuli. It has been suggested that the incidence of →polymodal receptors depends on context. For example, if a specific stimulus is intense enough to cause tissue damage, the following inflammatory response likely increases the number of responsive nociceptors, modulates their modality sensitivity and increases the overall incidence of polymodality (Emery and Wood 2019).

Different types of pain are processed by several different types of nociceptor and conveyed in fibers of different size (Dubin and Patapoutian 2010; Julius and Basbaum 2001; Scholz and Woolf 2002; Vasko 2009; Woolf and Ma 2007; Zhang et al. 2013).

Group III (Aδ) Fibers originate from two main types of nociceptors and target lamina I and deeper lamina V. The Type I variety are high-threshold mechanical (HTM) nociceptors with initially high heat thresholds (>50ºC), which declines upon longer exposure and sensitizes so that threshold is lowered. The Type II variety of receptors has high mechanical and low heat thresholds (Basbaum et al. 2009; Cevikbas and Lerner 2020).

Group IV (C) Fibers often display slow ongoing activity that is not perceived, although summed activation of fibers can cause pain perception in humans (Craig 2002). Most group IV (C) fibers respond to mechanical and thermal stimuli, while others respond only to heat. Most group IV (C) fibers are also sensitive to chemical nociceptive stimuli. They can be broadly divided into two groups that target distinct areas in the dorsal horn (Basbaum et al. 2009; Cevikbas and Lerner 2020, Häring et al. 2018). One group expresses $P2X_3$ →purinergic receptors (for ATP) and receptors for glia cell-derived neurotrophic factor (GDNF), and terminates almost exclusively within the deeper parts of lamina II) (substantia gelatinosa Rolandi) (Merighi 2018). The other, peptidergic, group synthesizes peptides such as substance P (SP) and →calcitonin-gene-related peptide (CGRP), expresses the nerve growth factor (NGF) receptor →tropomyosine receptor kinase A (TrkA), and somatostatin, and terminates more superficially in the dorsal horn (Basbaum et al. 2009; Cevikbas and Lerner 2020; Hunt and Mantyh 2001; Wu et al. 2010).

Many cases of congenital insensitivity to pain (human sensory and autonomic neuropathy type IV) are caused by mutations in TrkA (Pezet and McMahon 2006). There are also `sleeping´ or `silent´ nociceptors that constitute almost 25% of the group C fibers in humans skin and become mechanically responsive only after →sensitization by tissue injury (Cevikbas and Lerner 2020). They respond to heat and chemical stimuli (→capsaicin, →histamine) and likely play a role in inflammation (Basbaum et al. 2009; Frias and Merighi 2016; Schmidt et al. 1995).

A subset of free nerve endings called pruriceptors with afferents predominantly in group IV (C) and some in group III (Aδ) relay the sensation of itch, which is distinct from pain, as well as thermo-sensation and touch (Lay and Dong 2020). Possibly, all pruriceptors function as nociceptors in humans, but whether the reverse is true is as yet unclear (Cevikbas and Lerner 2020; Duan et al. 2017; Hoon 2015; Koch et al. 2018; LaMotte et al. 2014; Liu and Ji 2013; Luo et al. 2015; Ross 2011). There are histamine-dependent and histamine-independent group IV (C) fibers involved in itch sensation as well as a bunch of receptors for various agents (Lay and Dong 2020). Chronic itch in particular is only marginally related to histamine and is caused by other types of pruritogens. For example, →endothelin mediates itch behavior in mice (Cevikbas and Lerner 2020; Jeffry et al. 2011).

Some group IV or C cutaneous afferent fibers have a low threshold to mechanical stimuli and are involved in the sensation of affective touch or pleasant touch (Julius and Basbaum 2001).

4.4.1 Sensory Transduction Mechanisms

Transduction by different kinds of nociceptors involves different combinations of →ion channels and intracellular →signal-transduction mechanisms. Of particular importance are →transient receptor potential (TRP) channels, of which at least eight different types (→TRPV1, TRPV2, →TRPV3, →TRPV4, TRPM2, →TRPM3, →TRPM8, TRP ankyrin 1 (TRPA1)) are implicated in diverse aspects of nociceptive transduction and thermal encoding (Finnerup et al. 2021; Hung and Tan 2018; Jardín et al. 2017; Laing and Dhaka 2015; Mickle et al. 2015; Moore et al. 2018; Sexton et al. 2014; Satheesh et al. 2016). Moreover, →acid-sensing ion channels (ASICs) (Cheng et al. 2018; Deval and Lingueglia 2015; Lee and Chen 2018; Wemmie et al. 2013) and →hyperpolarization-activated cyclic nucleotide-gated (HCN) channels play important parts (Finnerup et al. 2021).

Transient receptor potential (TRP) channels are mostly found on the plasma membrane of cells. In addition to pain, they mediate sensations of hotness, warmth or coldness, different kinds of tastes, pressure, and vision. Most TRP channels are composed of 6 membrane-spanning helices with intracellular N- and C-terminals. They are non-selectively permeable to cations, including sodium (Na^+), calcium (Ca^{2+}) and magnesium (Mg^{2+}) (Laing and Dhaka 2015; Sexton et al. 2014). Many TRP channels are also sensitive to pungent chemicals from chili, garlic, peppermint, mustard, oregano, savory, clove and thyme. In addition to acute nociception, TRP channels also contribute to mechanical and thermal hyperalgesia. Normally, the threshold for activation of TRPV1 channels may be kept high by →$GABA_B$ receptors which thus prevent sensitization; this mechanism may fail under pathological inflammatory conditions and lead to peripheral hyperalgesia (Bente 2021).

Acid-sensing ion channels (ASICs) are neuronal voltage-insensitive Na^+ channels that are found in the →peripheral nervous system (PNS) and →central nervous system (CNS). They also exhibit low Ca^{2+} permeability. In mammals, ASICs are encoded by five genes that produce ASIC protein subunits: ASIC1, ASIC2, ASIC3, ASIC4, and ASIC5. In general, the role of the ASIC is to sense reduced levels of extracellular pH and result in a response or signal from a neuron. They may be sensors in the pain experience, because pain-causing inflammation lowers extracellular pH (Deval and Lingueglia 2015; Wemmie et al. 2013).

Mechanical nociception may also involve Piezo 2 ion channels (Anderson et al. 2017; Hill and Bautista 2020).

4.4.2 Mechanical Nociception

Cutaneous Mechano-nociceptors. Recent molecular-genetics methods have allowed to distinguish subsets of mechanical nociceptor afferents, including fast-conducting group Aδ and slow-conducting group C fibers, as well as innocuous touch receptors that interact with the mechanical pain pathway (Hill and Bautista 2020). The predominant cutaneous mechano-nociceptors are group Aδ (III) mechanical nociceptors, group Aδ mechano-heat nociceptors and group C (IV) polymodal receptors.

Calcitonin-gene-related peptide (CGRP) is an inflammatory →neuropeptide that is typically associated with peptidergic C-nociceptors. However, CGRP is also expressed in a subset of group Aδ fibers that detect noxious hair pull. In mice, a subset of Aδs is marked by the →G-protein-coupled receptor, neuropeptide Y2 receptor (NPY2R), and NPY2R fibers in the glabrous skin of the paws are required for proper timing of withdrawal responses to pinprick stimulation. A role complementary to that of Aδ fibers in mechanical pain is played by polymodal group C nociceptors, particularly during inflammation (Hill and Bautista 2020).

Mechano-heat nociceptors respond not only to mechanical stimuli but also to heat, usually above 50 °C. Cutaneous polymodal group C (IV) nociceptors respond to noxious mechanical, thermal and chemical stimuli. Their heat thresholds range from 41 °C to 50 °C, and they are also sensitive to chemical substances, such as potassium (K^+), →bradykinin (BK), →serotonin (5-HT) and capsaicin, the active ingredient of chili pepper (Frias and Merighi 2016). They →depolarize membrane potential by activating G-protein-coupled BK2 receptors (Willis 1996).

Various channels have been proposed to contribute to mechanical nociception, including TRP channels, degenerin/epithelial Na^+ channels (DEG/ENaC) and KCNK potassium channels, but their roles remain unclear (Basbaum et al. 2009). Recently, it has been proposed that an ion channel called TACAN is expressed in nociceptors and is responsible for their sensitivity to high-intensity mechanical stimuli, while →Piezo2 is broadly expressed in →mechano-receptors and nociceptors (Sharif-Naeini 2020).

Muscle Mechano-nociceptors. Due to their wide central distribution, high-threshold muscle afferents in groups III and IV have diverse roles. They have modulatory effects on spinal reflexes, may contribute to adjust muscle contractions during →muscle fatigue (→muscle

fatigue, neural factors) (Gandevia 2001) and to adjust heart rate, ventilation, blood pressure and vascular resistance during physical exercise (Decherchi and Dousset 2003; Laurin et al. 2015; Murphy et al. 2011). Group III muscle afferents are more mechano-sensitive than group IV afferents during skeletal muscle contraction, force production, dynamic/static muscle stretch and local intramuscular pressure; their response to a mechanical stimulus may be potentiated by chemical stimuli. Muscle group IV afferents are more sensitive to metabolites released into the interstitium by muscle activity because their activation usually starts after a delay during prolonged muscle contraction and continues to discharge until the withdrawal of muscle metabolites. They also sense temperature associated with muscle warming (Hayward et al. 1991; Laurin et al. 2015; Rotto and Kaufman 1988; Mense 1993).

Like their cutaneous counterparts, many muscle afferents of both groups III and IV are excited by algesic chemicals and metabolites released into active muscle, such as K^+, lactic acid, →arachidonic acid products (e.g., →prostaglandins), ATP, bradykinin (BK), and serotonin (5-HT). This excitation is mainly related to the activation of acid-sensing ion channels (ASICs), purinergic type 2X (P2X) and TRPV1 (transient receptor potential vanilloid 1) channels. Muscle pain can be experimentally induced by intramuscularly injecting neurotoxins such as capsaicin (TRPV1 →receptor agonist), ascorbic acid, carrageenan and hypertonic saline solution, known to activate group III and IV afferents (Laurin et al. 2015; Mense 1993). Some receptors respond to contraction during →ischemia and may thus be responsible for the aching muscle pain during ischemic exercise (claudicatio intermittens) (Willis 1996).

4.4.3 Chemical Nociception

The sensitivity of nociceptors to chemicals plays a paramount role in inflammatory pain. Sub-populations of group III-IV afferents are excited or modulated by a broad range of constituents in the inflammatory soup that accumulates around the primary tissue injury. It includes cells that release a variety of inflammatory molecules upon activation. Among these are immune cells, including inflammatory monocytes, →macrophages, and →neutrophils, which release molecules that can sensitize peripheral nociceptors. Immune cells act at the level of the cutaneous nerve terminals, peripheral nerve, →dorsal-root ganglion (DRG), or spinal cord to promote sensitization (Hill and Bautista 2020). But also nociceptive endings themselves release inflammatory ligands that promote →neurogenic inflammation. Group IV (C) endings release peptides and other irritants from their peripheral terminals via →axon reflexes, resulting in vasodilation, →phagocytosis and exacerbation of inflammatory symptoms such as pain and severe itching (Basbaum et al. 2009; Levine et al. 1993; Deval and Lingueglia 2015; Ito et al. 2001; Mense 1993; Scholz and Woolf 2002; Vasko 2009; Wemmie et al. 2013; Woolf and Ma 2007). Many noxious chemicals act on transient receptor potential (TRP) ion channels, which may evoke pain as well as itch (Cevikbas and Lerner 2020; Kittaka and Tominaga 2017; Luo et al. 2015; Ross 2011).

4.4.4 Thermo-reception

Thermo-reception can give rise to diverse reactions: various influences on body function such as maintenance of constant core body temperature, innate and learned motor behaviors such as quick responses to noxiously cold or hot objects, strong emotional reactions from pleasure to pain, rapid and acute percepts often coupled with tactile inputs during exploratory object manipulation. Thermo-sensibility shows a substantial inter-individual variability, based on genetics, sex, age, body-mass index, prior temperature experience and psychic state (Bokiniec et al. 2018; Vriens et al. 2014).

Thermo-receptor-activated Ion Channels. Transduction in thermo-receptors involves TRP ion channels whose expression on afferents is complex, however (Bokiniec et al. 2018; Kashio 2021; Laing and Dhaka 2015; Lewin et al. 2004; Palkar et al. 2015; Sexton et al. 2014; Stucky et al. 2009; Vriens et al. 2014). Noxious temperatures ≥ 42 °C activate TRPV1, TRPV2 and TRPM3 channels; TRPV1 channels are also activated by low pH and capsaicin (Frias and Merighi 2016). The TRPM2 channel is activated by warm temperatures above 35 C, but is not absolutely required for warm perception which, however, requires the cool-sensitive TRPM8 channel (Paricio-Montesinos et al. 2020).

Rather than using a →labeled-line code (Schepers and Ringkamp 2010), with receptor afferents firing only in response to warm stimuli, warm perception in mice may rely on signals from more than one receptor type to unambiguously detect skin warming. There are two populations of polymodal C fibers that signal warm. Warm excites one population and suppresses the ongoing cool-driven firing of the other. In genetically modified mice, in which the thermo-sensitive TRPM2 or TRPV1 ion channels are absent, warm perception is blunted, but not abolished. Loss or local pharmacological silencing of the cool-driven TRPM8 channel abolishes the ability to detect warm. It has therefore been proposed that it is the concurrent inhibition and excitation of these two polymodal channels that provide the sensory code for warm perception, which also does not require heat-activated TRP channels (Paricio-Montesinos et al. 2020).

Noxious heat responses in mice depend on a trio of TRP channels: TRPM3, TRPV1, and →TRPA1. Robust heat responses occur only if at least one of these TRP channels is functional. Combined genetic or pharmacological elimination of all three channels prevents heat responses in rapidly firing cutaneous C and Aδ afferent fibers. These triple knockout mice also show no withdrawal reflex to noxious heat while exhibiting normal nociceptive responses to cold or mechanical stimuli (Vandewauw et al. 2018).

Heat-evoked nociceptor activity may be modulated by →TREK-1 heat-sensitive potassium (K^+) channels. There may be other transduction mechanisms underlying thermo-sensation, including inhibition of K^+ →conductances or →Na^+-K^+ →ATPase, activation of pH-sensitive channels (Jordt et al. 2003; Patapoutian et al. 2003) or a Ca^{2+}-activated Cl^- channel called anoctamid that might be a noxious heat receptor (Vriens et al. 2014).

Cool and cold temperatures activate the channels TRPA1 and TRPM8 (Bokiniec et al. 2018; Talavera et al. 2020). TRPA1 has a threshold at temperatures perceived as painfully cold. TRPM8 is a calcium-permeable cation channel that is mainly responsible for the sensation of cold temperatures, and is also gated by cooling compounds such as →menthol and

eucalyptol (Latorre et al. 2011). Genetically modified mice that lack TRPM8 channels have severe noxious and innocuous cool-evoked behavioral and perceptual deficits (Paricio-Montesinos et al. 2020).

4.5 Central Processing of Nociceptive Signals

The central branches of nociceptive afferents terminate in the dorsal horn of the spinal cord or its trigeminal homologue in the brainstem, where they make →synaptic connections with a complex array of neurons that play different roles in nociceptive processing and pain. Nociceptive activity does not automatically reach higher centers and lead to pain perception. This depends on the rate of action potentials in primary afferents, temporal summation of pre- and postsynaptic signals and central influences (Dubin and Patapoutian 2010).

4.5.1 Spinal Processing

The spinal cord is no simple relay for nociceptive signal flow, but a complex network of interneurons and projection neurons which differ in terms of location, morphology, gene expression profiles, neurochemistry, patterns of inputs, excitability and discharge patterns (Braz et al. 2014; Cevikbas and Lerner 2020; Cordero-Erausquin et al. 2016; Duan et al. 2017; Gatto et al. 2019; Graham et al. 2007; Häring et al. 2018; Zeilhofer et al. 2012; Wu et al. 2010).

The intensity of a noxious stimulus is reflected in the extent and strength of spinal neuronal activation. Thus, as shown by autoradiographic, functional imaging studies, noxious heat stimuli of increasing intensity applied to the rat distal hindpaw elicited activation of increasing extent and strength on the ipsi- and contralateral side. Low stimulus intensities (45°C) activated the segment L4 in the somatotopic epicenter. As noxious stimulus intensities increased (49°C), activation extended from L2 to L5 contralaterally in the deep dorsal horn and ventral horn. These regions have neurons with bilateral receptive fields with ascending projections (Coghill 2020).

In the mouse, genetic methods have revealed distinct modular circuits made up of molecularly defined interneurons that process nociceptive (pain), pruritic (itch) and cutaneous mechano-sensitive (innocuous touch) stimuli. Excitatory interneurons transmit →somatosensory information and inhibitory interneurons operate as gates to prevent innocuous stimuli from activating nociceptive and pruritic pathways (Koch et al. 2018). The properties of these neurons can change depending on context; for example, depolarization may transform nociceptive-specific (NS) neurons into wide-dynamic-range (WDR) neurons (Berger et al. 2011; Sandkühler 2009). Neuron properties are also altered by the actions of several classes of →neuromodulators and neuropeptides (Zeilhofer et al. 2012).

4.5.1.1 Superficial Dorsal Horn

Lamina I contains several classes of modality-specific and morphologically distinct neurons that receive different inputs. They include spino-thalamic tract (STT) cells that respond to muscle or joint afferents or to slow mechanical touch, cooling or warming; viscero-ceptive cells with convergent input from cutaneous afferents; cells that are associated with referred pain; and neurons that respond to histamine and noxious chemicals and receive inputs from group IV fibers (Craig 2002, 2003; Jeffry et al. 2011).

Nociceptive-specific neurons in lamina I, which respond only to pinch and/or noxious heat, predominantly receive inputs from group III (Aδ) afferents and primarily transmit sharp pain that elicits fight-or-flight behavior. Polymodal nociceptive neurons receive inputs from polymodal group IV (C) afferents. They respond to noxious pinch, heat and cold, and transmit slow, burning pain. They are also involved in long-term responses, including sickness responses and immune functions (Craig 2003). Group IV (C) fibers from the skin terminate in a highly →topographic fashion in lamina II (substantia gelatinosa Rolandi) (Merighi 2018)), which may be a factor contributing to the good localization of cutaneous pain stimuli.

In parallel to polymodal transmission lines for itch, pain, thermosensation and touch, there appears to be a labeled line for itch starting with a small number of uniquely pruriceptive fibers and channeled through a specific `itch circuit´ in the spinal cord, at least in mice (Braz et al. 2014; Cevikbas and Lerner 2020; Craig 2002, 2003; Duan et al. 2017; Hoon 2015; Lay and Dong 2020; Liu and Ji 2013; Ross 2011). This may explain why the sensation of itching, in contrast to pain, is confined to the body surface. Inhibitory interactions between pain- and itch-related neurons explain why noxious cold, heat or chemical stimuli (`counter stimuli´) can reduce itch sensations (Ross 2011). Generally, neuronal circuits in the spinal cord and the brain, which mediate pain, itch and touch exhibit cross-modulation (Lay and Dong 2020). Chronic itch increases stress and anxiety, which in turn exacerbate itch, leading into a vicious cycle (Sanders and Akiyamam 2018).

4.5.1.2 Deep Dorsal Horn

Lamina V contains large neurons with widely distributed dendrites that receive small and large-diameter inputs from various sources. Almost all these cells are wide-dynamic-range (WDR) neurons because they are activated by various noxious stimuli, weak mechanical stimulation from the skin and by inputs from viscera, muscles and joints in varying proportions. Their usually large receptive field (RF) size can change as a result of both excitatory and inhibitory segmental processes. The activity can be inhibited from most of the remaining parts of the body via spinal and supraspinal mechanisms. Thus, prolonged noxious stimuli applied anywhere on the body surface may suppress the effects of noxious stimuli applied at other other sites. This diffuse noxious inhibitory control (DNIC) is triggered by peripheral group I and IV fibers, and involves supraspinal structures such as the peri-aqueductal gray (PAG), →rostral ventro-medial medulla (RVM) and descending pathways in the dorso-lateral →funiculi (Butler and Finn 2009; Hollins 2010; Le Bars 2002). Wide-dynamic-range (WDR) neurons can be →projection neurons and/or interneurons for polysynaptic withdrawal reflexes. They mimic many excitatory and inhibitory phenomena

related to pain sensation, such as hyperalgesia, →allodynia, referred pain or, perhaps, touch-induced analgesia (Willis 1996).

4.5.1.3 Touch-induced Analgesia

It is well-known that rubbing a skin area exposed to noxious stimuli often mitigates pain. This phenomenon of touch-induced analgesia is based on as yet incompletely understood mechanisms that block or suppress nociceptive transmission by coactivating large-diameter cutaneous afferents in the spinal cord (Duan et al. 2017; Mendell 2014) and/or at →sub-cortical and cortical levels (Mancini et al. 2015).

Rather than rubbing a skin area, electrically stimulating large-diameter afferents can relieve pain. This can be done by stimulating the dorsal columns of the spinal cord in humans suffering from intractable pain, in particular pain following nerve injury or peripheral vascular disease, and from angina pectoris (Linderoth and Meyerson 1995). Another way to stimulate large-diameter fibers is via →transcutaneous electrical nerve stimulation (TENS) or electro-acupuncture (Hollins 2010; Zhao 2008). TENS at low intensity, activating group Aα/Aβ (I/II) fibers and causing →paresthesia, elicits short-lasting analgesia. Mildly painful TENS at higher stimulus intensity, also activating group III fibers, causes long-lasting analgesia (Sandkühler 2009). Nociceptive signal transmission can also be curtailed by →presynaptic inhibition. Indeed, group C fiber input to lamina I can be presynaptically inhibited by group Aβ, group Aδ and group C afferents (Fernandes et al. 2020).

4.5.1.4 Referred Pain

Referred pain is perceived at a location other than the site of a painful stimulus. An example is ischemic pain brought on by myocardial infarction, in which pain is often felt in the neck, shoulders, and back rather than in the chest. In the thorax, general visceral afferent (GVA) pain fibers project to the same spinal cord segments that gave rise to the preganglionic sympathetic fibers. This arrangement provides an anatomical substrate to explain why the CNS perceives pain from the heart as coming from the somatic portion of the body supplied by the thoracic spinal cord segments 1-4. A plausible mechanism involves central sensitization, in which dorsal horn and/or brainstem neurons become more responsive after repeated stimulation by GVA neurons (Arendt-Nielsen and Svensson 2001). This explains why there is generally a delay in the onset of classical referred pain following an infarct.

4.5.1.5 Spinal Nociceptive Motor Actions

Withdrawal reflexes from noxious skin stimuli were originally considered the simplest centrally organized reactions to noxious stimuli (Clarke and Harris 2004; Sandrini et al. 2005). They were thought to be simple →flexion reflexes which would activate all flexor muscles and inhibit all extensor muscles simultaneously. However, studies in rats, cats and humans suggest that the reflex has a modular organization. In rats, each module controls a

single or a small number of synergistic muscles with similar actions, the innervating α-motoneurons receiving →multi-sensory input from the skin area the animal withdraws from. The weight of the input connections from a given palmar skin site to a reflex module is determined by how effective this module is in withdrawing from the skin site when the animal is in the standing position. Thus, there is a somatotopically organized sensory-motor transformation. Interneurons mediating the withdrawal reflex and determining the reflex strength in individual muscles are located in the deep dorsal horn in segments L4 and L5. These interneurons receive convergent inputs from tactile group Aß fibers and nociceptive group C fibers and are aligned as small groups in medio-lateral sequence corresponding to the somatotopical organization of the →α-motoneuron columns. This organization adapts to changing sensory and motor conditions (Schouenborg 2002, 2003).

In awake, unrestrained rats, brief thermal and mechanical noxious stimulation of group Aδ fibers from a paw activated a rapid multi-segmental motor program coincident with, or even preceding, withdrawal of the stimulated paw. This program included early head orientation and adjustments of the torso and the un-stimulated paws. This response could be inhibited by the rat´s posture, suggesting the existence of an endogenous analgesia system that gates access of nociceptive information to the ventral horn motoneuronal withdrawal circuits. This gate operates via →opioid- and non-opioid-dependent mechanisms (Blivis et al. 2017).

4.5.2 Supraspinal Processing

The complexity of pain experience in humans, often accompanied by fear, anxiety, depression and autonomic disturbances, makes it difficult to assign specific supraspinal structures and functions to the various components associated with pain onset and its progression. Recent neuroimaging studies have established that many different brain regions in various combinations are activated in the course of acute or chronic pain (Kuner and Kuner 2021; Tracey and Mantyh 2007).

4.5.2.1 Thalamus

Most likely, pain is a percept created by the →cerebral cortex and the thalamus which contributes to modulate cortical activity in perceptual →decision making, executive control, and attention, but exactly how the bi-directional cortico-thalamic interactions and the cellular and circuit mechanisms produce the pain percept is not well understood (Kuner and Kuner 2021).

The posterior ventro-lateral thalamus contains many nociceptive and thermo-sensitive neurons with properties similar to lamina I neurons, and is a processing station in the dedicated spino-thalamic-cortical line representing pain and temperature (Craig 2003). Nociceptive thalamic neurons are organized →somatotopically. Wide-dynamic-range (WDR) neurons with properties similar to the respective spinal lamina V cells have also been recorded in the above thalamic nuclei (Willis 1996). Thalamic nociceptive neurons in normal rats and humans display spontaneous discharge in various patterns, which become abnormal under pain conditions (Saab and Hains 2009).

4.5.2.2 Cerebral Cortex

Pain is a subjective experience in multiple dimensions: sensory-discriminative, affective/motivational, and cognitive, these aspects being processed differentially in a distributed brain network often referred to as `pain matrix´ (Chen 2017; Legrain et al. 2010). Multiple, highly interconnected cerebro-cortical regions receive parallel inputs from the thalamus. In humans, noxious stimulation in parallel activates somatosensory regions such as primary somatosensory cortex (SI) and secondary somatosensory cortex (S1, SII), the posterior insula, mid-cingulate cortex and amygdala. Other regions without direct spinal nociceptive input (the anterior insula, frontal →operculum, →precuneus (PCu), and →dorso-lateral prefrontal cortex, DLPFC) are activated next, and the posterior parietal cortex (PPC) and peri-genual cingulate cortex are activated last. Lesions of specific brain regions do not completely eliminate pain perception. For example, lesions of area S1 disrupt the ability to perceive light touch, but not the ability to perceive pain. This ability is also preserved with lesions to area S2, insula, ACC and PFC, as well as to regions providing sub-cortical input to the PFC (Coghill 2020). The precise activation patterns of cortical areas depend on the type of pain, and de-activation of other areas may also occur with activation (Neugebauer et al. 2009; Zhuo 2008). Primary somatosensory cortex (S1, SI), anterior cingulate cortex (ACC) and prefrontal cortex (PFC), for example →Brodmann´s area 10 (Peng et al. 2018), are activated more frequently and more robustly in individuals who are highly sensitive to pain than in insensitive individuals (Coghill et al. 2003). Mere anticipation of pain may also activate the pain matrix, whereas this activation and the subsequent pain may be reduced by the feeling to be able to control the intensity of an impending nociceptive stimulus (Brodal 2017).

Many human brain regions are activated in a fashion related to noxious stimulus intensity and perceived pain intensity. These regions include bilateral portions of the thalamus, contralateral SI, bilateral SII, bilateral posterior insula, bilateral anterior insula, bilateral anterior cingulate, and bilateral portions of the putamen. Thus, intensity-related information is widely distributed in regions ipsilateral to stimulation, as well as regions like the ACC that are typically associated with affective processing rather than sensory-discriminative processing (Coghill 2020).

Within the pain matrix, the primary somatosensory cortex (S1, SI) has been proposed to be devoted to more general sensory discrimination and intensity scaling as for touch and proprioception. The →opercular/insular region, including the →secondary somatosensory cortex (S2, SII) and the posterior insula of primates, is supposed to be the earliest truly pain-encoding region. The opercular/insular region is thought responsible for the subjective →recognition of pain, encoding of pain intensity, learning and memory of pain experiences (Chen 2017). Unpleasantness and motivational aspects are represented in insula, cingulate cortex and sub-cortical structures, e.g., the amygdala and →nucleus accumbens of the basal ganglia (Becerra et al. 2013; Bushnell et al. 2013; Chen 2017; Craig 2003; Neugebauer et al. 2009; Zhuo 2008). At a high integrative level, area 10 might contribute to evaluate and integrate sensory-discriminative pain information, affective-motivational aspects, pain modulation, stress, anxiety and fear response, and pain memory (Peng et al. 2018). It has been proposed that the above cortical network is not specifically related to pain representation but more generally is involved in detecting, orienting attention toward and reacting to →salient events of several sensory modalities. Thus, the anterior cingulate cortex

(ACC) and the insula are included in the so-called `saliency network´ which is activated by any event catching attention and raising →arousal (Brodal 2017; Legrain et al. 2010). In humans, lesions of the dorso-posterior insula reduce pain and temperature sensation, and its stimulation causes well-localized pain (Craig 2002, 2003; Tracey 2011). However, a patient in whom a herpes simplex encephalitis had lesioned the amygdala, ACC and insula had normal pain sensations to nociceptive stimulation (Brodal 2017).

Generalized cortical reaction to several sensory modalities is consistent with the spatio-temporal cortical representations of first pain and second pain, as assessed by →magnetoencephalography. First pain evoked by brief cutaneous laser pulses is associated particularly with transient activation of contralateral area S1, whereas second pain is related to longer-lasting activation of the ipsilateral anterior cingulate cortex (ACC), and either of the pain sensations activates area S2 bilaterally. These distinct distributions suggest different functions. The first pain may signal threat and provide precise sensory information about the noxious nature and location of the stimulus for an appropriate fast motor response such as a fast withdrawal, while the second pain has a strong affective component, attracts attention and elicits behavioral responses to limit further injury and optimize recovery (Ploner et al. 2002).

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5

Pain Plasticity and Modulation

CONTENTS

Abstract

• Pain modulation and neuroplasticity occur all along the nociceptive pathways, from peripheral nociceptors to cerebro-cortical levels, and involves many different mechanisms.

• Primary hyperalgesia results from both peripheral sensitization of nociceptors and central sensitization in the central nervous system, whereas secondary hyperalgesia results principally from central sensitization. Another form of central neuroplasticity is allodynia : pain resulting from what is normally a non-painful stimulus (e.g., touch).

• In peripheral sensitization, sensitivity of nociceptors can increase under a variety of pathophysiological conditions, such as tissue injury and inflammation. Increased sensitivity includes lowering of receptor threshold and increased, more sustained responsiveness to supra-threshold stimuli and expansion of receptive fields (RFs). The mechanisms leading to peripheral sensitization are manifold.

• Central sensitization leading to hyperalgesia and allodynia can outlast the primary cause of pain for days to years, and can spread to sites somatotopically remote from the primary cause. Pain-related sensitization occurs in many regions of the central nervous system (CNS) involved in pain processing The mechanisms underlying central hypersensitivity are complex and range from channelopathies to dysfunctional neuronal networks.

• Nociceptive processing at the spinal cord level and higher up is powerfully modulated by systems descending from forebrain sources. Forebrain structures can induce a state of stress-induced analgesia.

• Injuries during exercise or accompanied by stress, threat or emotion may not be immediately accompanied by pain. Conversely, recurrent or chronic pain accompanied by stress, anxiety or negative expectation can lead to stress-induced hyperalgesia/allodynia. Psychological factors are of considerable significance in modulating the severity of pain sensation.

• The modulation of nociceptive processing in the spinal dorsal horn is exerted by descending pain modulatory systems, both inhibitory and facilitatory. They start in the forebrain, but major executive stations are situated in the brainstem. Changes in the balance between descending inhibitory and facilitatory influences during chronic pain states contribute to their intensification and prolongation.

• All living organisms must be able to respond to noxious stimuli and retain in memory what they imply. There are various forms and mechanisms of plasticity, such as changes in synaptic efficacy, expression and function of ion channels and structural changes in cells synapses and neuronal circuits.

5.1 Introduction

The transition from acute pain to →chronic pain is still badly understood because of the many factors involved. Chronic pain typically results from interactions between environmental factors, inherited genetic risk factors, sex, developmental and medical history (Price and Ray 2019).

Acute and chronic pain symptoms involve a sensory dimension, an immediate →affective dimension, and sometimes a secondary affective dimension, termed pain-related suffering. Not surprisingly, pain modulation and neuroplasticity occur all along the nociceptive pathways, from peripheral →nociceptors to cerebro-cortical levels, and involve many different mechanisms (Boadas-Vaello et al. 2017; Coderre et al.1993; Heinricher et al. 2009; Kuner and Kuner 2020; Price et al. 2006; Treede 2016).

Neuroplasticity underlying →chronic pain has been investigated thoroughly in two situations: inflammatory pain and →neuropathic pain (Finnerup et al. 2021). Although they have some mechanisms in common, they differ with respect to aetiology, neuronal pathways, mechanisms, clinical features and treatability. Both types of chronic pain appear to result from plastic changes in cell properties, →synaptic transmission, network connections and anatomical structures (Kuner and Flor 2016), and cause epigenetic changes in chromatin structure, gene expression and thus neural functions (Descalzi et al. 2015; Finnerup et al. 2021; Martin et al. 2019). On the other hand, different neuronal pathways are indicated because, for example, ablation of →nociceptive neurons expressing the →tetrodotoxin (TTX)-resistant Na^+ channel $Na_v1.8$ abolishes inflammatory pain but not neuropathic pain (Costigan et al. 2009; Tsunozaki and Bautista 2009).

5.2 Peripheral and Central Sensitization to Pain

Chronic pain alters the sensory functions of nociceptive afferents, their central connections and subsequent processing stages (Finnerup et al. 2021). These alterations produce plastic changes in nociceptive signal transmission and processing on short- to long-term time scales, and create a pain memory (Price and Inyang 2015).

5.2.1 Hyperalgesia and Allodynia

→Primary hyperalgesia results from peripheral sensitization of nociceptors and →central sensitization in the →central nervous system (CNS), while →secondary hyperalgesia results principally from central sensitization. Another form of central neuroplasticity is →allodynia, i.e., pain resulting from what is normally a non-painful stimulus (Sandkühler 2009; Treede 2016). Allodynia often occurs not only at the site of the injury and →inflammation, but also at the corresponding site on the contralateral side (→mirror image allodynia) (Milligan et al. 2003). Hyperalgesia and allodynia are differentiated according to the stimulus evoking the pain, e.g., thermal or mechanical (in response to light touch or pressure) (Lolignier et al. 2015; Sandkühler 2009). Peripheral and central sensitization also occurs in chronic itch (Cevikbas and Lerner 2020).

5.2.2 Modulation of Nociceptor Sensitivity

→Sensitivity of nociceptors in skin and deep tissues can increase under a variety of pathophysiological conditions, such as tissue injury and inflammation. Increased sensitivity includes lowering of receptor →threshold, increased and more sustained responsiveness to supra-threshold stimuli and expansion of →receptive fields (RFs). It appears that sensitization of nociceptive group III (Aδ) and group IV (C) fiber endings seldom outlasts the primary cause of pain and is confined to the area of injury (Sandkühler 2009). Persistent pain is associated with de novo gene expression (Khoutorsky and Price 2018).

5.2.2.1 Peripheral Sensitization to Inflammation

Inflammation induces a complex, self-reinforcing, sequence of events. Activation of resident immune-competent cells leads to release of pro-inflammatory →chemokines, →cytokines, →growth factors, lipids, and reactive oxygen species and reactive nitrogen species (ROS/RNS), which induce local →degenerative processes, sensitize nociceptors and recruit silent nociceptors, and lead to expression of new receptors and →ion channels (Finnerup et al. 2021; Grace et al. 2016; McMahon et al. 2015; Pinho-Ribeiro et al. 2017). Pro-inflammatory influences also spread from the peripheral injury site to the →dorsal roots and →spinal cord (Cao and DeLeo 2009; Moalem and Tracey 2006; Watkins et al. 2007; White et al. 2005).

Many inflammatory chemical agents which excite nociceptors activate intracellular →signal transduction pathways and modulate →sensory receptor channels and →voltage-gated ion channels. Inflammatory agents so far identified include protons, →prostaglandins, →substance P, →bradykinin, →serotonin (5-HT), interleukin-1β (IL-1β), neurotrophins (→neurotrophic factors) and other endogenous chemicals. For example, the pro-inflammatory cytokine interleukin-1β (IL-1β), in addition to producing inflammation and inducing synthesis of several nociceptor sensitizers, also rapidly and directly activates nociceptors to generate →action potentials and induce pain hypersensitivity (Binshtok et al. 2008; Costigan et al. 2009; Hucho and Levine 2007; Julius and Basbaum 2001; Mense 1993; Merighi et al. 2008; Nicol and Vasko 2007; Pezet and McMahon 2006; Ren and Dubner 2010; Ren and Torres 2009; Scholz and Woolf 2002, 2007; Stein et al. 2009; Wang et al. 2006). Heat can render cutaneous group III (Aδ) mechanical nociceptors sensitive to heat (Willis 1996).

5.2.2.2 Peripheral Sensitization in Nerve Injury

Neuropathic pain is associated with peripheral nerve damage, →spinal cord injury (SCI), chemotherapy-induced →peripheral neuropathy, →diabetic neuropathy and alcoholic peripheral neuropathy (Carrasco et al. 2018). It involves a plethora of pathophysiological mechanisms (Berger et al. 2011; Finnerup et al. 2021) and incorporates a wide range of plastic changes at multiple levels of the sensory-motor neural network (Alles and Smith 2018; Bliss et al. 2016; Finnerup et al. 2021). Among the mechanisms associated with

neuropathic pain are mitochondrial dysfunction (Carrasco et al. 2018; Finnerup et al. 2021), inflammatory processes, peripheral and central sensitization (Alles and Smith 2018; Baron 2006; Costigan et

al. 2009; Saadé and Jabbur 2008; Watkins et al. 2007), →ectopic discharge (i.e., spontaneous action potential discharge activity that occurs away from the normal site of impulse generation) (Devor 2018; Finnerup et al. 2021) and nerve terminal →sprouting (Kuner and Flor 2016). The sensitivity of peripheral nociceptors is differentially altered in neuropathic pain, →group C fibers not being affected, low-threshold mechano-receptors (LTMRs) being implicated in mechanical allodynia (Finnerup et al. 2021).

Mitochondrial Dysfunction may be caused by free radicals, including oxygen and superoxide radicals and nitrogen reactive species (→nitric oxide), which lead to mitochondrial dysfunction, →glial activation and inflammatory responses (Carrasco et al. 2018).

Inflammation triggered by nerve trauma induces the complex sequence of events described above.

Intracellular Calcium Overload. Ca^{2+} enters cells in different ways including voltage-gated calcium channels and chemically gated channels (i.e., →glutamate). →Transient receptor potential (TRP) channels let pass Ca^{2+} and are activated by oxidative stress (Carrasco et al. 2018; Sun et al. 2020).

Injury Discharge sets in immediately and may initiate central sensitization, followed by abnormal firing in both injured and intact nerve fibers.

Ectopic Discharges can occur at different sites along →axons consequent to several changes. There are various avenues towards ectopic discharge generation. Nerve injury up-regulates the expression of prostaglandin E2 (PGE2) and its receptors EP1 and EP4 in the nerve and dorsal →ganglion, which eventually leads to activation of HCN2 channels promoting the generation and maintenance of spontaneous discharge (Tsantoulas et al. 2016). Inflammation of the nerve trunk releases pro-inflammatory cytokines: particularly →tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). TNF-α causes →demyelination and remodelling of the exposed axon membrane with *de novo* insertion of Na^+ channels (Watkins et al. 2007). Cytokines can also change the expression and properties of resident voltage-gated ion channels. Receptor proteins, in particular transient receptor potential (TRP) receptors on injured and intact nerve fibers, can also be up-regulated (Baron 2006), along with excitatory →adrenoceptors on nociceptive afferents (Pertovaara 2006) at three potential sites: axon tips of regenerating nociceptive afferents, receptive endings of non-injured un-myelinated afferents, and →dorsal-root ganglia (DRG).

Chronic Heat Sensitization. Injured sensory neurons become hypersensitive to chemical and thermal stimuli, such that normal body temperature elicits spontaneous activity when the threshold of noxious heat-sensitive TRPV1 channels is reduced to 38 °C (Costigan et al. 2009).

5.2.2.3 Sympathetic Modulation of Nociceptors

The →sympathetic nervous system and its peripheral →neurotransmitters normally modulate the discharge of a number of sensory receptors involved in tactile, stretch, and nociceptive sensation, and can change the membrane properties of nerve fibers (Passatore and Roatta 2009). Following peripheral nerve lesions and previous sensitization of the sensory receptors, →catecholamines released from →postganglionic sympathetic nerve terminals or into the blood circulation from the →adrenal glands can evoke or aggravate pain by exciting skin nociceptors and enhancing their responsiveness to pain stimuli. Several complex mechanisms are likely to underlie sympathetically mediated pain.

Sprouting of Postganglionic Sympathetic Fibers within Dorsal-Root Ganglia. Nerve injury can cause non-injured postganglionic sympathetic fibers to sprout around large axotomized →dorsal-root ganglion (DRG) cells, where they form basket-like structures (Ramer et al. 1999). The aberrant sympathetic input to DRG cells amplifies spontaneous and evoked activity and recruits silent neurons (Vrinten et al. 2001; Millan 1999), leading to sympathetically mediated pain through interactions between peripheral group II (Aβ) fibers and sympathetic efferents (Chung et al. 1997; Michaelis et al. 1996; Zimmermann 2001).

Expression of α_1- and α_2-Adrenoceptors on Intact Primary Afferents. Nerve injury can induce generation of varicosities in efferent sympathetic fibers and production of new α-adrenoreceptors (→adrenoceptors) on axotomized afferent neurons. This will increase sensitivity in primary sensory afferents to sympathetic activity and enhance excitability (Baron 2006; Perl 1999; Shyu et al. 1990). →Noradrenaline effects will vary depending on the mixture of adrenoceptors expressed. It is not clear whether noradrenaline acts directly on nociceptors or indirectly via prostaglandin release from sympathetic fibers.

In inflamed tissue, noradrenaline can also release →opioids from immune cells (Pertovaara 2006).

Indirect Modulation of Sensory Afferent Activity can result from modification of blood flow and vascular permeability. Pain enhancement is possible when vasoconstriction reduces washout of inflammatory mediators.

5.2.3 Central Hypersensitivity

It appears that hyperalgesia and allodynia require central sensitization, which may outlast the primary cause of pain for days to years and spread to sites →somatotopically remote from the primary cause (Sandkühler 2009). Pain-related sensitization has been recorded in many CNS regions involved in pain processing The mechanisms underlying central hypersensitivity are complex and manifold, and range from →channelopathies to dysfunctional neuronal networks to involvement of the →immune system (Alles and Smith 2018; Saab 2012).

5.2.3.1 Structural and Functional Reorganization in the Spinal Cord

Peripheral nerve injury elicits changes in primary sensory neurons that trigger reorganization and rewiring of central →synaptic connections (Costigan et al. 2009; Moore et al. 2000; Sandkühler 2009; Woolf and Salter 2000; Vrinten et al. 2001).

Aberrant Connections from Group II (Aβ) Fibers to Dorsal-Horn Neurons. Neurons in superficial dorsal-horn laminae normally receive direct input from small-diameter group III (Aδ) and IV (C) afferents. After peripheral nerve injury, there is a rearrangement of afferents within the →dorsal horn. Studies have shown (summarized in Woodbury et al. 2008) that after injury to spinal nerve afferents, large diameter (Aβ) axons `sprout´ and enter into laminae I and IIo of the dorsal horn, regions normally occupied by nociceptive afferents, giving rise to the possibility that there is an anatomical basis for mechanical allodynia. In support of the hypothesis, low-threshold →mechano-receptor (LTMR) afferents of mice were found after peripheral nerve axotomy to project into `pain-specific´ laminae of the thoracic dorsal horn (Woodbury et al. 2008). More recently, however, the sprouting hypothesis was disputed (Kuner and Flor 2016; Wu et al. 2010) on the grounds that LMTR arborizations are already present before nerve injury, so they cannot account for the allodynia. Nonetheless, Aβ fibers appear implicated in neuropathic mechanical allodynia by a central mechanism, but probably group C fibers play a role as well, suggesting that the exact contributions of different fiber types are state- and context-dependent and vary between disorders (Finnerup et al. 2021). In any case, there are enough opportunities for derangements because at least five different excitatory spinal →interneuron populations have been implicated in the development of mechanical allodynia (Gatto et al. 2019).

Hyperalgesia after Spinal De-afferentation. Subjects with trauma to →spinal roots or the →trigeminal system can experience burning pain projected to the →de-afferented skin region, a phenomenon called anesthesia dolorosa, or de-afferentation pain (Baron 2006). The pain, felt in an area that is numb when touched, is described as constant, burning, aching or severe. Reviews of neuropathic pain in animal models (Vrinten et al. 2001; Zimmerman 2001) focus on spinal cord mechanisms and describe a sequence that begins with the formation of an amputation neuroma at the site of nerve damage, followed by erratic mechano-sensitivity in dorsal-root ganglia and the dorsal horn; →long-term potentiation (LTP) of synaptic transmission; and attenuation of central pain inhibitory mechanisms including loss of opioid-mediated anti-nociception. Hyperalgesia is maintained by a high rate of discharge in small afferent fibers that release supra-normal levels of glutamate and →aspartate that act on NMDA receptors (NMDARs), and degeneration of presumed inhibitory interneurons in spinal laminae I-III.

5.2.3.2 Changes in Intrinsic Neuron Properties – Spinal Cord, Nerve Injury

Peripheral nerve injury and spinal cord injury generate particularly debilitating and hard-to-manage chronic pain states which are due at least in part to changes in intrinsic neuron properties, prominently of ion channels.

The precise patterns of ion-channel changes can vary widely in inflammatory pain or in various aetiologies of neuropathic pain, and are influenced by several other factors and include genetic mutations (Finnerup et al. 2021). Voltage-gated ion channels altered by inflammatory or neuropathic pain include Na^+ (Na_v) channels, K^+ (K_v) channels, Ca^{2+} (Ca_v) channels, →Ca^{2+}-dependent K^+ channels and →hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Baron 2006; Bennett et al. 2019; Carbone 2009; Costigan et al. 2009; Devor 2006; Dib-Hajj and Waxman 2019; Finnerup et al. 2021; Gold 2009; Habib et al. 2015; Rogers et al. 2006; Levinson 2009; Mathie and Veale 2009; Tsantoulas and McMahon 2014). The array of Na^+ channels changes properties, leading to spontaneous discharge and higher than normal firing rates in response to stimuli. For example, one responsible ion channel is the $Na_v1.3$ channel that is over-expressed in dorsal-horn neurons, as well in →ventro-posterior lateral (VPL) thalamic neurons following spinal injury (Waxman and Hains 2006). A large variety of potassium (K^+) channels, too, may be altered leading to increased excitability (Smith 2020).

Nociceptive inputs, in association with neuropathy-induced pain hypersensitivity, can also change the intrinsic response properties of WDR →projection neurons in the deep dorsal horn (Berger et al. 2011; Sandkühler 2009). The response patterns of WDR neurons are of three types: tonic slowly →adapting discharge, rhythmic →bursting, and →plateau potentials (Sandkühler 2009). The expression of any one of the patterns depends on a dynamic balance between excitatory metabotropic glutamate receptors and inhibitory →G-protein-coupled →$GABA_B$ metabotropic receptors (Benke 2021; Goudet et al. 2009). Normally, inhibition predominates and most cells show a tonic slowly adapting discharge pattern. A switch to the plateau state might be a key factor in central sensitization (Derjean et al. 2003).

Activation of $GABA_B$ receptors induces analgesia, while $GABA_B$ receptor antagonists enhances the sensitivity to →noxious stimuli. Global deletion of $GABA_B$ receptors produces hyperalgesia (Benke 2021).

Changes in Neuron Sensitivity. The dorsal horn hosts a plethora of neuron types, which are being characterized by modern genetic methods in mice. At least five populations of excitatory neurons are involved in neuropathic pain. For example, one group propagates signals underlying mechanical pain and are sufficient and necessary to mediate mechanical hypersensitivity in neuropathic pain. Another group of excitatory neurons in the deeper laminae is involved in mechanical pain and mechanical allodynia; it receives Aβ fiber input and projects to lamina I and II. The genetic ablation of yet another group of excitatory neurons selectively attenuated neuropathic mechanical and cold allodynia without affecting basal mechanical or thermal processing. In the dorsal-horn inhibitory →glycinergic neurons are more abundant in the more superficial laminae and →GABAergic interneurons are more prevalent in the deeper laminae, both groups receiving inputs from peripheral LMTRs. Ablation of glycinergic inhibitory neurons broadly induces mechanical, heat and cold hypersensitivity as well as spontaneous pain-related behavior in naive mice, and their chemogenetic activation alleviated neuropathic allodynia (Finnerup et al. 2021).

5.2.3.3 Shift in Anion Gradients

Since synaptic inhibition depends not only on neurotransmitter (e.g., →glycine and GABA) release and receptor density, but also on transmembrane chloride (Cl^-) concentration gradients, changes in these gradients will alter the potency of inhibition. Chloride gradients are maintained by transmembrane co-transporters, and the expression and/or function of such co-transporters are indeed altered in chronic pain states (Price et al. 2009).

Peripheral nerve injury can shift transmembrane anion gradients in lamina-I cells by down-regulating the potassium-chloride exporter KCC2 with a subsequent increase in the intracellular chloride concentration. Consequently, GABA and glycine release from →interneurons will →depolarize the cells instead of hyperpolarizing them, causing an overall increase in excitability (Baron 2006; Costigan et al. 2009; Lewin et al. 2004; Price et al. 2009).

5.2.3.4 Long-Term Synaptic Changes in Central Hypersensitivity

Hyperalgesia and allodynia following nerve injury and inflammation are in part due to activity-dependent pre- and postsynaptic synaptic changes, such as long-term potentiation (LTP) and increases in the density of synaptic spines (Baumbauer et al. 2009; Costigan et al. 2009; Grau 2014; Kuner and Flor 2016; Sandkühler 2009; Treede 2016).

Long-term potentiation (LTP) of →excitatory postsynaptic potentials (EPSPs) in rat dorsal-horn neurons of laminae I-III can be evoked by brief, high-rate tetanization of dorsal-root fibers in the group III to group IV range. LTP is also seen in wide-dynamic-range (WDR) cells in the rat dorsal horn after high-frequency stimulation of the sciatic nerve (Svendsen et al. 1997) and probably contributes to sensitization of spino-thalamic tract neurons (Willis 2002). Stimuli such as skin burns, contusions, inflammation, and nerve injury also evoke LTP.

Neuromodulators and LTP. Several modulatory factors influence signal transmission at spinal synapses that contribute to central hypersensitivity. Prolonged activity in group IV afferents opens presynaptic calcium (Ca^{2+}) channels, which releases glutamate and excitatory peptides such as substance P (SP), neurokinin A (NK A) and →calcitonin-gene-related peptide (CGRP), and induces slow →postsynaptic potentials (PSPs) (Dickenson 1997; Levine et al. 1993; Vrinten et al. 2001; Zamponi et al. 2009). In nociceptive dorsal-horn neurons, substance P elicits a late, slow depolarization (Dickenson 1997; Levine et al. 1993). The large depolarizing PSP opens voltage-gated Ca^{2+} channels and releases →N-methyl-D-aspartate (NMDA)-gated channels from magnesium (Mg^{2+}) block, Ca^{2+} inflow and a cascade of intracellular events that lead to LTP.

NMDA receptors (NMDARs) are also present at presynaptic endings of primary afferent terminals. In neuropathic but not inflammatory pain conditions, NMDAR activity is increased and can potentiate glutamate release from primary afferent endings and thus

enhance →synaptic plasticity (Deng et al. 2019).

→Kainate receptors primarily modulate nociceptive transmission and integration, and their dysregulation, dysfunction or abundance may disrupt the finely tuned process of glutamatergic transmission and can thus contribute to pain onset and sensitization (Li et al. 2021).

Metabotropic glutamate receptors are increasingly recognized as playing important modulatory roles in nociception and pain behavior, including peripheral and central sensitization (Goudet et al. 2009; Neugebauer 2002). The involvement of →glutamate receptors might make them targets for therapeutic intervention (Bleakman et al. 2006).

Nitric oxide (NO), a diffusible gas, appears to act as an anterograde neurotransmitter between primary afferent neurons and non-neuronal cells in dorsal-root ganglia and between different neuronal cell types in the spinal cord. Although not important for normal nociceptive processing, NO plays an essential role in central sensitization during inflammatory and neuropathic pain in conjunction with →cyclic guanosine monophosphate (cGMP), and several signaling pathways (Schmidtko et al. 2009). NO can activate both pro-nociceptive and anti-nociceptive mechanisms (Schmidtko 2015).

→Arachidonic acid, a prostaglandin precursor, is produced in the spinal cord in response to group IV fiber stimulation (Dickenson 1997; Zimmermann 2001) and may facilitate nociceptive transmission and enhance hyperalgesia and allodynia (Moore et al. 2000; Ito et al. 2001).

Nerve growth factor (NGF) is active in both peripheral and central sensitization and has complex multi-functional roles in the modulation of nociceptive processing through effects on the release of inflammatory mediators, nociceptive ion channel/receptor activity, nociceptive gene expression, and local neuronal sprouting effects (Barker et al. 2020; Finnerup et al. 2021; Lewin 1995; Mizumura and Murase 2015; Nicol and Vasko 2007; Pezet and McMahon 2006), and regulates the expression of →brain-derived neurotrophic factor (BDNF). BDNF is synthesized and released from central terminals of nociceptive afferents and increases the excitability of dorsal-horn neurons. It is markedly up-regulated in inflammatory conditions in an NGF-dependent fashion, and may play a role as a sensitizing modulator in inflammatory pain states by acting on postsynaptic →tropomyosine receptor kinase B (TrkB) receptors (Merighi et al. 2008; Moore et al. 2000; Pezet and McMahon 2006).

5.2.3.5 Decreased Inhibition

It has been suggested that neuropathic pain is also supported by loss of function of inhibitory interneurons in the dorsal horn and that several mechanisms are involved, including death or diminished activity of inhibitory interneurons, decreased transmitter release and reduced effectiveness of GABA and glycine as inhibitory transmitters (Gradwell et al. 2020; Hughes and Todd 2020; Todd 2015). Some painful conditions are known to decrease spinal GABAergic and glycinergic inhibition (Basbaum et al. 2009; Kuner and Flor 2016; Sandkühler 2009; Zeilhofer et al. 2012) as the result of group III

(Aδ) fiber de-afferentation. Loss of these relatively large afferents leads to degeneration of GABA-ergic and glycinergic spinal neurons with consequent reductions in levels of GABA and glycine and their conjoint receptors (Baron 2006; Costigan et al. 2009; Woolf and Salter 2000; Zimmermann 2001).

A subset of inhibitory interneurons, containing the marker parvalbumin (PV), act as modality-specific filters that prevent touch inputs from activating pain circuits. In mice with neuropathic pain, increasing PV activity significantly alleviates the mechanical allodynia. Conversely, selective ablation or silencing of PV interneurons induces mechanical allodynia in naive mice. Synaptic contacts from PV+ terminals to excitatory interneurons are decreased by nerve injury or ablation of PV neurons (Petitjean et al. 2015).

In neuropathic pain with allodynia resulting from →ischemic injury of the spinal cord, GABA content of the dorsal horn is decreased, and GABAergic presynaptic inhibition is impeded (Levine et al. 1993; Wiesenfeld-Hallin et al. 1997). Presynaptic inhibition is also reduced in inflammatory pain (Guo and Hu 2014). Inhibitory modulation of spinal nociceptive signal transmission exerted by descending pathways may also be disrupted via a number of mechanisms (Costigan et al. 2009; Sandkühler 2009). Still, the precise situation appears not quite settled (Todd 2015).

Central hypersensitivity induced by group IV fiber activation makes previously sub-→threshold inputs generate action potentials within the receptive fields (RFs) of spinal neurons. The RFs can also change more drastically (Wall 1988**;** Koerber and Brown 1995). Dynamic RF expansion up to nearly 400% in the rat dorsal horn can be caused by relatively brief (20s) barrages of C-fiber input (Cook et al. 1987). Dorsal-horn neurons with RFs adjacent to a cutaneous region exposed to heat injury can expand their RFs into the traumatized area (McMahon and Wall 1984). RF expansion linked to mechanical, chemical and inflammatory injuries and during polyarthritis has also been documented in neurons of the ventro-basal →thalamus (Coderre and Katz 1997). The appearance of new RFs sometimes results in faulty interpretation of the source of pain (Hoheisel et al. 1993). The underlying mechanisms include collateral sprouting, unmasking of normally inactive →silent synapses, reduction in pre- and postsynaptic inhibition and increased postsynaptic discharge activity.

Central sensitization also shows in the enlargement of RFs for nociceptive withdrawal reflexes in humans. Injections of →capsaicin dramatically expand the reflex RFs in both intact and spinal cord transected individuals (Biurrun Manresa et al. 2014). Moreover, patients with chronic pelvic pain exhibit a generalized expansion of reflex RFs in comparison with pain-free volunteers (Neziri et al. 2010).

5.2.3.6 Increase in Dorsal-Root Reflexes

Local excitation of nociceptors elicits →axon reflexes mediated by →antidromic discharges, i.e., backfiring into peripheral axon branches. Excitation of the branches releases neural mediators, such as substance P (SP), calcitonin gene related peptide

(CGRP), →vasoactive intestinal peptide (VIP), and gastrin releasing peptide (GRP). peptides, which contribute to →neurogenic inflammation and primary hyperalgesia (Kanashiro et al. 2020).

Antidromic discharges can also be generated and detected in →dorsal-root reflexes mediated by →presynaptic inhibition. Group II (Aß) fibers from mechano-receptors excite GABAergic interneurons, which presynaptically inhibit nociceptive afferent fibers and cause →primary afferent depolarization (PAD), which seems to be generated by non-GABAergic mechanisms (Hochman et al. 2010) and contributes to pain relief. Normally, PAD is not large enough to generate antidromic action potentials in nociceptive fibers, but under some conditions increased PAD generates action potentials that antidromically evoke neurogenic inflammation and →orthodromically excite spinal nociceptive neurons, leading to secondary hyperalgesia and allodynia (Carlton 2014; Cervero and Laird 1996; Willis 1999; Zeilhofer et al. 2012).

5.2.3.7 Activation of the Immune System

Inflammation and trauma of peripheral nerves or central nervous tissues are associated with activation of immune cells and immune-like →glia cells, →mast cells, →macrophages, →neutrophils, T lymphocytes and →astrocytes, which play complex roles in peripheral and central sensitization (Finnerup et al. 2021; Gwak et al. 2017; Ji et al. 2019; Kanashiro et al. 2020; Kuner and Flor 2016; McMahon et al. 2015). Neuro-immune dysregulation in the context of CNS injuries occurs as a consequence of the inflammatory response to SCI and cells (macrophages and T-cells). This response is necessary in the early post-SCI stages to close the injury site but the resulting scar prevents full tissue regeneration and leads to maladaptive neuroplasticity and chronic pain (Chambel et al. 2020). Inflammation early in life entails increased pain sensitivity later in life by priming immune components both peripherally and centrally (Karshikoff et al. 2019).

In chronic pain states, all systems involved in sensory, affective and →cognitive dimensions are affected by the activation of glia cells and the release of immune mediators. Generally, all nerves and neurons regardless of modality are affected by immune and glial activation (Cao and DeLeo 2009; Scholz and Woolf 2007; Watkins and Maier 2002).

After an initial noxious insult, sensory neurons activated by noxious stimuli release substance P, excitatory amino acids and →adenosine triphosphate (ATP). These in turn lead to the activation of glia and astrocytes. Activated glia and astrocytes increase their number, change their morphology and release pro-nociceptive mediators such as ATP, cytokines and chemokines (Chen et al. 2018a; Ji et al. 2019; Old et al. 2015). For example, within the dorsal horn, peripheral nerve injury activates →microglia (glia cells resident in the CNS), which up- regulates the expression of P2X and P2Y →purinergic receptors, e.g. $P2X_4$, which in turn leads to the release of BDNF and activation of its receptor, TrkB (Inoue and Tsuda 2018; Inoue 2021; Jarvis 2010; Tam and Salter 2021). Among the other released substances are prostaglandins, tumor necrosis factor, interleukin-1 (IL-1), interleukin-6 (IL-6) and nitric oxide (NO), which in turn change

neuronal and →synaptic functions via a multitude of mechanisms, and reduce the pain-suppressive effects of opioid drugs (Le Merrer et al. 2009) by contributing to opioid tolerance (Watkins et al. 2007). Paradoxically, opioids can even induce hyperalgesia (opiod-induced hyperalgesia) via a spectrum of mechanisms (Roeckel et al. 2016). Glia cells also influence synaptic transmission including →long-term depression (LTD) and long-term potentiation (LTP), and immune mediators modulate glutamatergic and GABAergic signaling (Austin and Fiore 2019). Finally, immune system activation affects neuronal excitability at multiple sites, from peripheral nerve to dorsal root to spinal cord and beyond (Basbaum et al. 2009; Costigan et al. 2009; Pinho-Ribeiro et al. 2017; Saab et al. 2008; Saab and Hains 2009; Saadé and Jabbur 2008).

Chronic stress contributes to the maintenance of chronic pain states, and vice versa. →Stress elevates the concentrations of →glucocorticoids. Since astrocytes and microglia express high glucocorticoid receptors, prolonged glucocorticoid exposure entails the activation and hypertrophy of glia cells, which in turn leads to maladaptive neuronal and glial plasticity with structural and functional changes and maintenance of neuropathic pain (Madalena and Lerch 2017).

5.2.3.8 Supraspinal Functional and Structural Changes in Chronic Pain

Supraspinal influences contribute significantly to the development and maintenance of chronic pain states and hyperalgesia (D´Mello and Dickenson 2008; Gebhart 2004; Heinricher et al. 2009; Lima and Almeida 2002; Merighi et al. 2008; Ren and Dubner 2007; Tracey and Mantyh 2007).

Functional and structural alterations of various kinds in association with inflammatory and neuropathic pain occur in numerous supraspinal structures, such as the →peri-aqueductal gray (PAG), →nucleus ruber, →midbrain →dopamine neurons, →locus coeruleus (LC), →rostral ventro-medial medulla (RVM), →hypothalamus, →thalamus, →hippocampus, →basal ganglia, →cerebellum, →amygdala, somatosensory cortex, →motor cortex, →insula, →anterior cingulate cortex (ACC), →prefrontal cortex (PFC) and →habenula (Boadas-Vaello et al. 2017; Costigan et al. 2009; Kuner and Flor 2016; Mitsi and Zachariou 2016; Saadé and Jabbur 2008; Shelton et al. 2012; Xiao and Zhang 2018; Zhuo 2018).

Chronic pain is associated with structural alterations including reduction (less often increase) in →gray matter in patients suffering from persistent pain (Brodal 2017). Furthermore, there are changes in →dendritic and synaptic structure, changes in neurochemistry, inflammatory responses, long-term plastic changes and functional reorganization in the brain (Bushnell et al. 2013; Kuner and Flor 2016; Saab 2012). Long-term-potentiation (LTP) is found in the amygdala, anterior →cingulate cortex (ACC), and insular cortex (Luo et al. 2014). For instance, in the ACC of rodents, different forms of long-term potentiation (LTP) contribute to chronic pain, in particular affective aspects and anxiety (Bliss et al. 2016).

The prefrontal cortex (PFC) plays a role in the network processing aversion and →reward, due to its dense connections with the amygdala, hippocampus, basal ganglia (→nucleus accumbens, NAc), peri-aqueductal gray (PAG), and dopaminergic midbrain structures. The medial prefrontal cortex processes ascending nociceptive inputs and is involved in both sensory and affective aspects of pain. In chronic pain states, hyperactivity of neurons in the basolateral amygdala leads to deactivation of the neurons in the medial PFC (Kuner and Kuner 2021). Acute and chronic pain states induce changes in neurotransmitters, gene expression, glia cells, and neuro-inflammation, and alter PFC structure, activity and connectivity (Ong et al. 2018).

The medial prefrontal cortex could promote the chronification of pain via cortico-→striatal connections. On the other hand, it exerts anti-nociceptive effects via descending connections to the →brainstem and spinal cord (below) (Ong et al. 2018). The lateral prefrontal cortex and rostral anterior insula seem to act as a pain-control system that alters →emotional and behavioral responses to various types of painful stimuli (Tracey and Mantyh 2007). Dopamine and serotonin concentrations are diminished in the →orbito-frontal cortex (OFC) and slightly increased in the amygdala, possibly contributing to disturbances of cognitive function (Neugebauer et al. 2009).

The expanse and degree of cortical reorganization and changes in cortical activation are notable in humans suffering from persistent pain, as well as phantom pain, a difficult to treat type of neuropathic pain (Aternali and Katz 2019; Giummarra et al. 2008; Zhuo 2008). In a mouse model of neuropathic pain, the activity of pyramidal neurons in the →primary somatosensory cortex (S1, SI) is persistently increased. This increase in activity is caused in part by increases in synaptic activity and NMDA-receptor-dependent Ca^{2+} discharges in apical tuft →dendrites and by shifts of local inhibitory activity in favor of pyramidal neuron hyperactivity (Cichon et al. (2017).

5.3 Descending Pain Modulation

Probably the most significant pain modulation is exerted by systems descending from →forebrain sources (Gamal-Eltrabily et al. 2021). Psychological factors are of considerable significance in modulating the severity of pain sensation (Bushnell et al. 2013; De Felice and Ossipov 2016; Hollins 2010; Tracey and Mantyh 2007; Treede 2016; Urien and Wang 2019). Well-known examples are the temporary absence of pain sensation accompanying injury, during exercise or during stress, threat or emotion, i.e., stress-induced analgesia (Brodal 2017; Butler and Finn 2009). Conversely, recurrent or chronic pain accompanied by stress, anxiety, depression or negative expectation can lead to stress-induced hyperalgesia/allodynia, a state of increased pain →intensity (Jennings et al. 2014; Zhuo 2017). In both types of stress-induced pain modulation, the endogenous opioid system plays an important role (Bagley and Ingram 2020; Ferdousi and Finn 2018).

5.3.1 Pain Perception Modulation Systems

The intensity of pain perception can be modulated by a great number of influences and underlying systems and mechanisms (Ossipov et al. 2011).

At cortical level, areas involved in the modulation of nociception include the prefrontal cortex (PFC), anterior cingulate cortex (ACC), ventro-lateral orbital cortex, insular cortex, motor cortex, and somatosensory cortices. The modulatory effects are mediated by cortico-cortical or cortico-subcortical interactions, by direct cortico-spinal projections, or by intermediate activation of brainstem structures, i.e., peri-aqueductal gray matter (PAG), locus coeruleus (LC), the raphé magnus nucleus (RM) and rostral ventro-medial medulla (RVM) (Gamal-Eltrabily et al. 2021).

The lateral prefrontal cortex and rostral anterior insula seem to act as a pain-control system that alters →emotional and behavioral responses to various types of painful stimuli (Tracey and Mantyh 2007). Pain relief has a rewarding effect engaging activation of midbrain dopamine neurons, release of dopamine in the nucleus accumbens (NAc), and opioid signaling in the anterior cingulate cortex (ACC) (Harris and Peng 2020; Kuner and Kuner 2021; Mitsi and Zachariou 2016; Navratilova et al. 2015). Anticipation and anxiety of pain that enhance pain experience (Sandkühler 2009), activate brain regions including the prefrontal cortex, →entorhinal cortex, anterior insula, amygdala, ventral brainstem areas and PAG (Neugebauer et al. 2009; Tracey and Mantyh 2007). The PAG plays a coordinative role in the management of threat, anxiety and fear by organizing changes in sensory processing including anti-nociception, →autonomic nervous activity and motor behavior (→fight or flight or →freezing) (Koutsikou et al. 2017; Roelofs 2017).

Brainstem structures could also be involved in mediating →placebo analgesic effects (De Felice and Ossipov 2016), via the prefrontal cortex, anterior cingulate cortex (ACC), insular cortex, amygdala, →diencephalon, and hypothalamus. Placebo analgesia may be confined to the body region where pain relief is expected (Benedetti 2013). The opposite effect, nocebo, may be induced when a subject expects an enhancement of pain (De Felice and Ossipov 2016). Expectations of future treatment results as well as →learning, ranging from behavioral conditioning to social learning, play pivotal roles in placebo and nocebo effects (Schafer et al. 2018; Wager and Atlas 2015). In addition to expectation-dependent placebo, there is an expectation-independent form (Schafer et al. 2018). Different mechanisms probably contribute to placebo effectiveness, including operational balance between the endogenous opioid system and the →cholecystokinin system, →endocannabinoids and →dopamine processing all along the nociceptive pathways (Corcoran et al. 2015; Finn et al. 2021; Guindon and Hohmann 2009; Wang et al. 2021; Wolf et al. 2020; Woodhams et al. 2017). Other anti-nociceptive substances include →orexin (Razavi and Hosseinzadeh 2017) and →oxytocin (Tracy et al. 2015). Placebo and nocebo appear to influence aspects of motor performance. For example, placebo enhanced →skeletal muscle force and reduces fatigue (Fiorio 2018).

While many pro-nociceptive and anti-nociceptive effects are mediated by brainstem structures (below), there are also direct cortico-spinal modulatory effects. For example, stimulation of the anterior cingulate cortex (ACC) in rats and mice facilitates spinal

sensory excitatory transmission, so that such →top-down facilitation may contribute to the process of chronic neuropathic pain (Chen et al. 2018b). By contrast, in mice, part of the →cortico-spinal tract (CST) originating in the S1/S2 somatosensory cortex exerts anti-nociceptive effects mediated by direct innervation of the dorsal horn. Tactile stimulation activates somatosensory CST neurons, and their cortico-spinal projections facilitate light touch-evoked activity of cholecystokinin interneurons in the deep dorsal horn. This represents a touch-driven spinal-cortico-spinal sensitization loop. In fact, reduction in somatosensory CST activity or transection of the CST selectively reduces behavioral responses to light touch without altering responses to noxious stimuli, but greatly attenuates tactile allodynia in a peripheral neuropathic pain model (Liu et al. 2018).

Anti-nociceptive and pro-nociceptive modulation of nociceptive dorsal-horn neurons is exerted by overlapping midbrain, pontine and medullary regions, the involved anatomical connections and neurotransmitter actions being complex (De Felice and Ossipov 2016; D´Mello and Dickenson 2008; Heinricher et al. 2009; Jennings et al. 2014; Lima and Almeida 2002; Mason 2001, 2005; Merighi et al. 2008; Ren and Dubner 2007; Saadé andJabbur 2008; Scholz and Woolf 2002; Tracey and Mantyh 2007; Vanegas and Schaible 2004; Wu et al. 2010; Yoshimura and Furue 2006; Zhuo 2017). It is likely that a disbalance between anti-nociceptive and pro-nociceptive effects contributes to chronic pain states (De Felice and Ossipov 2016).

The final descending pathways to the spinal cord are integrated into feedback loops including sensory inputs targeting various supraspinal structures. For example, PAG cells and some neurons in the rostral ventro-medial medulla (RVM) and ventro-lateral medulla (VLM) receive sensory inputs, including nociceptive signals, and cells in the dorsal reticular nucleus (DRT) are reciprocally connected with spinal dorsal horn (Heinricher et al. 2009). The RVM contains several classes of neurons that exert bidirectional control of nociception (De Felice and Ossipov 2016; Heinricher et al. 2009; Mason 2005). Both inhibitory and facilitatory descending pain modulation can be produced in the RVM. The dual RVM influences appear to involve anatomically distinct, independent spinal pathways and are mediated by different lumbar spinal receptors. Spinal nociceptive inhibition is mediated via descending projections from the RVM in the dorso-lateral →funiculi, whereas nociceptive facilitation is transmitted via the ventro-lateral funiculi (Bannister and Dickenson 2016; Urban and Gebhard 1999). The descending systems are also plastic (Bannister and Dickenson 2017).

5.3.1.1 Serotonergic RVM Cells

In rats, about 20% of the RVM cells projecting to the spinal cord are serotonergic (5-HT). The rest probably comprises GABAergic and/or glycinergic cells, which inhibit nociceptive processing in the spinal dorsal horn. RVM 5-HT cells could inhibit or facilitate nociception due to the existence of many sub-types of 5-HT receptors with opposing effects (De Felice and Ossipov 2016). Selective activation of RVM 5-HT cells in mice induces persistent pain sensitization (Cai et al. 2014). Hence, the facilitatory effect appear to predominate over inhibition (Bannister and Dickenson 2016).

5.3.1.2 Non-Serotonergic RVM Cells

The RVM in the rat contains three classes of non-serotonergic neurons with phasic pain modulating effects: Off, On and Neutral cells, at least some of which project to the spinal cord, especially to the dorsal horn (De Felice and Ossipov 2016; Foo and Mason 2003; Heinricher et al. 2009; Mason 2001; Porreca et al. 2002; Wu et al. 2010).

Off-cells exhibit a pause or reduction in firing just prior to a noxious heat-evoked tail flick or withdrawal reflex. They are inhibited by noxious heat, excited by PAG activation and by analgesic doses of opioids which make them become continuously active. They are continuously active during →slow-wave sleep (SWS) and only sporadically during waking. Off-cells provide for the *anti-nociceptive effects on nociceptive signal transmission* in the spinal dorsal horn (Heinricher et al. 2009).

On-cells are active just prior to a noxious heat-evoked tail flick or withdrawal reflex, excited by noxious heat anywhere on the body surface, inhibited by PAG activation and opioids, and show bursts of activity during waking but very little activity during slow-wave →sleep. On-cells become active over prolonged periods during acute inflammation. On-cells mediate *facilitatory effects on nociceptive signal transmission* in the spinal dorsal horn (Heinricher et al. 2009).

Neutral Cells do not react during nocifensive withdrawals or acute inflammation nor to micro-injections of opioids, cannabinoids, α_2-noradrenergic agonists or cholecystokinin. At least some Neutral cells are serotonergic (Heinricher et al. 2009). Neutral cells are believed to participate in responses to prolonged inflammatory nociceptive stimulation (Wu et al. 2010).

The evidence above implies that because On-cells are most active during waking, and Off-cells more active during slow-wave sleep, the former facilitate →alertness and awareness of a painful stimulus during the awakened state, while the latter suppresses during sleep. These behaviors change during inflammation and following nerve injury. For instance, in neuropathic pain models, On- and Off-cells show novel responses to non-noxious mechanical stimuli and enhanced responses to noxious heat (Heinricher et al. 2009).

5.3.1.3 Dorsal Reticular Nucleus and Ventro-lateral Medulla

The caudal medulla contains two further areas involved in descending pain control: dorsal reticular nucleus (DRT) and ventro-lateral medulla (VLM). Stimulation of the dorsal reticular nucleus facilitates nociception, while stimulation of the ventro-lateral medulla inhibits behavioral and dorsal-horn nociceptive responses. The →closed loops between DRT/VLM and the dorsal horn play a great role in central sensitization during chronic pain (Heinricher et al. 2009; Wu et al. 2010).

5.3.1.4 Noradrenergic Pain Modulation in the Pons

The PAG exerts its pain-modulatory effects in part via descending →noradrenergic pathways, which originate in →cell groups A5-A7, A5 and A6 in the locus coeruleus (LC) and A7 in the →pons. The PAG projects to A7 and LC, which connect reciprocally with RVM. LC also receives inputs from RVM, amygdala, thalamic nuclei and insula (De Felice and Ossipov 2016). In the dorsal horn, noradrenaline suppresses nociceptive signal transmission via several mechanisms including pre- and postsynaptic inhibition, activation of inhibitory interneurons and inhibition of excitatory interneurons (Pertovaara 2006; Yoshimura and Furue 2006). While, in a rat neuropathic pain model, activation of the spinally descending LC projection reduces spontaneous pain behavior, increases withdrawal thresholds and produces a positive affective bias, activation of the projection to the prefrontal cortex (PFC) produces aversion and increases spontaneous pain behavior. These differential effects have been suggested to argue for a modular functional LC architecture (Chandler et al. 2019).

Brainstem noradrenergic neurons are widely distributed and influence nociceptive responses in supraspinal structures, including the PAG, RVM, →mesencephalic →lateral reticular nucleus (LRN), hypothalamus, thalamus, amygdala, →striatum of the basal ganglia, and the →cerebral cortex. The effects can be facilitatory or inhibitory, depending on site of release and sub-type of adrenoceptor. Following inflammation or neural injury, central noradrenergic mechanisms change plastically, the net effect being an increase in the efficacy of pain control (De Felice and Ossipov 2016; Pertovaara 2006).

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6

Peripheral Tactile Processing

CONTENTS

Abstract

• Tactile sense, or touch, serves many functions, including object identification and localization, social communication, memory and motor control.

• Tactile sensitivity originates in five classes of cutaneous mechano-receptors: Merkel receptors, Ruffini corpuscles, Meissner corpuscles, Pacinian corpuscles, and free nerve endings. The first four types of receptor connect to group II (Aß) myelinated nerve fibers, the latter to unmyelinated group III (Aδ) or group IV (C) afferents.

• *Slowly adapting type-I (SAI) receptors* originate from Merkel disks in glabrous skin, respond statically to orthogonal skin indentation and are exquisitely sensitive to corners, points, curvatures and edges cutting through their receptive field (RF). Their small receptive fields and high density in fingertips, lips and tongue as well as the latter´s disproportionately large cerebro-cortical representation ensure a high spatial tactile acuity. This system is involved in form and texture perception.

• *Slowly adapting type-II (SAII) receptors* originate from Ruffini corpuscles, respond to perpendicular skin indentation and also signal tangential skin stretch, often in a direction-sensitive manner, which is important for the detection of an object´s motion across the skin and impending slip between the skin and an object.

• *Rapidly or fast adapting type-I (RAI; FAI) receptors* are Meissner corpuscles in glabrous skin and rapidly adapting hair follicle afferents, which react similarly to ramp-like perpendicular skin indentations and dislocations of hairs. Meissner corpuscle afferents react sensitively to very small protrusions on otherwise smooth surfaces that are tangentially slid over the skin and also respond well to low-frequency sinusoidal skin indentations.

• *Rapidly or fast adapting type-II (RAII; FAII) receptors* are Pacinian corpuscles that react only to the very edges of step- or ramp-like skin indentations, and are very sensitive to sinusoidal movements, their best frequencies lying between 250 and 350 Hz, whence Pacinian corpuscles have been linked to the sense of vibration.

• *Free nerve endings* are distributed widely throughout the body. Some unmyelinated afferents in group III (Aδ) or group IV (C) in hairy, not glabrous skin, have low thresholds to mechanical stimuli, have receptive fields (RF) of intermediate size, and respond particularly to slowly moving stimuli at a neutral skin temperature. They probably underlie affective touch.

• The multitude of cutaneous mechano-reeceptors is important for recognizing object properties for grasping and manipulation.

6.1 Introduction

The sense of touch is essential for daily activities throughout life. Gentle touch is critical for the healthy development of a newborn baby (Cascio et al. 2019). →Tactile acuity and postural stability decrease with age, which compromises fine manipulations and increases the incidence of falls due to reduced tactile sensation in the feet (Moehring et al. 2018). Touch is the first of the human senses to develop. However, tactile →perceptual →skill takes several postnatal months to develop fully (Bremner and Spence 2017). The human skin is the largest body organ and unique in containing a deformable sensory sheet (Yau et al. 2016). With an estimated 17,000 →mechano-receptors, it is an essential communication interface between body interior and exterior. Tactile sense includes perception of external stimuli (→exteroception) and body interior (→enteroception). It also includes movement and →spatial orientation arising from stimuli within the body itself (proprioception) (Abraira and Ginty 2013). It represents a wide variety of functions and purposes such as →alerting, →haptic exploration, object identification and localization, sense of →body-ownership, →motivation, social communication and →memory. It also plays an important part in motor control, particularly in grasping and manipulating objects (Bui et al. 2015; Goodwin and Wheat 2004; Juravle et al. 2016; Pruszynski et al. 2018). Accordingly, different types of functionally dedicated tactile receptors are distributed over body surfaces (Abraira and Ginty 2013).

6.2 Anatomy of Cutaneous Mechano-receptors

Cutaneous mechano-receptors in →primates fall into a number of classes and appear to serve distinct perceptual roles (Abraira and Ginty 2013; Johnson 2002; Lechner and Lewin 2013; Macefield and Birznieks 2009; Roudaut et al. 2012; Wheat and Goodwin 2009; Yau et al. 2016; Zimmermann et al. 2014). The receptors are distinguishable by their locations, accessory structures, tactile receptive field size and density, and by their responsiveness to mechanical stimuli. There are different sets of cutaneous mechano-receptors in glabrous and hairy skin, which accounts for much of the differences in response patterns to stimuli in contact with the skin (Macefield and Birznieks 2009; Wheat and Goodwin 2009).

6.2.1 Mechano-receptors in Glabrous Skin

Glabrous skin contains five types of cutaneous mechano-receptors with distinctive distribution patterns and tactile functions: Merkel disks, Ruffini corpuscles, Meissner corpuscles, Pacinian corpuscles and free nerve endings (Abraira and Ginty 2013; Moehring et al. 2018; Roudaut et al. 2012; Strzalkowski et al. 2018; Yau et al. 2016; Zimmermann et al. 2014):

Merkel Disks contain clusters of specialized epidermal Merkel cells associated with flattened nerve terminals (Merkel-neurite complex). In humans, they are distributed throughout the skin where they reside in the basal layer of the epidermis. Their density is particularly high in highly →sensitive skin areas including fingers and lips. Merkel cell clusters are innervated by myelinated group II (Aß) afferents. An individual cluster can be

innervated by two to three afferents, each of which can innervate several cell clusters (Abraira and Ginty 2013; Johnson 2002; Macefield and Birznieks 2009). Merkel cells activate afferent fibers via →adrenergic →synapses (Hoffman et al. 2018).

Ruffini Corpuscles, which are absent in macaques, lie in the dermis. They are encapsulated structures very similar in organization to Golgi tendon organs. Each is supplied by a single group II (Aß) afferent that branches within the corpuscle to intertwine with collagen fibrils (Abraira and Ginty 2013; Darian-Smith 1984; Johnson 2002; Macefield and Birznieks 2009).

Meissner Corpuscles are located in dermal papillae and abundant at the fingertips, in palms, soles of the feet, penis, clitoris, nipples and the tongue. Their group II (Aß) afferents end in fluid-filled encapsulated structures, which functionally isolate them from large, low-frequency deformations of the skin (Abraira and Ginty 2013; Johnson and Hsiao 1992). A single group II (Aß) afferent can innervate up to 17 Meissner corpuscles (Macefield and Birznieks 2009). Meissner corpuscles are very rare in hairy skin.

Pacinian Corpuscles are located in subcutaneous tissues as well as in many other tissues close to tendons, joints, in the genitals and mammary glands. Particularly impressive is the onion-like sheath enwrapping the central sensory ending. The capsule acts like a mechanical high-pass filter that filters out low-frequency tissue strain (Johnson and Hsiao 1992). Every Pacinian corpuscle is innervated by a single group II (Aß) afferent.

Free Nerve Endings. Endings without specialized auxiliary structures are distributed widely throughout the body. In the skin, they are found up to the lower strata of the epidermis. Most of them subserve →nociception, →chemo-reception and →thermo-reception. Nonetheless, some low-→threshold, unmyelinated afferents in group III (Aδ) or group IV (C) in hairy, not glabrous skin, are mechano-sensitive, have →receptive fields (RF) of intermediate size, and respond to skin indentation with adaptation, particularly to slowly moving stimuli at a neutral skin temperature (Ackerley et al. 2014; Cascio et al. 2019: Liljencrantz and Olausson 2014; Olausson et al. 2010). They probably underlie affective touch.

6.2.2 Mechano-receptors in Hairy Skin

Hairy skin is supplied with receptors and afferents that are similar in some respects to those in glabrous skin (Abraira and Ginty 2013; Lechner and Lewin 2013; Macefield and Birznieks 2009; Wheat and Goodwin 2009; Zimmermann et al. 2014). The counterparts of Merkel disks in hairy skin are referred to as `Haarscheibe´ or Merkel touch spots or Pinkus-Iggo receptors and have a structure similar to Merkel disks. Meissner corpuscles are very rare in hairy skin, where a similar function is carried out by hair follicle receptors. These have a diversity of structures, depending on the different types of hair follicle they innervate (Darian-Smith 1984; Lechner and Lewin 2013). Rodents and other animals have developed a highly specialized, exquisitely sensitive and complex whisker system, with which they explore their environment, particularly under dim-light conditions (Diamond and Arabzadeh 2013; Ebner and Popescu 2009; Feldmeyer et al. 2013).

6.2.3 Oral Tactile Receptors

The mechano-sensory innervation of the oral region differs somewhat from that of the hand in terms of mechano-receptor types, anatomy and distribution, although there are receptors with functional properties similar to those of the sensors described above. The oral epithelium contains specialized end organs called end bulbs of Krause which are innervated by sensory nerve fibers and express piezo2. This suggests that the bulbs of Krause may also participate in the detection and encoding of mechanical events occurring in the oral cavity. The bulb-neuron communication may contribute to complex fine motor skills such as speech or the ability to sense food textures (Moehring et al. 2018). Mechano-receptors on the inside of the lips and cheeks encode information related to movements of the upper lip during mastication, speech and intra-oral air pressure (Essick and Trulsson 2009).

6.3 Physiological Characteristics of Cutaneous Mechano-receptors

The anatomical features of cutaneous mechano-receptors provide some information concerning the ways in which tactile signals are detected and conveyed to the →central nervous system (CNS) for further processing.

6.3.1 Mechano-sensory Transduction

Mechanical stimuli impinging on the skin must first be →transduced into electrical signals (→mechano-electrical transduction). Different classes of cutaneous mechano-receptors react differently to mechanical stimuli depending on factors such as the mechanical properties of the skin structures interposed between surface and receptor, the depth of the end organs in the skin, the receptor morphology with its auxiliary structures, the extent of →axon terminal branching, the types of surrounding non-neuronal cells, and the distinct expression patterns and density of mechanically sensitive →ion channels in sensory endings (Moehring et al. 2018; Yau et al. 2016). Because external mechanical stimuli impinging on the skin must be transmitted to the receptors through the epidermis, the role of →keratinocytes has recently received more attention as well-positioned intermediaries between the external environment and sensory neuron terminals. They are equipped with →transient receptor potential (TRP) channels and modulate responses of sensory neurons by secreting →adenosine-triphosphate (ATP) upon mechanical stimulation (Moehring et al. 2018; Tsunozaki and Bautista 2009). Differential distributions of different ion channels (Ranade et al. 2015) play a role as well. Among the channels are →acid-sensing ion channels (ASIC), which appear to regulate and modulate receptors rather than directly serving as transducer channels (Omerbašić et al. 2014). In addition, piezo2 channels are present in the Merkel cell complex and in →dorsal-root ganglion cells in rodents and contribute to two-point tactile discrimination (Anderson et al. 2017; Moehring et al. 2018; Volkers et al. 2015; Walsh et al. 2015). Human patients with null mutations in piezo2 exhibited diminished sensitivity to light touch, vibration, and two-point touch discrimination in the glabrous skin (Chesler et al. 2016). Other mechanically sensitive ion channels, including potassium (K^+) channels, may modulate mechano-sensory transduction

(Moehring et al. 2018). Generally, cutaneous mechano-receptors produce discharge responses of high temporal precision (Saal et al. 2016). When a patch of skin overlying the receptor terminals of an afferent fiber is indented steadily, two broad classes of receptors can be distinguished: (1) slowly adapting (SA) receptors and (2) rapidly adapting (RA) receptors, sometimes referred to as fast adapting (FA). SA and RA/FA receptors have two subclasses; type I in superficial layers of the skin and type II in deep layers (Abraira and Ginty 2013; Johnson 2002; Yau et al. 2016).

6.3.1.1 Slowly Adapting Type-I Receptor System

The SA Type-I System originates from Merkel disks in glabrous skin and is involved in form and texture perception. Mice lacking Merkel cells due to a specific knockout display a complete loss of SAI firing patterns and female conditional knockout mice display a lack of texture discrimination (Maricich et al. 2012). Merkel cells express piezo2 channels that contribute to two-point tactile discrimination. Signal transfer from Merkel cells to SAI afferents has not yet been not completely elucidated, but may rely on →serotonin (5-HT) (Moehring et al. 2018). SAI afferents from Merkel disks respond statically to orthogonal skin indentation and are exquisitely sensitive to corners, points, curvatures and edges that pass through the receptive field (RF). Their small circular or ovoid RFs, high densities in fingertips, lips and tongue and their large cerebro-cortical →somatotopic representations ensure high spatial tactile acuity (Abraira and Ginty 2013; Johnson 2002). The RFs contain several (up to 7) spots of maximal sensitivity corresponding to the number of Merkel disks supplied by a single SAI afferent (Macefield and Birznieks 2009).

6.3.1.2 Slowly Adapting Type-II Receptor System

SAII afferents innervate the skin much less densely than SAI afferents and are thought to originate from Ruffini corpuscles in humans. Compared to SAI afferents, SAII afferents respond less sensitively to perpendicular skin indentation, but they respond to tangential skin stretch, often in a direction-sensitive manner (Abraira and Ginty 2013; Olausson et al. 2000). Directional sensitivity is important to detect an object´s motion across the skin, and in some cases to detect slipping between the skin and an object's surface. In the latter case, when grasping and lifting a fragile object for example, slip detection allows application of minimal force to prevent slipping without causing damage to the object (Abraira and Ginty 2013; Johnson 2002; Macefield and Birznieks 2009; Srinivasan et al. 1990).

Responsiveness to skin stretch also allows SAII afferents to react to joint position and/or movements, with many of them responding in a graded fashion to joint angle (Edin and Abbs 1991). Thus, populations of cutaneous mechano-receptive afferents can encode the orientation of human ankle movements (Aimonetti et al. 2007). Tactile afferents can also be activated by mechanical skin deformation during active arm movements, which may be a reason why neurons in the primate →primary somatosensory cortex (S1,SI) vary discharge properties during active arm movements (Cohen et al. 1994).

6.3.1.3 Rapidly or Fast Adapting Type-I (RAI/FAI) Receptor System

The RAI (or FAI) system originates from Meissner corpuscles, identified by location and morphology. Afferents from Meissner corpuscles in glabrous skin and rapidly adapting hair follicle afferents react similarly to ramp-like perpendicular skin indentations and dislocations of hairs, respectively. On average, the discharge rate increases with the velocity of movement, such that rate is related to velocity by a power function with an exponent of roughly 0.5 to 0.6 (Cohen and Vierck 1993). Meissner corpuscle afferents also react sensitively to very small protrusions on otherwise smooth surfaces that are tangentially slid over the skin. Single raised dots as small as 4 μm in height and 550 μm in width can excite them, such that with the surface movement, a row of Meissner afferents are activated sequentially, delivering a spatio-temporal activity pattern that signals direction and velocity of slip between skin surface and object (Schwarz 2016; Srinivasan et al. 1990). They also respond well to low-frequency sinusoidal skin indentations. When determining the lowest (→threshold) amplitude at which each sine wave elicits just one action potential, afferents from Meissner corpuscles respond most sensitively at frequencies of 30-40 Hz, and have therefore been associated with the sense of tactile flutter (Darian-Smith 1984; Johnson 2002; Macefield and Birznieks 2009; Romo and Salinas 2003). Again, rapidly adapting hair follicle afferents react similarly (Lechner and Lewin 2013).

6.3.1.4 Pacinian Corpuscles – RAII/FAII Receptor System

The PC system (Johnson 2002), also referred to as the RAII (or FAII) receptor system, reacts only to the edges of step- or ramp-like skin indentations in either direction. Pacinian corpuscles are very sensitive to sinusoidal movements, although at higher frequencies than Meissner corpuscles. Accordingly, they have been linked to the sense of vibration (Darian-Smith 1984; Verrillo 2009). Evidence suggests that they contribute to slip detection under appropriate circumstances (Srinivasan et al.1990).

6.3.1.5 Mechano-receptor Receptive Fields

The receptive fields (RFs) of afferents from Merkel and Meissner receptors are round to oval and small. The RFs range from 3 to 50 mm^2, corresponding to diameters of roughly 2-8 mm. The density of these fields is of primary importance for the acuity of spatial resolution. Density is maximal at the fingertips and falls off towards the wrist in two cascades, one in the middle of the terminal phalanx and the other at the finger base. The fingertip density of SAI and RAI afferents is 70 and 140 per mm^2, respectively, corresponding to an average center-to-center distance of 1.3 and 0.9 mm, respectively. This organization provides the basis and limit for the capacity to discriminate the location of two pointed stimuli (→two-point discrimination). Field size increases and field density decreases in proximal direction along the arm, reaching large values on the back. SAII (Ruffini) and RAII (Pacinian corpuscles) afferents have much larger receptive fields. Their density is much less than that of type I afferents, so they cannot be involved in precise spatial discrimination (Johansson and Vallbo 1983; Johnson 2002).

Receptive field sizes vary with stimulus →intensity. Due to the →visco-elastic properties of skin, deeper and faster skin indentations spread over wider skin areas. Hence, more remote receptors are activated. Spatial recruitment into a population of active receptors (population code) is an important mechanism of →intensity coding (Cohen and Vierck 1993; Pubols 1988).fingertip density of SAI and RAI afferents is 70 and 140 per mm^2, respectively, corresponding to an average center-to-center distance of 1.3 and 0.9 mm, respectively. This organization provides the basis and limit for the capacity to discriminate the location of two pointed stimuli (→two-point discrimination). Field size increases and field density decreases in proximal direction along the arm reaching large values on the back. SAII (Ruffini) and RAII (Pacinian corpuscles) afferents have much larger receptive fields. Their density is much less than that of type I afferents, so they cannot be involved in precise spatial discrimination (Johansson and Vallbo 1983; Johnson 2002).

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6.4 Feature Extraction

Why are there several classes of sophisticated cutaneous receptors with specific dynamic sensitivities? One possibility is that change is more important than constancy for survival. Therefore, receptors with high dynamic response sensitivity (novelty detectors) are needed. Another reason is that the nervous system analyzes objects by features and then conveys the parceled information in parallel pathways to integrative centers, re-synthesizing the features into a new brain-body (Graziano and Botvinick 2002) picture.

For the cutaneous senses, recent investigations into their firing patterns during simple object-grasping movements have yielded some insight into their differential responsiveness. Human subjects lifted, with thumb and index finger (→precision grip), a small object with varying surface properties. Load force in tangential or lift direction, grip force, the ratio between the two, object position and →acceleration were measured and mechano-afferent activity were recorded. The afferents responded differentially during different aspects of the motor task. Frictional properties were represented in discharges by certain populations of Meissner corpuscle afferents during the initial touch and at times later during small frictional slips (Johansson and Cole 1992). The object´s weight was signaled by transient responses of Pacinian corpuscles at lift-off, when →gravity was overcome by the lifting force. Because of high demands on the speed of information processing, which cannot be satisfied by a mean rate code, the sequence of initial spikes in ensembles of cutaneous afferents may play an important role in signaling the direction of fingertip force and the shape of surfaces (Johansson and Birznieks 2004).

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7

Central Tactile Processing

CONTENTS

Abstract

• This chapter is concerned with the coding of cutaneous tactile stimulus intensity, flutter-vibration sensation, motion sensation, tactile discrimination and recognition of object shape, and affective touch.

• Mechano-sensitive afferents from the face and mouth run through three branches of the trigeminal nerve, whereas afferents from most other parts of the body surface enter the central nervous system (CNS) via the spinal cord dorsal roots.

• Large diameter tactile-sensing fibers split into several branches, some projecting to various spinal cord loci, others descending and ascending in rostro-caudal direction. Ascending projections target supraspinal structures up to the cerebral cortex via several pathways: one through the dorsal columns to the dorsal column nuclei in the medulla oblongata, the other via synaptic stations in deep layers of the spinal dorsal horn. All pathways run through specific nuclei of the thalamus to areas of the primary somatosensory cortex and thence to the secondary somatosensory cortex and further areas.

• The `linearity hypothesis´ for touch posits that the intensity of subjective human sensation is linearly related to the depth of skin indentation. The discharge rate of intermediate neurons throughout the neuraxis is often linearly reated to indentation depth.

• Vibrotactile stimuli are perceived as having pitch and intensity, and are supposed to be processed through multiple neural channels. Flutter sensation occurs in the frequency band from about 5 to 40 Hz and corresponds well with the tuning curves of Meissner corpuscles. Vibration sensation occurs at frequencies between 50 and 400 Hz, this frequency band corresponding to that of Pacinian corpuscles.

• Detection and characterization of motion across the skin are biologically important for detecting potentially dangerous objects and for sensorily guiding object grasping and manipulation. The extraction of features such as stimulus motion, speed, direction and orientation require complicated interactions between neuronal assemblies. The analysis of these features starts in the periphery and continues up to the cerebral cortex.

• Everyday tactile experience with objects results from patterned activation of many sensory receptors which together provide a picture, frequently fragmented, of objects in terms of size, shape, texture, hardness, weight etc. The peripheral activation patterns of cutaneous mechano-receptors are not enough to construct complete object representations. These require additional integrative processes at the cortical level.

• Touch has an affective component in being neutral, pleasant or unpleasant. Pleasant (gentle, sensual) touch may be involved in emotional, motivational, hormonal and affiliative responses to caress-like contact between humans and contributes to social interactions. It may also be analgesic and anxiolytic.

• Sensory structures including those underlying touch sensations are plastic both during ontogenetic development and in adult life in response to differential sensory experience or to lesions, this plasticity depending on multiple cellular, synaptic and structural processes.

7.1 Introduction

The tactile senses serve a number of functions including →alerting, tactile stimulus →perception, tactile object identification and localization, →motivation, sense of →body-ownership, social communication with →con-specifics, and tactile memory. Tactile stimuli must be detected and coded as to →intensity, location and change in time (motion). Most important for motor control is that touch contributes to the →haptic identification and characterization of objects as to shape, size, weight, surface texture, compliance and thermal characteristics, these functions requiring the cooperation with other senses (Sathian 2016).

7.2 Overview of Central Projections of Tactile Afferents

Tactile innervation to the face and mouth is provided by three branches of the →trigeminal nerve. Large-diameter low-→threshold afferents enter the →central nervous system (CNS) and project to principal sensory trigeminal nucleus, with secondary neurons projecting to the contralateral side to join the medial lemniscus. Un-myelinated mechano-sensitive afferents (CT afferents) also project to laminae I and II of the →spinal cord dorsal horn in several mammalian species. The projection continues to the posterior ventro-medial thalamic nucleus (VMpo) and thence to the dorsal posterior →insula (Olausson et al. 2010).

Tactile afferents from most other parts of the body surface enter the CNS via the spinal →dorsal roots. After entering the spinal cord, large-diameter group II (Aß) afferent fibers from low-threshold mechano-receptors (LTMRs) split into several branches, some projecting to various spinal cord loci, others descending and ascending in rostro-caudal direction (Abraira and Ginty 2013; Bui et al. 2015). The rostral projections travel through several tracts and make contacts with the dorsal-column nuclei, →thalamic nuclei and ultimately the →cerebral cortex (Delhaye et al. 2018).

7.3 Tactile Afferent Projections to the Spinal Cord

The segmental organization of the spinal cord is reflected in →dermatomes, skin regions supplied by afferent fibers in a given dorsal root. The dermatomes of adjacent dorsal roots overlap extensively and vary with modality of sensation. For instance, overlap is less for pinprick pain than for light touch. As a consequence, section of a cutaneous nerve results in a circumscribed loss of sensation, whereas dorsal-root section does not produce extensive sensory deficit. Systematic mapping of the body surface onto the sequence of segments of the spinal cord provides a valuable diagnostic tool for the localization of →spinal root or →spinal cord injuries in →Brown-Séquard syndrome and →syringomyelia.

Local Spinal Projections. Cutaneous sensory afferents are heterogenous as to their anatomy, gene expression profiles, degree of →myelination and conduction velocities, electrophysiological properties, firing patterns, stimulus response, spinal connectivity and functions (Gatto et al. 2019). Afferents of cutaneous mechano-receptors send collaterals into

the spinal →gray matter. The collaterals display distinct distributions of →axonal terminations and patterns of terminal arborizations, in line with the receptor type (Abraira and Ginty 2013; Abraira et al. 2017). In rodents, cats and →primates, the highest density of large-diametercutaneous afferent terminals is found in laminae III-V. Some →interneurons located here and receiving inputs from these afferents are premotor in projecting to →motoneurons. Others are located more ventrally in laminae VI and/or VII (Bui et al. 2015). Branches of cutaneous afferents contact →projection neurons (e.g., dI1 and dI3 interneurons) as well as diverse →interneurons involved in a number of →reflex and other pathways, including interneurons exerting postsynaptic inhibition and →presynaptic inhibition (via dI4 interneurons). To a large extent, the projection cells and interneurons receive convergent inputs from a variety of afferent and descending pathways (Abraira and Ginty 2013; Abraira et al. 2017; Jankowska 1992; Windhorst 2007).

RORα Interneurons. In mice, →glutamatergic RORα interneurons are predominantly located in laminae II and III, are primarily innervated by afferents from a number of low-threshold mechano-cutaneous receptors, monosynaptically contact motoneurons as well as →cholinergic V0c interneurons that contact motoneurons and change their input-output gain. They also receive inputs from the →cortico-spinal tract (CST) and lateral →vestibulo-spinal tract (VST), indicating that signals descending from supraspinal sources may modulate or gate sensory transmission in the spinal cord. Genetically modified mice without RORα interneurons are impaired in sensing light touch on the foot sole, which does not lead to severe deficits in gross locomotion, but to deficits in precise foot placement (Bourane et al. 2015; Bui et al. 2015).

dI3 Interneurons. In mice, glutamatergic dI3 interneurons are located in laminae V-VII, monosynaptically contact motoneurons and likely receive their main sensory inputs from mechano-cutaneous afferents whose electrical stimulation evokes strong motor reflexes. Note that these interneurons also project to the →lateral reticular nucleus (LRN), a relay to the →cerebellum. Absence of these interneurons in genetically modified mice entails a reduction of grip force in the face of increasing loads and other deficits (Bui et al. 2015).

dI4 Interneurons are →GABAergic and mediate presynaptic inhibition (Bui et al. 2015). Somatosensory cutaneous afferents themselves receive two types of presynaptic inhibition: a →$GABA_A$-receptor-dependent form from low-threshold cutaneous afferents and an NMDA-receptor-dependent form from small-diameter afferents (Zimmerman et al. 2019).

7.4 Ascending Tactile Projections

→Somatosensory pathways are spatially organized such that, within tracts and nuclei up to the cerebral cortex, topological neighborhood relations are maintained at least roughly, and the different parts of the body are represented in an orderly →somatotopic manner.

Signals from large-diameter low-threshold, superficial and deep →mechano-receptors are conveyed to higher centers in several ways. One portion is carried by collaterals of a subset of primary sensory afferents that are split off after entry into the spinal cord and project through the →dorsal columns to the →dorsal column nuclei in the →medulla oblongata. The

other portion is carried by collaterals that project into the deep layers of the spinal dorsal horn and →synapse onto projection neurons directly or indirectly via various types of interneuron. For example, the mouse deep dorsal horn houses seven excitatory and four inhibitory interneuron sub-types with low-threshold mechano-sensitive inputs, each afferent contacting between four and eleven interneuron sub-types and each interneuron sub-type receiving inputs from at least one to three afferent classes. This convergence-divergence pattern provides for intense signal processing before the information is conveyed on to projection neurons (Abraira et al. 2017).

Dorsal Column-Medial Lemniscus System. At the dorsal-root entry zone, fibers containing group II afferents from skin, joints and deeper structures, and group Ia and group II muscle spindle afferents, ascend in the dorsal columns. (Abraira and Ginty 2013). The synaptic linkage of dorsal column fibers to neurons in the dorsal column nuclei is very strong as evidenced by the fact that a single →action potential in a sensory presynaptic fiber can evoke discharge in postsynaptic dorsal-column neurons (Rowe 2002). Axons of projection cells in these nuclei decussate to the contralateral side where they ascend in the medial lemniscus to the thalamic ventro-posterior lateral (VPL) nucleus. From here thalamo-cortical fibers project via the internal capsule to the somatosensory cortex.

Postsynaptic Dorsal-Column System. This system has an intermediate station in the dorsal horn with secondary neurons mainly in laminae IV and medial V. Some of these secondary neurons project via the dorso-lateral →funiculus to the dorsal column nuclei. Most postsynaptic dorsal-column neurons are excited by mechanical stimulation of →glabrous and hairy skin. A minority of the neurons respond exclusively to light mechanical stimulation, while the majority reacts to a wide range of stimuli, including pressure to skin, joint movements, →noxious mechanical stimulation and heat (Abraira and Ginty 2013; Maxwell and Réthelyi 1987).

In the mouse, a specific group of interneurons in laminae II/III projects to postsynaptic dorsal-column neurons, pre-motoneurons and motoneurons and receives afferent signals from innocuous light-touch receptors and descending signals from the cerebral cortex and cerebellum. They may be used for fast corrective motor responses during walking on uneven ground (Bourane et al. 2015).

Spino-cervico-thalamic System, a parallel system present in furred quadrupeds and primates, conveys cutaneous mechano-receptive information to the cerebral cortex (Brown 1981; Mountcastle 1984). The spino-cervical tract originates mainly from dorsal-horn neurons in laminae IV and a few in III and V. Spino-cervical neurons have been broadly classified into three groups: low-threshold, high-threshold and wide-dynamic-range (WDR) neurons. Low-threshold cells are excited by hair movements. High-threshold cells, which are rarely encountered, are activated by →noxious stimuli. Wide-dynamic-range neurons, which receive inputs from afferents of varied conduction velocities, respond to hair movements as well as to pressure or pinch (Abraira and Ginty 2013).

Spino-cerebellar Tracts. Tactile signals also reach the cerebellum that is involved in motor and other functions. Tactile signals are mediated via deep dorsal-horn neurons genetically identified in mice as →dI1 interneurons and giving rise to three pathways which also exist in

other mammals. The →rostral spino-cerebellar tract originates in more rostral (cervico-thoracic) segments. Two other tracts originate in more caudal (thoraco-lumbar-sacral) segments and are referred to as →ventral spino-cerebellar tract (VSCT) and →dorsal spino-cerebellar tract (DSCT). The spino-cerebellar tracts convey signals primarily from →skeletal muscle afferents and to a lesser extent from low-threshold cutaneous mechano-receptors. Spino-cerebellar connections are also established from dI3 interneurons via the LRN (Bui et al. 2015).

7.5 Processing of Skin Mechano-sensitive Signals in the Dorsal Column Nuclei

Neurons that receive input from vibration-sensitive afferents, rapidly and slowly adapting afferents from glabrous and hairy skin and joint and muscle stretch receptors are segregated and grouped within the dorsal column nuclei. This organization is maintained through successive processing stages up to the cerebral cortex (Mountcastle 1984).

Neuronal networks in the dorsal column nuclei provide significant signal processing. In addition to the principal relay neurons, there are interneurons that mediate pre- and postsynaptic inhibition, →recurrent inhibition among relay neurons and excitatory synaptic inputs that contribute to spatial localization and interpretation of spatio-temporal patterns of stimuli involving different classes of tactile mechano-receptors (Mariño et al. 1999; Mountcastle 1984; Windhorst 1996). Some of these processes may be involved in the movement-related gating of mechano-sensitive signal transmission (Chapman 2009; Cullen 2004).

7.6 Processing of Skin Mechano-sensitive Signals in the Thalamus

The →thalamus is an obligatory processing station for sensory information conveyed to the cerebral cortex. Both the medial lemniscus and antero-lateral systems terminate predominantly in the ventro-basal complex. Almost half of the synaptic inputs to neurons in the dorsal thalamus arises from the cerebral cortex and exerts modulatory functions by filtering and shaping thalamic neuronal responses to sensory inputs and by sharpening tactile receptive fields (RFs). Modulation occurs in the somatosensory, auditory and visual thalamic areas (Alitto and Usrey 2003).

Several neural processes present in the ventro-basal thalamus are capable of modulating and segregating different categories of mechano-receptor-related signals. Fiber systems descending from →cortical areas are engaged, which impose inhibitory as well as facilitatory influences on signal transmission by relay nuclei in the ventro-basal thalamus. Modality-specific thalamic cells are clustered to maintain differentiation of input signals on the way to the cortex. This allows deep sensory modalities originating in muscles and joints to be separated from skin modalities. Cutaneous representations are concentrated in the core, whereas deep modalities are restricted to the shell region (Mountcastle 1984).

7.7 Processing of Skin Mechano-sensitive Signals in Somatosensory Cortex

7.7.1 Cortical Connectivity Patterns

Primary targets of the somatosensory thalamo-cortical projections are the anterior parietal cortex (APC) containing the →primary somatosensory cortex (S1, SI) (Dijkerman and de Haan 2007), and the →secondary somatosensory cortices (S2, SII) in the →parietal →operculum (Sathian 2016) (for evolution in primates see Kaas 2004; for postnatal maturation in humans see Pihko et al. 2009).

Primary Somatosensory Cortex (S1, SI) is located in the →post-central gyrus of the →parietal cortex. It was long assumed that S1 on one side received tactile information exclusively from the contralateral body surface, but more recent evidence suggests also projections from the ipsilateral side (Medina and Coslett 2016; Tamè et al. 2016) and likely inter-hemispheric information exchange at S1 level, enabling the integration of touch signals from both body sides (Tamè et al. 2019). S1 consists of four areas: area 3a, area 3b, area 1 and area 2, arranged in anterior-posterior progression. They differ cyto-architecturally and in terms of connectivity patterns, carry separate body maps. and selective lesions entail different deficits (Sathian 2016).

Cutaneous mechano-sensitive inputs from skin and intra-oral mucosa arrive mainly in area 3b, but also in other S1 areas (Sathian 2016; Yau et al. 2016). Proprioceptive inputs from deep tissues, muscles and joints are represented mainly in area 3a, but distribute to all S1 areas (Sathian 2016; Yau et al. 2016).

Neurons in areas 3b and 1 receive convergent inputs from slowly adapting type-I (SAI) afferents and rapidly adapting (RA) afferents (Sathian 2016). The somatosensory cortex also receives →nociceptive inputs. Neurons in layer III of areas 3a and 3b project to area 1 and area 2, and area 1 to area 2. In this anterior-posterior direction, receptive field (RF) sizes and complexity increase (Sathian 2016). Areas 1 and 2 project further to →area 5 and →area 7 of the →posterior parietal cortex (PPC). In anterior direction, areas 3a, 1 and 2 project to motor cortical areas including →area 4 (→primary motor cortex) and →area 6, including the →supplementary motor area (SMA) (Fox 2009; Iwamura 2009a).

Layer V neurons project to →sub-cortical structures including the →striatum of the →basal ganglia, the cerebellum via the pontine nuclei, and the →ventral horn of the spinal cord, thus being involved in the planning, execution and dynamic modulation of movements. Layer VI cells project to the thalamus (Fox 2009; Iwamura 2009a). Responses in S1 are significantly shaped by intra-cortical horizontal connections including lateral inhibition (Tommerdahl et al. 2010).

Primary somatosensory cortex (S1, SI) receives →neuromodulatory inputs from →cholinergic, →dopaminergic, →noradrenergic and →serotonergic inputs (Jacob and Nienborg 2018; Rho et al. 2018).

Parietal Operculum. The parietal opercular cortex in the macaque contains the secondary somatosensory cortex (S2, SII), ventral somatosensory area (VS) and parietal ventral area (PV), which are possibly homologous to human fields OP1, OP3 and OP4, respectively. All fields carry a complete representation of the body surface (Sathian 2016). S2 has been divided into cytoarchitecturally and functionally different regions in various ways. It receives non-noxious cutaneous, proprioceptive and nociceptive inputs mainly from the nucleus ventralis postero-inferior (VPI) of the ventro-basal complex, the posterior nuclei (PO) and the nucleus centralis lateralis (CL) in the →intralaminar nuclei. S2 receives inputs from areas 3b, 1 and 2 of S1, and from areas 5 and 7, and feeds back to S1 (Iwamura 2009b). Region S2 is reciprocally connected with the insula, and projects to ipsi- and contralateral area 7b as well as to the ipsilateral →premotor cortex (Dijkerman and de Haan 2007).

Inter-hemispheric S1-S2 Connections. Inter-hemispheric connections via the →corpus callosum link S1 and S2 on both sides. The bilateral S2 cortices are reciprocally connected, and S2 is reciprocally connected to the contralateral S1. It appears, therefore, that the signals of a unilateral tactile stimulus are initially transmitted to the contralateral somatosensory cortices via thalamo-cortical connections, from where pre-processed information is then transmitted to ipsilateral somatosensory cortices via trans-callosal connections (Blatow et al. 2007; Eickhoff et al. 2008; Iwamura 2009a,b). In healthy, right-→handed humans, →functional magnetic resonance imaging (fMRI) showed that unilateral tactile finger (digits 1 and 2) or lip (upper and lower) stimulation by non-noxious repeated air-pressure pulses elicited contra- and ipsilateral S1 and S2 activations, with contralateral activations being stronger than ipsilateral ones (Blatow et al. 2007). Similarly, →magnetoencephalography in humans revealed short-latency activation of both ipsi- and contralateral S1 in response to a unilateral tactile flutter stimulus. Also, electrical median nerve stimulation evokes short-latency activation of ipsilateral S1 (Tommerdahl et al. 2010).

Human brain imaging has shown that brief tactile or electrical stimulation at different body locations activate not only contralateral S1 and bilateral S2, but also areas in the →superior parietal lobule (SPL) and the →inferior parietal lobule (SPL) [e.g., medial superior temporal cortex (→area MST)], the superior temporal polysensory area (area STP) in visual cortex, the supplementary motor area (SMA) and →cingulate motor area, and the insula (Beauchamp et al. 2009; Pleger and Villringer 2013).

Somatotopy in the Somatosensory Cortex. The primary somatosensory cortex (S1) carries multiple maps of the contralateral body surface and deep receptor structures. Different body parts are represented orderly, but disproportionately. In primate S1, the oral cavity, face, hand, arm, trunk, leg and foot are represented in the lateral-to-medial direction over the post-central gyrus (Iwamura 2009a).

The secondary somatosensory cortex (S2) does not have such a clear somatotopic organization as the S1 (Haggard 2006; Iwamura 2009b; Kaas 2005). The contralateral representation results from input from the ventro-basal thalamus, while the ipsilateral representation probably has its source in the contralateral S1 and S2. This implies that, as both representations are in register, there is a precise somatotopic mapping between contralateral cortices. In S2, the face is represented anteriorly, with medio-lateral strips representing hand, arm, trunk, leg and foot in posterior direction (Mountcastle 1984). Somatotopic representations of the face and multiple body parts are also seen in the

posterior parietal cortex (PPC); they are often multi-sensory maps with tactile and visual inputs and may be involved in object avoidance and defensive movements (Huang et al. 2012).

It seems evident that somatotopy in the somatosensory cortex of man and monkey represents optimal efficiency in the way the brain views the body. Body representation involves a montage of proprioceptive and tactile sensory information, accompanied by motor feedback signals and interpreted in the context of an →internal model of body geometry, which is adaptable with growth or with loss or deformity of body parts (Graziano and Botvinick 2002).

7.7.2 Properties of Cortical Processing

One principle of somatosensory information processing in S1 is that it becomes progressively more complex in the rostro-caudal direction (Yau et al. 2016). This is also suggested by the effects of lesions, which disturb the perception of light touch, →two-point discrimination, vibration sense, position sense, tactile object recognition as to size, shape, texture and motion. Damage to more posterior S1 and areas 5 and 7 results in difficulties in generating exploratory and manipulative finger movements (Iwamura 2009a).

Receptive Fields (RFs). Neurons of cortical area 3b in monkeys have the smallest RFs, which are confined to part of a phalange or to one or two phalanges of a finger. Functionally important finger parts, such as the tip, ventral glabrous surface and dorsal surface, are represented separately (Iwamura 2009a). The RFs are usually composite in that excitatory regions are partly overlaid or flanked with inhibitory ones. This composition, or the alignment of RFs, enables many cells in areas 3b and 1 to respond selectively to the *orientation of bars and edges* (orientation selecitivity), which is an elementary contour feature underlying shape perception (Yau et al. 2016). There is a general trend for RF structures and neuronal responses to become more complex in the antero-posterior direction, from area 3b to area 2, which contains neurons with RFs distributed over multiple digits and responding to cutaneous and proprioceptive inputs. Similar properties are found in neurons in secondary somatosensory cortex (S2). Area 2 and S2 neurons also prefer certain contour orientations, but at a larger scale, and in addition are sensitive to the degree and direction of contour curvatures (Gardner 1988, Iwamura 2009a; Yau et al. 2016). Very likely, the large and complex RFs of many cortical cells are also due to connections with →motor cortex, auditory, visual and thalamic areas, as well as callosal connections between somatosensory cortices involved in tactile responsiveness (Blatow et al. 2007; Iwamura 2009a) and activities such as reaching, grasping, manipulative movements and task-related postural adjustments.

Modal Properties. In the monkey primary somatosensory cortex (S1), neurons with cutaneous inputs mostly respond to convergent signals from different cutaneous mechano-receptors although, when tested under particular experimental consditions, they appear to be particularly responsive to an individual sub-modality (Saal and Bensmaia 2014). Thus, a population of slowly adapting (SA) neurons responds to static skin indentations with maintained increases or decreases in firing rate, and a class of rapidly adapting (RA)

neurons responds transiently. Some neurons with large receptive fields (RFs) react very sensitively and are probably related to stimulation of Pacinian corpuscles (Johnson 2002). Neurons in S1 are often sensitive to specific stimulus features, such as an edge or rough surface, or the direction and speed of a moving stimulus. The detection of motion direction may be facilitated by cells that have inhibitory RFs lying adjacent to excitatory ones. Some cells are activated only or better during active hand movements (active touch), possibly assisted by proprioceptive and motor signals (Saal and Bensmaia 2014), and some are facilitated or inhibited by →attention (Iwamura 2009a). The successive integration of sensory information leads to changes in map structure. In more anterior locations of somatosensory cortex, single neurons appear relatively more sensitive to one or the other sub-modality. In more posterior locations, place and modality specificity are replaced with an organizational principle found in `patchy´ maps that are intermediate between continuous (→topographical) and `scattered´ (randomized) maps. Such maps are also known from other sensory cortices, e.g., the auditory cortex and visual cortex (Johnson 2002). Cortical neurons receiving different proportions of modality-specific afferent inputs are differentially involved in different perceptual functions (Saal and Bensmaia 2014).

7.8 Tactile Object Identification and Recognition

Humans are good at identifying and recognizing objects even without vision. Objects are characterized by a variety of properties, including size, shape, weight, hardness, distribution of surface features such as edges, curvatures, texture. Often they are probed by tactile exploration through skin motion across objects. These properties are gauged from patterned activation of many →sensory receptors which together provide a frequently fragmented picture of objects (Sathian 2016; Yau et al. 2016). The activation patterns in peripheral sensory afferents do not suffice, however, to construct complete object representations (gestalt). These require additional integrative processes at the cerebro-cortical level and involve other senses such as proprioception and audition (Sathian 2016). Recognition also engages →memories from everyday tactile experience.

7.8.1 Perceptual Gestalt Principles

Object identification and recognition encompass elements such as personal thoughts and experiences, considered as a whole, and they proceed in stages. Several →Gestalt principles have been suggested to group individual stimulus elements into higher forms in the auditory and visual systems. For example, if a blindfolded subject grasps a bottle with spread fingers, the bottle surface is only partially sampled by touching and yet a holistic experience evolves, which is in essence a perceptual completion by filling in the gaps. Grouping principles help organize individual elements into forms or shapes of objects or parts thereof. The proximity of closely spaced stimulus elements makes them group together. For instance, if three dots are closer than surrounding dots, they may be perceived as a line or triangle. Elements with similar characteristics such as shape, size, texture, orientation, are perceived as belonging together (principle of similarity). How exactly these perceptual principles are neurally implemented in the tactile modality is still under investigation and the subject of vigorous debate, but it appears as if both early and higher-level cortical regions are involved (Gallace and Spence 2011). For example, neuroimaging

studies indicate that the →temporo-parietal junction (TPJ) of the cortex might play an important role in global gestalt.

7.8.2 Intensity Coding

Object hardness and weight are in part estimated from the intensity of skin indentations and pressure which must be faithfully measured and transmitted to the CNS. The `linearity hypothesis´ for touch posits that the →intensity of subjective human sensation is linearly related to the depth of skin indentation (Mountcastle 1984; Johnson 2002; Johnson et al. 2002). On a population basis, the discharge rates of slowly adapting (SA) afferent fibers from monkey glabrous skin and the firing rates of neurons in the dorsal column nuclei, ventro-basal complex of thalamus and monkey cerebro-cortical area 3b are all linearly related to stimulus intensity. Similarly, for hairy skin, both stimulus-response functions for sensation and sensory afferent discharge are power functions with about the same exponent of 0.5-0.6, again indicating linear transfer through intermediate stages (Mountcastle 1984). This complies with the observations in humans that the rate of stimulation of single slowly adapting (SA) afferents and the intensity of the evoked sensations are linearly correlated (Ochoa and Torebjörk 1983). Also, the amplitude of a flutter stimulus applied to a discrete forelimb site appears proportionally coded in the activation of contralateral area 3b and area 1 (Tommerdahl et al. 2010).

7.8.3 Flutter-Vibration Sensation

Some objects or parts thereof may vibrate, e.g., a smartphone. The sub-modality of →vibrotaction detects and estimates oscillatory stimuli imposed to the skin and underlying tissues. It is used to evaluate the vibratory frequency of static stimuli as well as of dynamic stimuli arising from relative motion of skin and object surface in exploratory motor acts (active touch). Vibrotactile stimuli are perceived as having →pitch and intensity, and are supposed to be processed through multiple neural channels (Hollins 2010). When the skin is stimulated with sinusoidal waveforms of sufficient amplitude, two different tactile qualities can be evoked depending on the modulation frequencies. Flutter sensation occurs in the frequency band from about 5-40 Hz and corresponds well with the tuning curves of Meissner corpuscles, whereas at frequencies between 50 and 400 Hz, the sensation changes to a different quality of vibration, this frequency band corresponding to that of Pacinian corpuscles. Above about 500 Hz, the periodic cycles are not resolved anymore and cause a stationary sensation (Mountcastle 1984). Subjective intensity estimation is probably related to a combination of signals from slowly adapting type I (SAI), rapidly adapting type I (RAI) and rapidly adapting type II (RAII) receptors (Hollins 2010). As mentioned, there are quality-matched cortical neurons corresponding to the slowly adapting (SA) and rapidly adapting (RA) peripheral receptors. The way in which both SA and RA neurons in cortical areas 3b and 1 respond to mechanical sinusoids in the frequency range of 5-40 Hz is similar and dependent on stimulus frequency and amplitude. RA neuron responses in S1 to flutter are mostly robust, sustained over time and entrained to the stimulus cycles, while those to vibration are usually transitory and only sustained in a very small S1 region. By contrast, neuronal responses in S2 to vibration are usually sustained for a much longer time, possibly due to stronger RAII inputs to S2 than to S1 (Tommerdahl et al. 2010).

It has long been assumed that low- and high-frequency signals (RAI and RAII signals, respectively) are conveyed and processed by independent channels up to the primary somatosensory cortex. However, there are many signs of interactions between these signals in S1 and between S1 and S2. For example, concurrent stimulation of a skin site with superimposed 25 Hz and 200 Hz (complex waveform) vibrations activated an S1 region that was substantially smaller than that activated by 25 Hz stimulation alone, indicating a suppressive influence of the 200 Hz stimulus on the response to 25 Hz. This has been interpreted as indicating that activation of Pacinian corpuscles accompanying cutaneous flutter stimulation triggers cerebral cortex mechanisms that sharpen the spatially distributed contralateral S1 response to the flutter stimulus. In humans, such a complex waveform improves tactile spatial acuity (Tommerdahl et al. 2010).

The perceptual detection and discrimination of vibrotactile stimuli, which involve →decision making, engage areas distributed in the →frontal cortex and parietal cortex, and likely sub-cortical structures. For example, in the monkey, the comparison operation underlying the discriminative decision between different vibration frequencies generates decision-related activity in distributed cortical regions including S2, →prefrontal cortex (PFC), medial premotor cortex, →ventro-lateral premotor cortex (PMv), and primary motor cortex (M1) (Romo and de Lafuente 2013).

Prolonged exposure to vibrotactile stimulation elevates absolute detection threshold and reduces the subjective intensity of sensation, presumably based on several peripheral and central mechanisms. In animal experiments, such stimulation is associated with a sustained reduction of cutaneous mechano-receptor sensitivity, depressed responsivity of neurons in the cuneate nucleus, and a reduction of the spatial extent of the responsive S1 region (Tommerdahl et al. 2010).

7.8.4 Motion Sensation

Detection and characterization of motion across the skin are biologically important, both in detecting potentially dangerous objects or in sensorily guiding object grasping and manipulation. The extraction of features such as stimulus motion, speed, direction and orientation require complicated mechanisms in the form of interactions between neuronal assemblies (Pei and Bensmaia 2014). The analysis of these features starts in the periphery and continues up to the cortical level.

Motion Sensitivity refers to the capability of detecting movement of a stimulus across the skin without much regard to its direction. At the periphery, this capability is probably provided by SA1 and RA afferents while they show only moderate sensitivity to the direction of motion when tangential forces are present (Pei and Bensmaia 2014). Cortical areas 3b and 1 contain motion-sensitive neurons, which also respond to light brushing or stroking, while those in area 2 need stronger, rubbing movements and are less frequent than in area 3b and 1 (Gardner 1988).

Tactile Speed. Cutaneous mechano-receptors are very sensitive to motion speed but also to texture. This requires cortical levels to disambiguate signals related to speed or texture, which probably involves integrating signals from SA1, RAI and RAII afferents. A sub-

population of neurons in areas 1 and 2 increase their firing with speed (Pei and Bensmaia 2014).

Direction Sensation. Sensitivity to motion direction is much more pronounced in S1 than in the periphery. Area 1 displays the strongest and most consistent direction tuning. A sub-population of neurons shows direction preference consistent across stimulus types and is invariant to changes in stimulus amplitude and motion speed (Pei and Bensmaia 2014). For their excitation, the stimulus need not traverse a continuous trajectory on the skin; rather, a series of points separated by as much as 9 mm and activated in an orderly time sequence suffices, indicating that direction-sensitive cells can integrate signals from quite separate points (Warren et al. 1986). To derive the motion direction of a larger object, the `aperture problem´ must be solved. Mechano-receptive afferents signal the local motions of differently oriented stimulus contours in limited peripheral receptive fields. These fractured pieces of information must be integrated at cortical level, taking into account, for example, different finger and hand configurations assessed by proprioceptive receptors. The `aperture problem´ also occurs in vision (Pei and Bensmaia 2014).

7.8.5 Discrimination and Recognition of Surface Texture

Surface texture is a feature of sensation and perception in several spatio-temporal senses (audition, touch, vision) and reflects repetitive spatial and/or temporal structure (Johnson and Hsiao 1992; Sathian 2016). Texture has several independent dimensions, such as hard-soft (compliance), rough-smooth, and slippery/sticky in some individuals (Hollins 2010; Johnson 2002; Sathian 2016). Roughness perception depends on the density, height, diameter, shape, and compliance of surface elements (Wheat and Goodwin 2009).

Signals from different cutaneous mechano-receptor sub-modalities may have differential roles in object surface recognition and manipulation (Macefield and Birznieks 2009; Saal and Bensmaia 2014). It has been hypothesized that roughness perception of a coarse surface uses a spatial code and depends peripherally on the mean absolute difference in firing rates between SAI afferents with receptive field (RF) centers separated by 2-3 mm. During object lifting or holding, SA afferents may sense the direction of skin stretch, hence, impending slip. They are not, however, responsive to slip of fairly smooth surfaces, nor do humans become aware of such an event. By contrast, the roughness perception of fine surfaces cannot be accounted for by a spatial code, but depends on motion between skin/object surfaces, which creates texture-specific vibrations generating particular temporal discharge patterns in Meissner and Pacinian corpuscle afferents. Thus, the duplex theory of roughness perception purports that roughness is mediated by a spatial code for coarse surfaces and a vibrotactile code for finely textured surfaces (Hollins 2010; Saal and Bensmaia 2014; Sathian 2016).

In macaques, differences in spatial surface features are reflected in discharge patterns of neurons in primary somatosensory cortex (S1) and parietal opercular cortex (Sathian 2016). During a texture discrimination task, the discharge rates of many neurons in S1 increased monotonically with spatial period, a proportion of them in a speed-independent way (Chapman et al. 2002). Neuroimaging in humans revealed texture-selective activation of parietal opercular cortex and of visual areas in medial occipital cortex. Connectivity

analysis suggests information flow from non-selective S1 (areas 3b, 1) to haptically texture-selective parietal operculum and thence to bi-modally texture-selective early visual areas, where haptic information is integrated with visual texture information. This route corresponds to the ventral somatosensory pathway (Sathian 2016).

7.8.6 Discrimination and Recognition of Object Shape and Size

Tactile object discrimination and recognition require more than the discrimination of micro-geometric properties. The estimation of macro-geometric object properties, such as edge orientations and curvatures and size indices such as edge lengths, surface areas etc., is a complex process that involves the participation of cortical areas beyond the somatosensory cortices, mainly because proprioception plays an important part (Yau et al. 2016).

7.8.6.1 Sensitivity to Edge Orientation

Orientation discrimination thresholds at the fingertip are about 20°. Peripherally, both Merkel (SAI) and Meissner (RAI) afferents appear to be involved in orientation discrimination. In macaques, orientation selectivity is found in primary somatosensory cortex (S1), particularly in areas 3b, 1 and 2, and in parietal opercular cortex and posterior parietal cortex (PPC) areas. In humans, discrimination of grating orientation activates the anterior part of the →intraparietal sulcus (IPS) and the presumed homologue of macaque →area V6 (Sathian 2016). Functional magnetic resonance imaging (fMRI) indicates some hemispheric dominance for form or location discrimination. In a study in which subjects were asked to direct attention to the orientation of gratings applied to the index fingertips, the left intraparietal sulcus (IPS) was selectively activated independently of which hand was stimulated. Paying attention to the stimulus location selectively activated the right temporo-parietal junction (TPJ) (van Boven et al. 2005).

7.8.6.2 Sensitivity to Curvature

Object shape is determined to a large extent by the distribution of edge and surface curvatures. SAI afferents encode object curvature during static contact, while RA afferents contribute during dynamic contact phases. Macaque area 2 contains shape- and curvature-sensitive neurons, and its ablation causes deficits in form perception. Further haptic processing of shape primarily involves IPS and →lateral occipital complex (LOC) (Sathian 2016).

7.8.6.3 Object Metrics

Object size and shape can be estimated from passive touch of a single extended skin surface patch or from touches of multiple skin patches, which requires metric representations of patch size and configurations. In the latter case, signals from different patches must be integrated.

Object size can also be estimated from passive touches of skin patches on multiple fingers, for instance on thumb and index finger during a →precision grip. This estimation requires a metric representation of fingertip distance which is a function of joint angles and segment lengths. While joint angles can be determined by proprioceptive receptors, no sensory receptors are known to measure segment lengths (Longo et al. 2010). In any case, object-size determinations require the inter-modal cooperation of several sensory modalities. In this cooperation, proprioception plays an important role, explaining the co-existence of proprioceptive with cutaneous inputs in somatosensory cortices (Yau et al. 2016). The inter-modal cooperation is well illustrated by two experiments. Cutaneous anesthesia increases the perceived size of objects held between fingertips. In the Pinocchio illusion, manipulations of proprioceptive signals from an arm/hand holding onto the nose lead to a perceived size change of the nose, which testifies to the flexibility and modifiability of the body schema (Badde and Heed 2016; Longo et al. 2010).

In any one touch event, only distributed fractions of an object´s surface usually cover the skin. For a full appreciation of its size and shape, repeated contacts must be established. This is often done by exploratory motor acts (active touch). In any case, it requires temporal integration, at least →short-term memory (→working memory) or, in the case of familiar objects, →long-term memory.

It is not clear how metrics are implemented in the CNS. The somatotopic maps in the somatosensory cortex do not appear to be of much help because they are heavily distorted and may give rise to distortions of distance perception. For example, the perceived distance between two touch points increases from regions of low receptor density to regions of high receptor density. This →illusion is much smaller, however, than can be accounted for by differences in →tactile acuity and cortical magnification, which suggests that there must be further mechanisms of tactile size constancy probably involving a central representation (internal model) of body metrics (Longo et al. 2010; Serino and Haggard 2010).

7.8.7 Human Brain Imaging of Object Discrimination

Tactile shape processing and perception activate somatosensory cortices S1 and S2. In addition, a distributed network of parietal and frontal brain regions is coactivated, possibly by contributing →memory and executive functions (Yau et al. 2016).

Complex form-discrimination was investigated in a study using →positron emission tomography (PET) in conjunction with cytoarchitectural mapping, yielding insights into which brain areas are activated during right-hand tactile finger stimulation (Bodegård et al. 2001). Volunteers discriminated roughness, brush velocity, edge length, curvature and object shapes by passive and active touch. Somatosensory cortical areas 3b, 1 and 2 were activated by all stimuli. Area 2 was activated significantly more and preferentially by surface curvature changes and shape. In similar ways, passive and active shape discrimination, but not the other stimuli, activated the anterior supra-marginal gyrus (aSMG) and the cortex lining the intraparietal sulcus (IPS), in addition to areas 3a, 3b, 1, 2, and motor areas including the dorso-lateral premotor area (PMd), primary motor cortex (M1) and supplementary motor area (SMA), and right (ipsilateral) cerebellar regions. These results suggest that object shape is computed in a hierarchical fashion by areas 3b, 1,

2, intraparietal sulcus (IPS) and anterior →supra-marginal gyrus (Bodegård et al. 2001).

7.9 Spatial Relations to Body and External Space

Especially for perceptive and motor purposes, the spatial relations of tactile stimuli and objects must be evaluated in a wider context, namely relative to body posture and/or to external space. It has been proposed that three types of body representations are involved in this process: a *superficial schema*, mediating localization of touch on the body surface; a *model of body size and shape*; and a postural schema, an online and up-to-date proprioceptive representation of the limbs in space as well as an offline representation of the most plausible spatial locations for a given touch (Tamè et al. 2019). Therefore, for spatial tactile localization, other senses must cooperate, in particular proprioception, working in an intrinsic →frame of reference, and vision, operating in an extrinsic reference frame. If both (or more) senses are available, they cooperate in a weighted fashion, with the weighting depending on a number of circumstances and contexts, and the different reference frames requiring →coordinate transformations from a skin-based into an extrinsic frame. Much of this processing ocurs in the posterior parietal cortex (PPC) (Badde and Heed 2016; Medina and Coslett 2010, 2016).

Vection. In stationary observers, moving large-scale sensory stimuli (visual and auditory) can induce illusory sensations of self-motion (i.e. →vection) in the direction opposite of the sensory stimulation. Tactile stimulation rotating around the waist leads to self-reported circular vection in a subset of human subjects, on average experienced in the same direction as the tactile stimulation. Importantly, perceived rotatory self-motion correlates with →balance (i.e., postural sway velocity and the standard error of the mean in the medio-lateral dimension) (Tinga et al. 2018).

7.10 Cross-modal Interactions in Tactile Perception

Many perceptual tasks are executed by more than one sense. Most importantly, the exploration and recognition of objects often occurs in cooperation of touch, proprioception and vision, but also hearing may occasionally contribute (Sathian 2016).

Vision has strong enhancing effects on tactile perception. For instance, viewing the body parts stimulated by tactile stimuli shortens →reaction times and improves tactile acuity. These effects do not depend on vision providing any specific information about the stimulus and are not mere side-effects of spatial attention. It has been proposed that these effects are mediated by →top-down influences on the primary somatosensory cortex (S1) exerted by →multi-sensory cortical areas, where tactile, visual and other signals converge. This is supported by several experimental results. For example, visual enhancement of two-point discrimination is abolished when S1 is transiently disturbed by →transcranial magnetic stimulation (TMS). Also, later components of somatosensory →event-related potentials in S1 are enhanced by vision of the stimulated body site, in particular when the tactile stimulation is task-relevant (Serino and Haggard 2010). Furthermore, the mere sight of touch to another person´s arm can influence activity of areas involved in somatosensory processing such as S1, S2, inferior frontal cortex and parietal cortex, and somatosensory

perception can be activated without actual touch by →mental imagery as well as by the anticipation of touch. In tests made on a synesthetic subject who felt touch while just observing touch, the anterior insular cortex (AIC) was activated whereas this was not the case in normal non-synesthetic subjects, suggesting a role for the insula in body-ownership (Rolls 2010).

On the other hand, tactile tasks activate visual cortical areas. For example, the task to discriminate the orientation of gratings applied to the immobilized fingerpad activates a site in the region of the human area V6 complex, which is also active during visual discrimination of grating orientation (Sathian 2016). Similarly, tactile motion perception activates the human MT complex (hMT+, human homologue of macaque →area MT), which is also responsive to →visual motion and auditory motion (Sathian 2016). Neuroimaging and →electroencephalographic (EEG) studies indicate that tactile object discrimination is associated with early activation of the lateral occipital complex (LOC), which also has a role in visual object perception (Allen and Humphreys 2009; Sathian 2016).

Hearing also contributes to some aspects of tactile perception. For example, writing with chalk on a (rough) blackboard causes tactile and audible vibrations. When the ears are plugged, the blackboard feels smoother than without plugs (Hayward 2008). When we rub our hands against each other, the feeling of dryness or moistness arises primarily from friction forces on the epidermis, but altering the →sound arising from rubbing changes the perception of dryness/moistness (Hayward 2008; Hollins 2010). Vibrotactile frequency discrimination is impaired by simultaneously presenting auditory tone (or →noise band) in a similar frequency range, suggesting the existence of frequency channels that can be accessed by tactile and auditory signals (Hollins 2010).

7.11 Affective Touch

Touch can be pleasant, neutral or unpleasant. Pleasant (→affective, gentle, sensual) touch may be involved in →emotional, →motivational, →hormonal and affiliative responses to caress-like contact between humans and contributes to social interactions (Cascio et al. 2018; Ellingsen et al. 2016; Gallace and Spence 2010; Lechner and Lewin 2013; Olausson et al. 2010; Rolls 2010). It may also be →analgesic and anxiolytic. In →neuropathic pain, the analgesic effects appear to fail, which enhances tactile →allodynia (Liljencrantz and Olausson 2014). More generally, affective touch may turn into the opposite when other sensory cues disqualify the toucher as unpleasant or dangerous (Ellingsen et al. 2016).

There appears to be a dedicated system for pleasant touch (Lechner and Lewin 2013; Olausson et al. 2010; Rolls 2010). In humans, some un-myelinated afferents (group C or IV) from hairy (not glabrous) skin are mechano-sensitive and respond to light touch and gentle stroking. In patients with neuronopathy, who specifically lack group Aδ fibers, tactile stimulation, presumably mediated by C-tactile fibers, elicited only vague, pleasant and difficult to localize sensations. In these patients and normal control subjects, soft brush stimuli to the right arm and thigh elicited somatotopically ordered activation of the left (contralateral) posterior insular cortex (Björnsdotter et al. 2009; Liljencrantz and Olaussson 2014). In general, positively affective touch and temperature activate the posterior insular

region, →anterior cingulate cortex (ACC), →orbito-frontal cortex (OFC), posterior superior temporal sulcus (STS), medial prefrontal cortex (PFC), in addition to →brainstem regions including the →peri-aqueductal gray (PAG) (Liljencrantz and Olausson 2014; Rolls 2010).

Tickling, which may be pleasant, can activate several somatosensory brain areas (Rolls 2010). Affective touch can be modulated by →cognitive influences acting on the anterior →cingulate cortex (ACC), orbito-frontal cortex (OFC) and ventral striatum of the basal ganglia (Rolls 2010). Neuromodulatory influences on ascending pathways mediating affective touch include →opioids and →oxytocin (Ellingsen et al. 2016).

7.12 Plasticity of Sensory Maps and Receptive Fields

Research over the past several decades has shown that sensory structures are plastic both during →ontogenetic development and in adult life in response to differential sensory experience or to lesions, this plasticity depending on multiple cellular, synaptic and structural processes (Feldman 2009; Navarro et al. 2007; Medina and Coslett 2010, 2016; Qi et al. 2014; Sammons and Keck 2015). Like other cortical areas, both S1 and S2 receive inputs from neuromodulatory systems such as the cholinergic →basal forebrain system and the brainstem →locus coeruleus (LC) and →raphé nuclei, which may play a role in cortical plasticity.

The ontogenetic emergence of somato-sensory maps is not yet well understood. The problem is to explain how at some synaptic stage along a sensory pathway, different groups of afferent nerve fibers from different body regions are segregated appropriately so as to contact different groups of segregated postsynaptic target neurons in a topographical manner. There are indications that both genetic and environmental influences contribute to set up these topographically ordered connections.

Detailed cortical maps may develop prenatally in the absence of sensory experience (Kaas 1988). On the other hand, cortical maps appear to follow instructions from peripheral receptor sheets, which in part explains the distortions of the homunculus which are closely correlated with peripheral receptor density. During development, extensive use or lack of use of a sensory input may lead to over- or under-representation at cortical level, respectively, and this can alter the normal course of development such that the changes are difficult to reverse (Kaas 2009; Sammons and Keck 2015). One among the many underlying mechanisms is the *pruning* of thalamo-cortical afferents due to sensory experience. Peripheral sensory input may reduce arbor size and provide for a higher spatial resolution of representation. Even in adult life, CNS representations of the peripheral sensory sheet are malleable in response to lesions or over- or under-use. Such changes may lead to mis-localizations of tactile stimuli (Medina eand Coslett 2016).

Hebbian →synaptic plasticity (→Hebbian learning), a mechanism that increases synaptic efficacy when a presynaptic cell persistently stimulates a postsynaptic cell, may be involved in fine-tuning topographic projections. Another concept is that there is a *gross map* of connections from the sensory sheet onto central receptive cells laid down by genetic programs (von der Malsburg and Singer 1988). These gross mappings establish *constraints* on any further refinements based on sensory experience. Fine tuning of these

connections depends on sensory experience in line with the Hebbian concept. Stimuli impinging on the peripheral receptor sheet correlate the firings of neighboring receptors. Even if, initially, the afferents of these receptors distribute to many cells at the next level of sensory processing, synaptic weights are distributed unequally, usually with the strongest synaptic contacts being assembled in the center of the arborization. If this applies to afferents from many neighboring receptors whose firings are correlated, these `center´ synapses to postsynaptic neurons will be strengthened, while less efficient connections will be down-regulated or eliminated, leading to functional tailoring of topological projections.

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8

Peripheral Processing of Proprioception

CONTENTS

Abstract

• To plan, generate and control appropriate movements, the central nervous system (CNS) needs information from proprioceptors about environmental conditions such as gravity, loads and resistances, geometric body configuration, ongoing movements with inter-segmental interactions, and neuromuscular conditions such as skeletal muscle fatigue. The most relevant body variables to be monitored are joint angles, muscle lengths and forces, and skin distortions.

• Proprioceptors contribute to a variety of functions. Via their central projections and connections, they contribute to reflex activities in the spinal cord and brainstem, to coordinative activities of the cerebellum and forebrain, and to conscious perception of limb position and movement, muscle force or tension, effort, and, arguably, the sense of balance.

• *Muscle spindles* are sensory receptors within the body of a muscle that primarily detect changes in muscle length. They consist of specialized muscle fibers lying in parallel to skeletal muscle fibers. They receive motor innervation from motoneurons and sensory nerve fibers (group Ia and group II afferents). Group Ia and group II afferents respond differently to muscle stretch and contraction. Their responses are differentially modulated by two types of fusimotor motoneurons.

• *Golgi tendon organs* (GTOs) have sensory endings that are enclosed by a capsule**.** Their sensory terminal branches intertwine with strands of tendon fibers at the transition to muscle fibers. About 5 to 20 muscle fibers from different motor units insert into a tendon organ. The afferent sensory fibers (group Ib) of Golgi tendon organs respond sensitively to twitch contractions of single motor units.

• *Joint mechano-receptors* are found in joint capsules, as well as in ligaments, disks and menisci. The form of their sensory endings is used to classify them as Golgi tendon organ-like, Pacini corpuscles (also smaller paciniform endings) and Ruffini-like endings, the former being associated with group I and the latter two with group II afferents.

• *Golgi tendon organ-like endings* have high thresholds to mechanical stimuli, and are completely inactive in immobile joints.

• *Pacinian corpuscles* have a low threshold to mechanical stress, but adapt rapidly. They are therefore silent during static conditions and when the joint is rotated at constant speed, but are very sensitive to acceleration and deceleration during movement.

• *Ruffini endings* have a low threshold to mechanical strain and may signal static joint position as well as amplitude and velocity of joint rotations in different directions of joint rotation.

• Many group III and group IV afferents respond to mechanical stimuli of various sorts and influence central neurons at various levels.

• Proprioceptive afferents project to various levels of the CNS, from the spinal cord to cerebellum and cerebral cortex.

8.1 Introduction

To plan, generate and safeguard appropriate limb and body movements, the →central nervous system (CNS) needs information from proprioceptors, the →sensory receptors located in →skeletal muscles, joint capsules and surrounding tissues as well as skin, that signal information to the CNS about position and movement of body parts (McCloskey and Prochazka 1994). Proprioceptors convey information about pertinent environmental conditions such as →gravity, loads and resistances, geometric body configuration, ongoing movements with inter-segmental interactions, and neuromuscular conditions such as →muscle fatigue

The most relevant body variables that need to be monitored by proprioceptors are joint angles, muscle lengths and forces, and skin distortion.

Joint Angles and Segment Lengths. Joint angles co-determine body configurations. The most direct sensory access to joint angles is provided by joint receptors and possibly ligament receptors. However, joint angles alone do not determine the position of a limb endpoint in space. What also needs to be measured in order to determine the position of a limb in space is limb segment length, which is estimated indirectly, because there are no direct physiological sensors for this variable (Serino and Haggard 2010).

Muscle Lengths. Since joint angles are co-determined by the actions ofs crossing them, sets of lengths give indirect information about joint angles, and these muscle lengths can be measured by muscle spindles. Although a number of challenges are presented by this indirect way of joint-angle measurement, muscle spindles have a prominent role in the awareness of body part position and movement (kinesthesia).

Muscle Forces. In association with load →torques, muscle forces determine joint torques and angles, and are signaled by Golgi tendon organs (GTOs).

Skin Distortions. Joint positions and movements cause skin distortions, which are detected by cutaneous mechano-receptors, whose responses could contribute to kinesthesia.

Proprioceptors encompass a fairly wide group of different →mechano-receptors and contribute to a variety of functions. The receptors contribute to →reflex activities at →spinal cord and →brainstem levels. Muscle spindles and Golgi tendon organs are also implicated in the maintenance of spine alignment and in realignment of fractured bones (Blecher et al. 2018). In addition, proprioceptors contribute to coordinative activities of the →cerebellum and →forebrain and to conscious →perception of limb position and movement, the sense of muscle force or tension, the sense of effort and, possibly, the sense of →balance. `Proprioception´ is often used interchangeably with kinesthesia, although in the strict sense kinesthesia means sense of movement while proprioception has a wider meaning.

8.2 Muscle Spindles

Muscle spindles are sensory mechano-receptors that lie in parallel with skeletal →muscle fibers. They are among the most complicated sensory receptors in mammals (Banks 2005; Banks et al. 2009; Bewick and Banks 2015). The human body contains about 25,000-30,000 muscle spindles, 4,000 in each arm and 7,000 in each leg (Prochazka 1996).

Large populations of muscle spindles are located in many but not all skeletal muscles (Botterman et al. 1978; Voss 1971; Holt et al. 2002). The intercostal muscles contain relatively large numbers of muscle spindles, whereas the diaphragm, digastric muscles, extraocular muscles in some species and the intrinsic laryngeal muscles contain very few or none. The neck muscles have very high densities of spindles that occur in complex arrays of 2-12 spindles, arranged in parallel or tandem, or in association with Golgi tendon organs (GTOs) (Bakker and Richmond 1982). In general, the number of spindles per muscle increases with muscle weight according to a power law (Banks 2006; Kokkorogiannis 2004).

Muscle spindle density may vary from muscle to muscle perhaps as a function of muscle type and task. In mixed muscles, the density of spindles tends to be higher in deep regions that often have a higher density of oxidative muscle fibers of slow twitch contraction (Banks et al. 2009; Kokkorogiannis 2004; Windhorst et al. 1989). Also, muscles involved in fine movements, for example, small muscles of the distal extremities, have notably higher numbers of muscle spindles (Botterman et al. 1978).

8.2.1 Intrafusal Muscle Fibers

A muscle spindle is composed of specialized striated muscle fibers, which in their middle part are surrounded by a spindle-shaped capsule. The number of these →intrafusal muscle fibers per spindle varies widely within individual muscles, between different muscles in a species and between species. Intrafusal fibers are attached at both ends via connective tissue to skeletal muscle fibers. There are two types of intrafusal fibers; →chain fibers and →bag fibers of two subtypes, bag_1 and bag_2, which differ in diameter. On average, a spindle has one or occasionally two bag_1 fibers, one bag_2 fiber and 3-5 chain fibers.

Chain Fibers are rapidly contracting →twitch fibers, with fusion frequencies beyond 100 pulses per second (Taylor et al. 1999).

Bag_1 Fibers contract slowly and weakly during repetitive activation, tend to stiffen rather than shorten and do not produce propagated →action potentials (Taylor et al. 1999).

Bag_2 Fibers have properties intermediate between chain and bag_1 fibers. They shorten substantially and more rapidly than bag_1 fibers, their fusion frequency being about 30 pulses per second (Taylor et al. 1999).

8.2.2 Motor Innervation of Intrafusal Muscle Fibers

Intrafusal muscle fibers are differentially innervated by motor axons that originate from several types of fusimotor neurons. Their actions have different influences on the discharge patterns of muscle spindle afferents. They are classified as dynamic or static, depending on the type of intrafusal fibers they innervate, and their respective effects on group Ia and group II afferent neurons that innervate the central part of the muscle spindle (Banks 2005; Boyd; Hulliger 1984; Taylor et al. 1999).

Dynamic →β-motoneurons or dynamic →γ-motoneurons preferentially innervate bag_1 muscle fibers, and sometimes bag_2 and chain fibers. They increase the stretch-sensitivity of the group Ia afferents by stiffening the bag_1 intrafusal fibers.

Static β- or γ-motoneurons contact bag_2 or chain fibers separately or together. They increase the firing rate of group Ia and group II afferents at a given muscle length.

8.2.3 Sensory Innervation of Intrafusal Muscle Fibers

Group Ia and group II afferent fibers connect to muscle spindles, with characteristic patterns of innervation.

Each muscle spindle is innervated by a group Ia afferent of large diameter (in cats: 12-20 μm corresponding to a conduction velocity of 72-120 m/s). Its primary sensory endings wrap around the central regions of intrafusal muscle fibers, forming annulo-spirals, which are extended upon lengthening of the sensory region. About 25-30% of group Ia afferents do not contact bag_1 fibers (Taylor et al. 1999).

A muscle spindle may be innervated by 0-4 group II afferents of smaller diameter than group Ia fibers (5-12 μm corresponding to a conduction velocity of 30-72 m/s). The secondary sensory endings of group II afferents form annulo-spirals around intrafusal chain fibers and flower-spray endings at bag_2 fibers, but rarely innervate dynamic bag_1 fibers (Taylor et al. 1999).

8.2.4 Mechano-sensory Transduction

Muscle spindles have traditionally been considered stretch receptors because they are excited by muscle stretch, but they also respond to shortening. The sequence of events in passive spindles leading to their excitation is as follows (Bewick and Banks 2015):

Muscle stretch → stretch of intrafusal muscle fibers → deformation of sensory endings → opening of stretch-sensitive →ion channels, →depolarizing →receptor potential → electrotonic spread of receptor potential to site of action-potential generator.

In the mammalian primary sensory ending, the current underlying the receptor potential is carried to about 80% by an inward sodium (Na^+) current and to about 20% by an inward

calcium (Ca^{2+}) current, followed by an outward potassium (K^{+}) current leading to a receptor-potential undershoot after cessation of stretch. The contributing mechanically sensitive ion channels have not been definitely identified but there are some candidates. There is evidence that the Na^{+} current flows through members of the →epithelial $Na^{\pm}$ channel (ENaC) and/or →acid-sensing ion channel (ASIC) families. The Ca^{2+} current appears to flow through ASIC members and/or voltage-gated Ca^{2+} channels and may involve →transient receptor potential (TRP) channels (Bewick and Banks 2015, 2021). In contrast, piezo2 has been claimed to be the main mechano-transducer in mouse proprioceptors, and its deletion in knock-out mice causes impairment of stretch-activated discharge in muscle afferents and of coordination in all limbs. Note that Piezo2 is a mechanically activated non-selective cation channel that is expressed in sensory endings of muscle spindles and Golgi tendon organs (Anderson et al. 2017; Woo et al. 2015).

As all vertebrate primary mechano-sensory nerve terminals, primary muscle endings contain small clear →synaptic-like vesicles that release →glutamate during stretch in a Ca^{2+}-dependent manner, the glutamate in turn activating an unusual →glutamate receptor. This glutamate system maintains and increases spindle responsiveness in a positive feedback manner (Bewick 2015; Bewick and Banks 2015).

8.2.5 Spindle Afferent Responses to Changes in Muscle Length

Group Ia and group II afferents from mammalian muscle spindles respond differently to muscle stretch and contraction. Passive muscle spindles, without fusimotor activation, show characteristic responses to repetitive ramp-and-hold muscle stretches (Hulliger 1984; Prochazka 1996).

During ramp-and-hold stretches, particularly group Ia afferents show a sequence of discharge components. During the ramp phase, the initial acceleration is associated with an initial discharge →burst and the subsequent constant-velocity lengthening with an elevated firing rate. This is followed by discharge adaptation during constant-length phase. The first two response components have often been interpreted as acceleration and velocity responses (Schäfer and Schäfer 1969; Schäfer 1973; Windhorst and Schmidt 1976). However, they depend on the pre-stretch condition of the muscle and are well expressed only after the passive muscle has been held at constant length for some time. Indeed, the group Ia discharge components are more closely correlated with respective force-related variables than with length-related variables, such that linear combinations of force (F) and the first time derivative of force (dF/dt) predict the entire time course of group Ia discharge during stretch (Blum et al. 2017).

Static responses of muscle spindle afferents often increase with an approximately linear discharge pattern with muscle extension, and sometimes curvi-linearly, depending on the spindle location in the muscle (Meyer-Lohmann et al. 1974).

Responses of spindle afferents in general exhibit non-linear →sensitivity to changes in muscle length and velocity and to modulation by fusimotor efferents. Group II afferents have lower sensitivity to changes in muscle displacement and velocity, while group Ia afferents exhibit the highest sensitivity to velocity. These generalizations seem to apply to

a variety of non-human species (Prochazka 1996), and also to humans although their mean firing rates (~10 pulse per seconds) are on average lower than in cats and the effects of fusimotor neurons on human muscle spindles are more modest compared with the cat (Macefield and Knellwolf 2018).

8.2.6 Spindle Afferent Responses to Sinusoidal Changes in Muscle Length

Spindle group Ia afferents are much more sensitive to small- than to large-amplitude muscle stretches, including those produced during high-frequency muscle vibration or tendon vibration.

Frequency Dependence. For both group Ia and group II afferents, the degree of discharge modulation is dependent on stretch frequency. At all frequencies, the sensitivity of primary spindle afferents is much greater than that of secondary afferents. The sensitivity change as a function of frequency is similar for either type, since the primary and secondary spindle afferent curves are practically identical if superimposed. At frequencies greater than 1 cycle/sec, sensitivity to sinusoidal stretch increased dramatically, reflecting high responsiveness to stretch velocity. The upward deviation of group Ia sensitivity beyond about 10 cycles/sec attests to an additional sensitivity for →acceleration. Similar response properties are shown by human muscle spindles (Kakuda 2000; Macefield and Knellwolf 2018).

Amplitude Dependence. Varying stretch amplitude at a constant modulation frequency of 1 Hz reveals a striking non-linearity in group Ia fibers, with an extremely high sensitivity at low amplitudes, that then declined drastically at higher amplitudes (Matthews and Stein 1969). This property, referred to as compression non-linearity, might permit group Ia afferents to detect small muscle length changes during movement (Hulliger 1984). By contrast, the secondary endings, which discharge when muscle is static and thus functionally provide position sense in a still muscle, exhibit low, constant sensitivity across the whole amplitude range.

8.2.7 Effects of Fusimotor Activation

→ß-Motoneurons exert effects on both skeletal and intrafusal muscle fibers, and thus may increase fusimotor activity in parallel with increases in extrafusal muscle activity so that intrafusal fiber properties are matched to the muscle and its load (Grill and Rymer 1987). γ-Motoneurons exert exclusive effects on intrafusal muscle fibers. Static γ-motoneurons are continuously active during movements such as locomotion, and dynamic γ-motoneurons increase group Ia stretch-sensitivity.

Dynamic Fusimotor Activation dramatically increases group Ia afferent responses during large-amplitude ramp stretch, through three possible effects: It stiffens the contractile poles of bag_1 intrafusal muscle fibers, it increases the pre-stretch spontaneous firing or the later static discharge and it can sustain group Ia afferent firing during muscle shortening (Morgan et al. 1985).

Dynamic fusimotor stimulation does not substantially alter the frequency response of group Ia afferents to small-amplitude sinusoidal length changes, and it usually has little effect on spindle group II afferents. Dynamic γ-motoneurons do increase muscle spindle sensitivity and they elevate spindle discharge in response to rate of change of muscle length during activities that require fast changes in muscle length.

Static Fusimotor Activation causes contraction of bag_2 and/or chain fibers, usually concurrently. The contraction greatly increases the pre-stretch spontaneous or later static discharge of both of group Ia and II afferents during large-amplitude ramp stretches. Static fusimotor activation, therefore, produces a substantial background bias to muscle spindle discharge.

In contrast to dynamic fibers, static fusimotor fibers usually reduce the dynamic responses of group Ia afferents to large-amplitude ramp stretches, as well as the frequency response to small-amplitude sinusoidal length changes. They also down-regulate the frequency response of group II afferents, and sustain group Ia afferent discharges during large-amplitude muscle shortening. Static γ-motoneurons are mostly used in the maintenance of postures and slower movements such as lifting.

After-effects of Fusimotor Activation. After activation of fusimotor fibers, mammalian muscle may show after-effects such as limb position-sense errors, muscle spasms, cramping and fatigue. Intrafusal after-effects may develop spontaneously when the muscle is held at constant length for some time and are influenced by fusimotor activation. The after-effects appear to result from residual changes in the intrafusal fibers themselves, which seem to involve a persistent increase in the number of cross-bridges between myosin and actin filaments, rendering the fiber or a portion of it less compliant and augmenting the effect of stretch on the sensory terminals (Emonet-Dénand et al. 1985). The effect is removed by large stretch, which exceeds the short-range →elasticity of cross-bridges.

The history of preceding muscle length changes and cross-bridge formation has consequences for muscle spindle responses and kinesthesia. If a muscle with its muscle spindles are stretched and then returned to the original test length, muscle fibers slacken and the spindle afferents discharge at a slower rate. If muscle fibers are caused to shorten and then allowed to return to test length, spindle afferents discharge at high rate. Muscle spindle discharge thus shows no precise and unique relation to muscle length. The lack of precision affects sense of limb position (Proske and Gandevia 2012).

8.2.8 Sensory and Descending Modulation of Fusimotor Activity

Fusimotor activity is changed and modulated in complex ways by many spinal sensory afferents of different kinds and by influences descending from various supraspinal sources. These influences in part diverge from those exerted on →α-motoneurons so that the activity patterns of both classes of motoneuron are not always closely coupled during motor acts (Hulliger1984; Prochazka 1996; Windhorst 1988).

8.2.9 Sympathetic Modulation of Muscle Spindle Discharge

Physiological studies performed on jaw elevator muscles in the rabbit show that →sympathetic activation modulates the resting discharge and sensitivity of muscle spindle afferents. The effects on resting discharge of spindle afferents are variable. Group Ia discharges are generally increased and group II discharges are decreased. Stimulation of the sympathetic supply to the muscles decreases sensitivity of spindle afferents to changes in muscle length (Roatta et al. 2002). Consequently, any condition which enhances sympathetic outflow to skeletal muscles, such as physical exercise and other →stress, should depress the sensitivity of spindle afferents to muscle length changes. An example of sympathetically mediated down-modulation of spindle feedback is the →fight-or-flight reaction. In this instance, precision and fine control of movements are momentarily compromised and replaced with a state of →arousal that increases blood pressure, blood sugar, and available →energy supply to skeletal muscle in preparation for potentially violent muscular actions.

8.2.10 Summary of Muscle Spindle Responses to Muscle Contraction

Because skeletal muscles are composed of contractile elements arranged in series with elastic elements (tendons or aponeuroses), even muscles kept isometric will shorten internally upon contraction, as will muscle spindles arranged in parallel with the contractile elements (Cronin et al. 2011). Provided the spindles discharge prior to contraction, they reduce their rate during contraction of the whole muscle, the muscle compartments and the individual →motor units.

The degree of discharge modulation during contraction of a single motor unit depends on the unit´s contractile strength and its location relative to the spindle (Cameron et al. 1981; Schwestka et al. 1981). The differentiated mechanical coupling between motor units and spindles has led to the concept of `sensory partitioning´, suggesting that intramuscular space is scanned differentially by sub-groups of muscle spindles or Golgi tendon organs (GTOs).

8.3 Golgi Tendon Organs

Golgi tendon organs (GTOs) are found in skeletal muscles in greatly varying numbers. Some intrinsic hand muscles with many muscle spindles are devoid of GTOs (Banks et al. 2009; Jami 1992; Prochazka 1996). In small muscles in general, GTO content is considerably variable. The reason is not immediately evident, given the importance of GTOs to proprioception and motor control (Houk and Henneman 1967). Nonetheless one suggestion (Jami 1992) is that muscle, joint and even skin receptors can compensate for absent or sparse afferent input to the CNS from GTOs.

8.3.1 Anatomy

Golgi tendon organs are structurally much less complicated than muscle spindles. The terminal branches of their sensory endings intertwine with strands of tendon fibers just at the transition to muscle fibers (→myotendinous junction). Golgi tendon organs are found not only at the main tendons, but also at insertions of muscle fibers with aponeuroses and deep tendinous sheets (Jami 1992). About 5 to 20 muscle fibers insert into a GTO. The GTOs sensory endings are encapsulated as well. The afferent fiber size falls into group Ib, so named to distinguish it from group Ia fibers. As noted above, GTO sensory terminals also express Piezo2 as →transduction channels (Woo et al. 2015).

8.3.2 Response Characteristics of Golgi Tendon Organs

Whenever the tendinous fibers running through the capsule of a tendon organ are stretched, the GTO´s Ib afferent is excited. This happens under two conditions: muscle stretch and contraction. Tendon organs were originally thought to be muscle stretch receptors, until it was realized that they are much more sensitive to the active force produced by muscle contraction and even contraction of individual motor units (e.g., Binder et al. 1977; Jami 1992). Hence, tendon organs are primarily active-force receptors, rather than stretch receptors. Active GTOs may also be unloaded by contractions of muscle fibers that by-pass the organ (Jami 1992; Mileusnic and Loeb 2006).

It has also been suggested that GTOs are able to monitor muscle damage resulting from repeated eccentric contractions. Such contractions cause an increase in passive muscle tension and GTO discharge (Gregory et al. 2003).

8.4 Joint and Ligament Receptors

Joint and ligament afferents also play roles in the perception of joint position and movement, and contribute to the coordination of posture and movement. They probably contribute to joint →stiffness and the functional joint stability. The receptors have distinguishing anatomical properties and distinct locations.

8.4.1 Anatomy

Joint mechano-receptors vary in both their location and anatomical shape. They are found in joint capsules and in internal joint structures such as ligaments, disks and menisci. The form of their sensory endings is used to classify them as Golgi tendon organ-like, Pacini corpuscles (also smaller paciniform endings) and Ruffini-like endings, the former being associated with group I and the latter two with group II afferents (Skoglund 1956; Gandevia 1996; Sjölander and Johansson 1997). Moreover, there are numerous free nerve endings with afferents in group III and group IV.

8.4.2 Response Characteristics

Joint afferents have a low →threshold to mechanical strain. These endings may signal static joint position as well as amplitude and velocity of joint rotations in different directions of joint rotation. Receptors that are tonically active at intermediate joint angles are found in several joints, e.g., the cat knee joint and the human toe joint. It has been suggested that these `mid-range´ afferents provide information on joint angles and/or limb movements, and it is likely that many of them arise from Ruffini-like endings (Macefield 2009). Golgi tendon organ-like endings have high thresholds to mechanical stimuli, and are completely inactive in immobile joints. Because of their high thresholds, these receptors have been suggested to measure the extremes of the joint´s normal movement range. Indeed, the majority of slowly →adapting joint afferents discharge near the extremes of joint movement, and respond to stresses in more than one axis of joint movement (Proske and Gandevia 2012; Sjölander and Johansson 1997). Paciniform endings have a low threshold to mechanical stress, but adapt rapidly. They are therefore silent during static conditions and when the joint is rotated at constant speed, but are very sensitive to acceleration and deceleration during movement (Sjölander and Johansson 1997).

8.5 Group III and IV Afferents

Group III and IV afferents are usually not listed under proprioceptors. But their roles in spinal motor control are underestimated although they are partly sensitive to mechanical stimuli and influence many neurons at spinal and higher levels.

Group III muscle afferents are more mechano-sensitive than group IV afferents during skeletal muscle contraction, force production, dynamic/static muscle stretch and local intramuscular pressure. Their response to a mechanical stimulus may be potentiated by chemical stimuli. Muscle group IV afferents are more sensitive to metabolites released into the interstitium by muscle activity because their activation usually starts after a delay during prolonged muscle contraction and continues to discharge until the withdrawal of muscle metabolites (Laurin et al. 2015). Among group III and IV muscle afferents are →nociceptive afferents which contribute to muscle pain (Mense 1993). Group III and IV afferents are also excited by muscle fatigue and contribute to its central regulation at various levels (Gandevia 2001; Taylor et al. 2016).

8.6 Central Projections of Proprioceptors

Proprioceptive afferents project to various levels of the CNS, from spinal cord to cerebellum and →cerebral cortex.

8.6.1 Spinal Projections of Proprioceptive Afferents

The projection patterns of cutaneous mechano-receptor afferents and deep mechano-receptor afferents are similar in some respects but differ in others. For example, there is the same gross →somatotopic pattern in that afferents from the legs project to the lumbo-sacral spinal cord and afferents from the arms to the cervical spinal cord, etc. Within the spinal cord, the projection patterns differ substantially.

Muscle spindle group Ia and II afferents and GTO group Ib afferents send collaterals to more ventral regions of the spinal →gray matter. Muscle spindle afferents reach lamina IX, where they contact →skeleto-motoneurons monosynaptically (for the development of this monosynaptic circuit see Imai and Yoshida 2018). They also reach other areas, where they synapse on →interneurons. Group Ib afferents from GTOs mediate effects on spinal motoneurons via interneurons and terminate in more dorsal laminae, in particular lamina VI. Joint afferents project widely in the spinal cord to produce reflex effects on many neurons, including skeleto- and fusimotoneurons.

8.6.2 Spino-cerebellar Projections of Proprioceptive Afferents

Signals from proprioceptors are relayed over several pathways to supraspinal structures. The cerebellum is heavily involved in motor control and several non-motor functions. In the cat, the cerebellum receives proprioceptive signals from the hindlimbs and lower trunk via the →dorsal spino-cerebellar tract (DSCT), the →ventral spinocerebellar tract (VSCT), and indirectly via spino-reticulo-cerebellar pathways, as well as through at least two olivo-cerebellar pathways (Bosco and Poppele 2001; Brodal 1981; Jami 1992).

8.6.3 Cerebro-cortical Projections of Proprioceptive Afferents

For the perception of body configuration and for cortical motor control, proprioceptive information reaches, via several ascending pathways, contralateral somatosensory area 3a, area 3b, area 1, area 2 and the →primary motor cortex (M1, area 4) (Naito et al. 2016; Proske and Gandevia 2012). Proprioceptive and cutaneous signals converge on neurons in areas 3a and 3b (Kim et al. 2015). Signal transmission from joint receptors to supraspinal structures appears to be powerful and could be the basis for the involvement of joint receptors in proprioception (Sjölander and Johansson 1997).

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9

Kinesthesia:

Integration in the Nervous System

CONTENTS

Abstract

• Kinesthesia, or kinesthetic sense, strictly means movement sense, but has also been used to refer either to proprioception alone or to the brain`s integration of proprioceptive and vestibular inputs.

• Kinesthesia is encoded and interpreted in the central nervous system (CNS) based on afferent signals from skeletal muscle, skin, joint and cutaneous proprioceptors. Motor commands generated within the CNS contribute to kinesthesia as well.

• High-frequency vibration of a muscle or tendon in a stationary limb induces powerful illusions of changed joint position and movement, suggesting that signals from muscle spindle group Ia afferents play an important role in movement sensations. The illusory movement perception induced by muscle-tendon vibration is associated with activation of widespread cerebro-cortical regions.

• In humans, trajectory information related to passive joint movements is encoded in the discharge patterns of ensembles of receptors belonging to all the muscles acting on a given joint. Ensembles of muscle spindle afferents encode the directions of active as well as passive movements of the wrist and the instantaneous trajectory of movement.

• The roles of joint receptors in kinesthesia are not yet firmly established. The interpretation of joint-receptor activity by the CNS is compromised because this activity is influenced by muscle contractions. One possibility is that activation of joint receptors by muscle contraction enables joint receptors to play a greater role in kinesthesia during active rather than passive movements.

• Cutaneous mechano-receptors excited by skin stretch provide information concerning underlying joint and muscle movements. One role may be to cooperate with other proprioceptors in making proprioceptive information more specific and localized. Cutaneous group IV afferents, for example, are sensitive to non-noxious mechanical stimuli and could thus contribute to kinesthesia, particularly after large-fiber sensory neuropathy.

• Sense of muscle force, sense of effort and sense of object heaviness are assumed to be distinct, partly generated by efference copies of motor commands and partly by sensory receptors including Golgi tendon organs, muscle spindles and pressure-sensitive cutaneous receptors.

• The combined activity of afferents of different modality may generate representations of global body geometry such as limb axis orientation, length and and loading, which may contribute to motor control and body schemata.

• Body schemata are flexible neural representations that relate position and movement of body parts to each other and to the external world.

9.1 Introduction

The sense of body position and movement reveals its importance for everyday life once it has been lost, this loss leaving the patient with a complete inability to coordinate his movements (Tuthill and Azim 2018).

Kinesthesia, the awareness of position and movement of body parts (Proske and Gandevia 2018), utilizes signals from →skeletal muscle, skin, joint and cutaneous proprioceptors, and →motor commands contribute to kinesthesia as well (Gandevia et al. 2006; Smith et al. 2009). It now appears that joint and cutaneous mechano-receptors contribute in particular to movement sense (Taylor 2009), while slowly →adapting cutaneous and muscle receptors appear to be required for position sense (Proske et al. 2000; Proske and Gandevia 2012).

The contribution of different sensory sub-modalities to kinesthesia is supported by the following experiment. When all types of proprioceptive afferent are fully intact and functioning, →thresholds for movement detection in the distal interphalangeal joint of the human middle finger are lowest. Detection of joint movements is impaired by digital anesthesia and by disengagement of the muscles caused by middle finger flexure at the proximal interphalangeal joint (Gandevia et al. 1983). In general, humans detect faster movements more easily than slower movements at all joints, and detect smaller velocity differences at slower mean velocities (Proske and Gandevia 2012; Taylor 2009).

9.2 Role of Muscle Spindles in Kinesthesia

Muscle spindle group Ia afferents are highly sensitive to small-amplitude, high-frequency length changes. Muscle vibration or tendon vibration with appropriately chosen parameters can drive group Ia afferent discharge at the vibration frequency. A large body of experimental evidence has established a critical role of muscle spindles in kinesthesia, even when their positions, multiple inputs and response properties make it complicated for the →central nervous system (CNS) to extract pure kinesthetic signals. Under certain circumstances, bodily →perception and egocentric frames of reference associated with muscle spindle activation can be misinterpreted, i.e., be illusory. Factors such as vibration frequency and →gravitational force can evoke illusory kinesthetic signals (Proske and Gandevia 2018).

Limb Position and Movement Illusions. In humans, high-frequency vibration of a muscle or tendon in a stationary limb induces powerful →illusions of changed joint position and movement. The illusions suggest that signals from muscle spindle group Ia afferents play an important role in movement sensations. The magnitude of the induced illusion depends on the amplitude and frequency of vibration, while the perceived movement velocity is to some extent correlated with the vibration frequency (Proske and Gandevia 2012; Taylor 2009). When an agonist muscle and an antagonist muscle are vibrated together, there must be a difference in vibration frequencies to generate an illusion, and the velocity of the illusion depends on this difference (Gilhodes et al. 1986). This is in line with discharge patterns of muscle spindle afferents during repetitive voluntary contractions. That is, the direction of a slow movement is specified by discharge rate, which is greater in the extending than in the shortening muscle, while the velocity of movement is indicated by

the difference in discharge rates originating from the agonist-antagonist muscles (Ribot-Ciscar and Roll 1998). Similar movement illusions can occur when an exposed tendon is pulled in a stationary limb**,** or when group Ia afferents of the ulnar nerve are electrically stimulated (Matthews 1988). As to be expected, vibration-induced muscle spindle excitation also disturbs motor tasks that depend on knowledge of the joint angle (Gandevia 1996).

Impact of Gravity. The →intensity of vibration-induced illusions is affected by changes in →gravitational load. Illusory arm movements are enhanced by 1.8 g conditions, but diminished in →micro-gravity. Under the latter conditions, unloading of the otoliths might reduce the vestibulo-spinal drive to →α-motoneuron and →γ-motoneurons, while increased gravitational load might make the arm feel heavier**,** as if producing enhanced resistance. Under 1.8 g, an individual making deep knee bends perceives downward movement as too fast, and the support surface moving upward against the feet, and vice versa for upward movement. Weightlessness also appears to alter the interpretation of proprioceptive messages (Lackner and DiZio 2009; Reschke et al. 1998).

Body Orientation. In addition to causing illusions of limb movements, muscle/tendon vibration also disturbs the sense of body orientation relative to the vertical. When the Achilles tendons in a restrained blindfolded subject were vibrated, the subject perceived a forward body tilt, and some subjects even felt continuous 360° pitch rotation of the body. These subjects also exhibited compensatory →nystagmus, very much like that occurring during real pitch rotation of the body (Lackner and DiZio 2000).

Propriogyral Illusions. Vibrating postural muscles of subjects standing in the dark can elicit illusions of visual target motion and of continuous body tilt and rotation. When vibration is applied to neck muscles, a small visual fixation target in a dark room is perceived as moving in like direction and velocity as the illusory body motion, which combination has been dubbed propriogyral illusion (Lackner and Levine 1979). It appears to be secondary to the eye movements induced by the vibration, presumably mediated via the cervico-ocular reflex (Popov et al. 1999).

Supraspinal Networks Involved in Kinesthetic Illusions. Illusory movement →perception induced by muscle-tendon vibration is associated with activation of widespread cerebro-cortical regions, the →basal ganglia and the →cerebellum. Vision, on the other hand, is able to suppress vibration-evoked illusions (Naito et al. 2016).

9.2.1 Coding of Joint Position in Passive Limbs by Muscle Spindles

During passive wrist-angle changes, human muscle spindles from wrist extensor muscles signal joint position by their →steady-state (hold) discharge rate and by two dynamic response components: the initial →burst and stretch responses, both of which are position-dependent. The recruitment thresholds of different afferents are distributed over the entire joint angle range of 110°, but individual afferents change their firing rates over limited ranges of roughly 15° only. The differences between individual spindles can probably be accounted for by the locations of spindles in different muscle regions exhibiting different extrafusal mechanical properties (Meyer-Lohmann et al. 1974). The representation of the whole range seems to require responses from populations of spindle

afferents with different recruitment thresholds and operative ranges, because the summed activity of the entire population of afferents is monotonically related to joint position (Cordo et al. 2002).

9.2.2 Joint-movement Detection in Passive Limbs

Even before direction is established, joint movements can be detected. Thresholds for joint movement show a large inter-individual variability linked to velocity and muscle history (Proske et al. 2000).

Velocity Dependence of Movement Thresholds. Thresholds for passive limb movement detection depend on velocity. Threshold minima are about 0.1° between 2 and 80°/s for human elbow and shoulder joints and about 0.8° between 20 and 80°/s for the finger distal interphalangeal (DIP) joint. For lower velocities, thresholds rise steeply (Hall and McCloskey 1983). Velocity dependence could in part be due to spindle response characteristics. When stretch velocities fall, so do the velocity components in group Ia afferents, and at very slow velocities they can subside completely, leaving a position-related response (Proske et al. 2000). The differences in movement detection thresholds at different joints may result from differences in the way fascicle lengths change in different muscles. When detection thresholds are expressed in terms of length change of muscle-fascicles, differences in proprioceptive acuity are not evident (Hall and McCloskey 1983). This provides another argument for major involvement of muscle spindles that measure changes in local →extrafusal muscle fiber lengths (Meyer-Lohmann et al. 1974; Proske et al. 2000; Windhorst et al. 1989).

Muscle History. →Thixotropy, the history-dependent →visco-elastic behavior of →muscle fibers, alters muscle mechanical properties following length changes or activation (Lakie and Campbell 2019). Thixotropy appears to affect →intrafusal muscle fibers more strongly than extrafusal fibers, and changes position and movement sense. When, for example, the human elbow joint is stiffened by co-contraction at 60°, movement detection thresholds subsequently determined at 90° are lower for extension than for flexion because flexor spindles are taut while extensor spindles are slack. Conversely, if the elbow joint is first stiffened by co-contraction at 120°, movement thresholds subsequently determined at 90° are higher for extension than for flexion because flexor spindles are slack while extensor spindles are taut. Thus, movement detection thresholds depend on the previous history of muscle contractions and length changes (Proske et al. 2000; Proske and Gandevia 2012).

9.2.3 Coding of Joint Movements in Passive Limbs by Muscle Spindles

Passively imposed, multi-directional ankle-joint movements in humans affect the activity of muscle spindle afferents originating in various muscles. For example, one study (Bergenheim at al. 2000) showed that spindle afferents from an ankle muscle during passive movements have different →preferred directions, as well as preferred locational sectors within which they generate sensory information. Spindle group Ia afferents from

one muscle never discharged throughout the whole trajectory. By contrast, all group II afferents discharged throughout most of the trajectory.

Several conclusions can be drawn from the Bergenheim experimental design and from other studies. First, trajectory information appears to be encoded in the discharge patterns of ensembles of receptors belonging to all the muscles acting on a given joint (Roll et al. 2000). Second, discrimination of different movement velocities depends on populations of afferents (Ribot-Ciscar et al. 2002). Third, the discharge patterns of spindle afferents recorded in response to imposed ankle and wrist movements can be used to drive multiple tendon vibrators to elicit illusions of the same movements (Roll et al. 2009). Fourth, and in line with the results of passive ankle movements, ensembles of human spindle afferents encode the directions of active as well as passive movements and the instantaneous trajectory of movement (Jones et al. 2001; Roll et al. 2009).

The code used is an ensemble code or population code. Paying →attention to different movement parameters (e.g., velocity or end position) elicits different patterns of fusimotor drive to muscle spindles suggesting that muscle spindle feedback is adjusted to the task requirements (Ribot-Ciscar et al. 2009). Group Ia afferent firing is also modulated by →emotions, i.e., increased by sad emotions evoked by particular music (Ackerly et al. 2017).

9.2.4 Joint-Angle Signaling during Active Movements

Passive joint movements are the exception rather than the rule. Most often, joint movements are associated with muscle contractions. In active muscles, spindles are not only affected by extrafusal contraction, but usually also receive fusimotor excitation. This combination of inputs to spindles presents a challenge to the CNS for the interpretation of signals from muscle spindles.

During precision finger movements associated with joint angle and muscle length changes, the discharge of human group Ia afferents that track a trapezoidal waveform on an oscilloscope screen, may hardly change their discharge rates. This implies that in these voluntary movements, the afferents do not code joint position, even though the subject experiences the change in position (Hulliger et al. 1982). Many spindle afferents show small changes in discharge during dynamic length changes, with a predominant increase during lengthening, and might thus signal the occurrence and direction of movement. However, the changes are small (Hulliger et al. 1985), and the degree of tracking precision required has only a small effect (Kakuda et al. 1997).

The interpretation of such findings is that during voluntary contractions, the fusimotor system is co-activated with the extrafusal main muscles. In this pattern of α-γ-co-activation, the fusimotor activity increases the bias of muscle spindle discharge so as to compensate for the contraction-induced internal muscle spindle shortening. In this way, fusimotor activity may prevent the spindles from losing their measuring capability, instead maintaining the→sensitivity of spindle afferents. On the other hand, fusimotor activity may also disturb detection and precision by making spindle discharge irregular and noisy.

9.3 Role of Joint Receptors in Kinesthesia

Removal of afferent input from joint receptors, e.g. by local intra-articular injection of anesthetics or by surgical removal of the joint, often has little proprioceptive effect but may reduce the movement acuity of some joints. These results do not indicate to what extent sensory endings in specific structures, such as joint capsules, ligaments and menisci, contribute to kinesthesia (Macefield 2009; Sjölander and Johansson 1997). Intraneural →micro-stimulation of individual joint afferents can evoke specific sensations referred to the joint of origin (Macefield 2009). However, the interpretation by the CNS of joint-receptor activity is compromised because this activity is influenced by muscle contractions. One possibility is that activation of joint receptors by muscle contraction enables them to play a greater role in kinesthesia during active rather than passive movements (Matthews 1988).

9.4 Role of Cutaneous Mechano-receptors in Kinesthesia

→Micro-neurographic recordings indicate that cutaneous afferents located in the dorsal skin provide information about movements of the hand and fingers. One role of cutaneous mechano-afferents may be to cooperate with other proprioceptors in making proprioceptive information more specific and localized. Although muscles controlling finger movements lie in the forearm and cross more than one joint, the proximity of cutaneous mechano-receptors to specific joints may provide more localized information that indicates which joint is moving.

9.5 Role of Small-diameter Afferents in Kinesthesia

Many small-diameter group III and group IV nerve afferents react to mechanical stimuli, so they might contribute to kinesthesia by providing information about muscle stretch, force and →muscle fatigue. Cutaneous group IV afferents are sensitive to non-noxious mechanical stimuli so they might contribute to kinesthesia after →large-fiber sensory neuropathy (Cole 2009a,b; Gandevia 1996). The majority of the free nerve endings around joints are normally silent, except when tissue is subjected to damaging mechanical deformation. Among the free nerve endings, a considerable number are chemo-sensitive and activated by certain ions including potassium (K^{+}), and inflammatory mediators such as →serotonin (5-HT), →histamine, →bradykinin and →prostaglandin. →Inflammation is normally accompanied by reduced threshold to mechanical probing and to joint movement (Schaible 2009; Sjölander and Johansson 1997).

9.6 Sense of Muscle Force, Effort and Heaviness

The sensations of muscle force, effort and heaviness are related since they are all associated with voluntary muscle contraction. They have commonly been thought as arising from →efference copies of motor commands relayed to sensory areas. This idea is compromised by the lack of proportionality between the decline in muscle force from muscle fatigue or →paralysis and the increase in sensation generated while trying to

achieve the required force. Other mechanisms have therefore been considered such as involvement of →sensory receptors like muscle spindles and Golgi tendon organs, although this also has problems (Proske and Allen 2019).

9.6.1 Sense of Effort

The sense of effort probably arises, at least in part, by transmission of an →efference copy of the motor command to sensory areas and is thought to be responsible for the commonly perceived increases in heaviness after muscle fatigue or paralysis (Proske and Allen 2019). It is accompanied by →cardiovascular effects. In paralyzed subjects attempting to contract muscles, blood pressure and heart rate increase in proportion to the intensity of the motor command and the perceived effort (Gandevia 1996).

Signals related to motor commands may also affect joint position estimation, because human subjects trying to move a paralyzed and anesthetized hand perceive an illusory hand displacement of up to 20°. These effects suggest that central effort-related signals contribute to joint position sense (Gandevia et al. 2006; Smith et al. 2009). Effects of muscle fatigue on position sense also support this supposition. For example, fatigue in human elbow flexor muscles correlates with positional errors, suggesting that positional cues are derived from the effort required (Proske 2005; Proske and Gandevia 2012).

9.6.2 Sense of Muscle Force

The sense of muscle force is distinctly different from the sense of effort and likely involves peripheral receptors including muscle spindles and Golgi tendon organs (Proske and Allen 2019; Proske and Gandevia 2012). History-dependent effects are also known for force estimation. Comparative studies in cats and humans suggest that, after a maximal muscle contraction, errors occur in force estimation, which can be explained by de-→sensitization of Golgi tendon organs (Thompson et al. 1990). There also is a sense of passive muscle force and stretch probably engaging muscle spindles (Proske and Allen 2019).

Protracted muscle tendon vibration generates, in addition to illusions, a →spinally mediated →tonic vibration reflex whose force can be accurately matched with a voluntary contraction of the other limb and is not associated with a sense of effort (McCloskey et al. 1974).

9.6.3 Estimation of Object Weight

Estimation of an object´s weight depends on combined sensations of muscle force, effort and movement. Muscle fatigue or paralysis elicit sensations both of increased heaviness and increased effort (Proske and Allen 2019; Proske and Gandevia 2012; Taylor 2009). Local pressure on the skin excites cutaneous and possibly local muscle and joint receptors, and muscular contraction excites joint, ligament and muscle receptors, including Golgi tendon organs (Gandevia 1996; Luu et al. 2011).

The weight of a limb seems to be sensed differently from that of external objects. When a standing subject raises a forearm, the force supporting it against gravity first increases up to the horizontal position and then decreases again. The changing force is not sensed accurately and the arm´s weight does not seem concentrated at the muscles or their attachments, where the forces required actually act. By contrast, the weight of an object held in the outstretched hand is fairly well estimated and localized to the hand. This suggests that the arm´s weight is already taken into account by an internal body representation (Lackner and DiZio 2000). The sense of force and heaviness cannot therefore rely on muscle tension alone.

9.7 Coding Strategies: Local vs. Global

How does the nervous system code limb position and movement? Does it specifically code local variables such as individual joint angles and muscle lengths, or does it code global variables such as the position and movement of the limb endpoint, and if so how (Bosco and Poppele 2001; Scott and Loeb 1994; Stein et al. 2004)? These questions have been addressed for two neuronal populations: mixed populations of sensory afferents consisting of spindle, Golgi tendon organ, cutaneous mechano-receptive and joint afferents, and cells of origin in the →dorsal spino-cerebellar tract (DSCT).

9.7.1 Coding of Limb Position and Movement by Sensory Afferents

Mixed populations of sensory afferents in the lumbar →dorsal-root ganglia of cats are able to encode hindlimb position and movement during general anesthesia. Muscle spindles contribute most to the process of position encoding, but cutaneous →mechano-receptors, in particular those overlying joints, are also important. Joint receptors might also be involved, although many fire only at the extremes of motion, and Golgi tendon organs contribute little without active muscle contractions. Thus, although the firing patterns of some afferents would probably be different under awake, behaving conditions, it seems evident that ensembles of different-type afferents in the →dorsal roots are able to encode global variables such as paw position and change of position (Stein et al. 2004).

9.7.2 Broad Tuning of Dorsal Spino-cerebellar Tract Responses to Limb Position and Movement

One of the major central projections conveying signals from muscle receptors to supraspinal structures is over the dorsal spino-cerebellar tract (DSCT) (Bosco and Poppele 2001). It should be noted, however, that the majority of DSCT neurons can also be driven, without phasic sensory inputs, by input from the spinal central pattern generators (CPGs) generating the basic rhythms for locomotion and scratch reflexes (Stecina et al. 2013).

In cats, the discharge of DSCT neurons varies broadly with hindlimb length and orientation, i.e., is related to global kinematic variables. Moreover, many DSCT cells respond to the direction of movement from one position to another. Thus, position and movement variables are coded simultaneously, but not independently because the movement response depends linearly on the magnitude of the position response. Moreover, in a proportion of DSCT cells, muscle force can alter the sensitivity to limb position (below). So it seems that responses to both movement direction and muscle force modulate the sensitivity of the kinematic response.

9.7.3 Population Coding in Dorsal Spino-cerebellar Tract Neurons

During passive hindlimb foot movements, various response components linked to kinematic limb variables are distributed across the DSCT population. Two response components correlate with limb-axis length and orientation and are integrated from proprioceptive signals arising in muscles, joints and cutaneous mechano-receptors. They are influenced by global limb configuration due to the coupling of different joints. For example, inputs from receptors modulated by changes in hip and knee angles are preferentially represented in DSCT discharges that denote limb orientation, whereas inputs from receptors modulated by changes in knee and ankle angles favorably represent limb length. Higher-order response components are however unrelated to limb orientation or length and instead appear to represent response dynamics, i.e. forces evoked by muscle contraction (Poppele et al. 2002). In a proportion of DSCT cells, muscle force alters the sensitivity to limb position uniformly across the entire workspace, implying the representation of kinetic variables along with kinematic variables (Bosco and Poppele 2001). During the stance phase of active stepping, DSCT neurons may encode global variables of limb mechanics, limb axis orientation and limb loading, the latter being closely linked with limb-axis length (Bosco et al. 2006). Moreover, many DSCT cells respond to movements of both hindlimbs, suggesting that they might encode inter-limb coordination (Poppele et al. 2003).

9.7.4 Proprioceptive Coding in Primary Somatosensory Cortex

In monkeys trained to reach for distributed targets, proprioceptive neurons in the S1 region of the →primary somatosensory sortex with →receptive fields (RFs) on the shoulder and elbow are broadly tuned for movement direction, similar to muscle spindle afferents and DSCT neurons. Many cells show phasic activity that covaries with movement, and tonic activity that covaries with maintained posture. Neuron discharge intensity varies considerably during kinematically similar active and passive arm movements, indicating that muscle contractions have a strong influence. These differences could originate from efference copies emanating from the →motor cortex or from properties of peripheral sensors whose discharge also depends on muscle contraction, and they might contribute to the sense of effort and muscle force.

Tonic S1 cells exhibit a hysteresis that depends on the direction of the preceding movement, akin to the behavior of muscle spindle afferents and joint receptors, although this cell feature might be averaged out in the population discharge.

Many S1 neurons show broadly tuned changes in activities that are dependent on the direction of external loads. Most often the strongest rate increases occur with loads opposite in direction to a cell´s preferred direction, indicating that the cell compensates for the load. However, the origin of load-dependence could be in the muscle-force sensitivity of peripheral receptors. Whether S1 neuron discharge is also interpreted in terms of more global variables such as arm position and movement remains to be determined (Prud´homme and Kalaska 1994).

9.8 Somatosensory Body Schemata

The sensation of body shape depends on signals from muscle spindle group Ia afferent fibers that convey positions and movements of body parts relative to each other (Massion 1992). The sensors also provide information on the conditions of body support, and on the →mass and →inertia of the body parts. The importance of large-fiber sensory nerve fibers in establishing a somatosensory body schema is emphasized by the fact that their loss in large-fiber →sensory neuropathy destroys the body schema (Blouin et al. 1993). Consequently, patients commit large errors in the extent and direction of fast goal-directed movements when they are deprived of visual information on the movement (Ghez et al. 1990). When subjects without sensory neuropathy are requested to perform fast forearm movements without visual guidance, vibration of the biceps brachii muscle tendon can change the initial arm position without the subjects noticing, yet they still attain the correct final destination. This indicates that the motor system may have access to a sub-conscious, correct body schema (Sittig et al. 1985).

9.8.1 Multi-sensory Integration of Body Schemata

Considerable →multi-sensory integration is necessary for awareness and management of most perceptual experiences, including body schema, i.e., the neural representation of one ´s own body posture and movement. For example, when a subject sitting in darkness fixates on a light attached to a hand and the related elbow flexors are vibrated, the hand and light are felt to move. A similar impression occurs with an acoustic target attached to the hand (Lackner and DiZio 2000). When lateral neck muscles are vibrated with the head fixed, the head is felt to move and small lights are perceived in darkness (Matthews 1988).

Somatosensory information that signals hand or limb contact with other body parts or environmental objects contributes to the proper perception of body dimensions and its relation with the external world. For instance, when subjects grasp their nose with the right fingers and the right biceps brachii muscle is vibrated, an illusion of biceps muscle lengthening and elbow extension is produced together with an illusion of nose elongation: the Pinocchio illusion (Lackner and DiZio 2005).

These phenomena demonstrate the power of proprioception in re-calibrating the →frames of reference of other sense modalities, such as vision and hearing. However, the relationship between vision and kinesthesia can change depending on context. For example, when the hand is viewed through displacing prisms, it is initially felt where it is seen. As soon as the hand is moved actively, the kinesthetic sensation is re-calibrated to enable accurate interaction between hand and object (Lackner and DiZio 2000).

9.8.2 Plasticity of Body Schemata

Body schemata appear to be partly determined genetically and partly acquired and modified through →learning (Gandevia 1996; Maravita and Iriki 2004; Martel et al. 2016; Matthews 1988). They seem to be operative shortly after birth, because phocomelic children sense their missing limbs (Berlucchi and Aglioti 1997). Even though inborn and fairly stable, important parameters such as estimates of the mass and length of individual limb segments are re-calibrated during body growth (Lacquaniti et al. 1992).

Body schemata change dynamically even in normal subjects. Muscle vibration that primarily excites muscle spindle group Ia afferents can produce illusory joint movements far beyond the normal range of joint movement, indicating that the body schema is easily extended without knowledge of anatomical constraints. For example, if the forearm is fixed horizontally against a wall and the elbow flexor muscles are vibrated, the whole body seems to rotate away from the lower arm. Or, if the head is actively rotated to one side and held there, it seems to return to the midline over some 10 minutes, indicating a change in body schema (Matthews 1988; Gandevia 1996; Lackner and DiZio 2000, 2009). And the perception of the subjective straight-ahead direction is perturbed in the absence of vision by vibration of the neck muscles, which outlasts the stimulation and returns to normal gradually (Karnath et al. 2002).

9.8.3 Neurophysiological Correlates of Body Schema Plasticity

In higher →primates, manipulated objects, clothes and tools may be incorporated and extend the body schema (Arbib et al. 2009; Giummarra et al. 2008; Maravita et al. 2003; Maravita and Iriki 2004). A neurological basis for such coding evidently resides in →multi-modal neurons of the premotor and →parietal cortex and the →putamen. The macaque intraparietal cortex contains neurons that respond to somatosensory stimulation within a given body somatosensory receptive field (sRF), and respond to visual stimulation in the adjacent →visual receptive field (vRF). When trained to use a tool to obtain food not reachable by the arm alone, the vRF of distal-type cell representation expands to incorporate the tool, whereas passive tool holding does not have the same effect. Similarly, the vRF of proximal-type neurons expands from a space covering arm use before tool use to a space covering arm plus tool after tool use.

During the learning phase of body schema plasticity, there is an augmented expression of →immediate-early genes, →neurotrophic factors and receptor →trkB, suggesting that a re-organization of neural circuitry has occurred. Behavioral and neuropsychological studies in humans support the notion that tools, by expanding the reaching space, can be incorporated

in the plastic body schema (Iriki et al. 1996).

9.8.4 Phantom Limbs

Visual, auditory and olfactory phantom sensations sometimes occur after deafferentation of sensory organs, which include pain and thermo-sensation, touch and movement sensation. They may occur spontaneously or be elicited by sensory stimulation. Immediately after limb amputation in humans, the patients often perceive their limb as perfectly normal, such that they may even try to move it. Some patients report referred sensations such that touch on an intact body part (e.g., the face) is felt as a sensation on the phantom limb (e.g., the hand). The phantom limb experience argues for the existence of central representation of body size and shape (Medina and Coslett 2016). Over time, the proximal parts of a phantom limb are felt to fade away such that, for example, the hand juts out from the shoulder or retracts into the stump, a phenomenon referred to as telescoping. The phantom arm may also simply shrink in size. A phantom limb may be seen as well as felt, or perceived as occupying anatomically unrealistic and unnatural postures (Berlucchi and Aglioti 1997; Frith et al. 2000; Giummarra et al. 2008; Katz 1992).

Central representations of body parts change after peripheral injuries, and may differ according to the type of lesion (Medina and Coslett 2016). These perceptions are explicable in terms of central re-organization of representational maps, since they do not occur in patients subjected to spinal transection, extensive rhizotomy or brachial plexus lesions before limb amputation.

In patients with phantom limbs, tactile sensibility is also altered. At the stump, detection thresholds are lowered for light touch, →two-point discrimination (spatial acuity) and point localization. The lowered thresholds are also compatible with cortical re-organization, in which surrounding representations take over the deprived area and acquire higher acuity of stump representation. The distal stump areas take over tactile and other sensory functions of the amputated hand (Katz 1992; Berlucchi and Aglioti 1997). However, referred sensations maintain modality-specificity.

9.9 Adaptation and Pathology of Proprioception

Physiological and pathological processes such as gravity, aging and neurological disturbances that affect large sensory fibers, the →brainstem and the →forebrain can alter proprioception. Patients with →Parkinson´s disease, for example, have a reduced ability to detect passive movements and to properly process proprioceptive information centrally (Proske and Gandevia 2012; Taylor 2009). →Chronic pain may also change proprioceptive and other elements of sensory processing and distort the body schema (Tsay et al. 2015).

Proprioceptive sensitivity declines and variability increases with age, in particular in the lower legs. The underlying reasons may be structural and functional changes in skeletal and intrafusal muscle fibers (Lord 2009; Proske and Gandevia 2012).

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10

The Vestibular System:

Anatomy, Functions, Synaptic Organization

CONTENTS

Abstract

• The vestibular system is involved in a large array of functions: coordination with visual inputs, locomotion and navigation; cognitive functions such as attention, spatial constancy, learning and memory; modulation of pain perception; affective and autonomic processes.

• The peripheral vestibular system within the inner ear detects gravity and linear translation as well as rotation and angular acceleration of head and body. Interaction between these signals in the brainstem distinguishes between gravity and acceleration and other inputs distinguish between passive and active head movements.

• The peripheral vestibular apparatus is made up of otolith organs and three semicircular canals.

• Sensory hair cells embedded in the epithelia of the otoliths detect gravity and linear translation. Sensory hair cells embedded in the epithelia of the semicircular canals detect rotational accelerations.

• Hair cells transmit membrane potential changes synaptically to primary vestibular afferents that project to the brainstem nuclear complex and the cerebellum. The peripheral vestibular neurons also receive an efferent innervation from the brainstem.

• The vestibular nuclei project, via separate pathways, to the cerebellum, to brainstem nuclei innervating extra-ocular muscles controlling eye movements and to spinal cord structures involved in upright posture, stance and locomotion. Pertinent vestibular projections are conveyed from the thalamus to the cerebral cortex, and via the thalamus and other pathways to the basal ganglia.

• Secondary neurons in the vestibular nuclei receive inputs from proprioceptive, cerebellar, oculomotor, cerebro-cortical and reticular sources. This convergence helps perform different complex functions.

• The physiological distinction between gravitational and translational accelerations is established by convergence of otolithic and semicircular canal afferents.

• The distinction between afferent signals generated by passive head rotation or active head movements is effected by signals generated in the cerebellum.

• Vestibular information reaches a number of interconnected cerebro-cortical loci via four or five pathways that are involved in the processing of vestibular signals. There is no unimodal vestibular cortex. In conjunction with other sensory signals, vestibular signals contribute to high-level functions, such as perceptual and cognitive functions.

10.1 Introduction

In most animals, relevant information required to monitor body orientation and movement in space is provided by the peripheral vestibular system. It is thought to have evolved from a primitive otolithic system (`statoliths´) in invertebrates more than 500 million years ago. In mammals, the vestibular system develops before birth and yields the ability to detect →gravitational vertical and →self-motion perception (Smith 2019).

Its outputs are used for diverse functions (Bigelow and Agrawal 2015; Cullen 2019; Eatock and Songer 2011; Fukushima et al. 2006; Green and Angelaki 2010; Hitier et al. 2014; Lackner 2014; Mast et al. 2014; Medendorp and Selen 2017; Mergner 2010; Pfeiffer et al. 2014; Shinder and Taube 2010; Ventre-Dominey 2014). These include stabilization of visual inputs in the face of environmental motion and self-motion by eye movements and head movements, gaze stabilization, maintenance of →balance in upright posture, locomotion and navigation and in voluntary, e.g. reaching movements. →Cognitive functions are also monitored, such as →bodily self-consciousness, →perception of verticality and self-motion, spatial visual constancy, →attention, spatial →learning and →memory. Vestibular signals also influence pain perception and →affective processes. To put vestibular signals into proper context, they must be integrated with visual, proprioceptive and other extra-vestibular signals (Britten and Arshad 2019; Cullen 2012). The →autonomic nervous system is also affected; the peripheral vestibular system co-regulates reactive blood re-distribution related to changes in body orientation (McCall et al. 2017).

10.2 The Peripheral Vestibular System and its Central Connections

10.2.1 Peripheral Vestibular System

The peripheral →vestibular apparatus (Dickman 2009) is one of the most complex sensory organs, whose phylogenetic origin is not quite clear (Braun 2009; Graf 2009a,b). The vestibular and auditory components are housed in the inner ear, in the labyrinths of the temporal bones on either side of the skull.

10.2.1.1 Labyrinth

The inner ear is divided into bony and membranous labyrinths. The membranous labyrinth, encased within the temporal bone, is a simple epithelial membrane, except at places where it becomes specialized into a sensory epithelium with →hair cells as →sensory transduction elements (Guth et al. 1998; Ó Maoiléidigh and Ricci 2019). It consists of an anterior chamber and the cochlear duct, which subserves hearing, and connects by way of the round saccule with the posterior vestibular apparatus. The peripheral vestibular apparatus is made up of otolith organs (saccule and utricle), and three semicircular canals. The space between bone and membrane is filled with →perilymph, while the membranous labyrinth is filled with →endolymph (Barmack and Pettorossi 2009; Kelly 1991; Lackner and DiZio 2005).

10.2.1.2 Otolith Organs

The otoliths detect →gravity and linear translations. The utricle and saccule each contain a sensory epithelium (macula sacculi and macula utriculi), which contains two types of sensory hair cells embedded in supporting cells. The hair cells (Guth et al. 1998) possess tens to hundreds of apical processes whose tips contact a gelatinous substance covering the macula and contain crystals of calcium carbonate or calcite, called otoliths (or otocones) (Ó Maoiléidigh and Ricci 2019; Strassmaier and Gillespie 2002). The longest process is the single kinocilium. The rest consists of actin-filled stereocilia, which decline in length in a direction away from the kinocilium. This arrangement gives the hair cell a functional direction. The macula of the utricle is almost horizontal and that of the saccule is nearly vertical (sagittal).

With the head erect, the otoliths of the utricle rest on the macula. When the head is tilted or →accelerated linearly, the otoliths´ weight or →inertia moves them from their rest positions so that the hair cell processes are deformed and initiate the sensory →transduction process. With linear translation at constant speed, the otoliths reach an equilibrium. By the same mechanism, the vertical macula of the saccule responds preferentially to vertical changes in head position (Kelly 1991). In summary, with the head upright, the utricle senses motion in the horizontal plane (e.g., forward-backward movement, left-right movement, and combinations thereof), while the saccule senses motions in the sagittal plane (e.g., up and down movement). Because the hair cells have a range of →spatial orientations, they can detect linear accelerations in several directions.

10.2.1.3 Semicircular Canals

The semicircular canals detect rotational accelerations. The horizontal semicircular canals on both sides lie in the same plane, thus building a functional pair. The common plane is slightly slanted upwards in a forward direction at an angle of ca. 15° with the horizontal (head) plane.
The planes of the vertical canals are roughly orthogonal to each other and to that of the horizontal canals. The planes of the vertical canals are oriented at angles of ca. 45° with the sagittal and frontal planes. This implies that an anterior vertical canal on one side builds a functional pair with the posterior vertical canal on the other side. The orientations of all these operational planes are aligned with those of extraocular muscles. Each semicircular canal dilates into an ampulla at one end. Each ampulla contains a crista ampullaris, consisting of a crest of sensory epithelium supported on a hill of connective tissue and lying at a right angle to the longitudinal axis of the canal. The crista carries a wedge-shaped gelatinous mass called cupula, which extends from the crista surface to the roof and lateral walls of the membranous labyrinth, forming a fluid-tight partition. The hair cells´ cilia project into, and make tight connections with, the cupula. The spatial orientation of the multiple stereocilia and single kinocilium have a single orientation.

When the head turns in the plane of the canal, the inertia of the endolymph causes it to press against the cupula, deflecting the hair cells´ cilia. If the head keeps rotating, the

endolymph eventually catches up with the canal, and the deflection of the stereocilia ends. If the head stops rotating, the moving fluid bumps into the suddenly arrested cupula, and this causes a feeling of turning in the other direction (post-rotatory sensation). The hair cells respond to angular accelerations and decelerations as low as $0.1°/s^2$ (Kelly 1991). After damage, hair cells can regenerate and facilitate functional recovery (Walshe et al. 2003).

10.2.1.4 Innervation of Hair Cells

There are two types of hair cells: Type I and Type II, distinguished by their shapes and by their afferent and efferent innervation. Hair cells do not form their own central →axons, but →synapse on →dendritic processes of bipolar neurons comprising Scarpa´s ganglion in the internal auditory canal. Centripetal processes of these →ganglion cells, the primary vestibular afferents, run in the vestibular portion of →cranial nerve VIII. Type I hair cells are surrounded by a calyx formed by one of the terminal branches of a thick or medium-diameter nerve fiber . Type II hair cells have multiple bouton-type afferent nerve terminals.

The peripheral vestibular neurons also receive an efferent →cholinergic (→nicotinergic and →muscarinergic) innervation from the →efferent vestibular nucleus (EVN) in the →brainstem, from where vestibular efferents project ipsilaterally, contralaterally or sometimes bilaterally to synapse on the primary afferents of Type I hair cells and directly on Type II hair cells (Dickman 2009; Mathews et al. 2017; Poppi et al. 2020).

10.2.2 Neurotransmitters and Neuromodulators in the Vestibular Complex

Neurotransmitters. The →neurotransmitter at the hair cell synapses with contacts to secondary neurons appears to be →glutamate, which activates a number of postsynaptic →glutamate receptor subtypes (Eatock and Songer 2011; Smith and Darlington 1996). Hair tufts at rest (not bent) release glutamate tonically, which evokes a sustained discharge of postsynaptic fibers at 90-100 spikes per second. Hair-cell →depolarization further increases presynaptic glutamate release and afferent discharge.

Hair cells are innervated by efferent nerve fibers whose cell bodies are located bilaterally in the brainstem. The neurotransmitters released include →acetylcholine, →**γ-a**mino-**b**utyric **a**cid (GABA), →calcitonin-gene-related peptide (CGRP) and →nitric oxide (NO) (Eatock and Songer 2011; Smith and Darlington 1996; Zenner and Gummer 1996). The efferents are thought to participate in a positive feedback loop, with vestibular afferents stimulating vestibular efferents to further enhance afferent activity (Eatock and Songer 2011).

At excitatory synapses between primary vestibular afferents and second-order neurons, glutamate released from primary afferent terminals activates postsynaptic →α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA/→kainate) receptors, →N-methyl-*X-7*D-aspartate (NMDA) receptors and metabotropic glutamate receptors (mGlu)

receptors. This receptor set provides the basis for fast →synaptic transmission as well as →synaptic plasticity. In fact, NMDA receptors are involved in →long-term potentiation (LTP) and →long-term depression (LTD), which may contribute to visuo-vestibular recalibration and vestibular compensation (Grassi and Pettorossi 2001). NMDA receptor (NMDAR)-mediated effects appear to be more important than →AMPA/kainate effects. NMDARs are unique in that they have a →glycine binding site that is necessary for NMDAR activation (Vibert et al. 1997). Secondary vestibular neurons utilize several neurotransmitters, including acetylcholine, →aspartate, glutamate, taurine, GABA, and glycine (Barmack and Pettorrossi 2009; Gliddon et al. 2005).

Neuromodulators. Various neurohumoral substances modulate signal processing in the →vestibular nuclei in a variety of ways. Elucidation of their diverse operational modes has been beneficial for effective pharmacotherapy against several disorders that affect the vestibular network.

Acetylcholine. →Muscarinic receptors and →nicotinic receptors expressed in vestibular hair cells and afferent neurons are involved in the efferent modulation of electrical activity by modulating potassium →M-currents (Pérez et al. 2009). Both muscarinic and nicotinic receptors are present in regions of the vestibular network, including the medial vestibular nucleus (MVN). Their presence accounts for the effectiveness of →atropine and →scopolamine as drugs against →motion sickness (Kohl and Homick 1983).

Dopamine. Dopaminergic pathways from the →midbrain play important roles in locomotion and voluntary movement. Dopamine modulates medial vestibular neurons both pre- and postsynaptically. Dopamine receptor →antagonists, particularly those acting on the D2-subtype, are used to treat vestibular disorders (Vibert et al. 1997).

Serotonin (5-HT). The serotonergic system emanating from the →raphé nuclei and related cell groups is involved in the control of various functions related to behavioral state. Serotonergic fibers densely innervate the vestibular complex. Serotonin (5-HT) has excitatory as well as inhibitory effects via different subtypes of receptors, and increases dynamic sensitivity required for fast reactions to external stimuli (Vibert et al. 1997).

Noradrenaline (Norepinephrine). →Noradrenergic inputs from the →locus coeruleus augment sensory-motor responses in situations requiring increased →alertness, →vigilance and selective attention (McBurney-Lin et al. 2019). The vestibular nuclei show regional differences in innervation density which serve to differentially alter vestibulo-ocular and vestibulo-spinal responses, as well as to facilitate adaptive changes in these responses (Vibert et al. 1997; Schuerger and Balaban 1999; Balaban 2002).

Histamine. Histaminergic neurons in the posterior →hypothalamus are involved in regulation and control of vigilance, neuro-→endocrine responsiveness (→neuro-endocrine axis), internal body temperature regulation and cerebral blood flow. Histamine modulates the vestibular system by excitatory actions on neurons of the vestibular complex. The histaminergic system is activated by vestibular inputs during sensory conflicts that induce motion sickness. This may explain the clinical efficiency of

anti-histamines in the treatment of vestibular disorders (Vibert et al. 1997).

Peptides such as →substance P, →neurotrophins and →opioids also modulate responses of vestibular neurons (Vibert et al. 1997; Matsuoka et al. 1984).

10.2.3 Vestibular Nuclear Complex and its Connections

According to its multifarious functions, the vestibular system is connected to many downstream structures in the →central nervous system (CNS).

Primary vestibular afferents in cranial nerve VIII enter the brainstem and divide into two fiber bundles. One bundle turns caudally and then passes into the vestibular nuclear complex. The other bundle ascends as →mossy fibers to the →cerebellum, where they distribute to several gyri, but primarily to the ipsilateral nodulus-uvula (Barmack 2003, 2009; Barmack and Pettorossi 2009).

The vestibular nuclear complex contains four main nuclei and smaller sub-nuclei with different inputs and outputs (Brodal 1981; Kelly 1991; Barmack 2003, 2009; Highstein and Holstein 2005). The main vestibular nuclei are: the superior vestibular nucleus (SVN) of Bechterev, medial vestibular nucleus (MVN) of Schwalbe, lateral vestibular nucleus (LVN) of Deiters and descending vestibular nucleus (DVN) (or inferior or spinal VN). The sub-nuclei include: the parasolitary nucleus (Psol), the Y group and the nucleus intercalatus (Staderini).

Since otolith organs signal gravito-inertial forces and semicircular canals signal rotational accelerations, the apparently clear functional division seems to call for independent processing of the different signals. This assumption is supported by the projection patterns of primary vestibular afferents. Afferents from the saccule and utricle tend to terminate in different overlapping regions of the vestibular nuclear complex (Newlands et al. 2003). Likewise, afferents from the different semicircular canals tend to terminate in different regions. On the other hand, inputs from otolith and semicircular canal in part converge onto single second-order vestibular neuron (Dickman and Angelaki 2002; McCall et al. 2017).

The vestibular nuclei project via separate pathways (Zwergal et al. 2009) to the cerebellum, to brainstem nuclei that innervate extra-ocular muscles which control eye movements, to structures of the →spinal cord, which are involved in upright posture, stance and locomotion, via the →thalamus to the →cerebral cortex (Barmack 2003; Shinder and Taube 2010), and via the thalamus and other pathways to the →basal ganglia (Stiles and Smith 2015).

Because of differential input-output connections, secondary vestibular neurons show different firing patterns that relate to eye and head movements. One major group is involved in the vestibulo-ocular reflex (VOR), which stabilizes gaze during head movements, and in smooth pursuit eye movements. The other group is independent of

eye movements (hence also called `non-eye movement neurons´) and is involved in posture and balance, self-motion perception and spatial orientation. The different groups receive different extra-vestibular inputs (Cullen 2012, 2019).

Outputs from caudal DVN, MVN and Psol influence the →nucleus of the solitary tract (NTS) and thereby modulate local changes in blood flow, blood pressure, heart rate and respiration rate (Barmack 2003; Barmack and Pettorrossi 2009).

The vestibular nuclei send a small number of efferent fibers back to the vestibular labyrinth, where they change the responses of primary afferents to vestibular stimulation; but little is known about the physiological role of the efferent system. It has been demonstrated that vestibular efferent activation follows specific behavioral and environmental cues, suggesting a context-dependent efferent activity. It has been suggested that the efferent innervation may participate in vestibular plasticity and vestibular compensation and/or operate as an →efference copy generated by the spinal cord during locomotion (Mathews et al. 2017). Finally, there are complicated connections between vestibular nuclei, both ipsilaterally and bilaterally.

Multi-sensory Interactions in the Vestibular Complex. For the complex functions subserved by the vestibular system, convergent information from other than vestibular sources is required and must be combined at several levels within the vestibular network. Secondary vestibular neurons receive additional inputs from proprioceptive afferents, →reticular formation, cerebellar and oculomotor sources, widely distributed →cortical areas (e.g., area 2, area 3a, area 6, area 7; parieto-insular vestibular cortex; →anterior cingulate cortex, ACC), in a way that differential patterns of →multi-sensory convergence define various groups of secondary vestibular neurons (Cullen 2012; Green and Angelaki 2010; McCall et 2017). From the visual system, they also receive →efference copies of eye or gaze →motor commands that are used to construct an internal 3D representation of the position and velocity of the head in space (Barmack 2003; Barmack and Pettorossi 2009; Henn 1999; Vibert et al. 1997). These signals derive from many brainstem and cerebro-cortical sources, among them the →accessory optic system (AOS) and pre-→striate visual cortex. Neurons in AOS detect information about self-motion that is combined with spatial information from primary vestibular afferents. Position and movement of the head relative to the trunk are signaled by neck proprioceptors involved in reflexive eye movements and postural reactions of trunk and limbs (Barmack 2003; Barmack and Pettorossi 2009; Cullen 2012; Green and Angelaki 2010). Disbalances or conflicts between sensory inputs may cause motion sickness (Bertolini and Straumann 2016).

10.2.4 The Cerebellum

The cerebellum is implicated in a plethora of functions, including oculomotor control, control of upright stance and locomotion, reaching and grasping and speech, timing and coordination of movement, prediction of sensory consequences of actions, error detection and correction, →motor learning, →classical conditioning (e.g. eyeblink conditioning),

and even attentional, →emotional, →motivational, →reward-related and cognitive functions (language, social cognition) (Ito 2006; Sokolov et al. 2017; Wagner and Luo 2020). The first three functions involve the vestibular system.

10.2.4.1 Cells and Circuits in the Cerebellum

Some important cell types and circuits in the →vestibulo-cerebellum are as follows.

Mossy fibers (*MF*) of pre-cerebellar neurons (*PCNs*) send branches to the →deep cerebellar nuclei (*DCN*) and vestibular nuclei (*VN*) as well as to cerebellar →granule cells (*GR*) via complex synaptic formations in so-called glomeruli (*GL*). The axons of granule cells branch to form parallel fibers (*PF*), which contact →Purkinje cells (PCs), →basket cells, →Golgi cells and →stellate cells (Ito 2006).

Climbing fibers (*Cl*) originate from neurons in the →medullary →inferior olive (*IO*) and send glutamatergic axon projections to the deep cerebellar nuclei (*DCN*) and vestibular nuclei (*VN*) as well as to contralateral Purkinje cells (*PCs*). Each fiber contacts 10-15 PCs (Azizi 2007). An individual Purkinje cell receives only one olivary axon, which climbs along its dendritic tree in spirals and makes up to 26,000 synaptic contacts with the Purkinje cell (Ito 2006).

The only output of the cerebellar cortex is provided by the inhibitory Purkinje cells (*PCs*), which target the vestibular nuclei (*VN*) and deep cerebellar nuclei (*DCN*), comprising the →nucleus fastiguus (fastigial nucleus), →nucleus interpositus (interposed nucleus) and →nucleus dentatus (dentate nucleus). Through these follower neurons, the PCs exert various actions including the activation and precise control of behavior by the suppression of PC inhibitory activity (Heiney et al. 2014).

Deep cerebellar nuclei (*DCN*) contain several groups of neuron in terms of morphology, neurotransmitter types and intrinsic properties: large glutamatergic →projection neurons that project to nuclei outside the cerebellum, including the red nucleus and the thalamus; medium-sized GABAergic projection neurons that project to the inferior olive (*IO*), two types of glycinergic projection neuron, which project to the cerebellar cortex or vestibular nuclei; and at least two types of GABAergic or GABAergic/glycinergic and glutamatergic →interneuron (Hori and Hoshino 2012; Uusisaari ad De Schutter 2011). The physiologial operation of this complex circuitry is poorly understood.

10.2.4.2 Neurotransmitters and Neuromodulators in the Cerebellum

Neurotransmitters. Granule cells and →unipolar brush cells (*UBs*) are glutamatergic. Purkinje cells, Golgi cells, stellate cells, basket cells and →Lugaro cells are GABAergic (Ito 2006; Hori and Hoshino 2012).

Transmission through glutamatergic mossy fiber-granule cell synapses in glomeruli allows for long-term potentiation (LTP) on the basis of NMDA receptors and metabotropic glutamate (mGlu) receptors (D´Angelo et al. 2005).

Single spike activation of parallel-fiber synapses on Purkinje cells generates fast postsynaptic currents via AMPA receptors, producing an →excitatory postsynaptic potential (EPSP) capable of activating a →simple spike (SS) discharge. Moreover, it generates slower signals, mediated by metabotrophic glutamate mGlu1 receptors resulting in Purkinje cell depolarization accompanied by sharp calcium (Ca^{2+}) elevation within dendritic regions (Ito 2006; Hoxha et al. 2016). At parallel fiber-Purkinje cell synapses, long-term depression (LTD) and long-term potentiation (LTP) occur. Additionally, at GABAergic synapses from molecular-layer interneurons to Purkinje cells, a special type of LTP called rebound potentiation (RP) takes place (Hirano 2018; Ito 2006).

A single climbing-fiber spike can elicit a pronounced, long-lasting EPSP which induces either a single →action potential or a →burst discharge (complex spike, *CS*). →Climbing fiber activation exerts depressant or facilitatory aftereffects on simple-spike activity, modulates parallel fiber-Purkinje cell synaptic transmission and has a remote action on terminals of Purkinje cell axons (Ito 1984).

Neuromodulators. The cerebellar cortex receives fibers from neuromodulatory brainstem systems that release serotonin (5-HT), noradrenaline, dopamine, histamine and acetylcholine (ACh). The parallel fiber-Purkinje cell synapses are modulated by several neurotransmitters, including serotonin, noradrenaline and acetylcholine (Hoxha et al. 2016). Signal transmission in the cerebellar cortex appears to be modulated both on a short-term and a long-term time basis by →monoaminergic, histaminergic and cholinergic fibers (Schweighofer et al. 2004). In addition, →orexin-containing fibers from the hypothalamus project to brainstem structures and the cerebellum (flocculus only) and may be involved in →fight or flight reactions (→stress). The cerebellum contains many more →neuropeptides, whose roles are not yet well understood, however (Ito 2006). The induction of cerebellar LTD requires spontaneous release by climbing fibers of corticotropin-releasing factor (CRF), which plays an important role in stress responses (Ito 2009).

10.2.4.2 The Cerebral Cortex

There is no unimodal vestibular cortex (Ferrè and Haggard 2015; Shinder and Taube 2010). Clinical case reports, brain imaging, caloric stimulation and electrical stimulation (Dieterich and Brandt 2010; Emri et al. 2003; Kahane et al. 2003; Ventre-Dominey 2014) in humans and other animals have shown that vestibular information, in collaboration with other senses, reaches a number of interconnected cerebro-cortical loci via four or five pathways that are involved in the processing of vestibular signals (Hitier et al. 2014). The cortical vestibular system is structurally and functionally lateralized with a dominance of the right hemisphere in right-handers and the left hemisphere in left-handers (Dieterich and Brandt 2018). Even the primary visual cortex (V1) in mice indirectly receives vestibular signals related

to head direction, which together with signals from →grid cells and →place cells in the medial →entorhinal cortex , motor signals, and visual signals may produce signals of self-motion, which together may be used in navigation (Chaplin and Margrie 2019).

10.3 Peripheral Signal Processing: Transduction in Hair Cells

→Mechano-electrical transduction (MET) in hair cells occurs by MET channels that are located near the tips of stereocilia at the base of the tip link filament that connects a shorter stereocilium to its next taller neighbor and are permeable to non-selective cation ions. When the stereocilia are deflected towards the kinocilium under experimental conditions, the MET-channel open probability increases, thus producing an inward →receptor current that depolarizes the cell, while deflections in the opposite direction decrease channel open probability, thus producing an outwardly directed →hyperpolarizing current (Qiu and Müller 2018). In the maculae of utricle and saccule, cells of all directional →sensitivities are intermixed, thus allowing detection and measurement of accelerations in all directions within their respective planes. Hair cells in the semicircular canal are oriented all in the same direction, so that endolymph motion leads to uniform changes in membrane potential.

Consequently, when the head turns around a vertical axis, hair cells in the horizontal canal of one side are depolarized and those on the other side are hyperpolarized. Both horizontal canals cooperate in a push-pull manner.

Mechano-electrical transduction has a very short latency, on the order of microseconds. Hair-bundle displacement in response to a mechanical stimulus produces slow relaxation with a →time constant similar to the slow →adaptation of the inward receptor current (Howard and Hudspeth 1987). It seems to be dependent on an elastic gating spring, which consists of a fine filament that runs from the tip of the stereocilia to that of its tallest neighbor. An →adaptation motor consisting of myosin-1c regulates filament tension**.** When the stereocilia are bent towards the kinocilium, the gating spring is first stretched and its tension then declines as the adaptation motor moves downwards (Gillespie 1995; Ó Maoiléidigh and Ricci 2019; Strassmaier and Gillespie 2002).

10.4 Primary Vestibular Afferent Discharge Patterns

10.4.1 Input Variables Coded by Primary Vestibular Afferents

Primary afferents from the otoliths are sensitive to linear force over a broad frequency range. During sinusoidal linear translation, most of them respond with signals that are in phase with or advance the force oscillation (McCrea et al. 2001). Each otolith afferent responds optimally to acceleration along a particular spatial direction, and the response to

acceleration in another direction is proportional to the cosine of the angle between acceleration direction and best orientation vector. Thus, for an angle of 90°, the change in discharge would be zero (`cosine gain rule´) (Chan et al. 2002).

Fluid mechanics within the semicircular canals play an important role in shaping the response of primary afferents. For low-frequency angular acceleration, fluid motion within each canal is proportional to angular acceleration, while at higher frequencies, →viscous forces result in real-time integration of acceleration, fluid motion thus being more closely related to velocity.

The discharge patterns of some primary vestibular afferents reflect frequency dependence while others signal acceleration, or an intermediate between acceleration and velocity even at high frequencies, so that fluid motion follows velocity (Highstein et al. 2005).

10.4.2 Parallel Afferent Channels

Primary vestibular afferents discharge regularly, irregularly or with a continuum of firing patterns between extremes of regular and irregular (Eatock and Songer 2011; Goldberg 1991, 2000; McCrea et al. 2001). Afferents from central vestibular epithelia tend to be thick and fast-conducting and encode phasic signals in irregular discharge patterns, while afferents from peripheral zones are finer and slower and encode more tonic signals in terms of regular patterns (Eatock and Songer 2011). If discharge pattern is of functional consequence, it seems likely to be conveyed over parallel pathways that connect differentially to neurons of different function. This turns out to be the case. Cells involved in vestibulo-ocular reflexes receive inputs from regularly and irregularly discharging afferents, and those participating in vestibulo-spinal reflexes receive inputs predominantly from irregularly firing afferents. It may be that different discharge dynamics compensate for the operation of reflexes under under varying behavioral circumstances controlled by vestibulo-ocular and vestibulo-spinal reflexes (Goldberg 2000).

10.4.3 Spatial Transformations

Three-dimensional (3D) head rotations rarely occur precisely in the plane of any particular pair of semicircular canals. Since the set of primary vestibular afferents from each semicircular canal responds only to that component of head rotation lying in the direction of the canal´s axis of rotation, 3D head rotation will usually change the discharge of afferents from more than one canal pair. This implies that three spatial components of the rotation are transformed into essentially three neural signals emanating from the cupulae (Robinson 1982). Similar considerations apply to the transformation of space coordinates into utricle and saccule discharge patterns.

10.5 Sub-cortical Processing

10.5.1 Discharge Patterns in the Vestibular Complex

Second-order neurons in the vestibular complex have relatively high spontaneous firing rates even at rest. Under resting conditions, the dynamic equilibrium of firing rates between neurons on both sides plays an important role in maintaining normal posture and eye and head position.

Discharge properties of vestibular nuclear neurons (VCNs) are more diversified and differentiated than those of primary afferents. For example, whereas otolith afferent discharges follow the `cosine rule´, VCN discharges do not. VCN phases vary with stimulus direction, suggesting ipsilateral and bilateral convergence of otolith afferents onto central neurons (Chan et al. 2002). Another example is the convergence of inputs from semicircular canals on both sides, which may result in differences between the spatial tuning properties of canal afferents and nuclear neurons (McCrea et al. 2001).

Second-order vestibular neurons with direct input from semicircular canal afferents are functionally distinct. One class of cells responds much less to acceleration during active than passive head rotation, while another class depends on current gaze strategy (Angelaki and Cullen 2008; Cullen and Roy 2004). Moreover, some neurons are more sensitive to low-frequency inputs and others to high-frequency inputs, suggesting that different frequency components play different roles in different behavioral contexts (McCrea et al. 2001).

10.5.2 Discharge Patterns in the Cerebellum

Recordings from Purkinje cells, mossy fiber terminals and interneurons in folia 8-10 of anesthetized mice showed that sinusoidal roll-tilt vestibular stimulation strongly modulates the discharge of climbing fibers and mossy fiber afferents, Roll-tilt onto the side ipsilateral to the recording site increases the discharge of both climbing fibers and mossy fibers. However, the discharges of Purkinje cell simple spikes (SSs) decrease during ipsilateral roll-tilt. When the vestibularly modulated discharge is blocked by a microlesion of the inferior olive (IO), the modulated discharge of CSs and SSs is also blocked. When the vestibular mossy fiber pathway is destroyed, vestibular modulation of ipsilateral CSs and SSs persists. Probably, climbing fibers are primarily responsible for the vestibularly modulated discharge of both CSs and SSs. Modulation of the discharge of SSs is likely caused by climbing fiber-evoked stellate cell inhibition (Barmack and Yakhnitsa 2015).

The caudal cerebellar vermis contains a group of Purkinje cells with responses that reflect an estimate of head tilt. These tilt-selective cells are complementary to translation-selective Purkinje cells, such that their population activities sum to the net gravito-inertial acceleration encoded by the otolith organs (Laurens et al. 2013).

Convergence of vestibular and neck proprioceptive inputs enables the computation of body motion in space, which appears to be done by neurons in the rostral fastigial nucleus. While `unimodal´ neurons respond exclusively to vestibular input similarly to neurons in the vestibular nuclei and thus encode motion of the head-in-space, `bimodal´ neurons respond to both vestibular and neck proprioceptor inputs and explicitly encode motion of the body-in-space (Brooks and Cullen 2009).

10.5.3 Distinction between Active and Passive Head Movements

Changes in primary afferent vestibular signals can result from passive, externally applied head motion (ex-afference) and/or from active head movements (re-afference). Since these two situations must be distinguished for accurate perception and motor control, the CNS must have mechanisms to do so. Vestibular primary afferents encode vestibular ex-afference and re-afference with equal fidelity, so a CNS mechanism must be central to the primary afferents. In fact, already secondary vestibular neurons selectively encode vestibular ex-afference implying that the re-afference is suppressed. In these neurons, discharge modulation is strongly attenuated during active head-on-body movements that receive direct vestibular afferent inputs (Cullen 2019).

It is thought that the central suppression signal is generated by the vestibular cerebellum by means of an →internal model. This model receives an efference copy of the motor command to the neck →skeletal muscles and computes an estimate of the expected proprioceptive feedback. This allows comparison with the actual proprioceptive feedback, resulting in a sensory →prediction error (i.e., ex-afference). When predicted and actual neck proprioceptive inputs match, a cancellation signal is generated by the cerebellum to suppress the re-afferent vestibular input. Indeed, neurons in the fastigial nucleus explicitly encode sensory prediction errors during self-motion (Cullen 2019; Cullen and Brooks 2015; for an elaborate model see Laurens and Angelaki 2017).

Vestibular cues to discriminate between tilt and translation do not suffice at low frequencies because semicircular canal signals are of poor quality at these frequencies. This may lead to →illusions unless other sensory (e.g., visual) inputs are recruited for help (Angelaki and Cullen 2008). Better estimates appear to be generated in the ceberellum.

Self-motion Perception includes the detection of angular and linear body motion, the instantaneous heading direction, traveled trajectory and traveled distance or time (Britton and Arshad 2019; Cheng and Gu 2018; Cullen 2019). It requires consciousness and thus cerebro-cortical processes. Self-motion perception depends on the integration of vestibular, visual, proprioceptive, auditory, and kinesthetic signals about body movement (Pettorossi and Schieppati 2014).

The required vestibular information is sent from the vestibular nuclei to the cerebral cortex via the thalamus. Responses of neurons in the ventral posterior lateral thalamus of macaques differ during externally applied (passive) head motion and actively generated self-motion. The responses of neurons that encoded passive rotations and translations were suppressed during comparable voluntary movement (~80% reduction). This

suppression only occurred if the actual sensory consequences of motion matched the motor-based expectation. Hence, the posterior thalamo-cortical vestibular pathway selectively encodes unexpected motion, thereby providing a neural correlate for ensuring perceptual stability during active versus externally generated motion (Dale and Cullen 2017).

The vestibular cerebellum also contributes to self-motion perception by integrating vestibular and extra-vestibular information (Britton and Arshad 2019). The cerebellar nodulus-uvula (lobules X and IX) is thought to create an internal model of spatial orientation. Some neurons combine otolith and semicircular canal inputs to distinguish tilt from translation (Straka et al. 2016).

The neck as important link between head and trunk and carrier of neck proprioceptors is of special importance for the perception of orientation and motion in space. This perception is strongly influenced by neck muscle vibration on short and long-term bases. Long-term neck proprioceptive inputs elicit plastic changes might adapt motion sensitivity to lasting or permanent head positional or motor changes (Pettorossi and Schieppati 2014).

Self-motion perception should go beyond that of straight translation or pure rotation and include the perception of curved trajectories. This can be achieved by the convergence of otolith and semicircular canal signals onto central neurons in the vestibular nucleus and cerebral cortex. Indeed, the convergent neurons typically exhibit stronger responses during a combined curved motion trajectory. Information about self-motion is also obtained by visual optic flow and is integrated with vestibular signals (Cheng and Gu 2018).

10.5.4 Gravito-inertial Force Resolution

To maintain spatial orientation requires the neural representation of orientation relative to gravity, as determined by head tilt. Tilting gravitational acceleration and inertial acceleration linked to translational motion are physically indistinguishable. Behavioral responses to tilts and translations are nonetheless different, so the brain must be able to compute the correct response to both acceleration components (Dakin and Rosenberg 2018; Laurens et al. 2013).

The required computations appear to be carried out in the vestibular nuclei and Purkinje cells of the cerebellar nodulus-uvula, which receive convergent inputs from otolith-driven and semicircular canal-driven signals. Such convergence requires a spatio-temporal transformation of →head-centered canal-driven signals into an estimate of head re-orientation relative to gravity. This signal must then be subtracted from the otolith-driven estimate of net acceleration to compute inertial motion (Angelaki et al. 2010).

10.6 Cerebro-Cortical Processing

10.6.1 Cerebro-cortical Vestibular Areas

Clinical case reports, brain imaging, caloric stimulation and electrical stimulation (Dieterich and Brandt 2010; Emri et al. 2003; Kahane et al. 2003) in humans and other animals have shown that vestibular information, in collaboration with other senses, reaches a number of interconnected cerebro-cortical loci via four or five pathways that are involved in the processing of vestibular signals (Hitier et al. 2014). There is no unimodal vestibular cortex (Ferrè and Haggard 2015).

Vestibular inputs distribute to widespread cerebro-cortical regions in humans. These regions include parts of →Brodmann´s area 2, area 3a, area 6, area 7, and of the →insula, the retro-splenial cortex, the parieto-insular vestibular cortex (PIVC), visual temporal Sylvian (VTS) area, →ventral intraparietal area (area VIP), vestibular cingulate area, para-acoustic area, →hippocampus and →parahippocampal cortex, and →frontal →cortical areas (Ebata et al. 2004; Hitier et al. 2014). The cortical system projects back to the brainstem vestibular nuclei to modulate vestibular reflexes.

Since the cortical regions with vestibular inputs are →multi-modal by also receiving →somatosensory, visual, sensory-motor and optokinetic signals, it has been suggested that they generate perception of the body and its parts relative to the environment (Ferrè and Haggard 2015) and contribute to posture control. For example, the PIVC could integrate its various inputs into a concept of head in space.

Parieto-insular Vestibular Cortex (PIVC). A central position within the system includes the PIVC, which receives inputs from all other cortical regions. Its precise location in humans is not clear (Hitier et al. 2014; Pfeiffer et al. 2014). In macaques, PIVC neurons respond to 3D rotational and translational vestibular stimuli, with all stimulus directions being represented (Chen et al. 2010). PIVC neurons also receive proprioceptive inputs, particularly from the neck during body movements independent of head movements. Integration of these inputs may thus represent body motion relative to the head (Hitier et al. 2014).

Anterior Parietal Cortex (APC). This region is considered a center for the integration of vestibular and somatosensory information from the head, neck and upper limbs and may play a role in distinguishing self-motion from object motion (Hitier et al. 2014; Pfeiffer et al. 2014).

Posterior Parietal Cortex (PPC). Human brain imaging reveals that vestibular stimulation activates area 39 and area 40 in the →inferior parietal lobule (IPL), which could correspond to monkey area 7. In the ventro-→parietal cortex (fundus of the →intra-parietal sulcus (IPS)),neurons respond in different proportions to visual, vestibular and somatosensory inputs. The ventro-parietal cortex may thereby construct a representation of subjective space and contribute to object location and motion relative to the head (Hitier et al. 2014). Neurons in the macaque PPC (medial and ventral intraparietal areas) display responses to vestibular stimulation with mixtures of components related to

position, velocity and/or acceleration (Klam and Graf 2003).

Medial Superior Temporal Area (Area MST). The →medial superior temporal area (→area MST) is considered to be important for →visual motion (optic flow) processing and has early been associated with compensatory and pursuit eye movements. It appears to also participate in information processing during head turning and linear acceleration. It may contribute to self-motion detection, in distinction to object motion, and helps to update spatial orientation (Hitier et al. 2014; Pfeiffer et al. 2014; Ventre-Dominey 2014).

Cingulate Gyrus and Retro-splenial Cortex. During human brain imaging, caloric stimulation activates the →cingulate gyrus and the retro-splenial cortex, the latter being important in navigation and →path integration (Hitier et al. 2014).

Hippocampal and Parahippocampal Cortices. These regions are involved in constructing spatial maps for orientation, navigation and spatial memory aided by various types of space-related cells, which in part use vestibular signals (Hitier et al. 2014; Smith 2019). Vestibular inputs that signal self-motion appear to be essential for the development and maintenance of spatial memory by brain areas including the hippocampus. When vestibular inputs are lost, spatial memory is impaired (Smith et al. 2010).

Frontal Cortex. Vestibular projections also reach two areas in the →primate frontal cortex, the →frontal eye field (FEF) and the supplementary eye field (SEF) that are involved in the control of eye movements, and during head movements interact with the vestibular system (Fukushima et al. 2006).

10.6.2 Self-orientation and Auditory and Visual Localization

Unusual patterns of vestibular stimulation elicit changes in perceived self-orientation and localization of auditory and visual stimuli, attesting to the interaction of several senses. For example, when subjects in a dark room are exposed to angular acceleration while viewing a head-fixed target, they experience motion and displacement of the target relative to their body (→oculogyral illusion) (Carriot et al. 2011). Similarly, when subjects with a →sound source fixed at some distance to their head are rotated on a slowly rotating platform, the sound source is perceived as directly overhead (audiogyral illusion). A →somatogravic illusion may occur during strong forward accelerations/decelerations during reduced visual information: Strong forward acceleration together with gravity creates a gravito-inertial vector rotated backward, inducing a pitching-up perception. A subject seated in a slowly rotating room with the left ear directed towards the room center will experience a rightward body tilt and see a luminous earth-horizontal line as displaced clockwise (→oculogravic illusion). Such effects suggest that a common reference frame for body sensory localization and localization of body relative to external space are modified (Lackner and DiZio 2005). Vestibular signals also contribute to the estimation of distance of objects in space (Török et al. 2017).

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11

Peripheral Auditory Processing: Anatomy and Functions in Hearing

CONTENTS

Abstract

• Hearing enables detection, perception, characterization and recognition of sounds and their localization in all directions relative to the head.

• Sounds consist of pressure oscillations in gaseous, liquid or solid media, which are funneled by the outer ear and transformed into vibrations of the tympanic membrane (eardrum).

• The middle ear transmits vibrations of the tympanic membrane via three small bones (ossicles) to the oval (round) window. This chain of mechanical links amplifies sound transmission.

• The inner ear contains the complex cochlea, is made up of three compartments or scalae: scala tympani, scala vestibuli and scala media.

• The scala tympani and scala vestibuli are filled with perilymph. The scala media is filled with endolymph and contains the organ of Corti. This organ is mounted on the basilar membrane (BM).

• The stapes in the middle ear acts on the oval window and makes it vibrate within its ligamentous suspension, thereby transmitting movements to the periplymph of the scala vestibuli. Part of the periplymph movement is imparted on the BM, making it move, in a complex, non-linear, spatio-temporal pattern. Inward movement causes a displacement wave that travels along the BM. As the wave travels, it grows in amplitude, peaks and then declines.

• The patterns induced in the BM depend on vibration frequency and amplitude. The BM is narrow and stiff near the oval window where it resonates with high frequencies, and is broad and flexible near the apex where it resonates with low frequencies.

• The maximum amplitude of a traveling wave corresponding to a high-frequency tone occurs close to the oval window, while that of a low-frequency tone is located closer to the apex. The cochlea thus maps frequencies along the longitudinal extent of the basilar membrane.

• The organ of Corti carries hair cells which are arranged in three rows of outer hair cells (OHCs) and one row of inner hair cells (IHCs). On its apical surface, each hair cell carries a bundle of stereocilia.

• Stereocilia of the OHCs are embedded in the overlying tectorial membrane, those of the IHCs are not. Motion of stereocilia in the direction of the longest stereocilium leads to depolarization, whereas motion in the opposite direction causes hyperpolarization.

• IHC depoilarization releases glutamate to activate type-I primary auditory afferents. Hair cells also receive efferent innervation that modulates responsiveness.

11.1 Introduction

It is of particular importance for higher `visual animals´ to sense the spatial layout of the environment when confronted by an array of objects, whether they are mates, predators or prey. While vision is the most accurate far sense, it has the drawback of usually being restricted at any time to spatial elements defined by the eyes´ momentaneous →visual field. By contrast, hearing has a more paramount scope by being able to localize →sounds coming from all directions relative to the head. The auditory system may thus →alert the animal and direct its →attention to non-visible objects and to particular sound sources within the background of other sounds (King et al. 2011). Localization of sounds must be complemented by a precise characterization and →recognition of sounds of interest. Such sounds also signal movements of the body and its interactions with the environment and, hence, the outcomes of actions and the nature of objects interacted with, examples being the rustle of fabric during movement, the sound of touching a chair etc. (Stanton and Spence 2020). Thus, hearing helps the animal identify important events and objects and track the changing position (self-motion), in combination with other sensory inputs (visual, vestibular, proprioceptive) (Campos et al. 2018).

11.2 Sounds

The auditory system has evolved for the purpose of detecting and perceiving sounds that are of survival value, in particular those related to prey, predators and communication with members of the same species (→con-specifics) (Eggermont 2001). Many animals have motor systems that emit and sensory systems that receive such vibrations.

Sounds are mechanical vibrations in gaseous, liquid or solid media. Oscillations of a tuning fork, for example, increase and decrease in local air pressure that radiate at a velocity of ca. 331 m/s at a temperature of 0° C. In water, the velocity of sound propagation is ca. 1,403 m/s (0° C) (York 2009).

A pure tone is a sinusoidal oscillation at a particular frequency and amplitude, and has thus →power only at that frequency. Frequency defines the tone´s perceptual correlate, →pitch (Oxenham 2018; McDermott and Oxenham 2008), and amplitude its loudness. Phase differences between the oscillations reaching the two ears are important for sound localization. Pure tones are rare in nature (Kanwal and Rauschecker 2007). Complex sounds consist of many components of many frequencies, amplitudes and phases. They are thus characterized by a complex frequency-dependent amplitude →spectrum. A repetitive saw-tooth-shaped pressure wave has a spectrum composed of a fundamental repetition frequency and multiples thereof (harmonics). Its pitch corresponds to the fundamental frequency. →White noise is an irregular (non-periodic) temporal sequence of →sound pressures, and has a power spectrum that is flat across the whole frequency axis. Band-passed noise (BPN) has power only within lower and upper frequency values (within a band). Most often, the parameters of a sound (frequency and amplitude) are not constant, but vary with time: frequency modulation (FM) and amplitude modulation (AM).

Complex communication sounds, such as animal →vocalizations and human speech, contain complex temporal structures with slowly and rapidly changing acoustic transients. For instance, speech contains components ranging from the slow (<10 Hz) rhythms of syllables and phrases to rapid (>100 Hz) temporal features (Lu et al. 2001). Human speech is not fundamentally different from animal vocalizations and contains basically the same three elements: →steady state, harmonically related frequencies; frequency-modulated sounds (FMs); and →noise bursts (Kanwal and Rauschecker 2007; Rauschecker and Tian 2000; Eggermont 2001). The understanding of vocalizations and music makes use of →Gestalt (unified whole) principles by which individual sensory stimuli are grouped together into units of →perception (Bizley and Cohen 2013; Jackendorff and Lerdahl 2006; Winkler et al. 2009).

The →intensity of a tone (loudness) is objectively measured on a scale devised by Alexander Graham Bell, inventor of the telephone. He realized that loudness increases according to the Weber-Fechner law as a logarithmic function of tone amplitude. This implies that loudness increases linearly by a constant unit whenever the amplitude increases by a constant factor. This allows us to define loudness as a relative scale on which amplitude is given as a ratio over a reference value. Hence, one deciBel (dB) is defined (e.g., Kelly 1991) as:

$$1 \text{ dB} = 20 \log_{10} P_t/P_r,$$

where P_t is the test sound pressure and P_r is the reference pressure value (physically defined as 20 $\mu N/m^2$). Thus, $P_t/P_r=10$ corresponds to 20 dB, $P_t/P_r = 100$ to 40 dB etc.

The normal hearing range of young human adults depends on frequency. The highest →sensitivity, here defined as the lowest threshold, is attained for tones between about 1-4 kHz. Below and beyond these frequencies, the sensitivity is less. The strongest loudness to be heard without discomfort or pain is about 120 dB, but sounds beyond 100 dB heard over longer periods can damage the inner ear.

Although loudness is a subjective term for the sensation of the intensity of a tone, the dB scale is an objective scale, on which the tone intensity can be measured by means of physical instruments. A subjective scale has been introduced, whose unit is the phon. The phon scale is defined such that it matches the dB scale at 1,000 Hz.

11.3 Requirements of the Auditory System

Several tasks are performed by the auditory system for the purpose of detecting, characterizing and localizing sounds (Griffiths and Warren 2002; Pickles 2015): analysis of the →auditory scene; →sensory transduction; source analysis; sound localization and evaluation; utilization of accessory motor systems.

Auditory Scene Analysis (Bizley and Cohen 2013; Feng and Ratnam 2000; Winkler et al. 2009) is the process by which the human auditory system organizes sound into perceptually meaningful elements. It parses complex and time-varying spectral patterns

of the acoustic environment into coherent →auditory objects, whose identification is aided by regularities in the acoustic scene. It also includes segregation and localization of different auditory objects, and comparison of the spectro-temporal patterns associated with each object with previously experienced ones, which requires →memory.

Mechano-electrical Transduction. This first step converts the sound pressure oscillations into neural signals for further processing.

Characterization of the Sound Source. This process yields information on the quality and quantity of the sound source. It relies on temporal variables such as on/off, response latency and duration; frequency analysis of complex sounds, including the discrimination and separation of frequency components, determination of center frequency and bandwidth of noise bursts, frequency-modulation rate and direction; sound intensity including amplitude modulation characteristics (Joris et al. 2004); enhancement of spectral and temporal →contrasts to improve bad →signal-to-noise ratios (SNRs) of natural signals; extraction and abstraction of behaviorally significant sound parameters.

Sound Localization in Space. The sound source is localized with respect to direction, distance and movement.

Evaluation. The sound source must be evaluated as to its biological significance, e.g., sexual status, food, threat, pleasantness, →emotion (Schirmer and Adolphs 2017).

Motor Systems are utilized which activate protective middle-ear muscle →reflexes, auditory orientation reflexes that aid in detecting novel, salient sounds, and acoustic →startle responses to abrupt, unexpected, intense stimuli (Metzner 2009).

11.4 Regularities in Natural Sounds

So-called `natural sounds´ are important for animal survival and include vocalizations, noises arising from wind, water and fire, and non-vocal sounds made by animals and humans for communication (Eggermont 2001; Theunissen and Elie 2014). The spectro-temporal structure of such sounds is not stochastic, but exhibits regularities, whose neural representations help parse the complex acoustic environment into auditory objects. For example, there are high-level auditory neurons that are exquisitely selective for con-specific calls (Theunissen and Elie 2014). These representations also enable perceptual continuity by making predictions about future sound-source behavior (Bizley and Cohen 2013; Winkler et al. 2009). Sound discrimination is improved by the use of an →efficient code (Beyeler et al. 2019) to represent the sounds of vital interest. In so doing, the auditory system has adapted its neural encoding mechanisms to the statistical structure of natural auditory information (Rieke et al. 1995; Theunissen and Elie 2014).

11.5 The Ear

The ear has a long evolutionary history (Fritzsch and Beisel 2001; Grothe et al. 2010; Manley and Köppl 1998). A novel feature of vertebrate ears is the development of secondary sensory neurons that connect the primary receptor cells constituted by →hair cells (below) to the brain (Fritzsch and Beisel 2001). Among mammals, humans are superior in terms of intensity and frequency discrimination and sound localization (Ridgway and Au 1999). →Ontogenetically, the development of outer, middle and inner ear depends on genes involved in →hindbrain segmentation and segment identity (Fekete 1999).

11.6 Funneling Sound: The Outer Ear

To be received and perceived, air pressure oscillations must first be transformed into →receptor potentials in auditory hair cells. This is done in several steps, the first one being the transformation of air pressure oscillations into vibrations of the tympanic membrane (eardrum).

Many animals are equipped with impressive movable pinnae that sub-serve several functions. They are used for the collection and filtering of sound: Pinna shape and size endow it with a particular resonance that contributes to filtering the transmission of sound. Pinnae also contribute to sound localization, due to different resistances to sound propagation regulated by the two pinnae. In humans, these processes play a minor role in sound localization. Outer ear resonance is most pronounced in the frequency range of speech. The external auditory canal enhances sound →energy around 270 Hz.

Sound is conducted through the external auditory meatus (auditory canal) and produces vibrations of the eardrum (tympanic membrane). In the auditory canal, resonance causes acoustic amplification at the eardrum of about 10 dB in the 2-4 kHz frequency range.

11.7 Transformation of Sound In The Middle Ear

Hair bundles of hair cells cannot survive in air, but must be bathed in a liquid environment. Sound pressure fluctuations in air must therefore be transformed into pressure vibrations in water, but the impedance of sound wave transmission is much higher in water than in air. Hence, the air-water boundary reflects sound and requires an amplification mechanism. This mechanism is supplied by the middle ear.

The middle ear transmits vibrations of the tympanic membrane via three small bones (ossicles) to the oval window, behind which the liquid phase begins. This chain of mechanical links amplifies sound transmission. This gain amplification is brought about by two factors. First, in humans the area of the tympanic membrane is greater by a factor of ca. 19 than the area of the oval window. Second, the ossicle chain is a lever system with a frequency-dependent amplification factor of 1.3 at a frequency of 1,000 Hz. In total, then, the amplification factor is ca. 24.

Sound transmission can be modulated by muscular action. Contraction of the stapedius muscle, which is connected to the stapes, reduces the transmission gain. This action is meant to be protective. Before chewing or speaking, the stapedius muscle contracts and thereby reduces the potentially damaging transmission of chewing or speaking sounds to the inner ear.

11.8 Decomposing Sound in the Inner Ear

Once sound pressure vibrations have penetrated into the final medium, sound analysis begins. More than a century ago, the physicist Georg Ohm suggested that the inner ear decomposes complex sounds into their frequency components (Kelly 1991). This analysis is performed by a sophisticated system of mechano-neural devices assembled in the cochlea. The analysis proceeds in steps.

In humans, the cochlea is about 34 mm long and spirals 2.5 times around the modiolus (Fettiplace 2020). The cochlea contains three compartments or scalae: scala tympani; scala vestibuli (continuous with the scala tympani at the helicotrema); scala media, which ends blindly at the apex. The scala tympani and scala vestibuli are filled with →perilymph. The scala media is filled with →endolymph and contains the organ of Corti. This organ is mounted on the basilar membrane (BM).

11.8.1 Frequency Dispersion

Frequency analysis of sound is accomplished in the cochlea (Oxenham 2018; Ulfendahl 1997; Robles and Ruggero 2001). The stapes acts on the oval window and makes it vibrate within its ligamentous suspension, thereby transmitting movements to the periplymph of the scala vestibuli. Because watery solutions such as the periplymph are almost incompressible, any inward movement at the oval window requires a compensatory outward window movement. However, because the helicotrema, where the scala tympani and the scala vestibuli meet, is too narrow to allow much fluid flow, part of the periplymph movement is imparted to the basilar membrane, making it move in a complex, non-linear, spatio-temporal pattern. Inward movement causes a displacement wave that travels along the basilar membrane. As the wave travels, it grows in amplitude, peaks and then declines. The patterns induced in the basilar membrane depend on vibration frequency and amplitude. The basilar membrane is narrow (100 μm) and stiff near the oval window where it resonates with high frequencies, and is broad (500 μm) and flexible near the apex where it resonates with low frequencies (von Helmholtz´s resonance theory) (Kelly 1991). Therefore, the maximum amplitude of a traveling wave corresponding to a high-frequency tone occurs close to the oval window, while that of a low-frequency tone is located closer to the apex. In this way, each cochlear site responds maximally to a particular characteristic frequency. What the cochlea does, then, is sort of a spatial Fourier analysis (→Fourier transform) by mapping frequencies along the longitudinal extent of the basilar membrane (→tonotopic map) (von Békésy 1960).

The amplitude of basilar membrane displacement is also a function of sound intensity. The minimum auditory threshold is at a sound pressure of about 20 μPa, which causes a basilar membrane movement of only 1 nm in amplitude (Fettiplace and Hackney 2006). The loudest tolerable sound (ca. 120 dB) shakes the basilar membrane by about ±10 nm. The input-output relation is thus non-linear (compression non-linearity) in that the output scales as the one-third power of the input (Hudspeth 2008). Close to the oval window compression non-linearity keeps displacement amplitudes in check to prevent damage to the hair cells (Robles and Ruggero 2001).

11.8.2 Mechano-electrical Transduction

The next step takes place in hair cells of the organ of Corti. The hair cells are arranged in three rows of 12,000-13,000 outer hair cells (OHCs) and one row of ca. 3,500 inner hair cells (IHCs). On its apical surface, each hair cell carries a bundle of stereocilia, modified →microvilli that contain actin filaments. Stereocilia of the OHCs are embedded in the overlying tectorial membrane, those of the IHCs are not. Oscillatory movements of the basilar membrane result in shearing movements between the tectorial membrane and the hair cell surface and in bending of the stereocilia, where stereociliary movements of the IHCs are probably caused by motion of the surrounding fluid, thus responding primarily to the velocity of basilar membrane movement (Fettiplace and Hackney 2006).

Very much like in vestibular hair cells, the bending and relative motion of stereocilia are thought to directly open →ion channels via a mechanical link from the top of one stereocilium to the side wall of its longer neighbor. These mechano-electrical transduction (MET) channels probably are large-→conductance cation channels, most permeable for calcium (Ca^{2+}) with some permeability for small organic cations. *In vivo*, these channels mainly conduct potassium (K^{+}) which is the most abundant cation in the endolymph (Douguet and Honoré 2019; Qiu and Müller 2018; Zheng and Holt 2021). Motion of stereocilia in the direction of the longest leads to →depolarization, whereas motion in the opposite direction causes →hyperpolarization (Fettiplace 2009; Fettiplace and Hackney 2006; Fettiplace and Kim 2014; Hudspeth et al. 2000; Pan and Holt 2015; Qui and Müller 2018; Vollrath et al. 2007). In mammals, the activation →time constant of the MET channel is extremely fast, probably less than 10 μs (Fettiplace 2009).

Hair-cell responses to stereociliary deflection initially overshoot and then adapt in fast and slower phases (Fettiplace 2009; Vollrath et al. 2007). The initial →adaptation is faster than in vestibular hair-cell stereocilia and may involve additional mechanisms such as Ca^{2+}-binding to the MET channels (to promote their re-closure and fast adaptation), accessory structures, voltage-dependent hair-cell properties and afferent →neurotransmitter release (Eatock 2000; Fettiplace 2009). The time constant of fast adaptation is inversely related to hair-cell characteristic frequency, allowing sensitivity to very high frequencies; the slower adaptation likely involves a non-muscle myosin (Fettiplace and Hackney 2006).

Sound Frequency Discrimination. In the course of vertebrate evolution, the range of the sound frequencies to be represented has extended upwards by recruiting different filter mechanisms for frequency discrimination. Non-mammalian hair cells developed a mechanism in which electrical resonance of receptor potentials is provided by →Ca^{2+}-activated K^+ channels, generating band-pass filters with center frequencies <1 kHz. This mechanism is not used in mammals In frogs and lizards, the electrical resonance is supplemented by a mechanical resonance of the sensory hair bundles that extends the upper frequencies up to 10 kHz. In the mammalian cochlea, some mechanisms interact. The locally varying mechanical resonance of the basilar membrane is amplified and sharpened by extra force supplied by OHCs: stimulation of the hair bundles elicits contraction of the OHCs´ cell bodies, which counteract fluid damping and boosts the motion of the basilar membrane. This mechanism creates narrow-band filters extending up to 100 kHz (Fettiplace 2020). Furthermore, the mechanical properties of the OHC stereocilia vary with location along the basilar membrane. Close to the oval window, the stereocilia are stiff and short, close to the apex, long and more flexible. This endows OHCs with different mechanical resonances matched to the changing resonance of the basilar membrane.

11.8.3 Signal Amplification

As compared to other →sensory receptors, e.g. olfactory receptors or photoreceptors, hair cells must operate, at threshold, with much smaller energy levels close to the thermal noise level. For example, in the chinchilla cochlea, at 9 kHz corresponding to a site 3.5 mm from the oval window, the threshold for nerve fiber excitation corresponds to a displacement of 1 nm and a velocity of 50 μm/s of basilar membrane motion (Ruggero et al. 2000). The stimulus limit of hair cells is very narrow, corresponding to a total excursion of their hair bundle of about 100 nm at the tip (Fettiplace and Ricci 2003). Reliable stimulus detection under these conditions might be mediated by the repetitive nature of sound oscillations, giving rise to mechanical resonance of the cochlea and ultimately the hair bundles. Although the surrounding endolymph heavily suppresses hair-bundle oscillations by →viscous damping, an active process that amplifies the hair-bundle oscillations could counteract it. Active amplification is suggested by the superb technical performance of the inner ear, with its high sensitivity and frequency selectivity, and by oto-acoustic emissions from the inner ear, whether occurring spontaneously or in response to stimuli. In mammals, the active process based on molecular motors might reside in OHCs, which contract upon depolarization and elongate upon hyperpolarization, thus explaining →reverse transduction of an electrical signal into a mechanical event. These active length changes might be effected by molecules in the basolateral plasma membrane and, via an unknown mechanism, be transmitted to, and enhance the sensitivity of, the IHCs. In lower vertebrates, the mechanism appears to reside in the hair bundles that can move actively (Ashmore et al. 2000; Avan et al. 2013; Brownell et al. 2001; Fettiplace et al. 2001; Fettiplace and Hackney 2006; Fettiplace and Ricci 2003; Hudspeth 2008, 2014; Hudspeth et al. 2000; Qiu and Müller 2018; Robles and Ruggero 2001). However, these potential mechanisms are still in question (Ren and Gillespie 2007).

11.8.4 Afferent Innervation and Glutamatergic Activation of Hair Cells

Innervation patterns of cochlear hair cells at their base are primarily responsible for the detection and measurement of sound. Each of the type I afferents innervates a single hair cell, but each IHC is innervated by as many as 10-20 afferents. The OHCs are innervated by the remaining 5-10% of the VIIIth nerve primary afferents (type II). Each type II afferent innervates many hair cells.

Upon depolarization, IHCs release →glutamate onto →α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA), →kainate and →N-methyl-D-aspartate (NMDA) receptors of type I primary afferents (Puel 1995). IHC glutamate has also a potent neurotoxic effect and may be responsible for damage to afferent nerve terminals and ensuing neuronal death, leading to noise-induced hearing losses (acoustic trauma), neural presbyacusis (age-related hearing loss), forms of sudden deafness or peripheral tinnitus (Puel 1995). Nonetheless, tinnitus probably has an additional, substantial cortical contribution.

Single-Tone Excitation. Cochlear nerve fibers display spontaneous activity at rates between a few spikes/s to 100-200 spikes/s (Evans 1974). Some fibers may phase-lock to the sine waves of single-tone stimuli for frequencies below 4,000 Hz. The response to single-tone stimulus is relatively simple and a function of frequency, stimulus level and time. The threshold stimulus level evoking a response that differs from spontaneous activity is a function of frequency with the threshold increasing from a minimum at the characteristic frequency, to higher levels toward lower and higher frequencies. These two branches define the frequency-threshold curve (FTC) or tuning curve and include the frequency-response area (FRA). Tuning curves vary among different cochlear nerve fibers. Plotted on a logarithmic frequency axis, the FTCs become increasingly narrow and asymmetric with increasing characteristic frequencies. Cochlear nerve fibers have been grouped into three classes (Frisina 2001). One class comprises fibers with high spontaneous firing rates and low thresholds. Conversely, fibers with low spontaneous rates and high thresholds fall into another class, and the third (medium) class comprises fibers with intermediate properties. It is important to note that, with higher sound levels, the tuning accuracy declines, implying that an individual cochlear nerve fiber is excited by a wide range of frequencies. Precise frequency determination would therefore call for sharpening mechanisms.

Cochlear Two-Tone Suppression. In most situations, single tones would be artificial stimuli, the common case being sounds with complex spectra. Because the non-linear dynamics of the basilar membrane are complex, corresponding interactions would be expected for natural sounds. This is exemplified by interactions of two tones. The best-known interaction phenomenon is two-tone suppression, implying that activity elicited by one stimulus (tone or noise) is suppressed by another tone over a restricted range of frequencies and intensities.

11.8.5 Efferent Innervation of Hair Cells

Outer hair cells are innervated by efferent →cholinergic nerve fibers originating in the medial nuclei of the superior olivary complex (SOC), while →synaptic transmission from inner hair cells to type-I primary afferents is controlled and/or regulated by efferent fibers →synapsing on afferent nerve terminals (Fettiplace 2020). Inner-ear efferents are closely associated with facial →motoneurons (→cranial nerve VII). They may be involved in the ontogenetic development of the cochlea by making transitory connections with IHCs and causing IHC afferents to fire rhythmically, which appears important in refining synaptic connections in the auditory system (Manley and Köppl 1998).

11.8.6 Representation of Sounds in Afferent Neural Firing

Re-encoding and transmission of sounds as hair-cell membrane potential changes is a complex process, because sounds have different dimensions that may all be biologically important for their identification. For instance, in human speech, vowel sounds differ as to the relative strengths of their harmonics, requiring a good capacity for frequency analysis. On the other hand, certain consonant sounds such as `ta´ and `da´ or `ba´ and `pa´ differ in voice onset time of a few tens of milliseconds, so that temporal analysis becomes important. Precise temporal information also subserves sound localization, which in many cases depends on time-of-arrival differences between the two ears. Encoding of these variables requires a well-balanced trade-off between frequency and temporal information. In addition, sound intensity must be encoded in some way. Conversion of hair-cell receptor potentials into afferent nerve fiber →spike trains will be described before considering the coding issue.

Sound intensity can be effectively encoded as mean discharge rate, since tone bursts of a particular frequency (e.g., 5 kHz), but of varying intensities, evoke afferent discharges tuned to that frequency, such that the mean rate increases with intensity, with an initial overshoot and terminal undershoot. However, coding of tone frequency requires a different approach.

The high tone frequencies heard by humans (up to 20,000 Hz) and more so by bats (up to 150,000 Hz) cannot be directly encoded by a 1:1 translation into neural discharge, i.e., one spike per oscillation, for two reasons. First, this would interfere with →intensity coding as described above. Second, neurons cannot fire at such high rates. There are two possibilities to encode high tone frequencies: phase locking and frequency labeling (Kelly 1991).

Phase Locking. Afferent spikes occur at a defined phase of the input cycle, thus coding the time of its occurrence. Phase locking may occur at up to 8,000 Hz, but due to limitation in discharge rate, phase-locked spikes cannot occur in response to each successive cycle. However, several fibers from the same cochlear region may respond to different cycles such that their synchronized ensemble discharge (ensemble code) could replicate the timing of successive input cycles (volley principle). The ensemble

discharge would need to be decoded by a subsequent neuron upon which the ensemble converges.

Frequency Labeling. The site of origin of an afferent fiber along the basilar membrane defines the meaning of its frequency code (place principle). This implies that frequency-dependent, ordered connections are operative (→tonotopic mapping) throughout the successive auditory processing stages as a special case of →labeled-line coding. Speech, for example, is encoded in combinations of firing rate, synchronized firing and interspike intervals. Cells in the →cochlear nucleus can extract either firing rate (→stellate cells) or firing synchrony (→bushy cells and →octopus cells) (Eggermont 2001). Precise timing of firing and its preservation through successive synaptic stages from the auditory nerve through →brainstem nuclei are ensured by a number of cellular specializations and adaptations, including fast-acting voltage- and transmitter-gated channels, and large nerve terminals that release large amounts of neurotransmitter (Trussell 1999).

11.8.7 Efficient Coding of Sounds in Auditory Nerve Spike Trains

The firing of each primary auditory nerve fiber reflects the temporal structure of an acoustic signal and its frequency content in a heavily filtered version. This duality necessitates a trade-off. On the one hand, accurate estimation of a frequency component requires that neural activity be assessed over many cycles. However, long assessment periods decrease the temporal accuracy. Since discrimination of natural sounds often requires accurate measurements of frequency as well as timing, the auditory system must find an optimal balance between timing and frequency analysis (Olshausen and O ´Connor 2002).

Primary auditory fibers encode natural sounds, for example those related to communication, more efficiently than broad-band (near white noise) stimuli. The rate at which the afferent spike train carries information is 2-6 times higher for natural stimuli, reaching up to 90% of the limit for information transmission set by the statistics of the spike response (Rieke et al. 1995). Efficient coding, adapted to statistical environmental properties, is also observed at higher processing stages such as the →inferior colliculus (IC).

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12

Central Auditory Processing: Pathways and Functions

CONTENTS

Abstract

• Central auditory processing depends on functional pathways that are organized for the most part tonotopically for the purpose of sound identification and sound localization.

• Primary auditory nerve fibers first target brainstem nuclei. Brainstem nuclei serve local reflex functions, but also provide for complex signal processing. There is an extensive, conspicuous crossing of connections, which has a functional basis in the need for binaural integration.

• The auditory cortical system consists of many interconnected areas that occupy a wide expanse, and is organized both hierarchically and in parallel. The hierarchical arrangement runs through at least four distinct levels, each containing several sub-divisions. Different areas are probably organized in two parallel main streams, one devoted to sound identification and the other to sound localization.

• The ventral sound-identification pathway starts in the brainstem and continues via the thalamus to the primary auditory cortex. The ventral stream is dedicated to auditory pattern and auditory-object identification and recognition.

• An alternative model suggests that the ventral pathway is primarily involved in perception of the temporal evolution of acoustic signals, which is important for perception of speech and vocalization.

• The dorsal sound-localization pathway starts in the brainstem and continues to the primary auditory cortex. In this circuit, several acoustic cues are exploited, based on the filter properties of the head and the ears.

• Acoustic cues involved in sound localization are computed in the dorsal pathway by comparing sound-pressure levels in the two ears. In animals with large heads and well-separated ears, interaural time differences are detectable when sounds arrive at different times from sources outside the sagittal plane.

• Deep layers of the superior colliculus contain an auditory map, where the locations of neurons are related to their directional sensitivities.

• The auditory system is plastic and can change its properties on short- to long-term bases.

12.1 Introduction

Two major tasks of the auditory system are to identify and to localize a salient sound source, which may originate from a wide spectrum of sources.

Sounds rarely occur in isolation in natural environments. Rather, they exist as complex mixtures that overlap and vary in time and frequency, occur within complex acoustic contexts, and they originate from different locations. The auditory system must therefore perform an →auditory scene analysis, i.e., grouping and segregation of different sounds to accurately identify and localize behaviorally relevant →auditory objects (Angeloni and Geffen 2018; Bizley and Cohen 2013; Cohen et al. 2016; Feng and Ratnam 2000; King et al. 2018; Nelken et al. 2014).

Sound identification starts in the peripheral auditory system which encodes acoustic features of speech, music, and →vocalizations such as →pitch, spectral envelope, amplitude modulationt, frequency modulation, and sound level dynamics. These features are progressively processed along the ascending auditory pathway and transformed into neural representations of the auditory cortex (Wang 2018).

Of great importance is the accurate localization of behaviorally relevant sound sources within a complex acoustic world (Ahveninen et al. 2014; Feng and Ratnam 2000; Middlebrooks 2015). This capacity contributes to the separation of sound sources and thus auditory scene analysis. Together with visual, vestibular, tactile, and proprioceptive signals, auditory cues contribute to self-motion perception, i.e., the estimation of a subject´s dynamically changing position relative to environmental events and objects during the maintenance of →balance, walking and driving (Campos et al. 2018). Spatial hearing helps localize prey, predators food, water, familiar members of the same species (→con-specifics), potential mates, and directs →attention, and often the gaze, towards events or objects of potential interest.

Despite the complexity of major auditory tasks, central auditory processing follows a few principles that depend on functional pathways, organized for the most part →tonotopically: At each →brainstem center and within the auditory portions of the →cerebral cortex, there is an orderly mapping of frequency to place, so that the spatial arrangement of structures subserves various frequencies, thereby enabling sound identification and sound localization.

12.2 Auditory Processing in the Brainstem

Primary auditory nerve fibers from the cochlea first target brainstem nuclei (Pickles 2015). These nuclei subserve →reflex functions and complex processing of auditory signals before being sent to higher structures. For example, connections from the medial superior olivary complex (SOC) to →trigeminal and facial →motoneurons innervating tensor tympani and stapedius muscles protect against high-→intensity sounds (Metzner 2009; Nieuwenhuys et al. 1978).

Auditory Reactions. Environmental features that are frequently novel are first detected by hearing; consequently the eyes and head are reflexly turned toward the source. This requires convergence of auditory, visual and oculomotor signals, and perhaps other sensory signals, as early in brainstem nuclei as the →inferior colliculus (IC) (Gruters and Groh 2012). An important role may also be played by connections from the inferior to the →superior colliculus (SC). The inferior colliculus bears a map of auditory space, and the superior colliculus (SC) carries maps of auditory, visual and somatosensory space. Proper congruence of these maps is established by →learning from experience.

Parallel Signal Processing. Auditory nerve fibers →synapse in the brainstem cochlear nucleus. The →cochlear nucleus contains at least seven morphologically and physiologically distinct principal cell types that project to subsequent nuclei in segregated pathways, each providing different representations of the acoustical signal (Yu and Young 2000). The ventral cochlear nucleus (VCN) contains three major groups of neurons: →octopus, →stellate, and →bushy cells. These cells extract different features of the spectral properties of sounds and send their signals on along parallel pathways. Two of these pathways carry temporal information. →Octopus cells feed monaural pathways and detect coincident firing among auditory nerve fibers. T stellate, (also called chopper cells) play an important role in pitch perception. They discharge →action potentials at various constant intervals that are integer multiples of 0.4 ms, irrespective of input frequencies. Chopper neurons build small networks incorporating different types of →neuronal oscillators, which correlate features of the acoustic input signal with each other or correlate the features of the input signal with →neuronal oscillations, with the temporal scale provided by the chopper neurons. This pattern is subsequently mapped spatially in the inferior colliculus (Bahmer and Gupta 2018). Bushy cells feed binaural pathways which serve to localize the azimuthal direction of sound origin. This function relies on comparisons of timing and intensity between the two ears (Oertel et al. 2017).

12.3 Organization of the Auditory Cortex

Auditory processing in the cerebro-cortical system (Romanski and Averbeck 2009) varies among species, and depends on habitat and communication function (Hackett 2015**)**. For example, monkey →cortical areas involved in auditory processing cover a large expanse. In the awake, passively listening rhesus monkey, the auditory system includes the entire superior temporal gyrus (STG) and large portions of the →parietal, →prefrontal, and →limbic cortices. Several auditory areas overlap with visual areas, suggesting that the auditory system, like the visual system, contains separate ventral and dorsal pathways for processing stimulus quality, location, and motion (Cohen et al. 2016; Poremba et al. 2003; Poremba and Mishkin 2007; Romanski and Averbeck 2009).

Monkey cortex has at least 20 interconnected auditory areas or →multi-modal regions, where even early auditory areas receive somatosensory and visual inputs from various sources (Smiley and Falchier 2009). This system is organized both hierarchically and in parallel. The hierarchical arrangement runs through three cortical auditory regions described as core, belt and parabelt. Each contains several sub-regions (Kaas and Hackett 2000; Kanwal and Rauschecker 2007; Recanzone and Sutter 2008; Romanski

and Averbeck 2009; Schreiner and Winer 2007). The parabelt projects to other regions of the cortex involved in auditory processing.

Core. The Core consists of three fields: primary auditory cortex (A1) (caudal), rostral field (R), and rostral temporal field (RT). All three areas have architectonic characteristics of primary sensory cortex with a well-developed layer IV of granule cells, and receive parallel projections from the principal or ventral nucleus of the thalamic medial geniculate body (complex). The Core fields carry →tonotopic maps of the cochlea (Kanold et al. 2014), with frequency reversals at their boundaries.

Belt. The belt surrounds the Core as a narrow (2-3 mm wide) band, compatible with a secondary sensory cortex. It receives inputs from the dorsal and magnocellular parts of the medial geniculate complex. The belt is connected with closely adjacent core, the parabelt region and the →prefrontal cortex (PFC). It consists of eight fields, each with a crude representation of the cochlea.

Parabelt. The parabelt receives most of its inputs from the belt region**,** and from several nuclei of the medial geniculate complex. It connects to the superior temporal gyrus (STG) and prefrontal cortex (PFC) as well as to the contralateral parabelt and belt.

Other Areas. The projections of parabelt to nearby and more remote prefrontal cortex (PFC), temporal cortex and →parietal cortex define a fourth level of auditory processing. These projection areas include the superior temporal polysensory (STP) area, the →frontal eye field (FEF) involved in oculomotor control, the →dorso-lateral prefrontal cortex (DLPFC) involved in spatial working memory, the ventro-lateral prefrontal cortex (VLPFC) involved in non-spatial, →multi-sensory characterization and →recognition of objects (Rämä 2008), the →orbito-frontal cortex (OFC) involved in multi-sensory →emotional and →motivational evaluation of stimuli.

In humans, the primary auditory cortex is situated in →Brodmann´s area 41 and area 42 in the superior temporal gyrus (*Heschl´s gyrus*) and is organized tonotopically. Low-frequency tones are represented laterally and high frequency tones medially. The `belt area´ in humans is most likely area 22 and part of area 42. Auditory association areas include the →planum temporale (Griffiths and Warren 2002), area 22 for the interpretation of sound, including speech (Wernicke´s area) and area 44 and area 45 for the control of speech (Rauschecker and Scott 2009).

The →insula seems to play an important role in auditory processing, since bilateral lesions lead to auditory →agnosia, manifested primarily in an inability to recognize or differentiate between sounds. The caudal insular cortex appears to be involved in representing vocal communication of sounds (Remedios et al. 2009). The insula in general is a multi-functional cortical region subserving visceral, sensory, motor, vestibular and somatosensory functions. It participates in temporal processing directed toward novel auditory stimuli, in allocating attention, in phonological processing and in visual-auditory integration (Bamiou et al. 2003).

Tonotopy or Cochleotopy. Terminations of primary auditory nerve afferents in the brainstem dorsal and ventral cochlear nuclei are organized spatially according to their origin from the cochlea. Tonotopy is represented on a global scale in the primary auditory cortex (A1) (Kanold et al. 2014). For at least three reasons, tonotopy is not sufficient alone for adequate pitch →perception. First, there are other sources of information related to pitch, such as temporal firing patterns (Griffiths et al. 1998).

For example, primary auditory nerve fibers fire synchronously, phase-locked to the waveforms of low-frequency tones or with amplitude modulation of high-frequency tones. Second, an individual auditory nerve fiber or central neuron may fire at the same rate in response to either low-level stimulation at its optimal frequency or to higher-level stimulation at other frequencies. Hence, it is the pattern of activity of many neurons, active at the same time, which provides unambiguous information regarding pitch. Third, the context and history of stimulation play a role in shaping an individual neuron's firing rate. One consequence is that humans are better at discriminating relative frequency relationships than at judging individual frequencies. Spatial organization per se is not clearly related to pitch perception, and how this and sound-→intensity perception are separated is still undetermined (Covey 2000).

12.4 Sound Identification and Sound Localization

Identification and localization of sound appear to be served by parallel systems that originate in the brainstem and project finally to auditory regions of the cerebral cortex (Bizley and Cohen 2013; Kanwal and Rauschecker 2007; Kraus and Nicol 2005; Rauschecker 2018).

The pathway associated with sound identification starts in the →stellate cells of the anterior ventral cochlear nucleus (AVCN) and the posterior ventral cochlear nucleus (PVCN) and computes spectral representations of sound. The temporal and spectral information is conveyed via the monaural nucleus of the lateral lemniscus (NLL) to the central nucleus of the inferior colliculus (ICC) and thence to the →thalamus and primary auditory cortex (Eggermont 2001; Gruters and Groh 2012). At the cerebro-cortical level, the ventral stream emanates from antero-lateral belt areas AL and ML (receiving inputs from AI and R) and projects ventrally via temporal cortical areas to ventro-lateral prefrontal cortex (VLPFC) and orbito-frontal cortex. The ventral stream is dedicated to auditory pattern and auditory object identification and recognition, using characteristic features such as timbre, pitch and loudness (Bizley and Cohen 2013; Brefczynski-Lewis and Lewis 2017). It has been hypothesized that the ventral pathway is organized hierarchically: In the early auditory cortex, neural activity is supposed to reflect auditory stimulus properties; in later auditory cortex, neural activity encodes the evidence leading to an auditory decision, and activity in the prefrontal cortex (PFC) then reflects the actual perceptual decision (Cohen et al. 2016). In humans, the superior temporal cortex also contains regions specific to speech perception and voice discrimination (Rauschecker and Scott 2009). Brain imaging studies in humans indicate that pitch tasks, spectro-temporal feature processing, phonetic and object recognition, and speaker identification are associated with the ventral stream (Read et al. 2002). An alternative model suggests that the ventral stream is primarily involved in perception of the temporal evolution of

acoustic signals, based on an accurate analysis of changes in spectral content, i.e., spectral motion, which is important for perception of speech (Kluender 2009) and animal vocalization (Belin and Zatorre 2000). There is also evidence from humans for lateralization of auditory functions. Speech sounds are processed primarily in the left cortex and music sounds in the right cortex, with this asymmetry being most prominent in the planum temporale (Tervaniemi and Hugdahl 2003).

The pathway for sound localization starts in the bushy cells of the AVCN, which target the superior olivary complex (SOC) (Eggermont 2001; Grothe et al. 2010; Oertel et al. 2017). This brainstem pathway also subserves fast reflex functions. The SOC then projects to the inferior collicus (IC), which provides a projection via the thalamus to the primary auditory cortex, and another projection via the external nucleus of the inferior colliculus (ICX) (Gruters and Groh 2012) to the superior colliculus (SC), the latter two structures bearing maps of auditory space. At the cerebro-cortical level, the dorsal stream starts from caudal belt areas CL and CM, projects to →posterior parietal cortex (PPC) and dorso-lateral prefrontal cortical (DLPFC) areas, and is mostly dedicated to the perception of auditory space and motion (Bizley and Cohen 2013; Middlebrook 2015; Rauschecker 2018; Rauschecker and Scott 2009; Recanzone 2000; Romanski and Averbeck 2009). Neuroimaging studies in humans have supported a posterior cortical `where´ pathway that includes areas such as the planum temporale (PT) and posterior superior temporal gyrus (STG), which are strongly activated by horizontal sound direction changes, distance changes and movement. However, these areas are also activated by other stimulus features (Ahveninen et al. 2014). Human brain imaging also indicates that identifying single sounds within words (phonemes), along with sound-localization tasks, are associated with the dorsal pathway (Read et al. 2002). The dorsal stream also exhibits a high temporal resolution suggesting a role in time processing (`when´), speech and language. It has been proposed that the dorsal stream embodies an →internal model of the outside world (including the own body), which incorporates important elements of a control circuit. As a consequence of head (and whole-body) movements during auditory scene analysis, the conversion of sensory-motor sequences into a unified experience may be one of the generalized functions of the dorsal stream. Requisites of these functions are to enable the coding and processing of ordered sequences and the implementation of sequence →memory in sensory perception (Rauschecker 2018; Rauschecker and Scott 2009).

The two pathways for sound identification and sound localization are not completely segregated. Some sound identification processes occur in the dorsal pathway and some localization processing occurs in the ventral pathway (Bizley and Cohen 2013; King and Nelken 2009).

12.5 Identification and Discrimination of Sound Properties

12.5.1 Sound Processing in the Auditory Cortex

Many response properties of neurons in the primary auditory cortex (A1) are strikingly similar to those of →sub-cortical neurons but sensitive to combinations of sounds, which cannot be predicted from their responses to tones. Cortical processing is heavily

influenced by the environmental contexts in which the sounds occur, by task demands and behavioral state. It integrates auditory and other sensory inputs, signals about current internal state, including →arousal level, deployment of attention, motor planning, and past experience (Angeloni and Geffen 2018; King et al. 2018).

Primary Auditory Cortex (Area A1). Along the ascending auditory pathway neurons display a progressively increasing stimulus selectivity, which is accompanied by changes in firing pattern. An auditory nerve fiber is primarily selective for one stimulus dimension, the frequency of a pure tone. In the layers of area A1 receiving inputs from the thalamus, sounds may be represented by cells that are tuned to pure tones or individual frequency components. However, in awake animals many neurons in area A1 do not respond to pure tones and are often found in the superficial layers. Such neurons are →sensitive to complex acoustical stimuli characterized by precise spectral and temporal combinations of two-tone pips. Thus, in awake animals, many cells display a stimulus selectivity defined in a multi-dimensional acoustic space, e.g., frequency, spectral bandwidth, sound intensity, amplitude or frequency modulation, and vocalizations (Wang 2018). Many auditory cortex cells also tend to extract pitch and to respond to timbre and location, and process binaural disparities. They might thus contribute to the representation of auditory objects, i.e., elements that produce an acoustic image with frequency and time dimensions. Their responses are highly adaptable and depend on context and experience, which may contribute to →perceptual learning. Moreover, they contribute to perceptual →decision making. Of importance is also the ability to predict natural sound sequences like speech and music (Rajendran et al. 2018). There is evidence indicating that area A1 neurons are sensitive to deviance or surprise and encode →prediction errors (Brefczynski-Lewis and Lewis 2017; Griffiths and Warren 2004; King et al. 2018; King and Nelken 2009; Nelken et al. 2014).

Tonotopy in Area A1. Center frequency is represented as several tonotopic gradients. Large groups of contiguous neurons that are tuned to one center frequency expand along iso-frequency strips. This frequency representation however depends on experience and is susceptible to long-term reorganization (Read et al. 2002). In the domestic cat, within and along each iso-frequency strip of and orthogonal to the cochleotopic gradient, there are multiple gradients representing discharge properties that are coded as time and intensity differences, in clusters of neurons with similar properties. A similar tonotopic organization is found in →primates (Schreiner et al. 2000; Read et al. 2002).

Belt and Parabelt. Areas A1 and R in the core region of the auditory cortex in marmosets contains a set of so-called `harmonic template neurons´ that do not respond or respond only weakly to pure tones or two-tone combinations but strongly to particular combinations of multiple harmonics. These cells can represent combinations of multiple harmonics and may play a role in processing sounds with harmonic structures such as animal vocalizations, human speech and music. In marmosets, neurons with pitch-selective responses are concentrated in a pitch center, which appears to be overlapping low-frequency portions of areas A1, R, and anterior-lateral (AL) and medio-lateral (ML) belt areas and which is similar to a pitch region in lateral Heschl's gyrus found by several human imaging studies. These pitch-selective neurons are tuned not only to low-frequency pure tones (<1,000 Hz) but also to missing fundamental harmonic complex sounds with a pitch near a neuron's BF (Wang 2018). In the awake behaving monkey,

cells in the rostral core auditory area (R) exhibit the sharpest frequency tuning, while area A1 neurons are tuned slightly less sharply. By contrast, cells in area CM are broadly tuned, probably because they integrate information across frequencies to sharpen their tuning for spatial acuity (Recanzone 2000). In the lateral belt areas of monkeys, neurons are tuned to the best frequency and bandwidth of band-pass filtered →noise, as well as to several con-specific vocalizations (Kanwal and Rauschecker 2007).

Two-tone Interactions in Area A1. In the cat, area A1 appears to be functionally divided into a ventral part where neuron discharge properties are more suited for narrow-band sound analysis, and a dorsal part with neurons for broad or multi-peaked frequency tuning and analysis of complex spectral patterns (Sutter et al. 1999). The structure of inhibitory side bands is more diverse in area A1 than in the primary auditory nerve or the inferior colliculus (IC). One to four suppressive side-bands flank an excitatory frequency-response area (FRA) in the dorsal pool of neurons of area A1, whereas the simple two-banded structure is less common (Sutter et al. 1999). In marmosets, approximately 80% of area A1 neurons are considered single-peak neurons when tested by a single pure tone. However, when these neurons are tested by two tones presented simultaneously, a significant proportion of the single-peak cells show facilitation or inhibition in their two-tone responses. The facilitation often occurs at frequncies harmonically related to the fundamental frequency, while harmonically related inhibition occurs less often (Wang 2018).

Representation of Temporal Transients. Auditory cortical neurons are not consistently synchronized with stimuli, so that the representation of rapidly occurring transients is more complicated. In area A1 of conscious marmoset monkeys, there are two populations of cortical neurons, one with stimulus-synchronized discharges and one not showing synchronization. The cells that display stimulus-synchronized discharges appear to represent slow sound sequences via a temporal code, while the cells that are not synchronized represent rapid transients through a rate code (Lu et al. 2001).

Perception of Sound Sequences in the Primary and Secondary Auditory Cortex. Speech and music are more than sequences of unrelated sounds; they contain pitch sequences over time, which form certain units of perception. In humans, the presentation of melodies activates the primary and secondary auditory cortices irrespective of the key or instrument used (Schindler et al. 2012). But music also arouses →affects and emotions (Jackendoff and Lerdahl 2006). Passive listening of non-musicians to pleasant music activates, in addition to primary and secondary auditory cortices, limbic and paralimbic regions, such as →amygdala, →nucleus accumbens, →hypothalamus, →hippocampus, insula, cingulate cortical areas, →orbito-frontal cortex (OFC) (Koelsch 2014). Activity of neurons in the auditory cortex reflects emotional and motivational contents and can distinguish between the positive and negative valence of sounds. Blocking these processes prevents animals from recognizing sounds as aversive or pleasant (Concina et al. 2019)

Auditory Imagery in the Human Cortex. Humans are good at mentally imagining auditory stimuli or scenes in the absence of auditory stimulation (auditory imagery), which is an important ability for speech and music (Keller 2012). Auditory imagery activates many of the same brain areas as actual auditory perception, including the

prefrontal cortex (PFC) and the →supplementary motor area (SMA) (Herholz et al. 2012; Hubbard 2010).

12.5.2 Tool Representation

Objects of particular interest for many animals including humans are tools whose identification requires the integration of information from several senses, e.g., audition, vision, proprioception. Brain imaging in humans identified an auditory tool network with regions in left anterior →inferior parietal lobule (IPL), bilateral posterior lateral sulcus, and left inferior pre-central sulcus (PCS). This network overlaps only partially with a visual tool network with regions in left anterior IPL and bilateral inferior temporal gyrus. The auditory and visual IPL regions showed a strong preference for tools versus other stimuli of the same modality, but also some multi-sensory response properties (Kassuba et al. 2020).

12.5.3 Intra-Species Communication

Complex communication sounds such as animal vocalizations and human speech contain complex temporal structures with slowly and rapidly changing acoustic transients (Lu et al. 2001). Production and recognition of species-specific vocalizations is important for survival and social interactions (Kanwal and Rauschecker 2007; Petkov et al. 2008). Non-human primates produce a wide variety of acoustic signals that encode the identity, sex, size, reproductive and motivational states in con-specifics. To recognize and distinguish species-specific `calls´ requires a →sensitivity to and selectivity for particular types of call. Sensitivity and selectivity in turn require a neuronal `combination-sensitivity´ that utilizes non-linear spectral and temporal integration of stimulus components. The manner in which sensitivity and selectivity are implemented differs widely between species. In bats, combination-sensitivity is found at sub-cortical levels and in the primary auditory cortex, while in monkeys it becomes prevalent only in the lateral belt of the auditory cortex (Kanwal and Rauschecker 2007). In the squirrel monkey, yet another site, the superior temporal gyrus (STG) is where species-selective vocalization is conveyed (Ghazanfar and Hauser 2001; Wang 2000). Another candidate `voice region´ in the monkey has recently been identified on the superior temporal plane, which shows sensitivity to the vocal identity of con-specifics. This region appears homologous to the human voice region in the upper bank of the superior temporal sulcus (STS), which is specialized for the recognition of human voices (Petkov et al. 2008). The antero-lateral belt region in monkeys shows the highest specificity for `monkey calls´ and the caudo-lateral region the highest spatial selectivity, indicating that these regions are the origin of specialized sound identification and location pathways, respectively. In the caudo-lateral region, the selectivities for both space and species-specific vocalizations often co-vary.

Perceptual Invariance. Acoustic communication signals are shaped by the physics of the sound-producing organs, the physical media they traverse, and the physics of the receptor organs. Vocal communication signals are also shaped by the perceptual mechanisms of the receiver, by the proximate behavioral states of the senders and receivers and by their

evolutionary history (Gentner and Margoliash 2003). As might be expected, acoustic communication and the wide diversity of behavioral constraints, including those between con-specific animals, encompass considerable variability. For example, perception of music involves a number of perceptual invariances. Another example, call recognition, requires recognition of a call type and its meaning despite large variations in pitch, amplitude and other parameters that vary with the emitter´s identity and mood and with noise background, which probably involves the →frontal cortex. For example, there are neurons in the frontal cortex of both bats and monkeys that respond selectively to a few call types, but not to a single type (Kanwal and Rauschecker 2007; Rauschecker and Scott 2009).

Multi-sensory Processing of Vocalizations. In social communication, vocalizations often concur with related visual stimuli, such as facial movements and expressions. Lip reading alone activates the auditory cortex in the absence of speech sounds (Calvert et al. 1997). Speech intelligibility increases when listening to someone´s voice and simultaneously watching lips move, which is particularly important in noisy environments. But there may be conflicts between auditory and visual signals. For example, when viewing one person articulating a syllable while listening to another person, listeners may report hearing a third syllable (the `McGurk effect´) (King 2009b). Auditory and visual signals must therefore be integrated at some site. In fact, many auditory cortical areas previously thought to be unimodal may actually be multi-sensory in responding to somatosensory and/or visual stimuli (Opoku-Baah et al. 2021). For example, in primary auditory and belt areas, neuron responses are influenced by somatosensory stimuli as well as visual object and face stimuli (Hoffman et al. 2008). Also, visual responses of some superior temporal sulcus (STS) neurons to images are modulated by simultaneously presented sounds (Stein and Stanford 2008). In addition, neurons in the ventro-lateral prefrontal cortex (VLPFC; area 12 and area 45) of awake macaques respond to animal and human vocalizations as well as to the corresponding facial gestures, and these responses interact with each other, resulting in enhancement or suppression (Romanski and Averbeck 2009).

Audio-visual Mirror Neurons in Premotor Cortex. Monkeys and humans are able to recognize actions by the sounds they emit. The monkey →ventro-lateral premotor cortex (PMv) contains neurons that fire when the monkey performs an action and hears the related sound. Most of these cells also discharge when the monkey observes the same action performed by another monkey (→mirror neurons). It has been proposed that such audio-visual mirror neurons might code the meaning of actions (Keysers et al. 2003).

12.6 Sound Source Localization

For humans, spatial hearing facilitates the detection and discrimination of sounds and voices against noisy backgrounds (Cohen and Knudsen 1999; Feng and Ratnam 2000; Grothe et al. 2010; King 2009b; Recanzone and Sutter 2008). Many vertebrates are adept at localizing sound sources. Humans, for example, are capable of a spatial resolution as great as 1-2 degrees of arc (Grothe et al. 2010; Kelly 1991), and bats may be even more adept. Owls can discriminate changes in sound location as small as 3° and can aim their heads to within 2° of a source (Bala et al. 2003). In primates with small heads that results

in short interaural distances, there appears to have been an evolutionary pressure to use high frequencies (below 125 Hz, though) for acute sound localization (Heffner 2004).

Sound localization is an extremely complex task because, unlike in the somatosensory and visual systems, the stimulus location cannot be mapped onto a sensory sheet, here the cochlea. Sound localization must instead be inferred from indirect acoustic cues generated by the interaction of the sound waves with the head and outer ears (Cohen and Knudsen 1999; Eggermont 2001; Grothe et al. 2010; King 2009b; King et al. 2001; Middlebrooks 2015; van der Heijden et al. 2019).

12.6.1 Spatial Acoustic Cues

Several acoustic cues can be utilized by the auditory system to detect and measure the direction, distance and motion of a sound source with respect to the head. All of them result from the interaction of the sound with the physical properties of body, head, and external ears, which reflect or absorb sound in a frequency-dependent way. The cues are based on the amplitude or timing of sound impinging on the eardrums.

There are three main categories of cues: Amplitude spectrum, frequency-dependent interaural level differences (ILDs), and frequency-dependent interaural time differences (ITDs) (Cohen and Knudsen 1999; Grothe et al. 2010; Joris and Yin 2007; King 2009a,b; Middlebrooks 2015; Recanzone and Sutter 2008):

Amplitude Spectral Analysis. The amplitudes of sounds arriving at one or both ears depend on the direction of sound impact in a frequency-dependent manner. Spectral cues are effective only if the sound has a broad frequency →spectrum and high enough amplitudes to detect peaks and notches imposed on the sound spectrum by the ears. When this is the case, spectral cues provide localization information, even in the vertical plane, and are able to circumvent back-front misperception in binaural cues. Filtering characteristics may even give rise to monaural cues (Grothe et al. 2010; King 2009b). However, cues based on interaural differences are more reliable and best suited for sound localization in the horizontal plane (Cohen and Knudsen 1999; Grothe et al. 2010; King 2009a,b; Konishi 2003).

Interaural Level Differences (ILDs) are computed by comparing →sound pressure levels at the two ears. This must be done by frequency-band discrimination, because the differences vary with frequency (Konishi 2003). The advantage of frequency-band discrimination is that ILDs become independent of stimulus spectrum. A disadvantage, at least in mammals, is that ILDs are of value only at high frequencies beyond roughly 1 kHz in humans and 7-10 kHz in small mammals. This is a special disadvantage for mammals with large behavioral ranges because they are dependent on long-range acoustic signals that are carried by low frequencies traveling long distances (Grothe et al. 2010). Another complication is that a particular frequency-specific ILD value corresponds to many different sound locations. Thus, taken alone, the ILD value is spatially ambiguous.

Interaural Time Differences (ITDs). In animals with large heads, separation of the ears is large enough to give rise to discernable interaural time differences (ITDs, up to about 800 μs in humans (Cohen and Knudsen 1999; Grothe et al. 2010; Eggermont 2001; Joris and Yin 2007; Konishi 2003; Vonderschen and Wagner 2014). If a sound source is straight in front of or straight behind the head, i.e., in the sagittal plane, a brief emitted sound such as a click will arrive simultaneously at the left and right ear. For other directions, ITDs can be resolved down to 10 μs in humans, corresponding to a path length difference of about 3.5 mm (Grothe et al. 2010; Eggermont 2001; King et al. 2001).

For frequencies that are low enough for primary auditory neurons to phase-lock to the sound waves, ITDs are measured as phase differences. At higher frequencies, ITDs are determined from amplitude envelopes (Cohen and Knudsen 1999). Delays of continuous tones can be reliably detected for frequencies below ca. 1,500 Hz on the basis of phase differences. Beyond this frequency, the tone wavelength is shorter than the interaural distance, so that the detection of phase or time differences becomes ambiguous. ITDs vary with sound frequency. Like interaural level differences (ILDs), frequency-specific ITDs are spatially ambiguous. Values of one particular ITD are not concentrated in one point, but are located along an `iso-ITD´ contour.

For narrow-band sounds, interaural level differences (ILDs) and interaural time differences (ITDs) are also spatially ambiguous because the same values can arise from multiple directions (referred to as ‘cones of confusion´). To arrive at an unambiguous estimate of direction, information from different cues must be integrated (Cohen and Knudsen 1999; King 2009b).

The above considerations impose several operational requirements on the functional structure of the sound-localization system: Spectral analysis of an internal model of the ear, binaural processing, parallel frequency-specific analysis, integration across frequencies, calibration and learning, and cross-modal integration of proprioceptive and vestibular signals (Cohen and Knudsen 1999; Grothe et al. 2010; King et al. 2001).

Spectral Analysis Based on an Internal Model of the Ear. Evaluation based on a comparison of the stimulus amplitude spectrum with the spectrum expected, taking into account the ear filter properties, requires an internal model of the ear filter properties. That is, the processing system must recognize the filter.

Binaural Processing. Any neural system exploiting interaural level differences (ILDs) and interaural time differences (ITDs) must receive inputs from both ears. This is enabled by extensive crossing of connections along the ascending projections.

Parallel Frequency-specific Analysis. Since interaural differences are the dominant cues in sound location, and interaural level differences (ILDs) and interaural time differences (ITDs) depend on frequency, the initial processing must be done for separate frequencies. This is accomplished in a tonotopic pathway, which extends from the cochlear nuclei to the auditory cortex, and carries information about both the identity and location of a sound. For spatial processing, frequency-specific signals are drawn from the tonotopic pathway at two levels: the brainstem and the cortex. The representations of auditory space are very different at these two levels, probably reflecting different functions in

relation to behavior (Cohen and Knudsen 1999). In addition to assisting in binaural processing, spectral analysis also contributes to localizing sound sources in the vertical dimension. For this spectral analysis, the dorsal cochlear nucleus appears to be of importance (King et al. 2001).

Integration across Frequencies. While the different cues are initially analyzed through parallel neural channels, the information must ultimately be pooled to arrive at consistent and accurate estimates of location.

Calibration and Learning. The neural processes underlying sound localization must be constantly re-calibrated, in particular during →ontogenetic growth, because the relation between source and body properties changes. The neuronal networks must thus be able to learn. The sound localization networks must also be able to adjust their tuning properties very rapidly to accommodate changing contexts of sounds (Grothe et al. 2010; King et al. 2011).

Cross-modal Integration. Since the →coordinate system of auditory space is anchored to the head, the orientation and movement of the head and ears must be taken into account using signals provided by the proprioceptive and vestibular senses. Furthermore, when a sound-source is visible, the two sources of information related to object location must be integrated so that auditory space is aligned with visual space. Since the construction of visual space also depends on eye movements, information about the latter must enter into the alignment of auditory and visual space maps (King 2009a,b).

12.6.2 Brainstem Processing of Interaural Differences

Binaural spatial processing starts in the brainstem. In mammals, the superior olivary complex (SOC) contains two divisions. The lateral superior olive (LSO) processes interaural level differences (ILDs). The medial superior olive (MSO) processes mainly interaural time differences (ITDs) (Grothe et al. 2010).

Processing of ILDs. Interaural level differences (ILDs) are processed in the mammalian LSO by excitatory and inhibitory interactions between inputs from the two ears (Grothe et al. 2010). The LSO contains multiple, frequency-specific maps of ILD.

Processing of ITDs demands exquisitely accurate temporal resolution of time differences, which are nearly two orders of magnitude shorter than the duration of action potentials. A popular model, the so-called delay-line hypothesis or →Jeffress model (Middlebrooks 2015), is based on studies in birds, in particular the barn owl. The basic idea is that the lateral position of a sound source is mapped onto the position of maximal activation within an array of binaural →coincidence-detector neurons that are tuned to different interaural time differences (ITDs). The tuning of a neuron for an interaural time difference (ITD) is determined by the difference in axonal conduction delay from each ear to the brainstem (Grothe et al. 2010; Joris and Yin 2007; Vonderschen and Wagner 2014). However, recent evidence from mammals suggests that the Jeffress model does not provide accurate descriptions of how interaural time differences (ITDs) are encoded in the mammalian auditory brainstem or of how ITD-sensitive neurons in MSO (and also LSO) contribute to

mammalian sound localization. The underlying mechanisms are not yet fully understood (Grothe et al. 2010; Joris and Yin 2007; Vonderschen and Wagner 2014).

Further Processing. Functionally segregated information is then conveyed to the central nucleus of the →inferior olive (IO), where neuronal sensitivities for interaural time and level differences may be sharpened by inhibitory interactions. From the inferior olive (IO), one pathway proceeds to the thalamus and cortex, which projects back to the inferior colliculus (Stebbings et al. 2014). Another pathway branches off to the external nucleus of the inferior colliculus (ICX) and the nucleus of the brachium of the inferior colliculus (nBIC), both of which convey binaural signals from the inferior olive (IO) to the superior colliculus (SC). The superior colliculus bears a spatial map of sound location, based mainly on interaural level differences (ILDs) (Cohen and Knudsen 1999; Grothe et al. 2010; King 2009a; King et al. 2001; May 2006).

The accuracy of perceptual sound localization is greater than the spatial tuning of individual auditory neurons, which is usually very broad. Hence, spatial information must be extracted from populations of neurons with a population code. Tuning of neurons to ITDs at low frequencies (<2 kHz) becomes sharper with progression from the superior olivary complex (SOC) through the IC to the auditory thalamus. The population code becomes more efficient by using fewer neurons to achieve a given acuity (Fitzpatrick et al. 1997).

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Motion Sensitivity. The recognition of changes in sound localization, i.e., sound motion, is crucial for many functions. Some sensitivity and direction selectivity to the motion of acoustical stimuli appears to be present in A1, but human and macaque imaging studies have emphasized the planum temporale as an important site for auditory motion processing (Chaplin et al. 2018).

12.6.3 Mapping of Auditory Space in the Superior Colliculus

The four →colliculi are what their name proclaims: small hill-shaped elevations on the dorsal roof of the →midbrain. All four are involved in hearing in different ways. The rostral bilateral pair of hills, collectively called superior colliculus (SC), is a vital structure that transforms →salient auditory, visual and somatosensory stimuli into orientating movements. It carries multi-sensory and →motor maps, spread out in superficial and deeper layers. These maps are by and large in register and ultimately serve to orient head and/or eyes to novel stimuli of different modality. Thus the motion vectors of the line of sight (gaze) are represented across the surface of the superior colliculus (Gandhi and Katnani 2011; King 2009a; May 2006; Stein and Meredith 1993; Stein and Stanford 2008).

In order to direct the gaze towards a novel acoustic stimulus, the locations of such stimuli are represented in a similar →topographic format (Cohen and Knudsen 1999). To perform this operation, two operational requirements need to be fulfilled: representation of an auditory map, and transformation from a frequency code to a topographic code.

Auditory Map. The deeper SC layers contain an auditory map, where the locations of neurons are represented according to their directional sensitivities. The horizontal meridian from nasal to temporal is represented from rostral to caudal in the superior colliculus, and the vertical meridian from inferior to superior is represented from medial to lateral in the superior colliculus.

Transformation of a Frequency-specific Code into a Topographic Code. The auditory map is not represented in the signals from cochlea to inferior olive (IO), but must be constructed anew. The transformation involves pooling of space-related information, distributed across different frequency-specific channels. As a result, neurons are broadly tuned for frequencies and narrowly tuned for a single sound location. In mammals, this transformation takes place in the external nucleus of the inferior colliculus (ICX) and the nucleus of the brachium of the inferior colliculus (nBIC). Output signals from these neurons are conveyed to the superior colliculus (SC), where they are arranged in a topographic map as described above. The precision of the auditory map in the superior colliculus (SC) varies across species. It is poor in rodents, excellent in barn owls, and intermediate in cats and ferrets. The sharp tuning of neurons in barn owls arises from their sensitivity to both interaural level differences (ILDs) and interaural time differences (ITDs) (Cohen and Knudsen 1999).

The auditory map in SC is essentially in register with the somatosensory map and the visual map. The somatosensory map is anchored to the body, the auditory →frame of reference for stimulus direction is →head-centered, and the visual reference frame is retino-centric. This implies that, for example, eye movements within the head shift the maps with respect to each other. Audio-visual integration of signals from external space must therefore take into account eye movements. In fact, auditory responses of SC neurons are modulated by eye position; hence their spatial sensitivity is re-aligned with visual coordinates (King 2009a,b; King et al. 2001; Stein and Stanford 2008).

12.6.4 Representation of Auditory Space in the Cortex

Spatial auditory processing in the human cerebral cortex probably engages a recurrent network of areas. It starts in the primary auditory cortex (area A1), then progresses through the planum temporale and projects to the inferior parietal lobule (IPL) and further to the →premotor cortex (PMC) and Brodmann´s areas 8, 9 and 46 of the dorso-lateral prefrontal cortex, with feedback connections from areas 9 and 46 to area A1 and planum temporale for active hearing (Van der Heijden et al. 2019).

The primary auditory cortex (A1) in mammals contains neurons that are tuned to sound-source location and others that are not. The former cells are preferentially sensitive to contralateral, ipsilateral or midline locations or to several different locations. In contrast to the superior colliculus (SC), there is no topographical organization into maps of

auditory space. Rather, cells with similar spatial sensitivities are clustered, with clusters of non-spatially tuned cells interspersed (Cohen and Knudsen 1999).

The spatial tuning of most cortical neurons is very broad, typically over 90° for a half-maximal response. However, cells in the caudo-medial belt (CM) show better spatial tuning than area A1 neurons, supporting serial processing in the `where´ pathway (Recanzone 2000).

Spatial sensitivity may also be expressed in temporal discharge characteristics such as latency, overall spike numbers, precise temporal patterns of discharge, and the coordinated activity of groups of neurons (King et al. 2001). Modeling studies with artificial neural networks suggest that in cat area A2, discharge patterns of neuronal ensembles signal the location of a stimulus. The relative spike counts and timing within the ensemble carry information about location, and location signaling by ensembles of moderate size approach the accuracy achieved by behaving animals. To achieve accuracy, it seems that the ensemble requires neurons that have different spatial sensitivities and location-specific differences in activity (Furukawa and Middlebrooks 2000).

An example of a cortical area that processes auditory space information is the mammalian frontal eye field (FEF). Lesions of the FEF, a region involved in eye movements, decreases a monkey´s ability to localize sounds. Cells in FEF discharge in relation to saccadic eye movements made to novel stimuli, including acoustic signals, in close functional association with the SC. In the avian homologue, electrical stimulation evokes →orienting eye and head movements (Cohen and Knudsen 1999).

Auditory Distance. Humans can estimate the distance of a sound source relatively accurately using several cues, including some that are pertinent to direction perception such as spectral cues, ILD and ITD. However, they tend to systematically underestimate far auditory targets and overestimate near auditory targets. Listeners are more precise when estimating the egocentric distance of targets conveyed by both visual and auditory cues than by an auditory target or a visual target alone, indicating that auditory cues can augment the visual estimation of egocentric distance when cues from both modalities are present (Campos et al. 2018). Distance processing probably involves a network of cortical areas including the planum temporale, superior temporal gyrus (STG), ventro-lateral premotor cortex (PMv) and →anterior cingulate cortex (ACC) (Kolarik et al. 2016). Little is known about how auditory distance is encoded by neurons. Some neurons in the superior colliculus (SC) of echolocating bats can signal object distance on the basis of delays between emitted ultrasonic vocal signals and the returning echo (King 2009a). In macaque monkeys, multi-modal neurons in ventral premotor cortex (PMv) represent acoustic distance in peri-personal space, and neurons in the planum temporale and posterior STG are sensitive to acoustic distance (Kolarik et al. 2016). The PMv of macaques is important in organizing arm and hand movements.

Looming Sounds. Rhesus monkeys show an orienting bias towards looming sounds. As in humans, it occurs for harmonic sounds from single sources, but not for broadband noise (Ghazanfar et al. 2002).

12.7 Auditory Perception of Self-motion

Self-motion through a complex environment is a delicate undertaking that requires the precise acquisition of information via as many senses as are momentarily available. Hearing is just one source in company with vision, vestibular signals, touch and proprioception (Campos et al. 2018). Hearing may contribute to self-motion perception by localizing the direction and distance of sound-emitting objects and their temporal changes (above).

Sounds can move relative to an observer due to his own movement (self-motion) or due to the movement of objects within the environment (object motion). During self-motion, the surrounding auditory scene moves globally as an acoustic flow in the opposite direction to the observer´s motion direction. This acoustic flow usually coincides with that of other sensory inputs such as dynamic visual inputs (optic flow), vestibular inputs, and proprioceptive inputs from the legs. This is usually not the case in object motion (Campos et al. 2018).

Acoustic flow perception is based on dynamically changing binaural and monaural cues. Changes occur in the loudness and amplitude of high-frequency content of a sound source. The relative motion can also lead to changes in pitch (→Doppler effect) and in azimuth (the angle between the positions of the listener and the sound source). This will dynamically change the associated ITDs, ILDs, and interaural differences in the frequency response of the sound arriving at the ears. The rate at which the spectral content of incoming sound changes can be used to estimate time to contact (Campos et al. 2018).

Self-motion perception can also be →illusory in analogy to visual self-motion perception induced in a stationary observer by motion of a large-scale surrounding, as for example in the train illusion (→vection). Likewise, a self-motion sensation can occur when a blindfolded stationary observer is presented with a moving global large-scale auditory environment, but this sesnation not as strong as visual self-motion sensation (Campos et al. 2018).

12.8 Auditory Influences on Upright Stance and Locomotion

Standing Balance. During quiet upright stance, humans sway to different degrees depending on circumstances (postural sway). Stationary sound cues can reduce the sway by anchoring the body to a stable environment as do visual fixations or light touch of a stable object. By contrast, dynamically changing auditory cues can disrupt standing balance, especially when they are incoherent, unrelated to, in conflict with, or competing with other sensory inputs to self-motion (visual, proprioceptive, tactile, vestibular). Hence, postural effects of audition on postural stability depend on the character of the auditory stimulus and its compatibility with other multi-sensory inputs (Campos et al. 2018; Väljamäe 2009).

Locomotion. Like other animals, humans are able under favorable circumstances to use echolocation in navigation and negotiating obstacles. Although this ability has been considered to be predominantly an acquired ability of individuals with visual impairments, there is evidence showing that sighted individuals are capable of using echolocation to estimate the distance and/or size of nearby objects to some extent (Campos et al. 2018).

12.9 Audition and Motor Actions

Hearing and motor actions are more closely related than might be presumed. In general, there are bi-directional influences between audition and action (Stanton and Spence 2020).

Sudden acoustic signals may elicit a →startle response or →orienting movement with appropriate body, head and eye movements involving a number of distributed systems. On the other hand, hearing sounds may be critical for signaling pleasant, unpleasant or dangerous actions or events and may facilitate appropriate motor reactions.

A meta-analysis of many brain imaging studies in humans listening passively to music revealed activations in the bilateral superior temporal gyrus, gyri temporales transversales (Heschl), insula, bilateral →pre-central gyrus, and bilateral →medial frontal gyrus. In addition, there was a widespread activation of motor areas including left and right dorso-lateral premotor area (PMd), right →primary motor cortex (M1, MI), and the left →cerebellum (Gordon et al. 2018).

Auditory imagery and auditory perception in particular of speech, music and non-vocal emotional vocalizations (such as laughter and crying) commonly activate frontal cortical regions, including the supplementary motor area (SMA) and the →pre-supplementary motor area (pre-SMA). These regions are connected to auditory cortical regions and have been implicated in various functions, e.g., motor timing and sequencing. They have also been suggested to facilitate motor responses to sounds and link auditory information with related motor schemes (Lima et al. 2016). In a →functional magnetic resonance imaging (fMRI) study, subjects listened to a musical rhythm, first in anticipation of finger tapping, and then tapped along with the musical rhythm. During listening in anticipation, the supplementary motor area (SMA), mid-→premotor cortex (PMC) and cerebellum were activated (Chen et al. 2008).

Listening to the sound produced by human body parts (e.g. clapping two hands) activates the →fronto-parietal `action observation network´ centered on the inferior frontal gyrus (IFG) and the inferior parietal lobule (IPL). Such activation might be somatotopically organized, with the left dorso-lateral premotor area (PMd) and the IPL being more responsive to the execution and hearing of hand movements than to mouth actions or to sounds that are not associated with human actions (e.g. environmental sounds, a phase-scrambled version of the same sound, or a silent event). Conversely, the more ventral regions of the left premotor cortex are more involved in processing sounds performed by the mouth. Blood oxygenation level-dependent (BOLD) signal in the left →ventro-lateral premotor cortex (PMv) is enhanced when seeing and hearing another individual tearing

paper as compared with viewing a silent video depicting the same scene or only hearing the sound associated with the observed action (Aglioti and Pazzaglia 2010).

12.10 Modulation of Auditory Processing

The ascending auditory pathways are complemented by a system of multiple descending connections (Grothe et al. 2010). Fibers descending from the superior olivary complex (SOC) target inner hair cells (IHCs) and outer hair cells (OHCs) and set up a fast feedback that adjusts the gain of signal processing to the overall sound level. Other descending systems from the inferior colliculus (IC) target lower brainstem nuclei (Gruters and Groh 2012). Cortical projections to the medial geniculate body and inferior colliculus (IC) chiefly target non-cochleotopic neurons. This system modulates the frequency-tuning characteristics of thalamic and collicular cells based on short-term experience (Eggermont 2001; Grothe et al. 2010; Read et al. 2002).

Auditory processing is modulated by →somatosensory and visual signals at all levels of central processing. For example, in normal subjects, jaw maneuvers can alter auditory perception or produce the sensation of tinnitus, probably mediated in part by projections from the trigeminal and →dorsal column nuclei to the cochlear nuclei (Wu et al. 2015). The inferior colliculus (IC), which is basically an auditory area, receives also signals related to somatosensation, vision, eye movements and position. These signals may play roles in attending to salient stimuli, perceiving and generating communication sounds, localizing sound sources, and distinguishing environmental from self-generated sounds (Gruters and Groh 2012). In primary auditory cortex A1, neuron responses to auditory stimuli are significantly modulated by auditory, visual or somatosensory stimuli (Wu et al. 2015).

Auditory processing is also modulated by movements. While this modulation has been shown during speech and other vocalizations, it also occurs during other sound-generating behaviors (Stanton and Spence 2020). Vocalization as well as head and neck movements activate the middle ear muscles and thereby dampen auditory responses to self-generated sounds. Sounds originating from movements from finger movements to locomotion act in the auditory brainstem and auditory cortex. It is thought that these motor-related signals act to suppress auditory responses to self-generated sounds in order to prevent sensory adaptation and to maintain the auditory system´s sensitivity to ex-afferent environmental sounds and to selectively suppress responses to predictable self-generated sounds (Schneider and Mooney 2018).

Auditory processing in the cochlear nucleus, inferior colliculus, thalamus and/or cortex (A1) is modulated by →neuromodulatory systems including →cholinergic, →dopaminergic, →serotonergic and →noradrenergic inputs (Concina et al. 2019; Jacob and Nienborg 2018).

12.11 Experience-dependent Auditory Learning

Rather than being a hard-wired system, the auditory system is rendered flexible by experience (Dahmen and King 2007; Edeline 1999; Herholz and Zatorre 2012; Irvine 2018a,b; King et al. 2011; Rauschecker 1999; Suga 2020; Syka 2002). This holds particularly for immature animals and under more restricted conditions for adults (Keuroghlian and Knudsen 2007; King 2009b). →Plasticity is present at sub-cortical levels, e.g., the inferior olive (IO), and in the auditory cortex, and also involves inhibitory circuits (Kandler 2004; Syka 2002). For experience-dependent plasticity to occur, an animal must be responsive to a stimulus, and the induced plasticity must be specific for the acoustic feature that the animal responds to (Keuroghlian and Knudsen 2007). Plastic changes occur on different time scales, from short to long.

On a short-term basis, milliseconds to minutes, various auditory functions can be modulated by →bottom-up and →top-down influences on neuron responses in the parallel-serial auditory processing streams (Jääskeläinen et al. 2007). The →receptive fields (RFs) of cortical neurons for frequency may change under various conditions (Edeline 1999). For example, by conditioning single-tone frequencies with electric shocks, primary cortical neurons of adult guinea pigs adapt their preferred frequency to that of the conditioned stimulus (Weinberger 1998). While plasticity of this sort may be most pronounced during development, it also occurs in adult animals, e.g., when the pattern of auditory nerve activity is changed by electrical stimulation or deafening (Eggermont 2008; Illing 2001; Knudsen et al. 2000; King 2009b; King et al. 2000, 2001). Rapid task-related changes in spectro-temporal receptive fields also occur during active listening, when attention is focused on salient acoustic features (Fritz et al. 2005).

On a longer time base, maps in auditory cortex may change depending on stimulus properties, behavioral relevance and the →reward value of a stimulus (Herholz and Zatorre 2012). Small, restricted lesions in the cochlea deprive the related frequency regions of the cortex of their inputs. These regions are then invaded by inputs to neighboring regions that represent different frequencies (Syka 2002). Hearing loss in children and adults resulting, for example, from extreme noise exposure, ototoxic drugs and aging, involves changes in cortical representation of frequency (Eggermont 2008). Conversely, expansion of cortical frequency representations occurs with training at a particular tone frequency. Early musical training expands the auditory cortex, and the early phonetic environment has a strong influence on speech development (Rauschecker 1999; Syka 2002).

Learning to play a musical instrument involves interactions between →cognitive systems, several sensory systems (touch, proprioception, audition, vision) and motor systems (primary motor cortex (F1, M1), →premotor cortex (PM), →basal ganglia, cerebellum), with related behavioral, structural and functional changes extending over time scales from days to years (Herholz and Zatorre 2012).

Macaques can learn to produce novel sound sequences with their hands by pressing levers on a keyboard (“monkey piano”). Awake functional magnetic resonance imaging (fMRI) showed that all sounds activated auditory midbrain and cortex, but listening to the sound sequences that had been learned by self-production additionally

activated the →putamen and the hand/arm regions of →motor cortex (Archakova et al. 2020).

Neuromodulatory systems may play a gating role in plastic processes (Dahmen and King 2007; Edeline 1999; Keuroghlian and Knudsen 2007). For instance, cholinergic neurons of the →forebrain nucleus basalis, which receives inputs from various brainstem nuclei, the hypothalamus, amygdala and frontal cortex, ramify ipsilaterally to the amygdala, reticular thalamic nucleus and the entire →neocortical expanse, and dramatically influence plasticity. The dopaminergic reward system may also modulate plasticity in animals and humans and thereby enhance musical training in humans (Herholz and Zatorre 2012).

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13

Early Visual Processing:

From Retina to Lateral Geniculate Nucleus

CONTENTS

Abstract

• The 2D projection of the 3D world onto the retina is an active process that is modulated by eye movements, adjustment of lens refraction to target distance and changes in pupil width, each resulting from actions within the central nervous system (CNS).

• The retina is an information-processing device with operational complexity comparable to the cerebral cortex. The mammalian retina contains about 100 cell types. Whereas each human eye contains on the order of 100 million photoreceptors, only about 1.5 million retinal ganglion cells (RGCs) project to higher CNS centers.

• RGCs send output projections to many brain regions: The thalamic lateral geniculate nucleus (LGN), which projects to the primary visual cortex; the midbrain superior colliculus (SC); other brainstem structures involved in pupil accommodation, control of eye movements and recognition of biologically important objects.

• The visual cortex of primates is represented by a number of distinct cortical areas, organized into two main streams: A ventral stream, from the primary visual cortex to the inferior temporal (IT) cortex which processes form, size, brightness, texture and color for conscious identification and recognition of objects: and a dorsal stream from primary visual cortex to superior temporal and parietal areas, which processes spatial object properties such as location, depth and motion, for visual guidance of motor actions.

• Two types of photoreceptors, rods and cones, are involved in night and day vision, respectively. They convert electromagnetic radiation into an electrical membrane potential change. Conversion is accomplished by the photopigments rhodopsin in rods and by three different opsins in cones. Rhodopsin is most sensitive to blue-green light. The opsins are sensitive to blue, green and red-yellow.

• Photoreceptor signals are transformed into action potentials by RGCs through complex vertical and horizontal cell interactions. Some types of RGC exert specialized functions such as local edge detection, orientation selectivity, detection of object motion and motion direction, and detection of approaching objects.

• Output signals from the retina undergo considerable transformation in the LGN through convergence and divergence of RGC-LGN connections, inhibition originating within and outside the LGN, altered discharge dynamics between RGC and LGN neurons, cortico-thalamic feedback and by projections onto LGN neurons from the brainstem and basal forebrain.

13.1 Introduction

Organisms have developed a sense for light very early on in evolution (Gehring 2014). The vertebrate retina evolved some 500 million years ago in chordates, and ever since the structures and functions of retinae have adapted to the species-specific niches together with various types of optical systems (Baden et al. 2020; Fernald 2004). An even larger variety of neural systems serves two general types of vision-dependent functions: →perception of the environment and guidance of motor behavior (Hayhoe 2017). To summarize the visual process in higher animals: It begins when the cornea and the lens of the eye focus light onto the retina, where the light is →transduced into neuronal signals. Feedback from the visual system causes the lens of the eye to adjust thickness in order to focus light on →photoreceptive cells of the retina, the rod photoreceptors and cone photoreceptors, which detect the photons and respond by producing →action potentials (Lamb 2016). Complex feedforward and feedback processes located in →thalamic and →midbrain ganglia and the visual cortex modulate these signals.

13.2 Optical Projection, Adjustment to Target Distance, and Pupil Control

The first representation of visual information about the three-dimensional (3D) outer world is the two-dimensional (2D) image on the retina created by a projection with some deficiencies (Artal 2015). Image representation is an active process that is influenced and modulated by eye movements, →accommodation to target distance and changes in pupil width. When objects need to to be seen sharply, light rays emanating from them are focused onto the retinal foveae, where photoreceptor density is greatest. To keep each eye in focus, many species, including →primates, change the curvature and hence the refractive index of the lens. This process, called accommodation for near vision is accomplished by the ciliary muscles (McDougal and Gamlin 2015).

Three components are involved in the accommodation reflex: The afferent limb, the efferent limb and the →motoneurons that are between the two limbs. The afferent limb is comprised of the retina and retinal ganglion cell (RGC) →axons of the →optic nerve, the →optic chiasm and the →optic tract, the lateral geniculate nucleus (LGN) and finally, its axonal projection to the visual cortex. The efferent limb consists of the Edinger-Westphal nucleus, the midbrain →parasympathetic →preganglionic nucleus that sends axons in the oculomotor (3rd cranial) nerve to the ciliary ganglion. Motor axons from the →ganglion innervate the ciliary body, a smooth muscle with suspensory ligaments attached to the lens that regulate the curvature of the lens and thus adapt the lens for near or far vision (Carpenter 1996; McDougal and Gamlin 2015; Trimarchi 1992).

The iris in humans constricts the pupil in bright light. It is encircled by contractile pupillary smooth muscle fibers. The sphincter pupillae muscles are innervated by parasympathetic fibers from the ciliary ganglion, which contract the sphincter muscles via excitatory →synaptic input from the Edinger-Westphal nucleus (McDougal and Gamlin 2015).

Pupil diameter is increased by radial dilatory muscle fibers (dilator pupillae), innervated by →sympathetic postganglionic fibers from the →superior cervical ganglion (McDougal and Gamlin 2015). Blood-born →adrenaline released from the →adrenal medulla also stimulates radial dilatory muscle fibers, causing pupil dilation (mydriasis) (Tank and Lee Wong 2015). Whereas parasympathetic pupillary constriction is normally continuous, →reflexive and graded as a function of light →intensity, pupillary dilation is activated intermittently, by →emotional states, →stress and severe pain (Carpenter 1996; Smith 2009).

13.3 Anatomy of the Retina

With respect to the vertebrate retina, the organization is similar despite structural variations between animals (Joselevitch and Kamermans 2009). The retina is an information-processing device with operational complexity comparable to the →cerebral cortex. The mammalian retina contains about 100 cell types: 3-4 types of photoreceptor, 50-70 types of →interneuron (horizontal, bipolar and amacrine cells), and more than 30 types of retinal ganglion cell (RGCs), which differ in morphology, physiology, spatial distribution and synaptic organization (Demb and Singer 2015) and give rise to some 40 visual pathways (Thoreson and Dacey 2019). Whereas each human eye contains on the order of 100 million photoreceptors, only about 1.5 million RGCs (Peichl 2009) project to higher centers of the →central nervous system (CNS). This convergence requires extensive data compression and an →efficient code (Beyeler et al. 2019; Carandini et al. 2005; Dhande et al. 2015; Field and Chichilnisky 2007; Jadzinsky and Baccus 2013; Sanes and Masland 2015).

There are three layers of cells: outer photoreceptors, intermediate cells and inner RGCs. Rod photoreceptors, making up about 95% of the human photoreceptors, are specialized for low-acuity, colorless scotopic (twilight or night) vision and may absorb single photons (Lamb 2016). But at higher mesopic light levels where both rods and cones are active, their interactions can influence color perception. Multiple cone photoreceptors are specialized for →photopic, high-acuity day vision, which make up barely 5% of human photoreceptors (Lamb 2016; Martin 2009; Molday and Moritz 2015; Thoreson and Dacey 2019). In the outer plexiform layer, photoreceptors connect to bipolar cells and horizontal cells, the latter feeding back to photoreceptors (Thoreson and Dacey 2019). In the inner plexiform layer, bipolar cells connect to RGCs and amacrine cells that in turn connect to RGCs. The vertical connectivity establishes *parallel functional channels* with extensive and varied lateral interactions that enable complex network processing (Demb and Singer 2015; Euler et al. 2014; Field and Chichilnisky 2007; Hausselt and Euler 2009; Martin 2009; Nassi and Callaway 2009; Thoreson and Dacey 2019).

Ganglion Cell Projections. Retinal ganglion cells (RGCs) send outward projections to many brain regions (Dhande et al. 2015). The *main retino-cortical pathway* is constituted by RGCs of each eye that send axons centrally in the optic nerve. The two optic nerves merge to form the optic chiasm, which gives rise to the two optic tracts. In the optic chiasm, RGC axons are re-arranged such that axons originating in the temporal retinal halves remain uncrossed,

while those in the nasal halves cross over to the contralateral optic tract. This arrangement ensures that information from the left visual hemi-fields is conveyed to the right hemisphere, and information from the right hemi–fields is conveyed to the left hemisphere. A small bundle from the fovea contains fibers that are both crossed and uncrossed, providing bilateral representation. Communication between regions beyond this central strip is conveyed by the →corpus callosum. The optic tracts project to the lateral geniculate nucleus (LGN).

RGCs also project to the midbrain →superior colliculus (SC) and to other →brainstem structures that are involved in pupil accommodation, control of eye movements and →recognition of biologically important objects (Dhande et al. 2015; Sewards and Sewards 2002). The SC connection to the →pulvinar nucleus of the →thalamus may act as rapid detector and first responder when survival requires quick responses to particular, often emotionally charged, ecological and social stimuli, and when visually guided reaching and grasping require fast execution during locomotion (Soares et al. 2017). The retino-collicular pathway may also contribute to processing of visual information that is not consciously perceived (→blindsight). Some specialized inner RGCs in mammals are intrinsically sensitive to light, using melanopsin as photopigment. They have diverse molecular, cellular and functional properties, project widely throughout the brain to assist in several functions. They help entrain the →circadian rhythms, drive the →pupillary light reflex to improve visual function, suppress →pineal →melatonin synthesis, modulate mood, →alertness, →learning, →sleep/wakefulness, regulate body temperature, and visual perception (Aranda and Schmidt 2021; Guido et al. 2010; Dhande et al. 2015; Peichl 2009; Schmidt et al. 2011; Do and Yau 2010). They may also influence color perception by interactions with cone and rod pathways (Thoreson and Dacey 2019). Some RGCs project to the →supra-chiasmatic nucleus (SCN) and →pretectum.

Centrifugal Retinopetal Connections. Vertebrates have retinopetal connections originating from various CNS structures, but their extent varies considerably between different animal species and their functions are still not well understood (Repérant et al. 2007). For example, →serotonergic inputs from the dorsal →raphé nucleus and →histaminergic inputs from the posterior →hypothalamus are thought to be involved in →arousal (Ghodrati et al. 2017). →Neuromodulation also originates in the retina. For instance, a special type of amacrine cells releases →dopamine that modulates changes between daylight and nightlight by acting on several retinal cell types via a number of mechanisms. High dopamine release tunes vision for photopic conditions, while low release tunes it for scotopic conditions (Roy and Field 2019).

13.4 Visual Processing in the Retina

Features such as light intensity, →contrast, contour orientation, direction and velocity of motion and →binocular disparity are derived from retinal neural transformations, by means of a number of operations controlled by specialized circuit elements (Jadzinsky and Baccus 2013). An important question is to what extent the retina dissects and/or combines the above variables to funnel the result into separate functional channels.

13.4.1 Duplicity Theory of Vision

The duplicity theory of vision is based on the existence of two types of photoreceptors, rods and cones that participate in night and day vision, respectively. In intermediate lighting conditions such as dusk, both rods and cones are co-active and must cooperate in some way in processing visual signals (Grimes et al. 2018). In fact, the two systems are not completely independent (Fain and Sampath 2018). Signals generated in rods are also fed into cone pathways, establishing 2-3 different rod pathways to RGCs (Peichl 2009) with different properties and →sensitivities (Sharpe and Stockman 1999). This may degrade spatial resolution in dim-light vision (Schneeweis and Schnapf 1995).

The density of photoreceptors varies across the retina. There are no receptors in the papilla, the →blind spot where RGC axons aggregate to form the optic nerve. Cones attain the highest density in the fovea, about 35,000 in an area of about 0.5 mm diameter (Dowling 1996), giving rise to the highest →visual acuity. By contrast, the fovea contains no rods, which explains the inability to sharply view small stars at night. Rods are most abundant several angular degrees away from the fovea.

The density of photoreceptors, and hence visual acuity and color perception, decline with distance from the fovea. This is impressively demonstrated by →retinitis pigmentosa, a →degenerative disease that progressively narrows the peripheral →visual field and leads to a severe loss of orientation and mobility in the environment. By contrast, age-related macular degeneration entailing loss of foveal vision does not significantly impair patients´ mobility. Peripheral vision functions well in recognizing objects and scenes thereby resolving the essence of a scene, and in visual search (Rosenholtz 2016).

13.4.2 Photopigments

Vision requires →sensory transduction that converts electromagnetic radiation into an electrical membrane potential change. This is accomplished by photopigments rhodopsin in rods and in three slightly different pigments (opsins) in cones (Hart 2009; Jacobs 2017). Rhodopsin is most sensitive to light of about 500 nm wavelength (blue-green), and the three opsins absorb maximally at 430 nm (blue), 530 nm (green) and 560 nm (red-yellow).

13.4.3 Phototransduction

Absorption of photons causes conformational changes in the photopigments, leading ultimately to closure of Na^+ channels and Ca^{2+} channels and subsequent membrane →hyperpolarization. Decreased intracellular Ca^{2+} concentration keeps the photoreceptor partially responsive even in bright light. This process is called adaptation; an important mechanism that enables the visual system to respond over a wide range of ambient illumination (Dowling 1996; Lamb 2016). Light adaptation in vertebrate photoreceptors involves an array of molecular mechanisms that extend beyond the →ion channel →conductance changes involving Na^+ and Ca^{2+} (Bownds and Arshavsky 1995; Pugh et al. 1999). Adaptation to mean light level and contrast level also occurs through synaptic depression at the output of bipolar cells (Demb and Singer 2015).

Between the photoreceptors as visual input elements and the RGCs as output elements, a complex interneuronal network performs extensive signal transformations. An important result of these transformations is the structure of the RGCs´ →visual receptive fields (RFs), which is at the basis of many retinal functions.

13.4.4 Retinal Ganglion Cell Receptive Fields

The discharge of an RGC can be influenced by light shone onto its →receptive field (RF), which has a particular spatial structure emerging from the retinal circuitry. Most retinal and other visual cells display maintained discharge even in the absence of illumination, so that light shone into different parts of their RFs can elevate or decrease their firing rate. In general, RGCs fall into two types with so-called ON-center or OFF-center RFs (Kuffler and Nicholls 1976). The properties of ganglion cell RFs are fluid and depend on several circumstances (Wienbar and Schwartz (2018).

13.4.5 Feature Extraction by Retinal Ganglion Cells

Some types of RGC are specialized for the extraction of important stimulus features: Edge detection, orientation, direction sensitivity, sensitivity to object motion and sensitivity to `looming´ objects (Dhande et al. 2015).

Local Edge Detectors and Orientation Selectivity. In rabbits and mice, some RGCs are excited by light or dark edges without preferred orientation restricted to their small RFs. Retinal ganglion cells (RGCs) in mice include edge-detecting types that extract and relay specific features from a visual scene such as local or global motion, direction of motion, stimulus orientation, contrast or uniformity, or the presence of large or small objects. Three such types of ON-OFF RGCs have recently been characterized morphologically and with physiological recordings of their light responses, receptive-field size and structure, and synaptic mechanisms of surround suppression. The three high-definition (HD) RGCs possess small receptive-field centers, consistent with their small dendritic fields, and strong surround suppression. They respond selectively to objects of specific sizes, speeds, and types of motion. These neurons represent a substantial fraction of mouse RGCs (Jacoby and Schwartz 2017).

Sensitivity to Motion Direction. An important feature of spatio-temporal retinal processing is the sensitivity of some RGCs to moving stimuli. For example, movement of a light spot in a →preferred direction can strongly excite a cell, while movement in the opposite direction may inhibit discharge. Some cells respond to edge movements in particular axes (e.g., up, down, forward, backward). A number of mechanisms at cellular and network levels, including facilitation, inhibition and division, account for direction selectivity and explain speed-tuned motion detectors (Clifford and Ibbotson 2003; Dhande et al. 2015; Hausselt and Euler 2009; Jadzinsky and Baccus 2013; Wei 2018; Wei and Feller 2011). One type of direction-selective cell projects to the brainstem for eye movement control, another via the LGN to the visual cortex (Dhande et al. 2015; Masland and Martin 2007). Some RGCs in frog, salamander and rabbit also respond to motion of patterns within their RFs different from motion in the surround. These cells have formerly been called `bug detectors´.

Sensitivity to `Looming´ Objects. Many types of RGCs communicate visual signals to the brain, along with the →sub-cortical brain regions that use those signals to build and respond to representations of the outside world. Some mouse RGCs thereby respond to looming objects, in particular to dark expanding objects overhead (Dhande et al. 2015).

Color Perception. Color vision is of immense biological importance for most animals and prevalent throughout the animal kingdom, but the mechanisms involved vary widely among species (Jacobs 2017).

13.5 Retinal Processes Underlying Color Vision

Color perception originates in the differential spectral sensitivity of cones, although rods contribute their share. The following network provides for separate signal pathways specialized for color opponencies (Martin 2009; Thoreson and Dacey 2019). The opponency concept stipulates that the cone photoreceptors are linked together to form three opposing color pairs: blue/yellow, red/green and black/white.

13.5.1 Spectral Sensitivity of Cones

Most non-primate mammals and some humans have two types of cone. Two thirds of female New-World monkeys, Old-World monkeys and normal humans have three types of cones; *short-wavelength-sensitive (S-)*, *middle-wavelength-sensitive (M-)*, and *long-waveform-sensitive (L-)*, resulting from a mutation of the M-type pigment (Conway et al. 2010; Gegenfurtner and Kiper 2003; Martin 2009; Thoreson and Dacey 2019). Some people are →color-blind because one of the three cone types is missing, resulting in dichromacy, the state of having only two types of functional cone cells.

Young and von Helmholtz Trichromatic Theory. Trichromacy in humans was first postulated by Young (1802) and then adopted by von Helmholtz (1911) (Thoreson and Dacey 2019). Both Young and Helmholtz mistakenly equated color sensations (e.g., of `red ´) with the stimulation of particular receptors (e.g., of long-wavelength receptors). Because `long-wavelength cones´ are most strongly excited by red light, they – and similar downstream neurons – are often called `red´ cells, although this is incorrect because `red´ refers to a perceived color, not a wavelength preference.

Signals from cone cells are ambiguous because the probability that a cone absorbs a photon depends on both the wavelength and the density of photons incident on the cone. Signals carrying information on wavelength must thus be generated by comparison among the relative activities of the three cones (Conway et al. 2010; Gegenfurtner and Kiper 2003; Martin 2009; Solomon and Lennie 2007; Thoreson and Dacey 2019). Hence, color percepts cannot be generated by a →labeled-line code, but need an →across-fiber code.

Hering´s Theory. The idea of comparing different wavelengths is inherent in Hering´s (1964) color-opponency theory. Hering posited that there are three dimensions or processes of color perception: red-green, blue-yellow and white-black (Hubel 1988). These are produced through the retinal network and appear at the level of RGCs and are reflected in the

→center-surround organization of their visual receptive fields (Conway et al. 2010; Thoreson and Dacey 2019).

Both theories require integration of signals across cones of different wavelength sensitivity. This type of integration also has a spatial aspect because there can be only one cone of a specific wavelength sensitivity at any retinal location (Brainard 2015).

In the trichromatic primate, two major pathways generating color opponency can be distinguished: the L- vs. M-cone pathway involved in red-green opponency and the S-cone pathway involved in blue-yellow opponency. This distinction is apparent at the bipolar cell level (Thoreson and Dacey 2019).

13.5.2 Red-green Pathway

Red-green opponency is conveyed by midget ganglion cells. In the central, macular region of the retina, L and M cones are tightly packed, with each cone contacting two midget bipolar cells. One of two bipolar cells responds to brightness increments (ON response), and the other to decrements (OFF response). Bipolar midget cells synapse with four types of midget ganglion cells that are characterized by their responses to light shone onto their receptive field (RF) centers: red-ON, red-OFF, green-ON, green-OFF. For example, shining a red spot of light into the center excites the red-ON cell. By contrast, the cell discharge is inhibited by green light in the surround. The reverse RF organization occurs in other cells. The opponent RF surround results from inhibitory actions of horizontal H1 cells that mediate L+M inputs. The RF center of a midget ganglion cell is small, ensuring high spatial acuity.

Midget RGCs project to parvocellular LGN neurons (Martin 2009; Thoreson and Dacey 2019). In the retinal periphery, midget bipolar cells receive inputs from two or more cones of potentially different spectral type and may converge on individual RGCs, such that spectral purity and spatial acuity deteriorate towards the periphery (Martin 2009; Thoreson and Dacey 2019).

Color-opponency requires lateral inhibitory mechanisms, which most likely are provided by horizontal cells and amacrine cells (Thoreson and Dacey 2019). For instance, one sub-type of horizontal cell (H1) receives excitatory inputs from M and L cones and inhibits cones and bipolar cells. The inhibitory surround of midget ganglion cells need not derive from spectrally pure cones, but could be constructed from `red´ (r), `green´ (g) and `blue´ (b) signals and would thus show a broad spectral sensitivity (Martin 2009; Thoreson and Dacey 2019).

13.5.3 Short-wavelength Pathway

S-cones underlie blue-yellow opponency, giving rise to ON and OFF pathways. The ON pathway involves S cone-selective ON bipolar cells which in turn excite small stratified (blue-on) ganglion cells in their center. The inhibitory OFF pathway presumably involves a diffuse OFF bipolar cell and a special sub-type of horizontal cells (H2) that collect inputs from L, M and S cones (Martin 2009; Thoreson and Dacey 2019).

The major OFF counterpart of the S-ON pathway involves a relatively rare OFF midget bipolar cell which in turn synapses exclusively with a single OFF midget ganglion cell. S-OFF midget ganglion cells from the central retina are thought to have an L+M surround arising by →negative feedback from the S cone that connects H2 horizontal cells. Intrinsically photosensitive RGCs can also show S-OFF/L+M ON opponent light responses (Thoreson and Dacey 2019). Since S-cones are rare, they contribute to chromatic vision, but not to spatial resolution (Martin 2009).

13.5.4 Broad-band Pathway

Similar to midget ganglion cells in the peripheral retina, parasol ganglion cells receive a mixture of inputs from all cones, predominantly L and M cones. They are therefore called `broad-band´ (Schiller and Logothetis 1990), being excited by white light shone into the center and inhibited by white light into the surround. Midget cells exhibit tonic discharges evoked during center illumination, while parasol cells exhibit a transient response, suggestive of a high sensitivity to temporal change. Parasol ganglion cells are not only larger and have larger dendritic and RFs, they respond better to changes in light intensity of low contrast than do midget ganglion cells, which respond to finer details, higher contrasts and color.

13.6 Anatomy of the Lateral Geniculate Nucleus

The lateral geniculate nucleus (LGN) of the thalamus is the first synaptic station for RGC axons in the retino-cortical pathway, but it is more than a simple relay station (Ghodrati et al. 2017).

Layered Organization. The LGN consists of six layers of cells, each cell receiving input from one eye. Optic nerve fibers from the ipsilateral eye terminate in layers 2, 3 and 5, and fibers from the contralateral eye in layers 1, 4 and 6. The layers are organized →retinotopically, in register with the retina so that overlying cells in different layers receive RGC inputs from corresponding retinal loci (Ghodrati et al. 2017; Usrey and Alitto 2015).

Cell Types. In primates, the LGN is differentiated according to the size of the principal projection cells. The lower two layers contain magnocellular (M) neurons making up about 10% of thalamo-cortical cells, and the upper four layers parvocellular (P) cells accounting for about 80% of thalamo-cortical cells. Very small koniocellular (K) cells (10% of thalamo-cortical cells) lie in three pairs of specialized layers (Casagrande 1994; Ghodrati et al. 2017; Hendry and Reid 2000; Usrey and Alitto 2015). In addition, inhibitory neurons influence LGN activity.

LGN Inputs. The LGN receives inputs from various sources: retina, cerebral cortex, →thalamic reticular nucleus (TRN) and brainstem (Adams and Horton 2009; Cudeiro and Sillito 2006; Field and Chichilnisky 2007; Ghodrati et al. 2017; Hirsch and Martinez 2009; Martin 2009; Usrey and Alitto 2015).

Retino-geniculate Inputs. In primates, P cells receive inputs from midget ganglion cells and other more rare cells. M cells receive inputs primarily from parasol ganglion cells and possibly some other cells. Koniocellular cells receive inputs from various types of RGCs, including small bistratified ganglion cells. They are the only LGN cells receiving signals from blue (S) cones and input from the superior colliculus (SC) (Ghodrati et al. 2017).

Cortico-geniculate Inputs. Retinal inputs make fewer synapses on LGN cells than are made by feedback inputs from visual cortex via cortico-geniculate axons. These feedback connections appear divided anatomically and functionally in close parallel with feedforward partitioning into magno-, parvo- and koniocellular pathways. Cortico-fugal axons excite LGN →projection neurons. They also excite intrinsic inhibitory LGN interneurons and inhibitory TRN cells, whereby LGN projection neurons are disynaptically inhibited by cortico-fugal axons. This mixed feedback is thought to exert a modulatory influence that augments signal transmission and sharpens RFs in the LGN (Hirsch et al. 2015; Usrey and Alitto 2015).

Thalamic Reticular Inputs. The thalamic reticular nucleus (TRN) consists of a thin shell of inhibitory neurons located between the thalamus and cortex. The visual segment of TRN has two parts. The first lateral part receives →topographically organized excitatory inputs from the LGN and →striate cortex and sends inhibitory feedback to the LGN. It additionally receives inputs from the →orbito-frontal cortex (OFC) and →dorso-lateral prefrontal cortex (DLPFC), probably mediating →attentional modulation, and from the →amygdala. The first part is thought to mediate emotional modulation, via the →basal forebrain and brainstem. The second (medial) TRN part is associated with the pulvinar and various regions of →extra-striate visual cortex (Ghodrati et al. 2017).

Brainstem Inputs target LGN and TRN cells and may thus modulate signal transmission through the LGN during arousal, attention and different states of wakefulness and →sleep. The brainstem inputs have also been associated with switching of LGN activity from →bursting to tonic discharge as well as with increases in →contrast gain. LGN receives a variety of neurochemical modulatory influences: →cholinergic inputs from the basal forebrain and →parabrachial nucleus (PBN), the superior colliculus (SC) and pretectum; dopaminergic inputs from the midbrain; →noradrenergic inputs from the →locus coeruleus (LC), →serotonergic inputs from the dorsal raphé nucleus and histaminergic inputs from the tubero-mamillary nucleus of the hypothalamus (Ghodrati et al. 2017; Hirsch et al. 2015; Jacob and Nienborg 2018; Usrey and Alitto 2015).

LGN Outputs: Geniculo-cortical Projections. Many but not all LGN cells send axons to the primary visual cortex (area V1). The majority of geniculate P, M and K cells project differentially to specific layers of area V1, which in turn connect differentially to other visual areas (Adams and Horton 2009; Sincich and Horton 2005). P cells project to area V1 layer 4Cβ, with collaterals to layer 6. M cells project to layer 4Cα, with collaterals to layer 6. K cells project to layers 2/3. This connectivity pattern establishes three parallel functional channels (Nassi and Callaway 2009).

While area V1 is the major target of geniculate fibers, a smaller projection also targets pre-striate or extra-striate areas, including area V2, area V3/V3A, area V4, →area MT/V5 (**m**iddle **t**emporal area/area V5) (Masland and Martin 2007). These areas also receive visual

information through other pathways that circumvent the LGN and involve the lateral-posterior pulvinar complex of the thalamus and the reciprocally connected superior colliculus (SC) (Grieve et al. 2000, 2009; Kaas and Lyon 2007; Shipp 2003). The pulvinar is reciprocally connected with →multi-sensory →cortical areas and activated by very diverse sensory inputs. It may be involved in arousal, attention, adaptive and flexible →recognition of biologically important objects, selection of →salient stimuli and fast behavioral responses (Froesel et al. 2020; Grieve et al. 2009; Sewards and Sewards 2002).

13.7 Visual Processing in the Thalamus

Formerly, the similarity of RF properties of retinal ganglion cells (RGCs) and LGN cells appeared to support the view that the LGN is a fairly simple relay station that adds sparse processing to retino-cortical signal transmission. Although these RF properties are indeed similar, the activity patterns of RGCs and LGN projection neurons differ appreciably, due to a number of factors and mechanisms (Ghodrati et al. 2017; Usrey and Alitto 2015):

Convergence-divergence. One to five RGCs can converge on an individual LGN projection neuron, and a single RGC can send divergent axon collaterals to different LGN neurons (Usrey and Alitto 2015). Convergence increases the →signal-to-noise ratio by averaging across inputs, and thereby the resolution of image representation (Hirsch et al. 2015). Divergence on the other hand reorganizes visual representation of space. It also produces synchronous discharges in LGN cells of the same class and in overlapping RFs, thereby strengthening signal transmission to cortical neurons (Ghodrati et al. 2017; Hirsch et al. 2015; Usrey and Alitto 2015).

Receptive Field Structures. Many RGC and LGN RFs are approximately circular and show structural similarities in having a concentric arrangement of antagonistic center-surround regions, which provide cells with sensitivities to stimulus size, spatial location, local contrast borders, phase and spatial frequency (Ghodrati et al. 2017; Hirsch et al. 2015). Cells whose RFs are not perfectly circular might show orientation sensitivity. For example, evidence indicates that monkey M and P cells are weakly sensitive to orientation, while a subset of K cells shows strong orientation sensitivity (Ghodrati et al. 2017). In addition, some cells exhibit sensitivity to motion and direction, which appears to occur particularly in cells of the koniocellular layers in rodents and marmoset monkeys (Dhande et al. 2015; Ghodrati et al. 2017; Usrey and Alitto 2015).

In addition to the classical receptive field (CRF), RGCs and LGN neurons often have a surrounding extra-classical RF, in which visual stimulation of either polarity suppresses excitability. This effect is stronger and more extensive in LGN neurons than RGCs (Ghodrati et al. 2017; Usrey and Alitto 2015). Similar extra-classical RF effects occur in the visual cortex.

Thalamic Inhibition. Two classes of inhibitory neurons exert effects on LGN projection neurons that help create the center-surround antagonism and influence cell discharge dynamics. Intrinsic inhibitory interneurons within the LGN receive excitatory inputs from RGCs and thus exert feedforward inhibition. In another type of inhibitory interplay, neurons in the thalamic reticular nucleus (TRN) receive collateral excitatory inputs from LGN

projection neurons and thus exert feedback inhibition (Ghodrati et al. 2017; Hirsch et al. 2015; Usrey and Alitto 2015).

Discharge Dynamics. Individual RGCs discharge more spikes per stimulus than their target LGN neurons. RGC spike pairs occurring at short-interspike intervals (less than 30 ms) are especially efficient in firing the LGN neuron, due to summation of →excitatory postsynaptic potentials (EPSPs). Through this `paired-spike enhancement´, high spike rates are preferentially transmitted through the retino-geniculate synapse which thus acts as a high-frequency filter (Ghodrati et al. 2017; Usrey and Alitto 2015).

Other Properties of P, M and K Cell Discharges. Compared to P cells, M cells have shorter latencies in response to visual stimuli. In addition, they have lower spatial resolution, are tuned to higher temporal frequencies, and they are much less sensitive to red/green →color contrast but more sensitive to luminance contrast.

K cells have poor spatial resolution, but larger RFs than P and M cells. In addition, they exhibit intermediate contrast sensitivity and temporal frequency responses, and are sensitive to blue/yellow contrast (Ghodrati et al. 2017).

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14

Cortical Visual Processing:

Form, Color, Depth, Motion

CONTENTS

Abstract

• The visual cortex of primates is represented by a number of distinct cortical areas, organized into two main streams: A ventral stream, from the primary visual cortex to the inferior temporal (IT) cortex which processes form, size, brightness, texture and color for conscious identification and recognition of objects: and a dorsal stream from primary visual cortex to superior temporal and parietal areas, which processes spatial object properties such as location, depth and motion, for visual guidance of motor actions.

• Visual recognition of shape and color and of object identification are thought to be the primary domain of the visual ventral stream from area V1 through the temporal lobe to the prefrontal cortex.

• In the ventral stream, neuronal responses on average increase in latency, receptive field (RF) size, complexity and sensitivity. Object detection and categorization are very fast processes and involve a network of cerebro-cortical areas. Some object categories such as the body and the face appear to receive special processing in specialized cortical areas.

• Representation of full 3D shape is also present in the dorsal stream for object-oriented actions such as reaching, grasping and manipulation.

• Color processing starts in the retina and continues through the lateral geniculate nucleus (LGN), primary visual cortex into the ventral and dorsal streams, with recoding taking place along the way.

• Depth and distance perception are required to estimate object shapes and the 3D world with its spatio-temporal arrangement of objects. Both distance and depth perception are based on monocular and binocular cues. The latter are provided by stereopsis, which is based on differences (disparities) between images cast on the two retinas.

• A requirement for normal stereopsis is that corresponding features in the two retinal images are identified correctly and fused into a single percept. This requires the existence of binocular cells with receptive fields in both retinas. Disparity sensitivity is thought to originate at cortical level, starting in primary visual cortex, and continues into the ventral and dorsal streams.

• Detection and evaluation of object motion, direction and speed starts in the retina and continues centrally. Because of the limited size of receptive fields (RFs), however, direction-selective neurons in primary visual cortex detect only the motion of local contours within the windows (apertures) of their small RFs. To deduce overall object motion, some sort of vector addition of the local motions must be performed, probably by neurons in the dorsal stream.

• Special mechanisms exist for the perception and interpretation of biological motion, e.g., dancing, running or walking. This capability develops early in life, lasts into old age and requires a large cerebro-cortical network.

14.1 Introduction

Visually guided behavior in a complex environment requires the identification and characterization of objects and their distinction from, and location within, an often-cluttered environment. Object characteristics are usually specified in terms of form (shape), location, motion and often color. Object →recognition involves →memory and →attention. These complex processes take place in widespread networks of →cortical areas (Orban 2009; van Essen et al. 1992).

14.2 Structures and Functions of Cerebro-cortical Visual Areas

In primates, almost 60% of →cerebral cortex is involved in visual processing in one or the other way (Verhoef et al. 2016).

14.2.1 Primary and Secondary Visual Cortices

Humans and macaque monkeys have been most intensively studied for higher visual functions. The early visual area V1, area V2, area V3, and →area MT/V5 are conserved in humans and macaques, while higher visual areas show greater differences between humans and macaques (Orban 2008; Orban et al. 2004; Sereno and Tootell 2005).

The human primary visual cortex (→striate cortex, →Brodmann´s (1909) cytoarchitectonic →area 17, or physiological area V1) is mostly located around and within the calcarine fissure (sulcus) on the medial surface of the occipital lobe. In macaque monkeys, much more of area V1 is visible on the external occipital surface. In both species, the secondary visual area V2 surrounds the primary visual cortex, and area V3 in turn surrounds area V2. The human visual cortex remains plastic into adulthood (Castaldi et al. 2020).

Retinotopy. The lateral geniculate nucleus (LGN) and the primary visual cortex are organized →retinotopically, so that the image carried by the visual stream preserves the spatial relationship of the image registered on the retinal field (Arcaro et al. 2019).

In the macaque, visual cortical areas have been analyzed by a number of methods, including histology and retinotopic mapping. Originally, mapping involved systematic probing with a microelectrode in the lateral geniculate nucleus or the primary visual cortex of an anesthetized monkey, in order to detect responses to images focused on the retinal field through contact lenses placed on the monkey's eyes (Van Essen et al. 1984; Connelly and Van Essen 1984; Sereno et al. 1994). More recently, →functional magnetic resonance imaging (fMRI) studies in conscious humans and monkeys have demonstrated that the retinotopic organization of macaque inferior temporal (IT) cortex is more extensive than previously described (Arcaro and Livingstone 2017; Conway 2018; White et al. 2017).

Nonetheless, retinotopic maps are seen in higher visual areas with decreasing precision, due in part to the increasing →visual receptive field (RF) size (Adams and Horton 2009; Sincich and Horton 2005; Grill-Spector and Malach 2004; Rousselet et al. 2004). New methods

using brain imaging and various tasks have revealed multiple areas in human →parietal cortex and →frontal cortex, which carry a →topographic map of visual space (visual map) (Silver and Kastner 2009).

Geniculate Afferents and Outputs. About 5-10% of the input to cortical neurons come from geniculate afferents. The rest stem from local neurons, other cortical regions, and →neuromodulatory systems (→cholinergic, →dopaminergic, →noradrenergic, →serotonergic); (Jacob and Nienborg 2018; Masland and Martin 2007). In the primary visual cortex, certain laminae and patches 150-200 μm in width are rich in the mitochondrial enzyme →cytochrome oxidase (CO). Patches, inter-patches and the different laminae receive differential projections from the different LGN cell classes and connect differentially to further visual areas, i.e., areas V2 to V5 and the →superior colliculus (SC) (Adams and Horton 2009; Felleman 2009; Sincich and Horton 2005).

Ocular-dominance Columns. Each primary visual cortex receives inputs from both eyes corresponding to the contralateral →visual field. These two topographical projections must somehow be put in register. Even so, geniculo-cortical fibers originating from different eye-specific LGN layers are kept fairly separate in area V1, with afferents related to the two eyes ending in different, interdigitating, vertical slabs of cortex that are called ocular-dominance columns (Adams and Horton 2008, 2009). Afferents from one geniculate layer terminate in every second slab. Visual stimulation of a single eye thus leads to activation of related cortical surface stripes.

Area V2 is an important link between area V1 and temporal and parietal cortical areas via area V4 and area MT/V5, respectively, and sends a massive feedback connection to area V1 (Sincich and Horton 2005). Area V2 is not organized according to →ocular dominance (Ts´o and Roe 1994), but is neurochemically differentiated into regions of different cytochrome-oxidase (CO) staining: thin and thick stripes of rich CO staining separated by pale `interstripe´ of low CO density (Adams and Horton 2009; Felleman 2009; Merigan and Maunsell 1993; Sincich and Horton 2005). The visual field is mapped discontinuously on area V2. Any area of the visual field is represented at least in triplicate across the thin-pale-thick stripes (Ts´o and Roe 1994). Aside from its value as a pathway marker, CO is indicative of oxidative metabolism and reflects overall neuronal activity over long time periods (Hevner et al. 1995).

Non-visual Sensory Inputs. Areas V1 and V2 also receive inputs from primary auditory cortex (A1). It seems that in area V1, there are independent channels for visual and auditory signals. The mechanisms responsible for coexistent auditory signals in the visual cortex are largely unknown. It appears, in any case, that auditory input facilitates visual perception (Petro et al. 2017). Conversely, responses to faces and objects can be recorded in primate auditory cortex (Hoffman et al. 2008).

14.2.2 Further Visual Areas and Cortico-cortical Projections

The visual cortex of primates is distributed into more than 30 anatomically distinct cortical areas that cover more than half the cortical surface in macaques and about a third in humans, and each connecting reciprocally with many other areas. The original scheme (van Essen et

al. 1992) has meanwhile been supplemented by →area V6, →area V6A, area AIP, and some more (Orban 2008). Many of these areas receive additional sensory inputs including touch and audition (Tompa and Sáry 2010). Regions in the parietal cortex and frontal cortex, and →sub-cortical structures such as the superior colliculus (SC) are involved in cross-modal interactions, and are evidently involved in poly-modal representations of space (Holmes et al. 2009; Driver and Spence 1998) and visually guided motor control (Sakata et al. 2009; Shin et al. 2009). Vision is thus the most extensively represented sensory modality. The connectivity between the visual areas is complex, encompassing more than 300 neural pathways (Felleman 2009; Felleman and van Essen 1991; van Essen et al. 1992). Several →extra-striate areas are connected by feed-forward anatomical links in a roughly hierarchical manner (Arcaro et al. 2019), and feedforward connections are differentiated according to sub-modalities, which are assumed to analyze different features and properties of the external world.

14.2.3 `What´, `Where´ and `How´ Cortical Visual Streams

Humans comprehend a complex scene rapidly and accurately by scanning across it, saccading at a rate of many times per second. Most humans possess a superb ability in categorizing complex natural scenes (Epstein and Baker 2019). For example, the presence of an animal and its details in a complex photograph can be rapidly detected by human subjects, and a neurophysiological correlate of this detection is observed in the →prefrontal cortex area in as little as 150 ms. A general impression of a scene can be obtained within about 100 ms (Fei-Fei et al. 2007), based on previous experience that predicts what to expect. A network of interwoven brain areas performs the representation and perception of objects and their relations.

A persuasive hypothesis (Ungerleider and Mishkin 1982; Ungerleider and Haxby 1994) predicts that different aspects of the external visual world are processed through different cortical processing pathways.

Form, size, brightness, texture and color are assumed to be processed in a →ventral visual stream from the primary visual cortex to the inferior temporal (IT) cortex (Tompa and Sáry 2010), with further connections to prefrontal cortex and →limbic system areas, This processing stream is also called the `what´ stream for conscious identification and recognition of objects, with →short-term memory and →long-term memory being of utmost importance.

Spatial object properties such as location, depth and motion were originally thought to be processed by a →dorsal visual stream from primary visual cortex to superior temporal and parietal areas, but the role of the dorsal stream has subsequently been re-interpreted and differentiated. Since the main function of the dorsal stream seems to be the organization and visual guidance of motor actions, it is also called the `how´ stream (Goodale and Westwood 2004; Goodale et al. 2004; Milner and Goodale 2008; Westwood 2009). On this view, object properties such as size, 3-D shape, orientation, slant, motion, and absolute distance relative to the body and effectors must be – and are – represented in the dorsal pathway (Erlikhman et al. 2018). Projections to prefrontal cortical area 8 and area 46 may subserve eye movement control and spatial →working memory, whereas projections to →premotor

cortical area F2, →area F7, →area F4 and →area F5 are involved in eye movements, reaching, grasping and manipulation. Direct and indirect projections to →medial temporal cortex (→hippocampal formation) may contribute to the control of navigation (Kravitz et al. 2011).

However, the two streams are no isolated modules due to many interactions between them, which calls for a more differentiated scheme (Milner 2017; Rosetti et al. 2017). Recognition of objects also depends on spatial aspects. At the tip of the temporal cortex (area TEd), object-sensitive neurons are intermixed with cells that encode environmental space (Connor and Knierim 2017). The recognition of objects is also closely linked to their significance and to →decisions that require actions. Thus, pathways for object-related information maintain reciprocal connections with sub-cortical and cortical structures, including the →striatum (→basal ganglia), →claustrum, →amygdala, the →hippocampus, →perirhinal cortex, →entorhinal cortex and prefrontal cortex (Oram and Perrett 1994b).

14.3 Form Processing

Visual recognition of shape and color and object identification are thought to be the primary domain of the ventral visual stream, although representation of full 3D shape also plays an important role for object-oriented actions such as reaching, grasping and manipulation and is present in the dorsal visual stream (Kastner et al. 2017; Orban 2011; Theys et al. 2015). The ventral stream starts in area V1, runs through the temporal lobe and connects to the prefrontal cortex. On the way, neuronal responses on average increase in latency, →receptive field (RF) size and complexity. On an initial, fast sweep of feedforward signal processing, the ventral pathway briefly analyzes several objects in parallel to attain a coarse representation, then a few objects are focused on for finer analysis by horizontal and re-entrant feedback connections (Hegdé 2008; Rousselet et al. 2004).

14.3.1 Form Processing in the Primary Visual Cortex

Neurons in primary visual cortex (area V1) are selective not only for shape cues, but also for texture, color, motion and depth (Orban 2008).

Different cells across area V1 have receptive fields (RFs) located in different visual field positions, with receptive field size increasing from central to peripheral. Cells with small concentric receptive fields in layer 4Cβ ensure that area V1 maintains a high-resolution fine-grained →topographical representation of the retinal image and provides for the spatial details of objects. In addition, area V1 is at the origin of successive processing that enables line detection, feature grouping and integration, leading to invariant object identification and recognition (Gur 2015). Representation and recognition of images are dependent on parallel representations of space by responses in area VI whereas other higher order, cognitive attributes are conveyed through integration, interpolation and convergence. These processes involve →top-down influences from other cortical areas: reentrant feedback pathways that convey higher-order visual information to antecedent cortical regions are superimposed on the feedforward pathway (Gilbert and Li 2013).

Top-down influences are distributed through descending pathways covering the entire →neocortex, and involve several types of cells with various contributions to →visual acuity.

Simple Cells in area V1 exhibit different receptive field structures. They have non-circular fields with specific →spatial orientation (Carandini et al. 2005; Hirsch and Martinez 2009). Simple cells are maximally excited when a light beam just covers a central longitudinal strip within the receptive field, whereas the cell´s discharge is inhibited by a beam applied outside and parallel to the central strip, or in an oblique orientation. There is no response when the entire field is illuminated. Simple cells are well suited to detect the orientation of short lines or →contrast borders. Acuity is highest when a light beam is focused centrally on the fovea, and decreases towards the peripheral visual field. The cells do not respond well, however, to the internal structure of the excitatory stripe, e.g., to individual dots and their arrangement, which indicates loss of spatial resolution due to integration (Gur 2015).

Complex Cells share orientation selectivity with simple cells, but without the location specificity and the sharpness (Hirsch and Martinez 2009). Their field is constructed from a number of discrete but spatially over-lapping sub-regions or sub-units (Carandini et al. 2005).

They react strongly to straight stimuli moving through the field at the correct orientation (Creutzfeldt and Nothdurft 1978; Hubel 1988). They could also play a role in detecting stationary straight lines under normal conditions when the eyes move (Hubel 1988). →Complex cells respond to contrasts in either direction, e.g., a bright line or bar on a dark background, and vice versa (Carandini et al. 2005; Oram and Perrett 1994b).

Origin of Orientation Specificity. It is not yet clear yet how orientation specificity of area V1 cells comes about. Several hypotheses have been proposed (Dhande et al. 2015; Hirsch and Martinez 2009; Orban 2008; Vidyasagar and Eysel 2015). Hubel and Wiesel (1962) proposed that →center-surround cells in the lateral geniculate nucleus (LGN), with on-centers aligned along the relevant orientation in space, converge onto orientation-specific simple cells. Inhibitory side-bands might be generated by alignment of LGN off-center neurons. Other mechanisms could also lead to orientation selectivity, perhaps in a complementary manner. Furthermore, LGN cells and retinal cells may show milder forms of orientation selectivity, which could be sharpened in area V1 (Dhande et al. 2015; Vidyasagar and Eysel 2015).

Contour Curvature. Some cells in area V1 known as `end-stopping cells´ are believed to play a role in coding curvature and tangent discontinuities (corners). Area V2 neurons have on average larger receptive fields (RFs) than cells in area V1, and relatively more are tuned to more complex local shape geometries, including curvature, angles and intersecting lines (Elder 2018).

Spatial Frequency Tuning. The receptive fields of simple and complex cells render them →sensitive to particular repetitive structures in the visual input. If the cells are tested with gratings of different spatial frequencies, they respond differently to different patterns. This amounts to →band-pass filtering of the visual input. Each cell thus visualizes the world filtered through its receptive field. Spatial frequency tuning is not invariant. Tuning varies if area VI neuron responses change from lower to higher frequencies (Hegdé 2008).

Receptive Field Modulation. Originally, a visual neuron´s receptive field structure appeared to result in invariable responses to stimuli. This has turned out to be a wrong supposition. Indeed, widespread influences from various sources modulate the responsiveness of what is now called the classical receptive fields (CRF) (Spillmann et al. 2015). For example, responses of area V1 neurons to oriented line segments within their CRFs are modulated by the texture of line segments that surround the fields. Neuron response is lower when the orientation of the surround pattern is the same as in the CRF, and is stronger when the orientations differ (orientation contrast). These effects segregate borders between textures and detect location and direction of changes in contour orientation, such as junctions or corners. Orientation contrast contributes to figure-ground segregation. Such contextual effects depend on short- and long-range horizontal connections between receptive fields RFs as well as top-down influences from higher visual areas (Spillmann et al. 2015).

Sensitivity to Motion Direction and Speed. Motion of contours may contribute considerably to shape →perception. Humans are good at extracting 3D object shape from motion cues (Domini and Caudek 2003). This capacity develops as early as two months after birth (Orban 2011). For example, the shadow of a contorted wire appears flat when the wire is stationary, but rotating the wire causes motion in the shadow, which suddenly appears three-dimensional. →Perception of motion and its after-effects (→motion after-effect) may result from contextual surround effects (motion contrast). Area V1 contains populations of direction- and speed-sensitive neurons (Orban 2008). Directional motion sensitivity in the CRF is strongly modulated in area MT/V5 by motion in the surround (Spillmann et al. 2015).

Temporal Receptive Field Changes. Many simple cells in area V1 develop orientation tuning within the first 40-80 ms of the response, and their ON and OFF sub-fields can change during stimulation, indicating that spatial and temporal response aspects are closely correlated (Wörgötter and Eysel 2000). The shape and size of receptive fields depend on the state of brain, as evidenced in the →electroencephalogram (EEG). They expand with a transition from non-synchronized to synchronized EEG, and shrink when stimulated with flashing light spots (Wörgötter et al. 1998).

Illusory Contours. Illusory contours evoke the perception of an edge without luminance or color change across it. This may serve to fill in gaps in incomplete stimuli and detect partly occluded or masked objects. Humans and non-human animals are able to perceive contours, almost without being aware of it. Early visual cortical regions such as area V1 and area V2 are thought to be responsible for forming illusory contours (Nieder 2002; Orban 2008; Spillmann et al. 2015; Weil and Rees 2011).

Contour Completion. Objects are partially occluded by nearer objects, separating them into image fragments. However, these fragments can be grouped together to create a representation of the partially occluded object. This process may start as early as in the primary visual cortex (area V1). For example, orientation-selective cells stop responding to a bar when it is partly occluded by a patch. They are also unresponsive when the patch has disparity, i.e., substantial inequality, making it appear to lie behind the bar. But they do respond when the patch has disparity so as to appear to lie in front of the bar (Sugita 1999). This has been interpreted as an example of the →Gestalt principle of good continuation (Spillmann et al. 2015). This concept is derived from Gestalt psychology, i.e., laws of

perception based on phenomena. In the case of contour completion, it means that because objects in the visual world are presented are often presented incompletely, the visual system reassembles the pieces, perhaps utilizing physiological mechanisms in multiple visual areas (Spillmann et al. 2015).

Surface Fill-in. Neurons in areas V1 and V2 that signal luminance contribute to the perception of surface lightness, for the purpose of characterizing an object surface in terms of brightness, color, texture, depth and so on (Peng and van Essen 2005), while other V1 and V2 cells are color-sensitive. Furthermore, there are filling-in and induction processes that depend on the borders and surrounds. For example, although the →blind spot and the vessels on the retina cause local `holes´ of information, they are successfully filled in. The filling-in probably involves an active process that makes use of surround information. Contextual signals propagating into a surface from its borders appear to play a significant role, and might be mediated via horizontal connections in area V1 as well as long-range feedback connections from higher areas (Albright and Stoner 2002; Paradiso et al. 2006; Spillmann et al. 2015; Weil and Rees 2011).

14.3.2 Form Processing in the Ventral Stream

Form processing in the ventral stream leads to fast and accurate recognition of objects embedded in complex backgrounds, which continues to develop postnatally until reaching the adult state (Grill-Spector and Weiner 2014; Ison and Quiroga 2008; Kersten et al. 2004; Kourtzi and Connor 2011). Face perception and recognition, for example, require about 16 years to mature (Grill-Spector et al. 2008). But object perception remains adaptable in adult age (Kourtzi and Connor 2011).

There are two ventral streams, one in each hemisphere. Each ventral stream primarily analyzes the contralateral visual hemifield, with integration occurring in structures such as the prefrontal cortex (Rousselet et al. 2004).

Precisely how and according to which principles object processing occurs at a neural level, remains controversial (Kourtzi and Connor 2011). One scheme proposes that neural object representations are constructed successively by integrating responses to structural elements. Indeed, neurons in the ventral pathway are sensitive to form and color (Merigan and Maunsell 1993), and the way they respond reflects successive stages of integrative computation leading to selectivity for increasingly complex stimulus features. In parallel, there is an average increase in receptive field size that is adaptable to different tasks (Rousselet et al. 2004). Another scheme emphasizes category coding. Both types of coding occur, but their interrelation is as yet uncertain (Kourtzi and Connor 2011).

14.3.2.1 Area V4 and Infero-temporal Cortex

Area V4 contains a retinotopic map that is less precise than in areas V1, V2 and V3 (van Essen and Zeki 1978). Many cells in area V4 of the macaque are selective for stimuli smaller than their classical receptive field (CRF). They have large non-classical suppressive zones surrounding the CRF (Gallant et al. 1996). Many area V4 cells are tuned jointly to the

location, orientation and curvature of local contour features (Elder 2018). Another response characteristic is the sensitivity to the relative position of structural elements to each other and to the whole object (Kourtzi and Connor 2011). Area V4 also contains neurons that respond to →binocular disparity with a bias towards near objects (Hinkle and Connor 2001).

From area V4 into the infero-temporal (IT) cortex, neurons need increasingly complex stimulus characteristics to respond (Kourtzi and Connor 2011; Orban 2008; Rousselet et al. 2004). In area CIT and area AIT, cells respond to complex features such as star-shaped stimuli or to combinations of features, such as a circular brown stippled area with a bar extending to the right. These features are not complex enough on their own to completely select for natural objects (Tanaka 1996, 1997). Moreover, there are IT cells that respond to particular configurations of surface fragments with sensitivity to surface curvature, orientation and 3D relative position (Kourtzi and Connor 2011). Evidently, an individual object cannot be represented by activity of cells within a single →cerebral column, except in the case of some special objects such as faces, but rather by the coordinated activity of several to many cerebro-cortical columns (Tanaka 1997).

14.3.2.2 Invariances in Form Processing

Objects known to a viewer are identified by reproducible constellations of features, which may still appear differently under varying circumstances such as change of size, retinal position, orientation, viewing angle, illumination, and partial occlusion. The task of the visual system is to recognize the object despite its changing appearance (Grill-Spector and Weiner 2014). This requires the capability to extract the invariant features from the changeable ones.

The infero-temporal (IT) pathway supports object recognition in the face of variations in retinal position, size, orientation, color, viewing angle and background (Booth and Rolls 1998; Elder 2018; Hoffman and Logothetis 2009; Ison and Quiroga 2008; Logothetis and Sheinberg 1996; Tanaka 1997; Tompa and Sáry 2010; Wallis and Rolls 1997). However, neurons with the highest selectivity for object identity are the least invariant to changes in position, size, contrast and clutter (Elder 2018).

Position Invariance (Tolerance). Perception of objects is rather tolerant to changes of their position on the retina. This invariance or tolerance may be supported by IT neurons with large receptive fields. But position information is still available in IT. There are other cells with small receptive fields and low position tolerance, which may represent objects at higher resolution (Tompa and Sáry 2010).

Orientation Constancy. A few cells respond equally to effective stimuli at all angles (Oram and Perrett 1994b; Tanaka 1997).

Size, Speed and Object Constancy. Monkeys and humans can accurately judge the size of objects up to 30 m., which requires estimates of object distance, size and movement speed as the object approaches or moves away. This ability requires that object size be scaled with distance, which in turn requires an estimate of distance. Viewing distance affects neuronal responses in area V4 In addition, objects need to be categorized and recognized as the same under different viewing conditions (Dobbins et al. 1998).

14.3.3 Object Categorization and Recognition

Object detection and categorization in humans are very fast processes, allowing them to get the essence of a scene at a glance before delving into details. Although training cannot speed up ultra-rapid categorization, expertise and familiarity with objects improve object recognition by decreasing →reaction time and error rates (Hedgé 2008). Of help are the location of objects in a natural environment and their positions relative to each other. Neural representations are sharper and perceptual sensitivity is greater when objects appear at their typical locations in the world. When objects appear in their typical relative positions, they are represented as groups, whereby they are more easily detected, recognized, and memorized (Kaiser et al. 2019).

Grouping visual stimuli into behaviorally relevant categories leads to re-organization of neural responses (Freedman and Miller 2008; Kourtzi and Connor 2011). In humans, category-specific cell responses occur in the →medial temporal lobe, including the →hippocampal complex, all of which receive convergent inputs from temporal cortical regions specialized for processing complex visual stimuli. In phylogenetically old vertebrates such as anurans, mechanisms to recognize prey and predators are innate and mediated by →brainstem structures. Mammals use →sub-cortical structures including the superior colliculus (SC) in addition to cortical structures. In →primates, early innate object recognition is supplanted with learned object recognition mediated by cortical structures (Sewards and Sewards 2002).

A large proportion of cells in the monkey IT cortex, in particular in area AIT and area STPa (**a**nterior **s**uperior **t**emporal **p**olysensory), are selectively responsive to particular objects and body parts (Gauthier and Logothetis 2000; Oram and Perrett 1994a,b; Rolls 2009; Tanaka 1997; Tompa and Sáry 2010; Wallis and Rolls 1997). Monkey IT cortex contains several functionally interconnected patches, in which neurons respond selectively to faces, these regions being separate from patches responding to facial expressions and objects (Tompa and Sáry 2010). Response properties are modified by experience, and change when novel faces appear, attesting to rapid →learning (Wallis and Rolls 1997).

Cells responding to different aspects of faces are also found in monkeys in the amygdala, ventral striatum, and prefrontal cortex (Gauthier and Logothetis 2000; Rolls 2009). The prefrontal cortex is also involved in processing information related to the identity of faces (O ´Scalaidhe et al. 1997). Cells in the anterior superior temporal sulcus (STS) react to particular body actions and postures (Peelen and Downing 2007).

In humans, brain imaging has revealed category-specific regions for ecologically important categories such as faces, bodies and their parts, places, buildings and, in literate humans, words and symbols, while some regions process objects and shapes more generally (Arcaro et al. 2019; Grill-Spector and Weiner 2014).

Face Areas. Face recognition is important for social communication and includes the determination of identity, sex, age, mood, →emotions, →intentions, thoughts, and direction of gaze. It is well-developed in humans but not monkeys (Rossion and Taubert 2019). In humans, it probably recruits a widespread network of areas located in the inferior occipital gyrus, fusiform gyrus (fusiform face area, FFA), anterior and posterior superior temporal

sulcus (STS), anterior temporal lobe and inferior frontal gyrus (IFG), with a right-hemisphere dominance (Arcaro et al. 2019; Duchaine and Yovel 2015). Facial expression is supposed to be processed in the amygdala and →insula; areas in the prefrontal cortex and the →orbito-frontal cortex (OFC) have been implicated in processing facial beauty. Activity in face-selective areas is also modulated by attention, expertise and →visual imagery, i.e., the ability to generate visual images through memory and →cognition, without any retinal input (Ishai 2007; Ishai et al. 2002).

Extra-striate Body Areas (EBAs). Bilateral regions called extra-striate body areas (EBAs) on the lateral brain surface adjacent to and sometimes overlapping with area MT/V5 have been suggested to be specialized for the visual perception of the human body and body parts (Kanwisher 2010). Another body-selective area, the fusiform body area (FBA) is situated in the fusiform gyrus, adjacent to and partly overlapping the fusiform face area (Peelen and Downing 2007).

Scene Areas. Neuroimaging in humans has revealed three cerebro-cortical retinotopic regions that respond selectively to scenes (e.g., landscapes, cityscapes, rooms): →parahippocampal place area (PPA), retro-splenial/medial parietal place area (RSC/MPA) and dorsal occipital place area (OPA). These areas are sensitive to low-level visual characteristic of scenes, such as high spatial frequencies, rectilinear junctions, edges at cardinal orientations. They also respond to higher-order stimulus structures, such as environmental boundaries defining the spatial layout of scenes, single objects modulated by spatial factors such as real-world size, spatial stability, navigational relevance. In relation to navigation, PPA and OPA primarily analyze the local spatial structure of scenes, the RSC/MPA encodes facing direction and location (Epstein and Baker 2019).

A problem inherent in the above-described mechanisms underlying object recognition arises from the integration across larger receptive fields, which destroys spatial resolution. It has been proposed that this resolution is provided in parallel by the fine-grained topographical representation in area V1 (Gur 2015).

14.3.4 Multi-sensory Interactions in Object Recognition

Object properties are also assessed by other senses such as gustation and olfaction, temperature sense, touch, proprioception and in part audition. →Psychophysics experiments that explore the relevance of visual imagery processes support the existence of →multi-sensory object representations. They suggest the existence of a multi-sensory representation, spatial in format, and flexibly accessible by both →bottom-up and top-down inputs (Lacey et al. 2007). The different modalities may provide redundant and/or complementary information on objects, which may improve recognition accuracy and speed. This requires the integration of different sensory signals into a common percept (Bizley et al. 2016).

Integration can result from convergence of modality-specific signals in multi-sensory association cortices or from more direct cross-modal influences from one modality-specific area onto another (Amedi et al. 2005). For example, monkey area V4 and posterior IT represent the visual and tactile material properties of objects (Komatsu and Goda 2018). And brain imaging in humans showed that the →lateral occipital complex (LOC), which is

presumably homologous to the macaque infero-temporal cortex, is activated selectively in response to both visual and →haptic 3D shape, in particular to the perception and manipulation of objects using the senses of touch and proprioception. LOC thus seems to be involved in the multi-sensory representation of objects (Sathian 2016). Cross-modal interactions also help establish the structure of peri-personal space i.e., which immediately surrounds the body (Macaluso and Maravita 2010).

14.3.5 Prior Knowledge in Object Recognition

Object recognition depends not only on sensory inputs that are ambiguous, but also on knowledge-based assumptions built into the visual system. For example, the perception of a solid form is biased towards convexity. When resolving convex from concave shapes based on shading, the light is assumed to come from above; and object perception is biased towards preferred views as if from a viewpoint above the scene, which occurs when handling most of the objects we manipulate (Kersten et al. 2004). The integration of individual visual items into a Gestalt also depends on experience and training. For example, chess experts outperform chess novices in the fast recognition of chess positions with multiple pieces, a process in which the →temporo-parietal junction (TPJ) appears to play a prominent role (Rennig et al. 2013).

14.4 Cortical Processing of Color

Color is a visual dimension whose neural representation has often been seen as segregated from that of form. This is probably a simplification, however (Rentzeperis et al. 2014). Color perception aids in the perception of objects and materials. Color accelerates object perception and facilitates the memory of objects (Witzel and Gegenfurtner 2018).

14.4.1 Color Coding in Primary Visual Cortex

It now seems clear that primary visual cortex transforms the geniculate inputs into new representations, with considerable convergence of LGN cells onto area V1 neurons, as already suggested by larger receptive fields in area V1 (Solomon and Lennie 2007). The primary visual cortex contains, besides many color-insensitive neurons, a variety of color-sensitive cells with different receptive field structures (Adams and Horton 2009; Conway et al. 2010; Johnson et al. 2008). There are color-opponent cells of two general types that are specific not to cones but to colors themselves: single-opponent cells and double-opponent cells. Single-opponent cells with circular receptive fields are excited by large color patches and could be important for the perception of color in extended regions. For example, these cells may be excited by a red spot shone into the center and inhibited by green light shone into the surround. In double-opponent cells with circular receptive fields, both the center and the surround are sensitive to opponent colors, e.g., double-opponent cells have a center that is excited by one color and inhibited by the other. In the surround, the pattern is reversed. For example, if the center is excited by green and inhibited by red, the surround will be excited by red and inhibited by green. Many neurons have opponent cone inputs that may enable them to detect →color contrast, color boundaries and contours and make perceptual

connections between form and color (Conway et al. 2010; Hurlbert 2003; Johnson et al. 2008; Shapley and Hawken 2002). Color-sensitive neurons are likely to receive inputs from both eyes and thus support binocular vision (Solomon and Lennie 2007).

14.4.2 Color Coding in the Ventral Stream

Functional magnetic resonance imaging (fMRI) of →alert macaque brains shows color-biased activity in various brain areas. A region encompassing area V4, area PITd and →area TEO contains luminance-independent, color-sensitive cells with some shape sensitivity that may contribute to hue perception and →color constancy. Other cells are weakly color-sensitive, but more strongly shape-sensitive (Conway et al. 2007; Conway and Tsao 2006).

Some cells in macaque area V4 are selective for stimulus form, independent of color, while others show conjoint sensitivity to both form and color (Oram and Perrett 1994b). The proportion of color-selective cells in infero-temporal cortex (IT) is high, with a uniform distribution of color preferences and a sub-population with narrow selectivity for color (Gegenfurtner and Kiper 2003). Color-sensitive cells in IT are highly concentrated in patches which multiplex hue and shape information, with shape-invariant hue information being much stronger in anterior than more posterior color patches (Chang et al. 2017). Infero-temporal neurons also contribute to color categorization (Conway et al. 2010).

In humans, lesions in area V4 produce mild deficits in color vision in conjunction with impairments in shape and texture discrimination, object recognition, and focusing of attention (Gegenfurtner and Kiper 2003).

14.4.3 Color Coding in the Dorsal Stream

Area V3 is considered the first stage of the dorsal processing stream and connects strongly to area MT/V5. Area V3 is also connected to area V4, which may explain why it contains color-selective neurons with similar incidences and properties as in area V1. These cells may be involved in processing motion defined by color. Area MT/V5 contains neurons whose responses are modulated by color stimuli, although less strongly than to luminance variations (Gegenfurtner and Kiper 2003).

14.4.4 Color Constancy

The color of a surface is perceived as being the same, even though illumination influences the wavelength composition of reflected light. Color constancy contributes to the categorization of an object, irrespective of the degree of illumination (Albright and Stoner 2002; Gegenfurtner and Kiper 2003; Heywood and Kentridge 2003; Shevell and Kingdom 2008; Zeki 1993). Most likely, several mechanisms at different levels result in comparisons between light reflected from different surfaces, such that overall effects of the source →spectrum are discounted (Gegenfurtner and Kiper 2003; Hurlbert and Wolf 2004).

In the retina, color constancy is thought to involve integration of chromatic signals through interactions between cones and horizontal cells (Vanleeuwen et al. 2007). In the visual cortex, contextual modulation (Albright and Stoner 2002) may occur. A cortical neuron excited by a red patch covering its receptive field would respond more strongly against a grey background than against a red background, as if correcting for the overall reddish illumination (Hurlbert 2003). Double-opponent cells in cortical area V1 that are sensitive to opponent colors in both the center and surround might also be involved. The organization of the receptive field might enable them to maintain constant responses despite global changes in illumination of theirfield. A change in illumination that increases the center response would simultaneously increase the surround response.

14.4.5 Color Disturbances of Cerebral Origin

Cerebral achromatopsia (Girkin and Miller 2001; Heywood and Kentridge 2003), a type of color-blindness in which most patients see the world in varying shades of grey, is caused by damage to the fusiform gyrus and lingual gyrus regions of the ventro-medial visual cortex. Many patients retain some hue discrimination, and may be able to distinguish borders between adjacent isoluminant colored patches so that they retain rudimentary form and motion sensitivity. Transient achromatopsia may accompany →migraine and →focal (partial) seizures, or result from vertebro-vascular insufficiency that affects wavelength-selective cells in areas V1 and V2. Color constancy may be selectively impaired in patients with circumscribed unilateral lesions in parieto-temporal cortex of the left or right hemisphere (Bartels and Zeki 2000; Moutoussis and Zeki 2000; Rüttiger et al. 1999).

14.5 Depth and Distance

Acting and navigating in a 3D world requires an excellent representation of the spatio-temporal arrangement of objects relative to each other and to the observer as well as the determination of object shapes (Verhoef et al. 2016). Object arrangement requires determining the →depth ordering of surfaces and their depth intervals, and fine-scale mechanisms are required for representing 3D surface geometry and object shape (Anzai and DeAngelis 2010). Both distance and depth perception are based on a number of different cues, both monocular and binocular, which require integration at some stage **(**Welchman 2017).

14.5.1 Monocular Depth Estimation

Segregation of image parts into foreground and background is an important aspect of the neural computation of 3D scene perception. To achieve segregation, the brain needs information such as monocular cues about →border ownership; that is, the belongingness of a contour to a specific surface that is represented in the image (Dresp-Langely and Grossberg 2016; Orban 2008; Spillmann et al. 2015).

Monocular cues include static elements such as object size as a function of distance, perspective, texture gradient, shading, motion, blur, degrees of brightness, relative haziness, and occlusion of one object by another, which requires the determination of border ownership (Welchman 2017). Motion cues such as →motion parallax provide a vivid impression of depth (DeAngelis 2000; Orban 2011). While each cue on its own may be insufficient to yield reliable 3D structure, the combination and integration of cues weighted according to task and available information would be expected to yield more reliable estimates (Welchman 2017).

Subsets of neurons in areas V1, V2 and V4 play important roles in monocular depth estimation. They encode not only local contrast borders, but also the side of the object to which the border belongs (Anzai and DeAngelis 2010; Spillmann et al. 2015). This `decision ´ is based on signals from far outside the classical receptive field (CRF), indicating that non-classical receptive-field surrounds may contribute to the determination of border ownership and, hence, figure-ground segregation and →depth-ordering (Albright and Stoner 2002; Orban 2008; Spillmann et al. 2015). Another mechanism contributing to depth-ordering is contour completion, where the goal is to group fragmented low-level edge elements into perceptually coherent and →salient contours (Ming et al. 2016).

14.5.2 Stereopsis – Binocular Depth Sense

Depth perception, including 3D appreciation of objects, is much more vivid with stereopsis which is based on differences between images cast on the two retinas. Binocular disparity contributes to several computations including object recognition, scene segmentation and sensory-motor transformations required for reaching, grasping and manipulation. However, between 5 and 30% of the human population have moderate to poor stereovision, indicating that it is not absolutely essential for survival (Verhoef et al. 2016).

14.5.2.1 Geometric Aspects of Binocular Vision

In adult humans, the eyes are roughly 65 mm apart. Hence, the retinal images of 3D objects differ in both horizontal and vertical dimensions, giving rise to horizontal disparities and vertical disparities. Disparity patterns in the visual field depend on 3D structure, gaze angle, viewing distance and eye alignment (DeAngelis 2000; Freeman 2009).

Horizontal Disparity. A fixated point *F* is projected onto the two foveae *f* and *f˝* and defines a circle called a horopter. In terms of binocular vision, `horopter´ refers to a line or surface containing all points in space whose images fall on `corresponding points´ of the retinas of the two eyes. Points on the horopter outside *F* fall onto extra-foveal retinal points with equal distance from the foveae; these retinal points are called `corresponding points´ and have zero disparity. Points within the horopter are projected onto non-corresponding retinal points with different distances from the foveae (*f* and *f´*, respectively), and cause positive (divergent or uncrossed) disparity. Points beyond the horopter cause negative (convergent or crossed) disparities. These relations can be altered with changing fixation.

Retinal disparities cover a broad range of amplitudes, and this range is divided into small and large disparities according to how the visual system processes them. There is a disparity limit of fusion, that is, there is a retinal point in one eye that could correspond to a retinal area instead of a point in the other eye. Thus, an an object stimulating slightly disparate retinal points could still be seen single. This area of correspondence representing the total amount of disparity compatible with single vision has become known as `‘Panum’s fusional area` (Qin et al. 2006). The disparity limit of fusion increases with stimulus size and eccentricity. Diplopia (double vision) can contribute to the qualitative sense of stereopsis, but only within limits. Outside these limits, diplopia presents a problem to the visual system and is dealt with by suppressing images from one eye (binocular rivalry) (Lin and He 2009; Patterson and Martin 1992; Gonzalez and Perez 1998). The best stereoacuity is achieved for small, isolated, moving objects with high contrast and frequency content, projected onto the fovea under good, constant illumination (Patterson and Martin 1992).

Vertical Disparity occurs when objects on either side of the vertical meridian are closer to one eye than the other and thus span different angles in the two eyes, providing an estimate, or perception, of surface slant, which cannot be determined from a pattern of horizontal disparities alone.

Curvature and Orientation Disparities are interocular differences in stimulus curvature and orientation and are important cues for the perception of slanted curved surfaces in complex scenes (Patterson and Martin 1992).

Dynamic Stereopsis. Temporal variables give rise to dynamic stereopsis. For instance, when an object in front of or behind a fixation point moves toward or away from the observer, a direction disparity occurs between its images in the left and right eye. When the object is outside the vertical meridian, its images in the two eyes also move at different velocities and contribute to stereoscopic sensing of 3D motion (Patterson 1999). The mechanisms underlying this motion in depth are different from those mediating the perception of lateral motion in the fronto-parallel plane or the perception of static depth (Patterson and Martin 1992). Information from the two retinas may reach more central visual structures with different delays when the eyes are differently illuminated. This leads to depth perception, as exemplified by the →Pulfrich effect: When an observer views a pendulum swinging in a frontal plane and one eye is covered with a filter that causes a delay of the visual stimulus, the pendulum appears to move in depth in an horizontal elliptical path (Gonzalez and Perez 1998).

14.5.2.2 Binocular Correspondence

A great problem for the →central nervous system (CNS) is the stereo-correspondence problem, implying that corresponding features in the two retinal images must be identified correctly and fused into a single percept (Verhoef et al. 2016; Welchman 2017). Psychophysical experiments have shown that the visual system uses similarities in orientation, motion direction and speed to help achieve binocular correspondence, Cortical cells with multiplex sensitivities to orientation, motion direction, speed and binocular disparity could be contributory. Many neurons in visual area V1, area MT/V5 and →area MST (medial superior temporal) that respond to binocular disparity are also tuned to orientation,

motion direction and speed. Finding corresponding features on the two retinas involves a search process in which the brain scans certain small zones fixed on the retinas. To reduce these zones, rotatory eye movements are important, involving the oculomotor system (Schreiber et al. 2001). Complex cells in area V1 may play a dominant role in the matching procedure because they have the required high spatial acuity and detailed internal structure of receptive fields (Poggio 1995).

14.5.2.3 Disparity-selective Neurons

Brain imaging in humans reveals widespread cortical responses to disparity, strong responses occurring around →area V3A. Disparity representations appear different in the ventral and dorsal visual streams, with highly specific and clustered representations in dorsal areas (Welchman 2017).

Binocular cells with receptive fields in both retinas are required for disparity detection and evaluation. Interocular interactions occur in the lateral geniculate nucleus (LGN), where neuronal responses in an eye-specific layer are suppressed or facilitated by stimuli presented to the non-dominant eye. The effects evidently result from interlaminar LGN interactions or cortico-geniculate back-projections (DeAngelis 2000).

Disparity sensitivity is thought to originate at cortical level, starting in area V1 (Anzai and DeAngelis 2010; DeAngelis 2000; Gonzalez and Perez 1998; Poggio 1995). In monkey area V1, simple and complex cells with non-circular receptive fields receive inputs from both eyes. Nearly all cells in the foveal region of areas V1 and V2, and most cells in higher areas are binocular.

Early Visual Cortex. Neuron responses to horizontal disparity in primary visual cortex have been divided into several categories, but may actually form a continuum. Stereoscopic and visual acuity decreases from the center to the periphery of the visual field, but disparity-sensitive cells occur at all eccentricities, i.e., distances between the receptive field center of a given neuron and points of fixation on the fovea. In area V1, neurons are sensitive to →absolute disparity in their classical receptive field (RF), but not →relative disparity, so that further processing downstream is required for computation of the latter. Area V2 contains some neurons with sensitivity to relative disparity in addition to cells with sensitivity to absolute disparity. Area V2 neurons also respond to stimulus borders defined by relative disparity. Similar results have been described for area 3 and area 3a, while relative disparity appears represented more strongly in area 4 (Anzai and DeAngelis 2010; Parker 2007; Verhoef et al. 2016). Cells in areas V1 and V2 are also sensitive to vertical disparities, with tuning functions resembling those of tuned excitatory and inhibitory cells. Similarly, cells in area MT/V5 respond to vertical disparity (Gonzalez and Perez 1998). As with other visual features, the sensitivity of binocular neurons is modulated by the surround (Albright and Stoner 2002).

Two-Streams of Corticofugal Visual Information. According to the two-streams hypothesis, visual information leaves the early visual cortex of the occipital lobe via dorsal and ventral streams. The ventral stream is involved with visual object identification and recognition and uses disparity information primarily for this pupose. The dorsal stream processes an object's spatial location relative to the viewer and uses disparity information for

the visual guidance of reaching and grasping actions (Verhoef et al. 2016).

Ventral Stream. Neurons involved in representing object shape should be sensitive to visual cues that vary with surface geometry, including spatial gradients in texture, velocity and binocular disparity. These sensitivities should be invariant to changes in position, scale and mean depth (Anzai and DeAngelis 2010). Binocular disparity activates many areas in the ventral visual stream (Verhoef et al. 2016). Ventral-stream areas, including area V4, show some sensitivity to absolute disparity and a marked sensitivity to relative disparity. Many neurons in area V4 are sensitive to 2D bar orientation and to orientation in depth, but are not yet selective for depth-independent 3D shape. Neurons in infero-temporal (IT) cortex, in particular in →area TE, are sensitive to the shape and curvature of 3D surfaces and may thus have a role in fine stereoscopic perception of object surface structure, 3D shape and place in space. Area TE cells often represent 3D shapes irrespective of the particular cues defining them, such as disparity, texture and shading (Anzai and DeAngelis 2010; Neri 2005; Orban 2008; Parker 2007; Verhoef et al. 2016).

Dorsal Stream. Reach-to-grasp movements require excellent spatial representations of objects in terms of distance, size, orientation and 3D shape including surface orientation and curvature. Indeed, such 3D representations occur in several dorsal-stream areas, e.g., area MT/V5, area MSTd, area CIP (**c**audal **i**ntra**p**arietal), area AIP (**a**nterior **i**ntra**p**arietal) (Anzai and DeAngelis 2010). This stream including area MT/V5 is predominantly sensitive to absolute disparity used for the control of vergence eye movements (Anzai and DeAngelis 2010; Neri 2005), although some sensitivity to relative disparity may be used to estimate the gradient of spatially extended surfaces and the separation in depth of such surfaces (Parker 2007). Many disparity-sensitive MT/V5 neurons have a center-surround structure, such that effects in the surround are antagonistic to the center. Neurons are generally suppressed when center and surround stimuli have the same disparity, with the suppression decreasing with increasing disparity differences. Area MST contains cells responsive to combined (rotatory) movements in depth and size changes. The lateral bank of area cIPS (**c**audal →**i**ntra**p**arietal **s**ulcus) with input from area V3A (with disparity-sensitive cells) contains neurons that are responsive to binocular disparity and tuned to the axis orientation of long and thin stimuli in 3D space. Other neurons that prefer broad and flat stimuli are tuned to the surface orientation in depth (Sakata et al. 2009).

14.5.2.4 Mechanisms Underlying Disparity Sensitivity

Disparity sensitivity evidently relies on several mechanisms that include neural connections and receptive field structures. Receptive field properties contribute to position disparity and phase disparity sensitivity in various ways (Anzai et al. 1999; Cumming and DeAngelis 2001; DeAngelis 2000; Freeman 2009; Gonzalez and Perez 1998; Welchman 2017).

Position Disparity. Shifts in position of the two receptive fields on the two retinas, as well as facilitatory and inhibitory interactions, can explain the various tuning curves of cortical cells (plots of firing rate, spikes/s, ordinate vs. disparity, degrees, abscissa; Tsao et al. 2003). Position disparities are restricted to small inequalities and cannot account for responses to large disparities.

Phase Disparity is based on asymmetries in receptive field profile. For example, even when simple cells have receptive fields that cover corresponding retinal areas, horizontal shifts of the ON- and OFF-subregions can account for disparity sensitivity. Phase disparities cover a wide range of disparities and, in addition, depend on orientation and spatial frequency.

14.6 Object Motion

The motion of objects and other environmental stimuli must be evaluated for perceptual and for motor purposes (Frost 2010). For reaching and grasping, motion signals from primary visual cortex (area V1) are sent via area V6 to visuomotor areas of the →superior parietal lobule (SPL), such as area V6A (dorso-medial pathway). For perception, motion signals from primary visual cortex (area V1) are sent via area V6 to area MT/V5, area MST and further areas (dorso-lateral pathway) (Galletti and Fattori 2018).

14.6.1 The Primary Visual Cortex´s Roles in Motion Processing

The visual system deduces direction of object motion from the direction of object contours (Adams and Horton 2009; Clifford 2009; Duncan et al. 2000). The primary visual cortex could contribute to this function because it contains many neurons with direction selectivity (Clifford 2009), including complex cells (above). Against this idea stands the small size of receptive fields (RFs) leading to the `aperture problem´ (Orban 2008).

Direction-selective neurons in area V1 register only the motion of local contours within the windows (apertures) of their small receptive fields, such that the directions of motion are perpendicular to the main axis of their receptive fields. To deduce overall object motion, vector addition of the local motions needs to be performed (described in detail in Bartels et al. 2008; Clifford 2009). There is evidence that neurons in area MT/V5 perform this operation (below). In fact, this area receives input from area V1 neurons that are directionally selective and respond only to the motion of the components of complex patterns (Movshon and Newsome 1996; Orban 2008).

Sub-cortical structures also contain motion-sensitive cells. Neurons in the →pulvinar (Grieve et al. 2000, 2009; Kaas 2019) can signal the true direction of plaid patterns, suggesting that they integrate different motion signals into a coherent moving percept (Merabet et al. 1998). Moreover, direction selectivity exists in the nucleus of the optic tract (NOT) and the →accessory optic system (AOS), which are connected to the oculomotor system ansd help stabilize eye movements (Clifford 2009).

14.6.2 Motion Processing in the Dorsal Stream

Area V6 is sensitive to both object motion and self-motion in both macaques and humans and has been suggested to subtract out self-motion signals so as to estimate object motion in a complex and dynamically changing environment (Galletti and Fattori 2018).

Area MT/V5 in the monkey plays a prominent role in motion processing (Born and Bradley (2005). It receives its dominant inputs from directionally selective complex cells in area V1, in part via area V6, as well as from nuclei of the pulvinar. When area V1 is lesioned and the V1 inputs to area MT/V5 are absent, other dorsal-stream areas receive visual inputs from the superior colliculus (SC) via pulvinar nuclei, thereby preserving some motion sensitivity, a phenomenon called `blindsight´ (Arina and Bridge 201; Kaas 2019).

Area MT/V5 is sensitive to pattern direction and speed gradients (Orban 2008). Local injection of ibotenic acid, a →glutamate receptor →agonist, compromises discrimination of motion direction and pursuit eye movements, while electrical →micro-stimulation in area MT/V5 influences perception of the direction of moving stimuli (Salzman et al. 1992). In humans, temporary inactivation of area MT/V5 by →transcranial magnetic stimulation (TMS) results in →akinetopsia (motion blindness) (Beckers and Zeki 1995).

Many area MT/V5 neurons are sensitive to both motion and depth, while subsets of area MT/V5 neurons are able to distinguish between intrinsic and extrinsic features, requiring integration of information related to direction of motion and depth (Duncan et al. 2000). Area MT/V5 outputs target several structures requiring motion information, including brainstem (superior colliculus, pontine →reticular formation) as well as frontal and parietal cortices. Parallel output channels have been proposed to subserve perceptual decisions about motion direction and to guide eye movements, possibly involving different signal-handling characteristics (Born and Bradley 2005; van Wezel and Britten 2002).

Some area MT/V5 neurons in monkeys signal direction of motion of chromatically defined contrasts, in particular when the luminance contrast is low (Croner and Albright 1999; Dobkins 2000). Motion direction can also be perceived using other contrast cues, such as spatial texture, temporal texture (flicker) and binocular disparity (Croner and Albright 1999).

For many neurons in areas MT/V5 and MST, the classical receptive fields (CRF) mapped with conventional stimuli such as bars or spots are surrounded by a region 50 to 100 times as large, from which responses to stimuli in the CRF can be influenced dramatically (Allman et al. 1985; Born and Tootell 1992; Tanaka et al. 1986). For instance, excitatory responses to moving bars in the CRF may be inhibited in direction- and velocity-dependent ways by stimuli moving in the surround, yielding an antagonist →center-surround organization. Surrounds may also exert facilitatory effects. Some cells with antagonistic surrounds could signal, for example, local motion contrast to detect object motion on a background, 3D shape perception from motion, `pop-out´ effects of targets in visual search (Allman et al. 1985; Born and Tootell 1992; Desimone and Duncan 1995; McMains and Kastner 2009).

Motion stimuli contribute to figure-ground segregation. For example, when a group of dots moves coherently on a background of randomly moving dots, it is perceived as a figure (Gestalt principle of common fate). This grouping is probably implemented by area MT/V5 neurons (Spillmann et al. 2015).

There are also cells in area MST and →posterior parietal cortex (PPC) that represent the direction of rotatory movements in space (Sakata et al. 2009).

14.6.3 Visual Perception of Body Movement

Humans are good at perceiving and interpreting →biological motion. They can rapidly and precisely distinguish movement patterns such as dancing, running and walking. This even occurs under severely reduced stimulus conditions, e.g., when a few small lights attached to main joints are the only stimuli that signal movements in a dark room (Frost 2010; Spillmann et al. 2015). These capabilities develop early in life and last into old age, and require a large cerebro-cortical network.

Non-human primates share some →skills related to visually perceiving body movement (Blake and Shiffrar 2007; Puce and Perrett 2003). In macaques, an eminent role is played by the superior temporal sulcus (STS), which is at the juncture of the ventral and dorsal streams. STS shows high selectivity to human form and motion within an →egocentric frame of reference, as opposed to an object-centric reference frame in which objects or their parts are coded relative to others.

STS contains predominantly visual neurons whose responses can be modulated by the motor system and the amygdala (Blake and Shiffrar 2007; Puce and Perrett 2003). Area STP (superior temporal polysensory) of the STS integrates form and motion information. Neurons in area STPa are specialized for processing different face, limb and whole-body motions, in a view- and direction-specific manner. Some neurons are sensitive to head view or direction of gaze and attention, and may be involved in reading the intention of others. Cells conjointly sensitive to body form and motion are also found in the amygdala (Brothers and King 1992), a structure involved in emotion, particularly fear.

Brain imaging in humans suggests that recognition of biological motion stimuli may differentially activate various systems. The superior temporal sulcus (STS) and its ascending limb in the inferior parietal cortex are activated by viewing motions of whole body, specific limbs, hand, mouth and eyes. The occipito-temporal cortex is activated by gaze aversion and opening and closing the mouth, perhaps as indicators of attentional and emotional states (Blake and Shiffrar 2007; Martin 2007; Puce and Perrett 2003).

14.6.4 Perception of Self-motion

During self-motion such as head and whole-body movements including navigation, large-scale retinal image changes occur referred to as optic flow (Britten 2008; Frost 2010; Lappe 2009). The optic flow field depends on the speed and direction of observer motion and on the depth structure in the scene. Optic flow is important for evaluating self-motion, perceiving object motion against a moving background, stabilizing gaze in space (optokinetic response, OKR) and thereby stabilizing the visual world (→spatial constancy), stabilizing orientation, posture and locomotion, and visually guiding navigation. In addition, Self-motion perception may use other sensory information. For instance, head movements are also signaled by the vestibular system, and the somatosensory system may signal changing pressures on the skin during motion and changing postures via proprioceptive signals (Medendorp 2011).

Two principal components of self-motion create different types of optic flow pattern: rotation about a vertical or other axis through the head, and gaze direction relative to directional heading (Britten 2008; Lappe 2009).

Various cerebro-cortical areas contain optic flow-responsive neurons, including area MT/V5, area MST, →area VIP, →area 7a and area FST (**f**loor of the **s**uperior **t**emporal sulcus). Area MST is most clearly related to optic flow. The dorsal part (area MSTd) contains neurons with large receptive fields that respond to directional translation, expansion, contraction, and rotation (Tanaka and Saito 1989; Orban 2008; Duffy and Wurtz 1995, 1997; Duffy 1998; Andersen et al. 2000). There are cells that are selectively responsive to different components, but most neurons respond to combinations (Andersen et al. 2000). Area MSTd also receives vestibular information on translational or rotational subject movements, which contributes to multi-sensory heading perception (Liu and Angelaki 2009). Nearly all MSTd neurons are sensitive to heading direction in 3D space (Orban 2008).

Most cells are position- and scale-invariant (Andersen et al. 2000). Binocular disparity and cues related to the changing size of objects may contribute to the perception of self-motion (Palmisano 1996). Speed gradients are detected and distinguished by different types of area MSTd neurons. The neurons prefer either a positive speed gradient or a negative gradient.

14.7 Visual Integration of Objects and Environment

In the monkey brain, the depth structure of objects and environment appears to be processed at three anatomical points, each for different purposes (Orban 2011): Area TE of the IT cortex in the ventral stream, intraparietal area CIP, and area MT/V5 in the dorsal stream.

The IT cortex contains many neurons that integrate depth cues and other attributes for 3D object recognition (Orban 2011). Area TE contains neurons with convergent texture and disparity sensitivities for surfaces (Orban 2011). Convergence of shape and depth information in the superior temporal sulcus (STS) appears to provide 3D recognition of objects (Janssen et al. 2000).

In area CIP, the depth structure of objects and the environment is extracted from texture and disparity, with some neurons also demonstrating perspective sensitivity, i.e., nonvisual sensitivity to paths of locomotion, and to the resulting changes in the network of directions and distances that spatially relate them to objects fixed in the surrounding environment. (Orban 2011). The relevant information on objects is transmitted to area AIP and thence to area F5 in the →premotor cortex to subserve grasping (Orban 2011). Area cIPS contains cells sensitive to binocular disparity and register 3D orientation of object axis and flat surfaces (Tanaka et al. 2001; Sakata et al. 2009).

The dorsal stream also includes areas where depth structure is derived from motion, which provides one of the most potent cues for depth perception. Properties of neurons in area MT/V5 suggest that this area is involved in both depth and motion processing. The center-surround organization of the neurons´ receptive fields allows them to detect image

discontinuities from velocity and depth differences (DeAngelis and Newsome 1999). The effects of disparity and motion direction are mainly additive (Bradley and Andersen 1998).

Disparity-sensitive neurons also contribute to motion in depth (Poggio and Talbot 1981). These neurons are dependent on input from cells with directional sensitivity in receptive fields of each eye. Cells with the same monocular directional sensitivities detect lateral object motion in their disparity range. Some cells in the dorso-medial portion of area MST are selective for a link between optic flow and binocular depth (Parker 2007). The motion information is transmitted to area AIP (for grasping) and other areas (Orban 2011).

14.8 Synesthesia

→Synesthesia is a neurological condition that affects many sensory modalities. It involves stimulation of one sensory or cognitive pathway, resulting in automatic, involuntary experiences in a second sensory or cognitive pathway (Bargary and Mitchell 2008; Hubbard 2007; Rich and Mattingley 2002; Robertson 2003). The two most common synesthetic dysfunctions are color-hearing cross-over effects that associate particular colors with particular →sounds, and grapheme-color synesthesia. In the latter case, specific graphemes such as alphabetical letters, numerical digits or punctuation marks are associated with specific colors; for example, the letter *R* is perceived as a blue color; blind people may have colored impressions of Braille signs. Some individuals sense smells associated with visualized colors, others describe music as movements of colored forms in visual space, or have specific auditory experiences associated with moving or flickering visual patterns (Saenz and Koch 2008). Traditional accounts of underlying neural mechanisms suggest that synesthesia is due to reduced inhibition of feedback from multi-sensory areas or to `cross-activation´ of brain areas concerned with the associated percepts.

14.9 Visual Working Memory

Memory is an essential component of visual perception and object recognition. In humans, tasks that utilize visuo-spatial working memory activate the →dorso-lateral prefrontal cortex (DLPFC), the right inferior posterior parietal cortex (PPC) and visual areas in the occipital cortex, with the PPC representing the →salience of stimuli and the goals of intended movements, and the DLPFC serving as an executive controller (Knudsen 2007).

Recognition and mnemonic storage, i.e., use of a system such as a pattern of letters, ideas, or associations which assists memory of objects, have been associated with the ventral stream from the primary visual cortex via the infero-temporal (IT) cortex to the hippocampus. The IT may contribute to the perception and spatial memory of places and paths, and the perirhinal cortex may contribute to the perception and memory of objects and the contents of scenes (Buckley 2005; Murray et al. 2007). The perirhinal cortex also appears to be concerned with evaluating stimuli as to their association with potential →rewards (Liu and Richmond 2000). In primates, the hippocampus contains `spatial view´ neurons that respond to the place where a monkey is looking and become active in tasks in which the location of objects and rewards must be remembered, thus contributing to actions in space and navigation (Rolls and Wirth 2018).

Mnemonic properties of IT neurons are expressed in two ways. First, stimulus selectivity of IT cells is acquired by learning. Second, IT cells link stimulus configurations that are associated temporally. The consolidation of these associations may require top-down feedback signals from the limbic system, in particular the hippocampal formation and the prefrontal cortex (Miyashita 1993; Miyashita and Hayashi 2000).

Visual amnesia is characterized by inability to remember visual surroundings and to learn new visual objects, patterns or faces, while →recall of consolidated visual knowledge is intact (Girkin and Miller 2001).

Working memory is closely related to attention. Attention determines whether visual items are stored in working memory for comparison with subsequent occurrences in scenes (Lamme 2003). Conversely, it has been argued that working memory controls top-down bias signals that direct attention (Knudsen 2007).

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Eye Movements:

Basics, Vestibulo-ocular Reflexes and Ocular Following Responses

CONTENTS

Abstract

• When the eye is rotated, three torque components emerge that are related to elasticity, viscosity and inertia. These torques are handled by six extraocular muscles, which are innervated by three cranial nerves and their associated motoneuron nuclei in the brainstem.

• Ocular motoneuron discharge properties reveal different components that are related to the mechanical torque components of elasticity, viscosity and inertia.

• Two two broad classes of tasks are performed by the oculomotor system: gaze holding (fixation) and gaze shifting. Fixation on a location in the visual field helps prevent slip of an image across the retina, such as might occur during movements of the head or the external environment. Two basic mechanisms counteract these sources of slip: vestibulo-ocular reflexes (VOR) and optokinetic responses (OKR).

• The vestibulo-ocular reflex (VOR) compensates for fast, large-scale image motion across the retina that would otherwise interfere with accurate vision. It originates in the semicircular canals of the vestibular organs and results in counter-rotation of the eyes in their sockets in the opposite direction to stabilize the line of sight.

• Three types of VOR compensate for head rotation, translation and tilting: rotatory (angular) VOR, translational VOR and tilt VOR. For the VOR to be precise, synaptic connections in the generating circuits must be continuously calibrated and adjusted.

• The gain and dynamic characteristics of the VOR can be appropriately modified on different time scales. In this process, the cerebellum plays an important role.

• Ocular following responses (OKRs) are initiated by slips of large segments of the retinal image. The simplest OKR response is a short-latency optokinetic nystagmus (OKN) that consists of a saw-tooth-like succession of slow following phases and quick resetting phases.

• If optokinetic stimulation persists long enough and light is suddenly switched off, the eyes produce a diminishing optokinetic after-nystagmus (OKAN), with the direction of the slow phases reversed.

• The OKR is organized by brainstem and cerebro-cortical areas, and by the cerebellum.

15.1 Introduction

Movements of the eyes are important for at least two reasons. First, vision is a sluggish process, so images need to be stabilized on the retina for periods of around 200 ms. Second, because seeing the entire retinal image with the same acuity would surmount the limited visual processing capacities, eye movements direct the line of sight onto important objects (Bremmer 2011). Eye movements and visual tracking are complex processes that involve considerable coordination prepared and executed by a vast network of distributed brain areas (Coiner et al. 2019).

15.2 Types of Eye Movement

Retinal stabilization is necessary for →transduction of light →energy in the form of photons into →action potentials for transmission through the visual pathways. Retinal stabilization employs two general types of mechanisms in vertebrates; gaze holding and gaze shifting. All vertebrates with visual systems utilize gaze stabilization, whereas gaze shifting occurs only if retinal specializations are present, such as the →primate →fovea, which permits scrutiny of a limited region of visual space at higher acuity (Glimcher 2003a).

Eye movements in primates can be further divided into several classes and sub-classes that contribute to →visual acuity (Robinson 1981; Carpenter 1996; Krauzlis et al. 2017; Lappi 2016; Moschovakis 2009):

Gaze Holding (Fixation) (Guitton 2009). Orientation and movement in the external world require a reference that should, at least temporarily, be stationary. →Fixation on a location in the →visual field helps prevent slip of an image across the retina such as might occur during movements of the head or the external environment. Accordingly, there are two basic mechanisms that counteract these sources of slip: the vestibulo-ocular reflex (VOR) and the optokinetic response (OKR).

Vestibulo-ocular reflex (VOR). Head movements elicit responses of afferent sensory fibers from the semicircular canals and otolith organs of the →vestibular apparatus, which cause the eyes to move in the opposite direction, even in the dark. When the retinal image is perfectly stabilized, the VOR has a *gain* of 1, which is defined as eye velocity, $\dot{E}$, divided by head velocity, $\dot{H}$ (e.g., Graf 2009a,b; Straka and Dieringer 2004; van der Steen 2009).

Optokinetic response (OKR). Slip of large segments of the retinal image elicits sequences of eye movements composed of slow following and fast resetting phases, a familiar example being the train nystagmus.

Gaze Shifting is necessary to direct the fovea onto image segments of current or future interest (Schall 2013; Tatler and Land 2011). During gaze shifting, three different types of eye movements can occur: saccades, smooth pursuit eye movements and vergence eye movements.

Saccades are very fast eye movements (up to 900°/s in humans), which may be as short as 20 ms (Krauzlis et al. 2017; Sparks 2002). Because vision is disrupted during these fast movements,

they must be interspersed with fixation periods, during which the gaze is kept stable, thus enabling capture of the details of a picture, which requires at least 200 ms. This succession explains the typical scanning of a picture, for example during reading. The brevity of saccades maximizes the number of viewable targets and minimizes the time, during which vision is poor due to fast image motion across the retina (Robinson and Fuchs 2001). Saccades may be combined with head and/or trunk movements, in particular when they are made to targets outside the current field of view (Tatler and Land 2011). Saccades may originate in two main sources. Endogenously driven saccades are voluntarily driven by goals or task demands. Exogenously driven saccades are driven →reflexively and involuntarily by →salient events in the environment. The history of previous saccades (for example to a →rewarded target) may influence the current target choice, irrespective of ongoing task demands or saliency (Mulckhuyse 2018). Saccades may also accompany smooth pursuit eye movements to catch up with the target. They occur during the VOR and OKR because the eyes must be re-positioned when approaching their movement limits. The saw-tooth-like succession of slow movements and fast, re-positioning saccades is called →nystagmus.

Smooth pursuit eye movements follow a target moving relatively slowly against a background (Krauzlis et al. 2017). The antagonist *optokinetic response (OKR)* to →retinal slip of the background image must be suppressed during smooth pursuit eye movements.

Vergence eye movements. In animals with forward-directed eyes and good depth →perception (stereopsis), the lines of sight of the two eyes must focus on the target. With the momentary target moving through varying distances, the two eyes must move through different angles or in different directions. These vergence movements must be closely coordinated with pursuit and saccadic eye movements (Mays 2009b), with accommodation of the lens (Mays 2009a), and less closely with changes in pupil size.

Micro-movements or →fixational eye movements occur while fixating a small spot despite efforts to hold the gaze absolutely fixated (Martinez-Conde et al. 2013; Otero-Millan et al. 2014). They have been proposed to play a role in the spatio-temporal encoding of spatial relationships (Rucci and Victor 2015). There are several forms of micro-movements: →Micro-saccades, ocular drift, ocular tremor and →torsional eye movements.

Micro-saccades, also called `fixational saccades´, are the fastest and largest of the micro-movements, They occur 1-3 times per second and carry the retinal image over several dozen to several hundred photoreceptor widths. They are usually conjugate, i.e., micro-saccades of both eyes are in the same direction and of similar amplitude. They scan small biologically important image regions, improve visual acuity, counteract →visual fading and filling-in. Micro-saccades share many characteristics with saccades, suggesting a common oculomotor origin (Hafed et al. 2015; Krauzlis et al. 2017). The →superior colliculus (SC) appears to play an important role in the generation of micro-saccades (Gandhi and Katnani 2011; Krauzlis et al. 2017; Otero-Millan et al. 2014; Schall 2013). During micro-saccades, like during larger saccades, visual processing is subdued, a phenomenon called `saccadic suppression´; and micro-saccades are associated with perceptual dislocations of visual objects (Krauzlis et al. 2017).

Ocular drift consists of a slow, low-frequency (<40 Hz) meandering movement around the target, occurs between micro-saccades and is under oculomotor control, and is in part coupled to

the vestibulo-ocular reflex (Rucci and Victor 2015). It helps improve the discrimination of high spatial frequencies (Krauzlis et al. 2017).

Ocular tremor is a high-frequency (spectral peak between 40 and 100 Hz) oscillation of small amplitude (ca. 15′′ of arc), occurs simultaneously with drifts, and is probably due to stochastic firing patterns of →motoneuron or fluctuations in ocular muscle contractions (Krauzlis et al. 2017). Drifts and →tremor may enhance the processing of high spatial frequencies (Otero-Millan et al. 2014).

Torsional eye movements occur around the line of sight, can produce binocular disparities, are usually conjugate and influence 3D perception of slant (Otero-Millan et al. 2014).

While some eye movements rely on fairly simple reflex mechanisms, others require sophisticated visual information and other processing before any movement can be made. This applies in particular to voluntary saccades and smooth pursuit, which enable identification of interesting objects in a visual scene cluttered with potentially important objects (Barnes 2008; Spering and Gegenfurtner 2008). The above movements have mostly been studied with head fixed under laboratory conditions.

In summary, under natural conditions, for example during locomotion, eye movements must be coordinated with head, limb and trunk movements, which requires the integration of several sensory systems and motor effectors spanning multiple →frames of reference (Lappi 2016). These movements thus involve a multitude of brain regions, including several high-ranking →cortical areas.

15.3 Orbital Mechanics

Fast and accurate eye movements to a new position require appropriately tailored neural commands to the extraocular muscles and precisely shaped muscle contractions. The neural structures generating these commands must take into account the mechanical properties of the eyeballs (globes), their suspension in the orbits and the muscles that move the eyeballs, which may be collectively called the →plant (Dean and Porrill 2009). Compared to limb movements, eye movements are fairly simple in mechanical terms: →Gravitational forces are virtually absent because the eyeball is restrained in its orbit except in the forward direction; the →inertial load (globe →mass) to be →accelerated is low, and there is a near-constant mechanical load that does not change much with movement. Nonetheless, the neural control of eye movements is a complicated process.

15.3.1 Extraocular Muscles that Move the Eyes

Eye movements are predominantly rotational: left-right, up-down, and →torsion around the axis of gaze. Translational movements are much restricted due to mechanical constraints, except for some propulsion/retraction motion in anterior/posterior direction. The rotational movements are controlled by three pairs of extraocular muscles. In part, these muscles are sub-divided into

muscle compartments in that different intra-muscular regions are differentially innervated to exert independent rotatory →torques (Demer 2015).

Medial and Lateral Rectus Muscles. With the eyeball in its primary position (gaze straight ahead), the lines of pull of the medial rectus (MR) and the lateral rectus (LR) span a horizontal plane that also contains the globe center. Hence, contraction of the medial or lateral rectus causes adduction or abduction, respectively. If the center moves out of this plane, however, rectus contractions have additional effects. For example, when the gaze is elevated, the plane moves above the globe center because the recti insert in front of the frontal plane through the center. Rectus contraction then creates an additional, eye-position-dependent torque of elevation. While this effect is small and nearly negligible, similar side-effects are more dramatic for the superior and inferior recti.

Superior and Inferior Rectus Muscles. These muscles have lines of pull that do not lie in the para-sagittal plane through the globe center. For example, for the superior rectus (SR) of the right eye, the line of pull is about 23° out of line with the para-sagittal (*Y*) direction. Hence, only when the eye is abducted (rotated to the right) by 23° from it primary position, does SR contraction cause pure elevation. By contrast, when the eye is fully adducted (rotated to the left), SR contraction additionally generates adduction and leftward roll around the line of sight (intorsion). Corresponding considerations apply for the inferior rectus (IR) muscle. In addition to its primary action (eye depression), the right IR has secondary actions, including adduction and extorsion.

Superior Oblique and Inferior Oblique Muscles. Actions of the rectus muscles may generate a side-effect, namely torsion, that calls for control by a third pair of muscles: the superior oblique (SO) and inferior oblique (IO). Because of their peculiar arrangement, the actions of SO and IO also cause secondary effects, although in primates, torsional movements are infrequent and small in amplitude (Carpenter 1996).

The mechanical conditions discussed above have a number of consequences that need to be taken into account by the oculomotor control system(s).

Interocular Synergies. In conjugate eye movements, the two eyes move in the same way. In this respect, the muscles of both eyes can be grouped into synergistic pairs, defined by their various primary and secondary actions. There are six such pairs: right LR and left MR (moving the eyes to the right); left LR and right MR (moving the eyes to the left); right SR and left IO (moving the eyes upward and leftward, and rolling them leftward); left SR and right IO; right IR and left SO; left IR and right SO.

Meshed Control of Coupled Variables. In general, contraction of each individual muscle exerts a complex three-dimensional (3D) effect. This implies that movement components parallel to the principal axes cannot be controlled independently by pairs of antagonistic muscles and their →motoneuron pools. Rather, each such component (for instance, elevation) involves the activation of more than one muscle. More generally, any particular eye movement must be organized by the concerted action of more than one muscle, except for a pure horizontal movement in the horizontal plane through the globe center. This in turn requires that the neural systems activating extraocular motoneuron pools must be meshed networks.

Position Dependence. The torques produced by extraocular muscles depend on the initial eyeball position, which must be taken into account by the neural oculomotor control system(s). This can be done by using sensory feedback or →internal models.

The planes of action of the extraocular muscles are close to those of the semicircular canals, which may have imposed their orientations on those of the eye muscles (Robinson 1982).

15.3.2 Muscle Composition and Motor Innervation

The extraocular muscles are innervated by three →cranial nerves and their associated →motoneuron nuclei: oculomotor nerve (III), trochlear nerve (IV) and abducens nerve (V). Extraocular muscles contain various types of →muscle fibers with different properties and functions (Büttner-Ennever 2008; Porter 2002; Scudder et al. 2002).

Global Muscle Layer. The global layer, next to the eyeball, has four types of large-diameter muscle fibers. Three types, each singly innervated, range from fatigue-resistant to fatigue-sensitive and appear to be the ones that move the eyeball. The fourth type exhibits very slow twitch contractions, similar to tonic, non-→twitch fibers in avian and amphibian species.

Orbital Muscle Layer. The orbital layer has two types of small-diameter muscle fibers. One type is fast-twitch, fatigue-resistant and singly innervated. The second is fatigue-resistant, multiply innervated and probably provides tonic tension.

15.3.3 Sensory Innervation of Extraocular Muscles

Humans can report eye position in darkness, and visual responses in many cortical areas are modulated by eye position, indicating the presence of extraocular proprioceptors (Wang et al. 2007). Muscle spindles are inconsistent across species, with some having muscle spindles in the orbital layer. They exist in humans, while in non-human primates, muscle spindles are absent, sparse or diminutive, and rats have no spindles. In goats and sheep, Golgi tendon organs have been identified. In all mammals studied, a particular and unique type of so-called palisade ending wraps around →myotendinous junctions of muscle fibers in the global layer (Büttner-Ennever et al. 2006; Dancause et al. 2007; Donaldson 2000; Maier et al. 1974; Ruskell 1999). In rats and New World squirrel monkeys, →stretch reflexes can be elicited despite the absence or sparsity of muscles spindles in extraocular muscles (Dancause et al. 2007). Stretch of extraocular muscles can also produce synchronized responses in neck and jaw muscles (Donaldson 2000; Ruskell 1999).

15.4 Oculomotor Dynamics

When the eye is rotated, three torque components in opposite direction emerge that are related to →elasticity, →viscosity and inertia (Dean and Porrill 2009; Robinson 1981).

Elasticity. Displacing the eye statically from its primary position generates an elastic torque due to connective tissue properties as well as the length-tension characteristics and slow de-activation of extraocular muscles.

Viscosity. Moving the eye dynamically generates a viscous torque from connective tissues and from →force-velocity characteristics of muscles.

Inertia. Moving the eye dynamically generates an inertial torque that is produced by the eyeball ´s →mass. This inertial load is small.

These torques must be counteracted during active eye movements by static and dynamic →muscle torques to attain and maintain the new position. The muscle torques that move the eyeball are net torques. For example, for horizontal movements of the right eye to the right, the net torque is the active LR torque minus the MR torque, and the opposite difference applies for the left eye.

15.5 Discharge Patterns of Extraocular Motoneurons

If the eyeball is to be moved rapidly and precisely, e.g., during saccades, the mechanics should be reflected in the discharge of extraocular motoneurons. In particular, elasticity, viscosity and inertia must be compensated for by specific components of motoneuron discharge. In fact, motoneuron discharge shows different components that are related to the mechanical torque components (Highstein 2009b; Sparks 2002).

When a monkey fixates, motoneurons fire at a nearly constant rate, the rate depending on eye position. More than 70% of the motoneurons fire in the primary eye position, the mean rate for many motoneurons being ca. 100 spikes/s. When a muscle contracts to move the eye in the `on-direction´, the static firing rate increases. When the antagonist muscle contracts, the same (agonist) motoneuron´s discharge rate decreases. The relationship between eye position and firing rate is linear. As exemplified by the different lines (green and red), different motoneurons are recruited into firing at different →thresholds (range -62° to 25°) and have different slope values (range 1.1-14.5 (spikes/s)/°) (Robinson 1981). In general, the motoneurons with the lowest thresholds (recruited earliest) have more shallow slopes than those recruited later (Scudder et al. 2002). Motoneuron discharge also varies with the velocity with which the eye passes through a given position. The velocity-related discharge component generates the muscle torque required to counteract the viscous plant properties, against which the desired eye velocity must be achieved. An additional early dynamic discharge component appears for very fast saccades (Robinson 1981).

The ocular motoneuron discharge thus contains static and dynamic components that affect the velocity of eye movement. There is a small delay of about 8 ms between discharge and eye position, due to conduction and →synaptic delays and the time taken for muscular excitation-contraction coupling (EC) (Robinson 1981).

15.6 Vestibulo-Ocular Reflexes

Vestibulo-ocular reflexes (VORs) are generated by passive head motion that elicit signals from the semicircular canals and otolith organs of the vestibular apparatus, and result in counter-rotation of the eyes in their sockets in the opposite direction (Glimcher 2003b). VORs thereby compensate for fast, large-scale image motion across the retina that would otherwise interfere with accurate vision (Graf 2009a,b; Straka and Dieringer 2004; van der Steen 2009), along with complementary visually evoked responses.

VORs ensure stability of gaze and posture, accurate perceptual orientation and sensation of self-motion. During active head movements, however, VORs would be counter-productive and must be suppressed, implying that the VOR control system must be able to distinguish between passive and active head movements (Cullen 2004; Green and Angelaki 2010; Lappi 2016). Compensatory eye movements due to the VOR are of different kinds, depending on the underlying sources and causes of motion related to head rotation, translation and tilting:

Rotatory (Angular) Vestibulo-Ocular Reflex. Head rotation excites the semicircular canals by angular acceleration and elicits the rotatory vestibuilo-ocular reflex (RVOR).

Translational Vestibulo-Ocular Reflex (TVOR). Head translation excites the otolith organs (utriculus and/or sacculus) by linear acceleration and elicits the →translational VOR (TVOR).

Tilt Vestibulo-Ocular Reflex. The signals from the otolith organs are also altered by head tilt that changes the impact of gravity on the otolith organs.

The RVOR operates as follows. When the head is rotated sinusoidally about a vertical axis in the dark, the RVOR generates eye movements around the same axis, but with slow phases in opposite direction to the head movement. Note that normally the gain of the RVOR (angular eye velocity, $\dot{E}$, divided by angular head velocity, $\dot{H}$) is close to 1. When the head rotation continues at the same speed, the initial eye movements return exponentially to zero, with a →time constant of some 20 s, because the vestibular system reacts to acceleration. When the rotation suddenly stops, the eye movements continue for a while, with the slow and fast phases reversed (post-rotatory vestibular nystagmus). These prolonged periods of eye movements in response to head acceleration or deceleration suggest the existence of a leaky integrator.

15.6.1 Dealing with Oculomotor Dynamics

In order to achieve its task, the RVOR must take into account the mechanics of the plant. Specifically, it must generate the motoneuron discharge pattern that reflects these dynamics.

During rotatory head movements, the semicircular canals produce signals proportional to head velocity, $\dot{H}$. These signals can be used directly to generate the motoneuron discharge component that is proportional to eye velocity ($\dot{E}$). What is also needed is a motoneuron discharge component that is proportional to eye position. This component could be generated by integrating in time the vestibular input. There is much experimental evidence that such integration is indeed performed

by neural integrators located in the →brainstem. There is evidence that these neural integrators are common to several systems controlling eye movements, such as those controlling vestibular reflexes, optokinetic responses, pursuit movements and saccades (Arnold and Robinson 1997).

15.6.2 Site and Structure of the Neural Integrators

Oculomotor neural integrators are located in the interstitial nucleus of Cajal (INC), the nucleus praepositus hypoglossi (NPH), medial vestibular nucleus (MVN), and possibly cerebellar flocculus (Dalezios and Moschovakis 2009; Fukushima and Kaneko 1995; Joshua and Lisberger 2015; Moschovakis 1997; Green and Angelaki 2010; Robinson 1981, 1989).

Despite much experimental work, the precise internal structure and physiological neuron properties of neural integrators are not well known. They consist of assemblies of neurons integrated in distributed networks and showing differing discharge patterns (Moschovakis 1997; Joshua and Lisberger 2015).

Eye movements in different directions engage integrators located in related brainstem regions, which affect horizontal, vertical and torsional eye movements:

Horizontal Integrator. For horizontal eye movements, the integrator is probably located in the nucleus praepositus hypoglossi (NPH) and medial vestibular nucleus (MVN) in the caudal →pons and →medulla oblongata (Fukushima and Kaneko 1995; Moschovakis 1997; Moschovakis et al. 1996; Arnold et al. 1999). The integrator for horizontal eye movements is not perfect, it `leaks´ with a time constant (T_n) of about 25 s, which is long enough for common eye movements of limited duration. Lesions or pharmacological inactivation of the integrator regions reduce T_n and this makes it impossible to hold the eye in an eccentric position, with the eye drifting back to a central position. Correction saccades then re-position the eye eccentrically, which leads to the phenomenon of →gaze-paretic nystagmus. Lesions to the cerebellar flocculus also reduce T_n, so the →oculomotor cerebellum may also be responsible for adjusting the time constant (Robinson 1989; Fukushima and Kaneko 1995).

Vertical Integrator. There is a separate integrator for vertical eye movements, which is distributed between the interstitial nucleus of Cajal (INC) in the→mesencephalon and the →vestibular nuclei (Dalezios and Moschovakis 2009; Moschovakis 1997).

Torsional Integrator. The INC may also be involved in torsional eye movements, and it may indeed be the torsional integrator, although the torsional integrator has a shorter time constant (<2.5 s) than the horizontal and vertical integrators (Fukushima and Kaneko 1995).

In summary, networks in the brainstem and →cerebellum produce appropriate inputs to motoneurons to compensate for mechanical plant properties associated with eye movements. (Blazquez et al. 2004; Green and Angelaki 2010).

15.6.3 Sensory-motor Transformations in the Rotational Vestibulo-ocular Reflexes

For the rotatory VOR (RVOR) to function properly, there must be not only the correct dynamics, but also the right matrix of reflex connections from the semicircular canals to the motoneuron nuclei (Graf 2009a,b; Robinson 1982). Head rotation creates a vector of vestibular activities that is transformed by the brainstem into a vector of motoneuron and muscle activations, which is subsequently transformed into eye movements in →head-centered coordinates. This sensory-motor transformation is enabled by two conditions. First, matrix-like connections from canals to muscles must be optimally adjusted, such that the respective planes of the strongly coupled canal-muscles are aligned. Second, secondary connections link the canal pairs to the muscle pairs (Graf 2009a,b; Robinson 1982).

15.6.4 Complexities of 3D Vestibulo-ocular Reflexes

The VOR had traditionally been considered a simple reflex because it used to be studied in one (e.g., horizontal) dimension with far fixation points implying parallel lines of sight. However, the situation is more complex and requires more elaborate computations. For example, since the eyes lie in front of the axis of head rotation, head rotation causes the eyes to also translate in space rather than simply to rotate. This in turn causes the two eyes to move through slightly different angles and the gain of the VOR to increase (Raphan and Cohen 2002). This effect becomes stronger the closer the viewed target. By and large, the VOR compensates for about 90% of eye translation that occurs during head rotation. It appears to do so in successive approximations using mechanisms working at different latencies (Snyder and King 1996). A similar effect occurs during pure head translation without rotation, the magnitude depending on translation amplitude and target distance. Head tilts excite the otoliths which initiate roll VORs at relatively small gains (ca. 0.6). Combinations of different head movements thus elicit complex 3D VORs, whose computations are made even more complicated by the different →coordinate systems used. The coordinate system of the semicircular canals is represented in the central vestibular system, →vestibulo-cerebellum and auxiliary visual structures. By contrast, no respective central representation exists for otolith input (Raphan and Cohen 2002).

15.7 Cerebellar Role in Vestibulo-Ocular Reflexes

The cerebellum has important roles in various types of ocular and somatic motor control, in particular in error detection, sensory-motor calibration, →adaption and →motor learning (Ito 2013; Kheramand and Lee 2011; Manto et al. 2012; Medina 2011). It also contributes to VOR regulation, across different time scales and through several functionally related anatomical connections.

15.7.1 Vestibulo-ocular Reflex Circuits

The VOR system consists of several parallel pathways with feedback, cell types and connections that are highly preserved across vertebrates (e.g., du Lac et al. 1995).

Direct Pathway. The classical `three-neuron arc´ includes vestibular →interneurons of two types: position-vestibular-pause (PVP) cells (Cullen 2009), which fire in relation to eye position and vestibular rotation, and pause during saccades, and flocculus-target neurons (FTN), which exhibit a fairly high background discharge. FTN neurons are inhibited by →Purkinje cells of the flocculus and ventral paraflocculus (VPFL) (together known as →floccular complex or floccular lobe) (Dash and Thier 2014; Highstein 2009a; Lisberger 2009; Voogd et al. 2012).

Indirect Pathways. Projections from the vestibular nucleus and the nucleus praepositus to the floccular complex include Purkinje cells that fire in relation to horizontal gaze velocity when there are interactions between vestibular and visual stimuli (Scudder 2009). There are additional indirect projections across the midline from vestibular afferents to contralateral motoneurons, and projections from the vestibular nucleus through the nucleus praepositus to motoneurons. The indirect pathways, like those that are direct, have discharge properties that are linked to the velocity of eye rotation during smooth pursuit eye movements.

15.7.2 Adaptation of the Vestibulo-Ocular Reflexes

For eye movements to be precise, synaptic connections between VOR- generating circuits must be continuously calibrated and adjusted. The gain and dynamic characteristics of the VOR can be appropriately modified on different time scales (Blazquez et al. 2004; Dash and Thier 2014; Highstein 2009c).

Online Modification. The conditions for VOR operations change during vergence eye movements when varying viewing distance, and during linear and rotational accelerations. Since the VOR must be corrected for eye translation and eccentric target location, complicated computations must be carried out that exceed those of the three-neuron reflex arc. The cerebellum appears capable of performing such computations. In the macaque, the discharge of Purkinje cells in the flocculus and ventral paraflocculus (VPFL) is modulated by viewing distance and the location of the head rotation axis, suggesting that these cells play a role in providing the corrections required by rotation-induced eye translation (Snyder and King 1996). Moreover, the VOR must be suppressable, for example when a fixated target moves exactly with the head (Ilg 1997).

VOR Adaptation is a much-studied example of motor →learning and is usually divided into acute and chronic components, both consisting of acquisition, consolidation and retention phases (Blazquez et al. 2004). Short-term adaptation is acquired over a period of hours in response to visual-vestibular miss-match, whereas long-term adaptation is acquired over longer periods. During →ontogenetic development, the network parameters must also be adjusted. For example, the neural integrator is calibrated in the first few months of life (Weissman et al. 1989). The VOR gain must then be adjusted to the juvenile growth of the eyes and to accommodate elderly weakening of extraocular muscles (Boyden et al. 2004; Ilg 1997). Other adjustments accompany changes in visual conditions, such as minimizing and maximizing the changes produced by visual aids such as glasses.

15.7.2.1 Characteristics of Vestibulo-Ocular Reflex Adaptation

To induce long-term adaptation, the magnification or direction of image projection onto the retina can be changed by using spectacles or prisms, or by moving the visual surround during head movements (e.g., Boyden et al. 2004; du Lac et al. 1995; Highstein 2009c; Ito 2013). In the initial unadapted state, the VOR is inappropriately calibrated to compensate for head turns with correct eye movements, resulting in retinal slip.

The initial 5 ms of the reflex do not change. Differently adapted VORs differ not only in response magnitude, but also in the temporal waveform, with the initial overshoot decreasing with increasing gain. The differences between modified and unmodified components suggest that different neuronal pathways are involved (du Lac et al. 1995). Other indications are that VOR increases and decreases exhibit different learning curves and are reversible to different extents (Blazquez et al. 2004; Boyden et al. 2004).

15.7.2.2 Adaptation Sites, Cellular Mechanisms and Signal Transmission

Two long-standing hypotheses, the Albus-Marr-Ito hypothesis and the hypothesis presented by Miles and Lisberger (1981), differ in three ways: where the plastic changes in VOR adaptation occur, what the instructive signals are, and how changes in neuronal discharge patterns originate (Boyden et al. 2004). There is supporting as well as conflicting evidence for both hypotheses. Most probably, this is due to the existence of multiple plasticity mechanisms. VOR adaptation is evidently associated with plasticity at two major sites: cerebellar flocculus and vestibular nuclei (Blazquez et al. 2004; Boyden et al. 2004; Broussard and Kassardjian 2004; du Lac et al. 1995; Gittis and du Lac 2006). Moreover, there may be plastic changes in the intrinsic excitability of Purkinje cells and vestibular nuclear neurons (Jang and Kim 2019).

The Albus-Marr-Ito hypothesis (Ito 1982, 2013) postulates that during the initial phase of visual-vestibular mismatch, pairing of retinal image slip and head motion causes synchronous activity in visually driven →climbing fibers and vestibularly driven parallel fibers. In this model, the climbing fibers signal retinal slip, which serves as the instructive signal guiding plastic changes in the cerebellum. Climbing-fiber activity in response to contraversive image motion causes →long-term depression (LTD) at synapses of parallel fibers carrying vestibular signals to Purkinje cells (Boyden et al. 2004). This picture has become more complicated for two reasons. First, in order to avoid depression all these synapses, LTD must be reversible by its counterpart, →long-term potentiation (LTP) (Grasselli and Hansel 2014). Second, there are other forms of use-dependent plasticity in the cerebellum: LTP and LTD of excitatory synapses and inhibitory synapses, and persistent changes in intrinsic neuronal excitability. They occur at various sites in cerebellar cortex and deep nuclei, and must cooperate in a complex way (D´Angelo et al. 2011; Gao et al. 2012). Lesioning and functional impairment of these areas prevent VOR adaptation (Blazquez et al. 2004; Boyden et al. 2004; du Lac et al. 1995). The brainstem sites of plasticity evidently enlarge the frequency range of VOR gain adaptation to higher frequencies (Porrill and Dean 2007).

The alternative hypothesis (Miles and Lisberger 1981) suggests that the cerebellar cortex, rather than storing the →memory trace, computes the instructive signal, which the Purkinje cells use to induce plastic changes in the synapses from vestibular afferents. According to this view, changes in Purkinje cell firing patterns result from changes in a motor →efference copy of eye movement commands created in the vestibular nucleus. The vestibular nuclei contain mechanisms of →synaptic plasticity such as long-term potentiation (LTP) and depression (LTD) and are therefore candidates for VOR adaptation (Gittis and du Lac 2006; Grassi and Pettorossi 2001; Menzies et al. 2010).

Probably, the cerebellar flocculus/paraflocculus is involved in the induction of plasticity, while the vestibular nuclei are the site of retention. In freely behaving mice exposed to a two-week visuo-vestibular mismatch, the VOR was reduced by 50%, the reduction depending on changes outside the flocculus/paraflocculus. Associated cellular changes occurred in the brainstem where the efficacy of →synaptic transmission between vestibular afferents and central vestibular neurons was decreased, supplemented by decreases in the spontaneous discharge rate and excitability of a sub-population of central vestibular neurons (Carcaud et al. 2017). A modulatory role on these plastic processes is played by →noradrenergic fibers from the →locus coeruleus (LC) (Pompeiano 2002).

Signal Transmission during VOR Adaptation. Changes in VOR gain should be associated with changes in neuronal activity if synaptic connections are altered. Indeed, many brainstem and cerebellar cells change their discharge patterns during VOR adaptation (e.g., Blazquez et al. 2004; Boyden et al. 2004; du Lac et al. 1995).

15.8 Ocular Following Responses

While in monkeys the VOR has a gain close to 1, in other animals including humans, the normal gain is below 1 and must therefore, in order to compensate for residual image motion, be complemented with visual backup mechanisms, each with its specific gain (Miles 1998). The most rapid mechanisms have such a short latency that they operate under →open-loop conditions, which requires adaptation.

There are at least two visual backup mechanisms for the VOR, together referred to as ocular following responses (OKRs) (Kawano 1999). The primitive response is the short-latency optokinetic nystagmus (OKN) that is elicited by large-scale image motions and consists of a saw-tooth-like succession of slow following phases and quick resetting phases. When this OKN persists long enough and light is then suddenly switched off, the eyes produce a diminishing optokinetic after-nystagmus (OKAN), with the direction of the slow phases reversed.

In the laboratory, ocular following responses are usually elicited by planar or circular motion of large textured images. The slow tracking phases of the optokinetic nystagmus (OKN) have two components: an early component (OKNe) with a fast initial rise in eye velocity, and a subsequent, delayed component (OKNd) with a gradual increase in eye velocity (Ilg 1997; Kawano 1999).

15.8.1 Transcortical Ocular Following Reflexes

Ocular following responses in primates are mediated by →sub-cortical and transcortical pathways. In macaques, for example, the required →visual motion signals come from visual cortical areas, rather than directly from the retina; in particular from →area MT/V5 and →area MST, which are specifically involved in motion analysis. These areas calculate the direction and velocity of visual stimuli moving through the visual field and transmit the information to the dorso-lateral pontine nucleus (DLPN), both directly and indirectly via the vestibulo-pontine and oculomotor systems. Visual motion signals also come from area V1, area V2 and area V3 (Distler and Hoffmann 2001).

Several visual transcortical reflexes help stabilize gaze in space. All of them operate with machine-like consistency at very short latencies (< 60 ms in monkeys, < 85 ms in humans) (Miles1998).

Radial-flow Vergence. An observer moving through the environment experiences optic flow. When the gaze is centered on an object in the focus of flow, radial expansion signals the approach of the object by means of ocular convergence (Miles 1998; Kawano 1999). Most probably, area MST neurons →sensitive to such flow patterns are involved in generating the responses because chemical MST lesions impair them (Takemura et al. 2007).

Disparity-dependent Ocular Following. A train passenger looking out the window experiences large-scale motion across both retinas, which elicits nystagmus. The tracking system must respond selectively to the motion of objects of interest, and disregard the motion of other objects in the scene. The earliest OKN is sensitive to →binocular disparity and is elicited only by objects moving in the vicinity of the fixation plane. It operates at such short latencies that perception is precluded (Miles 1998; Kawano 1999).

Disparity-dependent Vergence. Sudden changes of binocular disparity elicit vergence eye movements at very short latencies. This vergence mechanism corrects only for minor misalignments of the two eyes, within about 2 degrees, and helps prevent images from leaving the plane of fixation. This response could involve disparity-sensitive area MST neurons (Miles 1998; Kawano 1999), since MST lesions impair the responses (Takemura et al. 2007).

15.8.2 Cerebellar Role in Ocular Following Responses

To reiterate and underscore the role of the cerebellum in ocular following, cortical area MST sends strong projections to the dorso-lateral pontine nucleus (DLPN), which in turn sends a light →mossy fiber projection to the cerebellar flocculus and substantial projections to the dorsal paraflocculus (DPFL) and ventral paraflocculus (VPFL). Lesions and chemical inactivation of these structures decrease ipsilateral ocular following responses (Takemura et al. 2001).

Purkinje cell discharges are of two types during ocular following; →simple spike (SS) discharges and complex spike discharges.

Simple-spike Discharge of Purkinje Cells. During early phases of ocular following, motion of large-scale visual patterns strongly activates area MST neurons, DLPN neurons and VPFL Purkinje cells, which react before the eye movement at a progression of latencies suggesting information flow from area MST to DLPN to paraflocculus (Kawano 1999). The simple-spike (SS) discharge of VPFL Purkinje cells adequately represents the dynamic acceleration and velocity of eye movements, but not eye position (Gomi et al. 1998; Yamamoto et al. 2000). To generate the latter, the network from VPFL Purkinje cells to extraocular motoneurons must also incorporate a neural integrator (Yamamoto et al. 2000).

Complex-spike Discharge of Purkinje Cells. The climbing fiber input to Purkinje cells is also modulated during ocular following responses. The temporal complex spike (CS) patterns are similar to the simple-spike patterns when the sign is reversed and the magnitude is amplified ~50 times. Also, in individual cells, the →preferred directions of stimulus motion tend to be opposite for complex and simple spikes (SS). Complex spike discharge has both sensory and motor aspects, suggesting that the sensory aspects encode an error signal derived from retinal slip, but the discharge is already represented in the reference frame of dynamic →motor commands (Kobayashi et al. 1998).

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16

Saccades and Smooth Pursuit Eye Movements

CONTENTS

Abstract

• The neural organization of saccades, smooth pursuit and vergence eye movements is herein reviewed and discussed.

• Saccades are very fast eye movements triggered by a visual, acoustic, tactile or other stimulus, or performed voluntarily. Because vision is disrupted during saccades, they must be interspersed with fixation periods, during which the gaze is kept stable. Saccades may be combined with head and/or trunk movements, in particular when they are made to targets outside the current field of view.

• The neural excitation driving saccade-related motoneurons is generated by brainstem burst generators consisting of various types of neuron in complex networks. While the burst generators determine the metric and dynamic properties of saccades, they do not determine the time when saccades should take place and when they should stop.

• The neural commands driving the burst generators appear to be set up in highly interconnected frontal and parietal cortical areas, elaborated by the cerebellum and the basal ganglia and then funneled through the superior colliculus (SC), with feedback from the latter three structures routed back to the cerebral cortex via the thalamus.

• Growth, ageing, disease or injury may lead to consistent changes in saccadic metrics. To keep saccades accurate, continuous adjustments must be made to saccadic gain and dynamics. Saccade adaptation depends on several plasticity mechanisms at different sites.

• Smooth pursuit eye movements follow a target moving relatively slowly against a background. They are organized by a network that connects cerebro-cortical areas, basal ganglia, cerebellum and superior colliculus (SC).

• When targets change distance to the eyes, saccades and smooth pursuit eye movements must be accompanied by vergence eye movements and accommodation. These processes are closely linked.

16.1 Introduction

Gaze shifts, which include saccades, smooth pursuit eye movements and vergence movements, serve to direct the →fovea onto image segments of current or future interest. Commonly, gaze is directed to targets and their locations that are momentarily relevant. For example, saccades are often directed fast to →salient stimuli, including →emotionally laden (e.g., fear-evoking) stimuli (Mulckhuyse 2018). Moreover, eye movements precede or accompany body movements within natural task contexts such as locomotion, reaching, grasping and manipulations, requiring cocordination with these movements (Lappi 2016).

All mammals are capable of generating saccades and smooth eye movements that track the entire visual surround. Only →primates, however, use a combination of saccades and smooth pursuit. This ability co-evolved with new visual →cortical areas and their projections to →sub-cortical substrates (Lisberger et al. 1987; Ilg 1997; Ilg and Thier 2008; Krauzlis and Stone 1999).

Traditionally, the neural systems subserving saccades and smooth pursuit were considered as largely independent. Recent evidence, however, suggests a close relationship between the saccadic and smooth pursuit systems (Ilg 1997; Krauzlis 2005; Krauzlis and Stone 1999; Lappi 2016; Scudder 2009b).

16.2 Saccades

Saccades belong to a repertoire of →orienting behaviors that include movements of the eyes, external ears, head and/or body (Gandhi and Katnani 2011). Saccades have evolved as a necessary by-product of the vestibulo-ocular reflex (VOR) and the optokinetic response (OKR) in that the eyes need to be reset after the slow movement components produced by the →reflexes. But these quick phases appear to be linked to the head movements eliciting the reflexes and thus, in afoveate animals, do not attain independent importance. With the evolution of the fovea, the small central depression in the retina where →visual acuity is the highest and retinal cone photoreceptors are highly concentrated, fast re-orientation of the gaze towards salient stimuli became of essence. Moreover, in natural behaviors, saccades serve to seek information relevant to subsequent actions (Hayhoe 2017) and to look for targets in visual search (Clarke et al. 2019).

Saccades are guided by processes that presumably involve three factors: direct link between stimulus and →reward, expectation of a gain from the chosen action, and the uncertainty of such expectation (Gottlieb et al. 2014).

For good stereoscopic vision, saccades involve not only conjugate eye movements, but also →disjunctive (vergence) eye movements, both of which need to be tightly coordinated (Chaturvedi and van Gisbergen 1997; Mays 2009c).

Large saccades exceed the range of eyeball movements. For instance, this range is, from the primary position, about ±25° in cats and ±45° in monkeys (Sparks 1991). Therefore, large gaze shifts cannot be accomplished by eye movements alone, but must be complemented with head and/or body movements in a temporally and spatially coordinated way (Freedman 2008; Gandhi

and Katnani 2011; Isa and Sasaki 2002; Pelisson and Guillaume 2009; Sparks et al. 2001).

As useful as saccades are, they also create challenges to the visual system that must be overcome, such as (Parr and Friston 2017; Rolfs 2015):

• Rapid image motion across the retina during a saccade, which causes image smear that needs to be ignored.

• Saccades create temporal gaps in →perception that must be bridged.

• Retinal image motion created by saccades must be discerned from that caused by external world motion.

• The post-saccadic image must be connected to the pre-saccadic image to insure perceptual continuity.

• Relevant visual objects must be re-identified despite changed positions.

To counteract challenges to useful visual detection and perception, the saccadic system performs a number of sensory-motor transformations, integrations and a sophisticated coding system using body and/or head coordinated systems (Rolfs 2015; Girard and Berthoz 2005; Ramat et al. 2007; Sparks 2002).

16.2.1 Neural Control of Saccades

During a saccade, visual feedback cannot be used to guide the movement for two reasons. First, saccades often reach speeds in excess of 500°/s. This causes substantial blurring of the visual image, making it difficult to use visual cues for movement guidance. Second, saccades are generally of short duration (~45 ms for a 10° saccade) and visual information is not fully processed before the movement is over (Hopp and Fuchs 2002). This necessitates →feedforward control. The driving signal for the feedforward controller is the difference (error) between the current eye position and the desired (target) eye position (Scudder et al. 2002; Ito 2013).

The feedforward mode does not exclude feedback loops within the controller. It is generally agreed that local feedback is used to insure the accuracy of saccades despite considerable variability in their durations and trajectories (Scudder et al. 2002). This is achieved by continuously assessing, during the saccade, the instantaneous difference between the desired saccade amplitude and the current eye position derived from an →efference copy of the →motor command (Keller 2009b). Exactly which structures are involved in this feedback operation has been debated (Scudder et al. 2002).

16.2.2 Characteristics of Saccades

Saccade properties such as latency, duration and velocity have been well characterized, based mainly from studies of clinical disorders that disrupt saccade performance in humans (Ramat et al. 2007), and from analysis of how saccade properties are regulated by primate →brainstem

neurons (Moschovakis et al. 1996).

Latencies. The time between the presentation of a target and the start of a saccade, the saccadic →reaction time or latency, can vary considerably and give clues as to the neural pathways and amount of processing involved (Fischer and Weber 1993; Gezeck et al. 1997). The shortest-latency saccades are the express saccades, with a mean latency of ca. 70 ms in monkeys and 100-135 ms in humans. They are thought to be mediated by sub-cortical regions such as the →superior colliculus (SC) and oculomotor brainstem. At the other end of the spectrum, there are saccades with latencies of hundreds of milliseconds. These include anti-saccades, i.e. saccades in the direction opposite to the stimulus (Cutsuridis 2017), and memory-guided saccades (to memorized targets), which both require →cognitive processing in the →cerebral cortex. Saccades of intermediate latency, such as targeting saccades at ca. 180 ms, may also involve cortical areas such as the →frontal eye field (FEF) (Hopp and Fuchs 2002, 2004).

Duration and Velocity. For saccade amplitudes between 5° and 60°, duration increases linearly by about 2.5 ms for every degree of amplitude. For saccades between 0.03° and 20°, saccade amplitude and peak velocity are also related linearly. Velocity is highest for →alert subjects tracking a visual target and slow for anticipatory saccades, anti-saccades, and saccades directed towards remembered targets and auditory targets (Moschovakis et al. 1996).

Saccade latencies and velocities depend on context as well as other factors. For example, saccades are faster in anticipation of a stimulus of higher interest and of greater reward (Shadmehr et al. 2010).

16.2.3 Saccade-related Neuron Types

Brainstem and →cerebellar neurons are the predominant contributors in the control of saccades. Commands for horizontal and vertical saccades are produced by premotor neurons in the →pons and →medulla oblongata, whereas control of vertical saccades is executed by rostral →midbrain premotor neurons. In monkeys, the cerebellar cortex related to saccadic function is located in lobules VIc and VII of the vermis (Noda 1991; Sparks 2002).

To understand how saccades are influenced by neurons, it is important to remember what forces are needed to generate them. Saccades are driven by different force components (Ramat et al. 2007; Scudder et al. 2002): A *force pulse* precedes and continues during the saccade, to dynamically move the eyeballs; a *force step* holds the eye at its new position against the elastic restoring forces of extraocular muscles and connective tissues.

To generate the force components, extraocular motoneurons fire in →burst-tonic patterns that are driven by inputs from various pre-motoneuron networks. One type of input neuron produces the burst of discharge that drives the fast, velocity-related eye movement. This burst is superimposed on a position-related signal generated by a neural integrator. However, the neural integrators contain neurons whose discharge is not a pure eye-position signal but may also contain bursts of different strengths and slide components (Ramat et al. 2007; Schall 2013; Scudder et al. 2002; Sparks 2002).

Each of the saccade-related brain areas contains four classes of neurons; burst, burst-tonic, tonic and pause, whose discharges changes before, during and after saccades.

Burst Cells fire in relation to saccades directed into a specific area of space that defines their movement field. Based on the latency between burst start and saccade onset, bursts cells are further categorized as medium-lead and long-lead neurons (Moschovakis et al. 1996; Scudder 2009a; Scudder et al. 2002): Medium-lead burst neurons (MLBNs) directly contact extraocular motoneurons; long-lead burst neurons (LLBNs) have only sparse monosynaptic access to motoneurons in primates (Moschovakis et al. 1996).

Burst-tonic Cells produce a high-rate burst whose →intensity is related to the amplitude of saccades in particular directions (extraocular motoneurons being typical examples).

Tonic Cells produce discharges whose rate is related to eye position. Of particular importance are those found in the →vestibular nuclei, nucleus praepositus hypoglossi (NPH) and interstitial nucleus of Cajal (INC), which are thought to belong to the neural integrators.

Pause Cells fire constantly during →fixation and stop firing during saccades.

16.2.4 Brainstem Burst Generators

Diverse networks of brainstem burst generators project to extraocular motoneurons to differentially affect the properties of horizontal and vertical saccades (Moschovakis et al. 1996; Ramat et al. 2007; Scudder 2009a; Scudder et al. 2002; Sparks 2002).

16.2.4.1 Horizontal Saccades

For horizontal saccades to one side, the corresponding synergistic muscle pair, i.e., the ipsilateral lateral rectus (LR) and contralateral medial rectus (MR) muscles, is activated while the contralateral LR is inhibited. This type of coordinated horizontal saccade is organized by excitatory as well as inhibitory neurons (Büttner-Ennever 2008; Moschovakis et al. 1996; Ramat et al. 2007; Scudder 2009a; Scudder et al. 2002; Takahashi and Shinoda 2018).

Excitatory Burst Neurons (EBNs) fire bursts of →action potentials before and during horizontal →ipsiversive (on-direction) saccades, with an occasional contribution to vertical saccades. The number of spikes per burst is linearly related to the saccade amplitude in the on-direction. Burst duration is scaled to saccade duration, whereas intra-burst discharge rate is scaled to eye velocity as well as, to some degree, to saccade acceleration.

Inhibitory Burst Neurons (IBNs) have discharge properties very similar to those of their excitatory counterparts. Saccadic burst neurons in the brainstem →reticular formation caudal to the abducens nucleus exert an inhibitory →synaptic action on contralateral abducens motoneurons, thus contributing to ipsiversive horizontal saccades.

Horizontal Saccade Network. EBNs in the paramedian pontine reticular formation (PPRF) activate ipsilateral abducens motoneurons as well as internuclear neurons (INs) in the abducens nucleus. These INs mediate the excitation to the contralateral MR motoneurons. The EBN signal also goes to the horizontal neural integrator (HNI) in the nucleus praepositus hypoglossi-medial vestibular nucleus region (NPH-MVN), whose output also excites INs and LR motoneurons. In addition, in order to inhibit corresponding neurons on the contralateral side, EBNs excite ipsilateral IBNs in the nucleus paragigantocellularis dorsalis (PGD), which then inhibit contralateral IBNs, EBNs, HNI, INs and LR MNs.

16.2.4.2 Vertical Saccades

Downward Saccades. For downward saccades, the inferior rectus (IR) and superior oblique (SO) muscles on both sides must be activated. Two types of burst neuron (Moschovakis et al. 1996; Scudder 2009a; Scudder et al. 2002) create this pattern: excitatory downward burst neurons ($DMLB_e$), which have properties similar to those of EBNs; and inhibitory vertical burst neurons, which have similar discharge properties.

Upward Saccades require activation of the superior rectus (SR) and inferior oblique (IO) muscles on both sides, but also involve inhibition. This pattern is generated by excitatory upward burst neurons ($UMLB_e$), which have discharge properties similar to the horizontal cells, and inhibitory upward burst neurons ($UMLB_i$). The system is more complicated than that for downward saccades in that inhibition is heavily involved.

16.2.4.3 Straightening Saccades

The different burst generators for horizontal and vertical saccades must be coordinated for the huge variety of oblique saccades. If an oblique saccade is to be performed efficiently with a straight trajectory, its horizontal and vertical movement components should have equal duration, despite potentially different amplitudes. Otherwise, oblique saccades would show distorted trajectories. It has been hypothesized that equal component duration is assured by omnipause neurons (OPNs) (Ramat et al. 2007; Scudder 2009a; Scudder et al. 2002).

In monkeys, OPNs display a high background firing rate (50-200 spikes per second unrelated to eye position) during fixation or smooth eye movements, and stop firing before and during saccades in all directions (hence `omnipause´ from `omnidirectional´) for a period correlated with saccade duration. Omnipause neurons establish a complex →feedback system with virtually all pre-saccadic burst neurons. They provide inhibitory input to, and receive inhibitory input from, bilateral EBNs, IBNs, UMLBs, DMLBs, and others. Before the saccade, the EBNs and IBNs are tonically inhibited by the high background discharge of OPNs. This inhibition must therefore be suppressed to initiate a saccade, which is thought to be accomplished by putative inhibitory trigger neurons that receive input from the superior colliculus (SC) and frontal eye field (FEF). Once the saccade has been initiated, OPN suppression is maintained by EBN activity, possibly via latch neurons (Ramat et al. 2007; Scudder 2009a; Scudder et al. 2002). The firing pause of OPNs thus disinhibits burst neurons and allows them to discharge with a matching onset and duration during saccades. (Moschovakis et al. 1996; Scudder et al. 2002).

16.2.5 Inputs to the Brainstem Burst Generators

Although burst generators determine the metric and dynamic properties of saccades, they do not determine the time when saccades take place and when they stop. In order to initiate saccades, two types of input signal to the burst generators are required (Scudder et al. 2002): inhibition of OPNs; excitation of EBNs related to the desired saccade size.

Production and elaboration of these input signals appear to be generated in →frontal and →parietal cortical areas, elaborated by the cerebellum and the →basal ganglia and then funneled through the superior colliculus (SC), with feedback from the latter three structures routed back to the cerebral cortex via the →thalamus (Schall 2013; Voogd et al. 2012).

16.2.6 Roles of the Superior Colliculus in Saccades

The superior colliculus (SC) serves as a rapid detector and first responder when survival requires quick action. It is highly sensitive to ecological and social stimuli, and is active during visually guided reaching and grasping during locomotion (Soares et al. 2017). The SC is also involved in the organization of saccades and smooth pursuit movements (Parr and Friston 2017; Schall 2013; Veale et al. 2017). Moreover, it coordinates eye-head and eye-head-body movements, pinnae and whisker movements, sonar →vocalizations in bats, and is involved in →attention, →decision making, target selection, goal representation, motor preparation, and reward-related modulation. These various functions require →multi-sensory integration and sensory-motor transformations (Basso and May 2017; Gandhi and Katnani 2011).

16.2.6.1 Structure-Function Relationships in the Superior Colliculus

Input/Output. The superior colliculus (SC) receives inputs from the retina, visual cortical areas, the frontal eye field (FEF), supplementary eye field (SEF), →lateral intraparietal area (area LIP), the cerebellum, and the →substantia nigra. The SC sends signals to the burst generators via direct and indirect pathways. Both EBN and IBN sites receive inputs from the SC and the cerebellar caudal fastigial nucleus (CFN). The SC also projects to the →nucleus reticularis tegmenti pontis (NRTP), which sends →mossy fibers to both the →oculomotor vermis (OMV) and the CFN. In turn, →Purkinje cells in the OMV inhibit neurons in the ipsilateral CFN (Soetedjo et al. 2019).

Layered Structure. The superior colliculus (SC) is unique in being composed of superimposed sensory and →motor maps, spreading out in superficial and deeper layers, respectively (Basso and May 2017; Gandhi and Katnani 2011; Hirosaka et al. 2000; Isa and Saito 2001; Veale et al. 2017).

Sensory Maps. Neurons in the superficial gray layers of mammals receive visual inputs from the retina and visual cortex (Basso and May 2017; Walton et al. 2009a). Their →receptive fields (RFs) are arranged to form a →retinotopic map of the →visual field. One hemifield is mapped onto the surface of the contralateral superior colliculus (SC). The central field is represented rostrally, the peripheral field caudally, the upper field medially and the lower field laterally. In addition to visual signals, the deep layers receive auditory and somatosensory (tactile and noxious) signals

and non-sensory modulatory signals from widespread cortical and sub-cortical regions (McHaffie et al. 2005). The auditory and somatosensory maps in the deeper layers change with eye, head and body position, which is necessary because loci on the motor map specify the change in eye position required to look at a target (Walton et al. 2009a).

Motor Map. Cells in the deeper gray layers of the SC receive inputs from the substantia nigra, cerebellum, frontal eye fields and several sensory systems, and project primarily to brainstem circuits that generate saccades. Correspondingly, these neurons exhibit sensory responses or pre-saccadic command signals. The saccades commanded by the pre-motor cells vary with location in the intermediate layer to form a motor map that is aligned with the visual map in the overlying superficial layer (Basso and May 2017; Gandhi and Katnani 2011; Keller 2009c; Moschovakis 1996; Moschovakis et al. 1996; Lee et al. 1997; Scudder et al. 2002; Sparks 2002). Cells involved with small saccades lie rostrally in the superior colliculus (SC), those related to large saccades caudally, those firing with upward saccades are located medially, and those firing with downward saccades lie laterally in the superior colliculus (SC). This →topography is consistent with saccades produced during electrical stimulation (Gandhi and Katnani 2011).

Sensory-motor Correspondence. The spatial alignment of sensory and motor maps suggests that sensory information is directly transferred from sensory cells in the superficial layer to pre-motor cells in the intermediate layer (Isa and Saito 2001; Lee et al. 1997). Since the superior colliculus (SC) uses different reference frames to encode the spatial location of stimuli with different modalities, →coordinate transformations are needed to put them in register with one another and with the reference frame used to encode movement metrics (Moschovakis and Grantyn 2009).

16.2.6.2 Saccade-related Neurons in Superior Colliculus

Based on their discharge patterns, three classes of neurons that adjust saccade properties have been distinguished: build-up neurons (BUNs), saccade-related burst neurons (SRBNs) and fixation neurons. However, there are no clear boundaries that sharply demarcate the three types (Gandhi and Katnani 2011; Munoz and Wurtz 1995a,b; Moschovakis 1996; Moschavakis et al. 1996; Scudder et al. 2002).

Build-up Neurons (BUNs) or prelude neurons (Keller 2009a) project to EBNs, IBNs and OPNs. Their discharge rate rises slowly to a peak rate before saccade onset and then decays. These neurons have been suggested to be associated with target selection or motor preparation, or to indicate the error between the current eye and the target position for both saccades and smooth pursuit (Keller 2009a; Ramat et al. 2007; Scudder et al. 2002; Wurtz 2009).

Saccade-related Burst Neurons (SRBNs) (Hu and Sparks 2009) or tectal long-lead burst neurons (TLLBNs) (Moschovakis 2009b) discharge bursts with little prelude activity, leading saccades by ca. 20 ms. The burst rate is greatest for saccades with a particular preferred amplitude and direction (i.e., vector) and less for saccades with other vectors (both amplitude and direction), defining a `movement field´. The retinotopic coordinates of the preferred vectors are topographically organized. Neurons in the caudal SC discharge best for larger vector saccades and those more rostral in the SC for smaller vector saccades (Soetedjo et al. 2019).

Fixation Neurons or tectal pause neurons (TPNs) lie in the same layer as the build-up neurons (Guitton 2009; Munoz and Wurtz 1995a,b), but in the rostral superior colliculus (SC), where electrical stimulation stops ongoing saccades. They fire at a constant rate during fixation and pause during saccades. Hence, if they inhibit the more caudally located saccade-related SC neurons and excite OPNs, their firing pause might enable saccades by disinhibition. However, fixation-related neurons in rostral SC have also been described as firing bursts before small saccades; therefore, fixation could potentially be maintained by the activities of neurons with opposite →preferred directions (Gandhi and Katnani 2011). Fixation-related neurons are also present in other brain regions, such as the FEF, SEF, area 7a, area LIP, and the basal ganglia (Guitton 2009).

Some saccade-related neurons alter their discharge during saccade-vergence movements, and microstimulation of the superior colliculus (SC) induces vergence movements and lens accommodation (Gandhi and Katnani 2011).

16.2.6.3 Vector Decomposition and Spatio-temporal Transformation of Movement Commands

In the intermediate/deep SC layers, saccades are coded in terms of a place code, whereas brainstem burst generators code saccade metrics in terms of a temporal code, namely duration and firing rate. Hence, two operations in the SC are required: vector decomposition, the general process of breaking one vector into two or more vectors that add up to the original vector, and spatio-temporal transformation, wherein the SC encodes the position of targets in retinotopic space using a linear or a logarithmic mapping, depending on the species considered. (Moschovakis and Grantyn 2009).

Vector Decomposition appears to be implemented by →axon branches of TLLBNs, one branch directed to the ipsilateral →rostral interstitial nucleus (INC) of the medial longitudinal fascicle (riMLF) that encodes vertical saccade components, and another branch to the contralateral PPRF that translates horizontal saccade components (Moschovakis and Grantyn 2009).

Spatio-temporal Transformation. Several hypotheses have been proposed for spatio-temporal transformation (Moschovakis 2009a; Scudder et al. 2002). Common to all is the view that the superior colliculus (SC) uses →population coding to activate large ensembles of neurons in the intermediate/deep SC layers for every saccade. Some hypotheses assume that the SC determines the desired eye displacement, while the dynamics of the saccade are resolved downstream by a local feedback network that continuously compares the desired eye displacement with the current eye displacement during a saccade (Keller 2009b). However, alternative hypotheses suggest that the SC does not encode desired eye displacements (Krauzlis 2005; Optican 2005).

16.2.6.4 Local Feedback Loops

Saccades are too brief for sensory feedback to guide them precisely on target, and vision is reduced during saccades (Bremmer 2011). The task of guiding a saccade to a target can be theoretically accomplished by internal local feedback loops. Feedback would signal the current eye position, derived from an efference copy of the motor signal to extraocular motoneurons. A

comparator calculates the difference between the feedback signal and the desired change in eye position, resulting in a →motor error signal that drives the eye movement to target until the difference drops to zero (Optican and Pretegiani 2017).

Two anatomical structures were implicated in the operation of the feedback loops and the comparator; the superior colliculus (SC) and the cerebellum (Choi and Guitton 2006; Herzfeld et al. 2018; Krauzlis 2005; Scudder et al. 2002; Soetedjo et al. 2002). An alternative hypothesis theorizes that both the SC and cerebellum are involved, with the cerebellum using adaptive, velocity feedback and integral control to keep the saccade on target (Optican and Pretegiani 2017). Recent results suggest a key role for area LIP in saccadic error processing (Munuera and Duhamel (2020).

16.2.7 Eye-head Coordination

Eye and/or head and body movements that occur in a temporally and spatially coordinated manner bring about large-amplitude gaze shifts that exceed the limits of saccades (Gandhi and Katnani 2011; Pelisson and Guillaume 2009; Sparks et al. 2001). The eyes start moving first. The head moves later and more slowly. Eyes and head move in the same direction only during the active gaze shift. Subsequently the eyes must rotate back to keep the line of sight on target, because the head keeps moving towards the target. The relative contributions of eye and head movements vary with the amplitude of the gaze shifts, with initial eye position and with direction of gaze shift (Sparks et al. 2001). Head rotations contribute significantly for gaze shifts beyond 20°.

16.2.7.1 Role of the Vestibulo-ocular Reflex in Eye-head Coordination

As efficient as the VOR is in stabilizing gaze in many daily activities, it would be counterproductive during active gaze re-direction to new targets. The VOR is therefore reduced during eye-head gaze shifts and eye-head pursuit movements (Cullen 2009; Pelisson and Guillaume 2009; Scudder et al. 2002). Nonetheless, head motion signals may influence eye movements, as suggested by the decrease in eye velocity during the gaze shift while the head is accelerating. One possible source of the head motion signal is an efference copy of the head motion command. Another source could be afferent feedback from neck muscle receptors involved in the cervico-ocular reflex (Scudder et al. 2002).

16.2.7.2 Role of the Superior Colliculus in Eye-head Coordination

As the primary structure controlling →orienting, the superior colliculus (SC) is involved in combined eye-head movements. In cats and monkeys, electrical stimulation of the rostral SC evokes eye movements, stimulation of the intermediate SC evokes combined eye-head displacements, and stimulation of the caudal SC induces combined eye-head-body movements (Sparks et al. 2001; Scudder et al. 2002).

Superior Colliculus Activity. Discharge of SC neurons in the motor layers is best correlated with the amplitude and direction of gaze shifts, and only weakly with eye and head movement components. This suggests that the SC selects commands for eye and head movements concurrently (Sparks et al. 2001).

SC-Cervical Motoneuron Connections. There are several SC connections to cervical motoneurons innervating neck →skeletal muscles. While some connections are monosynaptic, most connections are oligo- to polysynaptic, which engage a staggered system of brainstem nuclei in the midbrain, →pons and medulla oblongata (Sparks 1991; Isa and Sasaki 2002; Moschovakis et al. 1996; Scudder et al. 2002). In the cat, one pathway runs through →reticulo-spinal neurons in the pons and medulla, another through neurons in Forel´s field H at the junction of medulla and →diencephalon. The former is primarily involved in controlling orienting head movements in the horizontal direction and the latter in the vertical direction. In both pathways, sub-groups of neurons are premotor neurons to both eye and cervical motoneurons, whereas other cells are designed for controlling either eye or head movements (Isa and Sasaki 2002).

Reticulo-spinal Long-lead Burst Neurons (RSLLBNs) receive predominant input from SC build-up neurons (BUNS). They fire directionally, with a preference for ipsilateral horizontal saccades. They might thus serve as head burst neurons (Scudder et al. 2002). But many reticulo-spinal neurons give off collaterals to extraocular motoneurons, providing the possibility of organizing →synergies of eye-head movements at this level (Sparks et al. 2001). The signals carried by these cells are often related to both eye position and neck muscle activity (Sparks 1991; Scudder et al. 2002).

16.2.8 Cerebellar Control of Saccades

The cerebellum is probably not involved in generating the commands for saccades, but in compensating for saccade inaccuracy, modulating saccade metrics and adapting them to prevailing circumstances (Moschovakis et al. 1996; Ramat et al. 2007; Robinson and Fuchs 2001; Scudder et al. 2002; Shadmehr et al. 2010). The effects of cerebellar lesions suggest these roles. Oculomotor vermis lesions render saccades →hypometric and slow down ipsiversive and contraversive saccades. When the fastigial nucleus is lesioned or inactivated chemically, saccades are slow, inaccurate and variable in size and speed in repeated trials. Normally, fastigial nucleus activity accelerates contraversive saccades and decelerates ipsiversive saccades (Kheramand and Lee 2011; Optican 2005; Robinson and Fuchs 2001).

16.2.8.1 Saccade-related Cerebellar Structures

Purkinje cells in the oculomotor vermis (OMV) and neurons in the ipsilateral caudal fastigial nucleus (CFN), also referred to as fastigial oculomotor region (FOR), are involved in the control of saccades (Iwamoto and Kaku 2010; Kheramand and Lee 2011; Ramat et al. 2007; Robinson and Fuchs 2001; Scudder et al. 2002). The cerebellum receives inputs from areas in the →frontal cortex and →parietal cortex, the superior colliculus (SC) and the nucleus praepositus hypoglossi (NPH), and projects to several neuron types of the brainstem burst generators (Robinson and Fuchs 2001; Voogd et al. 2012).

16.2.8.2 Neuron Types and Discharge Patterns in the Cerebellum

The cerebellar circuitry controlling eye movements is now understood at a level that is sufficient to link the roles of various cerebellar cell types and their discharge properties to saccade properties.

Purkinje Cells in the oculomotor vermis, flocculus and part of the paraflocculus receive inputs from pre-cerebellar long-lead burst neurons (PCLLBNs), medium-lead burst neurons (MLBNs), burst-tonic and tonic neurons via mossy fibers. While the →simple-spike (SS) discharge of individual Purkinje cells correlates only weakly with saccade kinematics and metrics, the population average encodes the velocity profile of saccades (Soetedjo et al. 2019).

Fastigial Long-lead Burst (FaLLB) Neurons. Purkinje cells project to the caudal fastigial nucleus (CFN), and mossy fibers of pre-cerebellar LLBNs give off collaterals to the (CFN). LLB neurons in the fastigial nucleus discharge in bursts during both ipsi- and contraversive saccades. Most CFN neurons fire bursts for almost all saccades, irrespective of direction and size. There is considerable variability in burst lead, firing rate and burst duration. Another feature of the bursts is that they are timed differently for ipsi- and contralateral saccades, starting early for the contralateral type and later for the ipsilateral. This suggests that the bursts are associated with the start of contraversive and the end of ipsiversive saccades (Robinson and Fuchs 2001).

16.2.9 Role of the Basal Ganglia in Saccades

The basal ganglia are instrumental in organizing saccades as a special form of orienting responses. The →multi-modal abundance of information processed by the basal ganglia during saccades calls for a selection strategy that encompasses a variety of mechanisms and associated structures. It seems likely that the basal ganglia are intimately involved in selecting stimuli for saccades (Hikosaka 2009a; Hikosaka et al. 2000, 2018; McHaffie et al. 2005). Roles in decision making and action selection have been suggested for other motor acts involving the basal ganglia, such as locomotion and arm and hand movements (Grillner et al. 2020). Action selection depends on attention, →motivation, →emotion and context and supervisory control over the basal ganglia by →prefrontal cortical areas. Action selection is partly based on previous experience and →learning, especially of associations between context, actions and their consequences, and on →habit formation using →reinforcement learning (Balleine and O ´Doherty 2010; Fee 2012; Graybiel and Grafton 2015).

The basal ganglia are also thought to be involved in movement execution (Turner and Desmurget 2010) and to control the speed, amplitude and frequency of goal-directed movements (Dudman and Krakauer 2016). These different aspects are probably taken care of by specialized basal ganglia `domains´, which are integrated in segregated circuits.

16.2.9.1 Basal Ganglia Anatomy

In higher mammals, the basal ganglia consist of bilateral sub-cortical nuclei in the →basal forebrain. There are three broad domains: the dorso-lateral, dorso-medial and ventral basal

ganglia (Groenewegen 2003; Hening et al. 2009; Humphries and Prescott 2010; Tewari et al. 2016).

The dorso-lateral basal ganglia contain the →striatum (consisting of →nucleus caudatus and →putamen), →globus pallidus (internal/medial and external/lateral segment), →substantia nigra pars reticularis (SNr), and the →subthalamic nucleus (STN). In the ventral basal ganglia, the striatum consists of →nucleus accumbens (core and shell).

The striatum, nucleus accumbens and STN form the major input stations of the basal ganglia, whose major output nuclei are →globus pallidus internus (GPi) and substantia nigra pars reticularis (SNr)

Basal Ganglia Inputs and Outputs. In primates, the basal ganglia receive excitatory inputs from various thalamic nuclei (Smith et al. 2009) and the entire cerebro-cortical mantle. Striatal medium-sized, spiny, →GABAergic and peptidergic neurons (MSNs) (Hikosaka 2009b; Nambu 2008) project to the external (→globus pallidus externus, GPe) and internal (globus pallidus internus, GPi) segments, both populated by large GABAergic neurons. Functionally, the GPi is joined by the substantia nigra pars reticulata (SNr). The major basal ganglia outputs, GPi and SNr, target sub-cortical structures involved in eye and orienting movements, vocalization, postural control, locomotion, as well as the cerebral cortex via the thalamus for hand and finger movements (Grillner and Robertson 2015; Grillner et al. 2020).

Oculomotor Circuit. The cerebro-cortical inputs to striatum and STN, as well as the output connections back to the cerebral cortex, are differentiated anatomically and functionally (Alexander et al. 1990; Heimer and van Hoesen 2006; Middleton and Strick 2000; Romanelli et al. 2005; Tewari et al. 2016). The oculomotor circuit is of primary importance in the control of eye movements (Hikosaka 2009a). Oculomotor neurons related to eye movements are clustered in regions of the →caudate nucleus, which receives inputs from FEF, SEF and →dorso-lateral prefrontal cortex (DLPFC) (Hikosaka 2009b; Hikosaka et al. 2000).

Disynaptic projections to FEF via the thalamus originate in the substantia nigra pars reticularis (SNr) (Hikosaka 2009c). The cortical-basal ganglia loop is complemented by loops through the SC. There are functionally segregated loops to and from the basal ganglia; one originating from the superficial SC layers and two from the deep SC layers, which course through different thalamic nuclei to the basal ganglia and return to the SC (McHaffie et al. 2005).

Neurochemical Control of Microcircuitry in the Basal Ganglia. Excitatory postsynaptic transmission is mediated by →glutamate in the striatum, STN and GPi/SNr. Inhibitory postsynaptic transmission is implemented by →γ-amino-butyric acid (GABA) in GPe, STN and GPi/SNr. →Neuromodulators of signal flow in the basal ganglia are →dopamine and the peptides →substance P, →dynorphin and →enkephalin.

Dopaminergic Neurons. There are at least three parallel pathways through which saccade-related signals are processed in the basal ganglia: a →direct pathway from cerebral cortex via striatum to SNr, an →indirect pathway from cerebral cortex via striatum to SNr through GPe and/or STN and a →hyper-direct pathway from cortex via STN to SNr (Grillner et al. 2020). – The striatal cells involved in the different pathways are differentially modulated by dopaminergic inputs from the *XVI-16*→substantia nigra pars compacta (SNc). Those cells that feed the direct pathway have

excitatory D1 dopamine receptors, while those feeding the indirect pathway have inhibitory D2 dopamine receptors (Gerfen and Surmeier 2011; Klaus et al. 2019; Nambu 2008). There are other →neuromodulatory (→cholinergic, glutamatergic, →histaminergic) inputs to the basal ganglia (Grillner et al. 2020).

Neurochemical Imbalance and Visual Dysfunction in Basal Ganglia Disorders. Neurochemical deficits within the basal ganglia such as in →Parkinson's Disease (PD) impair eye movement control (Armstrong 2017; Pretegiani and Optican 2017). PD is a progressive, neuro-→degenerative disorder caused by dopaminergic cell loss within the substantia nigra pars compacta (SNc), which in turn appears to be caused predominantly by genetic factors (Westerlund et al. 2010). This cell loss results in depletion of striatal dopamine and subsequent increased inhibitory basal ganglia output from the internal globus pallidus and the substantia nigra pars reticulata (SNr). Eye movement abnormalities in PD are more evident in voluntary than reflexive saccades in the initial stages, but visually guided saccades may also be involved at later stages. Generalized visual dysfunction in PD can impair visual acuity, visual fields, visual processing speeds, →contrast sensitivity, color discrimination, pupil reactivity, saccadic and pursuit eye movements, and motion perception. In addition, disturbance of visuo-spatial orientation, facial →recognition problems, rapid eye movement (REM) sleep behavior disorder, and chronic visual hallucinations may be present.

In →Huntington's Disease (→chorea), several neurochemicals are reduced in concentration in proportion to loss of caudate nucleus volume: the →energy substrate creatine, n-acetylaspartate, a neuronal marker and the excitatory →neurotransmitter glutamate (Padowski et al. 2014). Inability to suppress reflexive glances to suddenly appearing novel visual stimuli and delayed initiation of voluntary saccades, including predictive saccades, are early and consistent findings, Most patients, eventually, also exhibit slow saccades (Lasker and Zee 1997).

16.2.9.2 Basal Ganglia Operation in Saccades

It is generally accepted that inhibition plays a predominant role in the regulation of saccades within the basal ganglia (Grillner et al. 2020; Hikosaka 2009a,c; Shires et al. 2010). Otherwise, every possible stimulus would provoke saccades. During rest, the neurons in the output nuclei (SNr and GPi) discharge tonically at a fairly high frequency range (40-100 pulses per second), thus exerting a tonic inhibitory influence on their thalamic or brainstem target nuclei. In addition, in order to enable a saccade to a selected target, the second mechanism needs to be disinhibition. When long-lead burst (LLB) neurons in the caudate nucleus are excited by some cerebro-cortical inputs, they inhibit the SNr neurons, which stop firing and thus interrupt their tonic inhibition on superior colliculus (SC) cells.

Superior colliculus (SC) neurons are disinhibited and can be excited by other input sources to elicit a saccade. The role of the indirect GPe/STN pathway is not quite clear. However, when strong, it could act to maintain fixation and suppress saccades. In order to produce a saccade, the direct pathway needs to predominate, via cortical inputs that are different from those directed to the indirect pathway. In fact, not only do cortical inputs directly impinge on STN neurons, the caudate cells giving rise to the two pathways appear to be different and receive different cortical inputs (Hikosaka et al. 2000).

The picture is even more complicated, because SNr targets are not only saccade-related burst neurons but also inhibitory →interneurons in the superior colliculus (SC). In addition, neurons in the SNr and SC show various activity patterns, including discharges that precede saccades that appear to be related to selection, action choice, attentional shifts and →memory.

Moreover, In many cases, SC activity is not merely a mirror image of SNr activity (Shires et al. 2010).

16.2.10 Cerebro-cortical Control of Saccades

The highest level of oculomotor control is exerted by the cerebral cortex, where potential targets for gaze shifts are analyzed and decisions are made about the occurrence of eye movements, in cooperation with loops through sub-cortical structures such as the basal ganglia and cerebellum (Lynch and Tian 2006).

16.2.10.1 Eye Fields

The cerebral cortex of primates contains a network of intimately connected areas, referred to as →eye fields, which are involved in eye movements (Amiez and Petrides 2009; Lynch and Tian 2006; Medendorp et al. 2011; Schall 2015).

Many of the cortical eye fields receive direct information from various visual →extra-striate regions and send separate and differentiated projections to sub-cortical oculomotor structures, such as the basal ganglia, thalamus, reticular formation, superior colliculus (SC), pontine nuclei (and thence to the cerebellum), and receive feedback via the thalamus from the basal ganglia, cerebellum and SC. The various eye fields listed and characterized below exhibit neural activity closely related to eye movements. The primary visual cortex, area V1, also plays a direct role in eye movements (Tehovnik and Slocum 2007).

Prefrontal Eye Field (PFEF). The PFEF, located in the posterior part of area 46 of the dorso-lateral prefrontal cortex (DLPFC), contributes to generation and control of visually and memory-guided saccades. PFEF-damaged humans have difficulty suppressing saccades to a visual target in an anti-saccade task (Lynch and Tian 2006). The PEEF contains neurons which fire before, during or after goal-directed saccades and probably contribute to the control of purposive saccades and cognitive prefrontal functions such as performance monitoring, evaluating the outcome of previous decisions and making flexible changes in behavior (Funahashi 2014; Pouget et al. 2017).

Cingulate Eye Field (CEF). The CEF in the →anterior cingulate cortex (ACC) and surrounding cortex may contribute indirectly to gaze control by mediating motivational influences derived from previous actions (Schall 2015). ACC neuron discharge reflects positive and negative action evaluations, motor errors and reward (Pouget et al. 2017).

Frontal Eye Field (FEF). The FEF (Lynch and Tian 2006; Medendorp et al. 2011; Schall 2015; Vernet et al. 2014) is a node in a widespread network. In macaques, it is located in the rostral bank of the arcuate sulcus, while there may be at least two FEFs in humans. It has been

proposed that in macaques the FEF is at the core of a region in which several distinct areas, including area 45A and area 45B, are involved in parallel processing of different aspects of oculomotor behavior. Furthermore, there is a certain correspondence between some of the macaque and the human oculomotor fields, suggesting sharing of neural substrate for oculomotor control, gaze processing, and orienting attention in space (Borra and Luppino 2021). The macaque FEF receives inputs from other eye fields (SEF, PEF), extra-striate visual areas (e.g., →area MST), the substantia nigra and superior colliculus (SC), and projects to various regions in the frontal, occipital and parietal cortices (e.g., area V2, area V3, area V4, →area MT/V5, area MST, area LIP), to the basal ganglia, superior colliculus (SC) and pons. It has sub-regions concerned with saccades and with smooth pursuit eye movements each with differential connections to other structures. It also contributes to optokinetic nystagmus (OKN), vergence movements and lens accommodation (Vernet et al. 2014) It is also implicated in the selection of visual targets, allocation of attention, initiation and in programming of saccades, and in rapid correction of saccades before feedback is available (Murthy et al. 2007). FEF activity can be modulated by reaching and arm position and may thus contribute to eye-body coordination (Schall 2015).

Many cells in macaque FEF are involved in performance monitoring by showing internally generated post-saccadic discharge that is related to errors committed, as well as to task difficulty (Teichert et al. 2014).

Lesions or inactivations of the FEF produce mild deficits in generating saccades to briefly presented visual targets, to two or more sequentially presented targets, as well as severe deficits for saccades to remembered targets, in the selection of simultaneously presented targets, as well as contralateral →hemispatial neglect (Krauzlis 2005; Lynch and Tian 2006). FEF lesions also produce deficits of smooth pursuit eye movements.

→Micro-stimulation of the FEF elicits constant-vector saccades, whose direction and amplitude are independent of initial eye position. Electrical stimulation with longer trains elicits staircase gaze and eye movements, but no or only small head movements (Tehovnik et al. 2000; Sparks et al. 2001). FEF stimulation also elicits shifts of attention (Lynch and Tian 2006).

The FEF contains several populations of neurons. Some respond to visual stimuli predominantly in contralateral space, the responses being anchored to gaze direction (Medendorp et al. 2011); some are active during fixation (fixation neurons) (Guitton 2009); some fire before, during and after saccades (*movement neurons*); and some discharge during smooth pursuit (Lynch and Tian 2006; Schall 2015; Tehovnik et al. 2000; Wurtz et al. 2001).

Supplementary Eye Field (SEF). The SEF is located rostral to the →supplementary motor area (SMA) (Schall 2015). The connections of the SEF are similar to, but not congruent with those of the FEF. In addition to connections with oculomotor structures, the SEF has connections with parietal somatosensory areas, the dorso-lateral premotor (PMd) area, →cingulate motor areas, the supplementary motor area (SMA), and the forelimb area of the →primary motor cortex (M1) (Lynch and Tian 2006).

At most SEF sites, electrical stimulation produces saccades to a specific orbital position (the termination zone), where the eyes are held during prolonged stimulation. At posterior SEF sites,

stimulation can evoke →somatotopically ordered skeleto-motor responses. Some sites represent coordinated arm and eye movements to similar terminal positions. Lesions or inactivations of the SEF have weak, if any, effects on eye movements, but stronger effects on limb movements (Schall 2015; Sparks et al. 2001; Tehovnik et al. 2000). – While FEF neuronal activity is related to eye movements only, the SEF contains neurons whose activity is related to both eye and limb movements. The SEF is also involved in learning operations (Tehovnik et al. 2000).

The SEF has been proposed to be involved in the selection, monitoring and control of eye movements, in particular in the production of sequences of saccades (Schall 2015), as well as in the computation of →reward prediction error (Pouget et al. 2017; Stuphorn 2015). It may be specifically involved in coordinating eye movements with head and limb movements (Schall 2015).

Premotor Ear-Eye Field (PEEF). A new field dubbed `premotor ear-eye field (PEEF)´ has been suggested to be involved in auditory stimulus recognition and orienting processes, i.e. in orienting eyes and ears towards a →sound source. In the macaque, this field corresponds to area 8B which lies between →Brodmann´s area 6 and area 9, and is connected with auditory cortical areas, the superior colliculus (SC) and the cerebellum. Area 8B microstimulation evokes ear and/or eye movements, and neurons encode different auditory stimuli and ear and/or eye movements (Lanzilotto et al. 2013).

Area 7m, →precuneus in humans, is located on the medial wall of the hemisphere and has been implicated in oculomotor control as well as eye-hand coordination. In addition to extra-striate visual areas, it has connections with somatosensory areas and motor areas including SMA and PMd (Lynch and Tian 2006).

The activity of some area 7m neurons is related to eye movements, of some cells to hand position and movements, while the majority of cells are involved with combined gaze direction and hand reaching (Ferraina et al. 1997).

Parietal Eye Fields (PEF), Lateral Intraparietal Area (LIP). In the human PEF, up to seven retinotopic areas have been separated in the intraparietal sulcus (IPS) and →superior parietal lobule (SPL) (Medendorp et al. 2011). In the monkey, area LIP (Colby 2009) lies at the junction between the visual and saccadic systems, and contributes to the target selection and planning of saccades.

Damage to area LIP temporarily and mildly increases the latencies of saccades and smooth pursuit, while it significantly reduces visual attention in the contralateral visual field. Combined lesions of the FEF and area LIP induce much longer and stronger impairments than lesioning of each area alone. Electrical stimulation can elicit saccadic and smooth pursuit movements.

Many LIP neurons respond before saccades toward visual and acoustic targets and to remembered visual targets within their response field (Lynch and Tian 2006). Some LIP cells respond to visual stimuli, via a coarse but systematic topographical organization (Ben Hamed et al. 2001). Their responses are related to attention and reward (Krauzlis 2005). They also carry memory traces of potential target locations for saccades, which is updated or remapped during saccades. Area LIP neuron activity can be modulated by eye position (Colby 2009).

Areas MST and MT provide much of the information needed to scale saccade amplitudes to the speeds of moving targets (Krauzlis 2005). Although area MST projects to both the saccadic and smooth-pursuit FEF sub-regions, saccade-related activity has not been found in area MST. Damage, electrical stimulation and recordings demonstrate involvement in smooth pursuit (Lynch and Tian 2006).

Primary Visual Cortex. Electrical stimulation of the deeper layers of the primary visual cortex (area V1) evokes saccades into the receptive fields (RFs) of the neurons stimulated. These effects are probably mediated by projections of layer 5 neurons to the superior colliculus (SC) and thence to the brainstem burst generator. What role this projection plays under natural conditions remains to be elucidated (Tehovnik and Slocum 2007).

16.2.10.2 Multi-sensory Integration for Gaze Direction

Directing gaze toward a visible target requires information about retinal image location and relative eye and head positions. In monkeys, →posterior parietal cortex (PPC) neurons combine visual information with information on eye and head position or movement, and somatosensory and vestibular signals (Bremmer 2011; Gottlieb 2002). Hence, PPC neurons might represent target location in an extra-retinal →frame of reference.

In two adjacent cortical fields, area LIP and area 7a, modulation of visual signals is referenced to the body and to the world, respectively. Many neurons in area LIP respond to visual and acoustic signals; the receptive fields occupy the same spatial locations (Gottlieb 2002). Moreover, →area V6A contains neurons that respond to visual stimulation and to the position and movement of the eyes (Nakamura et al. 1999).

16.2.10.3 Internal Monitoring of Eye Movements

Eye movements are often composed of sequences of components. For example, when scanning the visual environment, saccades are sequenced to move from one target to the next, with intermittent fixation periods. For proper planning and execution of any movement component, the controller must keep track of what has happened. It can do so by using sensory information. But since this is influenced by the movement as well as the environment, an internal efference copy of the movement command would be needed for comparison.

For the cerebral cortex to plan a subsequent saccade, it needs corollary information about the command issued for the preceding saccade. A feedback pathway should exist from lower saccadic centers, such as the superior colliculus (SC) or brainstem burst neurons, to cortical centers, such as the FEF. There is evidence for such a pathway from the superior colliculus (SC) via the medio-dorsal thalamus to the FEF (Klier and Angelaki 2008; Sommer and Wurtz 2002, 2008).

16.2.10.4 Remapping and Visual Constancy

The visual world is sampled during short periods of fixation between saccades, during which fixational snapshots are assembled to yield a relatively stable representation of the external world (→spatial constancy, visual constancy or perceptual continuity) that is necessary for both →perception and guidance of eye, head and body movements (Medendorp 2011; Sun and Goldberg 2016; Wurtz 2018). Spatial constancy has two aspects that are required for perceptual continuity across saccades.

First, the perception of the swift retinal image motion during a saccade should be suppressed (saccadic suppression) across the saccade. This perceptual phenomenon is often assumed to result from active suppressive signals that are derived from eye movement commands. However, mechanisms activated by the saccade-induced image shifts themselves could account for a large part of saccadic suppression. Such mechanisms start in the retina, but might extend to higher processing stages (Idrees et al. 2020). To bridge the gap, visual →working memory helps carry the pre-saccadic perceptual contents across the saccade (Aagten-Murphy and Bays 2018; Prime et al. 2011).

Second, the substantial differences in retinal images before and after the saccade should still be interpreted as compatible with a continuous stable world (Higgins and Rayner 2015; Parr and Friston 2017; Rolfs 2015; Wurtz 2018; Zirnsak and Moore 2014).

Visual constancy is thought to be performed by spatial remapping, which implies that neurons shift their receptive field (RF) before or during the saccade to the location the RF will occupy after the saccade. Remapping occurs in the superior colliculus (SC), areas LIP and FEF, and extra-striate visual areas such as area V2, area V3, →area V3A, area V4, and the →parietal reach region (PRR) (Colby 2009; Hall and Colby 2011; Klier and Angelaki 2008; Sun and Goldberg 2016; Wurtz 2008, 2018; Zirnsak and Moore 2014).

A mechanism proposed to underlie remapping is generation of an efference copy of the eye-movement command to compensate for the sensory effects of eye movements. The efference copy is transferred from the superior colliculus (SC) via the medio-dorsal thalamus to the FEF (Sommer and Wurtz 2002; Wurtz 2018). Since monkeys and humans with thalamic lesions sometimes show deficits in spatial remapping, there may be alternative pathways that relay efference copies (Klier and Angelaki 2008; Medendorp 2011; Wurtz et al. 2011). However, it has been argued that the efference copy signal is too small and too slow to be effective (Bridgeman 2010).

Remapping also occurs during smooth pursuit movements and, more generally, during head and body movements (Medendorp 2011).

16.2.11 Saccade Target Selection

Although our richly textured visual world contains many interesting objects, only one at a time can be viewed with the fovea. This requires a selection and decision process about where and when to look, which in turn involves sensory processing, motivational evaluation and cognitive guidance. The selection of a saccade target coincides with the allocation of attention, which is

determined by a network of CNS structures (Glimcher 2003; Schall 2013).

Signal components related to the expected value of eye movements are expressed by neurons in many brain areas: The dorso-lateral prefrontal cortex (DLPFC), supplementary eye fields (SEF), nucleus caudatus, substantia nigra pars reticulata (SNr), and the superior colliculus (SC). The signals are rapidly updated when reward contingencies change, suggesting that the brain continuously evaluates the difference between reward expectation and reward outcome (reward prediction error) and learns from this error to correct its decisions. Neurons in the anterior →cingulate cortex (ACC) and supplementary eye field (SEF) carry signals about reward outcome and oculomotor behavior and may contribute to update reward value signals in parietal and prefrontal cortices. A role in initiating this process could be played by midbrain dopaminergic neurons, which respond to unpredicted events, and might gate the cortical and →limbic inputs to the striatum and thereby facilitate learning (McCoy and Platt 2005).

Targets for movements of eyes, arms and hands appear to be represented in a saliency map of the world, in which objects are enhanced that are immediately relevant to behavior. It receives →bottom-up and →top-down inputs. The former relate to important image features such as brightness, oriented edges, shape, color, motion and depth, the latter being associated with goals and expectations. The saliency map for saccades includes FEF, area 7a and area LIP, the basal ganglia and associated thalamic nuclei, and the superior colliculus (SC) (Goldberg et al. 2006; Gottlieb 2007; Gottlieb et al. 2009; Schall 2013; Veale et al. 2017; White et al. 2017).

In monkeys, target selection in areas 7a and LIP reflects the behavioral context and the monkey ´s motivation to act on an object of interest, based on object saliency, expectation of reward and long-term learned associations. Area LIP neurons may also be involved in decisions related to saccades. The discharge properties of single LIP neurons reflect both the direction of an impending gaze shift and the quality of the sensory information that instructs such a response (Shadlen and Newsome 2001; Gottlieb et al. 2009; McCoy and Platt 2005).

Target discrimination and selection in the FEF probably result from concurrent processing in the network of cortical areas. It occurs independently of when or even whether the saccade actually happens, so it is not linked to saccade programming (Schall 2015).

The basal ganglia contribute to selection processes. Saccade target selection depends on the target´s value or potential reward, which can vary flexibly on a short-term basis or more stably on a long-term basis (Hikosaka et al. 2018; Tatler et al. 2011). The flexible and stable values of visual objects appear to be processed separately by the head and tail of the caudate nucleus, respectively. The latter appears to select `good´ objects via the direct pathway, which enables saccades to them, and `bad´ objects via the indirect pathway, which suppresses saccades. Both pathways connect in parallel through different parts of the substantia nigra to the superior colliculus (Hikosaka et al. 2018). In part, target selection is based on stimulus-reward associations learned by →classical conditioning (Gottlieb et al. 2014).

The superior colliculus (SC) contributes to selecting a saccade target, in retinotopic coordinates, and initiating a movement with an appropriate initial direction and speed. This selection is influenced by attention, since SC neurons discharge when attention shifts toward spatially precise cues (Basso and May 2017; Krauzlis 2005; Optican 2005).

16.2.12 Saccade Adaptation

Growth, ageing, disease or injury may lead to changes in saccadic metrics. To keep saccades accurate, continuous adjustments must be made to saccadic gain (Dash and Thier 2014; Iwamoto and Kaku 2010; Scudder 2009c).

16.2.12.1 Characteristics of Saccade Adaptation

When saccades consistently miss their targets, their gain adapts to the new situation so as to hit the target again. Initial target misses can be induced experimentally by weakening eye muscles or moving the target while a saccade is underway. Changes in saccadic gain occur within 50-100 trials in humans and about 1,000 in monkeys (Soetedjo et al. 2019), the reason for the difference being unknown. The adaptive rate and magnitude vary widely within and across individuals.

There are two forms of adaptation with different time courses and different underlying mechanisms: short-term adaptation that develops within a few hours, and long-term adaptation which takes days. Short-term adaptation may rely on at least two memory systems of different temporal extent; seconds vs. minutes. Presumably, movement errors are first corrected by the short-term process and then gradually completed by the long-term process. Saccadic gain adaptation is relatively specific to step amplitude and direction and does not produce parametric changes in all saccades (Hopp and Fuchs 2002, 2004; Iwamoto and Kaku 2010; Robinson et al. 2006; Scudder 2009c; Straube et al. 1997). Adaptation of voluntary saccades, but not reflexive saccades (express saccades), also transfers to hand pointing movements; that is, when saccade amplitude is adaptively reduced, so is hand movement amplitude (Cotti et al. 2007).

16.2.12.2 Sites of Saccade Adaptation

Evidence indicates that the plastic sites for saccade adaptation lie downstream of the superior colliculus (SC) because the saccade-related activity of SC neurons does not change with adaptive increases or decreases in saccade size but is more related to the vector of the visual target, which does not change during adaptation (Soetedjo et al. 2019).

Saccade adaptation downstream of the SC depends on several plasticity mechanisms at different sites (Dash and Thier 2014). Different mechanisms likely underlie adaptation of voluntary vs. strongly reflexive saccades, inceasing vs. decreasing gain, short-term vs. long-term adaptation, and head-restrained saccades vs. head-unrestrained gaze shifts (Iwamoto and Kaku 2010).

Pharmacological manipulation of the oculomotor vermis (OMV: lobules VIc and VII) impairs the adaptation of saccade size. Moreover, the net saccade-related Purkinje-cell simple-spike (SS) activity is correlated with the adaptive changes. These results suggest that the OMV is a crucial site of plasticity for saccade adaptation. As Purkinje cells directly inhibit neurons in the caudal fastigial nucleus (CFN), the latter´s firing characteristics also change during saccade adaptation (Soetedjo et al. 2019).

In head-unrestrained gaze movements, adaptation appears to occur at sites upstream to where motor commands are split into commands controlling eye and head movements (Iwamoto and Kaku 2010). It appears that amplitude and directional adaptation occurs in separate places. Strongly reactive saccades to suddenly appearing salient visual stimuli are likely modified in the oculomotor vermis, fastigial nucleus and associated downstream structures, including the superior colliculus (SC) and the brainstem burst generator (Cotti et al. 2007).

16.2.12.3 Instructive Signals Guiding Saccade Adaptation

Saccadic gain changes must be guided by an instructive error signal. In most cases, the error signal originates from visual information about movement error. Proprioceptive input from extraocular muscles may also contribute to adaptation, but only in dis-conjugate saccades (Iwamoto and Kaku 2010).

When a target is stepped back during an initial saccade, the most efficient temporal window in reducing the gain is 80-100 ms after the end of the primary saccade. This and other evidence suggests that the instructive signal driving adaptation should be the visual error within the first 100 ms after the primary saccade (Scudder 2009c).

The adaptive changes in saccade-related Purkinje-cell simple-spike (SS) activity are driven by →climbing fibers which elicit complex spikes whose probability of occurrence, latency and shape reflect the motor error (and its amplitude) between the actual and desired saccade size (Herzfeld et al. 2018). The climbing fibers originate in that part of the →inferior olive (IO) that receives projections from the superior colliculus (SC). Incapacitating the SC prevents saccade adaptation. The SC therefore delivers the initial command that generates a saccade as well as the error signal that ensures that saccades remain accurate (Soetedjo et al. 2019).

16.2.13 Saccades, Vergence and Accommodation

Saccades in depth must be associated with changes in vergence and lens accommodation (Smith 2009). The coordination of the three reactions (`near trias´) is complicated by the fact that they are executed by different →plants and final common pathways. The →oculomotor plant executing saccades and vergence consists of the eyeball, the extraocular muscles, and the other tissues that are attached to it. The accommodation plant consists of the lens and ciliary muscles acting on it. The coordination of the near trias must occur at central sites upstream of the structures organizing saccades, vergence and accommodation.

16.2.13.1 Saccade-Vergence Interactions

Saccades and vergence interact. Vergence movements, usually slower than saccades, are accelerated by horizontal and vertical saccades, and horizontal saccades of the two eyes are of unequal size when occurring during vergence movements. The precise mechanisms are still not resolved (Mays 2009c).

Part of the interactions occur at motoneuronal and pre-motoneuronal levels. Most motoneurons show the same burst-tonic discharge pattern during saccadic and vergence eye movements, and the discharge of many saccade-related premotor neurons is also related to vergence. There exist some specifically vergence-related neurons in the mesencephalic reticular formation (MRF) (Coubard 2013).

When a visually guided combined saccade-vergence movement is perturbed by electrical micro-stimulation in the monkey superior colliculus (SC), the timing and the metric specification of both saccades and vergence are affected, such that the resulting movement is a weighted average (Chaturvedi and van Gisbergen 1999). This suggests that saccade-vergence interactions could occur at the level of the SC requiring, however, that a vergence signal is also encoded there.

16.2.13.2 Saccade-Accommodation Interactions

Separate plants and final common pathways execute saccades and accommodation, hence these effects must be coordinated at central sites. Among them are the superior colliculus (SC) that represents both accommodation and saccades, the vestibular nuclei that project to regions near the oculomotor nuclei, and interactions between omnipause neurons (OPNs) and →near-response neurons (below) of the →mesencephalic reticular formation (MRF) (Schor et al. 1999).

16.2.13.3 Vergence-Accommodation Interactions

Control Mode. Vergence has traditionally been considered a →closed-loop response to visual →binocular disparity (Mays 2009a). However, a recent `dual-mode´ theory holds that the initial response component is not controlled by visual feedback, but is triggered in an →open-loop mode by rapidly moving targets. Only the later, slow component uses disparity-driven visual feedback, tracks slowly moving targets and corrects for vergence errors of the initial component (Munoz et al. 1999). Accommodation is driven by optic blur caused by a mismatch between the distance of the object of interest and the refractory power of the lens (Mays 2009a).

Control System. Accommodation and vergence are coupled, although with some flexibility. Disparity-driven convergence can trigger accommodation, and vice versa, while blur-driven accommodation can elicit convergence (Mays 2009a; Mays and Gamlin 1995; Gamlin 1999). The control regions for vergence and accommodation include →preganglionic →parasympathetic neurons near the oculomotor nucleus (III) in the midbrain, neurons near to the oculomotor nucleus (III) and →pretectum, deep cerebellar and pontine reticular neurons, and cerebral cortex neurons.

Edinger-Westphal Neurons. Preganglionic parasympathetic neurons in Edinger-Westphal nucleus produce the accommodation component of the near trias. These cells exhibit a spontaneous firing rate, increase their rate linearly with accommodation and have a dynamic component related to accommodation velocity (Gamlin 1999).

Near-response Neurons are located dorsal and lateral to the oculomotor nucleus (III) and in a region in the pretectum (Mays 2009b). The behavior of some cells is related to vergence, that of others to accommodation, while the majority are involved in both behaviors. Many of these

neurons appear to project to the medial rectus (ML) area of the oculomotor nucleus (III) and also innervate Edinger-Westphal neurons (Mays and Gamlin 1995; Gamlin 1999; Mays 2009b).

Deep Cerebellar Nucleus Neurons. Discharge of tonically active neurons in the interposed nucleus decreases during the near-response. Many of these cells change their firing rate during both vergence and accommodation. Micro-stimulation in the interpositus region produces divergence and decreases accommodation. Interpositus neurons could also be involved in control of the far-response via its projection to the midbrain near-region (Gamlin 1999). Some cells in the posterior interpositus nucleus respond during divergence and accommodation, but not saccades (Robinson and Fuchs 2001).

Nucleus Reticularis Tegmenti Pontis (NRTP) Neurons. Inputs to cerebellar interpositus neurons could originate in nucleus reticularis tegmenti pontis (NRTP) and should thus show related activity. Some NRTP cells with a tonic discharge transiently increase their firing rate during the near-response as well as during the far-response (Gamlin 1999).

Cerebral Cortex. The NRTP receives inputs from the frontal eye field (FEF) region. In rhesus monkeys, a region immediately anterior to the saccade-related FEF region is involved in vergence and accommodation (Gamlin and Yoon 2000). Moreover, area LIP neurons transmit depth-related information to the superior colliculus (SC) (Gnadt and Beyer 1998).

16.3 Smooth Pursuit Eye Movements

Smooth pursuit eye movements in primates commonly track a small object as it moves across a patterned background. The goal is to keep the retinal target image on the high-acuity fovea by matching gaze velocity to target velocity. Since tracking errors occur, correction saccades (catch-up saccades) are used to realign target and gaze (Barnes 2008; Lisberger 2010; Ramat et al. 2007). Humans are able to also track somatosensory, acoustic and imaginary targets, but at a lower gain than visual targets (Ilg 1997). Emphasis is put on smooth pursuit of visual stimuli.

Smooth pursuit of visual stimuli involves several sub-processes that facilitate the detection of moving targets and their pursuit under various conditions. In particular, ocular tracking requires visual attention, the visual selection and motor selection of the moving target, which may not always be strictly coupled. Visual and motor selection can be spatially decoupled when pursuit is initially performed under open-loop forward control (below) (Souto and Kerzel 2021). These processes may vary between tracking unpredictable and predictable target motions (Barnes 2008; Fiehler et al. 2019; Fukushima et al. 2006; Spering and Gegenfurtner 2008).

Tracking of Unpredictable Target Motion. An unpredictable motion stimulus consists, for example, of a target step in one direction followed by steady motion in the opposite direction. Otherwise, target velocity may be changed during the motion (Robinson and Fuchs 2001). These prototypes are well suited to study the initiation of pursuit and the influence of visual inputs. There are other tracking signals, for example those constructed by superimposing several sinusoidal signals at non-harmonic frequencies (Barnes 2008).

Tracking of Predictable Target Motion. The use of repetitive time-varying motion stimuli permits the study of how and to what extent the pursuit system employs prediction to track a target (Barnes 2008). This paradigm is more akin to the natural situation in which an observer usually tracks targets whose dynamics he/she is familiar with and whose motion can therefore be predicted with some confidence (Lappi 2016).

16.3.1 Smooth Pursuit Control Modes

The smooth pursuit system uses diverse control modes that operate during different movement phases and under different conditions (Barnes 2008; Lisberger 2010): Open-loop forward control serves to rapidly track a target. Closed-loop →negative feedback adjusts for differences between target and eye velocities. Smooth pursuit also involves higher-order signal perception (Ilg 1997; Krauzlis and Stone 1999), velocity memory that originates in the retina (Murdison et al. 2013) and →velocity storage (Barnes 2008; Lisberger 2010). Smooth pursuit continues even when the target is momentarily occluded, which indicates that it can be driven by predictive mechanisms based on spatial memory (Lappi 2016).

16.3.2 Cortical Control of Smooth Pursuit

The posterior parietal cortex (PPC), →frontal cortex and supplementary eye fields (SEF) play prominent roles in the control of smooth visual pursuit (Ilg and Thier 2008; Voogd et al. 2012) that are essential for the analysis of →visual motion and target direction.

16.3.2.1 Role of the Posterior Parietal Cortex in Control of Smooth Pursuit

Areas MT/V5 and MST are concerned with the analysis of visual motion. Stimulation and lesions of areas MT and MST affect both motion perception and smooth pursuit in a direction-specific manner (Lisberger et al. 1987; Ilg 1997; Krauzlis and Stone 1999). Area MT/V5 has a retinotopic organization. Neurons in this area contribute to the initiation of pursuit by providing an estimate of target direction and speed (Lisberger 2010). The activity of visual-tracking neurons in lateral area MST (area MSTl) is correlated with retinal image slip, slow eye movements and slow head movements and are thought to encode the target direction in space.

Pursuit-related neurons in the dorsal MST (area MSTd) start firing more than 50 ms after pursuit onset and might have a role in eliminating eye-movement-induced optic flow components, thus facilitating the determination of heading direction (Ilg and Thier 2008). Neurons in area MSTd are tuned to focus on expansion of optic flow and encode it in an →eye-centered (gaze-centered) frame of reference during fixation and pursuit (Lee et al. 2011).

Stimulation of area LIP in the PPC can evoke smooth pursuit movements. Area LIP activity is modulated by eye-position and other →extra-retinal signals. Both area LIP and →area VIP contain directionally sensitive neurons that respond during pursuit. Area VIP cell responses resemble those in area MST (Bremmer 2011). Many cells in area 7 are active during fixation,

smooth pursuit, saccades, and visually directed hand movements. In addition, the →inferior parietal lobule (IPL) plays roles in visuo-spatial integration, orientation, and oculomotor control. An important feature of these cells is multi-sensory integration (Ilg 1997; Krauzlis 2005; Krauzlis and Stone 1999).

16.3.2.2 Pursuit-related Eye Fields in the Frontal Lobe

Frontal Pursuit Area (FPA). The FPA is reciprocally connected with areas MT, MST, LIP and VIP, and receives inputs in monkeys from thalamic nuclei that are targets of projections from the basal ganglia and cerebellum. FPA lesions or other methods of inactivation reduce the gain and eliminate the predictive component of pursuit, whereas stimulation evokes smooth pursuit movements and changes the gain of pursuit responses to new visual motion stimuli (Krauzlis 2005).

Pursuit neurons in FPA are tuned for every possible direction of movement, and code parameters such as eye velocity, gaze velocity, retinal image motion for target velocity. They are also involved in movement prediction (Fukushima 2003; Fukushima et al. 2006). During the course of pursuit, different neurons discharge within different time windows, such that the entire populations covers the whole movement time (Lisberger 2010).

Supplementary Eye Field (SEF). The majority of pursuit neurons in the SEF (Schall 2015) do not encode pursuit parameters or gaze velocity, and eye velocity coding is specific for task conditions (Fukushima et al. 2006). The largest activity changes occur when the target motion changes, especially with predictable timing (Krauzlis 2005).

16.3.3 Role of the Basal Ganglia in Control of Smooth Pursuit

Anatomical and physiological findings suggest that smooth pursuit may be regulated by signals through basal ganglia-thalamo-cortical pathways. The basal ganglia receive strong projections from the frontal pursuit area (FPA) (Lisberger 2010). When monkeys perform smooth pursuit movements, a subset of neurons in GPe and GPi modulate their firing (Yoshida and Tanaka 2009). The SNr appears to permit smooth pursuit by disinhibiting wanted and inhibiting non-wanted movements (Basso et al. 2005). Many neurons in the ventro-lateral thalamus discharge before or during the initiation of pursuit, the firing rate being proportional to the speed of target motion in a preferred direction. When the target is briefly extinguished during the maintenance of pursuit, the neurons continue firing, indicating that they carry extra-retinal, eye movement-related signals (Tanaka 2005).

16.3.4 Role of the Cerebellum in Control of Smooth Pursuit

The cerebellum has short-and long-term adaptive functions in smooth pursuit that support accuracy and adaptation of eye movements (Dash and Thier 2014; Ilg and Thier 2008; Krauzlis 2005). Neuronal recording suggests that the cerebellum is concerned with two important issues, namely spatial transformation and dynamic prediction.

16.3.4.1 Spatial Transformation

As in ocular following responses (OFRs), a spatial transformation takes place between floccular mossy-fiber inputs and Purkinje cell firing. Mossy-fiber inputs exhibit broad directional tuning curves with preferred directions in all four cardinal (horizontal and vertical) directions. Simple-spike (SS) discharge of Purkinje cells, on the other hand, is modulated most strongly during either horizontal (mostly ipsiversive) or vertical (mostly downward and slightly contraversive) pursuit. The preferred directions of Purkinje cells are well aligned with the principal axes of the →coordinate system, defined by the anterior and horizontal semicircular canals and by the pulling directions of eye muscles (Lisberger 2010; Robinson and Fuchs 2001).

16.3.4.2 Dynamic Prediction

Most floccular Purkinje cells fire a burst in the preferred pursuit direction during the initial acceleration phase, and a lower sustained discharge during the subsequent steady tracking phase (Lisberger 2010). The initial transient component probably results from visual inputs, seems to drive the initial acceleration of pursuit and is converted into a subsequent sustained eye-velocity-related signal via a positive feedback loop through the vestibular nuclei and nucleus praepositus hypoglossi (NPH). The floccular output targets brainstem networks that have adapted to take into account the dynamics of the oculomotor plant, and thus is itself predictive (Lisberger 2009). Purkinje cell responses are dominated by position and velocity components. Purkinje cell discharges carry a position component that could contribute to gaze holding (Lisberger 2010).

16.3.5 Role of the Colliculus Superior in Control of Smooth Pursuit

Although the SC has traditionally been regarded as a structure primarily involved in the organization of saccades (Walton et al. 2009b), its rostral part representing the central visual field is also concerned with smooth pursuit. Activation or inactivation of the SC changes the metrics of pursuit. Activity patterns of neurons in rostral intermediate and deep SC layers show complicated discharge patterns, suggesting that they are related to the location of the tracked target within the neurons' retinotopically organized response fields.

It appears that the distribution of activity across the SC is a real-time estimate of the retinal location of the eye for fixation, pursuit and saccades (Krauzlis 2005).

16.3.6 Role of the Brainstem in Control of Smooth Pursuit

The brainstem contains a diverse and complicated system of interconnected cell groups that enable coordination of pursuit and saccades (Krauzlis 2005).

Burst Generators. The paramedian pontine reticular formation (PPFR), rostral interstitial nucleus of the medial longitudinal fascicle (riMLF) and central mesencephalic reticular formation (cMFR) (Waitzman 2009) receive inputs from the frontal pursuit area (FPA). Subsets of neurons in these nuclei discharge only in relation to saccades, while others fire with pursuit and saccades. About half of the omnipause neurons (OPNs) decrease their firing rate during

pursuit in addition to pausing during saccades, so that they appear to modulate pursuit gain by inhibiting pursuit neurons in NPH and MVN (Krauzlis 2005).

Nucleus Praepositus Hypoglossi (NPH). This nucleus also receives projections from the FEF. NPH neurons discharge preferentially during ipsiversive horizontal pursuit. Their response patterns are similar to those of abducens motoneurons, which receive inputs from NPH and the medial vestibular nucleus (MVN) (Ilg 1997).

16.3.7 Smooth Vergence

Smooth vergence often accompanies other target-oriented smooth eye movements and can thus be regarded as a form of smooth pursuit (Fukushima 2003; Krauzlis and Stone 1999). Motion- and disparity-related cortical areas, in particular areas MT/V5 and MST, contribute to encoding vergence eye movements. Most neurons respond only during fronto-parallel pursuit or during vergence pursuit (Fukushima 2003).

The direction, magnitude and time course of the initial vergence velocity all appear to be encoded in the population activity of disparity-sensitive area MST neurons. This activity occurs early enough to contribute to vergence at short latency (Takemura et al. 2001).

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17

Skeletal Muscle: Anatomy, Action and Contractile Mechanisms

CONTENTS

Abstract

• The macroscopic functions of skeletal muscles, the microscopic mechanisms underlying contractility, and muscle fatigue are herein described.

• Skeletal muscles serve various macrocospic functions as motors, brakes, springs and struts. Bones, joints and ligaments restrain their movement ranges. Muscles exert complex actions at individual joints and across multiple joints. Conversely, several muscles often operate an individual joint.

• The microscopic anatomy and function of skeletal muscles are dominated by an intricate cooperation of proteins, particularly actin and myosin. The activation of this machinery by motor axon action potentials involves a chain of events referred to as excitation-contraction coupling (ECC).

• The peripheral mechanisms contributing to muscle fatigue are manifold and include changes in muscle metabolism and disturbances in excitation-contraction coupling (ECC).

17.1 Introduction

Motility is a widespread biological phenomenon that reaches its highest manifestation in the specialized tissue of →skeletal muscle. In humans, skeletal muscle comprises ca. 40% and 30% of body weight in men and women, respectively, and contains about 50-75% of all body proteins, attesting to its biological importance. It is thus extraordinarily involved in metabolism, →energy production and consumption, and thermogenesis (Csapo et al. 2020; Frontera and Ochalka 2015). Moreover, skeletal muscle synthesizes and secretes myokines, one of several hundred →cytokines or other small proteins (~5–20 kDa) and proteoglycan peptides that are produced and released by muscle cells (myocytes) in response to muscular contractions. Myokines subsequently exert auto-, para- and/or endocrine effects Thus, skeletal muscle can be classified as an endocrine organ as well (Das et al. 2019; Giudice and Taylor 2017; Iizuka et al. 2014; Delezie and Handschin 2018).

Skeletal muscle is the major executive arm of the nervous system, primarily in regard to motor activities (Heckman et al. 2009). But it also serves to express higher functions of the brain, of which we would have no knowledge if they were not communicated by muscles. Among these are `mental´ activities expressed by speech, song, and cries, by writing, gestures and facial expressions.

Skeletal muscles stabilize and move the skeleton in a highly orchestrated manner. They act conjointly with bones, joints, ligaments, tendons and aponeuroses to generate force and movement, maintain →balance and posture and resist →gravitational force. Skeletal muscle is a heterogeneous tissue, containing contractile and metabolic proteins along with elements of the excitation-contraction coupling (ECC) process, and is characterized by the ability to adjust size and functional properties in response to endogenous and exogenous influences.

In moving animals, many variables that determine muscle functions may change concurrently, such as the timing and →intensity of neural activation, muscle length and velocity of length change, as well as intrinsically generated and externally imposed forces (Biewener 2016; Huijing 1998). Under these conditions, muscles may exert various functions, including motor or braking actions, or acting as springs or struts (Dickenson et al. 2000).

Motors. In this function, muscles generate force while shortening, and thus produce positive →power. For example, the large pectoralis muscles of a bird generate considerable power during flight.

Brakes. Muscles may act as brakes. For example, because of large imposed strains, a leg extensor muscle of the cockroach, although capable of power production, actually acts as a brake during running, which slows the swing of the leg.

Springs. Muscles may transmit forces generated by others. For instance, in fish that generate most of their hydrodynamic forces with their tail fin, the power generated by anterior muscles is transmitted to the fin in part through the stiffening action of more posterior muscles. Also, some muscles of flies generate little or no mechanical power; yet they act as controllable springs to direct the forces of much larger power muscles, thus providing the means by which the nervous system can rapidly alter wing kinematics.

Struts. Under some conditions, muscles may work as struts. For example, in locomoting animals, →muscle fibers may be nearly isometric or even shorten under some conditions, while the tendon stretches. Under these conditions, muscles act as struts, permitting the →elastic tendons to store and release energy.

In summary, skeletal muscle is a multi-functional organ, not simply a contractile machine. The sections that follow focus on the properties and functions of supporting structures that act in cooperation with skeletal muscle, in particular bony and cartilaginous skeletons that stabilize body parts and the joints between skeletal structures. In addition, the actions of skeletal muscle and its contractile mechanisms, and mechanisms of →muscle fatigue will be dealt with.

17.2 Skeleto-muscular Determination of Movement Range

At a macroscopic level, skeletal and muscular elements both restrict as well as allow movements. As will be illustrated below, bones, joints, tendons, aponeuroses, ligaments and muscles, by restricting movement in various directions, impart mechanical advantage and efficiency of movement.

17.2.1 Bones, Joints and Ligaments

Bones, cartilages, articulation elements, capsules and ligaments co-determine and constrain the directions and ranges of movements (Alexander 1981; Matyas 2009). Joints that provide maximum motion in three dimensions include the ball-and-socket joint of the human hip, the shoulder joints and the eye. Less freedom is provided by saddle joints, such as the carpometacarpal joint of the thumb, which permit movements in all directions except axial rotation. Another restrictive type is the hinge joint, such as the elbow or the knee, which allows motion in only one plane (Alexander 1981). Cartilaginous rims, disks, joint capsules, ligaments of various sorts and muscle tendons further restrain movements.

Ergometrically, locking joints in some positions by ligaments can maximize power and efficiency by saving energy. The human knee exemplifies this principle. When humans stand upright, the center of gravity (COG) of body parts above the knees is situated anterior to the knees, which are thus kept extended without the need of quadriceps muscle activation (Alexander 1981).

17.2.2 Muscles and Tendons

Interactions between muscles and skeletal elements are complex and variable.

Dependence of Muscle Force on its Length. The contractile force produced by a muscle depends on its length, implying that it can move a joint efficiently only over a limited joint angle (Alexander 1981; Sandercock 2009a).

Musculo-tendon Architecture. Muscle fibers may be arranged more or less in parallel or in pennate patterns, which change during movement. The efficiency and direction of force transmission are determined by a muscle´s attachment to bones, the attachment locations, the course of tendons (possibly with pulleys and retinacular constraints), distribution of moment arms, and may vary depending on body posture and movement. Large moment arms or pennate architecture with short fascicles and long aponeuroses tend to increase the velocities of fascicular and cross-bridge motion for a given joint angle velocity, thereby reducing power output. Many muscles share common tendons, thus exerting →interaction forces among each other (Tsianos and Loeb 2017). Most skeletal muscles are composed of muscle fibers of different biochemical, histological and physiological characteristics, which underlie different neural control (Burke 1981, 2009).

Distributed Linkages by Extended Muscles/Tendons. The origins and insertions of a muscle may spread extensively across bones and other structures, such as subcutaneous bands of collagenous connective tissue, thereby reducing their relative mobility. Myofascial force transmissions are complex. Many muscles have distributed tendons, with variable moment arms across the insertion. Muscular forces can be transmitted at a distance through fasciae, albeit to different extents (Nichols 2018).

In-series Arrangement of Muscle Fibers. There is another architectural feature of skeletal muscle that imposes constraints (Roy and Edgerton 2009). The muscle fibers that comprise gross skeletal muscle are often shorter than the distance between tendons of origin and insertion. This implies that a muscle fiber must `cooperate´ with others by parallel or in-series junctions that connect them, so that tension is transmitted to a tendon or to layers of flat tendons (Loeb et al. 1987; Purslow 2020; Sheard et al. 2002). To efficiently transmit much of the force produced by any active muscle fiber to the tendon, the series compliance, or →stiffness, should be low. The compliance depends critically on the contractile state of the in-series muscle fibers. If these in-series fibers are slack and compliant, force transmission is weak. But if the in-series fibers contract, they are stiff and force transmission is strong. Thus, in order to avoid absorption of force by series-elasticity of non-active fibers, in-series muscle fibers should be activated simultaneously. However, this does not always happen (Sheard et al. 2002).

Muscle and Tendon Elasticity. Muscles resist extension, both when passive and during contraction, due to the actions of intra-muscle connective tissue, tendons and aponeuroses in series with muscle fibers (Purslow 2020). Proximal muscles of the limbs have long, parallel muscle fibers and short, if any, tendons, while the distal limb muscles have short, pennate muscle fibers and long tendons.

Tendons are much less extendable than passive muscles; but during movements like walking, tendons (and aponeuroses) may lengthen, thereby storing elastic energy and releasing it during shortening. Tendons also influence muscle speed, force and power (Alexander 1981; Biewener 2016; Magnusson et al. 2008; Raiteri 2018; Roberts 2016; Sandercock 2009b).

Advantages of Muscle/Tendon Elasticity. The elastic properties of muscles and in particular tendons also convey advantages in enabling storage and retrieval of energy (Biewener 2016; Roberts 2016; Sandercock 2009b; Zajac 1989). In very rapid movements,

elasticity can store the work of muscle contraction slowly and release it rapidly. When energy must be dissipated rapidly, such as in landing from a jump, energy stored rapidly in elastic elements can be released more slowly to stretch muscle contractile elements. Many intra-muscular structures have spring-like properties. Actomyosin cross-bridges, actin and myosin filaments, titin, and connective tissue all have the potential to store and recover elastic energy during muscle contraction. Yet, the primary elasticity resides in in-series

tendons (Roberts 2016). This is conspicuously demonstrated by hopping kangaroos that are particularly good at utilizing the →potential energy stored in their Achilles tendons during landing and taking the next leap (Baudinette 1994).

17.3 Expanding Degrees of Freedom

Muscles and their tendons expand freedom of movement. This allows them to serve multiple functions, move joints in multiple directions and work conjointly with several muscles and joints.

17.3.1 Muscle Multi-functionality

Many macroscopically defined skeletal muscles exert more than one function, either at a single joint with more than one →degree of freedom (DOF) or by spanning more than one joint. In other words, there are multiple ways for humans or animals to perform a movement in order to achieve a goal.

17.3.1.1 Complex Muscle Actions at Individual Joints

Even major hindlimb joints move in more than one direction. For example, muscles acting across the cat ankle joint exert significant →torques in flexion/extension, abduction/adduction and eversion/inversion directions (Lawrence III et al. 1993; Nichols 2018; Young et al. 1993). The three DOFs are controlled by several multi-functional muscles. Different torque directions are possible because different →reflexes activate ankle muscles. Activation of the medial gastrocnemius muscle, which contributes a substantial abductor torque, turns the body to the contralateral side, both abduction and plantar flexion initially being involved in this manoeuver (Nichols et al. 1993). During the stance phase of the normal cat step cycle, co-contraction of antagonists, such as that of triceps surae, tibialis posterior, peroneus longus and peroneus brevis (Abraham and Loeb 1985) serve to stabilize the ankle joint in the off-sagittal direction and promote movement trajectory in the sagittal plane (Lawrence III et al. 1993). Since different reflexes activate these muscles differentially, they also exert different torques on the knee in addition to the flexion torque (Bonasera et al. 1995).

17.3.1.2 Complex Muscle Actions at Multiple Joints

The majority of skeletal muscles crosses more than one joint. Multi-articular muscles are often quite long, undergo large length changes during natural movements, and consist of many short fibers interdigitated in series. Axial muscles often span many joints and are composed of muscle compartments arranged in series and/or in parallel (Loeb and Richmond 1994). Obviously, the capacity of such muscles to cause motion at one joint depends on the posture of all of the joints that they cross (Tsianos and Loeb 2017). An individual skeletal muscle may also influence remote joints through fasciae and →inertial coupling, these actions frequently being based on a complex internal architecture (Loeb and Richmond 1994; Nichols 2018). As examples, the head of the human biceps brachii acts on on shoulder and elbow joints, and the gastrocnemius muscle acts on both the knee and the ankle joints in complex multi-dimensional ways. Also, the →hamstring muscles of cats connect to the calcaneus through thickened portions of the crural fascia. Together with the tendons of origin and insertion, these structures transmit forces that lead to torques at the hip, knee and ankle joints with directions optimal for enabling the animal to leap at its prey (van Ingen Schenau 1994).

17.3.2 Joint Operation by Several Muscles

An individual joint is usually spanned by more than one muscle. For example, hip extension involves the adductor femoris and hamstring muscles, and ankle extension involves the soleus, the two heads of gastrocnemius, the plantaris and deep flexors. An extreme example is provided by the human head, which has only three DOFs relative to the trunk, but is operated by 23 muscles on either side of the vertebral skeleton (Sherk and Parke 1983).

Activation of the different muscles appears to be geared towards particular motor tasks. For example, the mono-functional brachialis muscle is active in any elbow flexion, but the bi-functional biceps brachii muscle is active during flexion only with the forearm supinated, not when it is pronated. Otherwise, another muscle would have to be activated to counter-act the biceps´s supinator action. This suggests that muscles are selected for action in a way that avoids co-activation of partial antagonists, thereby saving energy (Alexander 1981).

For many movements, mono-articular muscles at one joint can dissipate energy delivered by mono-articular muscles at another. A way around these opposing effects is to mobilize bi-articular muscles. This constellation of muscle activations may avoid or minimize the dissipation of energy, but it requires the co-contraction of partial antagonists in a task-dependent manner (Gielen et al. 1990).

Muscle multi-functionality, while affording advantages, also puts additional demands on neural control. The nervous system must be informed of the muscles´ peripheral actions and interactions, and take them into account when issuing commands for particular movements that depend on tasks and conditions.

17.3.3 Muscle Regionalization

In the →ventral horn of the →spinal cord, the somata of →motoneurons (MNs) innervating a macroscopically defined muscle are assembled in cigar-shaped →motoneuron pools extending in rostro-caudal direction. The location of different MN pools within the spinal cord is →somatotopically related to the location of their muscles in the periphery. This genetically determined →musculotopic map has three dimensions (Dasen 2017). The rostro-caudal location of a pool depends on the body part innervated (forelimb: cervical; trunk: thoracic; hindlimb: lumbar) and on the muscle location within a limb (Romanes 1951; Vanderhorst and Holstege 1997). There is also a transverse order in which dorso-ventral and medio-lateral MN locations are of importance. Thus, the more proximal axial and body-wall muscles are innervated by MNs in the medial (MMC; all spinal levels) and hypaxial (HMC; thoracic levels) MN columns. MNs innervating limb muscles lie in the lateral motor column (LMC) at both cervical and lumbar levels. The more ventrally located LMC MN pools innervate proximal limb muscles, and progressively more dorsal MNs project to more distal limb muscles. These locations co-determine the distribution of various →synaptic inputs to MNs (Dasen 2017; Goetz et al. 2015).

In many cases, the rostro-caudal location of individual MN somata within a pool is somatotopically related to the location of →muscle units within the muscle. Reasons for this relation may be manifold and are not completely elucidated. Many macroscopically defined muscles have heterogeneous internal structures and muscle compartments. Muscle heterogeneity is often expressed in terms of neuromuscular compartments (Chanaud et al. 1991; English et al. 1993; Loeb and Richmond 1994; Roy and Edgerton 2009; Windhorst et al. 1989) consisting of muscle groups and branches of the main muscle nerve that innervate them, sometimes separated by tendinous sheets. Even individual compartments may show heterogeneous distributions of muscle-unit types and activity. These compartments may have different mechanical actions and be activated differentially during various motor actions (Berchtold et al. 2000; Chanaud et al. 1991; de Ruiter 1995; English et al. 1993; Holtermann et al. 2009; Kernell 1998; Pratt et al. 1991; Windhorst et al. 1989).

17.4 Overview of Functional Muscle Anatomy

Muscle Cells (Myocytes). Muscle fibers in skeletal muscles, normally 10-100 μm thick and several centimeters long (Schiaffino and Reggiani 2011), are composed of long myofibrils of typically 1-2 μm diameter.

Muscle Extracellular Matrix (ECM). Muscle fibers are embedded in a surrounding that consists of various collagens, glycoproteins, proteoglycans and elastin. The ECM is important for effective muscle contraction and force transmission, and its texture and roles are affected by physical training and disuse, aging or various diseases (e.g., diabetes). In interaction with other cells, such as fibroblasts or →immune cells, the ECM regulates muscle development, growth and repair (Csapo et al. 2020).

Sarcolemma. The sarcolemma is the cell membrane of the muscle fiber. It consists of a plasma membrane, composed of polysaccharide containing thin collagen fibers. The surface layer of the sarcolemma fuses with a tendon fiber at each end of the muscle fiber.

Myofibrils. Each muscle fiber contains several hundred to several thousand myofibrils. Each myofibril is composed of about 1500 adjacent myosin filaments and about 3000 actin filaments, which, together, are responsible for muscle contractility.

Sarcomeres. The sarcomere, the fundamental contractile unit of skeletal muscle tissue, is defined as the segment between two neighboring Z-lines. Skeletal muscle fibers are striated, resulting from the alignment of sarcomeres. The sarcomere is the smallest contractile unit, usually measuring 2.0-2.5 μm from one Z-line to the next. In addition to many other proteins, sarcomeres contain two types of longitudinally oriented myofilaments: actin and myosin, the major molecular motors for force and power generation (Lin et al. 2017). Actin filaments are fixed at the Z-disk and extend into the two adjacent sarcomeres. The thicker myosin filaments cover the central portion of the sarcomere and are held together by structures appearing as transversal M-line. Where actin filaments are present alone (close to the Z-disk), the sarcomeres are optically **i**sotropic (I band). Overlap of myosin and actin filaments in the central part of each sarcomere gives rise to greater optical density and **a**nisotropy in polarized light (A bands). At normal rest length (2.0-2.5 μm), the sarcomere contains only myosin filaments in its middle portion, giving rise to the H zone (Ehler 2009; Gordon et al. 2000).

Myosin is a molecule of about 160 nm in length, consisting of two peptide chains. Each myosin molecule consists of a tail, a neck and two movable heads that under conditions of rest extend outward at about 90° from the longitudinal axis. The tails of many myosin filaments aggregate in the middle sarcomere region, while the heads protrude outward between the actin filaments to bind at specific binding sites. The myosin molecule contains two ATP-binding sites. The myosin heads contain →ATPase that is activated during contraction and splits →adenosine triphosphate (ATP).

Actin consists of a double-stranded linear assembly of **g**lobular molecules, G-actin, forming **f**ilamentous F-actin. This chain is twisted, with 13-15 actin pairs per full turn of about 750 nm . Polymerized tropomyosin with troponin molecules attached is positioned in both grooves of the actin double-strand.

Tropomyosin and Troponin. Troponin consists of three parts referred to as T, I and C. The T segment connects it to tropomyosin, a long molecule twisted around the actin double-strand.

Cytoskeletal Giant Muscle Proteins. The orderly assembly and stabilization of sarcomeres is maintained by three muscle-specific proteins, nebulin (Chu et al. 2016), obscurin and titin (Gautel and Djinovic-Carugo 2016; Lin et al. 2017). A single molecule of nebulin extends from the pointed ends of the thin filaments of actin and partially inserts into the Z-disks. A titin molecule anchors in the Z-disk and M-band, spanning half the sarcomere. Each of the giant molecules interacts with many different other protein ligands to regulate their activity and localize them at particular sites within or around surrounding sarcomeres. These include proteins that are structural, involved in signaling and the maintenance of

→homeostasis, or associated with intracellular membranes, particularly those comprising compartments of the sarcoplasmic reticulum (SR) (Kontrogianni-Konstantopoulos et al. 2009).

Sarcoplasmic Reticulum (SR). The myofibrils are surrounded by sarcoplasm, which contains the sarcoplasmic reticulum. The function of the SR is to store calcium (Ca^{2+}) ions, until they are released by muscle →action potentials that travel down the T-tubules. This triggers contraction of the muscle, which is terminated when Ca^{2+} is actively pumped back into the sarcoplasmic reticulum (Berchtold et al. 2000).

17.5 Overview of Skeletal Muscle Contraction

Skeletal muscles generate force by contraction of muscle fibers upon excitation by →skeleto-motoneurons. In adults, each skeleto-motoneuron, whose soma is located in the ventral horn of the spinal cord, innervates several to many muscle fibers, the whole complex called →motor unit because it constitutes the smallest unit of motor control. The motoneuron action potential travels down the myelinated motor axon (→action potential propagation) to the motor endplate (MEP) of the →neuromuscular junction (Rich 2009) and liberates →acetylcholine (ACh) from →synaptic vesicles in presynaptic →axon terminals. At the postsynaptic muscle fiber membrane (sarcolemma), ACh docks to →nicotinic acetylcholine receptors (AChRs), enabling current flow through sarcolemmal sodium (Na^+) channels and potassium (K^+) channels. The resulting →depolarization of the muscle-fiber membrane elicits an action potential that runs bi-directionally along the length of the fiber and enters the transverse tubules (T-tubules). Close contact of T-tubules with the sarcoplasmic reticulum (SR) leads to SR depolarization, release of Ca^{2+} and initiates the complex process of skeletal muscle contraction.

17.5.1 Motor Unit Action Potentials and Interference Patterns

It is possible to extracellularly record the action potentials of single muscle fibers. More often, however, intramuscular electrodes are used to record compound action potentials generated by muscle fibers belonging to one motor unit, referred to as the →motor unit action potential: MUAP. These potentials represent the sum of the muscle fibers´ individual action potentials, carried by volume conduction to the electrode tip. This technique provides insight into the normal patterns of motoneuron activity, and is also used to identify neurological disorders. When many motor units are active, the individual MUAPs intermix to yield an interference pattern, representing the successive activation of MSUPs that occurs with increasing strength of voluntary muscle contraction. Another, more integrative technique is to monitor the compound activity of many motor units by percutaneous recording with surface electrodes (surface →electromyography (EMG) (Lowery 2009).

17.5.2 Excitation-contraction Coupling

The chain of events continues with the conversion of sarcolemma depolarization into contraction mediated by Ca^{2+} release, referred to as excitation-contraction coupling (ECC) (Shishmarev 2020; Tupling 2009).

Calcium Release. In normal ECC, the all-or-nothing surface depolarization (muscle fiber action potential) is conducted inward through the branching array of T-tubules, and thus reaches the entire cross-section of the muscle fiber at each sarcomeric level. The T-system is closely associated with the longitudinal sarcoplasmic reticulum (SR), which serves as a large reservoir of Ca^{2+} ions. The T-tubule membrane contains dihydropyridine receptors (DHPRs) (voltage-gated Ca^{2+} channels, CaV1.1), which upon depolarization undergo complex conformational changes that are mechanically conveyed to the ryanodine receptors (RyR1s) in the adjacent SR membrane. This causes RyR1s to open and release large amounts of Ca^{2+} from the SR into the sarcoplasm, where at rest the Ca^{2+} concentration $[Ca^{2+}]_i$ is very low, e.g. 10^{-8} mol/l or less. $[Ca^{2+}]_i$ is kept low by the ATP-driven Na^+-K^+ pump (→Na^+K^+-ATPase), which maintains the sodium (Na^+) and potassium (K^+) ionic gradients, particularly in the T-tubules. The amplitude of the $[Ca^{2+}]_i$ transient depends on the amount of Ca^{2+} released and the intracellular Ca^{2+} buffers, including parvalbumin, →calmodulin (CaM), troponin C, ATP, and the ATP-driven Ca^{2+} pump which pumps the released Ca^{2+} back into the SR and causes relaxation. The liberated Ca^{2+} reaches the myofibrillar parts and initiates the contraction process by acting on troponin (Allen et al. 2008; Berchtold et al. 2000; Endo 2009; Fill and Copello 2002; Franzini-Armstrong and Protasi 1997; Hernández-Ochoa and Schneider 2018; Shishmarev 2020).

There are multiple Ca^{2+} entry and release pathways in skeletal muscle. One is active at negative membrane potentials and requires store depletion: store-operated Ca^{2+} entry (SOCE). The second is activated by membrane depolarization: excitation-coupled Ca^{2+} entry (ECCE). Their operation probably involves ryanodine receptors (RyRs), dihydropyridine receptors (DHPRs), inositol-1,4,5-trisphosphate receptors (IP(3)Rs), →transient receptor potential (TRP) channels, Ca^{2+} sensor proteins, and Orai1 Ca^{2+} permeable channels (Dirksen 2009). Orai1 Ca^{2+}-selective →ion channels are activated upon depletion of internal calcium stores, which is called the `store-operated´ or the `capacitative´ mechanism (Putney 2009).

Sliding Filament Theory. According to the sliding filament theory (Herzog 2009) proposed by H.E. Huxley and Hanson (1954) and A.F. Huxley and Niedergerke (1954), contraction occurs by actin and myosin sliding passed each other, until they touch in the middle of the H-zone or even beyond. Conversely, stretching a muscle involves sliding of I-filaments away from the center of the A-band, and when they stop overlapping with the A-rods altogether, no tension is developed. The sliding filament model ascribes the sliding motion to interactions between the myosin heads and the actin filaments.

Cross-bridge Cycling. At rest, when Ca^{2+} concentration is low, troponin-I inhibits the interaction between myosin heads, actin, ATP and magnesium (Mg^{2+}). When Ca^{2+} is released and binds firmly to troponin-C, the allosteric interactions between troponins I, C, and T, and tropomyosin free the binding sites on actin for the myosin heads. Myosin binds to actin, first weakly and then strongly. This binding induces actin to activate the ATPase, splitting the myosin-bound ATP to adenosine diphosphate (ADP) and phosphor (P_i). Upon release of P_i,

myosin heads reduce their angle from 90° to 45°, thus pulling in the actin filaments (power stroke) (Fitts 2008). These force-producing cross-bridges facilitate the formation of nearby cross-bridges, thus nonlinearly enhancing the process (Gordon et al. 2000). Detachment of the myosin heads from actin requires re-binding of ATP to the myosin heads. With Ca^{2+} still high, a new cycle can then begin. Many such cycles occur during a single muscle activation (→twitch). Shortly after its release, Ca^{2+} begins to be re-sequestered into the sarcoplasmic reticulum by the ATP-driven Ca^{2+} pump.

17.6 Muscle Fatigue

Muscle fatigue is a phenomenon of immense practical importance in both health and disease. In normal individuals, it is of particular importance in physically demanding occupations and in athletic competitions. Muscle fatiguability varies with muscle use, age and sex (Kent-Braun et al. 2012).

Many definitions of fatigue have been proposed. For example, muscle fatigue is evidenced by a decrease in maximal isometric force, shortening velocity, twitch relaxation speed, or power output (Allen et al. 2008; Enoka and Duchateau 2008). The mechanisms contributing to muscle fatigue have not been completely elucidated because of interacting processes occurring at different levels (Kent-Braun et al. 2012).

At the peripheral level, metabolic and physico-chemical changes within and around muscle fibers are primarily involved, including changes in→neuromuscular transmission, sarcolemmal excitability, excitation-contraction coupling (ECC), contractile mechanisms and metabolic energy supply (Bigland-Ritchie 1984; Gandevia 2001).

Peripheral metabolic and physico-chemical changes lead to activation of group III and IV muscle afferents, which cause effects all along the →neuraxis by affecting motoneurons and →interneurons in the →brainstem and →spinal cord and inputs to higher motor centers, thus contributing to what is called central fatigue (→Muscle fatigue, neural factors) (Amann et al. 2015; Taylor et al. 2016).

The relative importance of factors and sites depends on muscle fiber types and composition, state of training and fitness, the intensity, type and duration of muscle activity, muscle temperature, age and sex (Allen et al. 2008; Enoka and Duchateau 2008; Fitts 1994).

Different types of fatigue have been categorized, which depend on the type of muscle affected, the stimulus pattern, type of contractile activity, state of fitness and various neural factors (Allen et al. 2008; Amann et al. 2015; Kent-Braun et al. 2012).

High-frequency Fatigue. Continuous high-frequency muscle activation, generating near-maximal force, typically leads to rapid force decline followed by rapid recovery after stimulation offset. Part of the fatigue is due to occlusion of blood circulation above about 30-50% of maximal force. Fatigue develops more dramatically during dynamic exercise involving shortening contractions than during isometric contractions (Jones 1993).

Repeated Short Tetani produce slower fatigue development that depends on stimulation rate and duty cycle (fraction of time covered by contraction). This stimulation pattern simulates natural repetitive activities like walking, running, cycling, breathing etc. Initially after activity starts, fast →twitch fibers show a rapid decrease in force (phase 1), followed by a relatively constant force (phase 2), that terminates with a rapid decline in force (phase 3) (Allen et al. 2008).

Prolonged Low-frequency Force Depression. Low-frequency fatigue occurs after long-lasting low-frequency tetanic stimulation, after which force remains depressed over long periods, particularly in association with muscle stretch (Kent-Braun et al. 2012).

17.6.1 Metabolic Factors in Muscle Fatigue

When a muscle is maximally activated from rest, its metabolic rate increases dramatically, the increase being specific to animal species, muscle fiber type and form of exercise. The ratio of maximal to basal metabolic rate may vary from approximately 20 in slow mammalian muscle to approximately 500 or more in fast frog muscle (Ball 2015; Westerblad et al. 1991). The metabolic changes alter intra- and extracellular metabolite and ion concentrations that can influence muscle fiber function (Debold et al. 2016). Factors influencing these changes include the type of experimental preparation, pattern of fatiguing stimulation, type of muscle fiber, aerobic versus anaerobic conditions (with and without oxygen), and isometric vs. shortening contractions (Allen et al. 2008; Jones 2010; Lännergren et al. 1993).

Intracellular ATP Concentration is low and kept fairly constant by resynthesis from creatine phosphate (CrP), →glycogen and fatty acids (Ball 2015). ATP concentration falls late in fatiguing muscle because initially it is reconstituted by CrP. Fast muscles consume ATP, producing ADP and P_i much faster than regenerating it. The late decline in [ATP] (and concomitantly in [CrP]) can reduce Ca^{2+} pumping back into the sarcoplasmic reticulum, resulting in augmented resting $[Ca^{2+}]_i$. Transient increases in $[ADP]_i$ appear to be involved in reducing the maximal shortening velocity and in slowing relaxation (Allen et al. 2008).

Creatine and Inorganic Phosphate P_i Concentrations ([Cr] and $[P_i]$ increase early as a consequence of increased CrP breakdown. Whereas [Cr] does not appear to play a significant role in fatigue, the increase in $[P_i]$ is a major contributor. $[P_i]$ concentration can significantly and rapidly increase during intense fatigue, decreasing Ca^{2+} release from the sarcoplasmic reticulum, Ca^{2+} sensitivity of the myofibrils, and myofibrillar force production by a direct action on cross-bridge function, and may thus contribute to slow the rate of muscle relaxation (Allen and Trajanovska 2012; Fitts 2008).

Glycogenolysis. Glycogen is rapidly depleted during intense exercise by anaerobic →glycolysis and more slowly in aerobic exercise. Glycogen depletion may decrease Ca^{2+} release from the sarcoplasmic reticulum by unknown mechanisms (Allen et al. 2008; Cheng et al. 2018; Ørtenblad et al. 2013).

Anaerobic Glycolysis is turned on rapidly and leads to breakdown of glucose into lactate and protons (H^+), i.e., early →acidosis. A significant decrease in intracellular pH can reduce the Ca^{2+} sensitivity of the myofibrils, the number of high-force cross-bridges in fast muscle fibers and the force per cross-bridge in fast and slow fibers (Fitts 2008).

Metabolization of Pyruvate to Lactic Acid. Insufficient muscle oxygenation, for example during strong muscle contractions that occlude blood flow, promote anaerobic glycolysis. Consequently, pyruvate is metabolized to lactic acid, leading to intra- and extracellular acidosis.

Production of Reactive Oxygen Species and Reactive Nitrogen Species (ROS/RNS), such as peroxides, superoxide, hydroxyl radical, singlet oxygen, and →nitric oxide, peroxynitrite, increases with muscle activity and may exert various influences on myofibrillar proteins, impair sarcoplasmic Ca^{2+} release, depress myofibrillar Ca^{2+} sensitivity, and depress Na^+-K^+ pump activity leading to skeletal muscle fatigue (Allen et al. 2008; Cheng et al. 2016; Debold 2015; Fitts 2008; Powers and Jackson 2008; McKenna et al. 2008). Low physiological concentrations of ROS are required for normal force production, whereas high concentrations promote contractile dysfunction (Powers and Jackson 2008).

17.6.2 Disturbances in Excitation-contraction Coupling

Muscle contractions involve critical interactions between myofibril $[Ca^{2+}]_i$ and the muscle proteins actin and myosin, control of myofibril Na^+ and K^+ concentrations, proper functioning of the T-tubular voltage sensor and regulation of Ca^{2+} release and re-uptake by the sarcoplasmic reticulum. Malfunctioning of one or more of these processes will result in disturbances of excitation-contraction coupling (ECC) (Allen et al. 2008; Kent-Braun et al. 2012; McKenna et al. 2008).

Altered Excitability of the Sarcolemma and/or T-tubular System. According to the *membrane hypothesis of muscle fatigue*, →action potential propagation along the sarcolemma and into the T-tubules is compromised. Action potential generation and propagation are influenced by many factors, such as internal and external resistances of the muscle fiber, membrane resistance and capacity, and →resting membrane potential, which in turn is influenced by extra- and intracellular ion concentrations. Changes in the latter are most marked with continuous high-frequency stimulation (Allen et al. 2008; Kent-Braun et al. 2012; McKenna et al. 2008; Sejersted and Sjøgaard 2000).

Changes in K^+ and Na^+ Concentrations. Intense, repeated stimulus-evoked muscle contractions can increase intracellular Na^+ concentration, reduce intracellular K^+ concentration and elevate extracellular K^+ concentration, leading to cell membrane depolarization, Na^+-channel inactivation, impaired action potential generation and propagation, which in turn depress the Ca^{2+} release from the sarcoplasmic reticulum (Allen et al. 2008; Kent-Baum et al. 2012; McKenna et al. 2008).

Impaired T-tubular Voltage-sensor Activation. Voltage-sensor activation may be reduced by a decreased action potential and by voltage-sensor inactivation (Allen et al. 2008; Kent-Baum et al. 2012).

Changes in Ca^{2+} Dynamics. The Ca^{2+} dynamics and effects may be impaired by a reduced Ca^{2+} release from the sarcoplasmic reticulum and slowed Ca^{2+} re-uptake into the SR, as well as a decrease in Ca^{2+} sensitivity of myofibrillar proteins, which in turn may result from electrical and chemical changes listed above (Allen et al. 2008; Kent-Baum et al. 2012).

Inhibition of Actin-Myosin Interactions. Increased P_i and H^+ concentrations may inhibit the transition from the low- to high-force cross-bridge state and the release of ADP from the cross-bridge (Kent-Baum et al. 2012).

17.6.3 Recovery from Fatigue

After brief, high-intensity exercise in humans, voluntary force is typically restored within a few minutes due to recovery of central fatigue and peripheral fatigue associated with excitation-contraction coupling (ECC) and reperfusion of muscles. But recovery may remain incomplete for some hours. After long-lasting, low-intensity exercise, voluntary force typically shows rapid but partial recovery within the first few minutes, due largely to recovery from central fatigue (Carroll et al. 2017).

Force recovery after fatiguing stimulation shows different time courses depending on the pattern of stimulation. Recovery after continuous high-frequency stimulation is fast and occurs within the first seconds, whereas recovery after repeated low-frequency stimulation may take several hours. There is suggestive evidence that different time courses of recovery are associated with $[K^+]$ and $[Ca^{2+}]$ concentration gradients. It has been proposed that the fast component of recovery represents diffusion of elevated $[K^+]$ from the T-tubules. In addition, the time course of recovery of central Ca^{2+} release and force are both consistent with the time for diffusion of small ions out of the T-tubule (Allen et al. 2008).

17.6.4 Muscle Fatigue in Disease

A large array of disease states alters muscle fatiguability. In particular, fatiguability is enhanced in various neurological disorders, such as →stroke, →multiple sclerosis (MS), →Parkinson´s disease, →spinal cord injury, →Guillain-Barré syndrome, →myasthenia gravis and →myotonic dystrophy (Kent-Braun et al. 2012; Zwarts et al. 2008).

Specifically, in the rare, but particularly interesting cases of →mitochondrial myopathies leading to →lactacidosis (Edwards et al. 1982), symptoms of severe exhaustion, weakness and muscle fatigue during exercise are predominant features. Muscle fatigue may develop secondarily to →muscular dystrophies, loss of muscle tissue in cancer cachexia, general →inflammatory diseases, sepsis, burns, →acquired immunodeficiency syndrome (AIDS), chronic kidney failure, and normal aging, because the reduced muscle mass must work closer to their maximal capacity (Allen et al. 2008).

Muscle fatigue is also an important limiting factor in situations when functional electrical stimulation (FES) is used to help restore motor function following neurological damage, e.g., in →paraplegics (for references see Binder-Macleod and Barker 1991).

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18

Contractile Mechanics of Skeletal Muscle and Motor Units

CONTENTS

Abstract

• The macro-mechanics of skeletal muscles, motor units and their role in the gradation of muscle force, and plastic and non-linear muscle properties are herein described.

• Individual activations result in twitch contractions, whereas repetitive activations produce fused contractions that are rate-dependent

• Muscle force production depends on muscle length and speed of length change, giving rise to the force-length and force-velocity relationships, respectively.

• Macroscopic muscle force production can be graded by changes in activation rate and/or motor unit recruitment.

• A motor unit is comprised of a skeleto-motoneuron and the group of skeletal muscle fibers (muscle unit) it innervates.

• Muscle units vary in histochemistry, metabolism, contraction speed, tetanic force, and fatiguability. These properties co-vary with, and are matched to, properties of the innervating motoneurons, such as soma size, input resistance, duration of afterhyperpolarization (AHP), and speed of motor-axon action-potential propagation.

• Muscles are plastic: The match between motoneuron and muscle fiber properties can be altered depending on a number of factors.

• The force produced by a muscle or motor unit depends not only on the instantaneous neural input, but also on its preceding activation history.

18.1 Introduction

The macro-mechanics of →skeletal muscles and →motor units have mostly been investigated under laboratory conditions aimed at isolating individual factors that influence muscle behavior. Many of these factors interact, however, so that in real life muscle behavior is more complicated than described by any of the individual laboratory results (Huijing 1998). These macro-mechanics are highly complex and non-linear. They also depend on intra-muscular temperature, which may change depending on external temperature (James 2013). Furthermore, skeletal muscle shows short- and long-term flexibility and →plasticity.

18.2 Isometric and Isotonic Contractions

There are three general types of muscle contractile responses that generate force: isometric, isotonic, and eccentric. Isometric contractions are ideally measured and analyzed in laboratory studies by keeping the whole muscle or the →muscle fiber length constant and measuring the force generated. During isotonic contractions, force is kept constant and length is allowed to change. Muscles naturally contract almost isometrically when posture is maintained, whereas isotonic contractions occur more seldom because more often force changes along with length. Shortening contractions are also referred to as concentric contractions. Forced lengthening of a contracting muscle, an eccentric contraction, is a functionally important activity mode. It occurs mainly when someone walks down a slope or a staircase or slowly puts down a heavy load. Compared to concentric contractions, eccentric contractions require less motor unit activation and consume less oxygen and →energy. Unaccustomed eccentric exercise may cause muscle damage and delayed pain (Hody et al. 2019).

Two types of isometric contraction are evoked by electric shocks applied to motor nerves or directly to muscle. A contraction elicited by a single brief electrical shock evokes a twitch contraction. A train of electric shocks applied at short intervals before a twitch can relax evokes a fused contraction.

18.3 Twitch Contraction

The time course of a twitch contraction depends on the muscle´s composition of different types of motor unit. If a muscle is composed primarily of slow motor units, such as the soleus muscle, it produces a slow twitch that consists of an upstroke of force that follows excitation after a latency of a few milliseconds, followed by a relaxation phase that usually lasts roughly twice as long as the rising phase. The rates of force development and relaxation during a twitch correspond to positive and negative →yank, respectively, and reflect alterations in the contractile machinery due to pathologies, training or aging (Lin et al. 2019).

18.4 Contraction upon Repetitive Activation

Repetitive electric shocks evoke a sequence of individual twitches if the pulse interval exceeds the time course of the twitch. If the shock interval is shorter than the twitch time, twitches summate and produce a sustained contraction. At peak effective shock frequency, individual twitches are indistinguishable, that is they fuse into a complete →tetanus, during which the muscle exerts its full contractile force. The average tension developed is a sigmoidal function of the stimulus rate. The steepest portion of the S-shapedcurve spans the region in which rate modulation of muscle force output is most powerful. This portion is often called the *`regulatory range´*.

18.5 Length-tension Relation

The force produced during muscle or motor unit contraction also depends on the length at which the muscle is held. The →twitch forces and tetanic tensions of whole muscles and of motor units are all influenced by length in a way described by the length-tension relation (e.g., Heckman and Enoka 2004; Partridge and Benton 1981; Sandercock 2009; Zajac 1989).

Even a passive muscle exerts some force when stretched beyond a certain length. This *passive force* results from minor stretch of the sarcolemmal sheaths and intermingled connective and tendinous tissues, i.e., from parallel- and series-elastic elements including titin (Colombini et al. 2016; Holt 2019). Any *active force* generated by muscle contraction is added to the passive force. When passive force developed during electrical stimulation is subtracted from total force, *active force* is obtained and clearly depends on muscle length.

The length-dependency of active force has been explained in terms of the sliding filament model (Gordon et al. 1966; also Heckman et al. 2009; Sandercock 2009). Tension development of active sarcomeres depends on the degree of overlap of actin and myosin filaments. At long sarcomere length (3.65 μm), actin and myosin filaments do not overlap, and no force is produced. Shortening the sarcomere from 3.65 μm to 2.20 μm results in an increasing overlap of the actin and myosin filaments such that the number of cross-bridges and force production capacity increase proportionally, until a maximum is reached between 2.20 and 2.25 μm. Further shortening to 2.05 μm makes actin filaments touch in the middle or slide past each other, augmenting the resistance to shortening. This effect may be enhanced when myosin filaments touch the Z lines or even crimp. In general, the interaction of muscle length and active force is a complicated process. Sarcomere length will change during a contraction with constant muscle-tendon length, due to tendon stretch. Passive force therefore changes during the contraction (MacIntosh 2017).

The form of length-tension relations also depends on stimulation rates (Rack and Westbury 1969). At sub-tetanic rates and short muscle lengths, synchronous stimulation of →ventral root filaments innervating the isometric soleus muscle evoke separate twitches, with tension falling to zero after each stimulus. Increasing the muscle length passively increases the twitch duration, so that the twitches begin to coalesce and the tension no longer returns to zero. With further increments in muscle length the fusion between twitches becomes more complete, so that the tension fluctuation becomes a smaller proportion of the total

tension. As the contraction becomes more fused, the tension rises above the value obtained by graphical summation of the separate twitches, and if the tension fluctuations are then diminished further by changing from synchronous to distributed stimulation of the filaments, the tension rises to an even higher level. Hence, when length is increased, three factors act together to increase the muscle tension. Each stimulating pulse causes a more forcible contraction, the contractile activity lasts longer, and the longer duration in turn leads to a smoother contraction in which a higher tension can develop.

Active slack length and optimum muscle length move to higher lengths when stimulus rate is lowered. Obviously, length-tension relations of sub-maximally activated muscles are not simply scaled versions of those at maximal activation. There are other effects on the length-tension relation. Importantly, the length-tension relation depends on the preceding history of muscle length change, and changes in the course of sustained activation, due to →muscle fatigue or →potentiation/depression; it also changes during growth or →adaptation to immobilization (Huijing 1998).

18.6 Force-velocity Relation

The force produced by a muscle depends on the velocity of length change (Heckman and Enoka 2004; Lin 2009a; Partridge and Benton 1981; Roberts 2016; Zajac 1989).

Quantitative measurements of force-velocity relations typically proceed as follows. A muscle is initially held at isometric length by a mechanical stop supporting a set load. When the muscle is electrically stimulated so that the isometric force is greater than the load, removing the stop allows the muscle to shorten (shortening or concentric contraction). The initial shortening velocity is maximal for that load. However as the muscle shortens, velocity decreases, because the force it can produce decreases with shortening according to the length-tension curve. Ultimately, a →steady-state length is reached corresponding to that point on the length-tension curve, which yields the force that corresponds to the load. By contrast, when the load is greater than the isometrically generated muscle force, the muscle lengthens upon stop release (lengthening or eccentric contraction). Another important point is that the force-velocity relation depends on the rate of muscle activation, which will vary for different types of fiber (Joyce and Rack 1969).

The asymmetric force production during shortening (concentric) vs. lengthening (eccentric) contractions imposes differential strategies of neural control on the two types of movements (Duchateau and Baudry 2014). Indeed, recent human neuroimaging results using →electroencephalography (EEG) and →functional magnetic resonance imaging (fMRI) indicate that the brain puts more effort into controlling eccentric movements: longer-lasting and higher cortical signal amplitude (EEG) for eccentric movement preparation and execution, greater magnitude of cortical signals with wider activated brain area (EEG, fMRI).

In concentric (shortening) contractions, the initial shortening velocity is an inverse function of load. Several mathematical formulas and explanations for possible underlying mechanisms have been proposed for concentric contractions (Alcazar et al. 2019). A well-known hyperbolic function (Eq. 1) was proposed by A.V. Hill (1938):

$$(P+a)x(V+b) = (P_o+a)b = (V_{max}+b)a = \text{constant}, \quad (1)$$

where a and b are constants, P_o is the isometric tension at zero velocity and V_{max} is the maximal velocity attained with no external load. A number of studies have revealed deviations from this simple relationship in the high-force/low-velocity region, suggesting a double-hyperbolic function for concentric contractions. The increase in force in eccentric contractions has been proposed to fit an independent hyperbolic function (Alcazar et al. 2019; Sugi and Ohno 2019).

The physiologic basis of the force-velocity relationship is that force generated by a muscle depends on the total number of cross-bridges formed between actin and myosin filaments. Because it takes a finite amount of time for cross-bridges to attach, as filaments slide past one another faster and faster, i.e., as the muscle shortens with increasing velocity, force decreases due to the lower number of attached cross-bridges. Conversely, as muscle velocity decreases, more cross-bridges have time to attach and to generate force, and thus force increases. The maximal velocity V_{max} of a muscle fiber, determined by the rate of cross-bridge cycling, depends on the myosin isoforms contained in the fiber. Faster myosin isoforms allow for faster cycling rates and hence faster movements (Lin 2009a).

18.7 Gradations of Muscle Force

Although the control of posture and movement are interdependent, each imposes partially contrasting constraints on →skeleto-motoneurons (in brief: motoneuron) and the muscle fibers that they innervate (Kernell 1998).

Posture requires finely graded forces of low to moderate →intensity, often under near-isometric conditions. The contractions may last very long, sometimes hours in many anti-→gravity muscles, and thus require good endurance (fatigue resistance). Hence, the energy supply must be continuous, requiring an adequate capillary blood supply and good capacity for oxidative metabolism.

During muscle fatigue, the maximal →power output during shortening is reduced. Three factors may contribute to this reduction: a decrease in isometric force, a slowing of the maximal velocity of unloaded shortening and an increased curvature of the force-velocity relationship (Jones 2010; Kent-Braun et al. 2012).

Movements may be brief (ballistic) and thus regulated on a short-term basis, or repetitive like in locomotion, and may demand high contractile force and power. Endurance is of lesser importance. Energy must be rapidly mobilized from internal stores (→glycogen) and sometimes under anaerobic conditions (oxygen-free), since blood vessels may be occluded temporarily.

These requirements should be reflected in the functional organization of muscles and their innervation.

18.7.1 Functional Fractionation of Muscle

Muscle forces must be gradable finely and smoothly (Kernell 1992). This general requirement presents two challenges.

First, if all the fibers in a muscle were innervated by a single command motoneuron, force gradation below twitch tension would be impossible. One strategy would be to fractionate the muscle into smaller units, each controlled by the →central nervous system (CNS). The maximal fractionation achievable would be to have every muscle fiber innervated by an individual motoneuron. However, since individual skeletal muscles are often composed of many thousands of muscle fibers, this would require very large numbers of motoneurons to execute a graded contraction. As a compromise, a group of muscle fibers is controlled by an individual motoneuron, in a functional element referred to as a motor unit (Burke 1981, 2009; Heckman and Enoka 2004; Kernell 1992).

Second, there needs to be an efficient way of recruiting motor units. For example, finely graded postural tasks may require the availability of many small force increments and sustainable force production, while rapid strong movements would require the availability of fast contracting, strong motor units for short times.

18.5.2 Skeleto-motoneurons and their Muscle Units

In the →spinal cord, the somata of motoneurons innervating an individual macroscopic muscle and thus constituting a →motoneuron pool usually lie within long, narrow columns extending rostro-caudally in Rexed's lamina IX of the →ventral horn. →Brainstem motoneurons are often clustered in more compact nuclei. In mammals, a first classification of motoneurons distinguishes between skeleto- and fusi-motoneurons. The former comprise →α-motoneurons and →ß-motoneurons that innervate skeletal muscle fibers; and the latter comprise ß-motoneurons and →γ-motoneurons that innervate innervate →intrafusal muscle fibers in muscle spindles. ß-Motoneurons thus innervate both skeletal and intrafusal muscle fibers. This specific innervation pattern is the standard pattern in amphibia, while in mammals, including humans, ß-motor innervation is less common and varies between muscles (Hulliger 1984; Stifani 2014). α- and ß-Motoneurons have myelinated →axons in group Aα. γ-Motoneurons have myelinated axons in group Aγ, but are smaller and have a sparser →dendritic tree than skeleto-motoneurons (Moschovakis et al. 1991; Lüscher and Clamann 1992; Westbury 1982).

The somata of skeleto-motoneurons are among the largest in the CNS, having diameters of 30 to 70 μm and extensive dendritic trees yielding surface areas between 10^{-5} to 10^{-3} cm^2 (Brown 1981; Lüscher and Clamann 1992). Motoneurons vary in soma diameter, somato-dendritic surface, axon diameter, axon conduction velocity, biophysical properties such as input resistance, →rheobase, and membrane properties, such as specific resistivity and capacitance, and depth and duration of →afterhyperpolarization (AHP) (Binder et al. 1996; Burke 1981; Henneman and Mendell 1981; Kernell 1992; Rekling et al. 2000).

At early →ontogenetic stages, individual muscle fibers are innervated polyneurally by several motor axons, although this applies throughout life to extraocular muscles (Evinger and Baker 1991). During development, supernumerary motor terminals are withdrawn so that, in adult healthy mammals, each muscle fiber is innervated by only one motoneuron (mononeural innervation) (Ijkema-Paassen and Gramsbergen 2005; Jansen and Fladby 1990).

An individual motoneuron innervates between a few and a few thousand muscle fibers, depending on the type of muscle (Burke 2009; Clamann 1993; Heckman and Enoka 2004; Roy and Edgerton 2009).

18.7.3 Motor-unit Classification

A →muscle unit is the collection of muscle fibers innervated by an individual motoneuron, these muscle fibers having the same properties. Different muscle units vary in histochemistry, metabolism, contraction speed, tetanic force, and fatiguability (Berchtold et al. 2000; Clamann 1993). These properties co-vary with properties of the innervating motoneurons, such as soma size, input resistance, duration of afterhyperpolarization (AHP), and speed of motor axon →action potential propagation. Hence, motoneuron and muscle-unit properties are matched in functionally significant ways. Despite the essentially continuous variation, various criteria enable motor units to be classified into several categories (Burke 1981, 2009): *S*, slow-twitch, fatigue-resistant; *FR*, fast-twitch, fatigue-resistant; *F(int)*, fast-twitch, intermediate fatiguability; *FF*, fast-twitch, fatiguable. The different types of motor unit are specialized with respect to various features, such as contractile speed, force output, endurance etc., in order to fulfill the differential needs in motor tasks of varying strength and duration.

Other studies of muscle-fiber type diversity in motor units have identified a broader spectrum of properties that more precisely discriminate between the four major fiber types in adult mammalian skeletal muscles, leading to a different nomenclature: type 1 (slow-twitch muscles rich in →myoglobin and oxidative enzymes and specialized for more continuous activity), type 2A (fast-twitch oxidative glycolytic), type 2B (fast twitch glycolytic) and type 2X (fast-twitch glycolytic fibers whose contraction and half-relaxation times, fatigue resistance are intermediate between 2A and 2B fibers, and myosin heavy chain composition which differs from 2A and 2B types). Muscle fiber diversity across the four fiber types encompasses membrane excitation, excitation-contraction coupling, contractile machinery, all of which are functionally matched to the discharge properties of motoneurons within a motor unit (Schiaffino and Reggiano 2011).

18.7.4 Recruitment Gradation of Skeletal Muscle Force

Force-dependent recruitment of different numbers of motor units follows a pattern that →optimizes force output according to the demands of specific motor tasks (Kernell 1992).

18.7.4.1 The Size Principle

During many →reflexes and voluntary muscle contractions of increasing strength, motor units are usually recruited in a fairly stereotyped pattern. The mechanism behind this pattern was first formulated by Henneman (1957) as the size principle, which implies that orderly recruitment follows a sequence of increasing motoneuron size as expressed in motoneuron axon diameter. This hypothesis is still open to debate, because factors other than size contribute to recruitment order, such as specific membrane resistivity and →synaptic input distribution. (Binder et al. 1996; Burke 1981; Enoka and Stuart 1984; Heckman and Enoka 2004; Kernell 1992). Orderly recruitment of motor units has been demonstrated in various preparations and with different inputs to motoneurons, although the precision and stereotypy may vary (Binder et al. 1996). There are a few exceptions, the most notable being that high-threshold units are selectively recruited during lengthening (eccentric) contractions of the human soleus and gastrocnemius muscles, while the orderly sequence from low- to high-threshold units is observed in shortening (concentric) contractions (Nardone et al. 1989).

18.7.4.2 Reducing Force Oscillation

During maintained muscle contractions, the constituent contractions of recruited motor units should add up to smooth overall force profiles. However, smooth tetanic contractions of active motor units would prevent the rate gradation of force, and they would be metabolically demanding and fatiguing. But if individual motor units discharge at rates that cause unfused contractions, each produces an oscillating force contribution. Unless the force ripples contributed by the different motor units are asynchronous, they sum up to a vigorous oscillation (→tremor) that would prevent smooth force profiles. So the activities of the different motor units must be kept asynchronous. This requirement is non-trivial because it implies that synaptic inputs to motoneurons must not derive from a few individual command neurons causing large →excitatory postsynaptic potentials (EPSPs), but instead from populations of input neurons, each producing small EPSPs (Kernell 1992).

18.7.5 Rate Gradation of Muscle Force

A second possibility of grading muscle force exists at the single motor-unit level and involves the variation of discharge rate and contraction time course. This mechanism is needed to supplement force production, albeit to varying degrees. For example, in intrinsic hand muscles, motor-unit recruitment is more or less complete at 50% of maximal force, whereas in the biceps brachii, brachialis and deltoid muscles it continues beyond 80% of maximal force (Binder et al. 1996).

To generate →action potentials, a motoneuron must be →depolarized from its →resting membrane potential to →threshold. This is done naturally by excitatory synaptic inputs or experimentally by a depolarizing current injected by an intracellular electrode or by an extracellular electrode (Spielmann et al. 1993). When, via an intracellular electrode, a depolarizing current step is applied, producing a single action potential, the required

current is referred to as rheobase. In order to produce a sustained repetitive discharge at the minimal regular discharge rate requires about 1.5 times the rheobase current (Binder et al. 1996). Increasing the current strength further drives the motoneuron to higher firing rates.

18.7.5.1 Static Force-rate Relations of Different Types of Motor Unit

Since muscle-unit twitches are fairly long, they overlap and sum to a degree depending on the activation rate. Under isometric conditions, the static relationship between the firing rate and mean force output of a motor unit has a monotonic sigmoidal shape, similar to the force-rate relationship of the entire muscle. It starts at a minimum firing rate producing unfused twitches and extends up to a maximum rate at which twitches fuse smoothly and force is maximal. Motor-unit force is most easily altered by rate changes that occur in the steep part of the force-rate relation (`*regulatory range´*). The position of this regulatory range on the rate axis depends on motor unit twitch speed. It lies more to the left for slow and more to the right for fast motor units. The summation of successive twitches is often non-linear, showing depression or potentiation (Herzog 2009; Vandenboom 2009), particularly at the beginning of a pulse train, which may insure rapid force development.

18.7.5.2 Matching Motoneuron and Muscle-unit Rate Dependencies

In order for muscle units to contract efficiently, they must be activated in a way matched to their contractile properties. This implies that the discharge patterns of their motoneurons must be adjusted to muscle-unit properties (Heckman and Enoka 2004; Kernell 1992). This match has several aspects.

Minimum Discharge Rate. When voluntary muscle force is sustained at a level just above the recruitment level of a motor unit, the unit´s discharge is fairly regular and maintained. The minimum `recruitment´ rates vary between about 5 and 12 per second for different motor units (Freund 1983). A motor unit´s minimum regular firing rate usually corresponds to the lower end of the steep part of its force-rate relationship. It is mainly determined by the duration of motoneuron afterhyperpolarization (AHP). In anesthetized cats, AHP duration is inversely correlated with the lower limit of the rate of regular repetitive firing in response to maintained injection of constant depolarizing current (Kernell 1965, 1992). Such a relation also exists in human skeletal muscles (Gossen et al. 2003). On average, small motoneurons having long AHPs and innervating slow muscle fibers discharge regularly at lower rates than do large motoneurons, which have short AHPs and innervate fast muscle fibers.

Maximum Discharge Rate. The highest firing rates attainable by motor units appear to be great enough to cause contractile fusion. This maximum rate is higher in motoneurons with short than those with long AHPs as required by the differences in contraction speed of the respective muscle units (Kernell 1992).

Regulatory Range. The regulatory range, the steep portion of the force-rate relation, is matched to a corresponding *primary range* of motoneuron firing driven by depolarizing current. All motoneurons display a linear primary range, some motoneurons a subsequent secondary range with a steeper slope, and a few motoneurons exhibit a tertiary range of usually reduced slope. There appears to be a *rate match* between muscle units and their motoneurons. The steep portion of the force-rate relation of small, slow muscle units covers a low range (ca. 8-20 action potentials s^{-1}), which corresponds roughly to the primary firing range of their motoneurons. In comparison, the steep portion of large fast units covers a higher range (20-50 action potentials s^{-1}), which again corresponds roughly to the primary range of fast motoneurons (Kernell 1992; Kernell et al. 1999; Baldissera et al. 1998). At high sub-maximal forces, the force-rate relationship of motor units becomes less steep. This decrease in slope is compensated for by the increase in steepness of the relationship between firing rate and input current in the *secondary range* (Kernell 1992). That is, in the secondary range, a given increase in input current would create a higher increase of motoneuron firing than in the primary range, and this higher rate increase would push force upwards despite the lower force-rate slope.

Firing-rate Adaptation. In response to fast increases in excitatory input, motoneurons often discharge action potentials (spikes) at very high instantaneous rates, followed by adaptation to more sustained steady firing. The adaptation from the initial overshoot to a more sustained steady firing occurs in two or three phases (see Sawczuk et al. 1995; Kernell et al. 1999): an initial adaptation, complete within a few inter-spike intervals, a subsequent early adaptation, lasting usually about 2 s, and a slow late adaptation that may go on during the entire discharge (Binder et al. 1996). The initial discharge adaptation probably results from non-linear summation of afterhyperpolarization currents, whereas the slower phases of adaptation rely on other processes (Spielmann et al. 1993; Binder et al. 1996).

Short inter-spike intervals are important for increasing the speed of contraction and for enhancing force output by non-linear mechanisms. *Late adaptation* (increase in inter-spike intervals) is matched to the ongoing slowing of muscle-unit twitch contraction during muscle fatigue (→muscle fatigue, neural factors). Correspondingly, late adaptation occurs in spinal motoneurons. When cat lumbar motoneurons are injected with long-lasting rectangular depolarizing currents that make them discharge at an initially high rate, they subsequently adapt to lower rates. S-type motoneurons adapt not nearly as much as do FF-type motoneurons. Furthermore, the average force of FF-type motor units declines much more rapidly and drastically than that of S-type units. Thus, late adaptation of motoneuron discharge appropriately parallels the decline of force over time, being more prevalent in F-type than in S-type motor units (Kernell and Monster 1982; see also Spielmann et al. 1993).

Firing-rate adaptation properties studied in cat lumbar motoneurons were found to be similar in lumbar motoneurons of pentobarbital-anesthetized rats. Motoneurons of S-type muscle units had slower AHP time courses and more slowly conducting axons than F-type muscle units. It was argued that the `speed match´ between motoneuron and muscle unit helps ensure that barely recruited motoneurons begin firing at a rate “that is optimally suited for the subsequent gradation of force” (Bakels and Kernell 1993).

18.7.5.3 Compensation of Muscle-unit Dynamics by Motoneuron Discharge

Muscles and their constituent muscle units are sluggish to varying degrees, depending on muscle-unit type. Motor units exhibit rate-modulated force properties characteristic of →low-pass filtering (e.g., Partridge and Benton 1981; Zajac 1989). When sine-wave currents are applied to axons innervating a motor unit, force declines with increasing current frequency. On the other hand, the gain of the motoneurons innervating the motor unit is amplified over the same frequency range. Evidently, the gain in amplitude is associated, at least in part, to input currents in the motoneurons that develop over the same frequency domain where the force response of the muscle is attenuated. The amplitude gain effectively compensates for the low-pass filter properties of the muscle response (Baldissera et al. 1984, 1998).

18.7.5.4 Potentiation and Depression

Many muscle-unit properties appear to be taken care of in a feedforward way by matched motoneuron properties. However, there are other, non-linear properties that may make feedforward nervous control very difficult or impossible (Partridge and Benton 1981).

The force produced by a muscle or motor unit depends not only on the instantaneous neural input, but also on its preceding *activation history*. For example, two successive twitches usually do not sum linearly. In an overlapping pair of twitches, the initial force rise of the second twitch may be depressed, while the force during the relaxation phase usually is more or less increased and prolonged (facilitation or potentiation), depending on the muscle (Parmiggiani and Stein 1981). For example, when a single S-type motor unit of the cat medial gastrocnemius muscle is stimulated with subsequent pulses, a second stimulus following the first stimulus after 10 ms adds a disproportionately large amount of tension in relation to the first twitch, while the third and fourth stimuli do not recruit as much additional force. With an inter-stimulus interval of 50 ms, all successive twitches are potentiated, and this potentiation nearly disappears again at an interval of 100 ms (Burke et al. 1976). Individual twitches may also be potentiated after longer preceding activation or after short tetanic stimulation (→post-tetanic potentiation, PTP) (Kostyukov and Levik 1994; Vandenboom 2009). These phenomena are found in both slow and fast motor units, although to different extents (Burke et al. 1976; Niemann et al. 1986). Post-tetanic potentiation (PTP) may be a mechanism to lessen the loss of force during fatiguing maintained contractions. Since, at the onset of activation, many motor units start firing at a high rate, their twitches may be potentiated for seconds. The force of FF units first declines steeply and then exhibits an intermediate hump, which probably results from potentiation. This transiently opposes the fatigue proceeding in parallel (Kernell and Monster 1982).

The magnitude and duration of post-tetanic potentiation (PTP) in skeletal muscle fibers depends on a number of factors, including muscle fiber type, species, temperature, sarcomere length and stimulation paradigm. Early studies performed on both intact and permeabilized muscle fibers established that the primary mechanism for modulation of PTP was phosphorylation of myosin, a modification that increased the Ca^{2+} sensitivity of contraction. More recent work from a variety of muscle models indicates the presence of additional mechanisms for PTP that may involve altered Ca^{2+} handling, whereby

stimulation-induced elevation of resting Ca^{2+} increases the Ca^{2+} occupancy of troponin C, or of other Ca^{2+} buffers such as parvalbumin, or increases weakly bound cross-bridges as a necessary precursor to attaining the strongly bound, force-generating state (see Vandenboom et al. 2013).

The cellular mechanism responsible for PTP, in general, has been characterized at a number of synaptic junctions, from the calyx of Held, a giant →glutamatergic synapse in the auditory brainstem (Korogod et al. 2005) to the skeletal →neuromuscular junction. The mechanism involves slow-release →presynaptic vesicles, somewhat remote from the presynaptic release sites, which are activated by high free calcium (Ca^{2+}) that binds to →calmodulin (CaM) (Balakrishnan et al. 2010). CaM then activates myosin light chain kinase (MLCK), leading to activation of myosin II, a molecular motor in the presynaptic terminal, which drives relocation of →acetylcholine-containing vesicles in the slow-release pool to presynaptic membrane release sites.

18.7.5.5 Catch-like Muscle Properties

Another non-linear property might contribute to rate gradation of muscle force. In invertebrate (Wilson and Larimer 1968) and mammalian muscles (Burke et al. 1970; Grottel and Celichowski 1999; Kostyukov and Levik 1994), the so-called catch-like property means that the precise temporal patterning of stimuli influences force output over long time spans. For example, in a slow cat motor unit (Burke et al. 1970), force rise during repetitive activation is much faster when the stimulus sequence starts with a much briefer than average interval (e.g., 10 ms). When a brief interval is injected later, the force suddenly rises in a step-like fashion. Conversely, a longer-than-average interval results in a step-like decrease in force.

Two mechanisms have been proposed to explain the force-enhancing effects of the high-rate →burst in catch-like-inducing trains: increased sarcoplasmic Ca^{2+} concentration and increased →stiffness of the series-elastic elements of muscle (Binder-Mcleod and Kesar 2005).

Short intervals between successive spikes (`doublets´) that might elicit the catch-like force enhancement have been observed under various circumstances in humans and animals (e.g., Andreassen and Rosenfalck 1980; Bawa and Calancie 1983). It appears that they may be particularly effective during muscle fatigue (Binder-Macleod and Barker 1991; Binder-Macleod and Landis 1994), since doublets seem to occur more often in this condition.

18.7.5.6 Hysteresis

Post-tetanic potentiation (PTP) and the catch property may also underlie the hysteretic relationship between force and activation rate when a muscle or motor unit is stimulated with a sequence of stimuli whose rate is modulated rhythmically (Partridge and Benton 1981; Wilson and Larimer 1968; Binder-Macleod and Clamann 1989). For example, when a cat medial gastrocnemius motor unit is stimulated with a temporally symmetric triangular pattern, the produced force is typically asymmetric in that it is greater, at the

same stimulus rate, on the down-swing than on the up-swing. This is particularly conspicuous after plotting force vs. stimulus rate at the same instants in time.

It is not only activation history that determines the force produced, but also the history of length change (Herzog 2009; Lin 2009b; Nichols and Cope 2004). An active muscle develops higher forces during lengthening than during shortening. Thus, when the muscle is slowly lengthened and then shortened again at the same speed, the forces at corresponding lengths are greater during the lengthening than the shortening phase. Conversely, the lengths corresponding to the same forces are longer during the shortening than during the lengthening phase. This yields a strong hysteresis in the length-force plot. In addition, the final endpoints of length attained by an active muscle depend on the previous length history (Herzog 2009).

In summary, the length-tension hysteresis and dependence on previous direction of length change may leave the muscle at unpredictable steady lengths despite identical activation patterns and applied loads (Kostyukov and Levik 1994; Kostyukov et al. 1995).

18.8 Motoneuron and Muscle Plasticity

While it is well known that several motoneuron properties are well matched to those of the muscle fibers they innervate, and there should be reciprocal influences between motoneurons and muscle fibers, the question is which mechanisms are at work to enable these matches.

What seems clear, is that it is no longer sufficient to describe the variation of functional motoneuron characteristics simply as fast or slow, because all properties seem continuously graded. Furthermore, there is cytochemical evidence for several, seemingly independent parameters of functional specialization (Kernell et al. 1999).

During embryonic development, a →recognition process establishes an early match (Kernell et al. 1999). Growing motoneuron axons recognize different classes of muscle fibers, with the result that functionally homogeneous muscle units arise based on mutual cell recognition. Motoneurons as well as muscle fibers are largely pre-specified as fast or slow. Motoneuron axons growing into the muscle then select, by cell recognition, the corresponding muscle fibers (Jansen and Fladby 1990). In neonatal cats and rats, afterhyperpolarizations and twitches are initially longer than in adults. Over the first postnatal weeks, isometric twitches quickly become faster, but while the twitches of fibers destined to be fast remain fast, the twitches of muscle fibers destined to be slow (e.g., soleus) slow down. The secondary slowing of soleus muscle fibers appears to depend on slow motoneuron activity. The postnatal decrease in afterhyperpolarization duration, especially in `fast´ motoneurons, occurs later than the speeding-up of isometric twitches, which seems to reflect a retrograde influence of muscles on their motoneurons (Kernell 1998).

Adjustments are also possible throughout adult life. Muscle properties can be manipulated by many procedures. Changes occur during altered nutrient supply, environmental conditions such as →hypoxia, different types of physical exercise, electrical stimulation or

denervation, rehabilitation after trauma, injury and disease, →paralysis, limb immobilization and space flight (Berchtold et al. 2000; Flück and Hoppeler 2003; Gardiner et al. 2005; Hoppeler 2016; Huijing 1998). Early self- and cross-re-innervation experiments demonstrated that, for example, the fast flexor digitorum longus (FDL) muscle became slow-contracting and the slow soleus muscle contracted more rapidly after their severed nerves had been cross-united (Buller et al. 1960).

Two important factors underlying these changes in muscle-fiber properties could be muscle loading and the pattern of neural activity reaching the muscle. In fast-twitch muscles, synchronous low-rate stimulation for 3-24 h per day leads to a decline in muscle-fiber diameter, decline in muscle force, increase in contraction time, increase in endurance, shift from glycolytic to oxidative enzyme activities, and increase in capillary density around the stimulated fibers (Pette and Vrbová 2017). The reverse conversion from slow to fast characteristics is more complex and variable and never quite complete. Nonetheless, under-use creates a general trend for muscles to express a fast phenotype with respect to contractile and regulatory proteins and to up-regulate enzymes of →anaerobic glycolysis (Gordon 1995). These anterograde (motoneuron-to-muscle) influences appear to have a counterpart in retrograde effects of muscle properties on motoneuron properties. Sufficient numbers of slowed muscle fibers seem able to prolong motoneuron afterhyperpolarization (Kernell 1998, 1999). Moreover, increases or decreases in physical activity change biophysical motoneuron properties, although little is as yet known about the underlying mechanisms (Gardiner et al. 2005).

Motoneuron properties also change with various physical exercise or disuse regimes (Button and Kalmar 2019; Gardiner et al. 2005). For example, when rats had been exposed to 12 weeks of voluntary wheel running, `slow´ motoneurons with AHP half-decay times ≥20 ms, but not `fast´ motoneurons with AHP half-decay times <20 ms, exhibited more negative (→hyperpolarized) →resting membrane potentials and action potential thresholds, as well as greater afterhyperpolarization (AHP) amplitudes. These adaptations likely reflect changes in the density, localization, and/or modulation of →ionic channels in different cell types that probably enhance fatigue resistance during rhythmic firing (Beaumont and Gardiner 2002). In a recent study, a 5-week resistance training, involving a voluntary progressive weight-lifting program, in which animals had to lift against resistance to access food, evoked adaptive changes in both slow- and fast-type motoneuron properties. In fast motoneurons, thes changes comprised a higher input resistance, a lower rheobase, a decrease in the minimum current required to evoke rhythmic firing, an increase in the maximum frequencies of the early-state firing and the steady-state firing, and an increase in the slopes of the frequency-current (*f*/*I*) relationship. The latter two changes were also observed in slow motoneurons. These adaptations may contribute to increase tetanic force production following resistance training (Krutki et al. 2017).

Changes in the opposite direction may occur with decreased physical activity. For example, following 2 weeks of hindlimb suspension, rat hindlimb motoneurons showed smaller antidromic spike amplitudes, increased rheobase, faster membrane →time constants, lower cell capacitances, depolarized spike thresholds, smaller AHPs, and faster minimum and maximal firing rates, consistent with the shift in muscle fiber characteristics toward a faster, fatiguable phenotype (Cormery et al. 2005). Indirect methods applied to humans have yielded more varied results (Button and Kalmar 2019).

Muscle function changes during ageing, due to a plethora of structural and functional adaptations, which occur not only in the peripheral neuromuscular system (neuromuscular junction, motor units), but also the central nervous system (CNS), e.g. degeneration of the human cortex and →spinal cord (Borzuola et al. 2020).

Muscle Non-linearities. ”Muscle, the motor” (Partridge and Benton 1981) does not only move, but also serves as brake, spring, and strut (Dickenson et al. 2000). As springs, muscles may transmit forces generated by other muscles. When it acts as a constant spring or strut, its force output depends non-linearly on its length (length-tension relation). While moving, its force output depends non-linearly on the direction and velocity of shortening or lengthening (force-velocity relation) (Lin 2009a; Partridge and Benton 1981; Roberts 2016; Tsianos and Loeb 2017; Zajac 1989). Muscle contractile effects also vary with the lever-arm changes occurring during movement (Windhorst 2007).

Muscle Time-dependent Properties. Muscle properties change even during a single movement as a result of potentiation, fatigue, injury, disease as well as longer-term physiological and morphological changes that depend on activation, length, and loading history; some muscles exhibit phenomena like yield and sag (Tsianos and Loeb 2017). Muscle force output depends on the preceding length change (Kostyukov and Levik 1994), and on the history of its activation and contraction as expressed in hysteresis and the catch property (Binder-Macleod and Clamann 1989; Burke et al. 1970, 1976; Lin 2009b; Partridge and Benton 1981; Wilson and Larimer 1968). Muscles and tendons adapt to load and use conditions (Tsianos and Loeb 2017).

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19

Upright Stance: Fighting Gravity

CONTENTS

Abstract

• This chapter lays out the biomechanics and spinal neural circuits involved in the organization of quiet upright stance in humans and quadrupeds.

• Quiet upright stance is constantly challenged by gravity and needs to be maintained by dynamic active processes, but it most often is the foundation for other activities. Standing perfectly still is a rare occurrence because arms and hands are generally moving.

• Static equilibrium is attained when gravitational and vertical ground reaction forces cancel each other. To do so, the vertical gravitational force vector emanating from the body′s center of mass (COM) must project within the base of support spanned by the support points. Dynamic equilibrium in addition depends on the velocity of the moving COM.

• The requirements for attaining stable quiet stance are more demanding in humans than in quadrupedal animals. In humans, the body is constantly swaying. Sway must be measured, which involves cutaneous and proprioceptive mechano-receptors, as well as vestibular and visual signals.

• A fundamental requirement for upright stance is generation of skeletal muscle forces and joint stiffness to keep the body upright against gravitational forces. One basic mechanism is the stretch reflex, set up by muscle spindles and their connections to skeleto-motoneurons.

• The stretch reflex is complemented by other neural circuits, including reciprocal Ia inhibition, recurrent inhibition and presynaptic inhibition, as well as reflex connections of group II muscle spindle afferents, group Ib afferents from Golgi tendon organs (GTOs), and group III and IV afferents.

• The patterns of connectivity from these various afferents to skeleto-motoneurons and fusimotor neurons are mostly, but not exclusively, mediated by interneurons, are characterized by large-scale convergence and divergence and thus build complex networks. A similar convergence-divergence principle governs the connections from neural tracts descending from supraspinal structures to interneurons and motoneurons.

• The reflex effects from group Ia and GTO afferents onto motoneurons may serve the reflex regulation of muscle and joint stiffness and of inter-joint coupling.

• In addition, the convergence of segmental afferents of different modalities enables the representation of global variables of body geometry, such as limb orientation, length and loading, which may guide motor maintenance of upright posture.

19.1 Introduction

Terrestrial animals standing and walking with their body above the ground must cope with and counteract the ever-present →gravity. Gravity has had a enormous influence on the evolution of living forms, and shapes and constrains the →perception and interactions with the environment. Humans in particular have evolved a vertical, biped posture that has elevated their line of sight, freed the arms and hands to interact with objects and enabled metabolically efficient walking (Dakin and Rosenberg 2018). In upright stance on legs, animals and humans must maintain erect body orientation and equilibrium, which requires postural orientation and postural equilibrium or →balance (Horak 2009).

Postural orientation includes positioning of body segments relative to each other and to the environment. Of particular importance is the orientation of the body to gravity. Trunk orientation is an important variable to be controlled because it determines the orientation of the limbs relative to objects to be interacted with. Trunk and head position together determine the head´s position in space, which is essential for interpreting sensory data from head-based chemical, auditory, vestibular and visual sensors. Thus, during complex tasks, many animals stabilize their heads in space in order to keep the retina and →vestibular apparatus in a relatively constant position in relation to the environment (Horak and Macpherson 1996; Massion 1998).

Postural equilibrium, or balance in the narrow sense, is defined by the state in which all the forces acting on the body balance out. This state can be static or dynamic. In static equilibrium, the body stays in the desired position and orientation, while in dynamic equilibrium, it moves in a controlled way, in order to prepare for and execute voluntary movements (Haddad et al. 2013; Horak and Macpherson 1996; Lalonde and Strazielle 2007).

19.2 Biomechanical Challenges to Upright Stance

Quiet stance is often depicted as a state completely different from movement but, in fact, quiet stance needs to be maintained by active processes. The →central nervous system (CNS) must: (i) have a postural body schema anchored to the vertical, (ii) provide for upward thrust generated by actively contracting anti-gravity muscles and for →stiffnesses of joints as a first defence against perturbations, (iii) provide for a battery of internal mechanisms that cope with internal or external perturbations, including movements of the arms and hands, which elicit inter-segmental →inertial forces (Balasubramaniam and Wing 2002), (iv) organize proper coordination of muscle activities at different joints; (v) insure that these muscle activities are finely calibated and balanced in order not to jeopardize equilibrium and stability.

19.2.1 Basic Definitions

Forces. During quiet stance, the forces acting on the body are the gravitational force pulling the body and its parts vertically downward, and the counteractive forces exerted by the support surfaces (→ground reaction forces).

The ground reaction forces are distributed over the areas of contact between the feet or paws with the support surface, but are often represented as a lumped vertical vector at the →center of pressure (COP), which is the weighted average of all distributed pressures in the contact area.

Static Equilibrium is attained when the gravitational force vector and the lumped vertical ground reaction force vector cancel each other, i.e., have equal magnitude but opposite direction. To do so, the vertical gravitational force vector emanating from the →center of mass (COM) of the body must project within the →base of support (BOS) spanned by the support points. Since the body is segmented and gravity →accelerates each individual segment, the COM can lie outside the body, depending on postural orientation.

The severity of the challenge to maintain static equilibrium depends on the number of feet on the ground at any time, and on the height of the COM above the support base. For example, a cat standing quietly with four feet on even level ground has its COM well balanced above a fairly broad base of support. By contrast, a standing human´s much greater COM, centered at about the second lumbar vertebra at a relatively greater height, must be balanced over a relatively smaller base. The challenge to equilibrium is even greater when balancing on tiptoes, standing on stilts, or standing on one foot. Many two-legged animals are extremely proficient at one-foot standing, for instance storks or flamingos, at rest or asleep.

Dynamic Equilibrium depends, in addition, on the velocity of the moving COM. If the COM is moving fast enough to exceed the limits of the base of support, the body is dynamically unstable. Conversely, the body may be dynamically stable even if the COM is outside the base of support but is moving toward it with sufficient velocity (Maki 2009). This situation is typical of locomotion. During walking, running, sprinting, galloping or jumping, erect body orientations have to be balanced and stabilized dynamically. During locomotion, some feet are off the ground. This reduces or temporarily abolishes a support base. In any case, the COM rarely projects into the support base. In addition, the forces and →torques are much greater, because the body must not only to be supported against gravity but also be propelled, requiring inertial forces.

19.2.2 Human Quiet Stance

Stabilization of static equilibrium is a dynamic process because the body is always in motion. Even during quiet stance, the human body sways (postural sway; Chap 20), the degree depending on several factors, among them age (Haddad et al. 2013), health condition (Schoneburg et al. 2013), degree of physical training (Kiers et al. 2013),

viewing conditions (Nardone and Schieppati 2010), and simultaneous →cognitive tasks such as gaze shifts toward precise targets (Bonnet and Baudry 2016). Hence, keeping the COM above the support base requires continuous, more or less large postural adjustments (Mergner 2010). Such adjustments involve not only the sensory-motor system, but also the →autonomic nervous system, both systems sharing some neural structures (Sibley et al. 2014).

The problem of keeping the humans erect is especially challenging because the human body consists of a linked series of segments that are able to move relative to each other in various directions (Hsu et al. 2007; Ivanenko and Gurfinkel 2018; Sasagawa et al. 2013). In order to analyse the problem, a first approximation is to assume that the segments are coupled rigidly above the ankle joint so that the body is seen as stiff, behaving like an inverted pendulum, pivoted around the axis through the ankle joints (Morasso et al. 2014; Peterka 2018). In this model, the COM is located at height h above and on average about 4-5 cm in front of the ankle joint. The line connecting COM and the ankle joint is inclined forward by an angle, θ_{sw}.

The body weight (→mass times gravity constant, g: $m.g$) exerts a dorso-flexor torque at the ankle, accelerating the body forward. In order to keep the body from falling forward, an oppositely directed ground reaction force, R, must balance the gravitational downward force. This force is the net result of all the distributed forces occurring across the foot-surface contact areas. It is usually measured by force plates that permit determination of the center of pressure (COP).

19.2.3 Quadrupedal Quiet Stance

In quadrupeds standing quietly on a horizontal surface, the vertical projection of the COM and the →spatial orientation of limb segments vary little. This constancy is a result of →biomechanical constraints inherent to the skeleto-muscular apparatus and of neural processes. (Lacquaniti et al. 1984).

Quiet standing involves some relatively invariant strategies, as shown in cats trained to stand freely on a platform equipped with small force platforms:

(i) When the support platform is tilted forward and backward (pitch direction), the cats tend to keep the vertical orientation and the length of their limbs relatively constant. The orientation of the cat's trunk remains roughly parallel to the surface while the projection of the COM onto the support surface changes, depending on tilt angle (Lacquaniti et al. 1984, 1990).

(ii) Loading the cat´s forequarters with 10-20% of its weight does not appreciably change the limb geometry in terms of length and orientation angle, despite a considerable forward shift in projection of the COM and an increase in contact force vectors at the front paws (Lacquaniti et al. 1990).

(iii)

(iii) The contact force vectors at the paws remain closely aligned with the vertical, so that the torques at the proximal joints (scapula and hip) are close to zero and the torques at other joints do not change much (Lacquaniti et al. 1990).

(iv) When cats are trained to stand with different distances between forefeet and hindfeet, the trunk remains oriented largely parallel to the support surface and the internal limb geometry remains about the same, although the limbs have to be levered at the girdles to accommodate the changes in stance distance. The directions of the ground reaction forces covary with the limb axes. Forelimb joint torques therefore remain the same, and vary only slightly in the hindlimb (Fung and Macpherson 1995). The torques at scapula and hip and the tangential forces at the paws may differ substantially from those during normal stance and thus require greater →energies (Lacquaniti and Maioli 1994).

Thus, in the maintenance of stance posture, trunk orientation and intra-limb geometry are constrained in order to minimize muscular effort or →energy expenditure. The constraints probably are both mechanical and neural in nature. Mechanical constraints are determined largely by joint configurations, capsules, ligaments, and →visco-elastic properties of →skeletal muscles. Neural constraints are mainly determined by →spinal →reflexes, such as pathways from muscle spindle group Ia afferents and Golgi tendon organ (GTO) group Ib afferents to →skeleto-motoneurons (motoneurons innervating skeletal →muscle fibers, including →α-motoneurons and →β-motoneurons; in brief: α-motoneurons) (Fung and Macpherson 1995).

(v) Since contact forces at the paws and joint torques vary independently of limb geometry, the two sets of kinematic (movement-related) and kinetic (force-related) variables seem to be controlled independently by the central nervous system (CNS) (Lacquaniti and Maioli 1994).

These findings suggest that the maintenance of quiet stance requires an →internal model of body geometry, which serves as a reference to control actual body geometry (Lacquaniti and Maioli 1994; Lacquaniti et al. 1997). The neuronal implementation of this internal model and, hence, its location in the →neuraxis are not yet well understood. However, the above studies suggest that the →spinal cord is able to define and maintain certain variables of body geometry such as limb orientation, limb lengths and loading. These variables can be generated by the convergence of proprioceptive afferents of diverse modality (Chap 9) and used to guide the proper motor output needed to assure stance. But this requires a complex sensory-motor transformation.

19.3 Central Representation of Posture

For the perception and control of body orientation in space, the CNS must have a reference, to which it can relate body orientation, and this reference is the earth vertical, of which the CNS must create and incorporate a representation. Furthermore, it must create a representation of the body′s configuration, i.e., a postural body schema constructed from sensory signals (Dakin and Rosenberg 2018). Strangely, humans value verticality as aesthetically attractive, but only when they stand upright themselves (Gallagher and Ferrè 2018). Perhaps, this could have something to do with the fact that

lines in the world, urban as well as natural, have higher probabilities to be vertical or horizontal than to show intermediate orientations. These tendencies are reflected in the sensitivities of cerebro-cortical cells, first in primary visual cortex, where greater numbers of cells respond preferentially to vertical than oblique orientations (Dakin and Rosenberg 2018).

19.3.1 Estimation of the Earth Vertical

Subjective verticals are what their names proclaim: subjective. A variety of experimental paradigms have been used to probe their construction. In the subjective visual vertical (SVV) task, human participants align a visually presented line with the perceived vertical. In the subjectic haptic vertical (SHV) task, subjects align a hand-held lengthy object with the perceived vertical, and in the subjective postural vertical (SPV) task, they align their body orientation with the perceived vertical (Dakin and Rosenberg 2018). These estimates may differ from each other. For example, when the body is roll-tilted, SVV and SHV elicit different patterns of errors, with SVV generally being biased towards the body and SHP remaining accurate or being biased away from the body. Evidence has been provided to suggest that the two measures access different but related estimates of the gravitional vertical (Fraser et al. 2015). Hence, the relation or subjective estimates to gravity are modifiable and subject to various influences.

Various mental paradigms including lesions or pathological loss of sensory inputs have been used to determine the influence of varying conditions and sensory inputs on the accuracy and precision of verticality estimates (Dakin and Rosenberg 2018).

The subjective vertical is constructed from various sensory sources: vision, vestibular signals, proprioceptive signals from →mechano-receptors located in muscles, tendons and joint capsules as well as from cutaneous mechano-receptors (tactile) signals from the foot soles play major roles (Gurfinkel et al. 1995). These various sensory signals are noisy and at times ambiguous and are therefore integrated, in order to improve the accuracy and precision of verticality estimates, but the →multi-sensory integration requires the transformation of the →frames of reference of the different modalities (Dakin and Rosenberg 2018).

19.3.1.1 Cutaneous Signals

The distribution of pressure on the foot soles and of foot-tissue deformation varies with body orientation. For example, about 0.5 mm of vertical oscillation in the calcaneus (forefoot) of a quietly standing humans is associated with about 0.5 degrees of body tilt, or about 0.7 cm of COP displacement (Ivanenko and Gurfinkel 2018). Foot-sole deformation can be sensitively monitored by cutaneous mechano-receptors, whose discharge properties indicate whether the body is perpendicular to the ground or not. Vibration of various parts of the foot soles lead to →illusory perceptions of whole-body leaning, with the orientation and amplitude depending on the particular stimulation patterns. The perceptions are at times accompanied by kinesthetic illusions along the

longitudinal body axis (Roll et al. 2002).

19.3.1.2 Proprioceptive Signals

Proprioceptive signals arising from the ankle joints aid in determining whether the body is perpendicular to the ground or not, and contribute to the perception of body orientation relative to vertical. But it is not only proprioceptors from the ankle, rather from along the entire body that contribute to postural orientation. For example, vibration of dorsal neck muscles activates muscle spindle Ia afferents in subjects with eyes closed, which induces forward body sway. This occurs because the CNS interprets dorsal neck muscle vibration as muscle lengthening related to head flexion on the trunk. Since vestibular signals tell the CNS that the head remains stationary in space, head flexion should be due to backward body tilt. This illusion is then actively counteracted by forward body tilt (Ivanenko et al. 1999; Kavounoudias et al. 1999; Pettorossi and Schieppati 2014).

The manner in which the CNS integrates proprioceptive information from different body parts is not well understood, but the process appears to follow fairly simple vector-summation rules. Thus, postural responses evoked by vibrating neck and ankle muscles together may equal the sum of the effects evoked by vibrating the muscles at different body levels individually (Kavounoudias et al. 1999; Roll et al. 1989).

Proprioceptors other than muscle spindles can contribute to the perception of vertical. For example, lateral gastrocnemius tendon vibration induces either backward falling of the whole body or, when the back is fixed, an illusion of forward movement of the whole body. This illusion disappears in →micro-gravity, when the subject´s feet are fixed to the floor in the absence of body weight. Postural sway is restored when stretchers attaching the hip to the floor are added, so as to exert forces comparable to the body weight. This suggests that load receptors that normally monitor the effects of gravity on the body segments are involved. In addition to cutaneous pressure receptors in the foot sole, load receptors may include joint receptors and receptors monitoring the muscle effort needed to oppose gravity, such as the Golgi tendon organs (GTOs).

Somatosensory loss can lead to various disturbances o verticality estimates (Dakin and Rosenberg 2018)

19.3.1.3 Vestibular and Graviceptive Signals

Vestibular signals provide indications of the head´s position and motion in space, as well as trunk motion (Mergner 2010; Chap 10). Dysfunctions of the vestibular system can lead to biases or loss of precision in verticality estimation, augmenting the reliance on other sensory sources (Dakin and Rosenberg 2018).

In many vertebrates, determination of body orientation also depends on proprioceptive signals from cervical structures, as well as trunk →graviceptors whose activity indicates the earth vertical. There appear to be at least two afferent systems that involve graviceptors. One originates in and around the kidneys, with projections to the

→cerebellum and →neocortex. Graviceptors are also located in tissues supporting large blood vessels and abdominal viscera (Mittelstaedt 1997, 1998). In the caudal intraparietal (CIP) area of macaques, gravity estimates of vestibular and somatosensory signals change the visual orientation preferences of neurons, which occur with changes in head and body orientation, into the direction of the gravity-centered representation, but the approximation is incomplete (Dakin and Rosenberg 2018).

19.3.1.4 Visual Signals

Whenever the visual surround is stationary and head-trunk-leg linkages are rigid, →visual motion can signal body motion. However, when the →visual field is rotated around the line of sight, the perceived verticality is biased and induces ocular torsion. Large-field angular visual motion occurs naturally during head tilts, and induced experimentally biases orientation perception as if the head were tilted relative to gravity and may elicit abnormally large postural sway in patients with spino-cerebellar →ataxia type 6. Neurons which might contribute to head-orientation estimates exist in the cerebellum, →brainstem, and →ventral intraparietal (VIP) area. Motion signals and signals from semicircular canals can be integrated to improve estimates of changes in head tilt. Appropriately, neurons in the vestibular complex integrate visual and vestibular rotation signals (Dakin and Rosenberg 2018). Thus, when visual signals are used to estimate the earth vertical, they must be calibrated using other sensory information. Clearly, the CNS cannot rely on any single sensory modality, but must make use of various sources of information and integrate them into an estimate of the earth vertical.

19.3.2 Determination of Global Control Variables

There are two main views as to which global variables are controlled in upright stance. One is that →recognition of body configuration in the CNS is the main determinant. The other is that the COM location is the more critical variable.

Body Geometry. One hypothesis holds that the CNS primarily controls body configuration relative to the earth vertical. In quadrupeds, this would mean that what is regulated during stance is the orientation and length of the leg axes with respect to the vertical, or of the trunk axis relative to the support surface. In humans, it would be the body axis linking body segments along a line from head to feet, oriented with respect to the earth vertical (Gurfinkel et al. 1995).

Projection of COM into Support Base. Several observations support the notion that the vertical projection of the COM into the supporting area is the major factor in the control of upright stance. In humans under normal gravity conditions, both the body´s COM projection and the body trunk axis can be regulated simultaneously. By contrast in micro-gravity, subjects with their feet fixed to the floor respond to a request to adopt a vertical posture by positioning the COM close to the ankle joint axis, with the trunk axis inclined forward (Clément et al. 1984). When asked to bend their bodies forward or backward, they keep their COM projection close to the ankle joint axis, like in

normo-gravity (Massion et al. 1997).

The two views need not be mutually exclusive. It has been suggested that the top global variable is body geometry, which then secondarily determines the COM projection within the biomechanical constraints (Lacquaniti et al. 1997).

It has also been hypothesized that the nervous system specifies a referent orientation that is changed when, for example, the body leans forward. The nervous system would then tilt the referent orientation forward, which would reduce →vestibulo-spinal drive to the ankle extensor muscles and secondarily let the body follow the gravitational force until the new position is reached. There is evidence for this suggestion: Vestibulo-spinal activity is reduced while cortico-spinal activity remains constant (Zhang et al. 2018).

19.4 Anti-gravity Thrust and Stiffness

The maintenance of upright stance requires actions of a chain of anti-gravity muscles along the body, which prevent the loose collection of bones from collapsing under the impact of gravity. These anti-gravity muscles must produce an upward thrust and provide for joint stiffnesses in preparation for internal and external disturbances. While supraspinal structures contribute to accomplish these tasks, so do networks at the spinal cord level.

19.4.1 α– and γ–Rigidity

In quadrupeds, inactivation of the cerebellum by anemic decerebration causes intense →rigidity due to activation of α-motoneurons innervating the extensor muscles (Pollock and Davis 1930, 1931). Severing the neuraxis at the level of the →midbrain →colliculi induces a rigidity in anti-gravity extensor muscles that is strong enough to support the body weight during standing and depends on the integrity of the reflex loop (Sherrington (1898). These classical models of upright posture have been interpreted as α–rigidity not dependent on the reflex loop (Pollock and Davis 1930, 1931), and as γ-rigidity or `reflex standing´ (Sherrington 1898), in which α-motoneurons are indirectly excited by →γ-motoneurons and which is thus associated with exaggerated extensor →stretch reflexes (Granit 1970). Hence, in addition to α-motoneurons, γ- motoneurons may have powerful effects on motor output. In normal animals, α- motoneurons and γ-motoneurons are commonly co-active, supported by some activity of β-motoneurons that innervate both →extrafusal and →intrafusal muscle fibers (Grill and Rymer 1987).

19.4.2 Monosynaptic Stretch Reflex Circuit

Group Ia afferents from primary muscle spindle endings form monosynaptic and oligosynaptic linkages to homonymous and synergistic α-motoneurons, but also to other α-motoneurons (below). On average, the strongest monosynaptic connections are made with α-motoneurons involved in postural tasks, particularly those innervating anti-

gravity muscles (Lüscher and Clamann 1992). Those →motor units that are predominantly active during postural tasks, S-type units with small α-motoneurons, receive the strongest monosynaptic Ia afferent input. In faster forms of human locomotion such as running and sprinting, during which larger α-motoneurons are recruited, monosynaptic Ia reflexes appear to significantly contribute to triceps surae activation during the stance phase (Capaday and Stein 1987). Monosynaptic group Ia connections are complemented by monosynaptic connections of group II muscle spindle afferents, mainly with homonymous and synergistic α-motoneurons (e.g., medial gastrocnemius group II afferents with triceps surae α-motoneurons), at a strength of about half that of monosynaptic group Ia connections. In addition, there are weaker di- and trisynaptic excitatory and inhibitory connections (Stauffer et al. 1976). The monosynaptic group II-α-motoneuron connections might assist the Ia-α-motoneuron connections. The homonymous and synergistic connections establish a closed feedback loop with additional inputs from fusimotor neurons (ß-motoneurons and γ-motoneurons).

A strong stretch reflex action has the advantage of counteracting external and motor disturbances. For example, when an active limb extensor muscle slightly yields under the impact of gravity or an accidental internal decrease of muscle force, its muscle spindles are stretched, raise their discharge rate and reflexly excite their homonymous α-motoneurons, which increase anti-gravity muscle contraction to resist the yield. A disadvantage is that, with too high a gain, it is prone to instability due to the unavoidable signal transmission delays in the loop. Indications of this risk are the possible contribution of the stretch reflex to physiological →tremor and clonus in →spasticity.

19.4.3 Input-Output Relations of α-Motoneurons

Coordinating the activities of muscles acting at different joints requires complex neuronal interactions. The input-output relations of spinal neurons are characterized by widespread convergence and divergence, the patterns differing between different systems. These patterns play major roles in the functions of spinal reflex systems.

19.4.3.1 Distribution of Monosynaptic Group Ia Effects on α-Motoneurons

Skeleto-motoneurons (in brief: α-motoneurons) receive multifarious direct or indirect inputs from themselves via excitatory recurrent →axon collaterals (recurrent facilitation), →recurrent inhibition via Renshaw cells, reciprocal Ia inhibitory interneurons, a plethora of other spinal →interneurons, proprio-spinal neurons, sensory afferents of all types, and several supraspinal structures. The distribution patterns depend on the animal species, the muscles innervated (e.g., extensors vs. flexors) and their roles in posture and movement. The supraspinal structures include →cerebral cortex, cerebellum, and →brainstem structures, including the →vestibular nuclei, →nucleus ruber, and the →reticular formation (Baldissera et al. 1981).

Group Ia afferents from a muscle make monosynaptic connections to wider sets of α-motoneurons innervating more or less synergistic muscles in the hindlimb and forelimb of cat and non-human primates (Baldissera et al. 1981; Eccles et al. 1957; Eccles and Lundberg 1958; Edgley et al. 1986; Hongo et al. 1984). This `Ia synergism´ has been interpreted as contributing to muscle synergies during locomotion and →skillful grasping (Schomburg 1990).

In humans, heteronymous monosynaptic group Ia connections to α-motoneurons innervating muscle in the lower limb are more widespread than in the cat or the baboon. Whereas in the latter species they mainly link α-motoneuron pools of muscles acting synergistically at the same joint, transjoint group Ia connections between α-motoneurons innervating ankle and knee muscles are almost the rule in humans (Meunier et al. 1993). α-Motoneuron pools innervating thigh and shank muscles, even seeming antagonists, are linked by heteronymous group Ia feedback connections. This has been interpreted by the demand for varying synergies during different activities. For example, tibialis anterior and quadriceps muscles are co-active while leaning backwards from vertical stance, gastrocnemius and →hamstring muscles while leaning forward, gastrocnemius and quadriceps during vertical displacements, and tibialis anterior and hamstrings during reciprocal vertical displacements of the feet. It has been proposed that alternative context-dependent patterns of reflex actions (e.g., soleus to quadriceps or hamstrings) may be appropriately selected by directing →presynaptic inhibition of group Ia afferents not required in a particular motor action (Meunier et al. 1993).

19.4.3.2 Distribution of Group II Afferent Effects on α-Motoneurons

As noted above, α-motoneurons receive monosynaptic inputs from group II muscle spindle afferents which might support the group Ia monosynaptic effects (Kirkwood and Sears 1974; Stauffer et al. 1976). The monosynaptic group II effects are probably not that significant, however. Stronger contributions to extensor →muscle tone might be provided by oligosynaptic group II-α-motoneuron connections. But these contributions would likely not result from phasic reflex responses to the sway-related muscle length oscillations because group II spindle afferents have a low sensitivity to small-amplitude length changes (Matthews and Stein 1969). Instead the extensor support may be tonic, maintained by a fusimotor loop enhanced by descending signals from supraspinal sources to γ-motoneurons and to the interneurons in the group II pathway. Dynamic group II-mediated reflexes occur in response to larger-amplitude external stance perturbations (Chap 20).

Group II afferents feed alternative excitatory and inhibitory interneuronal pathways to both extensor and flexor α-motoneurons, these pathways being independent. Group II reflex effects from many muscles converge onto α-motoneurons, mediated by subsets of interneurons with a more restricted convergence from extensor and flexor muscle afferents and a limited divergence of excitatory and inhibitory interneurons to different α-motoneuron pools. These interneurons also receive, in various proportions, convergent inputs from group Ia, group Ib, low-threshold mechano-receptor (LTMR) afferents,

joint afferents, muscle group III and group IV afferents including →nociceptive afferents, and from various descending tracts including the →cortico-spinal, →rubro-spinal, →reticulo-spinal and →vestibulo-spinal tracts (Jankowska 1992; Schomburg 1990) .

Due to the wide convergence and divergence, interneurons with strong group II inputs are probably involved in various types of reflex actions, including short- and medium-latency stretch reflexes (SLR and MLR, respectively) and the transcortically mediated stretch reflex (Côté et al. 2018; Edgley 2001; Jankowska 1992; Jankowska and Edgley 2010; Lundberg et al. 1987; Schomburg 1990). In humans, the oligosynaptic homonymous and widely distributed heteronymous reflex effects mediated by group II afferents and associated interneurons can be significant and are modulated during stance and movements (Marchand-Pauvert et al. 2005; Schieppati and Nardone 1997; Simonetta-Moreau et al. 1999).

19.4.3.3 Distribution of Group Ib Afferent Effects on α-Motoneurons

Under some conditions such as upright stance and the stance phase of locomotion, additional reflex support for extensor muscles comes from GTO group Ib afferents.

Group Ib afferents are supposed to convey force feedback particularly from contracting muscles (Jami 1992; Nichols 2018). Group Ib effects are mediated by excitatory and inhibitory interneurons (Côté et al. 2018; Jankowska 1992) that are integrated with other reflex pathways and task-dependent (Jankowska and Edgley 2010). The task-dependency is exemplified by radically different group Ib reflex effects during quiescence (e.g., while lying) vs. quiet upright stance and the locomotor stance phase (Chap 20).

Group Ib Afferent Effects on α-Motoneurons during Quiescent States. In reduced immobile preparations, group Ib afferents exert di- or trisynaptic inhibition on homonymous α-motoneurons and closely related synergistic α-motoneurons (autogenic inhibition), as well as di- or trisynaptic excitation on antagonist α-motoneurons. This pattern was traditionally referred to as the inverse myotatic reflex (Nichols 2018).

Group Ib Afferent Effects on α-Motoneurons during Quiet Stance. During quiet stationary stance in →alert cats, a contrasting pattern was observed while activating the Golgi tendon organs (GTOs) in hindlimb extensors by intramuscular stimulation with chronically implanted electrodes and recording →electromyographic (EMG) reflex responses in various hindlimb muscles. Stimulation of every hindlimb extensor muscle tested evoked excitatory EMG responses that were widely distributed among hindlimb extensor muscles, thus reflecting a positive force →feedback system. For example, stimulation of ankle extensors typically excited extensor and flexor (tibialis anterior) muscles at the ankle and hip but not knee, whereas stimulation of hip extensors typically excited only extensors at all three joints. However, intramuscular stimulation of either the lateral gastrocnemius or medial gastrocnemius inhibited the soleus muscle while exciting other extensors at the ankle and more proximal joints. Similar activation

patterns are seen in standing cats with physiological loading of the left hindlimb by sudden unloading of the left forelimb or right hindlimb: widespread activation of left hindlimb extensors but initial inhibition of the soleus muscle; co- activation of extensors and flexors at ankle and hip. These patterns of force feedback can function to support the body weight during stance (Pratt 1995).

The group Ib reflex effects are probably supported by facilitating signals from the cortico-spinal tract (CST) and rubro-spinal tract with mono- to oligosynaptic connections with the intercalated interneurons, while the dorsal reticulo-spinal tract and the →noradrenergic reticulo-spinal tract exert inhibition (Schomburg 1990; Jankowska 1992).

In cats, group Ib afferents exert widespread excitatory and inhibitory reflex effects that reach almost all α-motoneuron pools of the ipsilateral limb, i.e., α-motoneurons that innervate muscles crossing different joints and axes of rotation, and depend on the context and task of motor acts (Côté et al. 2018; Jankowska 1992; Nichols 2018; Schomburg 1990). The distribution of excitatory effects is at least partially reciprocal to that of inhibitory effects (Schomburg 1990; Jami 1992; Jankowska 1992). The intercalated excitatory and inhibitory interneurons are shared to a large extent with group II afferents and in part even group Ia afferents from muscle spindles (Jankowska and Edgley 2010).

In addition to α-motoneurons, other types of spinal neurons are affected by group Ib interneurons (Côté et al. 2018; Jami 1992; Jankowska 1992; Schomburg 1990; Windhorst 2007): γ-motoneurons, group II and group Ib interneurons, cells of origin of the →ventral spino-cerebellar tract (VSCT), and cells of origin of the →dorsal spino-cerebellar tract (DSCT) in Clarke´s column (Bosco and Poppele 2001).

19.4.4 Input-Output Relations of γ-Motoneurons

In order to supply enough anti-gravity force during upright stance, direct activation of extensor α-motoneurons from descending tracts might be assisted by their indirect activation via the reflex loop boosted by fusimotor inputs to muscle spindles. This might suggest that inputs to α-motoneurons and γ-motoneurons should be similar to assure their proper co-activation. However, things are more complex.

In cats, the patterns of sensory inputs to α-motoneurons and γ-motoneurons are different. γ-Motoneurons receive no group Ia input nor reciprocal inhibition, both in flexor and extensor γ-motoneurons and irrespective of whether they are static or dynamic (Appelberg et al. 1983a). Group II fibers have mixed excitatory and inhibitory oligosynaptic effects on static and dynamic γ-motoneurons (Appelberg et al. 1982b, 1983b). Joint afferents from intra-articular ligaments exert potent effects on γ-motoneurons (Johansson et al. 1991). Group III and group IV afferents activated by intra-arterial injection of metabolites exert differential effects on the dynamic and static varieties of γ-motoneurons (Johansson et al. 1993). By contrast, in humans, hypertonic saline injection into the tibialis anterior muscle does not change muscle spindle discharge (Smith et al. 2019).

γ-Motoneurons receive inputs from the →motor cortex, cerebellum, nucleus ruber, reticular formation and vestibular nuclei, in part independently of α-motoneurons (Windhorst 1988). In particular, while in cats rubro-spinal effects on α-motoneurons and both classes of γ-motoneurons are similar (Appelberg et al. 1982a), dynamic γ-motoneurons are separately controlled from a →mesencephalic area for dynamic control´ (MesADC) close to the nucleus ruber (Appelberg et al. 1975). This specific control locus might be important for setting the dynamic sensitivity of group Ia afferents to muscle length changes (Chap 8) and thus for the detection of small and rapid deviations from the desired values, which occur during upright stance.

19.4.5 Input-Output Relations of Reciprocal Ia Inhibition

In addition to controlling the activity of agonist muscles, antagonist muscle activity must be controlled as well. An important mechanism to organize the coordination of muscle activities around joints is reciprocal inhibition.

If a group of syergistic muscles is to be activated under some condition, their antagonists had better not in order not to impede the agonist action. This can be done by complementing the excitatory monosynaptic group Ia action on synergistic α-motoneurons by an inhibitory action of the same group Ia input on antagonist α-motoneurons. The latter action is mediated by reciprocal Ia inhibitory interneurons and occurs during the stretch reflex and during directed voluntary muscle contractions (Baldissera et al. 1981; Côté et al. 2018; Hultborn 1976; Jankowska and Edgley 2010; Nichols 1994).

α-Motoneurons and `corresponding´ reciprocal Ia inhibitory interneurons are closely linked in that they receive similar patterns of inputs, prominently from group Ia afferents, but also from other sensory afferents and supraspinal structures via spinally descending tracts. Inhibition of hindlimb α-motoneurons from the cortico-spinal, rubro-spinal, reticulo-spinal and vestibulo-spinal tracts is largely mediated via reciprocal Ia inhibitory interneurons (Baldissera et al. 1981; Jankowska 1992; Hultborn 2001; Lundberg et al. 1987; Schomburg 1990). For example, activation of an extensor α-motoneuron pool by the vestibulo-spinal tract coincides with inhibition of the antagonist flexor α-motoneurons by collaterals of extensor-activating tracts. Reciprocal Ia inhibitory interneurons receive inputs converging from group Ia fibers originating in more than one muscle.

Co-contraction of muscles acting around a joint increases joint stiffness, e.g., during safety stance or gait on slippery surfaces. Under these conditions, however, a reciprocal inhibition of the antagonist muscles would be counterproductive. Thus, when subjects co-contract the antagonist muscles around say the ankle joint, reciprocal Ia inhibition between the antagonist α-motoneurons is strongly diminished. One possible mechanism underlying this effect is the facilitation of Renshaw cells which inhibit reciprocal Ia inhibitory interneurons. Monosynaptic group Ia →H-reflexes and stretch reflexes are depressed in antagonist muscles, presumably because of increased presynaptic inhibition

of group Ia afferent terminals on motoneurons (Nielsen 2016).

The axons of reciprocal Ia inhibitory interneurons reach α-motoneurons at quite some distance (Jankowska 1992). As judged by the occurrence of recurrent facilitatory postsynaptic potentials (RFPSPs) in cat hindlimb α-motoneurons (below), RFPSPs are widely distributed, although usually weak (Hultborn et al. 1971; McCurdy and Hamm 1994; Trank et al. 1999; Turkin et al. 1998).

19.4.6 Input-Output Relations of Recurrent Motoneuron Actions

In cats, earlier work showed that α-motoneurons directly connect to each other via recurrent collaterals that build excitatory →synapses on other α-motoneurons and thus exert recurrent facilitation (Cullheim et al. 1977, 1984). In mice, this influence is fairly strong, purely →glutamatergic and apparently distributes over quite some rostro-caudal distance (Bhumbra and Beato 2018). In neonatal mice, activation of α-motoneurons has effects on locomotor functions mediated via glutamatergic recurrent collaterals, but whether this effect persists into adulthood is not known (Falgairolle and O´Donovan 2019).

In cats and mice, α-motoneurons exert complex recurrent inhibition (mediated via Renshaw cells) of α-motoneurons, γ-motoneurons, reciprocal Ia inhibitory interneurons, other Renshaw cells, and cells of origin of the ventral spino-cerebellar tract (Alvarez and Fyffe 2007; Jankowska and Edgley 2010; Katz and Pierrot-Deseilligny 1998; Windhorst 1990, 1996, 2007). The recurrent inhibition of spontaneously active reciprocal Ia inhibitory interneurons and Renshaw cells indirectly produces recurrent facilitation in the target α-motoneurons, eliciting recurrent facilitatory postsynaptic potentials (RFPSPs). even in homonymous and synergistic α-motoneurons (Haase et al. 1975; Hultborn et al. 1971; McCurdy and Hamm 1994; Trank et al. 1999; Turkin et al. 1998).

In the cat, recurrent inhibition links many α-motoneuron pools, some of which are located in different spinal segments and innervate muscles in different limb segments. The reciprocal connections often differ in strength. Recurrent inhibition is particularly expressed in anti-gravity muscles that stabilize joints during upright posture and the stance phase of the locomotor step cycle. The distribution pattern partially overlaps with that of `Ia synergism´ (Baldissera et al. 1981; Eccles et al. 1961; Katz and Pierrot-Deseilligny 1998; Windhorst 1996). In humans, too, heteronymous recurrent inhibitory connections between α-motoneurons innervating muscles in the lower leg are widely distributed with a pattern very similar to that for heteronymous monosynaptic group Ia excitation (Meunier et al. 1994; also Katz and Pierrot-Deseilligny 1998).

Recurrent inhibition is influenced by signals descending from supraspinal sources. In cats, Renshaw cells receive modulating inputs from the →motor cortex, cerebellum, nucleus ruber, reticular formation and vestibular nuclei, in part independently of inputs

of the same origin to α-motoneurons (Windhorst 1988). In humans, heteronymous recurrent inhibition declines during voluntary quadriceps and soleus muscle contractions, and as compared to sitting, recurrent inhibition is weaker during standing and the late stance phase of walking (Iles et al. 2000). The recurrent inhibition from quadriceps to tibialis anterior muscles, but not to soleus, α-motoneurons is reduced when the quadriceps and tibialis anterior muscles are required to co-contract for maintaining upright stance, for example while leaning backwards (Barbeau et al. 2000).

Adult Renshaw cells do not receive group Ia afferent inputs. Renshaw cells can be inhibited by a range of electrical and natural stimuli including touch and pressure applied to ipsi- and contralateral body regions, with →noxious stimuli often being most effective (Wilson et al. 1964). Stimulation of the ipsilateral gastrocnemius nerve at group II strength depresses recurrent inhibition and excites extensor α-motoneurons possibly by disinhibition (Fromm et al. 1977). In cats, activation of group III and IV afferents by intra-arterial injection of →bradykinin, →serotonin (5-HT), lactic acid and KCI transiently raised or lowered the spontaneous firing rate (if present) and almost always decreased the antidromic response of Renshaw cells to motor-axon stimulation (Windhorst et al. 1997).

The functions of recurrent inhibition and facilitation are still discussed controversially, and many hypotheses have been advanced ever since their discovery more than half a century ago (Windhorst 1996, 2007). Some functions probably relate to the organization of moment-to-moment activities of target neurons. Thus, one suggestion concerns the influence of recurrent inhibition on the short-term fluctuation of α-motoneuron discharges based on the finding that synchronous recurrent inhibition produced marked short-term modulation of α-motoneuron spike timing and instantaneous firing rate (Obeidat et al. 2014). This could be of importance for the force development because short interspike intervals nonlinearly enhance the force output of motor units (`catch property´; Chap 18). Another but related role might be that Renshaw cells, together with group Ia afferents, contribute to increase the dynamic sensitivity of α-motoneurons so as to phase-advance motor output and thus to compensate for phase lags induced by signal-transmission delays in the stretch reflex circuit (Matthews 1994, 1997). This could reduce the risk of instability and tremor. In a similar vein, recurrent inhibition has been suggested to influence the short-term α-motoneuron synchronization and thereby tremor (Edgley et al. 2021; Maltenfort et al. 1998; Uchiyama and Windhorst 2007; Williams and Baker 2009). The wide distribution of recurrent inhibition could contribute to these effects by injecting de-correlating →noise into the spinal neuronal system.

19.4.7 Input-Output Relations of Presynaptic Inhibition

Different motor tasks may require different patterns of proprioceptive feedback to regulate spinal motor control functions. Presynaptic inhibition is an adaptable mechanism to control the inflow of sensory inputs into the spinal cord (Quevedo 2009; Rudomin 2009; Rudomin and Schmidt 1999).

Presynaptic inhibition acts by decreasing the efficacy of →synaptic transmission from presynaptic terminals of sensory afferents to spinal neurons, the effects being mediated via inhibitory →GABAergic or →glycinergic interneurons contacting the terminals of

sensory afferents (Koch et al. 2017; Quevedo 2009; Rudomin 2009; Rudomin and Schmidt 1999).

The behavioral effects and the discharge patterns of interneurons mediating presynaptic inhibition are now being studied in mutant mice. Presynaptic inhibition of cutaneous and proprioceptive afferents appears to be executed by different interneurons.

dI4 Interneurons are GABAergic and mediate presynaptic inhibition of low-threshold mechano-receptive (LTMR) afferents (Bui et al. 2015). Somatosensory cutaneous afferents themselves receive two types of presynaptic inhibition: a $GABA_A$-receptor-dependent form from LTMR cutaneous afferents and a form acting on small-diameter afferents and dependent on →N-methyl-D-aspartate (NMDA) receptors (Zimmerman et al. 2019).

RORβ Interneurons. In locomoting mice, presynaptic inhibition appears to be exerted by a group of interneurons expressing the RORβ orphan nuclear receptor, which form inhibitory synapses on myelinated proprioceptive afferents from flexor muscles. Many of the RORβ interneurons are glycinergic and exert their inhibitory actions primarily on group Ib, group II and group III afferents, as opposed to group Ia monosynaptic afferents. In mutant mice lacking RORβ function, the presynaptic inhibition of sensory transmission is degraded and leads to →ataxic (`duck´) gait characterized by exaggerated flexion movements and alterations of the step cycle (Koch et al. 2017).

It is well known from animal and human studies that presynaptic inhibition can be set to different mean levels and modulated dynamically during rest, locomotion and voluntary movements. For example, the monosynaptic transmission from group Ia afferents to α-motoneurons is presynaptically inhibited more strongly during stance than rest (lying), and more strongly during running than walking (Katz et al. 1988; Stein 1995; Nardone and Schieppati 2004).

Presynaptic inhibition is subject to influences from segmental sensory afferents and spinally descending pathways, which modulate its strength and probably distribution in a task- and context-dependent way. The synaptic efficacy of spindle group Ia and II, GTO group Ib and cutaneous afferents is differentially altered by activity in the same groups of afferents as well as by signals descending in cortico-spinal, rubro-spinal, reticulo-spinal and vestibulo-spinal tracts, as well as by raphé-spinal →serotonergic and →locus coeruleus (LC)-spinal noradrenergic systems (Quevedo 2009; Rudomin 2009; Rudomin and Schmidt 1999).

Presynaptic inhibition has a particularly complicated distribution pattern. Some gross functional input-output patterns in cat hindlimb are as follows. Group Ia muscle spindle afferents from both flexor and extensor muscles are inhibited presynaptically by group Ia and Ib afferents in flexor nerves, while group Ib afferents are inhibited only by group Ib inputs from both flexor and extensor muscles (Rudomin and Schmidt 1999). Group II muscle spindle afferents terminating on interneurons in the spinal intermediate zone are strongly inhibited presynaptically by afferents of their own kind (Jankowska et al. 2002). The terminals of cutaneous afferents are also subject to presynaptic inhibition. The distribution of presynaptic inhibition might contribute to →synergy formation, although the precise way it does is unknown (Windhorst 2007).

Little is known about a specific role of presynaptic inhibition in quiet stance. It might co-determine the synaptic efficacy of the Ia-motoneuron connections, which varies with sway direction and position (Tokuno et al. 2008). Between three conditions of quiet standing on inclined platforms (horizontal foot placement, toes up, toes down), the stance stability varies, but presynaptic inhibition of soleus group Ia feedback appears unaltered (Mezzarane and Kohn 2007). Presynaptic inhibition increases with eye closure and when standing on a foam mat relative to standing on a rigid platform, more so in elderly than young people (Baudry and Duchateau 2012).

19.4.8 Multi-modal Convergence of Sensory Afferents on Spinal Interneurons

The functions of proprioceptive muscle afferents have often been neatly separated: group Ia afferents = muscle length plus velocity monitors; group II afferents = muscle length monitors; group Ib afferents = muscle force monitors; joint afferents = joint angle monitors; some cutaneous mechano-receptor afferents = proprioceptive afferents in so far as they measure skin distortion over joints (Prochazka 1996; Edin and Abbs 1991). However, the convergence of different proprioceptive afferents onto common interneurons blurs this picture.

In the cat spinal cord, group Ia and II muscle spindle afferents as well as group Ib afferents from Golgi tendon organs (GTOs) of wide muscular origin converge on interneurons in varying proportions and in part random patterns, these interneurons then projecting on to α-motoneurons that innervate muscles across the limb (Jankowska 1992; Jankowska and Edgley 2010; Schomburg 1990). The entire interneuron population receiving convergent proprioceptive inputs may show some differentiation and fractionation as to the combinations of inputs. For example, subsets of lumbar interneurons receive convergent inputs from both group Ia and group Ib afferents that have co-excitatory, co-inhibitory or mixed reflex effects on the interneurons. Convergence occurs for afferents from the same muscle, or from different muscles acting at the same joint or at different joints. Interneurons with Ia-Ib convergence may project to all α-motoneuron pools in the hindlimb and to contralateral α-motoneuron pools (Jami 1992; Jankowska 1992; Schomburg 1990). However, as pointed out by Edgley (2001): "...giving 'nicknames' to groups of interneurones on the basis of a characteristic input gives a simple indicator to which group they belong, but it is important to remember that what the neurones actually do depends on all of the inputs, as well as on the outputs".

The roles of group III and IV afferents are underestimated in spinal motor control. Group III muscle afferents are more mechano-sensitive than group IV afferents during skeletal muscle contraction, force production, dynamic/static muscle stretch and local intramuscular pressure. Their response to a mechanical stimulus may be potentiated by chemical substances, such as those accumulating during physical exercise, →muscle fatigue or →inflammation. Muscle group IV afferents are more sensitive to metabolites released into the interstitium by muscle activity because their activation usually starts after a delay during prolonged muscle contraction and continues to discharge until the withdrawal of muscle metabolites (Laurin et al. 2015). Both types of afferent may contribute to adapt cardio-vascular and motor functions (Decherchi and Dousset 2003).

Activation of group III and IV muscle afferents by intra-arterial injection of potassium chloride (KCl), →bradykinin, →arachidonic acid, serotonin (5-HT), lactic acid, and hypertonic saline has varied effects on α-motoneurons, γ-motoneurons, Renshaw cells and other interneurons mediated by many different known and unidentified interneurons (Johansson et al. 1993; Kniffki et al. 1981; Rossi et al. 2003; Windhorst et al. 1997), and spatially facilitates excitatory and inhibitory pathways from low- to medium-→threshold cutaneous and joint afferents as well as from group lb and group II muscle afferents (Schomburg et al. 1999). Little is known about the hidden roles that group III and group IV afferents play during normal movements under non-noxious and non-fatigue conditions.

The complex structure of the pre-motoneuronal networks, characterized by widespread inputs and outputs as well as extensive convergence, suggest that they exert sophisticated functions. Two important ones are stiffness regulation and maintenance of body geometry.

19.4.9 Reflex Regulation of Muscle and Joint Stiffness

For the maintenance of upright posture, the stiffnesses of muscles and joints are important for counteracting deviations of vertical stance from the optimal values. Several systems have been suggested to be engaged in providing stiffness, at the levels of individual muscles and joints and at the level of multiple joints and the whole limb.

Limbs of standing animals and humans must be able to resist internal and external disturbances through joint stiffness derived from at least three sources: passive stiffness from connective tissues and the visco-elastic resistance of passive muscle to stretch; active stiffness provided by the resistance of contracting muscle; and reflex-mediated stiffness resulting from the actions of the stretch reflex, which recruits additional α-motoneurons and increases the firing rate of already active α-motoneurons (Duysens et al. 2000; Houk and Rymer 1981; Horak and Macpherson 1996; Nichols and Huyghues-Despointes 2009).

Monosynaptic stretch reflexes and reciprocal Ia inhibition may play roles in stiffness regulation. Group Ia feedback may function largely to regulate the stiffnesses of individual muscles or synergistic groups (Nichols 2018).

Monosynaptic Stretch Reflexes. When an active but →de-afferented (non-reflexive) soleus muscle is extended by a ramp-and-hold stretch in a decerebrate cat, force first increases steeply due to the muscle´s intrinsic stiffness, which is commonly attributed to elasticity of existing actin-myosin cross-bridges. This elasticity has only a short range of operation, which when exceeded by continuing stretch, breaks down so that the muscle `yields´. When the active but de-afferented muscle is contracting during a ramp-and-hold release, the fall in force is more dramatic than the rise in the first case. With an intact reflex, the force changes are larger than the mechanical response for stretch and lower for release. In both cases, however, there is a substantial reflex contribution, a genuine `stretch´ response and an `unloading´ response, which become more symmetrical. This `linearization´ has been ascribed to asymmetric changes in muscle activation by the

reflex. That is, the reflex action dominates responses to lengthening but are less prominent in response to shortening, because activation of group Ia muscle spindle afferents induced by stretch is much larger than the de-activation induced by release (Nichols and Houk 1976).

It has been suggested that, rather than regulating muscle length or muscle force as individual variables, the stretch reflex serves to regulate stiffness as a compound variable (Houk 1979; Houk and Rymer 1981). Length would be signaled by muscle spindle afferents and positively fed back to α-motoneurons, while force would be signaled by Golgi tendon organs and be fed back negatively to α-motoneurons. The combined action of both autogenetic feedback systems would provide for stiffness regulation. The concept of stiffness as a compound variable was later modified because in the decerebrate cat, the →sensory receptors primarily responsible for reflexive eccentric contraction (muscle length increases) are most likely the muscle spindles and their group Ia afferents, which have just the right non-linear dynamic stretch-response properties to predict the impending decline in muscle force and preempt it by reflex action (Houk et al. 1981). It would seem reasonable to also include group II afferents from muscle spindles in this scheme.

Reciprocal Ia Inhibition may be involved in the regulation of muscle and joint stiffness. For instance, when the anti-gravity muscle soleus is stretched, its autogenetic stretch reflex increases its stiffness. At the same time, the antagonist tibialis anterior shortens, which reduces the strong reciprocal inhibition onto soleus and further increases its stiffness (Nichols 1989; Nichols and Koffler-Smulevitz 1991). It has also been suggested that excitatory force feedback increases muscular stiffness and interjoint coupling (Nichols 2018).

Joint Stabilization. Similarly, the ankle abductor muscles [peroneus brevis (PerB); peroneus longus (PerL)] and adductor muscles [tibialis posterior (TP); flexor digitorum longus (FDL); flexor hallucis longus (FHL)] are linked by mutual reciprocal inhibition. Thus, PB and TP share strong, length-dependent, short-latency inhibitory reflexes most likely mediated via Ia reciprocal inhibition. Just as reciprocal inhibition between soleus and TA stiffens the ankle joint against sagittal perturbations, reciprocal inhibition between PerB and TP could stiffen the ankle joint against non-sagittal perturbations (Bonasera and Nichols 1996), which stabilizes the ankle. This is supported by intracellular recordings showing that recurrent facilitatory →postsynaptic potentials (RFPSPs) predominate in the recurrent projections to PerB α-motoneurons, which during locomotion are co-active with hindlimb extensors and its adductor antagonist, tibialis posterior (Turkin et al. 1998).

In the cat and human, soleus group Ia afferents establish monosynaptic connections with PerB α-motoneurons and might contribute to the lateral stabilization of the ankle during stance and the stance phase of locomotion. They are more frequent and stronger in humans than cats, possibly related to the greater need for foot stabilization in plantigrade bipedal stance and gait in humans (Meunier et al. 1993).

The extensor digitorum brevis (EDB) receives RFPSPs from various sources. It can be active during stance as well as swing and often co-contracts with antagonists of the hindpaw and extensors of the hip and ankle. Co-activity of EDB and its antagonists

during stance may increase paw stiffness. RFPSPs from extensor α-motoneuron pools to EDB α-motoneurons may increase EDB motor output and thus contribute to regulate the degree of co-contraction and hence stability (Trank et al. 1999).

19.4.10 Reflex Regulation of Inter-joint Coupling

Perturbations to the whole limb cannot be mastered by only adjusting the stiffness of individual joints, but must be counteracted by coordinated stiffnesses across joints at a global level. This requires the common regulation of α-motoneuron pools innervating muscles at different joints.

It has been suggested that GTO force feedback and its spinal processing play major roles in organizating trans-joint stiffness adjustments. Functionally important effects of force feedback have been revealed by physiological experiments. The pattern for cat ankle and knee muscles is fairly complex, but appears to show the following main features (Nichols 1994, 2018):

Across-joint Coupling. Force feedback is not distributed homogeneously among anti-gravity synergists. For example, group Ib input from the gastrocnemius muscles strongly inhibits the soleus muscle, but not vice versa, and there is no inhibition between the gastrocnemii. This is probably because the soleus is a mono-articular muscle while the gastrocnemii are bi-articular. This is also suggested by the pattern among the knee extensors. Thus, inhibitory force feedback may mediate coordination across joints (Nichols 2018).

Across-axis Coupling. Inhibitory force feedback also links muscles across axes of rotation. If muscle groups are defined by common mechanical actions and group Ia-α-motoneuron connections, this type of inhibitory force feedback links muscles of different groups. For instance, triceps surae muscles provide inhibitory force feedback to the peroneus muscles (ankle abductors) and the tibialis posterior (ankle adductor), i.e., muscles operating at different axes (flexion/extension and abduction/adduction) (Nichols 2018).

Generally, the global mechanical properties of the limb may be regulated by the integration of distributed feedback from GTO afferents and muscle spindle afferents. Inhibitory force feedback is predominantly inter-muscular and distributed. Together with length feedback, it may manage limb mechanics at a higher, more global level. Collectively, all sources of force feedback as well as length feedback determine the mechanical properties of the limb as a whole (Lyle and Nichols 2018; Nichols 2018).

The distribution of muscle activations and stiffnesses across the limb provides the kinetic basis for global kinematic invariants such as limb orientation, length and loading, which are expressions of an internal model of body geometry (Lacquaniti and Maioli 1994; Lacquaniti et al. 1997). These variables can be generated by the convergence of proprioceptive afferents of diverse modality and used to guide the proper motor output needed to assure stance. But this requires complex sensory-motor transformations which are performed by the pre-motoneuron network.

In summary, it may be presumed that the spinal neural networks perform sophisticated but hidden operations to solve "...some of the most complex problems in motor control and, in that sense, spinal mechanisms are much more sophisticated than many neuroscientists give them credit for" (Poppele and Bosco 2003). Specifically, the vertebrate spinal cord is able to solve, at least to some degree, the degrees-of-freedom problem, the problem of complex spatial sensory-motor transformations, and the inverse dynamics problem (Poppele and Bosco 2003), as well as to cope with inter-segmental interactions, kinetic and kinematic specifications, non-linear and time-dependent muscle properties including muscle fatigue. Many of the involved interneurons likely are engaged in multiple functions.

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20

Postural Sway and Responses to Perturbations of Stance

CONTENTS

Abstract

• Quiet upright stance is constantly challenged by gravity leading to postural sway. Upright balance is endangered by interior and exterior perturbations, requiring appropriate counter actions.

• Internal perturbations include self-generated body-part movements which change the distribution of body mass; external perturbations include exterior forces acting on the body.

• Postural responses to counter external stance perturbations can be roughly divided into two classes: fixed support, feet-in-place strategies that return the center of mass (COM) over the foot support, and change-in-support strategies where the feet are not necessarily kept in place.

• Sensory signals that elicit postural reactions come from cutaneous mechano-receptors in the foot soles, muscle spindles, vestibular receptors and visual receptors.

• Postural responses are organized along the neuraxis, including spinal cord, brainstem, cerebellum, and the cerebral cortex.

• Muscle fatigue and pain influence the stability of upright stance.

20.1 Introduction

Quiet upright stance is constantly challenged by internal and external influences. The most important external influence is →gravity, which causes the body to continuously sway. Postural sway can be augmented or decreased by various factors. Equilibrium is most dramatically endangered by exterior perturbations, such as pushes or sudden changes in stance support, and its maintenance calls for fast and appropriately scaled corrections by musculo-skeletal and neural mechanisms. Serious internal perturbations are self-generated body-part movements, which change body geometry and →mass distribution and must be anticipated and taken into account by the →central nervous system (CNS) (Mackinnon 2018). →Emotional and →affective states, e.g., anxiety or fear elicited by external stimuli such as threats, change behavior and postural stability (Lelard et al. 2019). Postural stability also deteriorates with age due to increasing →cognitive and brain structural changes, particularly in unstable stance conditions and with diminished sensory input (Sullivan et al. 2009).

20.2 Postural Sway Control in Humans

Even when trying hard to stand absolutely still will a subject sway more or less strongly depending on circumstances, such as the quality of the support base.

The →center of mass (COM) and the →center of pressure (COP) are constantly moving during upright stance. The COP wanders rather slowly in both antero-posterior and medio-lateral direction, the antero-posterior sway excursions are correlated in both legs, and time records of both COM and COP are almost in phase.

In order for the COM to remain in a safe and fairly constant position between the two feet, the dynamic range of the COP excursions must be larger than those of the COM. The rationale is that, if COP is ahead of COM, it →accelerates COM backward, and if COP is to the right of COM, it accelerates it to the left, etc. The excursions of COM have lower frequencies and amplitudes than those of COP. In the long run, the average COP must be equal to the average COM (Winter et al. 1998, 2003). Remarkably, the COP excursions are of about the same amplitude (1-2 cm) in rats, cats, dogs, horses and humans, despite the substantial differences in COM heights (Ivanenko and Gurfinkel 2018).

Postural sway may also have advantages. Swaying movements might provide important sensory information to the CNS concerning the interaction between body and environment (Haddad et al. 2013), by defining deviations from a normal or reference state. Such a reference comes as a *perception of upright* that emerges from →multi-sensory integration of several sensory signals (Kheradmand and Winnick 2018). The subjective reference is not fixed, but adapts to slow changes in inclination of the support surface. Faster oscillations occurring during upright stance are usually superimposed on the slow changes.

The slow and fast processes suggest the existence of at least two organizational levels in postural control: a conservative level that constructs and controls the set point and the distribution of muscle activities in posture, and an operative level that controls equilibrium on a faster time scale

to compensate for external and internal perturbations (Ivanenko and Gurfinkel 2018; Mezzarane and Kohn 2007).

20.2.1 Potential Mechanisms of Sway Control

The COP wanderings reflect COM movements in space, and these in turn are due to joint-angle movements. It might be tempting to assume that a good method to block, or at least mitigate, the joint movements, would be to co-contract antagonist muscles around the joints in order to increase joint →stiffness. Maybe surprisingly, however, voluntary co-activation of agonist-antagonist leg and trunk muscles does not stabilize vertical posture but may rather lead to postural destabilization as indicated by experiments on young healthy humans. When these were standing with no additional muscle coactivation, low co-activation or high co-activation, an increase in co-activation led to a significant increase in the postural sway speed reflected in faster rambling and trembling COP trajectories (Yamagata et al. 2017). There must be other means, therefore.

An older hypothesis propounded that body sway in the sagittal plane is largely controlled by ankle-joint stiffness (Winter et al. 1998, 2001, 2003). Joint stiffness results from three sources: passive stiffness of connective tissues and the elastic resistance of passive (relaxed) →skeletal muscle to stretch; active stiffness provided by the resistance of contracting muscle; and reflex-mediated stiffness resulting from the actions of the →stretch reflex, which recruits additional →α-motoneurons and increases the firing rate of already active α-motoneurons. While relaxed muscles do contribute some part to joint stiffness, the relative quantity is difficult to measure and thus not well known. Active muscle contraction also contributes relatively little during quiet upright stance because only relatively few →motor units are active and fire at sub-maximal rates (Lakie and Campbell 2019). Because the first two contributors do not suffice to stabilize quiet upright stance, both sensory feedback and predictive CNS mechanisms have been suggested to be involved.

20.2.2 Role of Sensory Receptors in Sway Control

Neural sway control requires sway sensation. Indeed, conscious humans can subjectively →perceive and quantitatively evaluate postural sway (Schieppati et al. 1999). In principle, several →sensory receptors could contribute relevant signals: vestibular, visual, cutaneous and proprioceptive receptors, the latter including muscle spindles, Golgi tendon organs, and joint receptors (Chiba et al. 2016; Forbes et al. 2018; Peterka 2018). Sensory feedback from Golgi tendon organs, joint receptors and cutaneous receptors in the plantar foot surface has little if any effects. A prominent role have muscle spindle primary endings with group Ia afferents because of their exquisite sensitivity to muscle length changes. Body sway during unperturbed upright stance induces length variations in leg muscles induced by rotations around the ankle joint. However, during human upright stance, internal lengths of soleus and gastrocnemius muscles change, on average, by shortening during forward sway and lengthening during backwards sway (paradoxical movements) (Loram et al. 2005a, b). Simulations using a biologically based neuro-musculo-skeletal inverted-pendulum model suggest that reciprocal inhibition might contribute to this effect (Elias et al. 2014).

Leg proprioception changes with age, decreasing in sensitivity, acuity and central integration of the proprioceptive signals. These changes lead to greater body sway, an increase in antagonist muscle co-activation, a greater reliance on visual information, and ultimately impair postural control (Henry and Baudry 2019).

Sensory Thresholds. Experimental threshold determinations in standing humans revealed that, with all sensory inputs available, the thresholds for the perception of sway were very small. Equivalently low thresholds were obtained for the perception of passive ankle movements when only proprioception from the legs was operative. The thresholds for perceiving visual movement were higher than the proprioceptive thresholds at slower velocities of movement, but there was no difference at higher velocities. Visual and proprioceptive thresholds were thus low enough for the perception of sway in normal stance. By contrast, vestibular thresholds were an order of magnitude larger and beyond the largest sway movements (Fitzpatrick and McCloskey 1994). →Micro-neurography of muscle-spindle afferents from the human triceps surae muscle indirectly suggests that spindles are in part sensitive enough to sense ankle movements during quiet standing (Peters et al. 2017).

Effects of Cutaneous Mechano-receptors. Cutaneous receptors in the foot sole could play a part in detecting and monitoring body sway (Kavounoudias et al. 1998; Meyer et al. 2004a). Quiet upright stance goes along with a specific distribution of body weight over different contact areas between feet and surface. Thus, when the body tilts forward, the pressure on forward foot areas increases and that on the rear foot zones decreases. Similarly, right-and-left differences in pressure between the two feet indicate medio-lateral sway.

Anesthesia of the foot soles has relatively little effect on body sway, however. With the eyes closed, it increases COP velocity but not magnitude. Anesthesia of the whole foot sole influences anterior-posterior sway, whereas forefoot anesthesia mainly affects medio-lateral sway (Meyer et al. 2004a).

Artificial stimulation of cutaneous receptors in the foot soles demonstrates effects on posture. Vibratory stimulation of the fore and rear foot soles of standing subjects produces →illusions of body lean and change posture. Vibrating each zone separately produces spatially oriented body tilts, as measured by COP shifts. Tilt direction is opposite to the plantar site vibrated. The change in the relative pressures produced by co-vibrating two zones induces postural adjustments that oppose the simulated body deviation (Kavounoudias et al. 1999).

Plantar cutaneous afferents evidently play a moderate role in normal stance regulation if the eyes are closed, or if the subject stands on one leg only, but may become more important with the loss of other sensory modalities, e.g., proprioception in →peripheral neuropathies (Meyer et al. 2004a).

Effects of Vision. Humans are able to stand quietly in the dark. However, vision improves postural stability provided the visual surround is stable. The extent of improvement depends on stance width, support surface and availability of other sensory inputs. For example, if the vestibular or somatosensory system is impaired, leading to postural instability and a tendency to fall, vision stabilizes posture (Guerraz and Bronstein 2008; Honeine and Schieppati 2014).

Eye closure increases sway, depending on circumstance (de Freitas et al. 2009; Mezzarane and Kohn 2007; Peterka 2018). Several sources may contribute to the stabilizing effects of available vision. First, spontaneous body oscillations may cause the image of the environment to move on the retina and generate optic flow; i.e., an image of objects in the external world that drifts across the retina. Second, signals related to eye movements may contribute: for example, a copy of a →motor command (→efference copy) or of the extraocular muscle afferents (re-afferences) accompanying eye movements (Guerraz and Bronstein 2008). Indeed, eye movements toward precise targets reduce postural body movements (Bonnet and Baudry 2016).

Multi-sensory Integration. Generally, sway is smallest when multiple accurate sensory sources are available and are combined to reduce variability of an internal estimate of orientation. With eyes open, deranging proprioceptive signals by standing on a compliant foam surface increases sway, With eye closure or in darkness, sway increases. Standing on a foam surface with eyes closed forces the sway control system to rely on the noisy orientation signals from the vestibular system and thus further increases sway. Such experimental results can be used to estimate the relative contributions (weights) of different senses to →balance control. The temporary loss or diminution of any contributing sense must be compensated for by re-weighting the contributions of the remaining senses (Chiba et al. 2016; Peterka 2018; Rasman et al. 2018).

It seems likely that several neural mechanisms are required to control postural sway. Sway-related presynaptic modulation and →recurrent inhibition (Baudry and Duchateau 2012; Tokuno et al. 2008) and →spinal, stretch reflex-mediated sway control (Hellebrandt 1938) have been proposed but now seem unlikely (Loram et al. 2005a,b; Vieira et al. 2010).) The source of modulation might be supraspinal, but at the present time there is insufficient evidence to support the proposal.

20.3 Postural Responses to External Stance Perturbations

Upright stance is readily perturbed by internal and external influences that exceed the range of postural sway or compromise the neural control of stance (Rasman et al. 2018). Internal perturbations that change the distribution of body mass are compensated for by →anticipatory postural adjustments, while external perturbations call upon immediate mechanical counter-forces, sensory responses and central multi-sensory integration (Bronstein 2016; Jacobs and Horak 2007; Nonnekes et al. 2015; Peterka 2018). During discrete perturbations to standing balance in humans, the first line of defence is a large →yank (derivative of force with respect to time), which is produced by the combination of the initial muscle stretch and intrinsic short-range stiffness of muscle (Lin et al. 2019).

20.3.1 Anticipatory Postural Adjustments to Self-generated Movements

Movements of body parts while standing will change the position of the center of mass (COM), and exert →inertial inter-segmental →interaction forces between the body segments. Thus, rapid →voluntary arm movements produce predictable perturbations of balance. The CNS must take these actions into account in advance in order to preserve equilibrium, in a way precisely

calibrated to movement direction and velocity (Dakin and Bolton 2018; Haddad et al. 2013).

A voluntary arm movement is preceded by anticipatory postural adjustments. Leg movements occur in advance of arm raising and serve to stabilize the trunk against the effects of the arm raising action. In addition, anticipatory whole-body postural adjustments are made involving the hand and arms in a grip task. The grip force increases before the load force produced by the arm. Early changes in grip force and →ground reaction forces and →torques are positively correlated, suggesting a common predictive basis, i.e., a →predictive internal model of the body for the anticipatory adjustments in upper and lower limbs (Balasubramaniam and Wing 2002).

20.3.2 Postural Strategies to Counter External Stance Perturbations

Postural strategies select and weight objectives to be achieved, such as COM stability and geometry. They can be roughly divided into two classes: fixed support, feet-in-place strategies that return the COM over the foot support, and change-in-support strategies where the feet are not necessarily kept in place (Horak 2009; Maki 2009; Ting 2009).

Several strategies are available to counter external stance perturbations, For example, two fixed-support strategies might be utilized to counter different perturbations of a surface that supports a quietly standing human subject. When the support surface is translated backwards, inducing forward body sway, either of two possible reactions takes place: an ankle strategy and a hip strategy (Horak 2009).

In the execution of the ankle strategy, ankle, knee and hip extensors as well as paraspinal muscles are activated to produce an extensor torque around the ankle joints and thus rotate the body backwards for forward sway. This strategy is most often used when the entire foot has safe contact with a stable ground. It maintains vertical alignment of legs and trunk (Horak and Macpherson 1996; Horak et al. 1997; Maki 2009; Ting 2009).

The hip strategy involves activation of the neck, abdominal and quadriceps muscles for backward sway. This strategy is often chosen in response to larger and faster perturbations and when the ankle strategy would not help, e.g., while standing on a narrow or compliant surface. But experience and task focus also play a role. The hip strategy permits fast COM movement and gaze stabilization by counter-rotating the head against the hip rotation (Horak and Macpherson 1996; Horak et al. 1997). Complex postural reactions also occur when the support surface is suddenly rotated, for example in the pitch plane with toes up or down.

Additional strategies to counter external stance perturbations would be to change the support by stepping (stepping strategy) or reaching for support with the hands (→reach-to-grasp postural strategy) (Horak 2009; Horak and Macpherson 1996; Horak et al. 1997; Maki 2009).

The stepping strategy is associated with early activation of hip abductor muscles and co-contractions of ankle muscles. The step frequency depends on the displacement and velocity of the pull relative to the →base of support. The →threshold boundary has a forward limit that, when crossed, always induces the subjects to step irrespective of how slowly they are pulled. As the pull velocity is increased, the threshold position producing a step shifts nearer to the ankles.

Older subjects step more often than young subjects (Mille et al. 2003).

20.3.3 Initial and Predictive Scaling

In neurologically healthy subjects, the trajectories of joint angles and torques change gradually with increasing amplitude (Park et al. 2004). The initial responses are in part closely related to the sensory input. Responses must be initiated within 70-100 ms of perturbation onset and are thought to be pre-programed feedforward responses.

In the initial phase, the amplitude of longer-lasting perturbations must be predicted on the basis of prior experience with repeated occurrences. Thus, postural responses are appropriately scaled to the amplitudes of predictable (e.g., repeated) perturbations, but not to those of unpredictable perturbations (Horak et al. 1997; Maki 2009). Only later response phases can be shaped by sensory feedback (Maki 2009).

20.3.4 Muscle Synergies

Muscle synergies are thought to be flexible, centrally organized spatio-temporal patterns of muscle activation organized to achieve motor goals such as ground reaction forces during stance perturbation, COM shifts in standing, foot and limb kinematics during walking and hand kinematics (Torres-Oviedo et al. 2006; Krishnamoorthy et al. 2003; Ivanenko et al. 2004, 2006; Ting 2007; Weiss and Flanders 2004).

Both locomotor central pattern generators (CPGs) in the →spinal cord as well as systems that descend from supraspinal structures distribute excitation and inhibition to various →motoneuron pools to help organize muscle synergies.

Proprioceptive feedback contributes to →synergy organization in two general ways. First, it can trigger synergies during corrective postural adjustments and adjust the recruitment of centrally organized synergies to behavioral constraints. Second, spinal connections between proprioceptive afferents, →interneurons and motoneuron pools link these pools into synergies and fine-tune the activations of individual muscles.

20.4 Sensory Triggering of Postural Reactions

External perturbations that drive the COM movements beyond the limits of postural sway excite more sensory receptors, and more strongly so. Thus, the same sensory signals from cutaneous →mechano-receptors, proprioceptors, vestibular receptors and visual receptors, which in quiet stance reign in postural sway, now elicit appropriate postural reactions (Deliagina et al. 2014; Forbes et al. 2018). The CNS relies on multiple sources of sensory information to determine the choice of strategy used to control balance (Bronstein 2016; Honeine and Schieppati 2014; Morasso et al. 2014).

In cats and rabbits, postural reactions appear to be organized by an array of distributed sub-systems. The spinal cord contains networks that generate postural limb reflexes (PLRs) driven by stretch and load receptors of the limbs (Sect 2.7). But these somatosensory signals are also sent to supraspinal structures where they contribute to form postural commands transmitted to the spinal cord through the →vestibulo-spinal tract (VST), →reticulo-spinal tract, →rubro-spinal tract and →cortico-spinal tract (CST). In humans, the →cerebral cortex does not appear to be involved in triggering the initial, short-latency phase of postural reactions to external perturbations (Deliagina et al. 2014).

20.4.1 Cutaneous Inputs from the Foot Soles

In humans, plantar cutaneous mechano-receptors play a moderate role in quiet upright stance. Their importance in postural reactions to lateral accelerations of a support surface appears to be larger. Loss of plantar sensation may contribute to reduce balance and increase the risk of falls in patients with peripheral neuropathies (Meyer et al. 2004b).

In the cat with an intact cerebral cortex, supported by some means and with the hindlegs hanging free and flexed, light touch of the sole skin will lead to limb extension. When skin contact is slowly withdrawn, the foot will follow so as to resume contact. This behavior, called the magnet reaction (Roberts 1967), illustrates the significance of cutaneous inputs from the foot sole in searching for support.

Further evidence for the importance of cutaneous afferents in postural control is that →pyridoxine (vitamin B6) in high doses produces selective →large-fiber sensory loss accompanied by disturbances of quiet upright stance. After being trained to stand on a movable platform under control conditions, cats given toxic doses of pyridoxine display →ataxia. Excursions of the body center of mass (COM) in the direction opposite to that of platform translation are also exaggerated, and the time at which the COM subsequently reverses direction is delayed (Stapley et al. 2002).

20.4.2 Proprioceptors and Stretch Reflexes

Muscle spindle afferents, particularly group Ia afferents, appear well suited to signal →biomechanical and perturbation characteristics. In anesthetized cats, horizontal support-surface perturbations of the intact hindlimbs produce broadly tuned, but directionally sensitive discharge patterns of spindle afferents which are also very sensitive to small perturbations (Henry and Baudry 2019; Honeycutt et al. 2012).

In normal standing human subjects, a sudden upward tilt on a rotating supporting platform (toes up) elicits short-latency (SLR) and medium-latency (MLR) →electromyographic responses to stretch in the soleus and the flexor digitorum brevis muscle (Nardone et al. 2000; Bove et al. 2003). While the SLR is probably a typical stretch reflex mediated by group Ia muscle spindle afferents and their monosynaptic linkages to motoneurons, the MLR appears to involve activation of group II muscle spindle afferents that affect motoneurons through a lumbar interneuronal network. The SLR does not seem to play a role in the maintenance of quiet stance since it is not sufficiently powerful to prevent falling (Carpenter et al. 1999). Likewise, during

the stance phase of walking in humans, stretch of the anti-gravity ankle extensor muscles evokes sizeable stretch reflexes including an SLR and MLR component (Grey et al. 2001).

Proprioceptors responsive to early stretch or release of paraspinal, pelvic and hip muscles may be instrumental in triggering postural reactions whenever roll-trunk movements are involved. Neck muscles also react to perturbations at latencies shorter than those of ankle muscles. But in paraspinal muscles, the maximal responses are roughly 90° out of phase of the initial stretch reflexes. Disparities in timing indicate that local stretch reflexes and postural reactions are controlled by different processes and are modulated separately, but adequately, coordinated (Carpenter et al. 1999).

In patients with →diabetic neuropathy who have no monosynaptic →Achilles tendon reflexes and weak or absent →patella reflexes, postural strategies and synergies are relatively normal, although there are some changes in timing and amplitude (Nardone and Schieppati 2004). It seems that stretch reflexes contribute little torque to corrections for stance disturbances (Horak 2009).

For trunk stabilization in response to perturbations in the sagittal plane, intrinsic muscle properties, muscle spindle feedback with acceleration and short latencies, and inhibitory Golgi tendon organ feedback appear to suffice (van Dieën et al. 2018).

Tendon vibration of muscles around the ankle joint to activate muscle spindle afferents evokes specific brain activations measured with →functional magnetic resonance imaging (fMRI). Activations are seen in primary sensory cortex and secondary sensory cortex, secondary associative areas, and →basal ganglia. Multiple voxel clusters (Woo et al. 2014) are significantly correlated with muscle spindle activity and excursions of the center of pressure (COP) in the anterior-posterior direction (Goble et al. 2011). Cerebral activity might be relevant for the control of the COM as indicated by the finding that it is increased when upright stance is threatened (Ozdemir et al. 2018).

20.4.3 Vestibular Receptors

Cats subjected to bilateral →labyrinthectomy show abnormal responses to sudden pitch and roll rotations of a support platform within the first post-surgery week. In normal cats, the downhill extensor muscles are activated and the uphill extensor muscles are inhibited to keep the body aligned with the earth vertical. By contrast, in labyrinthectomized cats, the downhill extensor muscles are inhibited and the uphill extensor muscles are activated, which further de-stabilizes upright posture (Deliagina et al. 2014; Macpherson et al. 2007).

Vestibular inputs in cats might provide a reference to the earth vertical. Without this reference, they would compute an incorrect estimate of the initial COM motion relative to the earth vertical, and align their limb axes perpendicular to the support surface using proprioceptive information (Macpherson et al. 2007).

Humans have vestibular thresholds above the largest sway movements, therefore there is no major role for vestibular signals in the control of normal quiet stance. Nonetheless, patients with

vestibulo-cerebellar lesions exhibit increases in COP movements in all directions. Patients with bilateral vestibular loss experience difficulties in keeping balance when standing with their feet in tandem arrangement, particularly with closed eyes (Morton and Bastian 2004).

Large-amplitude perturbations of a support surface in pitch elicit vestibular signals from otoliths; large perturbations of roll elicit signals from semicircular canals. These signals would therefore be expected to contribute to postural reactions. However, humans with bilateral vestibular loss are able to select and trigger an appropriate early hip strategy when exposed to sudden translations of surface support (Runge et al. 1998).

Galvanic Stimulation. →Galvanic vestibular stimulation (GVS) with DC current through the skin over the mastoid processes activates fibers of the vestibular nerve fibers in humans and experimental animals. Stimulation excites a wide range of central vestibular neurons, including those related to both the semicircular canals and the otolith organs.

Maintained current elicits a large sway in the direction of the anodal electrode, but only with the head upright, not with the head bent (Cathers et al. 2005; Fitzpatrick and Day 2004; Forbes et al. 2015; Hlavacka 2009; Keshner 2009; Manzoni 2009). Thus, vestibular effects on sway and posture involve interaction with various sensory inputs by →multi-modal convergence on →vestibular nucleus neurons.

Vestibulo-spinal Tract (VST) Fibers target premotor interneurons all along the spinal cord and and lumbar motoneurons (by weak monosynaptic connections) and are predominantly set up in the lateral vestibular nucleus (LVN) (Deiters). There is also a distinct vestibulo-spinal projection, predominantly via the medial vestibular nucleus (MVN) (Schwalbe), that targets neurons related to upper-body muscles, particularly neck and some forelimb muscles (McCall et al. 2017). Vestibulo-spinal projections in the decerebrate cat contribute to anti-gravity thrust, and to adjustments of head/body orientation in space in response to static and dynamic disturbances of position (Keshner 2009; Manzoni 2009). If, for example, the head-body is tilted to the left, the left extensor muscles are activated and the contralateral flexor muscles de-activated. Generally, however, such actions interact with effects elicited by visual and proprioceptive receptors (Manzoni 2007).

Vestibulo-spinal reflexes (VSRs) interact with →cervico-spinal reflexes originating in neck proprioceptors. Their efficacy is also modulated by the anterior cerebellar vermal cortex, ascending spino-vestibular pathways, →noradrenergic inputs from the →locus coeruleus (LC). VSRs are also affected by the sleep-wake cycle (Keshner 2009; Manzoni 2007, 2009).

20.4.4 Visual Signals

Moving Visual Scenes induce or enhance postural sway in both animals and humans. In a study conducted with dogs trained to stand quietly on a movable table, sinusoidal oscillation of the visual surround generated consistent, frequency-dependent changes in body position. At low frequency oscillation, body position changes tended to lead the position of the optokinetic stimulus, while at higher frequencies of visual oscillation, body position changes lagged the

optokinetic stimulus. The results demonstrate a strong visual component of the postural control system (Talbott 1980). This has been further demonstrated in humans using several test paradigms, for example: moving or tilting rooms, projected displays simulating a moving wall, tunnel, floor or ceiling, or visual roll rotations, otherwise known as roll vections. In response to fore/aft motion of the entire visual environment, subjects sway in the direction of motion. The largest effect of a rhythmic sinusoidal motion of the visual scene occurs at frequencies around 0.2 Hz, at which the body motion is phase-locked to the →visual motion (Guerraz and Bronstein 2008).

Vection is an illusion of body tilt opposite to the stimulus. Subjects attempt to compensate for this illusion by tilting in the direction of the stimulus. Adults standing naturally and quietly on fixed ground are rarely de-stabilized by moving visual scenes but de-stabilization may occur under more difficult stance conditions, such as tandem or one-footed stance (Horak and Macpherson 1996).

20.4.5 Influence of Gaze Direction on Visually Induced Postural Sway

The direction of visually induced body sway depends on signals that detect eye-in-orbit and head-on trunk position. Signals indicating eye position in orbit and head position on the trunk can redirect visually evoked sway, that is, re-organize the system linking vision to postural muscle activities (Wolsley et al. 1996). The required eye-in-orbit and head-on-trunk position signals could be of proprioceptive origin, because vibration of extraocular and neck muscles has a strong influence on posture (Pettorossi and Schieppati 2014).

20.4.6 Influence of Gaze Direction on Postural Responses to Neck Proprioceptive and Vestibular Stimulation

Gaze direction also strongly affects the direction of postural responses elicited by dorsal neck muscle vibration or galvanic vestibular stimulation. Symmetric (relative to the spine) neck vibration evokes body sway in the direction of the head´s naso-occipital axis, whether the head and trunk are straight ahead (forward sway), or the head or the head/trunk are rotated together. Basically the same occurs with lateral eye deviations, with eyes open or closed. Hence, head rotation re-orients postural responses according to the head-on-feet position. These findings emphasize the importance of viewer-centered reference frames for interpreting neck and visual signals (Ivanenko et al. 1999).

20.4.7 Vestibular-somatosensory Interactions

Postural responses to galvanic labyrinthine stimulation depend on head position. When the head is oriented forward, the induced body sway is oriented largely in the frontal plane. When the head is oriented to the right, the postural reactions occur in the sagittal plane. In this case, the postural reactions appear to be governed by asymmetric otolithic inputs in the sagittal plane instead of in the frontal plane, as in the case of the straightforward head position (Massion 1998).

20.4.8 Vector Summation Principle

Vector summation appears to play a role in multi-sensory integration in support of upright stance and posture, at least under restricted conditions. For example, proprioceptive signals from the tibialis anterior muscle and plantar cutaneous signals sum vectorially. Isolated tibial anterior vibration induces forward whole-body tilt, whereas isolated plantar forefoot vibration evokes backward tilt. The respective tilt amplitudes depend on vibration frequency. Combined stimulation at different frequencies produce postural shifts that correspond to the expected vectorial sum of individual shifts evoked by isolated stimulation of tactile and proprioceptive sensory inputs (Kavounoudias et al. 2001). As another example, proprioceptive signals from tibialis anterior or soleus muscles altered by vibration and vestibular signals altered by binaural galvanic current induce body leans equivalent to the sum of responses evoked by the galvanic and vibratory stimulation alone (Hlavacka et al. 1995).

20.4.9 Haptic Stabilization

→Haptic contact, i.e. contact by touch, produced for example by lightly touching a stable external wall, serves to provide a reference value for anchoring posture. In normal humans or in patients with abnormal postural control due to labyrinth defects, diabetic neuropathy, cerebellar disorders, or alcoholism, body sway can be reduced by even light contact of the index finger with a non-supportive surface. In blindfolded normal subjects, postural sway can be reduced by as much as 50% within about 200 ms of finger contact (Honeine and Schieppati 2014; Lackner and DiZio 2000, 2005; Wing et al.2 011). The haptic sway reduction does not result from muscle spindles in finger muscles, but from effects of other afferents (Silva et al. 2019).

20.5 Influence of Muscle Fatigue on Stance Control

In humans, intense exercise that fatigues the whole body increases postural sway (Paillard 2012). Trunk →muscle fatigue affects postural control, in particular sway velocity (Ghamkhar and Kahlaee 2019). Fatigue of ankle extensor muscles reduces the stability of quiet upright stance (Ledin et al. 2004). Muscle fatigue increases COP velocity as well as mean and median frequency without enlarging the range of oscillations. This suggests that fatigue changes the way in which postural stability is controlled, without much affecting the detection and response capabilities of the sensory-motor system (Corbeil et al. 2003). Since head position is important for the evaluation of upright posture, changes in sensory signals originating from neck muscles may be expected to affect postural control. This seems to be the case since fatigue in neck muscles increases postural sway, particularly in the absence of vision (Schieppati et al. 2003; Corbeil et al. 2003; Gosselin et al. 2004).

20.6 Influence of Pain on Stance Control

20.6.1 Influence of Pain on Quiet Stance

Painful stimuli applied to the dorsum of the feet increases excursions and mean velocity of postural oscillations with increasing stimulation →intensity. Since →nociceptive stimulation of

the hands does not affect control of posture, the painful stimulus probably produces its postural effects via sensory-motor processes rather than through cognitive resources related to pain →perception. Sensory-motor mechanisms might reduce perception of →muscle torque, suppress signal flow through tactile neural systems, distort the →body image or disturb the integration of →multi-sensory information required for postural control (Corbeil et al. 2004).

20.6.2 Influence of Pain on Stance Perturbations

A →noxious stimulus applied to a body part triggers the withdrawal reflex. Withdrawal reflexes were once considered the simplest centrally organized reactions to noxious stimuli (Clarke and Harris 2004; Sandrini et al. 2005). However they are not all that simple.

When a quadruped is standing quietly on all four legs and the skin of one leg is pricked, the leg is withdrawn from the noxious stimulus by activation of the flexor muscles. Flexor activation is associated with ipsilateral inhibition of the weight-supporting extensor muscles. Since, for example, withdrawal of the left hindleg distributes more body weight onto the unstimulated legs, there must be more extensor excitation to prevent the animal from yielding under its body weight. The supporting forces of the diagonally opposite leg are slightly reduced, while those in the other two legs are increased. The increase of extensor forces in the contralateral hindleg is exerted by a crossed extension reflex via di- and polysynaptic pathways (Jankowska 1992). To shift the COM farther into the remaining triangular base of support, the vertebral columotoneuron is bent away from the stimulated left hindleg.

Withdrawal reflexes do not occur in stereotyped fashion every time the stimulus is applied, rather they depend on state and context (Sandrini et al. 2005). This is a particularly demanding task for humans who have to balance a vertically extending body mass above relatively small support surfaces provided by one or two feet. It is therefore not quite as easy as for quadrupeds to withdraw a noxiously stimulated limb. When human subjects are instructed to stand freely and either the plantar or dorsal surface of one foot is electrically stimulated at a strength producing pain, the reflex muscle activations in the lower limbs are complex. Only those nociceptive reflex responses that serve to avoid the stimulus without jeopardizing limb support are activated. This attests to the modifiability of withdrawal reflexes.

More insight into underlying neural processes has been gained by recent experiments on rats. In awake, unrestrained rats, brief thermal (laser) or sharp mechanical stimulation of group Aδ fibers were applied to a paw. In quadrupedal stance, rats reacted with an early movement of the head toward the stimulation site, followed, or nearly simultaneously accompanied by, movement of the stimulated limb and the contralateral forelimb and then by movement of the contralateral hindlimb and ipsilateral forelimb, very much as described above for cats. In bipedal upright stance on hindlimbs, movement of the head and hindlimbs was delayed or suppressed completely. To prevent destabilizing leg withdrawal requires an inhibitory mechanism that temporarily suppresses segmental nociceptive responses. This gate has been hypothesized to operate by an →opioid action at the spinal level that may include deep →dorsal horn laminae and perhaps also the ventral cord and by →glycinergic and GABAergic inhibitory networks (Blivis et al. 2017).

Patients suffering from chronic work-related neck pain or →whiplash-associated disorders exhibit larger sway areas (i.e., areas that circumscribe COP trajectories) during quiet stance. In addition, stability is reduced during more challenging postural tasks such as standing on one foot or on both feet in tandem arrangement, as well as during postural perturbations (Michaelson et al. 2003).

20.7 Role of Spinal Interneurons in Stance Control

In the decerebrate rabbit in which the head and the vertebral columotoneuron and pelvis were rigidly fixed, anti-phase flexion/extension movements of the hindlimbs caused by tilts of a supporting platform elicited postural limb reflexes (PLRs). Neurons in spinal segments L5-L6, which presumably contributed to the generation of PLRs, could be divided into two groups: F-neurons activated during flexion of the ipsilateral limb, E-neurons activated during extension of this limb. There was also a group of non-modulated neurons. F- and E-neurons were intermingled and scattered across the whole cross-section of the →gray matter. The phase of modulation of a neuron was determined mainly by sensory input from the ipsilateral limb. The majority of neurons received mono- and polysynaptic sensory inputs from both limbs, with the inputs being linearly summated. Sensory inputs from the →receptive field (RF) of a neuron (determined at rest) can be responsible for the tilt-related modulation only in some of the neurons (Zelenin et al. 2015).

F- and E-groups are inhomogeneous. They could contain segmental and propriospinal interneurons, as well as the ascending tract neurons, some of which may be implicated in supraspinal postural feedback loops, while others may be involved in sensory perception. The ascending neurons may include, e.g., →spinocerebellar tract neurons, which receive inputs from group I and II afferents. However, presumably at least some of the recorded F- and E-neurons are premotor interneurons that activate and inhibit extensor α-motoneurons, respectively. Mixed sources of afferent inputs characterize different sub-populations of neurons (Zelenin et al. 2015).

In mice, inhibitory $V0_D$ CINs, and possibly excitatory $V0_C$ interneurons, contribute to upright body orientation. Roll platform tilts initiate corrective PLRs including activations of the extensors on the down-side tilt and inactivation of extensors on the opposite side. It has been suggested that these INs contribute to the left-right coordination. The ablation of these INs disinhibits the activity of extensor α-MNs on the opposite side (up-tilt) and decreases the activity of α-MN on the ipsilateral (down-tilt) side, leading to a decrease of the efficacy of postural corrections (Zelenin et al. 2021).

20.8 Role of Supraspinal Structures on Stance Control

Functional neuroimaging in humans reveals that several brain regions contribute to stance control and stability. The key nodes involve the brainstem, cerebellum, basal ganglia, →thalamus and several →cortical areas (Dijkstra et al. 2020).

20.8.1 Role of the Brainstem in Stance Control

In the cat, changes in support, either by translation (Honeycutt et al. 2009) or by drops of individual foot supports (Stapley and Drew 2009) evoke whole-body postural responses showing that, in addition to the spinal cord, the brainstem is involved in maintaining upright posture.

Reticulo-spinal neurons in the ponto-medullary reticular formation (PMRF) contribute to →startle responses and postural responses to stance perturbations (Nonnekes et al. 2015). Lesions involving these structures produce deficits in postural control during standing and locomotion. In addition to inputs from other supraspinal structures, PMRF neurons receive sensory inputs from the limbs and distribute outputs to multiple limb muscles, thus contributing to muscle synergies. PMRF neurons respond strongly to external stance perturbations at short latency and before the initial EMG changes in limb muscles, indicating that they assist in organizing the initial synergistic muscle activations. They also respond to voluntary movements that tend to destabilize stance and require anticipatory postural adjustments (Stapley and Drew 2009).

In cats, rubro-spinal tract neurons contribute to send supraspinal posture-related signals to the spinal cord. While maintaining balance on a periodically tilting (left-right) platform, the firing rates of many rubro-spinal tract neurons were periodically modulated, with the amplitude and phase of responses being determined primarily by sensory input from the corresponding contralateral fore- or hind-limb, whereas inputs from other limbs made a much smaller contribution. This suggests that the rubro-spinal system may be primarily involved in intralimb coordination rather than in interlimb coordination (Zelenin et al. 2010). The →nucleus ruber receives major inputs from the cerebellum.

20.8.2 Role of the Cerebellum in Stance Control

The →cerebellum plays a major role in sensory-motor coordination. Among the functions coordinated are posture and stance. Most heavily involved in the control of balance are the cerebellar vermis and associated fastigial nucleus and the →floccular complex, which appear to control extensor →muscle tone to maintain upright stance and balance.

In cats and monkeys, lesions of the vestibular nuclei or fastigial nucleus produce changes in upright postural tone and balance functions, including impaired righting responses and frequent falls backward and toward the lesioned side. Lesioned cats show ipsilateral limb flexion and adduction combined with contralateral limb extension and abduction (Morton and Bastian 2004).

Damage to the cerebellum in humans may have an array of causes and also a plethora of symptoms in various combinations. The effects on stance control include increased postural sway, abnormal oscillations of the trunk (titubation), poor control of equilibrium during movements of other body parts and increased or decreased responses to perturbations. Patients with anterior →cerebellar cortical atrophy exhibit increased COP movements in the anterior-posterior direction and ataxia of stance and gait. Patients with vestibulo-cerebellar lesions exhibit increases in COP movements in all directions, ataxia of head and trunk during sitting, standing

and walking, and increased frequency of falling (Grimaldi and Manto 2012; Morton and Bastian 2004; Nardone and Schieppati 2010; Timmann 2009).

Although there is varied evidence for a cerebellar contribution to →motor learning, the cerebellum´s integrity is not essential for short-term adaptation of postural responses to translational platform perturbations. Patients with cerebellar damage can predict perturbation amplitudes based on previous experience, but they are unable to use this information to modify the gain of an adaptive postural response (Schwabe et al. 2004).

20.8.3 Role of the Basal Ganglia in Stance Control

The contribution of the basal ganglia to upright stance in healthy people is not well understood. The basal ganglia send outputs to brainstem systems facilitating extensor muscle tone. The importance of the basal ganglia is underscored by impaired stance in →Parkinson´s disease. Parkinsonian patients show several balance dysfunctions in the control of upright stance and locomotion. They exhibit axial ataxia with narrow stance, stooped posture, flexed hips and knees, increased muscle tone especially of flexors, axial stiffness with muscle co-contractions, postural inflexibility, difficulty in turning around the vertical axis, slowed and reduced force development in postural responses to disturbances, and fear of falling (Lalonde and Strazielle 2007; Nardone and Schieppati 2010; Park et al. 2015; Rinalduzzi et al. 2015; Schoneburg et al. 2013). Balance disturbances and the associated risk of falling do not respond well to →dopaminergic (→L-DOPA) therapy, indicating that deficits in other than dopaminergic systems are involved, possibly including deficits of →noradrenaline due to cell loss in the locus coeruleus (LC) (Grimbergen et al. 2009). Parkinsonian patients are also variously impaired in nociceptive, thermo-sensory and tactile sensation. In particular, the processing and utilization of proprioceptive information and the integration of different types of sensory inputs to guide movement are disrupted, which may degrade motor performance and stability (Conte et al. 2013; Konczak et al. 2009; Rinalduzzi et al. 2015; Schoneburg et al. 2013).

20.8.4 Role of the Cerebral Cortex in Stance Control

It has been suggested that distinct neural systems, some which interact, are responsible for posture (holding still) and movement. Distinct motoneurons and interneurons involved in gaze control, head movements, arm movements, locomotion and posture exhibit phasic movement-related discharges or a sustained discharge during posture maintenance (Ivanenko and Gurfinkel 2018).

In line with this distinction, the discharge patterns of individual neurons in the →primary motor cortex (F1) of macaques represent mechanical loads during posture and movement tasks. About half of the neurons that express load-related activity do so exclusively during either posture only or movement only. These load representations suggest distinct specialized control processes for posture and for movement (Kurtzer et al. 2005).

Human and non-human subjects with cortical lesions that spare the brainstem exhibit abnormal postural responses to external perturbations, indicating that postural equilibrium is influenced by the cerebral cortex. Behavioral evidence also suggests cortical involvement, because postural responses are modified by complex cognitive-motor processes that are thought to be mediated by the cerebral cortex (Jacobs and Horak 2007).

20.8.4.1 Cortical Activity in Humans

→Positron emission tomography (PET) used to study brain activity in neurologically healthy humans yielded different results during the maintainance of different standing postures. Compared with supine posture, standing with feet in parallel activated the anterior cerebellar lobe and the right visual cortex (→Brodmann area 18/19). Standing on one foot activated the anterior cerebellar vermis and the lateral posterior lobe ipsilateral to the weight-bearing side. Standing with feet in tandem activated the anterior and posterior vermis, the visual association cortex as well as the →midbrain. Standing with closed eyes activated Brodmann area 8 and area 9 in the →prefrontal cortex (PFC). These findings underline the importance of the cerebellar vermis for stance control and suggest roles of cerebro-cortical areas in visual control functions (Ouchi et al. 1999).

The intensity of brain activation depends on the relative weights of different sensory inputs. For example, using →functional near-infrared spectroscopy (fNIRS) and posturography, there was a bilateral activation in the temporal-parietal areas (superior temporal gyrus, STG, and →supra-marginal gyrus, SMG) when both vision and proprioception were degraded, enforcing reliance on primarily vestibular information in the control of balance (Karim et al. 2013).

→Electroencephalographic (EEG) recordings show changes in cortical processes that occur before and after perturbation of stance. The pre-perturbation changes evidently originate in →supplementary motor area (SMA) and sensory-motor cortices and apparently reflect preparation of motor responses. The post-perturbation changes most likely originate in →anterior cingulate cortex (ACC) and SMA and reflect general errors in detection and planning of later stages of the postural reaction associated with behavioral goals and environmental constraints (Bolton 2015).

20.8.4.2 Motor Cortex Activity in Cats

In cats maintaining equilibrium on periodically tilting platforms, →pyramidal tract neurons (PTNs) in the forelimb representation of the →motor cortex discharge periodically in correlation with the frontal-plane platform tilts. For example, a PTN in the left motor cortex shows strong activity in all cases in which the right forelimb is standing on the platform, while the activity is much reduced when the leg is lifted. This suggests that PTN discharge modulation depends primarily on tilt-related somatosensory inputs from the contralateral limb of the corresponding girdle. It has been proposed that PTNs are involved in the postural feedback control of contralateral limbs (Deliagina et al. 2008).

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21

Biomechanics of Locomotion

CONTENTS

Abstract

• An understanding of the principles of biomechanics is a starting point for understanding locomotion. Locomotion first requires an appropriate initial body posture, then proceeds to a rhythmic locomotor state, aided by central pattern generators (CPGs) and sensory feedback that ensure energy- and movement-efficient locomotion.

• Vertebrates vary stride length by varying gait in order to locomote at different speeds. During walking or running, upright stance is altered by moving the center of mass (COM) outside the base of support (BOS) in order to achieve balance stabilization.

• Biomechanical actions of skeletal muscles on movements are often derived from their anatomical sites of origin and insertion.

• The primary function of a muscle is to re-distribute energy among segments. Muscle force can cause significant segmental energy re-distribution irrespective of whether the muscle produces mechanical work by shortening, dissipates energy by lengthening, or neither by remaining isometric.

• A common set of spatially fixed locomotor muscle synergies can be recruited in combinations via several pathways, including central pattern generators (CPGs), brainstem structures involved in balance control and corticofugal motor command pathways for voluntary gait modification.

• Human locomotion is kinematically complex because of multiple interactions of body segments that change the contribution of legs through the cycle and maintain delicate balance.

• For bipedal animals like humans, the maintenance of balance during walking and running is particularly challenging because the center of mass (COM) is relatively high above the base of support (BOS).

• The transition from quiet upright stance to steady-state walking or running (gait initiation) challenges balance because it involves a change in the base of support (BOS) and a progression of the center of mass (COM). Gait initiation starts from a postural phase and involves anticipatory postural adjustments (APAs). The following foot-lift phase stretches from heel liftoff to toe clearance, in which the COM moves forward and towards the stance leg. The subsequent execution phase ends at swing-foot contact with the support surface.

• Gait termination is a complex process. It depends on ambulation speed (walking to running) and the time in the step cycle at which the decision to stop is taken. It poses a risk of falling, particularly while moving at higher speed. It requires deceleration of forward body momentum and attainment of stable posture.

• Quadrupedal and bipedal locomotion have some features in common, but differ in various aspects imposed by the specific requirements of environment, locomotor styles and body configurations.

21.1 Introduction

Locomoting supports life-sustaining and life-enhancing behaviors. Locomotion has put strong evolutionary pressures on developing efficient, rapid, adjustable movement patterns, and has therefore been very influential in determining the morphology and physiology of animals (Katz 2015).

Locomotion takes a variety of forms, depending to a large extent on the medium through which the animal moves, from fairly solid substrates such as soil or sand, to more fluid media like water, or to lofty media like air. The spatio-temporal patterns of the required force production and, hence, the mechanical and physiological means used to move may vary widely (Dickenson et al. 2000).

The muscular and skeletal systems of a locomoting organism must allow for sufficient →degrees of freedom (DOFs), different locomotor speeds, adaptability, stability, appropriately orchestrated →skeletal muscle forces and →energy efficiency.

Locomotion must be accessible to and controllable by →volition and high-order processes associated with it. These processes should be able to initiate, change or stop locomotion.

Particular emphasis is given in the sections that follow to terrestrial locomotion in bipedal or quadrupedal animals that are moving from place to place over ground. Characteristics and challenges to terrestrial locomotion are described first.

21.2 Biomechanics of Terrestrial Locomotion

Terrestrial locomotion puts high demands on the stability of the muscular, skeletal and nervous systems. It requires an appropriate initial body posture before transitioning to a rhythmic locomotor state. Rhythmic pattern generation organized by neural central pattern generators (CPGs) ensures efficient locomotion during change of gait or speed (Frigon 2017). In addition, muscle activities must be adjusted to leg →kinematics and →kinetics during different gaits. CPG activities must also be able to react to changing external environments such as wind resistance and terrain, and to internal adjustments in muscular, skeletal and nervous properties during locomotion.

21.2.1 Bipedal Locomotion

Human walking and running are confronted with several general challenges. The most important challenge, whose solution is as yet poorly understood, is to ensure →balance during the movement (Reimann et al. 2018). When the legs are moving, the trunk, head and arms must be dynamically stabilized. The trunk and, in particular, the head as a base of important sensory organs, should be kept erect and oscillation-free as much as possible. All of the adjustments must be achieved dynamically in the presence of rapidly changing ground supports (Winter 1995). Equivalent demands must be met in quadrupeds.

21.2.1.1 Bipedal Gaits

Vertebrates vary gait in order to locomote at different speeds (Frigon 2017). Humans generally walk at low speeds and run at high speeds. Gait transitions are triggered by determinants that are still not quite clear, but may involve metabolic and mechanical efficiency, mechanical load, plus →cognitive and →perceptual factors (Kung et al. 2018).

Bipedal walking implies that one foot is on the ground most of the time (single-support phase), and two feet are on the ground for a short period (double-support phase). By contrast, the running pattern lacks double-support phases, but contains phases without any ground support at all. Moreover, the duty cycle (the fraction of the stride duration, for which each foot is on the ground) decreases slowly with increasing walking speeds and then drops abruptly at the transition to running, namely by ca. 35%. In addition to duty cycle, there are other gait variables that change smoothly within one gait and discontinuously between gaits.

In walking, each leg repetitively proceeds through a stance phase and a swing phase. The body´s center of gravity (COG) moves up and down during each leg´s stance phase. In addition, the COG oscillates medio-laterally. The COG moves forward along the medial border of each support foot, and during single support it is →accelerated away from the support foot towards the future position of the swing foot. During the stance phase, the support leg´s COP moves forward from heel strike to toe-off.

21.2.1.2 Bipedal Kinematics

Human locomotion is kinematically complex because of multiple interactions of body segments that change the contribution of legs through the cycle and delicate balance.

Vertical Body Motion. An energetically important aspect is the vertical displacement of the COM throughout the stride. It is desirable to minimize this displacement, and there are →biomechanical mechanisms to achieve this (Lee and Farley 1998). Forward translation of the point of ground contact during the stance phase reduces vertical COM displacement, because foot contact is established by the heel at stance onset and by the toes at stance end. The vertical COM displacement is further reduced because the stance limb, rather than being a rigid strut, is compressed during the stance phase. However, the stance leg is kept relatively straight, presumably in order to reduce the →torque around the knee and thus the energetically costly muscle force relatively low (Kuo and Donelan 2010). The pelvic girdle rotates about a vertical axis through about ±3° at normal walking speeds; this rotation increases with speed, resulting in an effectively greater leg length and a longer stride length and radius, thus reducing the vertical pelvis excursion. During the first half of the stance phase, the stance-leg knee flexes and the stance-leg ankle dorsi-flexes, reducing effective leg length. Just before toe-off, the foot of the stance leg is plantar-flexed. Thus, even during normal human walking, there is a complex interaction of component motions, which vary individually (Bianchi et al. 1998a).

When humans switch from walking to running, the peak →ground reaction force increases by ca. 50%, and the trajectory of the COM changes drastically (Alexander 1989; Dickenson et al. 2000; Lee and Farley 1998). Thus, even during normal human walking, there is a complex interaction of component motions that vary individually (Bianchi et al. 1998a).

Degrees of Freedom (DOFs). Vertical and forward COM motion in the sagittal plane is characterized by two degrees of freedom (DOFs) that depend on the combined motions of all lower-leg segments. The control of COM motion by the →central nervous system (CNS) is simplified if the leg motions were also controlled by two variables, but this seems unlikely.

The segment motions appear to go through complicated rotations, and the segments´ elevation angles follow individual trajectories. However, when plotting the trajectories against each other, the elevation angles turn out to be linearly related. This is the same rule of planar co-variation that applies to quiet upright stance. The specific orientation of the plane in angle space reflects the phase relations between the elevation angles and thus the timing of inter-segmental coordination. For example, this plane rotates slightly, but consistently, along its long axis with increasing walking speed (Bianchi et al. 1998a,b).

The rule of planar co-variation reduces the degrees of freedom (DOFs) of lower-limb angular motions in the sagittal plane to two and thus to the same number as that of COM motion (Lacquaniti et al. 2002). It also simplifies the control problem, because the CNS does not have to control all joint angles individually.

In some respects, backward walking is a time-reversed version of forward walking, because the trajectories of the thigh, shank, and foot elevation angles are essentially time-reversed relative to the corresponding trajectories in forward walking. The changes in elevation angles co-vary along a plane during the whole gait cycle in both forward and backward directions. The phase relationship among elevation angles is maintained with a simple reversal of the delay. However, →electromyographic (EMG) activation patterns are drastically different in forward and backward walking, as is the organization of the muscle synergies. The magnitude of EMG activity integrated over one gait cycle generally is greater in backward gait than in forward gait, suggesting a greater level of energy expenditure in the former than in the latter gait (Grasso et al. 1998).

Forward and Backward Walking. On a split-belt treadmill, normal humans can easily adapt so that the right and left legs walk in different (opposite) direction. These walking adaptations are stored independently for each leg and do not transfer across directions (Choi and Bastian 2007).

Walking along Curved Paths. While walking along a curved path, stride length and stance-phase duration differ between legs, and the COM moves toward the concave trajectory side, enabled by appropriate foot yaw orientation, body tilt in the frontal plane and pelvis rotation over the stance leg (Godi et al. 2019),

Running. In running, the lowest COM position is reached at mid-stance, where virtual leg compression is considerable. This allows recovery of energy in the late stance phase. Another important factor is that the heel-contact angle of the leg with respect to the vertical is smaller in running than walking, which reduces the reactive and decelerating backward force (Lee and Farley

1998).

21.2.1.3 Bipedal Kinetics and Energetics

The speed of unperturbed locomotion is given by the product of stride length and stride frequency. Any combination of speed, stride length and frequeny is associated with a metabolic or energetic cost that is influenced by properties of the organism, environment and task. It has been proposed that, under these restraints, the CNS selects a movement strategy and pattern that minimizes energy cost. How the CNS does so remains to be elucidated (Croft et al. 2019).

Changes in the mechanical energy of the COM have been derived from calculations based on force-plate measurements of vertical and horizontal ground reaction forces (Cavagna et al. 1976). From the horizontal force and body →mass (m), the COM´s forward speed (v_f) and →kinetic energy due to forward motion (E_{kf}) can be calculated, such that $E_{kf} = (1/2)mv_f^2$. Other calculations like this yield the →gravitational →potential energy (E_p), and the small kinetic energy due to vertical velocity, $E_{kv} = (1/2)mv_v^2$. The total energy then is $E_{tot} = E_{kf} + E_p + E_{kv}$.

In walking, the changes in potential and forward kinetic energy are out of phase so that changes in total energy are minimized. This has led to the notion of energy recovery. In the ideal inverted-pendulum model, the forward kinetic energy (E_{kf}) would be partially converted into vertical potential and kinetic energy ($E_p + E_{kv}$) during the ascent of the COM and be recovered during the descent. This cyclic conversion is not ideal, though, and energy is lost on the way. Most of the energy needed for unperturbed level walking is dissipated at the leading leg´s collision with the ground, where the downward COM movement is re-directed into an uphill movement. The collision occurs occurs over an extended phase beginning at heel-strike and typically extends slightly beyond double-limb support. Much of the energy lost during collision is probably due to the knee which flexes while producing an extension torque. Some energy is also dissipated in soft tissues, such as the heel pad, cartilage, viscera, and vertebral disks. The energy restoration process uses several mechanisms, involving active muscle contractions. The collision is followed by a rebound phase, in which the leg straightens during the first half of single-limb support and thus performs positive →work generated by the knee extensors. In addition, as the hip extends during the stance phase, the associated torque performs positive work that can compensate for the subsequent heel-strike collision. Another possibility to regenerate energy is to apply ankle push-off late in double-limb support phase. Yet another mechanism to inject restorative energy into the system is to actively swing the leg back and forth, which costs metabolic energy. The energy costs or walking increase with either longer or wider steps (Kuo and Donelan 2010).

During running, E_{kf} and (E_p+E_{kv}) change in phase, therefore E_{tot} undergoes large oscillations. There is little exchange and recovery of energy as occurs during walking, and the energy consumption is therefore much higher. Nonetheless, by cyclically stretching and recoiling, tendons store and release energy and thereby reduce muscle work which would be much greater without tendons (Biewener 2016; Magnusson et al. 2008; Roberts 2002).

21.2.1.4 Biomechanical Muscle Actions

The biomechanical actions of skeletal muscles on movements are often derived from their anatomical sites of origin and insertion, although this notion is oversimplified. The body segments exchange kinetic and potential energy throughout a movement, with energy flowing into or out of the segments. Thus, the force that a muscle generates accelerates not only the segments of origin and insertion, but also other segments and joints via inter-segmental interactions (Zajac et al. 2002). Two examples concerning the soleus muscle may suffice to make the point.

First, during walking, the stance foot is on the ground in mid-stance (~20–40% gait cycle). The active soleus muscle, which develops only an ankle extensor torque, accelerates the shank and the foot as well as the thigh and trunk segments. Similarly, the soleus not only accelerates the spanned ankle joint into rotation, but also the other unspanned joints, such as the knee and hip. Thus the soleus decelerates the thigh and the shank and accelerates the trunk, causing energy flow from the leg to the trunk while at a nearly constant length. The soleus thereby delivers translational energy to the trunk because its contribution to the hip inter-segmental force has a component that is collinear with the translational velocity of the trunk. Most of the energy exchange caused by the soleus, while acting nearly isometrically in mid-stance, is due to changes in horizontal kinetic energy of the segments (Zajac et al. 2002).

Second, isometric as well as shortening of the soleus muscle can re-distribute segmental energy by accelerating some segments and decelerating others. However, the energy gain of the accelerated segments exceeds the energy reduction of the decelerated segments by the amount of muscle work produced. For example, later into stance (~40–60% gait cycle), the soleus muscle continues to decelerate the thigh and shank and accelerate the trunk while acting concentrically. Here, the energy gain of the trunk exceeds the energy reduction of the leg because the soleus produces work by shortening and also by releasing stored musculo-tendon →elastic energy (Zajac et al. 2002).

In summary, the primary function of a muscle could be to re-distribute energy among segments. Muscle force can cause significant segmental energy re-distribution irrespective of whether the muscle produces mechanical work by shortening, dissipates energy by lengthening, or does neither by remaining isometric (Zajac et al. 2002).

Still, muscle activity also contributes to tuning the biomechanical properties of joints. For example, the →stiffness and →viscosity of the swinging leg´s ankle joint are increased just before heel strike, which would help dampen the shock of ground collision, and most likely results from coactivation of antagonistic soleus and tibialis anterior (TA) muscles (Lee and Hogan 2015).

21.2.1.5 Bipedal Muscle Activation Patterns

At least half of the over 50 muscles in the lower limb of humans contribute to active leg motion during walking. It would be extremely demanding for the CNS to organize the activity of each individual muscle; instead, it appears to organize several basic, properly timed and distributed activity patterns to groups of muscles (Aoi and Funato 2016; Lacquaniti et al. 2012). A common set

of spatially fixed locomotor muscle synergies are recruited via several pathways for voluntary gait modification during forward and backward walking (Chvatal and Ting 2012).

Muscles show rhythmic activation patterns that exhibit high variability between strides when humans are walking in the forward direction. Nonetheless, many leg and trunk muscles exhibit characteristic individual activity profiles when averaged over several steps and several individuals. In fact, individual muscle activations are composed of relatively few activity profiles. The CNS produces only 4-5 basic patterns, each one timed at a different phase of the gait cycle, and distributes them in appropriately weighted combinations to the group of muscles engaged in particular tasks during locomotion. These basic patterns are conserved across subjects of different weight, height and mass distributions, plus, across different locomotor speeds, amplitudes and directions and across different gravitational loads (Ivanenko et al. 2006; Lacquaniti et al. 2012).

21.2.1.6 Maintenance of Balance during Bipedal Locomotion

Maintaining balance during walking and running is particularly challenging for bipedal animals. In humans, the →center of mass (COM) is relatively high above the →base of support (BOS). Moreover, the BOS is comparatively small, being determined by two feet or even only one foot on the ground at a time in the step cycle. Because during a stride the vertical COM projection rarely falls into the BOS, bipedal gait is inherently unstable, even in normal unperturbed gait on even ground. The COM fluctuates in all directions around the mean trajectory.

Possible perturbations of normal gait come in unexpected and expected forms: slip, trip, jostle, descent of foot in hole, obstacle crossing and change in direction. Expected perturbations such as visible obstacles can be anticipated and gait can be adapted through a feed- forward control process. Unexpected perturbations such as slips are basically controlled in feedback (reactive) mode. Small perturbations do not need a complete phase-resetting of the gait cycle, while large perturbations usually require to change the step strategy. The compensatory reactions consist of a series of muscle activations, many of which are below the threshold latency of voluntary reactions (Duysens and Forner-Cordero 2018).

Small perturbations in the anterior-posterior walking direction are less challenging than those in the medio-lateral direction. To dynamically stabilize gait, the latter perturbations must be detected and counteracted by active patterns of muscle activations to be organized by the CNS (Kuo and Donelan 2010).

There are several strategies or motor actions that act against medio-lateral perturbations, one or the other which dominates depending on conditions. One is to move the trunk from side to side, another is to produce active eversion/inversion torques at the ankle and a third is to modulate push-off by the stance foot. Another simple solution is to make lateral adjustments to swing-foot placement by active hip abduction or adduction (Kuo and Donelan 2010; Reimann et al. 2018).

During the stance phase, the stance leg can contribute to gait stability by means of active →muscle torques at the ankle joint. For example, contraction of lateral ankle muscles generates torques that

shift the COP medially, which can secure slight medial fluctuation of the COM (Reimann et al. 2018).

During the double-support phase of walking, ground contact of both legs enables a redistribution of weights if needed. In this phase, the leading leg is in front of and slightly lateral to the trailing leg; weight shifts between the legs thus affect lateral balance. Such a weight shift can be performed by modulating the plantar-dorsiflexion angle of the trailing ankle, which would change the way the trailing leg pushes off against the ground. A stronger push-off with the left leg will accelerate the COM forward and to the right, and a weaker push-off will accelerate the COM backward and to the left (Reimann et al. 2018).

Swing-foot placement appears to depend on passive and active effects of swing-leg kinematics as well as COM position and acceleration during the preceding swing phase, and on active neural control using COM estimation based on proprioceptive, vestibular and visual feedback (Bruijn and van Dieën 2018). For example, in the stance phase, muscle spindle activity arising in the stance-leg hip abductor muscles contributes to the control of the subsequent medio-lateral foot placement in relation to the kinematics of the CoM, and thus to the medio-lateral stabilization of gait (Arvin et al. 2018).

21.2.1.7 Gait Initiation in Humans

Having dealt with the intricacies of steady-state bipedal locomotion, it is worth reassessing the transition from quiet upright stance to steady-state walking and the reverse. Both transitions challenge stability. The transition from upright stance to walking, referred to as gait initiation, challenges balance because it involves a change in the base of support and a progression of the center of mass (COM). For example, when the left foot is lifted, the left part of the support base is lost and the COM is accelerated toward the left. This transition may cause instability with a risk of falling (Yiou et al. 2017).

Gait initiation is traditionally divided into three successive phases. A postural phase (1) precedes the swing-heel liftoff and involves →anticipatory postural adjustments (APAs). The foot-lift phase (2) stretches from heel liftoff to toe clearance, in which the COM moves forward and towards the stance leg. The subsequent execution phase (3) ends at swing-foot contact with the support surface (Hase and Stein 1998; Yiou et al. 2017).

Anticipatory postural adjustments (APAs) are complex responses to perturbations organized by the CNS in a predictive way. APAs in the antero-posterior direction include a backward shift of the →center of pressure (COP) that promotes the initial forward propulsion before toe-off, scaled according to intended step length and speed. The propulsion is generated by bilateral inhibition of the plantar-flexor muscle activity and the subsequent activation of ankle dorsi-flexor muscles. APAs in the medio-lateral axis involve COP shifts toward the swing leg and ensuing COM shift in the opposite direction, i.e., toward the stance leg. Such shifts are promoted by activation of the stance-leg hip adductor, rectus femoris and ipsilateral tibialis anterior muscle (TA) muscles, and by bilateral silencing of the soleus muscles silencing (Yiou et al. 2017).

Anticipatory postural adjustments (APAs) on their own do not fully stabilize balance in the medio-lateral direction. Precise lateral placement of the swing foot after the swing phase, which enlarges the support base, appears to be more important. Foot placement is primarily adjusted by the hip abductor muscles of the swing leg (Yiou et al. 2017).

21.2.1.8 Gait Termination in Humans

Gait termination occurs in three conditions: goal completion, fear and →startle (Duysens and Forner-Cordero 2018). It is a complex process. It depends on ambulation speed (walking to running) and the time in the step cycle at which the decision to stop is taken. It poses a risk of falling, particularly while moving at higher speed. It also requires deceleration of forward body momentum (product of mass and velocity), plus, attainment of stable posture (Hase and Stein 1998). Two mechanisms are used to decelerate forward body momentum. The swing leg increases braking force during footfall, and the stance leg decreases push-off force. If the two mechanisms are insufficient to achieve a stable upright position, additional procedures include elevating body position by rising up on the toes, or taking an additional step (Hase and Stein 1998).

In the anterior-posterior plane, deceleration associated with gait termination during rapid stopping proceed as follows. At the time of foot contact, prior soleus (SOL) activation extends the ankle and places the foot flat on the ground, thereby impeding further forward leg movement. Soleus and vastus lateralis actions keep body position behind the forward leg. Gluteus medius and erector spinae actions prevent hip flexion and forward trunk movement, thereby stabilizing the COM behind the forward foot. The other (stance) leg reduces push-off power by strong tibialis anterior (TA) activation and by diminishing soleus activity, which, together, reduce ankle plantar flexion and produce backward momentum. Biceps femoris muscle and gluteus medius muscle (GM) actions keep the hip extended and the leg behind the body (Hase and Stein 1998).

The EMG changes occur within 150-200 ms in most leg muscles and are closely coupled. This suggests that these muscle synergies are stored as motor programs that can be easily and quickly accessed when necessary (Hase and Stein 1998). The programs are flexible, however, and are dependent on walking speed. Thus, the muscle synergies change in the stance leg, while being relatively robust in the swing leg (Crenna et al. 2001).

Stopping from running poses higher demands, to which adults and pre-pubertal children respond with different strategies. During deceleration, children approach the stop at higher relative speed, with lower momentum, higher and more anterior position of COM. They use fewer and relatively longer step lengths over a relatively longer distance and longer time (Cesar and Sigward 2015).

21.2.2 Quadrupedal Locomotion

21.2.2.1 Quadrupedal Gaits

Quadrupedal mammals walk at low speeds, trot at intermediate speeds and gallop at high speeds. Quadrupedal locomotion incorporates as many as six differentiable gaits. Walking, trotting and

galloping are the prominent ones. The gaits differ strikingly, as assessed by a range of variables (McMahon 1984).

21.2.2.2 Quadrupedal Kinematics

Stride Phases in Quadrupeds. The basic kinematic features of undisturbed cat hindlimb walking can be quantified using various measures. The different joint angles show complex changes throughout the stride. In particular, the trajectories of the knee and ankle angles divide the step cycle into a flexor phase and three extensor phases. Transitions between phases are not synchronized across joints. A much simpler picture appears when measuring the segment orientation angles, all of which essentially show a roughly sawtooth-like pattern divided into forward-swing (FS) and backward-swing (BS) phases. However, there are systematic differences in FS onset and termination (Shen and Poppele 1995).

Common Features of Quadruped and Biped Locomotion. Human and quadrupedal walking kinematics have some features in common. For example in both the cat hindlimb and human lower-leg segment, elevation angles at the hip, knee and ankle exhibit planar co-variation in the sagittal plane. Moreover, the phase ordering between the elevation angles shifts systematically with speed both in cat and man, which may reduce the oscillations, and thus the dispersion of kinetic energy increases rapidly with speed (Lacquaniti et al. 2002).

Corrections for External Perturbations during Locomotion. Locomotion can be easily perturbed by external influences, e.g., by collisions with objects. A crucial problem in quadruped walking is lateral stability. In awake cats, external perturbations challenging this stability elicit reactions that depend on the relative timing of the perturbation and step cycle phase. For example, in awake cats whose anterior body was suspended and whose hindlimbs walked on a treadmill, a lateral push to the hip region, say from the left, caused a rightward deviation of the caudal trunk. If the push was applied at the end of the stance phase or during the swing phase of the left hindlimb, this limb´s trajectory deviated to the right (inward), which landed the foot in a more medial position to regain stability. Conversely, the corrective step was directed outward when the push was applied contralaterally. The electromyographic (EMG) patterns in the corrective limb showed strong changes of the hip abductor and hip adductor activity in the perturbed as compared to the unperturbed step (Karayannidou et al. 2009).

21.2.2.3 Quadrupedal Kinetics and Energetics

Vertical displacement of the COM depends on two variables in quadrupeds: the mass distribution between fore- and hind-quarters and the relative phase of leg motions. If the mass is assumed to be equally distributed between the fore- and hind-quarters, and the limbs cycle at evenly spaced time intervals, the pendular movements of the fore- and hind-quarters offset each other and the COM follows a flat trajectory. Deviations from these conditions lead to vertical COM displacements. For example, if most of the body mass is carried by the fore-quarter, the COM more closely follows the movements of the fore-quarter. If both limbs on one side move almost synchronously, the COM moves up and down at the mean amplitude of fore- and hind-quarters (Griffin et al. 2004). The COM motions determine energy exchange, expenditure and recovery, with similar considerations

applying in walking quadrupeds as in human walking. In walking, the maximum values of mechanical energy recovery are lower for quadrupeds (30–65%) than for bipeds (70–80%) (Griffin et al. 2004).

21.2.2.4 Quadrupedal Muscle Activation Patterns

In normal quadrupedal locomotion, there are three main muscle activation patterns exhibited by →skeleto-motoneurons (for brevity, referred to as → motoneurons, as long as → γ-motoneurons are excluded). Extensors are active during late swing and most of the stance phase, hip and ankle `flexors´ are active during swing; and `retractors´ are active during late stance and early swing. Retractor muscle activation may serve to complete the backward movement of foot and toes, to complete the extensor thrust of late stance phase, and then to lift the foot off the ground for forward swing (Yakovenko et al. 2002). Walking up and down a series of steps changes the kinematics, kinetics and muscle activation patterns.

21.3 Timing of Locomotor Phases

Spinalized and decerebrate cats while walking on treadmills adjust their hindlimb stepping rate to a considerable speed range between 0.1 and 1 m/s. At higher speeds, walking/trotting sometimes gives way to galloping. Increased step rate is achieved primarily by shortening the stance phase, while the flexion phase remains nearly constant. These adjustments indicate a substantial role for sensory feedback in switching between different locomotor phases, especially in regulating the stance phase duration (Pearson 2008).

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22

Spinal Neural Control of Locomotion

CONTENTS

Abstract

• Effective and efficient terrestrial locomotion in vertebrates is achieved through complex interactions between neural networks located in the forebrain, brainstem and spinal cord.

• A fundamental requirement for locomotion is the generation of rhythmic motoneuron discharges by central pattern generators (CPGs) in the brainstem and spinal cord, and by autonomous pacemakers, whose rhythm is set up by intrinsic ion channel conductances and influenced by a wide variety of chemical neuromodulators. Proprio-spinal connections coordinate different CPGs, depending on movement speed and gait.

• During locomotion, motoneuron and interneuron activities are modulated by persistent inward currents, Ca^{2+} current and Na^{+} current, which generate excitatory plateau potentials, reduce action potential afterhyperpolarization, lower discharge threshold and increase synaptic efficacy.

• Sensory feedback in local or distributed rhythmic networks during locomotion infuences the transition between locomotor phases, reinforces ongoing motor output, shapes muscle discharges and contractions, and affects the timing of motor activity throughout the gait cycle.

• During locomotion, spinal reflexes at various sites can be modulated in intensity or even reversed by presynaptic inhibition and proprioceptive feedback from muscle spindles, depending on the gait phase. Several types of reflex control mechanisms are involved: reciprocal Ia inhibition mediated by inhibitory interneurons, recurrent inhibition via Renshaw cells, cutaneous reflex modulation and tendon reflexes.

22.1 Introduction

Casual observation of adult human locomotion gives the false impression that it is a seemingly simple task. In fact, how individual →skeletal muscles fulfill the mechanical requirements of the locomotor task is quite complex; and how it is accomplished has been for a long time debated (Cappozzo and Paul 1997). A first approach to understanding a complex locomotor task such as human walking is to understand the basic mechanics of the multi-segmented body using simple mechanical models without muscles. Such models have limited →degrees of freedom (DOFs), and while they demonstrate that the inherent dynamic properties of the multi-segment system can be exploited to generate locomotion (Zajac et al. 2003), living organisms require muscle activities organized by the →central nervous system (CNS).

For terrestrial locomotion, the CNS must make context-dependent choices and produce adequate activities: initiate and stop locomotion, select the direction and the appropriate speed and associated gait pattern. During the locomotor phase, the CNS must generate basic patterns of rhythmic muscle activities, coordinate different limb activities, maintain →balance and equilibrium during the dynamic movements, and adjust the basic locomotor pattern to changing contexts and behavioral goals. These tasks are organized differentially but coordinatively by neural networks stretching from the →spinal cord through the →brainstem to the →forebrain. The most taxing demands on locomotor control arise when an animal must adapt its gait patterns rapidly while moving through a cluttered, uneven environment during navigation. This requires complex contributions from different areas of the →cerebral cortex, the →basal ganglia and →cerebellum (Ferreira-Pinto et al. 2018; Grillner and El Manira 2019).

22.2 Central Pattern Generators

A fundamental requirement for locomotion in all vertebrates is the generation of rhythmic →skeleto-motoneuron (in brief →α-motoneurons) activities by central pattern generators (CPGs) in the spinal cord and brainstem (Catela et al. 2015; Grillner and El Manira 2019; Katz 2015; Steuer and Guertin 2019). The CPGs are autogenous in the sense that they do not depend on afferent sensory feedback or spinally descending signals for their basic rhythm-generating function. In many vertebrate species, the isolated spinal cord and brainstem are capable of producing quite elaborate motor output patterns similar to those recorded in normal animals. For instance, after pharmacological pre-treatment (e.g., bath application of the →monoamines →serotonin (5-HT) or →noradrenaline), the rabbit and cat lumbo-sacral cord, separated from the rostral CNS by transections at low thoracic level and from movement-related sensory inputs by →paralysis, is capable of producing complex well-organized motor output patterns (fictive locomotion). These can be recorded as rhythmic →burst firings of α-MNs activity in lumbar →ventral roots or peripheral nerves (Brocard et al. 2010; Cazalets and Bertrand 2000; Goulding 2009; Guertin 2013; Rossignol et al. 2006). In cats, many fictive activity patterns of hindlimb uni-articular muscles closely resemble those in normal freely walking cats. However, the patterns of bi-articular thigh muscles differ from neurally intact preparations, possibly due to sensory feedback (Markin et al. 2012).

22.2.1 Multiplicity of Central Pattern Generators

In quadrupedal mammals such as rodents, cats and dogs, the global CPG is divided into sub-units. The trunk and each limb have at least one CPG (Cazalets and Bertrand 2000; Frigon 2017). Rhythmogenic capabilities are widely distributed along the spinal cord. Crucial elements of the forelimb CPGs are located in the upper thoracic and lower cervical spinal segments, whereas those of the hindlimb CPGs are located in the upper to mid-lumbar segments (Frigon 2017; Grillner and El Manira 2019).

For each limb joint, Brown (1911) postulated two neuronal half-centers, each driving flexor muscles simultaneously during the swing phase or extensor muscles simultaneously during the stance phase, with reciprocal inhibition between the half-centers insuring alternating activities. There are alternative hypotheses to this symmetric model (Ausborn et al. 2018; Dougherty and Ha 2019). In any case, Brown´s half-center hypothesis does not hold because the step cycle is divided into four phases: the stance (support) phase, the swing (flexion) phase and two intercalated transitional phases. During the lift-up phase at the end of the stance phase, double-joint muscles such as the semitendinosus muscle (hip extensor and knee flexor) are activated; and during the foot´s touch-down at the end of the swing phase, several muscles, including the short dorsi-flexors of the foot, are transiently active. The →electromyograhic (EMG) activity of muscles active during lift-up and touch-down occurs partially in between the activity of the main flexors and extensors. These complex activity patterns persist after →de-afferentation (Grillner and El Manira 2019). Still, the half-center terminology is used to date (e.g., Ausborn et al. 2018; Duysens and Forner-Cordero 2018).

Locomotion is an immensely complex action because of the many degrees of freedom (DOFs) to be controlled. It has been suggested that this problem is relieved by muscle synergies, i.e., coordinated activities of small groups of synergistic muscles. These synergies have been proposed to be organized by groups of →interneurons (dubbed `motor synergy encoders´) in the medial deep →dorsal horn (lamina V), which receive inputs from sensory afferents and descending →motor commands (Levine et al. 2014; Osseward and Pfaff 2019).

Fore- and Hindlimb Coordination. Fore- and hindlimb CPGs in quadrupedal animals show some differences because fore- and hindlimb functions are different. While hindlimbs produce the bulk of forward thrust, the forelimbs must support the head and are used for propping and steering (Yamaguchi 2004). Proprio-spinal connections coordinate the different CPGs in ways that depend on movement speed and gait (Côté et al. 2018; Frigon 2017). Different gaits require different coordination for leg and back →kinematics, and for forward walking and backward walking. Consequently, different patterns and synergies of muscle activations are necessary. These requirements support the concept of multiple subsidiary pattern generators that are coupled differently according to circumstances.

Location of CPG Networks. In the spinal cord of the neonatal rat, the CPG for hindlimb movements spreads over the lower thoracic region and throughout the lumbar region, which also contain the α-MNs controlling leg muscles. Similar distributions appear to exist in other vertebrates including the turtle, chick and cat. In humans, there appear to be a lumbar and a sacral CPG level, both controlling the legs. The lumbar level (segments L3-L5) controls mainly upper leg muscles, while the second one the lower leg muscles (Ivanenko et al. 2006). However, not all segments are equally important for all aspects of CPG function, suggesting that there is a hierarchical

organization of the hindlimb CPG, with the rostral segments playing a leading role in rhythm-generation (Duysens and Forner-Cordero 2018; Kiehn and Butt 2003). In the transverse plane, the medial part of lamina VII, lamina VIII, and lamina X contain all the CPG elements required to generate ipsilateral flexor-extensor and left-right alternation.

22.2.2 Central Pattern Generators in Humans

The autonomy of the isolated spinal cord for generating locomotor rhythms is far greater in the spinalized rat or cat than in →primates, including humans. The (debated) existence of CPGs in humans is inferred indirectly from various observations and becomes apparent when cortical influences are weak, such as in newborns and →sleeping people, and in patients with →spinal cord injuries (Klarner and Zehr 2018; Minassian et al. 2017; Zehr and Duysens 2004).

Pattern generation in humans precedes the development of posture (upright stance). Step-like movements are present at birth (`newborn stepping´), characterized by digitigrade stepping, i.e., by standing on the ball of the foot with toes reaching the ground first. They occur spontaneously or can be elicited by sensory stimuli. Stepping also occurs in anencephalic infants, implying that spinal coordination is possible without cortical control. Digitigradestepping normally disappears after several weeks. At about 9 months of age, children start to adapt their innate pattern to external conditions, with polysynaptic reflexes acquiring increasing importance (Dietz 2003). In human infants under 12 months of age, i.e., before the onset of independent walking, the neural circuitry for producing rhythmic alternating activities in lower limbs, stepping in different directions, correcting for disturbances in a well coordinated manner, and adjusting to different circumstances such as loading are all well developed (Yang et al. 2004).

22.2.3 Structure of Central Pattern Generators

Locomotor CPGs in several vertebrate species are composed of and divided into sub-components. Each utilizes genetically and molecularly diverse interneuron sub-populations with different →ontogenetic developments, which play different roles within networks and are subject to →neurotransmitter modulation (Brocard et al. 2010; Burke et al. 2001; Catela et al. 2015; Deska-Gauthier and Zhang 2019; Gosgnach et al. 2017; Gordon and Whelan 2006; Grillner and El Manira 2019; Guertin 2014; Haque and Gosgnach 2019; Lu et al. 2015; Osseward and Pfaff 2019; Taccola and Nistri 2006; Zhong et al. 2012).

In the mouse, the precise nature of, and wiring among, these interneurons and α-MNs is being revealed using multifarious methods. The interneurons involved are classified as →V0, →V1, →V2a, V2b, →V3 and dI6. *V0 interneurons* can be divided into a dorsal inhibitory sub-population ($V0_D$) and a ventral excitatory sub-population ($V0_V$), both responsible for coordinating left-right alternation, the dorsal subset at slow locomotor speeds and the ventral subset at higher speed; a small fraction of these cells, the →cholinergic $V0_C$ interneuron sub-population, acts to control the input/output gain of α-MNs. V1 interneurons are mostly inhibitory and include Renshaw cells, reciprocal Ia inhibitory interneurons (which derive from yet another progenitor domain) and a diversity of others, and are involved in regulating flexor-extensor alternation and step frequency. *V2a interneurons* are excitatory and involved in left-right alternation and are required for robust

locomotor patterns. *V2b neurons* are inhibitory and, together with V1 cells, secure the flexor-extensor alternation on one side at faster locomotor speeds. V3 interneurons are excitatory cells with primarily commissural projections, but also ipsilateral connections between two groups of ventro-medial and ventro-lateral V3 interneurons and α-MNs, which in turn recurrently excite the V3 cells. Subgroups of V3 interneurons also contact Renshaw cells, reciprocal Ia inhibitory interneurons, as well as V2b cells and other, unidentified, commissural interneurons. V3 interneurons are thought to balance locomotor output across the midline and thus to help maintain a stable and robust locomotor pattern. →dI6 interneurons are made up of different subgroups. One inhibitory subset sends →axons to ipsilateral and contralateral targets, including MNs and possibly Renshaw cells as well as cholinergic neurons (possibly $V0_C$ interneurons). Another inhibitory subset sends commissural axons to targets in close proximity to commissural neurons in the intermediate →gray matter, but not to MNs. Both subsets fire rhythmically during fictive locomotion, and their ablation causes defects in left-right alternation (Chopek et al. 2018; Gosgnach et al. 2017; Griener et al. 2017; Haque and Gosgnach 2018; Zhang et al. 2014). Whether α-MNs belong to CPGs has been debated. In neonatal mice, activation of α-MNs has effects on CPG functions, but how this effect is mediated and whether it persists in adult mice is not known (Falgairolle and O´Donovan 2019).

Locomotor activities have two aspects: rhythm-generation and pattern-formation. Rhythm means the timing or regularity, and pattern is the coordinated recruitment of α-MNs in sequence (Dougherty and Ha 2019).

Rhythm-generating Networks. Rhythms may be generated by potential →pacemaker neurons which oscillate spontaneously due to an assortment of →ion channels in their cell membranes and then impose their intrinsic rhythmic activity onto the network (Ramirez et al. 2004). The →ventral horn of the spinal cord hosts rhythm-generating neurons, i.e., local, ipsilaterally projecting, excitatory interneurons, which can convert tonic input into rhythmic output. Besides, there are other cells which project ipsilaterally to coordinate the flexor and extensor rhythms and commissurally to coordinate rhythm generation on both sides (Dougherty and Ha 2019).

Rhythms can also be produced by neuronal oscillatory network(s) (→neuronal oscillations), whose rhythm is an emergent property of inter-neuronal connections, or by a combination of the two mechanisms (Kiehn 2016). Rhythm-generating networks may include reflex network(s). It has been suggested that these networks generate the vertical (up and down) component of limb movement during a step (Deliagina et al. 2019). In any case, neuronal networks generating rhythmic motor activities are multi-functional and continuously reorganize and reconfigure themselves according to the task at hand and the context in which they operate (Briggman and Kristan 2008).

Pattern-formation Networks organize the spatio-temporal patterns of muscle activations, shape the required excitatory and inhibitory neuronal signals and distribute them in various combinations to the different →motoneuron pools that generate coordinated muscle activation patterns; for example, the fundamental locomotor pattern of alternating flexor and extensor activity (McCrea and Rybak 2008). In newborn mice, so-called V1 and V2b interneurons, sub-populations of which are the progenitors of reciprocal Ia inhibitory interneurons, are essential for securing the reciprocal pattern of flexor and extensor motor activity (Zhang et al. 2014). It has been suggested that pattern-formation networks generate the horizontal (forward and backward) component of limb movement during a step (Deliagina et al. 2019).

There are two basic views as to how these aspects are organized. The first view posits a two-layer organization of two separate networks (Dougherty and Ha 2019; Rybak et al. 2015). The rhythm-generating network would generate the rhythm and be upstream of the pattern-formation network which would connect to α-MNs (Deska-Gauthier and Zhang 2019; Dougherty and Ha 2019; Duysens and Forner-Cordero 2018). The second view contradicts this separation. Indeed, even in the two-layer model, rhythm and pattern are related insofar as flexor-extensor alternation and left–right coordination are determined by the rhythm-generating layer (Dougherty and Ha 2019). But the alternative hypothesis additionally posits that rhythm and pattern would emerge from a common complex network of interconnected ipsilateral →glutamatergic interneurons and inhibitory commissural interneurons. The ipsilateral glutamatergic interneurons would form a recurrent circuit driving the locomotor rhythm. Furthermore, they would provide direct excitation to α-MNs, which in turn could profoundly influence the function of the locomotor CPG by recurrent connections (Grillner and El Manira 2019).

22.2.3.1 Pacemaker Neurons

Pacemaker neurons are individual neurons that are intrinsically capable of rhythmic burst discharge enabled by an assortment and distribution of diverse membrane ion channels (Brocard 2019; Brocard et al. 2010; Grillner 2006; Kiehn 2016; Ramirez 2009; Ramirez et al. 2004; Straub 2009). These ion channels underlie the bursting property and include →persistent Na^+ ($I_{na}p$) currents; low-voltage-activated Ca^{2+} (LVA I_{ca}) currents; →hyperpolarization-activated (I_h) inward currents; →Ca^{2+}-dependent K^+ ($I_{K(Ca)}$) currents and slowly activating K^+ currents (I_A); the former three active during →depolarization and the latter two during repolarization (Straub 2009). Individual pacemaker neurons rarely dominate the rhythm in a mammalian oscillatory network. Most often, closely timed bursts of several pacemakers initiate new activity states through orchestrated interactions of many network cells (Brocard et al. 2010; Dougherty and Ha 2019; Ramirez et al. 2004).

The mouse spinal cord hosts so-called Shox2 nonV2a and Hb9 interneurons whose pacemaker properties are mediated by activation of T-type Ca^{2+} currents and →persistent Na^+ currents. The cells receive inputs from sensory afferents and directly contact α-MNs. Hypothetically, subsets of rhythm-generating neurons may be responsible for different locomotor speeds or contexts and might be controlled differently by descending systems. For example, the cuneiform nuclei and →pedunculopontine nucleus (PPN) control high and low speeds, related to escape and exploration, respectively (Dougherty and Ha 2019).

Pacemaker properties can emerge gradually due to increases in extracellular potassium (K^+) and decreases in extracellular calcium (Ca^{2+}) concentrations resulting from discharge activities of neuron populations (Brocard et al. 2013). Bursting patterns are flexible due to their dependence on →neuromodulators and non-linear mutual interactions with →synaptic mechanisms.

22.2.3.2 Oscillatory Networks

It has been possible to characterize CPGs anatomically, physiologically and pharmacologically in various types of invertebrates and some kinds of lower vertebrates (Ferreira-Pinto et al. 2018; Katz 2015). For example, the neurons constituting the CPGs for swimming in the lamprey and the Xenopus tadpole have been identified and their connections described (Archavsky et al. 1993; Grillner 2006; Roberts et al. 2000). Much less is known as yet about the networks constituting mammalian CPGs (Brocard et al. 2010; Gordon and Whelan 2006; Goulding 2009; Kiehn 2016; Zhong et al. 2012). Candidate CPG neurons have been characterized genetically, anatomically and molecularly and divided into numerous groups with different properties and functions (Côté et al. 2018; Gosgnach et al. 2017; Guertin 2013, 2014; Kiehn 2016; Ziskind-Conheim and Hochman 2017).

CPG networks possess diverse and variable characteristics at the cellular, synaptic and network level (Getting 1989; Pearson 1993; Marder and Calabrese 1996). In addition, CPG networks vary in sign (excitation or inhibition), strength and time course of action, neurotransmitter release properties, and multi-component synaptic potentials. At the network level, various neuronal network interactions are crucial constituents of CPGs, including mutual excitation, recurrent excitation, →recurrent inhibition, reciprocal inhibition, feedback inhibition and parallel excitation-inhibition (Getting 1989).

22.2.3.3 Neuromodulation of Central Pattern Generators

Neuromodulators are known to influence CPG activity and adaptability to a large variety of circumstances and demands that can activate an inactive CPG (Díaz-Ríos et al. 2017; Guertin 2014; Harris-Warrick 2011; Sharples et al. 2014). Under normal conditions, spinal locomotor networks need synaptic drive from supraspinal systems for activation. Inactive locomotive networks in reduced preparations can sometimes be driven into fictive locomotion by electrical stimulation of supraspinal structures, such as the →mesencephalic locomotor region (MLR) (Ferreira-Pinto et al. 2018). In spinalized preparations including isolated spinal cords, bath application of neuromodulatory substances mimics descending influences on the CPG network.

Neurotransmitters and Neuromodulators. A large variety of neurotransmitters and neuromodulators have important influences on locomotion and supportive posture. Neuromodulators alter the frequency and/or burst properties such as amplitude and duration of CPG output. They do so by changing the electrical properties of intrinsic CPG neurons and α-MNs, or by modulating the synaptic connections between the neurons (Díaz-Ríos et al. 2017; Guertin 2013, 2014; Miles and Sillar 2011; Perrier and Cotel 2015; Sharples et al. 2014; Sławińska et al. 2014).

Neuromodulator Sources. The source of neuromodulators may be intrinsic or extrinsic to the CPG. An example of the former case is the →endocannabinoid system, which is dispersed, not bound to a specific fiber system, and modulates locomotor activity in an activity-dependent manner by changing synaptic interactions between CPG neurons (El Manira and Kyriakatos 2010). In the latter case, neuromodulators are mostly released from nerve fibers descending from the →brainstem and →diencephalon. →Dopaminergic fibers descend through fiber tracts from the →hypothalamus, noradrenergic fibers originate in the →locus coeruleus (LC) and Kölliker-Fuse nucleus, and serotonergic (5-HT) fiber tracts arise in the →raphé nuclei (RN), to innervate α-MNs and dorsal-

horn interneurons (El Manira and Kyriakatos 2010; Grillner 2006; Heckman et al. 2008; Hultborn et al. 2013; Jordan et al. 2008; Miles and Sillar 2011; Perrier and Cotel 2015; Sharples et al. 2014; Sławińska et al. 2014; Sławińska and Jordan 2019; Whelan 2009).

Monoamines. In spinal animals, →receptor agonists acting on conjoint dopaminergic, noradrenergic and serotonergic (5-HT) receptors, particularly in combination, induce rhythmic patterns that resemble walking and swimming in intact adult animals (Guertin 2013, 2014; Kiehn and Butt 2003; Sharples et al. 2014). Monoaminergic signals descending from the brainstem increase with the speed of locomotion, as well as during →fight or flight reactions (Heckman et al. 2005, 2008). Serotonergic effects on motor output are more complicated for a number of reasons, including strength of serotonergic input and receptor types activated (Perrier and Cotel 2015). In behaving cats, the activity of serotonergic neurons in the raphé nuclei is positively correlated with the tonic level of motor activity (→muscle tone) and often increases before locomotion. During prolonged treadmill locomotion leading to →muscle fatigue, serotonergic neurons gradually reduce their initially elevated firing activity. The ensuing disfacilitation of α-MNs may contribute to the development of central fatigue (→muscle fatigue, neural factors) (Fornal et al. 2006; Jacobs et al. 2002; Perrier and Cotel 2015).

22.2.3.4 Alteration of Motoneuron Properties during Locomotion

Modulating influences during locomotion alter the discharge properties of α-MNs and interneurons and the ways they transform synaptic inputs into →action potential sequences (McCrea 2001; Heckman et al. 2005, 2008; Power et al. 2018; Rekling et al. 2000). Excitatory drive potentials are unveiled, inhibitory synaptic potentials are reduced, firing →threshold is lowered and depolarizing inward current is enhanced and prolonged. Consequently, α-MNs become more excitable.

Plateau Potentials. Rhythmic depolarizing locomotor drive potentials (LDPs) result in part from plateau potentials that affect action potential firing rate and duration (Schmidt and Jordan 2000). The generation of plateau potentials involves →dendritic voltage-dependent →persistent inward currents (PICs) carried by sodium (Na^+) and calcium (Ca^{2+}) currents . PICs are subject to neuromodulation, in particular from descending serotonergic and noradrenergic influences (Binder et al. 2020; Heckman et al. 2008; Hultborn et al. 2013). These influences distribute diffusely in the spinal cord and are not specific to particular α-MN pools. Moreover, PICs tend to prolong the effects of synaptic inputs beyond their duration. These effects can however be spatially restricted and temporally controlled by actions of inhibitory inputs, e.g., those exerted by reciprocal Ia inhibition (Johnson and Heckman 2014). Plateau potentials based on PICs also occur in spinal interneurons (Abbinanti et al. 2012; Tazerart et al. 2007).

Reduction in Afterhyperpolarization. During fictive locomotion, the α-MN →afterhyperpolarization (AHP) is reduced leading to increased firing rates (Brownstone et al. 1992; Power et al. 2018). Serotonin changes intrinsic α-MN properties by blocking the K^+ current underlying the late AHP and thereby unmasking a →voltage-gated Ca^{2+} current leading to plateau potentials (Schmidt and Jordan 2000).

Changes in Motoneuron Firing Threshold. The threshold for spike firing is shifted in the hyperpolarized direction, which reduces the amount of depolarizing current needed to excite the α-MN (Krawitz et al. 2001; MacDonell et al. 2015). Threshold hyperpolarization is induced by serotonin and noradrenaline but does not depend on the persistent inward current (PIC) (Power et al. 2018).

Changes in Late Spike Frequency Adaptation (SFA). Under normal non-locomotor conditions, supra-threshold sustained or intermittent current injection into α-MNs may elicit discharges whose rate slows down over tens of seconds. During fictive locomotion in cats, late SFA was absent, contributing to increased α-MN excitability (Brownstone et al. 2011).

Changes in Synaptic Efficacy. Most importantly, the PICs amplify and prolong depolarization and firing elicited by excitatory synaptic inputs, depending on the level of monoaminergic input (Heckman et al. 2008; Hultborn et al. 2013).

There is indirect evidence that α-MN excitability is also modulated during cyclic movements in humans and depends in complex ways on frequency, →power output and muscle studied, but the exact mechanisms underlying this modulation are unknown (Power et al. 2018).

22.3 Interactions between Sensory Feedback and Central Pattern Generators

The importance of muscle proprioception for normal locomotion is easily appreciated by effects of its loss or diminution. In the mouse, locomotor patterns deteriorate after genetic elimination of proprioceptive feedback from muscle spindles and Golgi tendon organs. This elimination entails the loss of interjoint coordination and alternation of flexor and extensor muscles. Group Ia and group II muscle spindle afferents influence predominantly the patterning of flexor muscle activity, while group Ia, group II and group Ib afferent actitivities determine the pattern of extensor muscle firing (Akay et al. 2014). Proprioceptive muscle spindle afferents also co-determine the speed of locomotion, which is mainly determined by activity of extensor muscles. In mice, feedback from muscle spindles of ankle extensor muscles regulates muscle activity strength as gait speed increases (Mayer et al. 2018).

Proprioceptive feedback reinforces ongoing motor output, shapes muscle activities and contributes to timing the transitions between the different locomotor step phases, It also plays an important role in adjusting the basic locomotor rhythm to environmental conditions and in compensating for unexpected perturbations (Büschges 2005; Duysens and Forner-Cordero 2018; Hultborn and Nielsen 2007; Pearson 1993). Various sources of sensory feedback change throughout the gait cycle, and all known spinal reflex pathways are modified during locomotion. Sensory information most appropriate for the particular step phase is selected by the CPGs (McCrea 2001).

22.4 Timing of Locomotor Phases

Spinal and decerebrate cats adjust their hindlimb stepping rate while walking on treadmills to a considerable speed range between 0.1 and 1 m/s. At higher speeds, walking/trotting sometimes gives way to galloping. Increased step rate is achieved primarily by shortening the stance phase, while the flexion phase remains nearly constant. These adjustments indicate a substantial role for sensory

feedback in switching between different locomotor phases, especially in regulating the stance phase duration (Pearson 2008).

22.4.1 Stance-to-Swing Transition

The stance-to-swing transition and activation of flexor muscles are promoted by two groups of afferent signals, hip-position-related and load-related signals (Duysens et al. 2000; Duysens and Forner-Cordero 2018; Grillner and El Manira 2019; McCrea 2001; Pearson 2008).

Hip-position-related sensory feedback occurs during walking, for example when a cat´s hip angle reaches →threshold extension (Duysens and Forner-Cordero 2018). The extension phase is curtailed while the flexion phase is promoted. The hip-angle effect at the end of the stance phase likely results from stretch of muscle spindles in hip flexor muscles (e.g., iliopsoas) and certain ankle flexors,e.g., extensor digitorum longus EDL) and tibialis anterior (TA), at the end of the stance phase (Pearson 2008). Of particular importance for this muscle-length-dependent effect may be a group of interneurons identified in the cat's mid-lumbar segments, which receive monosynaptic excitatory input from group II muscle spindle (and other) afferents from hip muscles, and have been hypothesized to be involved in the phase switch from extension to flexion (Windhorst 2007).

In walking humans, →stretch reflexes and reciprocal Ia inhibition contribute to switching from extension to flexion. The ankle flexors tibialis anterior (TA) and extensor digitorum longus (EDL) are stretched in the late stance phase between heel off and toe off ground. Muscle spindle group Ia afferents are excited during this period and help activate their agonist α-MNs, and reciprocally inhibit their antagonist soleusα-MNs (Capaday et al. 1990).

Load-resisting reflexes during the stance phase assist in the transition to swing in many species. Declining extensor force and group I afferent discharge from Golgi tendon organs and muscle spindles in late stance may release flexor muscles from inhibition and thus help initiate the swing phase (Duysens et al. 2000; Duysens and Forner-Cordero 2018; Grillner and El Manira 2019; Lam and Pearson 2002; Pearson 1993, 2008). However, release from inhibition is conspicuous only in animals with reduced descending control and only weakly so if at all in intact cats and normal adult humans. By contrast, in newborns and infants without powerful cortical control, both the hip position and the limb loading are strong signals for regulating stepping (Capaday 2002; Pearson 2008; Zehr and Duysens 2004). Yet, a recent computer simulation study (Ekeberg and Pearson 2005) suggests that a force-related signal at the end of the stance phase is crucial for regulating the stance-to-swing transition while a hip-extension signal alone would not guarantee normal locomotion.,

22.4.2 Swing-to-Stance Transition

Sensory signals related to hip position are probably also of importance in regulating the swing-to-stance transition in cat locomotion (Duysens and Forner-Cordero 2018; McVea et al. 2005; Pearson 2008). Stretch reflexes in →hamstring muscles, such as the bi-functional semitendinosus muscle (hip extensor and knee flexor), may contribute to decelerate hip flexion and knee extension at the end of the flexion phase when the hamstrings are rapidly extended and muscle spindles are

activated. The magnitude of hamstring activation correlates linearly with the speed of knee extension (Duysens et al. 2000; Pearson 1993). Stretch of ankle extensor muscles appears not to contribute to the initiation of the swing-to-stance transition (McVea et al. 2005).

22.5 Modulation of Reflex Systems during Locomotion

Spinal reflexes can be modulated in size or even reversed in sign depending on the step phase. Modulation, gating or complete re-organization of reflexes can occur at various sites and include several mechanisms (McCrea 2001). These include some already discussed, such as skeleto-motoneuron properties, and others including →presynaptic inhibition, fusimotor inputs to muscle spindles, and modulation of interneural pathways.

22.5.1 Modulation of Stretch Reflexes, H-reflexes and Presynaptic Inhibition

Presynaptic inhibition provides a mechanism by which information flow through the CNS may be regulated at the first →synapse in the CNS. Inhibition of this type is thought to contribute to the regulation of both spinal reflexes and ascending pathways (Lidierth 2006; Rudomin and Schmidt 1999). A general principle of presynaptic inhibition appears to be that afferents of one modality most strongly influence those of the same modality. The specificity extends to subclasses of afferents that most strongly inhibit afferents of their own subclass, e.g. slowly adapting →mechano-receptors are most strongly depolarized by other slowly adapting mechanoreceptors (Schmidt 1971).

Presynaptic inhibition is task- and phase-dependent. It changes from rest to stance to locomotion and between different phases within a gait cycle (Quevedo 2009; Windhorst 2007). In cats, the amplitude of →primary afferent depolarization (PAD) due to presynaptic inhibition may vary in phase with the locomotor rhythm (Dubuc et al. 1988; Dueñas et al. 1990; Gossard and Rossignol 1990).

In humans, monosynaptic group Ia reflexes to skeleto-motoneurons are reduced by pronounced presynaptic inhibition, and reflexes from group II afferents and Golgi tendon organ afferents through interneurons become more important (Nielsen 2016). In cats, it persists throughout fictive locomotor activity and outlasts it (Gosgnach et al. 2000). Monosynaptic group Ia-motoneuron transmission is also rhythmically modulated throughout the locomotor cycle (Schomburg and Behrends 1978). Group Ia afferents themselves can contribute to significant phase-dependent presynaptic inhibition of monosynaptic Ia transmission, and this inhibition can be altered by concomitant activation of cutaneous mechano-receptor afferents, but only for a restricted part of the step cycle (Ménard et al. 2003).

Stretch reflexes, although oligosynaptic rather than purely monosynaptic, are rhythmically modulated throughout the step cycle. For example, in a decerebrate cat preparation, the soleus stretch reflex was deeply modulated and reached its peak at or before the peak in soleus background electromyograhic (EMG) activity, thus providing for maximal reflex-mediated →stiffness before or during foot impact (Akazawa et al. 1982).

In humans, too, short-latency soleus stretch and →H-reflexes (short-latency spinal reflexes elicited by electrical group Ia afferent stimulation) are deeply modulated during the gait cycle. Both reflexes are depressed during the swing phase, may increase in the late swing phase, are strong at heel contact, and progressively increase in amplitude from mid to late stance phase (Côté et al. 2018).

The modulation of stretch and H-reflexes over the gait cycle probably depends on several processes, including changes in α-MN excitability, and in postsynaptic and presynaptic inhibition, such that these changes may at least in part be effected by the CPG (Côté et al. 2018). Presynaptic inihibition plays an important role.

In the mouse, presynaptic inhibition appears to be exerted by interneurons expressing the RORβ orphan nuclear receptor, whose genetic nullification leads to →ataxic gait characterized by exaggerated flexion movements and alterations of the step cycle (Koch et al. 2017).

Presynaptic inhibition also contributes to interlimb coordination. Force-sensing afferents recruited during the stance phase modulate transmission of sensory signals in the contralateral swinging limb via presynaptic inhibition (Hochman et al. 2013).

Where and how the phasic modulation of presynaptic inhibition originates is controversial, but is generally attributed to movement-related sensory feedback (Brooke et al. 1997) or to central factors; namely, that the CNS adjusts the excitability of the spinal circuits in anticipation of movement-related events rather than as a consequence. This does not exclude the possibility that peripheral feedback could augment excitability changes produced centrally (Lavoie et al. 1997; Schneider et al. 2000).

22.5.2 Modulation of Fusimotor Spindle Innervation

The most sophisticated means of modulating the impact of proprioceptive feedback from muscle spindles during locomotion is via fusimotor activity. In amphibia, activation of extrafusal and →intrafusal muscle fibers is coupled to innervation from →β-motoneurons. In mammals, the existence of →γ-motoneurons and their influence on α-MNs offers additional possibilities. The relationship between activation patterns of α-MN and γ-motoneurons during various motor acts has been the subject of intense research over the past half a century. Results from a considerable number of investigations have led to vigorously debated concepts and the emergence of two primary hypotheses regarding fusimotor influences on skeleto-motor neurons (Windhorst 2007).

22.5.2.1 Servo Control Hypothesis

An early concept (Merton 1953) proposes that the →feedback system set up by group Ia muscle spindle afferents and their monosynaptic connections to homonymous skeleto-motoneurons functions as a →servo control system (follow-up servo hypothesis). This concept is applicable to locomotion, with the CPG supplying the motor command. According to this proposal, in slow and precise voluntary movements, descending motor commands impinge primarily on γ-motoneurons. These activate muscle spindles, which reflexly activate α-MNs to cause a muscle contraction. This indirect form of muscle activation has the advantage of reduced sensitivity to internal disturbances

such as muscle fatigue, and resistance to unexpected interference by the external world with the intended locomotor event (Houk and Rymer 1981).

The quality of a servo system depends critically on the loop gain. For effective suppression of disturbances, the loop gain needs to be high. However, in a feedback system with considerable signal transmission delays, high gain may cause oscillations (Rack 1981). It has been argued that under some conditions, the monosynaptic stretch reflex loop might contribute to physiological and pathological →tremor or clonus. However, in studies prompted by the follow-up servo hypothesis, it turns out that the stretch-reflex gain in animals and humans is modest in most circumstances, depending on input amplitude. Moreover, in humans, activation of γ-motoneurons does not precede that of skeleto-motoneurons, as required by the servo control hypothesis (Windhorst 2007).

22.5.2.2 Servo-assistance Hypothesis

In humans and animals, many movements are produced by concomitant activation of γ-fusimotor neurons and skeleto-motoneurons. The servo-assistance hypothesis, in its strict version (Matthews 1972), proposes that the primary activation of a muscle is via its skeleto-motoneurons, whose activation is supported by feedback from muscle spindle afferents and excited in parallel by γ-motoneurons. Fusimotor action would provide a temporal template of the intended movement so that spindle discharge would, ideally, be constant. Counterbalancing of muscle length-dependent changes in spindle discharge would be provided by static fusimotor neurons, whereas dynamic fusimotor neurons would be differentially activated, as determined by motor task, to ensure a high spindle →sensitivity to muscle length disturbances. In general, however, the discharge patterns of muscle spindle afferents and the implied fusimotor inputs during locomotor movements are not constant, nor are they simple or uniform.

22.5.2.3 Skeletomotor and Fusimotor Activation Patterns during Movement

How γ-motoneurons are activated in relation to skeleto-motoneurons has not been settled unequivocally (Hulliger 1984; Murphy and Martin 1993; Ellaway et al. 2015; Windhorst 2007). This is due, in part, to the different muscles and movements investigated and the different preparations and recording methods used. The preparations employed range from awake, freely moving animals and humans to reduced preparations from muscle spindle afferents in conscious humans or cats. However, recordings from muscle spindle afferents and fusimotor fibers give only indirect clues as to which type of fusimotor neuron does or does not modulate its discharge in parallel to skeleto-motoneurons.

During movement in conscious cats, the discharge rates of muscle spindle afferents from hindlimb muscles are strongly modulated by both changes in muscle length and fusimotor inputs (Prochazka and Gorassini 1998). The precise spindle discharge pattern depends on the particular parent muscle and its type of contraction during movement (Liddell and Phillips 1944; Murphy and Martin 1993; Prochazka and Gorassini 1998). This mode of firing-rate modulation is at variance with the servo-assistance hypothesis, because fusimotor activity does not compensate for internal length changes in order to make spindle discharge constant throughout the step cycle. The averaged activity of group Ib Golgi tendon organ afferents are well correlated with EMG recordings, agree with force measurements during normal cat locomotion, and support the notion that ensembles of Golgi tendon

organ afferents signal whole-muscle force (Prochazka and Gorassini 1998).

In humans, spindle afferents exhibit a variety of discharge patterns in various muscles during voluntary or reflexly elicited contractions. Group Ia afferent discharge may hardly change during a precision finger movement. On the other hand, muscle spindle afferent discharge rate may be modulated during movement. Human muscle spindles in general monitor muscle length and velocity in routine movements of moderate speed as long as opposing loads are small (Al-Falahe et al. 1990). The responses of muscle spindles in human forearm muscles are also broadly tuned to the direction of wrist movement (Jones et al. 2001).

22.5.3 Support of the Stance Phase

Three general mechanisms contribute to the support of body weight during the locomotor stance phase: (1) →Visco-elastic properties of muscles and other tissues provide stiffness and →load compensation during weight bearing. (2) Sensory feedback and associated CNS control systems help provide anti-→gravity thrust, ensure stability and regulate limb →biomechanics. (3) Signals from supraspinal structures provide excitatory drive to extensor α-MNs (Windhorst 2007).

22.5.3.1 Visco-elastic Properties vs. Reflex Actions

In intact walking cats, paw ground contact is normally signaled by cutaneous and muscle mechano-receptors. When ground contact is prevented by suddenly opening a trapdoor just before footfall, the contact-related signals are absent and the foot keeps descending before a corrective →flexion reflex occurs. Within the first 40 ms or so, a period far outlasting the monosynaptic stretch-reflex latency of ca. 10 ms, there are no extensor EMG differences between control and trapdoor trials, implying that the initial part of the muscle contraction after ground contact is normally generated by the CPG and not by reflex activity. This in turn suggests that weight support during the initial extensor phase relies heavily on visco-elastic properties of previously active extensor muscles rather than on a reflex-generated stiffness. But in decerebrate walking cats, loss of ground support may reduce the ankle extensor EMG activity by 50% to 70% (Donelan and Pearson 2004a). Sensory feedback and reflexes thus appear to play some role in stance support.

22.5.3.2 Load Receptors

The →sensory receptors involved in supporting extensor muscle activity during the locomotor stance phase are referred to, in general, as load receptors, although they signal different biomechanical variables (Duysens et al. 2000; Duysens and Forner-Cordero 2018). Main load receptors include Golgi tendon organs of the ankle extensors, and cutaneous mechano-receptor afferents from the foot sole. Accessory load receptors include muscle spindles in the ankle extensors and →joint receptor afferents from Ruffini endings and Pacinian corpuscles.

22.5.3.3 Muscle Spindles

Group Ia and group II afferents originating in muscle spindles play diverse roles with varying degrees of importance in supporting stance. These roles go beyond just supporting the body weight during the stance phase because the activation of extensor muscles also provides the main propelling thrust and thus increases with walking speed. In mice, feedback from muscle spindles in ankle extensor muscles contributes to the strength and speed-dependent amplitude modulation of muscle activity, while muscle-spindle feedback from the knee extensor muscles is unimportant for speed-dependent amplitude modulation. Genetically ablating muscle-spindle feedback leads to an inability to walk at higher speeds (Mayer et al. 2018).

Group Ia Muscle Spindle Afferents. Some evidence appears to argue against an important role for extensor group Ia afferents and their reflex actions. For example, the cyclic modulation of H-reflexes, which is assumed to result from increased presynaptic inhibition, but bypasses the muscle spindle (Schieppati 1987), is generally smaller during walking than standing.

Other evidence suggests that feedback from group Ia spindle afferents might play a role in the stance phase. Muscle spindle afferents reinforce ankle extensor activity during the early stance phase of gait. As much as 30-60% of the activity of soleus muscle, which undergoes a lengthening contraction during stance, results from reflex action of predominantly group Ia afferents (Yang et al. 1991). However, several lines of evidence suggest that in late stance, neither group Ia nor cutaneous afferents reflexly contribute to background soleus EMG activity (Cronin et al. 2011). During running, group Ia afferents that are activated by triceps surae stretch after ground contact enhance extensor EMG after 35-45 ms, i.e., via a short-latency spinal stretch reflex. Group Ia afferents may thus contribute to the subsequent vigorous shortening required to propel the body (Dietz et al. 1979).

Results obtained from locomoting decerebrate cats suggests that about 50% of extensor muscle contraction results from spindle group Ia afferents (Severin 1970). The importance of monosynaptic group Ia connections to α-MNs may depend on the task. After the nerves to the triceps surae muscle in cats are cut and re-sutured to insure motor →re-innervation, walking on level ground and uphill on a ramp appears almost undisturbed. By contrast, the ankle joint yields excessively when walking down a ramp, and the ankle-knee inter-joint coordination is disrupted. This argues for an important role of local proprioceptive feedback from extensor group Ia afferents in regulating stiffness of extensors during lengthening contractions and in inter-joint coordination (Abelew et al. 2000).

Group Ia Oligosynaptic Reflex Pathways that depend on locomotor phase have been described in cats (Whelan 1996; Burke 1999). In part, these pathways are shared with group Ib afferents from Golgi tendon organs. During the stance phase in fictive locomotion, but not in the flexor phase nor in the absence of locomotion, disynaptic excitatory connections from group Ia afferents from hip, knee and ankle extensor muscles to ipsilateral extensor α-MNs become operative. This excitatory reflex may contribute to the enhancement of extensor activity and increase in force production during stance (Angel et al. 1996; McCrea 2001). There is an equivalent in flexor α-MNs that receive disynaptic group I →excitatory postsynaptic potentials (EPSPs) during the flexion phase of fictive locomotion and fictive scratching (Burke 1999).

Group II Muscle Spindle Afferents. The contribution of group II muscle spindle afferents to stance support is not yet quite clear. They do not appear to be of much significance in the cat (Donelan et al. 2009). Their discharge is low and poorly modulated during locomotion, and their effects on extensor α-MNs are negligible (McCrea 2001; Donelan and Pearson 2004b). In humans, group II muscle spindle afferents from extensors could play a more important role, but perhaps predominantly when the normal extensor muscle activity is perturbed.

22.5.3.4 Golgi Tendon Organs

During locomotion, reflex actions of group Ib afferents from Golgi tendon organs are re-organized from their state at rest (Duysens and Forner-Cordero 2018). At rest, extensor group Ib afferents exert autogenic, di- or trisynaptic inhibition on homonymous and synergistic α-MNs. During locomotion, extensor group Ib afferents activate ipsilateral extensor α-MNs and inhibit flexor α-MNs, these effects being modulated in size in different locomotor phases. Various findings confirm that group Ib afferent volleys can reset the locomotor phase to extension and indicate that the locomotor-related EPSPs in extensor α-MNs during →L-DOPA- and MRF-generated fictive locomotion are mediated by the extensor component of the rhythm generator, and at least some of the interneurons of the 1b pathway make significant contributions. A functional consequence of resetting in normal locomotion might be to accommodate variability of load signals during the stance phase, thus promoting or prolonging the extensor phase (Gossard et al. 1994).

In distinction to group Ia afferents, group Ib afferents evidently have access to the CPG, since their excitation can reset the locomotor rhythm and entrain the locomotor rhythm upon rhythmic stimulation, whereas group Ia muscle spindle afferents fail to do so. Extensor group group Ib afferents indirectly excite extensor muscles, which amounts to a reinforcing positive force feedback that helps regulate extensor force**,** depending on the loading conditions of the whole limb (Duysens and Forner-Cordero 2018). The gain of the homonymous positive force feedback pathway in the cat medial gastrocnemius (MG) muscle is estimated to range from 0.2 at short muscle lengths to 0.5 at longer muscle lengths, accounting for 20% and 50% of total muscle force, respectively. The length dependence is due to the intrinsic length-tension relation of muscle. On the other hand, the gain of the pathwaythat converts muscle force to α-MN depolarization is independent of length (Donelan et al. 2009; Donelan and Pearson 2004a).

22.5.3.5 Cutaneous Mechano-receptors in the Foot

Cutaneous mechano-receptors are well suited to signal mechanical deformation of the sole and ankle when loaded. Recordings from cutaneous nerves in cats and humans reveal discharge activity related to footfall and the stance phase (Duysens et al. 2000). In intact walking cats and humans, electrical stimulation of cutaneous sural afferents from the foot during the stance phase can enhance ankle extensor muscle activity, although at a fairly long latency. Conversely, unloading signaled by withdrawal of load-related cutaneous inputs can trigger flexion (Duysens et al. 2000; Zehr and Duysens 2004). Evidence suggests that in late stance neither group Ia nor cutaneous afferents from the foot reflexly contribute to background soleus EMG (Cronin et al. 2011).

22.5.3.6 Plasticity of Stance Support System

The reflex system that reinforces stance must be precisely calibrated to provide support without jeopardizing stability. This requires plastic processes that adapt the system to prevailing circumstances. Several lines of experimental evidence verify the importance of plastic reflex processes during stance. For example, after cutting nerves to the lateral gastrocnemius (LG), soleus and plantaris muscles in the cat, stimulation of the synergistic medial gastrocnemius (MG) nerve becomes progressively more effective in prolonging the extensor burst duration (Lam and Pearson 2002). Also, in conscious walking cats the magnitude of MG bursts during the stance phase increases progressively to compensate for the loss of extensor thrust. Early MG EMG activity, generated before paw ground contact by central drive, increases gradually over a one-week period. The mid-stance portion of the MG EMG burst, driven centrally and by sensory feedback, increases rapidly within the first few days.

Experiments in walking humans suggest that in mid and late stance, Golgi tendon organ activity reflexly contributes to soleus activity and thereby provides positive force feedback (Cronin et al. 2011). During locomotion, the excitatory autogenic force feedback is predominant in the gastrocnemius muscles and moderately reduced in other muscles. Inhibitory inter-muscular force feedback can persist but is re-distributed to distal muscles as compared to rest and may be involved in inter-joint coordination (Nichols 2017).

The early increase of mid-stance activity appears to be related to an increase in reflex gain from MG afferents to homonymous α-MNs, possibly via facilitation of the disynaptic pathway (Pearson and Misiaszek 2000; Lam and Pearson 2002). Further evidence for the importance of plasticity in the stance support system is that recovery of mid-stance activity after cutting LG, soleus and plantaris nerves is impaired by →pyridoxine, a drug known to selectively destroy large afferents from leg muscles of mammals (Pearson et al. 2003).

22.5.4 Cyclic Modulation of Reciprocal Ia Inhibition

There is convincing evidence that reciprocal inhibition contributes significantly to flexor-extensor alteration during locomotion (Kiehn 2016; Grillner and El Manira 2019; and other studies below). During the hindlimb stance phase of cat locomotion, flexor muscles are not co-active with extensors. Counteracting flexor activity can be partially avoided by reciprocal Ia inhibition during the stance-phase. Extensor skeleto-motoneurons are co-active with groups of corresponding reciprocal Ia inhibitory interneurons that receive monosynaptic excitation from extensor group Ia afferents and project to flexor α-MNs. Rhythmic modulation of these interneurons may come from extensor group Ia afferents, the CPG and descending tracts.

During fictive locomotion in the cat, α-MNs and reciprocal Ia inhibitory interneurons with corresponding group Ia inputs are active largely in phase. The quadriceps-related reciprocal Ia inhibitory interneurons are mainly active during the extension phase of the step cycle. Since these interneurons usually become active before their corresponding α-MNs, they appear to receive independent excitation, presumably from the CPG. In addition, reciprocal Ia inhibitory IPSPs in α-MNs are largest during the off-phase, indicative of reciprocal Ia inhibitory interneuron facilitation and its contribution to motoneuronal hyperpolarization (Pratt and Jordan 1987).

The strength of reciprocal Ia inhibition between antagonist ankle muscles in humans generally declines from quiet stance to walking to running, with locomotor speed being the major determinant (Kido et al. 2004). Moreover, reciprocal Ia inhibition is rhythmically modulated during walking, in line with the cat data (Petersen et al. 1999; also Lavoie et al. 1997). Part of the rhythmic modulation of reciprocal Ia inhibition during locomotion may involve presynaptic inhibition of reciprocal Ia inhibitory interneurons or of their terminals on α-MNs (Enríquez-Denton et al. 2000).

Inputs from spinally descending fibers can modulate the activity of reciprocal Ia inhibitory interneurons. The →vestibulo-spinal tract (VST), for example, monosynaptically excites both extensor α-MNs and corresponding reciprocal Ia inhibitory interneurons. In decerebrate cats walking on a treadmill, a large subset of vestibulo-spinal neurons discharge rhythmically around a substantial mean rate. The majority of these neurons fire just before or during the stance phase of the ipsilateral hindlimb. Another rhythmical source derives from contralateral commissural interneurons, which modulate both reciprocal Ia inhibitory interneurons and Renshaw cells (Welniarz et al. 2015).

22.5.5 Cyclic Modulation of Recurrent Inhibition

Renshaw cell discharge in cats during fictive locomotion is modulated in phase with input α-MNs. Flexor and extensor Renshaw cells start firing after their related α-MNs. Extensor Renshaw cells fire maximally at the end of the extension phase when the α-MNs begin to hyperpolarize and decrease their firing rate. Flexor Renshaw cells discharge maximally during middle to late flexion when flexor α-MN discharge starts declining (Pratt and Jordan 1987). Blockade of cholinergic motor axon synapses on Renshaw cells by the →nicotinic receptor antagonist mecamylamine drastically reduces or abolishes their discharge without disrupting the locomotor rhythm. This suggests that Renshaw cells are not an integral part of the CPG, nor do they control the locomotor timing or that of the discharge of α-MNs and reciprocal Ia inhibitory interneurons (Noga et al. 1987; Pratt and Jordan 1987). Similar results were obtained in the isolated spinal cord of newborn mice, in which Renshaw cell activity was inhibited during activity of their associated α-MNs, but by what interneurons is unknown to date (Nishimaru et al. 2006, 2010). However, in genetically modified mice, the reduction of Renshaw cell output did not influence drug-induced fictive locomotion in the neonatal mouse or change gait, motor coordination, or grip force in adult mice (Enjin et al. 2017). The role of Renshaw cells in locomotion remains to be elucidated.

Heteronymous recurrent inhibition from quadriceps α-MNs to tibial anterior α-MNs in humans depends on background α-MN discharge level, measured by EMG, and is similar during both walking and standing for matched EMG levels. Recurrent inhibition from quadriceps α-MNs to soleus α-MNs is diminished in the early phase and enhanced in the late locomotor stance phase, unlike quiet stance. This modulation apparently promotes soleus activation at the swing-to-stance transition and deactivation at the stance-to-swing transition (Lamy et al. 2008).

A more general role for recurrent inhibition during locomotion may be to de-correlate α-MN discharges that tend to be correlated by common driving inputs (Radosevic et al. (2019).

22.5.6 Cyclic Modulation of Cutaneous Reflexes

Reflex effects of cutaneous mechano-sensitive afferents are subject to task and phase modulation. Cutaneous input provides important details, on a step-by-step basis, regarding the terrain an individual encounters while walking, which is particularly relevant under demanding situations (Barthélemy et al. 2011; Brooke et al. 1997; Burke 1999; Ruff et al. 2014; Zehr and Stein 1999).

Differential Cutaneous Reflex Modulation in Locomoting Cats. In quiescent preparations of the cat, cutaneous reflex effects from the hindlimb usually have at least trisynaptic latencies. Di- or trisynaptic effects are more often seen in fictive or other locomotor states, indicating that the mediating reflex pathways are gated by the CPG. Moreover, reflexes from different nerves are modulated differentially with locomotor phase. For example, the superficial peroneal (SP) nerve innervates the dorsal surface of the distal hindpaw and the medial plantar (MPL) nerve the ventral surface. The disynaptic EPSP evoked by SP stimulation in a flexor digitorum longus (FDL) α-MN is maximal during the first third of flexion. By contrast, disynaptic components of the MPL-stimulation response are maximal during the extension phase and disappear completely throughout the flexion phase, leaving only small later components. This differential modulation indicates that different sets of last-order interneurons mediate the reflexes (Burke 1999). In humans, cutaneous reflexes are phase-modulated not only in the legs, but also during arm cycling and natural arm swing of walking (Zehr and Duysens 2004).

Stumbling-corrective Reaction. Some cutaneous reflexes are complex motor reactions; for example, the $\rightarrow$stumbling-corrective reaction. When a swinging hindfoot meets an obstacle in a forward-walking intact cat, the leg must be lifted above the obstacle to avoid stumbling. The appropriate reaction is evoked by activation of cutaneous receptors on the foot´s dorsal surface. The flexor muscles are excited at short latency, which induces additional limb flexion that lifts the paw above the obstacle. If, instead, the stimulus is applied during the stance phase, the extensor phase is enhanced. This phase-dependent gating of two alternative pathways is due to the CPG (Grillner and El Manira 2019). This reflex pattern can also be elicited in chronic spinal cats during walking, indicating that the responsible circuitry resides in the lumbar spinal cord and involves oligosynaptic pathways (Forssberg 1979). During backward walking, cutaneous receptors on the ventral surface of the foot elicit a well-organized stumbling-corrective response, thus providing an instance of task-specificity (Zehr and Stein 1999). Human infants below 12 months of age who have not yet developed independent walking show phase-dependent stumbling-corrective reponses to light touches applied to the foot, with the responses being location- and task-specific (Lam et al. 2003).

Cutaneous Reflex Modulation and Sign Reversal in Humans. Some lower-leg reflex responses to cutaneous nerve stimulation in humans are amplitude-modulated or even reversed in different phases of walking (Barthélemy et al. 2011; Yang and Stein 1990; Brooke et al. 1997; Zehr and Stein 1999). Short-latency (40-50 ms) responses probably mediated in the spinal cord appear to be suppressed and substituted by functionally more important longer-latency (70-80 ms) responses that may take a transcortical reflex route (Barthélemy et al. 2011). Sign reversal, first demonstrated in chronic spinal cats (Forssberg et al. 1975), shows up as follows. During swing, tibial nerve stimulation evokes an excitatory reflex response in the tibialis anterior (TA) muscle, which reverses to an inhibitory response at the swing-to-stance transition. During quiet stance, there is no reflex. The phase-dependent sign reversal of this cutaneous reflex is possibly due to the existence of parallel reflex pathways, which are alternately opened and closed by the CPG. In addition, vision influences cutaneous reflex modulation according to whether or not stepping requires precise foot

placement (Ruff et al. 2014).

Functions of Cutaneous Reflexes during Locomotion. Functional interpretations of cutaneous reflexes and their modulation during gait are still somewhat speculative due to a number of experimental limitations (Brooke et al. 1997; Côté et al. 2018; Zehr and Stein 1999). →Nociceptive reflexes may act as phase-dependent protective responses. Thus, during stance, the knee is stabilized by co-contraction of antagonist thigh muscles and prevented from collapse on contact with a →noxious stimulus. Excitatory responses in the TA muscle may serve to withdraw the foot during swing and to dorsi-flex the ankle during stance to maintain →balance. Reciprocal inhibitory responses occur in ankle extensor muscles. These responses may be a trade-off between avoidance of the noxious stimulus and preservation of balance and the rhythm of locomotion (Brooke et al. 1997). Reflexes to non-noxious stimulation of the three major lower-leg cutaneous nerves (sural, tibial and superficial peroneal) are functionally important particularly during swing and the swing-to-stance transition and show a strong `local sign´. For example, stimulation of the sural nerve during swing elicits withdrawal of the foot from the stimulus site, predominantly by knee flexion and ankle dorsi-flexion (DF). In the late stance phase, the reflex primarily evokes hip and knee flexion as well as ankle dorsi-flexion to allow for accommodation of the stance limb to uneven terrain. This would be effected by activation of the medial gastrocnemius (MG) and tibialis anterior (TA) muscles acting in concert to evert and dorsi-flex the foot. The putative contributions of MG to plantar flexion (PF) and eversion (EV), and of TA to dorsi-flexion (DF) and inversion (IN) are shown by the dotted lines. The vector effect of the sural reflex would act to stabilize the foot in case of pressure activation of the lateral foot border caused by uneven terrain (Zehr and Stein 1999).

Phase-dependent Interaction of Cutaneous and Muscle Reflexes. Cutaneous reflexes act in concert and alternation with muscle reflexes, and they do so in a phase-dependent way. During swing and the swing-to-stance transition, cutaneous reflexes rank first because muscle sensory feedback is expected to be weaker than during stance. By contrast, during stance and the stance-to-swing transition, muscle reflexes rank higher in stance support and stability (Zehr and Stein 1999).

22.6 Inter-limb Coordination

In terrestrial locomotion of quadrupedal mammals and humans, movements of the four limbs must be properly and flexibly coordinated. Intra-spinal pathways, somatosensory feedback from the moving limbs and descending pathways from supraspinal structures implement coordination. Mechanical linkages between trunk and limbs also contribute to stabilize multi-limb movements (Danner et al. 2019; Frigon 2017; Klarner and Zehr 2018; Rybak et al. 2015; Zehr et al. 2016).

22.6.1 Coordination of Bilateral Limbs

Coordination of bilateral leg activities must be flexible to allow for different gaits, with alternating activities in walking and synchronous activities in gallop and hopping, and to respond differentially to perturbations depending on step phase (Frigon 2017; Nishimaru 2009).

Cats and humans are able to walk on split-belt treadmills, where each belt runs at a different speed. Movements of the two legs are well coordinated in that each limb affects the spatio-temporal behavior of the other. Adult humans can also easily walk with their legs moving in opposite directions (Choi and Bastian 2007). In both infants and adults, initiation of swing in one leg is contingent on the other being in the stance phase (Dietz 2003; Reisman et al. 2005; Zehr et al. 2016).

The required flexibility of left-right coordination involves complex neuronal networks. The coordination of bilateral activities is mediated by commissural interneurons whose axons cross in the ventral commissure (Côté et al. 2018; Goulding 2009; Kiehn 2016; Maxwell and Soteropoulos 2020). The importance of this bilateral communication has been demonstrated in transgenic mice with specific genetic mutations, in which the perturbation of commissural neurotransmitter balance entails severe perturbations in left-right coordination and pharmacological blockade of inhibition leads to complete loss of alternation (Goetz et al. 2015).

In the cat and rodent lumbar spinal cord, sub-populations of excitatory and inhibitory commissural interneurons receive different combinations of inputs from segmental afferent inputs, e.g., from group I and II muscle afferents, and from supraspinal sources, including fastigial neurons, →cortico-spinal tract, →rubro-spinal tract, →reticulo-spinal tract and vestibulo-spinal tract neurons (Frigon 2017). In the cat, commissural interneurons located mainly in lamina VIII are rhythmically acrtive during fictive locomotion and excited monosynaptically from reticulo-spinal pathways, and others in lamina VIII and laminae VII-VI are excited polysynaptically from reticulo-spinal pathways or are not excited (Matsuyama et al. 2004). A dorsal sub-population of inhibitory commissural interneurons projects monosynaptically to contralateral α-MNs, and a group of ventral glutamatergic interneurons exerts contralateral inhibition via reciprocal Ia inhibitory interneurons and Renshaw cells. These interactions may allow commissural interneurons to function in various reflex, locomotor and voluntary movements (Jankowska 2008; Kiehn 2016; Welniarz et al. 2015). Furthermore, so-called V3 interneurons are excitatory commissural interneurons that ipsilaterally mutually excite each other and α-MNs. They form direct connections with contralateral rhythm-generating circuits and appear to play key roles in gait transitions and in limb coordination because their acute silencing produces uneven gaits in freely moving adult mice (Chopek et al. 2018).

22.6.2 Coordination of Fore- and Hindlimbs

Special cortico-spinal control comes into play when humans walking upright have their hands free and engaged in various activities. There are situations, however, in which humans use quadrupedal movements, for example in crawling and swimming (Frigon 2017; Zehr et al. 2016).

Evidence indicates that inter-limb coordination during human locomotion is organized in a way similar to that in the cat. During normal walking, when humans do not use their arms and hands for specific non-locomotor purposes, they move them in concert with the hindlimbs as infants and cats do. Swinging of the arms is functionally important in stabilizing trunk rotation, i.e., counteracting torsion-related trunk movements. Arm and leg movements under these conditions are locked at a fixed frequency relationship (Dietz 2003; Zehr et al. 2016).

Reciprocal long and short proprio-spinal connections link the cervical and lumbar CPGs through a complex network of descending and ascending connections between CPGs (Côté et al. 2018; Frigon 2017). These links are cyclically modulated (Klarner and Zehr 2018; Zehr et al. 2016). For example in humans during rhythmic movements of one foot, H-reflexes in the upper limbs are cyclically modulated. During human treadmill walking, large inter-limb cutaneous reflexes can be evoked in a reciprocal manner from hand to foot and from foot to hand, and are phase-modulated. Stimulation of the human superficial radial nerve during walking results in suppression of activity in the tibialis anterior muscle at the end of swing. This suggests that the responsible proprio-spinal pathways are gated and modulated by CPG activity (Dietz 2003; Zehr and Duysens 2004).

The mechanisms mediating the coordination between fore- and hindlimb CPGs in humans and other mammals are gradually being unravelled. Intermediate thoracic networks play an important role. For example, in isolated neonatal rat spinal-cord preparations activated by →N-methyl-D-aspartate (NMDA), serotonin and dopamine, this role includes transverse (left-right) neuronal projections as well as upward signal transmission from low-threshold lumbar afferents whose stimulation evokes left-right alternating activity in the cervical CPGs (Juvin et al. 2012). In rodents, so-called V2a interneurons establish ipsilateral cervico-lumbar projections while so-called V0v interneurons provide long excitatory commissural projections (Grillner and El Manira 2019).

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23

Supraspinal Neural Control of Locomotion

CONTENTS

Abstract

• Effective and efficient terrestrial locomotion in vertebrates is achieved through complex interactions between neural networks located in the forebrain, brainstem and spinal cord. The spinal cord needs sensory feedback for timing, support and adaptive functions. In addition, spinal cord motor networks need signals from supraspinal sources to prepare for and effect changes in posture and gait.

• Supraspinal systems encompass motor drive and motivational networks in the prefrontal cortex, limbic system and basal ganglia, network components in the cerebellar cortex, the deep cerebellar nuclei, rubro-spinal, reticulo-spinal and vestibulo-spinal tracts of the medulla and the tecto-spinal network in the dorsal part of the midbrain.

• The posterior parietal cortex (PPC) plays important roles in transforming sensory information into motor plans. The PPC exhibits rhythmic discharge activity during locomotion, and plays a critical role in obstacle avoidance.

• The motor cortex appears to contribute more to the execution rather than the planning of movements during gait modifications. Neurons in the motor cortex discharge rhythmically in conjunction with gait phases during locomotion and are important for proper foot placement, stepping over obstacles and error detection.

• The inferior olive in the medulla and its axonal projections to the cerebellum constitute an error detection and correction network involved in motor control during locomotion.

• The cerebellar cortex and deep cerebellar nuclei contribute to shaping of locomotor-rhythmic muscle patterns, stance and gait, maintenance of balance and equilibrium and they help adapt locomotor patterns to behavioral goals.

• Rudimentary, stereotypical locomotion and effects on limb muscle tone persist after forebrain ablation that leaves brainstem and spinal cord systems intact. Nonetheless the forebrain plays important roles in sophisticated functions like error detection and corrections, obstacle avoidance, precise foot placement and navigation.

• Navigation between two far points in space is the most complex form of locomotion and puts high demands on several sub-systems of the central nervous system (CNS). It requires (1) representation of the initial spatial location and directional heading in the environment, (2) representation and selection of a goal, (3) selection and computation of a route to the goal, (4) updating of position/heading underway, (5) memorization of the starting position to be able to return quickly, (5) integration of information about body motion in the environment using olfaction, touch, audition, vision and information about self-motion from proprioceptive and vestibular signals, optic flow, and motor efference copy.

• There are several navigational strategies, which are not mutually exclusive but may co-operate depending on conditions. Among them are landmark navigation and path integration.

23.1 Introduction

Animals locomote through the environment using external and internal cues. The former include various sensory stimuli and the latter appetitive drives such as hunger, thirst, search for safety, shelter and reproduction. These cues are used to make basic decisions regarding approach or avoidance of objects, with special importance placed on →affective state, →motivation, →reward expectancy and →cognitive factors (Kim et al. 2017).

Effective and efficient terrestrial locomotion in vertebrates is achieved through complex interactions between neural networks distributed throughout the →central nervous system (CNS) (Mackinnon 2018). →Spinal cord mechanisms alone are unable to provide sufficient vigor and speed to ensure lateral stability and deal with foreseeable obstacles. To do so, the spinal cord needs sensory feedback for timing, support and adaptive functions. In addition, it needs signals from supraspinal sources that prepare spinal motor output networks for changes in posture and gait, before and during locomotion (Armstrong 1988; Drew and Marigold 2015; Ferreira-Pinto et al. 2018; Garcia-Rill et al. 2003; Grillner and El Manira 2019; Ruder and Arber 2019; Sharma et al. 2019; Takakusaki et al. 2016).

23.2 Overview of Supraspinal Sub-systems

Sensory Systems including olfaction, touch, audition and vision aid in guiding and modulating locomotion. New and unexpected stimuli →arouse the subject and initiate appropriate actions, calling into action several higher-order systems involved with motivation, cognitive function and anticipatory planning (Ferreira-Pinto et al. 2018; Kim et al. 2017).

Drive and Motivation. Locomotion can be initiated by different sub-systems that provoke various behaviors: →appetitive behavior triggered by internal needs (including hunger and thirst), reproductive behavior and exploratory behavior requiring planning or cognitive decisions, →defensive behavior or escape behavior in response to a fearful encounter with a predator (Ferreira-Pinto et al. 2018; Kim et al. 2017; Sinnamon 1993; Swanson 2000; Takakusaki et al. 2008). The →limbic system directs locomotion toward the pursuit of goals which, in part, is determined by motivational brain systems. The limbic system, →prefrontal cortex (PFC) and →basal ganglia receive →dopaminergic inputs and operate as a reward system, as well as modulate →attentive, →emotional and motor functions (Alcaro et al. 2007; Heimer and van Hoesen 2006; Schultz 2015). Besides the dopaminergic cells involved in reward, a large proportion of neurons in the →substantia nigra pars compacta (SNc) of mice, not overlapping with reward-responsive dopaminergic neurons, transiently increase their activity before self-paced movement initiation and increase the probability and vigor of future movements (da Silva et al. 2018). The mouse lateral hypothalamus contains several groups of →orexin/hypocretin neurons which slowly modulate appetite, →energy balance, metabolism, feeding, arousal, motivation, reward seeking and other functions, but also have faster effects on various central motor structures involved in locomotion, thus promoting rapid locomotion initiation (Karnani et al. 2020).

Decision Making and Action Selection. →Decision making involves several brain areas that initiate approach or avoidance. For example, the →superior colliculus (SC) triggers appropriate locomotor responses to novel visual stimuli, via the SC connection to the →mesencephalic locomotor region

(MLR)). The limbic system contributes to decision making, when triggered by approach or avoidance of external objects. For example, the limbic basolateral →amygdala drives decisions for approach toward reward-promising stimuli, while the central amygdala can suppress feeding in response to aversive stimuli. Either of the two regions exerts effects by projections to the lateral hypothalamus (Ferreira-Pinto et al. 2018; Kim et al. 2017). The basal ganglia also play a central role in decision making and action selection (Grillner and El Manira 2019; Grillner et al. 2020; Klaus et al. 2019; below).

Transformation Systems. Visually guided locomotion requires interactions between systems organizing eye movements and locomotion. These systems thus share common neural substrates, in particular the meso-pontine →tegmentum and cerebellar vermis (Srivastava et al. 2018). Transformation systems use information concerned with the direction and distance of gaze targets in an →eye-centered →frame of reference, translate it into a target in a →locomotor frame of reference and update internal spatial representations based on →somatosensory, proprioceptive and vestibular signals. The updated representations are used to control future motor action (Lappi 2016).

Adaptive Systems utilize higher-level sensory-motor systems to organize and fine-tune anticipatory planning and execution of gait modifications in response to upcoming events (Drew and Marigold 2015; Takakusaki et al. 2016).

Higher–order supraspinal sub-systems such as those described above utilize three principal descending pathways that influence locomotion.

Medial System. The medial system is part of the →cortico-bulbo-spinal system, receives cerebro-cortical influences via the →cortico-bulbar tracts and descends via the →reticulo-spinal (RST), →rubro-spinal (RuST) and →vestibulo-spinal (VST) tracts in the ventral and medio-ventral →funiculi of the spinal cord. It coordinates synergistic axial and proximal limb →skeletal muscle activities, including neck movements and eye movements, adjusts erect posture and →muscle tone and assists in the →orientation of head and body (Holstege 1996; Lemon 2016). During locomotion, the medial system helps ensure lateral stability and produces step-by-step regulation of the level of muscle activity. In addition, the medial system assists in modifications of posture that anticipate and accompany voluntary movements (Drew et al. 2002; Takakusaki et al. 2016).

Lateral System. The lateral system includes the →cortico-spinal tract (CST) and the →rubro-spinal tract (RuST), a lateral constituent of the cortico-bulbo-spinal system (Holstege 1996; Lemon 2016). The lateral system exerts fine control and voluntary modifications of gait. In cats, →motor cortex, →pyramidal tract or cortico-spinal tract (CST) lesions do not produce gross or long-term locomotor deficits as long as locomotion is simple. For example when the pyramidal tract is severed, cats are still able to walk on even ground. However, cats challenged to walk in more demanding circumstances, such as walking on the rungs of a ladder, show long-lasting deficits after cortical lesioning (Liddell and Phillips 1944). In addition, cats with large lesions of the spinal dorso-lateral funiculi are unable to modify their gait sufficiently to step over obstacles attached to a treadmill belt

after the lesion. Lesioning procedures involving the lateral system demonstrate that in cats, the medial pathways, including the reticulo- and vestibulo-spinal pathways, are unable to fully compensate for damage to the lateral pathways (Drew et al. 2002). In humans, many fibers in the cortico-spinal tract (CST) make monosynaptic connections to →skeleto-motoneurons innervating arm, back and leg muscles and are active in uncomplicated locomotion and even hopping (Nielsen 2016).

In mice there is a direct cortico-spinal pathway from the →primary somatosensory cortex (SI, S1), which modulates the lumbar locomotor network. Stimulation of this pathway enhances the speed of locomotion, while inhibition has the opposite effect and ultimately terminates locomotion. In freely moving mice, activity of pyramidal cells in S1 correlates with the speed of locomotion and starts before movement onset (Karadimas et al. 2020).

Proprio-spinal C3-C4 System. The C3-C4 proprio-spinal system of the cat mediates disynaptic excitation to forelimb →motoneurons from the cortico-spinal, reticulo-spinal, rubro-spinal, and →tecto-spinal tracts (Alstermark and Isa 2012). Evidence suggests that this group of C3-C4 proprio-spinal neurons in the cat are involved in precise voluntary target reaching movements of the forelimb, as well as in accurate foot placement, akin to a dynamic reaching movement superimposed on the locomotor movement (Grillner 2006).

23.3 Brainstem Systems Controlling Posture and Locomotion

After →forebrain ablation in cats that leaves →brainstem and spinal cord systems intact, locomotor activity is preserved, although in a stereotypical fashion (Takakusaki and Okumura 2008; Whelan 1996). Cats acutely decerebrated by brainstem transection anterior to the superior colliculi (SC) and in front of the →mammillary bodies can spontaneously alternate between quiescent behavior and periods of organized walking, with the legs being able to fully support the body. Such spontaneous locomotor behavior is rarely seen in cats with transections placed only a few millimeters more caudally, which suggests that the posterior hypothalamic/subthalamic locomotor region (SLR) is endowed with a special enabling function in locomotion which, if ablated, prevents spontaneous locomotion (Karnani et al. 2020; Kim et al. 2017). Since this region is not related to the →subthalamic nucleus (STN), it is more properly called diencephalic locomotor region (DLR). It has been suggested that DLR may be engaged in locomotion triggered primarily by emotional stimuli. When the paws of a pre-mammillary cat are put in contact with a treadmill, they may readily start locomoting in a well coordinated manner, being able to change gait from slow walk through trot to gallop with increasing belt velocity (Grillner and El Manira 2019).

The mouse lateral hypothalamus contains several groups of orexin/hypocretin neurons which, in addition to being slow modulators of whole-body physiology, appear to have a key role in sub-second-scale sensory-motor transformations, self-initiated movement and diverse mobile behaviors. They respond to olfactory, tactile and visual stimuli, as well as to social interactions with a female conspecific. The responses are causally involved in rapid control of spontaneous and sensory-evoked motor output, suggesting a broad and rapid influence on locomotion initiation. Orexin/hypocretin neurons innervate multiple CNS sites that drive or modulate locomotion, including the substantia nigra, →nucleus accumbens, motor cortex, →locus coeruleus (LC) and spinal cord (Karnani et al. 2020).

Animals with a CNS reduced to →cerebellum, brainstem and spinal cord exhibit robot-like locomotor capability (Armstrong 1988; Whelan 1996) that is neither goal-directed nor adapted to the environment, indicating that these qualities must be supplied by the forebrain (Grillner et al. 1997).

Regional stimulation studies provide further clues as to how brainstem systems are involved in locomotion. Stimulation of the dorsal tegmental field (DTF) in the moving cat suppresses postural and locomotor behavior, inducing the cat to stop locomoting and then recline. By contrast, stimulation of the ventral tegmental field (VTF) elicits the opposite by augmenting posture in a sitting cat, followed by standing and spastic locomotion. Stimulation of the MLR induces a cat to walk, run, gallop (`forced galloping´) or jump depending on stimulus strength, with the ability to avoid obstacles retained. Stimulation of the subthalamic locomotor region (SLR) makes a sitting cat locomote in a way that looks like searching behavior and an `→alerting reaction´ (Mori et al. 1989). The subthalamic locomotor region (SLR) projects directly to the spinal cord and also to the MLR (Kim et al. 2017).

23.3.1 Mesencephalic Locomotor Region

The anatomical constitution of the physiologically defined MLR was debated for some time (Ferreira-Pinto et al. 2018; Garcia-Rill et al. 2019; Grillner and El Manira 2019; Kim et al. 2017). Some investigators suggested that the MLR comprises several cell groups in the →pedunculo-pontine nucleus (PPN) and the nucleus cuneiformis (CnF). In the mouse, PPN stimulation activates primarily slower forms of locomotion (walk and trot), potentially related to foraging and exploratory behavior. Stimulation of the CnF tends to elicit fast locomotion (gallop and bound) and may be related to escape behavior (Duysens and Forner-Cordero 2018; Ferreira-Pinto et al. 2018; Grillner and El Manira 2019; Ruder and Arber 2019). In mice, →glutamatergic excitatory neurons in both the PPN and CnF can control slower alternating locomotion while only glutamatergic neurons in the CnF are required for high-speed synchronous locomotion (Caggiano et al. 2018; Josset et al. 2018). Photostimulation of GABAergic neurons in the MLR suppresses locomotion (Sharma et al. 2019).

The MRL in the wider definition contains glutamatergic, GABAergic and →cholinergic neurons (Ruder and Arber 2019). In the mouse, the glutamatergic cells are necessary and sufficient for locomotion, encode locomotor state and speed, and are selectively innervated by the basal ganglia (BG) (Roseberry et al. 2016). The glutamatergic MLR cells also project to rostral brain structures through which they might have an indirect effect on locomotion. The PPN connects with most BG nuclei as well as with dopaminergic neurons in the →ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), the →thalamus, and the →basal forebrain. GABAergic cells appear to have a negative impact on locomotion through local and distant circuit mechanisms. Cholinergic cells appear to exert a modulatory rather than a driver role, at least partially mediated by direct influences on the substantia nigra compacta (Snc) and the ventral tegmental area (VTA) (Ferreira-Pinto et al. 2018).

The MRL influences the central pattern generator (CPG) via the ventro-medial medullary reticular formation (v-MRF), and the locus coeruleus (LC) and →raphé nuclei (RN) with respective descending fiber tracts (Grillner and El Manira 2019; Takakusaki 2013). For example, modulatory

→serotonergic (5-HT) neurons in the raphé nuclei receive inputs from the MLR and send their →axons via the ventro-lateral →funiculus to innervate the CPG and lumbar α-MNs and via the dorso-lateral funiculus to innervate dorsal-horn interneurons (Sławińska and Jordan 2019).

Part of this descending influence is probably mediated by brainstem neurons in the →reticular formation (Ferreira-Pinto etal. 2018; Ruder and Arber 2019). In the mouse, the brainstem hosts functionally heterogeneous neuron sub-populations that have differential effects on locomotion. Glutamatergic neurons in the lateral paragigantocellular nucleus support high-speed locomotion and can tune locomotor speed through inputs from glutamatergic neurons of the MLR. Intermingled inhibitory →glycinergic neurons can induce different forms of behavioral arrest. Descending pathways from these sub-populations with opposing funtions communicate with distinct spinal effector circuits (Capelli et al. 2017). Selective activation of so-called →V2a neurons in the rostral mouse →medulla oblongata stops ongoing locomotor activity (Bouvier et al. 2015).

There is considerable evidence that the MLR can facilitate or reduce skeletal muscle tone. The locomotion-executing system involving the MLR in parallel facilitates muscle tone via the locus coeruleus (LC) and the raphé nuclei (RN), which activate extensor →α-motoneurons. Furthermore, the vestibulo-spinal pathways contribute to anti-→gravity extensor muscle tone, in particular by monosynaptic connections to extensor α-MNs. The MLR integrates information from the sensory-motor cortices, limbic system, and basal ganglia. It is also influenced by →midbrain dopaminergic neurons in the substantia nigra pars compacta (SNc) via two pathways, one ascending to the basal ganglia and the other descending to the MRL, the latter pathway promoting locomotion (Ryczko and Dubuc 2017). In humans, lesions in this area due to micro-infarction evoke →astasia and gait →ataxia.

23.3.2 Muscle-tone-inhibitory System

The muscle-tone-inhibitory system includes the PPN portion where cholinergic neurons, which suppress postural muscle tone, are located; the pontine reticular formation (PRF); and reticulo-spinal neurons of the medulla oblongata that inhibit extensor α-MNs directly or via inhibitory →interneurons. Large muscle tone-related systems interact and balance each other via inhibitory influences (Takakusaki and Okumura 2008). The cholinergic PPN is also part of the phylogenetically conserved reticular activating system (RAS), which additionally includes the locus coeruleus (LC) and raphé nuclei (RN). The RAS is involved in the control of the sleep-wake cycle, arousal and posture-locomotion, possibly in the context of →fight or flight reactions (Inglis and Winn 1995; Garcia-Rill et al. 2003).

23.3.3 Cerebellar Locomotor Region

The cerebellar locomotor region (CLR) corresponds to the hook bundle of Russell. This site contains crossing fastigio-fugal fibers which, when stimulated by trains of electrical pulses in decerebrate cats, augments the postural tone of neck, trunk, fore- and hindlimb extensor muscles. Stimulus pulses also evoke well-coordinated locomotion when the paws contact a moving treadmill. These observations indicate that the fastigial nucleus contributes to locomotion (Mori et al. 2004; Takakusaki and Okumura 2008). The CLR also contributes to excitation of the ventro-medial

medullary reticular formation (v-MRF).

23.4 Goal-directed Locomotion

Cats, rabbits and rodents retain goal-directed locomotion after the entire →cerebral cortex has been ablated, leaving the →hypothalamus and basal ganglia intact. Kittens →de-corticated neonatally can live for many years and are capable of complex behaviors (Bjursten et al. 1976; Ebbesen and Brecht 2017).

Drive and motivation for locomotor behavior stem from the limbic system, hypothalamus and brainstem regions, in particular, a mesolimbic dopaminergic (ML-DA) system that is recognized for its central role in motivated behaviors, various types of reward, and, more recently, in cognitive processes (Alcaro et al. 2007). The hypothalamus and upper midbrain contain a collection of nuclei that are thought to constitute the `behavior control column´ involved in organizing and coordinating some principal types of animal behavior. The rostral segment of this column of brainstem nuclei is involved in controlling ingestive and social behaviors, whereas the caudal segment is involved in controlling general exploratory or foraging behaviors that have locomotor and →orienting components (Swanson 2000).

Rostral Segment. This segment stretches from the →pre-optic area to pre-mammillary nuclei and plays a critical role in regulating three basic classes of goal-oriented behavior. Ingestive or appetitive behavior employs locomotion to advance the animal towards an incentive and consummative stimulus. Defensive behavior incites and employs locomotion to turn away and distance the animal from a threatening or →noxious stimulus; activation of this system entails escape, flight, running and jumping. Reproductive behavior employs locomotion for mating purposes.

Caudal Segment. This segment encompasses the mammillary body and substantia nigra nuclei and plays critical roles in the expression of exploratory behavior and foraging behavior, including locomotion and →orienting movements of the eyes, head and neck and upper limbs.

The excitatory effects of the drive-providing systems on brainstem locomotor systems must be controlled and counterbalanced by more sophisticated systems that put decisions on behavior in a wider context (Penner and Mizumori 2012). In this →decision-making process, the basal ganglia are intimately involved.

23.5 Roles of the Basal Ganglia in Locomotion

The basal ganglia play complex roles in the control of locomotion-related behavior, such as help decide what to do (action selection) and if and when to do it (self-paced movement initiation), specification of continuous variables of movement execution such as vigor, feedback gain control, movement →learning (Balleine and O´Doherty 2010; Ferreira-Pinto et al. 2018; Graybiel 2008; Grillner and El Manira 2019; Grillner et al. 2020; Klaus et al. 2019; Park et al. 2020; Schultz 2015, Turner and Desmurget 2010). These different aspects are dependent on specialized domains that are incorporated into circuits within the ventral basal ganglia and the dorso-medial and dorso-lateral →striatum (Liljeholm and O´Doherty 2012; Penner and Mizumori 2012).

Ventral Basal Ganglia. The ventral basal ganglia (VBG), consisting of the nucleus accumbens, olfactory tubercle, ventral →pallidum, substantia nigra and subthalamic nucleus (STN), are involved in several functions related to locomotion. The VBG send projections to the lateral hypothalamus, lateral pre-optic area, mesencephalic locomotor region (MLR), pedunculo-pontine nucleus (PPN) and brainstem dopaminergic cells (Heimer and van Hoesen 2006; Humphries and Prescott 2010; Penner and Mizumori 2012; Voorn et al. 2004). The ventral striatum receives dopaminergic inputs from the ventral tegmental area (VTA) (Grillner and El Manira 2019).

The VBG circuitry influences locomotion in various ways, such as initiating and modulating locomotion. Local administration of dopamine activates dopamine receptors type 1 (D1R) on striatal →projection neurons and can elicit locomotor activity. This is blocked by inactivating the MLR, which shows that the locomotor initiation is channeled via the MLR (Grillner and El Manira 2019). The shell of the nucleus accumbens organizes unconditioned, innate reward-related locomotion whereas the core organizes approach behavior (Kim et al. 2017).

Dorso-medial Striatum. This region includes the →nucleus caudatus with connections to wide cerebro-cortical regions and is integrated in *associative circuits* (Penner and Mizumori2012). Some regions in the →primate prefrontal cortex (Tanji and Hoshi 2008) with connections to the dorso-medial →striatum appear to be involved in different aspects of decision making, which influences the initiation and routing of locomotive behavior.

Dorso-lateral Striatum. Neural circuits associated with decision making and locomotor behavior in the dorso-medial striatum are known to interact with neural circuitry in the dorso-lateral striatum, including the →putamen. Evidence from a range of species suggests that the putamen strongly influences (1) decisions and related locomotor behaviors that are flexible, goal-directed and sensitive to feedback, and (2) decisions and related locomotor responses that are relatively automatic or habitual (Balleine et al. 2007).

The →globus pallidus, in conjunction with the →substantia nigra pars reticulata (SNr), suppresses locomotion. Active avoidance behavior, a form of decision making, utilizes the same neural circuitry, i.e, the output of the basal ganglia through the substantia nigra pars reticulata (Hormigo et al. 2016). In the mouse, optogenetic activation of the →direct pathway from D1R striatal neurons to SNr leads to activation of glutamatergic neurons in the MLR and initiation of locomotion, while activation of →indirect pathway from D2R striatal cells leads to inhibition of glutamatergic MLR neurons and cessation or reduction of ongoing spontaneous locomotion (Grillner et al. 2020; Roseberry et al. 2016). However, these pathways are not absolutely separated, neither anatomically nor functionally. For example, both D1- and D2-expressing neurons are active during movement initiation and execution, and their activities are sufficient to bidirectionally modulate the speed of ongoing movement without affecting action selection (Ferreira-Pinto et al. 2018). The dorsal striatum receives dopaminergic inputs from the substantia nigra pars compacta (SNc) (Grillner and El Manira 2019).

Parkinson´s Disease: Gait Disturbances. How the multiple basal ganglia functions interact in normal organisms is not well understood, but can be gleaned from pathological disorders such as →Parkinson´s disease, which produces gait disorders, in addition to disorders of eye movements, upright stance and arm and hand movements. Gait disorders include gait akinesia, gait bradykinesia and deficits in posture and equilibrium control. Gait →akinesia refers to difficulty in initiating locomotion. Parkinson's patients afflicted with gait bradykinesia walk slowly with shuffling and dragging feet, reduced step size and increased stance phase. Often, after the start of walking, patients

exhibit flexed forward posture and →hypokinetic steps, forcing them to increase their cadence as if to catch up with the advancing →center of mass (COM). Trunk rotation is reduced and concomitant arm movements may be reduced or asymmetrical during walking. Gait is unstable, with difficulty navigating around obstacles, with a tendency to suddenly fall without cause (Boonstra et al. 2008; Schoneburg et al. 2013).

Proprioception may also be reduced and contribute to the gait disorders (Dietz 2013). In addition, normal increase in leg extensor muscle activity with increasing body load is reduced, indicating that a change in →threshold or bias in load receptor function has occurred. These patients are therefore dependent on visual information to stabilize gait (Dietz 2002, 2013).

23.6 Role of the Cerebellum in Locomotion

The cerebellum assists in shaping rhythmic muscle activity patterns and in maintaining →balance and equilibrium. It also helps to adapt locomotor patterns to changing contexts and behavioral goals (Grillner and El Manira 2019; Thach and Bastian 2004). Muscle force is also affected. The cerebellum modulates timing, rate and development of muscle force, thus coordinating motions at various joints and possibly between limbs. It also helps control upright posture during locomotion (Morton and Bastian 2004, 2007; Thach and Bastian 2004).

The cerebellum receives abundant information from central →motor commands and sensory events (Jörntell 2017). It is bidirectionally connected with the basal ganglia, the dentate nucleus with its projection to the striatum, and the subthalamic nuleus (STN), which projects to the cerebellar cortex (Bostan and Strick 2018).

23.6.1 Divisions of the Cerebellum Related to Locomotion

The cerebellar cortex and →deep cerebellar nuclei are concerned with stance and gait, but with different degrees of influence and diverse functional specializations (Grimaldi and Manto 2012; Morton et al. 2004; Thach et al. 1992; Thach and Bastian 2004).

Cerebellar Vermis and Nucleus Fastiguus are specialized for anti-gravity stance (Thach and Bastian 2004). This area is active primarily in bilateral movements involving muscle tone, posture, equilibrium in stance and locomotion of the whole body. Transient or permanent inactivation of the nucleus fastiguus (fastigial nucleus) in monkeys impairs stance and gait. Sitting, standing and walking are impaired. Frequent falling to the side of the fastigial lesion occurs, while leaving isolated limb movements relatively normal (Thach et al. 1992; Thach and Bastian 2004).inactivation of the nucleus fastiguus in monkeys impairs stance and gait. Sitting, standing and walking are impaired. Frequent falling to the side of the fastigial lesion occurs, while leaving isolated limb movements relatively normal (Thach et al. 1992; Thach and Bastian 2004).

Cerebellar Intermediate Hemisphere and Nucleus Interpositus. The nucleus interpositus (interposed nucleus) is implicated in bending of limbs and paw placement during locomotion in cats as well as in reaching and grasping in humans and monkeys (Low et al. 2018). It modulates →reflexes involved with placing movements, stepping and maintenance of joint/limb position (Thach and Bastian 2004). It regulates and coordinates spatial and temporal organization of →skilled

arm and hand movements, as well as tone and associated posture of ipsilateral limbs. In monkeys, interpositus impairment produces extensor muscle bias, failure to lift the foot from the ground and a strong →action tremor (3-5 Hz) during arm reaching. Impairment of the overlying cortex causes hyper-flexed locomotor movements (Thach et al. 1992; Thach and Bastian 2004). Genetic manipulation and ablation experiments in mice identified a subset of glutamatergic neurons in the nucleus interpositus which give rise to nucleo-cortical →mossy fibers that preferentially target a specific forelimb-related region of the cerebellar cortex and primarily project to a restricted region of the motor thalamus linked to the caudal forelimb area of the motor cortex. In the mouse, diphtheria toxin-mediated ablation and optogenetic stimulation disrupted locomotion and skilled reach by altering limb positioning and timing (Low et al. 2018).

Cerebellar Lateral Hemisphere and Nucleus Dentatus are concerned with coordination of skilled movements of hands and fingers and speech, and control of complex, exteroceptively guided movements, movement planning and mental imagination of movement. The lateral hemispheric areas are involved in cognitive and linguistic skills (Ito 1984; Thach et al. 1992; Thach and Bastian 2004). Damage produces symptoms more pronounced in the upper than the lower leg (Dichgans and Diener 1985). They include →hypotonia, →hyporeflexia and →asthenia. In monkeys, nucleus dentatus (dentate nucleus) impairment does not interfere with standing and sitting, but the leg and paw are lifted higher than normal in the swing phase during walking. Damage to the lateral hemisphere and dentate nucleus also produces deficits of reaching and grasping (Thach et al. 1992; Thach and Bastian 2004).

23.6.2 Cerebellar Discharge Patterns during Locomotion

Rhythmic Proprioceptive Inputs. During locomotion and scratching in cats, the cerebellum receives information via the →spino-cerebellar tracts about mechanical events in the musculo-skeletal periphery.

During the stance phase of active stepping, →dorsal spino-cerebellar tract (DSCT) neurons can encode limb axis orientation and limb loading, the latter being closely linked with limb-axis length (Bosco et al. 2006). During fictive locomotion, the majority of DSCT neurons are driven by central pattern generators (CPGs) for locomotion and scratch, suggesting that these neurons are involved in distinguishing between locomotion-induced re-afference i.e., resulting from movement of body parts, and ex-afference resulting from external perturbations (Fedirchuk et al. 2013; Stecina et al. 2013).

→Ventral spino-cerebellar tract (VSCT) neurons show phasic cycle-related activity during fictive locomotion and signal activity in spinal interneurons (Fedirchuk et al. 2013). Initial →axon collaterals of VSCT cells target last-order inhibitory interneurons in disynaptic reflex pathways to hindlimb α-MNs from muscle spindle group Ia afferents from antagonist muscles, and/or from group II afferents and from Golgi tendon organ group Ib afferents from synergistic muscles (Jankowska and Hammar 2013).

Granule Cell Discharge. Using *in vivo* patch-clamp recordings in mice walking on a cylindrical treadmill, the entire step sequence could be predicted from input excitatory postsynaptic currents (EPSCs) and output spikes of a single →granule cell (Powell et al. 2015). Hence, even at the level

of the cerebellar input layers, significant correlates of motor kinematics, associative learning and behavioral context are present (Narayanan and Thirumalai 2019).

Purkinje Cells. Interpositus neurons receive inhibitory inputs from →Purkinje cells lying in the intermediate and paravermal portion of lobule V of the anterior lobe overlying nucleus interpositus anterior. Step-related →simple-spike (SS) discharge patterns of these Purkinje cells exhibit much variation in timing of their rhythmic activities. The average population activity of Purkinje cells is in phase with the activity of interpositus cells, despite the inhibition that Purkinje cells exert on interpositus cells.

The cerebellar cortex probably does not create the rhythmic interpositus activity, but may rhythmically shape activity. The main rhythmic drive may arise from collateral projections of mossy fibers and →climbing fibers to the nucleus interpositus. Similar relations hold for Purkinje cells in the lateral vermis, which project to the lateral vestibular (Deiters) nucleus (Armstrong 1988).

Lateral Cerebellum. Neurons in the dentate nucleus of pre-collicular decerebrated cats are relatively unresponsive during unperturbed treadmill walking. Discharges are modulated when the treadmill is momentarily turned off and then on again. The perturbation results in cessation of discharge modulation (Schwartz et al. 1987).

A number of studies have established that during locomotion, rhythmic activity is widely distributed across populations of neurons in numerous cerebellar compartments (Armstrong 1988). The deep cerebellar nuclei, nucleus fastigius and nucleus interpositus, both contain a high proportion of cells that exhibit step cycle-related modulation of their discharges, in association with visual, visuomotor and saccade-related activities. In conscious cats walking on a horizontal ladder, Purkinje cells and dentate cells show step-related rhythmic discharge modulations or increase their firing rate before saccades. The visual inputs probably originate in the dorso-medial visual cerebral cortex and are mediated via pontine nuclei to the lateral cerebellum. By combining visual responses with saccade-related activity, the lateral cerebellum may contribute to the visually guided coordination of body and eye movements (Marple-Horvat et al. 1998; Marple-Horvat and Criado 1999).

The cerebellar output targets various structures, among them the →vestibular nuclei, →reticular nuclei and the red nucleus, which send descending tracts to the spinal cord.

Interpositus Neuron Discharges during Locomotion. Most nucleus interpositus neurons discharge rhythmically during forelimb locomotion. The phasing of cell activity throughout the step cycle shows substantial individuality, but the summed activity of the cell population is also modulated rhythmically. The highest activity is attained during the swing phase and the lowest during the stance phase. The nucleus interpositus may contribute to stance and swing activity via its actions on rubro-spinal tract neurons. Since the interposito-rubro-spinal pathway is organized →topographically, individual muscles or groups of muscles might be controlled and fine-tuned individually according to their roles in the step cycle (Armstrong 1988; Schwartz et al. 1987).

23.6.3 Brainstem Neuron Discharge during Locomotion

Lateral Vestibulo-spinal Tract (LVST) Neurons. The vestibulo-spinal system contributes significantly to maintaining posture and equilibrium during stance and locomotion. An important component, excitatory postural drive to anti-gravity extensor muscles, originates in the lateral vestibular (Deiters) nucleus. In cats, this is partially accomplished by monosynaptic excitation of extensor α-MNs and disynaptic inhibition of flexor α-MNs (Grillner et al. 1970). In mice, vestibulo-spinal neurons distribute their axons widely throughout the spinal cord and make →synaptic contacts with various classes of interneurons involved in locomotion, i.e., commissural interneurons, as well as so-called →V2a interneurons (involved in left-right alternation), V0c interneurons (modifying α-MN gain in a task-dependent way), and RORα interneurons (dorsal premotor interneurons involved in touch sensation and fine motor control) (Witts and Murray 2019).

Many studies of the discharge patterns of lateral →vestibulo-spinal tract **(**LVST**)** neurons in locomoting cats were carried out in reduced preparations under different conditions and thus yielded varying results (Matsuyama and Drew 2000). For example, in decerebrate cats walking on a treadmill, about a third of the LVST neurons fired tonically, while another large subset modulated discharge rhythmically around a substantial mean rate that contributed a tonic background to postural support. The rhythmically active portion consisted of several groups with different phase-related discharge patterns. The majority fired just in advance of or during the stance phase of the ipsilateral hindlimb, contributing to extensor activity in an appropriate phase-dependent way (Orlovsky 1972a). In another study in decerebrate cats, LVST neurons shifted their activity from tonic, locomotor-unrelated activity during slow walk to phasic, locomotor-coupled →bursting during fast walk. With asynchronous hindlimb movements (i.e., during trot), increasing locomotor speed results in double-bursting, which switched to a single burst in each step cycle with symmetrical hindlimb movements (i.e. during gallop) (Mori et a. 1988).

A study in intact cats revealed different groups of LVST-neurons. A large group showed two peaks and two troughs of activity in each step cycle, with one peak time-locked to extensor muscle activity in the ipsilateral hindlimb and the other in anti-phase. A second group showed a tonic or irregular discharge interrupted by a single brief period of decreased activity just before the onset of swing in the ipsilateral hindlimb. A third group showed a single peak of increased activity time-locked to either extensor or flexor muscle bursts of a single limb. These discharge modulations could be sculpted by excitatory and inhibitory inputs, the latter provided by cerebellar Purkinje cells and the former stemming from several sources, including sensory inputs from the limbs, the neck and the vestibular labyrinth (Matsuyama and Drew 2000).

Reticulo-spinal Tract (RST) Neurons. The reticular formation (RF) receives command inputs from the motor cortex, but also signals from the vestibular nuclei (Matsuyama and Drew 2000; McCall et al. 2017). The MLR-reticulo-spinal system provides tonic drive to the central pattern generator (CPG) and contributes to fine-tuning rhythmic activities in groups of functionally related muscles. Step-related rhythmic discharges occur in neurons of the MLR, and rhythmically discharging RST neurons exert short-latency excitatory actions especially on flexor α-MNs. The rhythmicity of RST neuron discharge originates from the MLR and to a large extent from the cerebellum (Armstrong 1988). In a study on intact cats, RST neurons showed three activity patterns. The first group included cells showing phasic activity related to flexor or extensor muscle activity, with one or two clear phasic activity bursts. The second group contained cells that were

phasically active but whose activity was not time-locked to the activity of any of the recorded muscles. The RTS neurons in the third group were unrelated to locomotor movements (Matsuyama and Drew 2000). Rubral neurons also respond to hindlimb movements, and this influence could contribute to locomotor duscharge modulation (McCall et al. 2017).

Rubro-spinal Tract (RuST) Neurons. The →nucleus ruber (rubral or red nucleus) receives major afferent inputs from the cerebellar nucleus interpositus and weaker inputs from the motor cortex and the spino-rubral pathway. Descending rubro-spinal proejctions exert excitatory actions mainly on flexor skeleto-motoneurons. In decerebrate cats walking on a treadmill, about a sixth of the RuST neurons fired tonically, while the others rhythmically modulated their discharge in different phase relations to the step cycle; the vast majority discharged just before and during the swing phase (Orlovsky 1972b). In a later study, the discharge of lumbar-projecting RuST neurons was modulated in relation to the →intensity and frequency of the rhythmic α-MN efferent activity in the contralateral hindlimb. The average firing rate was minimal at the transition between the extensor and flexor efferent bursts and increased progressively to reach a maximum in the second part of the flexor burst. Comparison of the rubro-spinal activities during real and fictive rhythmic motor activities revealed only minor influences of phasic afferent inputs (Arshavsky et al. 1988). In awake cats trained to walk on a treadmill, RuST neurons related to the forelimb showed more diverse discharge patterns. During unobstructed locomotion, the vast majority of cells with a →receptive field (RF) confined to the contralateral forelimb was phasically active. The highest activity of most neurons occurred around the swing phase of locomotion. Slightly more than half of the neurons were phasically active during both swing and stance. Some neurons showed multiple periods of phasic activity within the swing phase (Lavoie and Drew 2002).

The RuST helps support and fine-tune flexor muscle activities during swing. The rhythmicity of rubro-spinal neuron discharge originates, to a large extent, from the cerebellum (Armstrong 1988).

23.6.4 Error Correction during Locomotion

Locomotion can be easily perturbed by external influences, e.g., by collisions with objects, or by internal errors in programming and execution.

In humans, fast and slow adjustments can be discerned during step preparation, initiation, unobstructed and obstructed gait. Fast adjustments occur both during stepping and gait. Even step adjustments appear to be further modifiable online, e.g., when avoiding obstacles during tripping (Potocanac and Duysens 2017).

In awake and decerebrate cats walking with their hindlimbs on a treadmill, a lateral push to the hip region induces changes in foot landing of the swing hindlimb, which are appropriate to regain stable walking (Karayannidou et al. 2009b; Musienko et al. 2014). It has been suggested that these reactions are generated by neuronal structures in the brainstem, cerebellum and spinal cord, while the forebrain (particularly the motor cortex) seems to play a secondary role (Musienko et al. 2014).

The cerebellum is intimately involved in locomotor adaptation to short and long-term perturbations. These are signaled by climbing fibers which are thought to serve as error detectors. The mossy fibers provide information about the ongoing movements in each step cycle via the dorsal spino-

cerebellar tract (DSCT), but the majority of DSCT cells also receives locomotor drive from CPGs. Moreover, mossy fibers transmit, via the ventral spino-cerebellar tract (VSCT) and the spino-reticulo-cerebellar tract (SRCT), →efference copy information about the motor commands sent by the CPGs to the flexor and extensor muscles. This provides phasic feedback mediated by the cerebellum to the vestibulo-spinal, reticulo-spinal and rubro-spinal tracts (Grillner and El Manira 2019; Stecina et al. 2013)).

Climbing fibers originate in the →inferior olive (IO). The IO receives motor command signals from the sensory-motor cortex, and sensory feedback from the periphery. From a comparison of the two, a mismatch signal should be detected and error correction can be made by altering the motor command output.

Although error correction by the IO seems to play a fundamental role in locomotor control (Apps and Garwicz 2005), findings from some studies raise caveats concerning the underlying mechanism. For example, error signals have been described mostly in the complex spike discharge of cerebellar Purkinje cells (Ebner et al. 2011), but there are mixed reports as to whether the discharge of IO cells and the complex spike activity of Purkinje cells are modulated rhythmically and phase-bound to the locomotor rhythm. Complex spikes fail to occur at fixed times during stereotypical unperturbed walking in conscious cats, despite the vast sensory inputs the IO receives. This may in part be due to movement-related and phase-dependent gating of self-generated sensory inputs. Evidence to support this assumption (Apps 1999; Pardoe et al. 2004) is that substantial climbing fiber responses (CFRs) are evoked in all phases of the locomotor step cycle in conscious cats by electrical stimuli that activate cerebro-olivo-cerebellar (COCP) and spino-olivo-cerebellar (SOCP) pathways. The largest COCP responses occur during the stance phase, and the smallest responses occur during the swing phase of the ipsilateral forelimb step cycle. SOCP responses recorded at the same sites are largest during the swing phase and smallest during the stance phase. The results imply that IO neurons remain excitable throughout. Differences between SOCPs and COCPs in their pattern of step-related modulation are unlikely to have arisen solely through inhibition at the level of the IO. The different patterns of modulation suggest that climbing fiber signals conveyed by COCPs and SOCPs are likely to affect information processing within the cerebellar cortical C1 and C3 zones at different times during locomotion**.**

If the IO is indeed an error-detection device, complex spikes elicited in Purkinje cells by olivary climbing fibers should respond to unexpected perturbations of ongoing movements. There is in fact supporting evidence from ferret and cat experiments (Bloedel and Lou 1987; Armstrong 1988) that perturbations to locomotor movements evoke complex-spike discharges. These discharges are correlated with enhanced simple-spike responses, suggesting that activation of climbing fibers selects a particular population of sagittically aligned Purkinje cells and their related cells in the →deep cerebellar nuclei. This, in turn, might lead to the selection of a particular error-correcting motor response.

23.6.5 Locomotor Adaptation and Learning

Normal walking is often fairly stereotyped with symmetric step lengths and step times. Studies performed on human volunteers reveal, however, that when regularity associated with walking is disturbed, movements are gradually modified to restore kinematic features through an error-based learning process, in order to maximize economy of gait (Finley et al. 2013). This locomotor adaptation

is a special type of →motor learning. It can be effectively studied by letting a subject walk on a split-belt treadmill on which one leg is exposed to a belt speed higher than that of the other leg.

Humans adapt to suddenly imposed differences in belt speed during split-belt walking. This capacity develops slowly throughout childhood and adolescence (Torres-Oviedo et al. 2011). Initially, adult subjects walk with unequal step lengths, but gradually adapt to steps of equal length (Finley et al. 2013). Adaptation proceeds at fast and slow time scales. Reactive feedback produces more rapid adaptation, while predictive feedforward mechanisms mediate slower adaptation. The two types of adaptation are differentially affected by cerebellar damage. Rapid adaptation is not impaired, while slower practice-dependent adaptation of step length and double-support are. Adaptation to split-belt walking is associated with reductions in →electromyographic (EMG) activity in various muscles of both legs with a reduction in metabolic →power, suggesting that minimization of energy expenditure may be an important factor in driving adaptation (Finley et al. 2013). Moreover, like other forms of →motor adaptation, locomotor adaptation has longer-lasting →memory effects: recall, i.e., the retrieval of previously successful adaptations, and faster re-learning in response to repeated exposures to the same perturbation, reflecting an increased sensitivity to errors (Mawase et al. 2017).

In cats walking on a treadmill, exposure of one forelimb to a belt speed higher than that of the other limbs is an effective means of eliciting motor learning. In this paradigm, the normal coordination of limb movements is disturbed, and climbing fiber responses are induced at high probability in Purkinje cells of the cerebellar vermis. After a number of steps in the perturbed locomotion, the cats regain inter-limb coordination and stability. The cerebellum is the most likely site responsible for this adaptation since adaptation takes place in decerebrate cats, while inter-limb coordination is seriously impaired in spinal cats, and mechanical lesions or cooling of the cerebellum induces disturbances of locomotion **(**Yanagihara and Kondo 1996). Specific involvement of cerebellar climbing fiber adaptation seems speculative, however, since evidence was not presented that climbing fiber discharge intensity diminishes in association with inter-limb coordination and stability.

23.7 Role of the Cerebral Cortex in Locomotion

Stronger challenges arise when skilled locomotion is required in an uneven environment cluttered with potential obstacles. To deal with such complexities requires excellent spatio-temporal vision, appropriate gait modifications, in particular precise foot placements, anticipatory planning and exact feedback-controlled execution. These functions involve cerebro-cortical regions including the visual cortex, →posterior parietal cortex (PPC) for planning and sensory-motor transformations and the motor cortex for execution (Drew and Marigold 2015; Duysens and Forner-Cordero 2018; Higuchi 2013).

23.7.1 Role of Vision in Locomotion

Excellent vision is of essence as well as proper coordination between the locomotor and oculomotor systems in. order to maneuver through a complex and ever-changing environment (Duysens and Forner-Cordero 2018; Higuchi 2013; Hollands and Marple-Horvat 2001; Srivastava et al. 2018). Walking subjects must control the direction of heading and make navigation decisions by keeping track of the surrounding scene, and if the ground is rough,

must also select suitable footholds for the next steps, depending on the energetic costs and benefits involved. The necessary information is sampled by the visual system using sequential gaze re-directions in order to inform the subsequent action (Hayhoe and Matthis 2018).

Visual disturbances during walking require fast responses to avoid falling. When young human subjects walk in a virtual-reality cave and are confronted with the perception of a fall to the side, changes occur in the modulation of the ankle push-off, in swing-leg foot placement and in stance-leg ankle roll. The adjustments in gait accelerate the body in the direction opposite of the visually induced fall stimulus. The accompanying rapid changes in ankle-muscle activity suggest the existence of a direct reflexive pathway from the visual system to the spinal cord (Reimann et al. 2018).

When humans are required to land the swinging foot on safe target footholds, visual information is used in an intermittent rather than a continuous manner. Visual information is sampled during discrete intervals that occur during a specific phase of the gait cycle, before the step to that foothold has been initiated. Humans need visual information about upcoming footholds, at the latest, during the second half of the preceding step. Once the foot leaves the
ground, visual information about the upcoming target is not needed. The reason may lie in the kinematics and dynamics of the moving body, which under normal conditions of unperturbed locomotion are tuned to energy efficiency and dynamic stability. Using visual information at strategic intervals during the gait cycle to modify these variables may allow the body and swing leg to follow their natural trajectory and thus preserve the benefits of passive biomechanics (Barton et al. 2017). In experiments with transiently reduced vision, accurate saccades and subsequent accurate steps onto the next footfall target (stepping stone) werealmost always made even when the information had been invisible for as long as 500 ms (Hollands and Marple-Horvat 2001).

The coupling of locomotion and eye movements depends on the difficulty of the traversed terrain. In a flat terrain, subjects use stable step lengths and durations, without using gaze to locate specific footholds. In medium-difficult terrain, subjects look two steps ahead and slow down so that the necessary visual information can be gathered in time. In rough terrain, subjects often look ahead 2-3 steps and slow down. Within a step duration of about half a second, subjects often make two or three fixations to exclude unsuitable footholds and find new saccade targets on a time scale of 100 or 200 ms (Hayhoe and Matthis 2018).

23.7.2 Role of the Posterior Parietal Cortex in Locomotion

The posterior parietal cortex (PPC) provides an estimate of subject position with respect to objects in its path, and transforms sensory information into motor plans (Drew and Marigold 2015). It receives inputs from the visual cortex and sends strong projections to →frontal motor areas and, via the pontine nuclei, to the lateral cerebellum, which, in turn, projects via the thalamus to the motor cortex (Drew et al. 2008a). PPC exhibits rhythmic discharge activity during locomotion, and plays a critical role in obstacle avoidance.

Rhythmic Discharge. Most neurons in cat parietal →area 5 discharge rhythmically with step-related phasing, even when walking on a flat surface without the necessity of tight visual control. This activity is probably not driven by somatosensory inputs. It could be set up by ascending input from spinal central pattern generators (CPGs). Parietal discharge patterns change dramatically when

cats need to place their feet carefully while walking on the rungs of a horizontal ladder. Modulation of rhythmic neuron activity is usually more pronounced, resulting in a double-peak discharge. One peak usually occurs in swing, and the other one in stance. Visual information is evidently integrated with locomotor activity in the →parietal cortex by enhancing and re-ordering its pattern. It also seems that the PPC exerts its influences independently and directly on →sub-cortical and spinal locomotor-related structures (Beloozerova and Sirota 2003).

Obstacle Avoidance. Many cells in cat area 5 increase their discharge rate at the beginning of the step that precedes the obstacle, or even 2-3 steps in advance, irrespective of whether the ipsi- or contralateral limb can clear the obstacle (Drew and Marigold 2015).

The PPC is also a critical structure for spatial memory. Quadrupeds must ensure that when the forelimbs have stepped over an obstacle on the ground, the hindlimbs will also do so despite the obstacle being out of sight. Cats are able to remember an obstacle they have stepped over with the forelegs for many minutes, and use this spatial memory to step over the obstacle with the hindlegs (Drew and Marigold 2015).

PPC neurons in area 5 show activity that is strongly correlated with the location of an obstacle relative to the body (McVea and Pearson 2009). An important function of the PPC may be to plan adequate foot placement so that a required gait modification is initiated at the right time and place to clear an obstacle (Drew and Marigold 2015). Damage to the PPC in cats leads to difficulties in making a reaching movement to a moving target, but not a stationary target. It also causes an inability to step smoothly over an obstacle without hitting it, and a deficit of forelimb-hindlimb coordination (Drew et al. 2008a).

23.7.3 Role of the Motor Cortex in Locomotion

The motor cortex evidently contributes to the execution rather than the planning of movements during visually guided gait modifications by modulating the activity of groups of synergistic muscles which are active at different times during the gait cycle (Drew and Marigold 2015).

Humans with lesions of →premotor →cortical areas, including →supplementary motor area (SMA), often show disturbances of gait initiation and freezing of gait (Takakusaki et al. 2008). In bipedally walking monkeys, inactivation of the hindlimb region of the →primary motor cortex (F1, M1) by local →muscimol injection produces →paresis of the contralateral hindlimb, while injection into the trunk/hindlimb region of the supplementary motor area (SMA) disturbs postural control during locomotion without →paralysis. In cats, damage to the motor cortex, pyramidal tract or cortico-spinal tract (CST) results in locomotor deficits, including changes in limb trajectory, inability to step over obstacles, dragging of the paw and difficulty with precise paw placement (Drew et al. 2008a).

Rhythmic Discharge in Motor Cortex. Non-invasive methods of recording and stimulation in humans, such as neuroimaging, →transcranial magnetic stimulation (TMS) and electrical stimulation, and coherence calculations between different electromyographic (EMG–EMG) as well as between electromyographic (EMG) and →electroencephalographic (EEG) signals, demonstrate that rhythmic modulation of motor cortex and cortico-spinal tract (CST) activity accompanies walking (Barthélemy et al. 2011).

Recordings taken from neurons in the motor cortex of conscious, walking cats and rabbits show that the neurons discharge rhythmically in conjunction with gait phases during locomotion and are important for proper foot placement, stepping over obstacles and error detection (Armstrong 1988; Beloozerova et al. 2003; Drew and Marigold 2015; Marple-Horvat et al. 1993).

The quadruped motor cortex is not significantly involved in the initiation of simple locomotion. However, in awake cats walking on a treadmill, a large percentage of cortical neurons were phasically modulated and discharged most intensely during the swing phase of the step cycle (Lavoie and Drew 2002). This modulation appears to be caused by signals ascending from the spinal structures (`limb controllers´) generating rhythmic movements of individual limbs or combinations thereof (Zelenin et al. 2011). In cats standing on a roll-tilted platform, roughly half of the recorded →pyramidal tract neurons (PTNs) exhibited a positional response by increasing their activity with either the contra-tilt (20%) or the ipsi-tilt (27%). During walking, PTN discharge was modulated rhythmically, and tilts of the supporting surface evoked additional positional responses by modulating the response magnitude in 58% of PTNs (Karayannidou et al. 2009a). PTNs fall into dissimilar groups that fired in different gait phases. PTNs preferentially received somatosensory inputs from shoulder, elbow and wrist, and discharged in relation to movements of those forelimb joints (Stout and Beloozerova 2012). During forward walking and during backward walking, the discharge of some motor cortical cells was modulated by inputs from only one girdle, whereas that of the other neurons received inputs from both girdles. Half of the forelimb-related neurons and a third of the hindlimb-related neurons received inputs only from their own girdle when this girdle was leading and from both girdles when this girdle was trailing, suggesting some flexibility of the functional roles of individual neurons (Zelenin etal. 2011).

Precise Foot Placement. Rhythmic activity is strongest during walking over difficult terrain, where precise foot placement and close visuo-motor control are required (Beloozerova and Sirota 2003). Under these conditions, the cortico-spinal system seems to be of particular importance for →volitionally starting and stopping locomotion, adjusting its speed, and precisely placing limbs (Drew and Marigold 2015).

Stepping over Obstacles. Studies in awake cats prepared for chronic testing have shown that pyramidal tract neurons (PTNs) increase their discharge rate during tasks that require precise, accurate placement of fore- and hindlimb paws in order to step over obstacles while walking on a treadmill. The studies (Drew et al. 2002, 2008a) demonstrate that a large percentage of PTNs discharge early in swing, in phase with the activity of knee flexors. Other PTNs discharge slightly later, in phase with ankle flexors, while still others discharge at the end of swing, in phase with digit dorsiflexors. Thus, it can be concluded that different sub-populations of cortical neurons modify the activity of selected groups of close synergistic muscles during different parts of the swing phase. Hypothetically, these modifications are mediated in part by groups of interneurons that assist in establishing the fundamental locomotor rhythm. This provides a means by which the changes specified by signals descending from the motor cortex may be smoothly, and appropriately, incorporated into the locomotor cycle (Drew et al. 2008b).

But negotiating obstacles also involves sub-cortical structures. For example, when awake cats stepped over an obstacle fixed to the treadmill, discharge patterns in motor cortex and nucleus ruber showed some similarities in that sub-populations in each structure exhibited a single peak of increased firing rate centered around the swing phase. However, there were also dissimilarities. First, all of the rubral neurons showed increased firing during the gait modifications, while only

63% of the cortical cells showed increased and 30% decreased activity. Furthermore, some rubral cells discharged during both swing and stance, and some neurons exhibited multiple peaks of activity during swing, similar to cells during unobstructed locomotion. Also, changes occurred in the magnitude, duration and timing of the cell discharge patterns, together with the appearance of new periods of neuronal activity during the gait modification. Hence, both rubral and cortical cells probably contribute to specify the appropriate spatio-temporal muscle activations necessary to produce the change in limb trajectory required to step over the obstacle, but they do so in somewhat different ways (Lavoie and Drew 2002).

Error Detection. Fast responses to errors are essential when precise foot placement is required. For example, in cats walking on a horizontal ladder, a subset of neurons in the forelimb motor cortex including PTNs increase firing rate when the contralateral limb unexpectedly steps onto an unstable rung. The onset latency to increased discharge ranges from 20 to 100 ms. Some cells also respond to ipsilateral rung descent at latencies from 35 to 80 ms. Hence, the motor cortex is rapidly informed about gait perturbations and could, via the cortico-spinal tract (CST), assist spinal reflex mechanisms in producing a compensatory change in motor output (Marple-Horvat et al. 1993).

23.8 Navigation

Navigation between two far points in space is the most complex form of locomotion and puts high demands on several sub-systems of the CNS. It requires (1) representation of the animal´s initial spatial location and directional heading in the environment, (2) representation and selection of a goal, (3) selection and computation of a route to the goal, (4) updating of position/heading underway, (5) memorization of the starting position to be able to return quickly, (5) integration of information about body motion in the environment using olfaction, touch, audition, vision and information about self-motion from proprioceptive and vestibular signals, optic flow, motor efference copy (Bremmer 2005; Calton and Taube 2009; Penner and Mizumori 2012; Poulter et al. 2018; Rochefort et al. 2013; Taube 2007). There are several navigational strategies during locomotion, which are not mutually exclusive but may co-operate depending on conditions (Wehner et al. 2016). Among them are landmark navigation (or piloting) and →path integration.

23.8.1 Landmark Navigation

Salient environmental cues are used in landmark navigation to determine current position and direction. The sensory information needed can come from the olfactory, tactile, auditory or visual senses. Mental representations of the spatial areas may also be necessary, so that they become familiar and imprinted in →memory (Loomis et al. 2001; Collett and Collett 2002).

Cognitive spatial maps may be valuable in establishing mental representation of spatial areas. The maps contain information about the external environment independent of one´s location, such as topological information about relative spatial relationships between →landmarks and metric information about distances. The existence of such maps is supported by the ability to take novel routes or shortcuts.

23.8.2 Path Integration

In path integration, the current position and direction relative to the starting values are determined without the use of external landmarks. This strategy relies solely on internally available information (→idiothetic cues), and can be used to return to the starting position. Path integration is employed by a large variety of animals, from insects to humans (Aflalo and Graziano 2008; Collett and Collett 2002; Etienne and Jeffery 2004; Loomis et al. 2001; Mittelstaedt and Mittelstaedt 2001; Poulter et al. 2018; Taube 2007; Wehner et al. 2016). Path integration requires an initial reference vector and an estimate of the current position and direction of the path travelled, often from the starting position (Taube 2007). This calculation requires continuous monitoring of intermittent self-generated motion, in particular direction and speed (Sheeran and Ahmed 2020).

Distance travelled might be calculated from various sources such as, an efference copy of motor outflow, from proprioceptive signals, from vestibular or somatic →graviceptor signals (Lackner and DiZio 2005; Mittelstaedt 2000; Patla 1997), or from vision (Lappe et al. 1999; Warren et al. 2001). Memory must then store continuously updated values of current distance and direction, relative to the initial reference values.

Location, direction and movement are encoded by different classes of neurons within the limbic system and posterior parietal cortex (PPC) (Taube 2007; Whitlock et al. 2008).

23.8.2.1 Neural Representation of Location and Direction

Ensembles of neurons in the →hippocampal formation (→boundary cells, →place cells, →grid cells, →head direction cells) encode an animal´s location and orientation in the environment (Poulter et al. 2018).

Boundary Cells in the subiculum, parasubiculum and medial →entorhinal cortex discharge in response to boundaries, such as vertical surfaces or cliffs, often at a particular distance and in the direction of the animal´s current location (boundary vector cells) (Poulter et al. 2018). There is suggestive evidence that the →receptive fields (RFs) of boundary cells, similar to those of place cells and grid cells, rotate coherently with head direction to provide global orientation for the three types of cells (Bush et al. 2014).

Place Cells that fire in specific, stable and spatially limited place fields within the environment were first found in the rat →hippocampus (O´Keefe and Dostrovsky 1971) and later in the subiculum, entorhinal cortex and striatum (Etienne and Jeffery 2004; Moser et al. 2008, 2014; Penner and Mizumori 2012; Taube 2007). To anchor their space fields in space, place cells need →multi-modal sensory inputs, in part mediated via boundary cells (Bush et al. 2014; Wiener et al. 2002). Among these inputs, visual inputs are most important when available. If not, motion-related idiothetic cues become more relevant. However, since path integration tends to accumulate errors, idiothetic information is insufficient and must be re-calibrated with respect to environmental landmarks. All these types of information come from a number of cortical areas (Taube 2007). The cerebellum might assist in constructing hippocampal space maps by integrating sensory information from different

sources, transforming reference frames, distinguishing externally generated from self-generated vestibular signals, and sending this information to the hippocampus, possibly indirectly via navigation-processing cerebro-cortical areas (Rochefort et al. 2013).

Grid Cells. Grid cell discharges in the medial entorhinal cortex fire at high rates in response to events at multiple locations within an environment, such that the locations form a repeating hexagonal grid-like pattern. The grid map is dynamically updated during the animal´s movement and depends on motion signals provided by proprioceptive, vestibular and optic-flow signals. Grid cells may also receive information on changes in position by speed cells in the medial entorhinal cortex. As the designated name infers, cell firing is related, mostly linearly, to running speed (Poulter et al. 2018). Integration of discharge activity could provide estimates of the distance travelled (Bush et al. 2014; Moser et al. 2008, 2014; Taube 2007).

Head Direction Cells. Distinct populations of neurons encode an animal's spatial head direction irrespective of its location, working like a compass although without dependence on the earth's electromagnetic field. Such cells occur in several limbic areas, thalamus, striatum, posterior cingulate and other cortical areas. The head-direction signal may primarily derive from vestibular signals related to angular head velocity, but is likely updated along the way by motor efferent signals, proprioceptive signals and landmark cues. Vestibular signals reach the entorhinal cortex and hippocampus via several stations and pathways, where they are integrated with place signals (Etienne and Jeffery 2004; Jacob et al. 2014; Penner and Mizumori 2012; Taube 2007; Wiener et al. 2002; Yoder and Taube 2014).

Information about motion speed is processed by the hippocampus and entorhinal cortex based on motor and sensory signals provided by upstream sources (Sheeran and Ahmed 2020).

23.8.2.2 Encoding of Goal and Route Computation

Navigation requires representation of goals, such as simple approach and avoidance, following odor trails, moving toward prominent visual beacons or using geometric maps based on spatial relationships. A procedure is then needed to calculate the route from the initial location to the goal. The posterior parietal cortex (PPC) has been proposed as the site that integrates signals of →spatial orientation in immediately surrounding space with representation of the goal. The correct route to the goal is then established, and prefrontal and motor areas subsequently execute the plan (Calton and Taube 2009; Whitlock et al. 2008).

In humans, the medial parietal region (MPR), including the →posterior cingulate cortex (PCC; area 23 and area 31) and the retro-splenial cortex (area 29 and area 30) (Kravitz et al. 2011) are involved in navigation based on route knowledge. The MPR in monkeys appears to contribute to route-based locomotion by integrating sensory (visual) and motor signals related to location and self-movement (Sato et al. 2006). Information processing from parietal to retro-splenial cortex appears to follow a gradient from →egocentric to →allocentric frames of reference (Clark et al. 2018).

In monkeys and humans, spatial information appears to be transmitted from the posterior parietal cortex to the medial temporal lobe via direct and indirect projections through the posterior →cingulate cortex and retro-splenial cortex (Kravitz et al. 2011).

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24

Preparation and Planning of Arm and Hand Movements

CONTENTS

Abstract

• Processes occurring during the preparation phase of arm and hand movements generally involve perception of potential target objects and determination of their identity and location, decision making about an appropriate object to interact with, and task rules regarding a movement goal that determines how and what to do with the object.

• Motor planning in a more restricted sense requires selection of an effector and an action, movements that include joint trajectories and/or muscle activations, and planning of anticipatory postural adjustments.

• Indirect signs of preparation and planning processes in the brain have been obtained by electroencephalographic (EEG) recordings in humans. More complex actions such as reaching and grasping are signaled by preceding preparatory EEG activity that is stronger and starts earlier than in simple movements such as finger tapping.

• In humans and non-human primates, various representations in the central nervous system (CNS) of space and time utilized in reaching movements have been elucidated from psychophysical, neuropsychological and electrophysiological measurements.

• Despite the critical importance of timing in movement planning, the underlying structures and mechanisms are not well understood.

24.1 Introduction

→Voluntary movements such as goal-directed reaching, grasping and manipulation of objects require →skilled hand and arm movements that are initiated and designed to respond to goal, context and conditions, and can change throughout the movement (Hughlings Jackson 1931). Skilled forearm movements may have their evolutionary precursors in food-handling →behavior, precise stepping, and in arboreal locomotion of monkeys (Grillner and Wallín 2004; Karl and Wishaw 2013). They require excellent cerebro-cortical visuo-motor coordination.

Voluntary arm and hand movements need time to prepare before starting. During this period, there are no overt changes in →skeletal muscle activity, and movement preparation is independent of movement initiation. It has been shown that preparation ameriolates performance by lowering →reaction time, and longer preparation delays generally lead to better movement quality (Papaioannou and Dimitriou 2021). The processes occurring during this phase include →perception of potential target objects, determination of their identity and location, →decision making that selects an appropriate object to interact with, task rules that determine what and how to do with the object (movement goal) and whether to initiate the action at all considering the potential costs, efforts and risks. Once a positive decision has been taken and a movement goal is defined, motor planning starts. This stage involves selection of an action and an effector, the movement trajectory including its velocity, the joint trajectories and skeletal muscle activations, appropriate preparation of peripheral-plant properties, and the planning of →anticipatory postural adjustments (Mirabella 2014; Wong et al. 2015).

24.2 Signaling Movement Preparation and Planning in the CNS

24.2.1 Cerebral Cortex

Indirect signs of preparation and planning processes have been demonstrated by →electroencephalographic (EEG) recordings in humans. The first recording in response to self-initiated simple movements such as finger flexion revealed a slowly rising negative potential over frontal-central scalp areas starting 1-2 s before movement onset, initially referred to as a `Bereitschaftspotential´ (BP) (Kornhuber and Deecke 1965) or readiness potential (RP) and later as motor-related cortical potential (MRCP). Later, this potential was differentiated and components often started even earlier (2.8 s) (e.g.,Bozzacchi et al. 2012). The early MRCP could be associated with unconscious readiness for the upcoming action and increasing cortical excitability. The major contribution to this potential is attributed to the bilateral →pre-supplementary motor area (pre-SMA; area F6) and →cingulate motor areas. There is a later steep rise of the MRCP during the last 400-500 ms before movement onset that reflects movement preparation and is often associated with the decision to move and increasing excitability of →premotor →cortical areas. This late phase is probably generated predominantly by premotor and motor areas and peaks in the motor potential, which is primarily generated by the →primary motor cortex (area F1, area M1) contralateral to the arm to be moved and coincides with movement onset. A positivity after movement onset has been associated with somatosensory feedback (re-afferent potential) and activity in the →primary somatosensory cortex (S1, SI) (Di Russo et al. 2017).

More complex actions such as reaching and grasping are reflected in preparatory EEG activity that starts earlier and is stronger than in simple movements. For example, in real grasping, it starts 3 s before movement onset in parietal areas. These actions require higher-level →cognitive processes and visuo-motor and other sensory-motor transformations, from perception and →recognition of objects to decisions on the final movement goal. They involve an intricate cerebro-cortical network of areas in the →prefrontal cortex (PFC) and →parietal cortex (Di Russo et al. 2017).

Studies in rodents and non-human →primates have revealed long-lasting changes in brain neuronal activity occurring before movements (Svoboda and Li 2018). Specifically, in primates such activity precedes hand and arm movement in various areas of →cerebral cortex, including the →parietal reach region (PRR) in the →posterior parietal cortex (PPC), dorso-lateral premotor area (PMd), primary motor cortex (area F1, area M1), and in the →thalamus, →basal ganglia and the →cerebellum. Preparatory activity patterns vary with kinematic movement variables such as direction, distance, and speed (Shenoy et al. 2013).

Even in primary motor cortex, usually conceived as the upper end of the executive arm, signs of motor preparation precede the onset of movement by well over a hundred ms. →Pyradimal tract neurons (PTNs) fire in advance of movement onset and might be involved in starting a reach-to-grasp movement (Lemon and Kraskov 2019). Not surprisingly, preparatory activity occurs in structures receiving inputs from cortical structures, e.g., in the →spinal cord, where such activity occurs in cervical →interneurons of monkeys before arm or wrist movements (Fetz et al. 2002).

24.2.2 Cortico-thalamo-cerebellar Interactions

The →frontal cortex is reciprocally and intensely connected with the cerebellum, in part via the thalamus. Importantly, neurons in mouse anterior lateral motor cortex (ALM) and specific thalamic nuclei show selective persistent activity that instructs future actions. During a tactile discrimination task with a delayed directional response, ALM and thalamic neurons exhibited selective persistent delay activity that predicted movement direction. It has been suggested that the thalamus might be a center of motor preparation and that persistent activity requires reciprocal excitation across multiple brain areas (Guo et al. 2017). This network can be extended by inclusion of the cerebellum. In mice, preparatory activity was observed in both the frontal cortex and →nucleus fastiguus, seconds before movement onset. A transient perturbation in the fastigial nucleus disrupted correct subsequent responses, without hampering movement execution, and silencing frontal cortex activity abolished preparatory activity in the cerebellar nuclei (Gao et al. 2018). Again in mice, the cerebellar output neurons in the dentate nucleus and cells in the ALM showed similar preparatory activity before →reward acquisition, and silencing the former suppressed the latter. This suggests that preparatory activity is controlled by learned decreases in →Purkinje cell firing under supervision of →climbing fiber inputs signaling reward delivery (Chabrol et al. 2019).

24.3 Motor Planning

Motor planning involves several selections as to the action to be taken, the effectors to be used and the anticipatory adjustments needed.

24.3.1 Action Selection

There is evidence that more than one potential action is planned and held in store before a decision is made to execute one or change a started action. The decision depends on several factors, such as external sensory cues, anticipated action outcomes, implicit →memory of recent perceptual, cognitive or motor experience, and →attention (Song 2017; Wong et al. 2015). These various action options (→affordances) are represented in multiple frontal and parietal areas (Andersen and Cui 2009; Chapman et al. 2010; Cisek and Kalaska 2010). When subjects are requested to make rapid reaches to a target on a screen and the target is signaled from the beginning, reach trajectories are fairly straight to the goal. When there are two equally likely potential targets, subjects first aim between the targets and correct the trajectory. The distance between potential targets influences the initial trajectory direction. The density of potential targets in the display also plays a role, because the initial trajectory selects the more closely adjoined targets. Evidently, during the planning phase of a fast reach, trajectories are selected by simultaneously encoding multiple potential target locations during the reach. The distance and density distribution of potential targets co-determine the initial trajectory planning (Chapman et al. 2010).

Investigations in non-human primates have shown that the choice between competing reaching options is reflected in neural activities in several cortical areas (Cisek and Kalaska 2010). The prefrontal cortex (PFC) has been conceived of as an `executive control´ station supervising the task rules and the selection of actions, possibly in connection with the basal ganglia (Cisek and Kalaska 2010; Haggard 2008; Hazy et al. 2007; Tanji and Hoshi 2008; Wong et al. 2015). The pre-supplementary motor area (pre-SMA; area F6) appears involved in the selection and preparation of movements, particularly in the determination of when to start a movement depending on →motivation and external contingencies (Rizzolatti et al. 2014). Brain imaging in humans has suggested that pre-SMA is particularly active when subjects have to select the appropriate response on-line, when a change or update of the motor plan is required or a response to an unpredictable visual stimulus (Sakai et al. 2000).

In general, neural activity in the monkey →motor cortex before movement onset correlates with the direction, extent, speed and curvature of the following movement (Wong et al. 2015). Activities in the dorso-lateral premotor area (PMd) initially carry simultaneous representations of potential movement options and later reflect the selection of the action to be executed (Cisek and Kalaska 2005). Activity in PMd and area F1 is modulated by arm and wrist postures, but activity in ventro-lateral premotor cortex (PMv) is not (Wong et al. 2015). There are indications that the →lateral intraparietal area (area LIP) and parietal reach region (PRR) are involved in selecting eye movements and reaching movements (Andersen and Cui 2009). As in eye-movement planning and locomotion, the basal ganglia may say `yes´ or `no´ to competing action options (Hazy et al. 2007; Grillner et al. 2013; Houk et al. 2007; Humphries and Prescott 2010).

24.3.2 Effector Selection

An important selection involves a suitable effector to carry out hand and arm movements. For example, either hand might be used in feeding, object grasping and manipulation and in communicative gestures. The decision on which to choose depends on past experience, context, sensory input, effector availability, and handedness (Goble and Brown 2008). Handedness is widespread across vertebrates and invertebrates (Versace and Vallortigara 2015). Which hand to use depends on the leading sense employed for searching. Thus, there appears to be a right-hand/left-hemisphere specialization for visually guided grasping and a left-hand/right-hemisphere specialization for →haptic exploration (Stone and Gonzalez 2015). However, the left hemisphere appears to play a crucial role in the visual control of reach-to-grasp movements independently of handedness (Gonzalez et al. 2006). Handedness is an important factor in reaching because the dominant hemisphere/limb system may be specialized for controlling limb trajectory dynamics while the non-dominant system may primarily control limb position (Sainburg 2005).

The final selection of an arm and hand appears to result from competition between action plans initiated in parallel for each limb. The posterior parietal cortex (PPC) is involved in the choice of right vs. left arm and hand for unilateral reaching, but with a hemispheric asymmetry. Transient inactivation of the left caudal intraparietal sulcus (cIPS) by →transcranial magnetic stimulation (TMS) biases the choice towards the left hand, while TMS of the right PPC does not (Oliveira et al. 2010).

In the monkey →premotor cortex, neural activity suggests that two potential reach movements with either of the two arms are planned in parallel until a decision for one arm is made (Cisek and Kalaska 2010).

Movement preparation involves the setting of peripheral plant mechanics, e.g., muscle →stiffnesses, to enable efficient movement. In part this may include setting stretch-reflex sensitivity by altering fusimotor muscle spindle inputs. In fact, it has been shown that in humans group Ia afferent activity decreased when preparing to reach for targets in directions associated with stretch of the spindle-bearing muscle. As expected from this result, whole-arm perturbations during reach preparation revealed a modulation of stretch-reflex gains in shoulder and upper arm muscles. This suggests that central preparatory activity may tune muscle-spindle sensitivity in order to set muscle stiffnesses required for the task goals (Papaioannou and Dimitriou 2021).

24.3.3 Selection of Anticipatory Postural Adjustments

Movement of a body part changes the body configuration, exerts dynamic inter-segmental interactions between body parts, changes the location of the →center of mass (COM) and thus alters the postural equilibrium of the body. Appropriate compensations must therefore be prepared in parallel with planning arm and hand movements. →Supplementary motor area (SMA proper; area F3) could be involved in organizing anticipatory postural adjustments that accompany hand and arm movements, since individuals with damage to area F3 show deficits in postural adjustments when required to raise their arm while maintaining upright posture (Massion 1992; Rizzolatti et al. 2014; Romanelli et al. 2005).

24.4 Initial Conditions and Transformations

Planning and preparation of goal-directed reaching movements of the hands and arms involve several steps (Buneo and Andersen 2006; Gielen 2009; Krakauer and Shadmehr 2006).

24.4.1 Determination of Hand and Target Positions

Goal-directed reaching movements require the determination of hand and target positions, from which a vector (→motor error) can be computed to guide the hand to target. The target position can be assessed by vision or, if this is temporarily unavailable, remembered from previous experience. Information about target distance from the body is assisted via pupillary vergence, directed at the region immediately surrounding the body where reach needs to be directed. In addition, the hand and arm are localized by proprioceptive signals from muscle spindles and joint receptors. The different signals are represented in the neural activity of several fronto-parietal areas concerned with hand/arm movements (Battaglia-Mayer 2019). These signals and hand/arm movements are represented in different →frames of reference between which transformations must be performed (below). From the various sources of information a →motor command is generated.

24.4.2 Sensory-motor Transformations

In order to plan and prepare for goal-directed reaching movements, sensory signals must be transformed into motor commands. An important interface for sensory-motor transformations is the posterior parietal cortex (PPC), because of its strategic position between sensory and motor areas and its input-output connections. For example, PPC →area V6A and area LIP are involved in visuo-motor transformations needed for arm/hand and eye movements to →salient targets and for eye-hand coordination in reaching. The medial intraparietal area (area MIP) integrates visual and somatosensory information for reaching. Area AIP is important for the visual control of hand-object interactions, such as grasping, and to some extent for reaching (Vesia and Crawford 2012). In general, different sub-regions of the PPC show a degree of preferential functional specialization for certain actions. But eye, arm and hand movements are interdependent, and the involved areas are thus anatomically connected and contain mixtures of neurons firing in association with all these movements (Hadjidimitrakis et al. 2019).

24.4.3 Context- and Task-dependent Coordinate Systems

Arm, hand and eye movements occur in different contexts and under different conditions. For example before and during hand motion, the initial hand position and the target position may be visible or not (e.g., only remembered). The differences in conditions also co-determine the type of reference frame used by the →central nervous system (CNS).

In human and non-human primates one method used to reveal reference frames utilizes →psychophysical measurements, for example an error analysis of reaching movements (Engel et al. 2002; Gordon et al. 1994; McIntyre et al. 2000). For example, in a study involving human subjects, target and cursor positions were displayed on a computer screen and vision of the hand

and arm was blocked to prevent visual corrections. Reaching movements were found to be planned in a →hand-centered coordinate system with direction and extent of hand movement as the planned parameters. Directional errors due to blocked vision were greater than reach errors for both slow and fast movements. It was concluded that direction and reach are separately specified in the brain (Gordon et al. 1994).

In other human reaching studies, three types of errors have been defined for end-points derived from repeated hand movements to the same target position. One is a constant error, defined as the systematic deviation of mean hand end-position from the target position. A second is the variable error that defines the variance of the individual end-points around the mean. The third type is local distortion, that reflects the fidelity with which the relative spatial target configuration is maintained in the formation of the end-points (e.g., Battaglia-Mayer et al. 2003).

An assortment of coordinate systems that guide hand/arm reaching centered on eye-, head- and body in monkeys, have been elucidated and their respective cortical locations identified, and are described in the paragraphs below.

Eye-centered (Gaze-centered) Coordinates. →Learning new visuo-motor mapping after an experimentally induced error between →perceived and actual finger position involves a →spherical coordinate system (distance, azimuth, elevation) centered between the two eyes (Battaglia-Mayer et al. 2003). Eye-centered frames are also suggested by neurophysiological evidence (Cohen and Andersen 2002). Eye-centered coordinates are represented in area LIP for saccade planning and in the parietal reach region (PRR) for planning of reaching movements, irrespective of the modality of the stimulus. In addition, the →dorso-lateral premotor cortex (PMd) and →ventro-lateral premotor cortex (PMv) contain neurons that encode the location of reach targets in eye-centered coordinates (Buneo and Andersen 2006). Both areas also contain neurons that encode target location in hand-centered reference frames and in mixed eye-hand frames.

Head-centered Coordinates. In the monkey →ventral intraparietal area (→area VIP), the somatosensory system represents tactile receptive fields (RFs) in →head-centered coordinates, while →visual receptive fields are represented in distributions between head- and eye-centered coordinates (Avillac et al. 2005).

Eye- and Head-centered Coordinates. In monkey posterior parietal cortex (PPC), reaching to auditory targets is encoded in eye-, head- and mixed coordinates (Andersen and Cui 2009).

Body-centered Coordinates. Reaching with an invisible hand reshapes the end-point error distribution, suggesting that there is a →shoulder-centered or body-centered →frame of reference. Shoulder-centered frames are also used for reaching to kinesthetically perceived targets (Battaglia-Mayer et al. 2003).

Mixed Coordinates. Some neurons in monkey posterior parietal cortex (PPC), including PPR neurons, encode target position relative to the eye *and* hand Similarly, some PMd neurons encode reach goals in combined eye-centered and limb-centered coordinates or in unidentifiable coordinate frames. Neurons in PMd encode the relative position of eye, hand and target, which may provide an advantage for eye-hand coordination. Such neurons with mixed coordinates possibly play a role in the transformation between the different reference frames (Andersen and Cui 2009; Battaglia-Mayer 2019; Batista et al. 2007; Buneo and Andersen 2006; Chang and Snyder 2010).

Temporal Evolution of Reference Frames. In parietal area 5d, neurons code the hand position relative to the gaze before presentation of the reach target, and then relative to the target after its appearance (Bremner and Andersen 2014).

Allocentric Frame of Reference. When targets are embedded in a geometrically structured space, visual context influences pointing errors. It has therefore been suggested that target position could be defined in an →egocentric frame of reference or an →allocentric (object-centered) frame, depending on the context of the visual background, available sensory information, task constraints and cognitive context (Battaglia-Mayer et al. 2003). However, the existence of allocentric reference frames independent of egocentric frames has been disputed (Filimon 2015).

24.4.4 Coordinate Transformations

Since the CNS uses different reference frames depending on context and task, the required →coordinate transformations depend on the same circumstances. In general, they involve different posterior parietal cortex (PPC) and motor areas in partially specialized ways (Andersen and Buneo 2002; Battaglia-Mayer et al. 2003; Crawford et al. 2011; Medendorp et al. 2008). It is important to note, though, that coordinate transformations are also performed by →sub-cortical structures, including the cerebellum and the spinal cord (Windhorst 2007).

24.4.5 Timing of Movements

Movements must be planned in space and time. While the spatial aspects have been well studied, the temporal dimension is less well-understood despite its critcal importance, particularly in skilled movements such as goal-directed reaching, grasping, manipulation, tool use, music playing and speech. Timing goes beyond organizing the correct order of sequential elements of movements. It involves precise timing of these elements relative to an external or internal reference point, e.g., a stimulus or joint state. Several kinematic and dynamic variables are important for timing, such as the variability of the spatial trajectory in time, the interval between an external stimulus and the maximum position, velocity or force of a movement as well as between movements produced using the same or different effectors (Kornysheva 2016).

The neural substrates of timing in the CNS are still being elucidated and discussed, exactly because there apparently is no single universal clock but a number of distributed structures and mechanisms involved in timing (Kornysheva 2016). Among the structures are the cerebellum (Ashe and Bushara 2014; Breska and Ivry 2016; Yamaguchi and Sakurai 2014), the basal ganglia and the premotor cortex (Merchant et al. 2014, 2015), which might use different mechanisms but also interact with each other (Petter et al. 2016).

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25

Defensive and Reaching Movements

CONTENTS

Abstract

• This chapter describes how arm and hand movements are organized to regulate defensive and reaching movements, and calls attention to the neural circuitry they employ.

• The fronto-parietal cortex, brainstem and spinal cord play essential roles in defensive hand and arm movements.

• Defensive movements in primates against threats intruding into peri-personal space and moving towards the body engage a fronto-parietal cortical network composed of an extended ventral intraparietal area (VIP) and the dorsal part of premotor area F4.

• Aiming, pointing and reaching movements of the hands and arms during defensive movements utilize a variety of kinetic and kinematic tracking rules and strategies.

• In humans during the planning phase of reaches or grasps, many fronto-parietal areas are active for contralateral as well as ipsilateral actions.

25.1 Introduction

Hand and arm movements are very versatile and complex and for their instantiation involve, in addition to the peripheral executive instruments, wide regions of the →central nervous system (CNS): the →fronto-→parietal cortex, →brainstem and →spinal cord. Beyond that, the →cerebral cortex not only contributes to prepare, plan and execute movements, but even to their observation or imagination which excites virtually the same sensory-motor cortical network which supports the execution of that same action (Savaki and Raos 2019).

This chapter describes how arm and hand movements are organized to regulate defensive and reaching movements, and calls attention to the neural circuitry they employ.

25.2 Neuronal Networks and Organization

The major cerebro-cortical motor output targeting brainstem and spinal cord structures leaves the →motor cortex in front of the principal sulcus. While the →primary motor cortex (area M1, area F1) has classically been conceived as being organized in a →somatotopic manner, more recent studies have shown that activation of different parts of the motor cortex evoke different meaningful patterns, thus exhibiting a map of complex behavioral actions. Such action maps have been described in species from rodents to →primates (Graziano 2016). Similar regions exist in the rostral →posterior parietal cortex (PPC) of primates (Kaas et al. 2013). The underlying neural mechanisms have not yet been elucidated completely, but their →topographic differentiation suggests specialized organizations for different behaviors.

25.2.1 Fronto-parietal System for Defensive Movements

Defensive movements in primates against threats intruding into peri-personal space and moving towards the body engage a fronto-parietal cortical network distinct from those involved in other arm/hand movements. This neural system is composed of an extended parietal →area VIP and the dorsal part of →premotor →area F4.

25.2.1.1 Effects of Cortical Micro-stimulation and Lesions on Defensive Movements

Premotor Cortex. Even in the anesthetized monkey, electrical intracortical →micro-stimulation (ICMS) evokes movements typically used to defend the body against objects that are near, approaching or touching the skin. It evokes mainly contralateral movements, including blinks, squints, lifting the upper lip in a facial grimace, shrugging of the shoulder, turning aside the head, blocking arm movements, and defense-related centering eye movements (Graziano 2006; Graziano et al. 2002). Activity in the motor cortex elicits not only excitatory effects on →motoneurons resulting in movements, but also complex inhibitory effects that are often hidden from view and easily overlooked (Ebbesen and Brecht 2017). Damage to area F4 in monkeys and damage in humans produce reaching

deficits and →hemispatial neglect in peri-personal space (Brozzoli et al. 2014; Rizzolatti et al. 2014).

Parietal Areas. Micro-stimulation of area VIP evokes complex movements, including eye closure, grimacing, head withdrawal, elevation of the shoulder, and hand movements to the space beside the head or shoulder. In macaques, defensive movements engage area VIP, area PEip (intraparietal sector of area PE), →secondary somatosensory cortex (S2, SII) and premotor area F4 (Graziano 2006; Graziano and Cooke 2006). In various primates, micro-stimulation of distinct regions in the rostral PPC, which are connected to specific motor and premotor areas, evokes aggressive hand-to-body, hand-to-mouth and other movements (Kaas et al. 2013).

25.2.1.2 Neuronal Discharge Patterns during Defensive Movements

Area F4. Frontal area F4 in monkeys contains neurons that discharge during defensive movements, e.g., in response to an air puff to the cheek (Cooke and Graziano 2004; Graziano and Cooke 2006). Defensive movements can be elicited by several sensory modalities, and this zone therefore contains a high proportion of →multi-modal neurons that respond to tactile, visual and auditory stimuli. The tactile receptive fields are on the contralateral face, shoulder, arm or torso. Many neurons also respond to visual stimuli, with the →receptive fields (RFs) adjacent to the corresponding tactile receptive fields. That is, →visual receptive fields are anchored to a particular body part and move with it, indicating a body-part-centered →frame of reference (Brozzoli et al. 2014; Fogassi et al. 1996). Neurons with tactile receptive fields on the side or back of the head often repond to nearby acoustic stimuli. Visual responses are often selective for object motion toward the tactile receptive fields. Some neurons fire with simple movements, others during movements directed towards the mouth, the body or toward particular space locations (Graziano 2006).

Area VIP is also a polysensory area that integrates tactile, vestibular, auditory and visual signals in →head-centered coordinates, and appears to be involved in the →perception of self-motion and object movements in peri-personal space. Neurons in monkey area VIP and area PEip have visual and tactile response properties. Tactile receptive fields are mostly located on the face and arm, and visual receptive fields are confined to peri-personal space near the tactile receptive fields (Graziano and Cooke 2006). In humans, a similar →multi-sensory area is located in the anterior →intraparietal sulcus (IPS) (Kastner et al. 2017).

25.3 Rules in Reaching

Aiming, pointing and reaching movements of the hands and arms have been studied in detail in the laboratory under restricted conditions, including those that have importance in defensive maneuvers. They have revealed →invariants, i.e., tracking rules and strategies for movement control that implicate a variety of control schemes in humans and non-human terrestrial vertebrates.

25.3.1 Kinematics

Kinematics, by definition the branch of mechanics that deals with motion without reference to the →masses or forces involved in it, include straight trajectories, curvatures and bell-shaped velocity profiles when pointing, aiming and reaching.

Straight Trajectories. Many planar reaching movements follow a fairly straight path with only slight curvature. For example, when subjects are asked to move an object (e.g., a cursor on a screen coupled to a computer mouse), the movement path is straight, which has been interpreted as evidence that the central nervous system´s (CNS) plans reaches in external space (→kinematic trajectory planning in task space) (D´Avella 2009; Gielen 2009).

Curvatures. When subjects are asked to make point-to-point movements in darkness, the end-point trajectories are curved, which has been interpreted as →kinematic trajectory planning in joint-angle space (Gielen 2009). Trajectories are also more curved during movements in the vertical plane and during unconstrained 3D movements (Flash et al. 2009). It has been argued that the amount of curvature depends on the degree of constraint imposed on a movement. Whereas curved movements occur persistently with unconstrained movements, straight paths are associated with `compliant´ motions, i.e., motions constrained in a plane by external contact etc. These differences have been taken to indicate that constrained and unconstrained movements are planned differently (Desmurget et al. 1998).

Bell-shaped Velocity Profiles. Another kinematic regularity shows up in single-joint movements from one angle to another. Such movements exhibit roughly symmetrical, bell-shaped velocity profiles, suggesting smooth trajectories. However, when speed is coupled with high precision demands, the primary movements may be imprecise and must be amended by small corrective movements that lead to multi-peaked velocity profiles.

Single-joint rules cannot be generalized to multi-joint movements because the latter involve additional rules for inter-joint coordination (Gottlieb et al. 1996). For example, if the wrist is taken as the arm end-point, its position is determined by shoulder and elbow joint angles, whose →degrees of freedom (DOFs) exceed those of 3D space, providing for →redundancy that the CNS must resolve by selecting one among the infinite possible trajectories (D´Avella2009; Flash et al. 2009). Nonetheless, bell-shaped velocity profiles are seen also in 3D hand movements.

End-point Errors. In planar target-directed reaching movements, the end-point errors are distributed in ellipses, whose long axes are in the direction of movement. This `extent variability´ increases with movement amplitude, but with a different relation than the variability perpendicular to it (i.e., direction variability´), suggesting that the direction and extent of a reaching movement are controlled independently (Gordon et al. 1994).

Trade-offs. Everyday experience demonstrates that fast movements are usually less accurate than slow ones. This general relationship, which has many stipulations, is known as the speed-accuracy trade-off or Fitts´ law (Bogacz et al. 2010; Gawthrop et al. 2007; Guigon et al. 2008; Plamondon and Alimi 1997). Several hypotheses have been advanced to explain this relationship, based on the notion that the initial movement part is a fast impulse-like primary sub-movement covering distance, followed by corrective sub-movements (homing phase) based on sensory feedback that takes more time (Elliott et al. 2010).

25.3.2 Kinetics

The study of forces that cause motion (for example →torque, →gravity, friction, etc.) can be classified into two groups; Linear and angular motion. With respect to reaching, a rule referred to as 'linear synergy' has been proposed for two-joint human reaching tasks involving the shoulder and elbow joints. It states that the dynamic, non-gravitational components of →muscle torques at the elbow and the shoulder are similarly shaped, biphasic, nearly synchronous and symmetrical across wide ranges of speeds, loads and directions. The dynamic components, i.e., the torque pulses, are related almost linearly to each other. The relative scaling changes smoothly and regularly with changing movement direction. Such relationships, since they are found in infants, may be inborn. Kinematic regularities are thought to emerge from these dynamic rules through the mechanics of the peripheral musculo-skeletal system (Gottlieb et al. 1996, 1997; Zaal et al. 1999). According to this view, the CNS arranges such movements in kinetic terms (→kinetic planning in joint-torque space), thereby reducing →redundant degrees of freedom (DOFs) (D´Avella 2009; Gottlieb et al. 1996, 1997). The →skeletal muscle activations underlying reaching movements may be constructed by combining a small number of time-varying muscle synergies which depend on direction and speed and are organized at spinal and cortical levels (D´Avella and Lacquaniti 2013).

Impact of Gravity. In planning and executing reaching movements, the CNS has to deal with the ever-present force of gravity. It has been proposed that, for this purpose, the CNS contains an →internal model of gravity, which is assumed to be encoded in the vestibular cortex (La Scaleia et al. 2019). This model could be used to predict and compensate for gravitational effects on reaching trajectories, which might simplify motor planning by enabling invariant trajectories. Alternatively, the internal model of gravity could be used to predict its mechanical effects, so that motor planning could exploit gravity as an assistive force to accelerate downward movements and as a resistive force to decelerate upward movements; this would help →optimize the effort needed to move. This strategy would be visible in direction-sensitive kinematics. When human subjects are asked to perform arm movements in different directions under 1G (gravity on the earth surface) and 0G (zero gravity during parabolic flight) conditions, kinematic differences between the conditions gradually diminish during repeated exposure to the zero-G phase, supporting the effort-optimization hypothesis (Gaveau et al. 2016).

25.3.3 Fronto-parietal System for Reaching

Reaching and pointing movements can be made independently of grasping an object, but in most cases, reaching aims at grasping and manipulating objects (reach-to-grasp movements: →prehension).

Reach-to-grasp movements are more complex than pure reaching movements and may recruit more brain regions. In monkeys, visually guided prehension activates a very extensive and densely interconnected network of →cortical areas including and covering almost the entire →parietal cortex (Evangeliou et al. 2009). Similarly widespread activations can be seen in humans (Grafton 2010; Vingerhoets 2014).

A model developed for the monkey proposes that reaching and grasping are broadly organized in two interconnected parallel functional pathways, a dorso-medial and a dorso-lateral pathway (Battaglia-Mayer and Caminiti 2019; Galletti and Fattori 2017; Maranesi et al. 2014; Murata et al. 2016; Turella and Lingnau 2014), which may have different evolutionary origins (Karl and Wishaw 2013).

The dorso-medial network is predominantly concerned with reaching and includes areas in the →superior parietal lobule (SPL) and frontal →area F2, the caudal portion of dorso-lateral premotor area (PMd); it has been proposed to consist of two parts, a `dorsal reaching system´ and a `lateral reaching system´ (Battaglia-Mayer and Caminiti 2019).

The `lateral grasping system´ encoding purposeful hand actions is formed by parietal →area PFG as entry point, area AIP in the →inferior parietal lobule (IPL), and the secondary somatosensory cortex (S2, SII), as well as by premotor →area F5, ventro-caudal →prefrontal area 46, and part of area 12. It can be recruited by inputs from area F6 (Battaglia-Mayer and Caminiti 2019).

The `dorsal reaching system´ organizes fast reaching and its online control and also incorporates a grasping-related component. It receives essential proprioceptive signals about hand position from anterior parietal →primary somatosensory cortex (S1) and area PE and visual information about target location from →area V6A and →area 7m. The →coordinate transformation from retinal to limb coordinates underlying fast reaching appears to occur in area PEc, area PEa, area MIP, which is, in part, co-extensive with the so-called →parietal reach region (PRR). Outputs go to area F2 and, less strongly, to →supplementary motor cortex (SMA; area F3), rostral cingulate motor area (CMAr) and ventral cingulate motor area (CMAv), which all project to the primary motor cortex (M1) (Battaglia-Mayer and Caminiti 2019).

The `lateral reaching system´ forms a complementary sidepath with the parieto-occipital area Opt as the entry point and →area PG and its projection to the arm-dominant domain of the `dorsal reaching system´. This sidepath has been proposed to be recruited in eye and hand movements involved in object construction, tool use, and interception of moving targets, which need input signals conveyed by the →visual motion-sensitive middle temporal area (→area MT) and middle superior temporal area (→area MST) (Battaglia-Mayer and Caminiti 2019).

These pathways are not independent because, for example, area AIP and area V6A are connected reciprocally (Galletti and Fattori 2017). In addition, probably to ensure close cooperation between grasping and eye movements, the dorso-medial pathway has connections with area AIP (with a prime role in grasping), area PG, area LIP, area VIP, and visual motion-sensitive area MST (Grafton 2010).

Brain imaging, →electroencephalography (EEG) and →electrocorticographic (EcoG) recordings in humans show that arm and hand movements activate bilateral sensory-motor, parietal and premotor areas (Bundy and Leuthardt 2019; Chettouf et al. 2020). Activation is stronger for contralateral movements, thus exposing a degree of hemispheric specialization (Vesia and Crawford 2012). Parietal reach-related regions include the superior parieto-

occipital cortex (SPOC), →gyrus angularis and mid-posterior intraparietal sulcus (mIPS) (Vesia and Crawford 2012), as well as regions in the more rostral superior parietal lobule (SPL) and →precuneus (Kastner et al. 2017; Vingerhoets 2014). The pure transport component of right-hand reaching particularly activates left SPOC and the left rostral SPL (Cavina-Pratesi et al. 2010). There may be several functions of motor activity in ipsilateral cortex: inter-hemispheric inhibition and facilitation to maintain the balance of excitation and inhibition between the hemispheres, contribution to the planning and execution of voluntary movements, bilateral planning of movements with contralateral execution, maintenance of an →efference copy of the state of the ipsilateral limb to facilitate the coordination of bimanual movements, and driving proximal muscle activity for maintenance of posture (Bundy and Leuthardt 2019; Chettouf et al. 2020).

25.3.4 Effects of Cortical Lesions on Reaching Movements

Area V6A. Lesions in area V6A of macaques results in errors in reaching toward a visual object in the peripheral →visual field, as well as defective grasping and properly orienting the wrist and opening the fingers to scale them to object size. Similar deficits (→optic ataxia) occur in human patients with lesions of the superior parietal lobule (SPL) (Andersen et al. 2014; Galletti and Fattori 2017; Turella and Lingnau 2014).

Premotor Cortex. Unilateral lesions in monkey premotor areas posterior to the arcuate sulcus (area F4 and area F5) lead to contralateral visual and somatosensory neglect in peri-personal space and deficient use of the contralateral hand (Brozzoli et al. 2014; Cléry et al. 2015). In humans, lesions of area PMd result in persistent, mild to moderate, contralateral weakness of shoulder and hip muscles and a disturbance of movements requiring temporal coordination of bilateral proximal muscle groups. However, hand and finger function is preserved (Freund 1987). Complex →skilled movement sequences may fragment into their individual components. There may also be a loss of smoothness and characteristic speed of movement, rendering them clumsy and awkward (Luria 1963).

25.3.5 Reaching-related Neuronal Activity

Neuronal activity correlated with various variables of reaching movements are widespread over many cerebro-cortical and →sub-cortical structures.

25.3.5.1 Reaching-related Neuronal Activity in the Cerebral Cortex

Reaching movements require determination of initial hand and target positions, from which a →motor error can be computed. These positions can be derived from proprioceptive signals, visual signals, →allocentric cues, gaze-direction, eye vergence. The different signals influence reaching-related neural activity within several fronto-parietal areas that are concerned with hand/arm movements (Battaglia-Mayer 2019; Battaglia-Mayer and Caminiti 2019; Chen and Crawford 2020).

Furthermore, various action-related variables need to be specified. Representational models of cerebro-cortical neuronal activity have postulated that motor variables, such as the direction, endpoint, spatial trajectory, velocity and output forces, are coded and represented in single-cell activity in various brain regions, using specific reference frames and kinematic-to-kinetic transformations (Ebner et al. 2009; Kalaska 2019; Shenoy et al. 2013). For various reasons, however, these models are not satisfactory in explaining the complexity of neural activity during the planning and execution of movements. New perspectives and methods are being developed to reveal hidden patterns in multi-neuron ensemble rather than single-neuron activity (Kalaska 2019).

Area V6A. As a core region of the dorso-medial pathway, area V6A contains neurons modulated by reach direction and amplitude, but there are also neurons that encode wrist orientation and grip formation, as well as the shape and →affordance of graspable objects. Area V6A thus appears to encode object properties for the purpose of action during reach-to-grasp movements (Fattori et al. 2017).

Some neurons in area V6A are modulated by gaze direction in 3D space and eye vergence, thereby contributing to the coding of peri-personal space (Cléry et al. 2015). But there are also `real-position´ cells (also in area VIP and in premotor cortex), whose visual receptive fields do not move with gaze and thus encode the real spatial loci of graspable objects. Furthermore, many area V6A neurons are responsive to the direction and speed of moving stimuli and may thus be involved in organizing reaches for and grasps of moving objects as well as avoidance of obstacles during self-motion (Galletti and Fattori 2017).

Area 5. Discharge patterns of neurons in →area 5 are complex. During target reaching, discharge of many neurons is monotonically related to the initial hand position or target location or to a combination of the two (Lacquaniti et al. 1995). Many cells encode target locations simultaneously in →eye-centered and limb-centered coordinates, and populations of them encode the direction of shoulder movements without being strongly related to force, thus coding primarily kinematic variables, in distinction to primary motor cortex (Andersen and Buneo 2002; Kalaska 2009).

Area MIP neurons mostly encode the direction of movement rather than the location of visual stimuli, are influenced by somatosensory stimuli and reaching, and may also be engaged in detection and correction of movement errors (Andersen and Buneo 2002; Buneo and Andersen 2006; Galletti and Fattori 2017).

Some discharge properties recorded from the PPC suggest that it contains a →forward internal model for online trajectory control and error correction. Such a model would require an efference copy of →motor commands and an internal model of the effector dynamics, the requisite information being available to the PPC. Because the PPC projects to →cerebellum via the →pons, it is possible that the two areas comprise a functional loop responsible for monitoring and updating the internal state of the limb for online control (Mulliken et al. 2008).

Area PMd neurons provide information about the target and the body part used to execute the reaching movement (Hoshi and Tanji 2004). Many cells are tuned to the direction, distance and speed of movement, and are influenced by arm position (Batista et al. 2007). When monkeys perform visually guided, delayed reaching movements, neuronal activities in Pmd

and →ventro-lateral premotor cortex (PMv) change differentially. During the delay between a cue and the planning phase, a population of area PMd neurons initially show kinematics-related activity that also, increasingly, reflects movement dynamics. Area PMd also contains neurons with grasp-related activity, supporting the notion that the dorso-medial pathway is involved in organizing reach and grasp movements (Fattori et al. 2012; Turella and Lingnau 2014).

Primary Motor Cortex. Among all supraspinal motor systems, the primary motor cortex (area F1, area M1) is most strongly coupled to spinal motor output, particularly in primates. Analysis of discharge properties suggests that area F1 is involved in several reaching-related tasks: spatial target location, hand position, arm posture, movement direction, distance and speed, tangential velocity and →acceleration, reaching accuracy, joint motion or joint torque, load and muscle activation and force output.

Discharge properties of area F1 neurons can change with behavior, context and task (Fetz 1992; Ebner et al. 2009; Kalaska 2009; Reimer and Hatsopoulos 2009; Scott 2008). Some cells fire maximally in the direction of hand movements with sinusoidal tuning functions (Georgopoulos et al. 1982). Others discharge more in relation to motion of external targets or fire when no movements are being made, for example in →motor imagery when a subject imagines performance of an action or while observing others move. The temporal response profiles vary widely among neurons (Churchland and Shenoy 2007). Many area F1 cells whose discharge patterns show complex relations to movement variables, or are unmodulated during movement, contribute to muscle activations (Cheney et al. 1991; Fetz 1992; Kalaska 2009). Other area F1 discharges may reflect internal workings of the network that are not directly related to movement (Schieber 2011; Shenoy et al. 2013). Area F1 neurons may also be involved in representing somatosensory and visual stimuli, action selection, →working memory, →decision making, and `mirror neuron´-like representations of actions (Ebbesen and Brecht 2017). In summary, there is no simple relation of area F1 neuron discharge patterns with →biomechanical movement or other variables. It has therefore been suggested that the brain does not preprogram and directly specify a desired motor outcome, but can control the motor actions only indirectly by changing neurophysiological variables, such as activation →thresholds (Feldman 2019). In fact, on the way to the spinal cord, cortico-fugal signals underlie many influences, including sensory signals from the biomechanical periphery, reaching the cortex as well as the spinal motoneurons.

In mice trained to perform food-pellet retrieval tasks with a forelimb, sub-groups of →cortico-spinal neurons (CSNs) in somatosensory and motor cortex are activated in specific loci and in precise temporal sequences. CSNs from the caudal or rostral forelimb area control reaching or grasping, respectively, and both are active in the transitional pronation step. Ablation of rostral CSNs produces defects in grasping/pronation while not affecting reaching and retrieval steps. By contrast, ablation of caudal CSNs entails deficits in goal-directed reaching but not grasping. Through parallel descending projections, these CSNs preferentially connect with specific spinal premotor →interneurons and recruit specific extensor vs. flexor and distal vs. proximal muscle groups responsible for specific movement steps (Wang et al. 2017).

25.3.5.2 Reaching-related Neuronal Activity in the Basal Ganglia

Rapid target-oriented movements under constraints of time and accuracy are often characterized by late irregular multi-peaked velocity profiles. For example, in response to perturbations of the visual target, the primary movement is, initially, relatively unchanged, while the movement´s total extent is altered by changes in the number and extent of discrete corrections in motor activity. Related neuron discharges in primary motor cortex (area F1) and →globus pallidus internus (GPi) are modulated appropriately. For example, when a monkey turns a rotating handle to move a cursor horizontally on a screen that exhibits position and velocity required to reach the target, neuron discharges in area F1 precede the primary and corrective movements, suggesting that the neurons produce motor commands for both types of movement. By contrast, the GPi neuron projecting to the primary motor cortex area F1 (area M1) reduces its discharge rate before the primary movement and the two small motor corrections. The reduction might reflect disinhibition of the →thalamo-cortical system involved in organizing the movements (Houk et al. 2007). Brain imaging in humans performing goal-oriented arm movements also indicates that the →basal ganglia are involved in contextual, feedback-driven decisions that determine corrective sub-movements (Tunik et al. 2009).

25.3.5.3 Reaching-related Neuronal Activity in the Cerebellum

Neuronal discharge patterns that accompany reach to grasp motor events have been analyzed most thoroughly in awake performing macaques. →Purkinje cells discharge →simple spikes (SS) in phase with movement and are positively correlated with one or more forearm muscle →electromyogram (EMG) activities during a sequential reaching and button-pressing task. About a quarter of the cells pause during movement and are negatively correlated with some muscle activities (Miller et al. 2002). In reach-to-grasp movements, Purkinje cell simple spike discharge is modulated independently by grasp aperture or grip force (Mason et al. 2006). In →nucleus dentatus neurons, discharges are consistently activated during self-paced movements and start firing before movement onset (Mink and Thach 1991a,b). Some studies have demonstrated that →nucleus interpositus cell firing correlates with position and force or velocity and force, but others reported no correlations with any movement variables. The inconsistencies can be accounted for by the hypothesis that interpositus neurons are engaged most strongly in coordinated whole limb movements with an emphasis on hand use, rather than in single-joint movements (van Kan et al. 1993).

25.3.5.4 Reaching-related Neuronal Activity in the Brainstem and Spinal Cord

The mutually connected cerebral cortex, basal ganglia and cerebellum send their outputs to brainstem and spinal cord via different pathways.

Superior Colliculus (SC). The SC is a multi-layered structure located on the dorsal roof of the →midbrain and is a vital station that transforms →salient auditory, visual and somatosensory stimuli into orientating movements. Sensory, association, and motor areas of the cerebral cortex provide major inputs to the SC. The superficial layers are primarily visual and project to the deeper layers, which additionally receive inputs from both

somatosensory and auditory sources, as well as from the basal ganglia and cerebellum. The deeper layers project to brainstem structures containing gaze-related →burst neurons, and to regions in the spinal cord and medullary reticular formation (MRF), which produce head turning (May 2006). Temporary localized inactivation of SC in monkeys impairs target selection in reaching movements (Song et al. 2011). Further evidence that the SC is involved in arm motor control is that arm movements can be elicited by electrical stimulation in deep SC layers (Philipp and Hoffmann 2014). The SC contains neurons, intermingled with eye-movement-related cells, whose activity is related to arm reaching. The arm-related cells may receive inputs from premotor area F5 and contribute to reach-to-grasp movements and eye-hand coordination (Borra et al. 2014).

Nucleus Ruber. In cats, rats and primates, neurons in the magno-cellular region of the nucleus ruber (red nucleus), including rubro-motoneuronal cells, increase their discharge rate during the execution of voluntary movements, in most cases before the onset of the movement; the discharge may be correlated with different parameters of the movement, such as the velocity or the temporal characteristics of the EMG activity that produces that movement. It has been suggested that the red nucleus may play a particular role during coordinated, multi-articular movements such as reaching, particularly when these movements involve the use of the hand e.g., reach-to-grasp (Lavoie and Drew 2002). In magno-cellular neurons of the macaque, which receive direct input from the nucleus interpositus, discharge bursts related to voluntary movements of the distal arm and leg have been recorded, with firing rates of a sub-population being closely correlated with movement velocity (Gibson et al. 1985a,b). They resemble the interpositus neurons in firing at high rates during reaching and grasping (van Kan et al. 1993). During free-form movements, rubral neuron discharge is correlated with the activities of a particular set of muscles, leading or lagging neuron discharge up to roughly 150-200 ms (Miller et al 1993).

Reticular Formation (RF). The RF receives strong command inputs from the motor cortex and transforms these commands into behaviorally appropriate descending signals. Individual →reticulo-spinal tract neurons distribute their terminals diffusely on both sides along the →neuraxis. In cats, a subset of forearm-related reticular neurons discharged prior to the onset of activity in the prime flexor muscles during the reach of the ipsilateral limb. In a sub-population of this subset, the initial discharge change was time-locked to the GO signal during reaches of either limb, this early discharge hypothetically contributing to the →anticipatory postural adjustments that precede movement. In some cells, the initial change in firing rate was reciprocal for reaches with the left and right limbs, although activity during the movement was non-reciprocal. It has been suggested that these activities facilitate the interlimb coordination and help generate the muscular activity patterns that provide postural support in response to voluntary movements or unpredictable perturbations.on both sides (Schepens and Drew 2006).

Pre-motoneuronal Spinal Interneurons. Monkey cervical spinal neurons exhibit discharge patterns that resemble those of supraspinal neurons, before and during voluntary hand movements. Many pre-motoneuronal interneurons show preparatory activity prior to voluntary hand movements (Cohen et al. 2010), which are associated with force and spatial tuning to force direction. Some interneurons behave as expected for reciprocal Ia inhibitory interneurons or Renshaw cells (Fetz et al. 2002). The discharge patterns of interneurons mediating →presynaptic inhibition of sensory inputs are not well known, but when these

GABAergic interneurons are genetically ablated in mice, reaching movements become severely perturbed and show marked forelimb oscillations, presumably because the gain of sensory feedback is increased (Fink et al. 2014).

25.3.6 Sensory Updates and Reaching Corrections

During homing in on the target, many fast pointing movements exhibit irregularities in the velocity profile, which have traditionally been interpreted as corrective sub-movements performed to improve the accuracy of target capture (Elliott et al. 2010). While the primary sub-movement is planned or underway, changes in target position might require correction or arrest of the initial movement. The same structures that are involved in organizing the primary movement might also organize the corrections (Archambault et al. 2015; Battaglia-Mayer et al. 2014; Gaveau et al. 2014).

Corrections of reaching movements must also occur in response to external perturbations, and depending on the body position, postural responses may also be required. For example, if while standing, external perturbations perpendular to the moving arm´s trajectory during goal-directed reaching, upper-limb motor corrections are required, but additionally lower-limb motor responses are needed to maintain whole-body →balance. Hand motion was immediately altered by the perturbation, while changes in the →center of pressure (COP) occurred after 100 ms, when lower-limb EMG responses were already present. Upper-limb EMG responses to mechanical perturbations were evoked first (50 ms), and lower-limb muscle activity occurred immediately after (60 ms). This suggests that the lower-limb responses were indirectly evoked by input from the upper limb, possibly through involvement of cerebro-cortical areas. Corrective postural adjustments were modulated by upper-limb behavioral context, e.g., target shape (Lowrey et al. 2017).

In order to come up with an accurate and fast reach control, the brain needs several types of information. The Optimal Feedback Control (OFC) hypothesis postulates that the brain estimates the state of the world and the body using a combination of sensory feedback from various modalities, as well as forward predictions about the consequences of the commanded action generated by a forward internal model. This state estimate is then used by a feedback controller to control and correct action. What is unclear as yet is how the forward prediction signals and the multi-modal feedback signals with their different delays and frames of reference are integrated into a coherent multi-modal state estimate (Oostwoud Wijdenes and Medendorp 2017). This integration must be flexible since not all sensory modalities may always be available simultaneously. Proprioceptive, visual and vestibular signals are most important.

25.3.6.1 Role of Proprioception in Reaching

The role of proprioception in reaching movements can be estimated using several methods. One is to mechanically disturb the execution of reaches by mechanical perturbations that activate proprioceptive afferents.

Mechanical perturbations of hand and arm movements are sensed by proprioceptive and cutaneous mechano-receptive signals. In humans, arm and hand muscle stretches evoke staggered reactions that are detectable by →electromyography (EMG) (Scott 2016). A very short-latency →reflex (ca. 30 ms) is mediated via spinal pathways, followed by longer-latency response components at ca. 60 ms and ca. 75 ms via supra-spinal →reticular, cerebro-cortical and possibly cerebellar pathways (Kurtzer 2015; Macefield 2009; Scott 2016).

In the human arm, short-latency reflexes contribute to postural hand control in the face of mechanical perturbations by producing sophisticated corrective responses. Thus, reflexes in the elbow muscle were tuned to correct for the hand displacement irrespective of the direction of the perturbation-induced deviation of hand position from the the target position (Weiler et al. 2019).

Many studies have indicated that longer-latency reflexes are in part mediated by transcortical routes. The monkey primary motor cortex (area F1, area M1) receives somatosensory feedback, mediated primarily through the primary somatosensory cortex (S1, SI), that gives rise to transcortical reflexes at relatively short and long latencies (Scott 2016). Cortico-spinal neurons are sensitive to proprioceptive (>60%) and cutaneous →mechano-receptive (30%) input from their field of action, which is referred to as `tight input-output coupling´. In the monkey →dorso-lateral premotor cortex (PMd), cells respond less intensively to somatosensory inputs in preparation for ensuing movements (Humphrey and Tanji 1991). →Long-latency stretch reflexes are flexible, adaptable to sensory conditions and movement goal, and may incorporate internal models of the mechanical properties of limb and environment (Pruszynski 2014; Scott 2016; Shemmell et al. 2010).

Mechanical perturbations during the execution of reaching movements evoke corrective responses. For reaches aimed at targets of different sizes, the same perturbation elicits different corrective responses, indicating that the compensatory response is task-dependent, independently of the perturbation itself. Mechanical perturbations produce two effects: a physical one by actively altering the limb's trajectory (away from the target), and a sensory one altering the central estimation of limb state. To get access to the second process, a purely sensory disturbance is required, as was often used for vestibular or visual disturbances. A possibility is to use muscle vibration or tendon vibration to alter the muscle afferent input without changing the hand´s trajectory. At the right frequency and amplitude, muscle vibration activates mainly muscle spindles in relaxed muscles and additionally Golgi tendon organs during active contractions. This activation should change the estimated, but not the actual, limb position and velocity. In humans, during vibration of the biceps brachii muscle or triceps brachii muscle, the corrective responses to the same physical perturbation were larger when reaching to the narrow compared to the wide target, in a direction-dependent way. The earliest detectable difference between these target-specific corrections was at about 100 ms, likely reflecting a task-dependent feedback control policy rather than a voluntary response (Keyser et al. 2019).

25.3.6.2 Role of Vision in Reaching

The precision of visually supported reaching and pointing at a target depends on the accuracy of →retinotopic mapping, and on the position and movement of eye and head. Precise reaching requires precise vision of the target. Reaching thus facilitates the generation of quick and accurate saccades to foveate the target, i.e., to fixate the highest resolution region of the image on the center of the retina. When a target is presented to a monkey, neurons in the rostral →superior colliculus (SC) start the required firing pause earlier in combined reach-gaze movements than in isolated gaze movements (Reyes-Puerta et al. 2011).

Hand pointing is more accurate when a target is presented in a structured visual background, emphazising the importance of allocentric cues. In patients lacking afferent sensory feedback (→de-afferentation), vision of the hand prior to movement onset improves accuracy.

Also important is good depth perception, as indicated by impaired pointing performance in monocular vision (Crawford et al. 2004; Desmurget et al. 1998, 2005).

The role of vision is also demonstrated by motor responses to sudden target jumps. When another target is suddenly presented during ongoing movement to an initial target, hand and arm movements need to be adjusted to accomplish accurate reaching. This usually occurs smoothly, implying that the movement kinematics are influenced by visual and proprioceptive feedback mechanisms (Archambault et al. 2015; Battaglia et al. 2014; Desmurget et al. 2005; Sarlegna and Mutha 2015). →Transcranial magnetic stimulation (TMS) of the left PPC in humans disrupts hand path corrections that normally occur during target jumps, but it has no effects on reaching movements to stationary targets. This indicates that the PPC computes a dynamic motor error signal from internal representations of hand location and target location, which is used to correct ongoing movements (Desmurget et al. 1999).

In target-jump experiments performed on monkeys, neurons in fronto-parietal areas are active during both direct and corrected reaches. After a target jump at the onset of the initial movement, changes in neuronal activity occur in PPC area 5, PMd area F2 and primary motor cortex (area F1, area M1). Changes in area PMd lead the others. Hence, area PMd might be involved in decisions on initial and changed motor plans, PPC appears to estimate peripheral kinematics and compute a novel trajectory, and area F1 is concerned with the fine-tuned movement implementation (Archambault et al. 2015; Battaglia et al. 2014).

Proprioceptive–visual coordination is also required when reaching for a stationary target while the body is moving. Hand kinematics must be adjusted according to the relative motion. Optic flow could play a role in this adjustment since abrupt motion of the visual background induces short-latency trajectory corrections, possibly implicating area MST (medial superior temporal) in the →extra-striate cortex (Gomi 2008).

25.3.6.3 Role of Vestibular Signals in Reaching

For the proper control of a number of voluntary movements, humans and other animals use vestibular information, as shown to occur during passive rotation during reaching, arm-reaches involving trunk movements, and →galvanic vestibular stimulation (Reichenbach et al. 2016). Relative motion between objects and body occurs during reaching while the body is moving. Vestibular information in combination with neck proprioceptive signals serves to maintain the initial hand position and planned hand trajectory unchanged during body motion. They also predict and counteract body-rotation-induced torques, i.e., centrifugal and →Coriolis torques, which are thus accurately estimated by the brain (Blouin et al. 2015). Galvanic vestibular stimulation, which produces the →illusion of a body rotation, also results in online and task-dependent movement adjustments during the hand movement. Latencies of reach corrections in response to vestibular perturbations seem to be substantially longer than corrections in response to visual and proprioceptive perturbations, i.e., about 176–240 ms. Movement corrections to visual target jumps during passive body acceleration suggests that visuo-motor feedback gains are modulated by vestibular input (Oostwoud Wijdenes and Medendorp 2017). In right-handed humans, the posterior part of the right medial intraparietal sulcus processes vestibular signals during a goal-directed reaching task. The processing of vestibular signals in the right cortex differs from the processing of visual and proprioceptive signals, which occurs predominantly in the left posterior parietal cortex (Reichenbach et al. 2016).

25.4 Interception of Moving Targets

A moving object might represent a threat when approaching a subject or a target for grasping. In order to avoid collision with a subject or target, the time remaining before potential contact needs to be estimated. Studies in humans have suggested that the brain extrapolates future object motion from instantaneous object position and velocity. For this estimation, the brain uses several sources: visual, vestibular, tactile and proprioceptive cues derived from short- and →long-term memory of object kinematics, →cognitive cues such as expectations and beliefs, familiarity with the object and an internal model combining multi-sensory information about gravitational forces acting on the object (internal model of gravity).

Visual motion extrapolation and the estimation of future trajectories depend on an extended network including areas in the posterior parietal cortex (PPC), the posterior →insula, retro-insular cortex and →temporo-parietal junction (TPJ), and the basal ganglia and cerebellum (Lacquaniti et al. 2013; Bosco et al. 2015).

In monkeys, neurons in posterior parietal cortex (PPC) and primary motor cortex (area F1, area M1) respond to the direction and velocity of stimulus motion and are modulated by the time elapsing between target motion onset and arrival at the interception point. →Area 7a is more closely bound to stimulus motion features, and area F1 to hand action, suggesting a gradual sensory-motor transformation between these areas. Some motor cortex cells show a predominant relationship to hand kinematics, and others to initial target velocity. Furthermore some cells are task-specific, being active only during target interception and not during reaching to stationary targets (Battaglia-Mayer et al. 2006; Merchant and

Georgopoulos 2006; Merchant et al. 2009). The →lateral intraparietal area (area LIP) has a high percentage of neurons maintaining activity across a visual gap, thus they probably represent inferred target motion (Bosco et al. 2015).

25.5 Bilateral Interactions between Upper Limbs

Many actions require cooperation and coordination of the upper limbs. Bimanual movements are diverse, context-dependent, highly flexible and adaptive. Some motor activities involve bilaterally symmetric actions, while others include alternating arm movements or differentiated actions of each hand. Interactions between upper limbs are subject to coordination constraints. Depending on movement complexity, they engage complex and widespread neural mechanisms (Rueda-Delgado et al. 2014; Swinnen and Wenderoth 2004; Theorin and Johansson 2007).

Rhythmic movements of two limbs are easy to perform and relatively →stable when performed in phase (iso-directional). On the other hand, anti-phase (anti-directional) movements require more →attention and may transit to in-phase movements at higher frequencies (Baldissera and Tesio 2017). Bimanual movements are also simpler to perform at simple frequency ratios (1:1 or 2:1) than at more complicated ratios (3:2 or 5:3), the latter tending to transit to simpler ratios at higher frequencies (Rueda-Delgado et al. 2014). Furthermore, there are spatial constraints placed on movements in different directions or with different amplitudes. For example, it is easier to coordinately move both limbs in the same direction or in opposite directions than in complex intermediate directions (Swinnen and Wenderoth 2004).

There is evidence showing that the difficulty of performing two movements in different directions may arise from interference of anticipatory postural adjustments that are dispatched from the cortex to insure a stable basis for voluntary movements (Baldissera and Tesio 2017).

Coordination constraints may be overcome, at least in part, by linking a bimanual task to cognitive and perceptual cues such as an auditory rhythm, and by training and →motor learning (Klaiman and Karniel 2006; Klapp and Jagacinski 2011; Oliveira and Ivry 2008; Swinnen and Wenderoth 2004).

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26

Grasping and Manipulation

CONTENTS

Abstract

• This chapter describes the basic mechanics underlying arm and hand movements in grasping and manipulation, and the neural networks that support them. An overview of motor disorders that impair grasping and manipulation is also provided.

• Grasping and manipulation of objects are more diverse and versatile in humans than in non-human primates, although macaques employ a large variety of grip types.

• Grasping of objects is usually closely coupled with reaching (reach-to-grasp movements).

• Reach-to-grasp movements consist of a hand transport phase, a superimposed grasping phase during which the hand is oriented and pre-shaped for the grasp, and a subsequent phase in which the object is transported or manipulated.

• To properly grasp and lift an object, several factors must be counterbalanced to properly adjust grip force. For example, the grip force must overcome forces of gravity and inertia, but must be slightly larger than the minimum required to prevent dropping.

• Humans can reach for and grasp objects without vision, guided by memory, although visual conditions affect memory-guided grasping.

• Reaching and grasping are thought to be organized in two parallel functional pathways of the fronto-parietal cerebral cortex; a dorso-medial pahway and a dorso-lateral pathway.

• Cells in the ponto-medullary reticular formation of macaques discharge during fine finger movements associated with object manipulation.

• Cervical proprio-spinal neurons have been identified in humans, monkeys and cats, which contribute to precision grasping with thumb and index finger.

26.1 Introduction

Human beings are exceptionally adept in the ability to reach, grasp and interact with objects in the environment. Arm and hand movements concerned with grasping and manipulation of objects are present at birth and proficiently skilful by the age of four years (O´Shea and Redmond 2021).

Grasping is widespread among tetrapods (Sustaita et al. 2013). There are many different ways of grasping, manipulating and holding an object. For example →primates use different effectors such as torso, arm, hand, fingers, foot and mouth under natural circumstances (Macfarlane and Graziano 2009). Grasping and manipulation of objects are more diverse and versatile in humans than in non-human primates (Lewis 2006), although macaques also employ a large variety of grip types (Macfarlane and Graziano 2009).

The processes involved in object handling are immensely complex. To organize accurate and dexterous manipulation, the →central nervous system (CNS) must take into account an object's intrinsic properties (e.g., size, shape, texture, hardness), biomechanical characteristics of the hand, fingertips and skin and of joint kinematics, as well as interaction dynamics (forces, pressure, torsion) (O´Shea and Redmond 2021). All major senses, including vision, proprioception, audition, taste and olfaction, contribute to the →multi-sensory characterization of objects and play roles in organizing grasping and manipulation (Betti et al. 2021).

Successful grasping and manipulation of objects require anticipatory planning and predictive cognitive-motor processes that anticipate action outcomes and take into account *motor goals* and object properties, as well as reactive sensory-motor processes that provide important error-based information for movement adaptation (O´Shea and Redmond 2021; Schneider and Hermsdörfer 2016). Sensory-motor →memory of an object or similar ones is of considerable importance. Even fine movements involving small →masses (e.g., finger flexion) are accompanied by →anticipatory postural adjustments usually confined to the arm (Cavallari et al. 2016). Accordingly, the organization of grasping and manipulation involves many diverse neural structures.

26.2 Organization of Grasping

Evolution of the complex human hand, consisting of 27 bones and 18 extrinsic and 18 intrinsic →skeletal muscles, allows for a large number of mechanical →degrees of freedom (DOFs) which enable flexibility and dexterity (Santello et al. 2013). The fingers and thumb possess 25 DOFs (O´Shea and Redmond 2021), due to the constraints by connective-tissue interactions between adjacent fingers, the presence of multi-tendon, multi-digit muscles acting on several fingers and their patterns of neural innervation, so that even during the most sophisticated behaviors, different fingers do not move completely independently of each other (Latash and Zatsiorsky 2009; Santello et al. 2013; Schieber 2009; van Duinen and Gandevia 2011; Weiss and Flanders 2004)

26.2.1 Kinematics

In a common view, reach-to-grasp movements consist of a hand transport phase, a superimposed phase during which the hand is oriented by the wrist and pre-shaped for the grasp, and a subsequent phase in which the object is grasped, manipulated or transported. The three phases require different sensory information and computational processes and are associated with different muscle synergies (Gerbella et al. 2017). The kinematics and timing of reach-to-grasp movements depend on the size and location of objects, but in different ways in humans and macaques (Castiello and Dadda 2019).

Although hand transport and grip aperture have originally been considered convenient variables to describe reach-to-grasp movements, this view has recently been contested on account of various findings. For example, object size →illusions have no or little effect on grip aperture and the variability in grip aperture is independent of object size. Furthermore, various variables of the wrist movement depend on object size and many variables describing grip formation depend on object distance. Thus, the components underlying reach-to-grasp movements are not independent of each other, and so are the organizing neural structures (below). Alternatively, grip formation may be described as emerging from the movements of the digits in space (Smeets et al. 2019).

An object can be grasped in many different ways, depending on the object´s visual and other properties, its meaning and the goal of the grasp, which require selection of appropriate grasp sites and grip forces (Castiello and Begliomini 2008; Gerbella et al. 2017; Grafton and de C Hamilton 2007; Schneider and Hermsdörfer 2016; Smeets et al. 2019). Humans and monkeys use specific hand shapes for individual objects (Castiello 2005; Santello et al. 1998). For any particular object there will be a set of learned grip prototypes, from which an appropriate one can be selected (Castiello and Begliomini 2008; Grafton and de C Hamilton 2007). The fingertips approach the contact points more or less perpendicularly to the surface, which reduces the risk of slip and increases grip stability. As in pointing movements, grip accuracy is inversely related to movement speed, thus conforming to the speed-accuracy trade-off, but for multiple effectors (Smeets et al. 2009, 2019). The accuracy of finger placement depends on the object´s weight and friction, with the required accuracy being highest for heavy and slippery objects (Soechting and Flanders 2008).

In a →precision grip, the thumb and finger move relatively independently of each other during the transport phase, such that grasping appears equivalent to simultaneous pointing with two digits (Smeets et al. 2009). In a →power grip, the fingers and sometimes the palm clamp down on an object with the thumb making counter pressure. While adopting specific hand shapes to different tasks, including precision and power grips, the joint angles of the digits do not vary independently; they show relationships that suggest several basic →synergies (Latash and Zatsiorsky 2009; Santello et al. 1998).

In humans, kinematic synergies (correlations between joint angles during multi-joint movements) have been reported to occur in the configuration of the entire hand during reach-and-grasp movements, the spatio-temporal coordination between thumb and index finger movements as well as in the coordination of tip-to-tip finger movements (Grinyagin et al. 2005). Final postural hand configurations corresponding to various grasp types are

encoded as kinematic synergies in several → (Leo et al. 2016). In non-human primates, premotor →interneurons in the cervical →spinal cord may be involved in organizing the spatio-temporal patterns of hand muscle synergies during a voluntary precision grip task (Takei et al. 2017).

26.2.2 Kinetics

In a study of the kinematics and kinetics of index finger and thumb movements, humans performed opening and/or closing (tip-to-tip) movements of two amplitudes (grip apertures) and two velocities. The joint torques calculated by modelling scaled linearly with different grip apertures. Especially with the lower aperture and during slow movements, some of the thumb joints moved only marginally implying that torques between joints were redistributed. With increasing movement velocity, the synchronization among the joint torques increased (Grinyagin et al. 2005).

In grasping and lifting an object, forces exerted at contact points are adjusted so that the object is not crushed or dropped. This means that several factors must be counterbalanced to properly adjust grip force, such as weight and load, frictional resistance, →torques, and →inertial forces and locomotion (Schneider and Hermsdörfer 2016; Zatsiorsky et al. 2005). To lift and hold an object, the grip force must overcome forces of inertial →gravity and inertia, which is only slightly larger than the minimum needed to prevent slip.

26.2.3 Object Stabilization

Several conditions are required to ensure stable grasping. For example, in a precision grip, the thumb and index finger need to be placed in positions on the object surface so that the line connecting the finger contacts is perpendicular to the surface on both sides, and projects above or through the object´s center of gravity. In addition, grip forces applied by the differentdigits involved in grasping must be coordinated to maintain the object´s rotational equilibrium (Soechting and Flanders 2008).

The →motor command that organizes stability appears to be separate from the command that controls the magnitude of grip force necessary to prevent slippage (Zatsiorsky et al. 2004). In five-digit grip tasks, grip forces exerted by pairs of digits tend to be synchronized. One underlying mechanism could be the tendency of →motor units in different muscles to discharge synchronously (Santello and Fuglevand 2004).

26.2.4 Anticipatory Grip Adjustments

When the properties of an object to be grasped are not sufficiently known before contact, they must be predicted. The initial predictions may be based on an →internal model of the object derived from vision and memory of previous experiences with the same or similar objects. In the construction of this model, the →parietal cortex and →cerebellum may play

an important role (Grafton 2010; Nowak et al. 2007, 2013; Schneider and Hermsdörfer 2016).

If a first attempt at lifting an object fails due to an under-estimation of its weight, grip force will be appropriately adjusted in the next attempt. However, explicit knowledge does not always help. When a glass of water is lifted, set down and half emptied with a straw and lifted again, grip force is not reduced despite the knowledge of the reduced weight. By contrast, when two previously experienced objects are stacked, human subjects appropriately scale their grip force at the first lift. Explicit knowledge of the individual weights apparently allows them to build a new internal object model from the previous individual ones (Davidson and Wolpert 2005; Schneider and Hermsdörfer 2016). Unconscious anticipatory grip force adjustments occur when a grasped object is transported through space, during which the cerebellum plays a role in the predictive control of grasping (Nowak et al. 2007).

26.2.5 Visually Guided and Memory-guided Grasping

Although vision plays an important role in guiding motor actions such as grasping (O´Shea and Redmond 2021), humans can reach for and grasp objects without vision, guided by previous experience, i.e. by memory. Nonetheless, visual conditions do influence memory-guided grasping kinematics. For example, an object appears relatively smaller when placed aside a larger object than aside a smaller object, and the question arises as to whether this `size-contrast illusion´ influences memory-guided grasp kinematics as assessed by peak grip aperture, i.e., the separation between thumb and index finger. When an object is visible until the onset of movement, the illusion has no effect on grasp aperture. When vision is occluded well before movement onset, peak grip aperture is larger. Essentially the same results are achieved when the movement is delayed after visualizing the object. Direct vision until movement onset apparently triggers a response that differs when object information has to be retrieved from memory (Goodale 2014; Milner and Goodale 2008). Upon reach completion, →haptics based on tactile and kinesthetic inputs play an important role in object manipulation and exploration (Stone and Gonzalez 2015).

26.2.6 Fronto-parietal System for Visually Guided Grasping

In most cases, reaching aims at grasping and manipulating objects (reach-to-grasp actions). In macaques, *reaching-to-grasp* movements are organized by a dorso-medial network running through the →superior parietal lobule (SPL) including →area V6A and some areas in the →intraparietal sulcus (IPS), the dorsal →premotor cortex including →area F2 (caudal portion of dorso-lateral premotor area (PMd) plus ventral premotor →area F4 (Borra et al. 2017). The *`dorsal reaching system´* organizes fast reaching and its online control and also incorporates a grasping-related component. The *`lateral reaching system´* forms a complementary sidepath (Battaglia-Mayer and Caminiti 2019).

The *`lateral grasping system´* is a large-scale network of →cortical areas (Borra et al. 2017). It is formed by parietal →area PFG as entry point, area AIP in the →inferior parietal lobule (IPL), and the →secondary somatosensory cortex (S2, SII), as well as by premotor →area

F5, ventro-caudal →prefrontal area 46, and part of area 12. It can be recruited by inputs from area F6. Embedded in this network is the mirror neuron system, which uses area PFG as an intermediate node for information transfer from superior temporal areas to area F5 (Battaglia-Mayer and Caminiti 2019). While different sub-regions of the →posterior parietal cortex (PPC) show a degree of preferential functional specialization for eye, arm and hand movements, they are anatomically connected and contain mixtures of neurons firing in association with all these movements, which is required because these movements are interdependent (Hadjidimitrakis et al. 2019).

Area AIP, area PFG and area F5 are conceived of as extracting →affordances for hand-object interactions by transforming the visual representation of objects into potential movement representations (Binkofski and Buccino 2018; Borra et al. 2017; Castiello and Begliomini 2008; Gerbella et al. 2017; Janssen and Scherberger 2015). They are also involved in defining action goals and selecting possible actions. Area AIP receives the required visual information about the size, shape, orientation and motion of objects indirectly from primary visual cortex (area V1). Area AIP receives more elaborate visual information about object identity from →inferior temporal cortex (area TEa and area TEm), from →prefrontal cortical (PFC) area 12 about object identity and and rules for action selection. The secondary somatosensory cortex (S2, SII) contributes properties encoded in visual →working memory, and from area 46 about higher-order goals information on hand actions (proprioceptive) and on tactile object properties. The granular frontal opercular (GrFO) area integrates →limbic information and possibly assigns →emotional and subjective value to stimuli and actions. A similar role may be played by a sector in the dysgranular →insula (area Id), which could signal internal states of the body.

Area F5d (dorsal area F5) is the output station of the *lateral grasping network*. It carries →somatotopic movement representations of the hand and mouth and connects with the →reticular formation, the hand field of →primary motor cortex (area F1, area M1) and the cervical spinal cord (Borra et al. 2017).

Area F2vr may also be involved in reaching and grasping, mostly in wrist rotation, and sends projections to the primary motor cortex (area F1, area M1), →brainstem and spinal cord. Another area involved in both reaching and grasping is area V6A, especially its dorsal part (Fattori et al. 2017; Gerbella ert al. 2017). may also be involved in reaching and grasping, mostly in wrist rotation, and sends projections to the primary motor cortex (area F1, area M1), →brainstem and spinal cord. Another area involved in both reaching and grasping is area V6A, especially its dorsal part (Fattori et al. 2017; Gerbella et al. 2017).

26.2.6.1 Grasp-related Neuronal Discharge Patterns

Area V6A and Area PMd regions of the dorso-medial reach-to-grasp pathway exhibit neuron discharges related to reach direction and amplitude, wrist orientation and grip preshaping in monkeys.

Area V6A contains populations of cells showing grasp-related activity modulated by wrist orientation or grip type and encoding the visual properties and shape of graspable objects and

affordances (Fattori et al. 2017). Area V6A receives inputs from the motion-sensitive visual area V6 and contains visual neurons with →receptive fields (RFs) in the contralateral visual field and, less numerously, somatosensory neurons responding to upper arm movements. Besides, many cells respond to reaching, gaze changes and saccades (Borra et al. 2017; Galletti and Fattori 2017). It has been proposed that area V6A serves as a comparator of the desired and current hand positions and configurations, such that the resulting error signal updates the motor output and corrects reach direction, hand orientation or grip aperture (Fattori et al. 2017).

Area F2 in caudal PMd contains grasp-related neurons that encode object features, location and motion relative to the peri-personal space and extra-personal space. Most neurons respond to specific orientations of visual stimuli and corresponding wrist movements, and are selective for grasp type (Maranesi et al. 2014; Raos et al. 2004). Homologous areas in humans are also active during grasp planning and are sensitive to object angle and motion (Borra et al. 2017; Grafton 2010; Maranesi et al. 2014). In both PMd and →ventro-lateral premotor cortex (PMv), intermixed neurons are specific for either reach direction or grasp type, thus supporting reach and grasp integration. →Area F7, the rostral part of PMd, contains neurons exhibiting discharges related to eye movements and arm movements and coding positions in space of targets for reaching.

Area AIP, Area PFG and Area F5 in the dorso-lateral grasping network of the macaque contribute to selecting and organizing object-oriented hand actions based on object properties and goals of grasping.

Area PFG has been suggested to be involved in the definition of action goals and in the fine control of grasping and manipulation. Many area PFG neurons respond differentially to specific action goals, e.g., grasp-to-eat or grasp-to-place. These neurons show activity related to hand, mouth or hand-and-mouth movements, and respond to visual and somatosensory stimuli in peri-personal space. Area PFG is connected to the superior temporal polysensory (STP) area that integrates signals from auditory, somatosensory and visual areas. Many cells also show mirror neuron activity (Borra et al. 2017; Gerbella et al. 2017). In addition to grasp-related activity, neurons in area AIP, area PFG and area F5 encodes object size, 3D shape and orientation, as well as reaching and gaze information (Borra et al. 2017; Janssen and Scherberger 2015; Turella and Lingnau 2014).

Discharge properties recorded from macaque area AIP provide convincing evidence that *visual-dominant cells* and *visual-and-motor cells* represent 3D shape, size and orientation of objects for manipulation, whereas motor-dominant cells are predominantly active during grasping and holding in dark and light. Certain types of visual-and-motor neurons (*mirror neurons*) are active when the monkey grasps an object or observes an object to be grasped (Borra et al. 2017; Murata et al. 2000, 2016; Sakata et al. 2009; Castiello and Begliomini 2008).

When there are several possibilities of grasping an object, neural activity in area AIP reflects these options (Cisek and Kalaska 2010). Representation of 3D object features in area AIP is transferred to premotor areas F2 and F5 (Castiello and Begliomini 2008).

Area F5 transmits somatotopic movement representation of the hand and mouth. It receives projections from the posterior parietal cortex (PPC), ventro-lateral prefrontal cortex (VLPFC), and connects to the reticular formation and the hand field of primary motor cortex (area F1, area M1) and to the cervical spinal cord. It contains neurons encoding specific hand, mouth and hand-and-mouth movements. Grasp-related neurons show discharge properties reflecting grip type, as well as the final goal or →intention of the action such as eating or placing an object, this information probably coming from the →prefrontal cortex (Bonini et al. 2012; Borra et al. 2017; Gerbella et al. 2017). Area F5 contains different types of neurons with response properties similar to those in area AIP, but with a stronger prevalence for motor representation (Borra et al. 2017; Raos et al. 2006).

Visuo-motor (canonical) cells in area F5 respond to 3D objects of different size, shape and orientation even when no action is required, and thus build a realistic object representation that →optimizes grasping. Visuo-motor neurons have been proposed to automatically translate visual object features into a potential motor action. Area F5 cells are active during grasping, holding, tearing, or manipulating. Most `grasping neurons´ encode specific types of hand configuration, such as precision grip, whole hand →prehension, finger prehension, and fire during movement.

Some cells code either objects or observed actions (Borra et al. 2017; Giese and Rizzolatti 2015; Raos et al. 2006; Rizzolatti et al. 2014).

Visual-dominant cells in area AIP have been proposed to establish the first step in the transformation of object properties into motor representations by area F5 visuo-motor neurons (Gerbella et al. 2017).

Mirror neurons in macaque area F5 are active during performance of an action or when the monkey observes the action or a similar one. Some cells also discharge when a monkey observes his own hand action (Kurata 2018).

Other cells (*audio-visual mirror neurons*) respond to characteristic action-related →sounds. Thus, neurons in PMv discharge both when the monkey performs a specific action and when it hears or sees the same action performed by another individual (Keysers et al. 2003). Mirror neurons are also found in area AIP and other parietal areas (Borra et al. 2017; Janssen and Scherberger 2015).

A mirror-neuron system has also been suggested, based on brain imaging studies, to exist in humans. One presumed location is in →Broca´s region, where mouth, hand and foot movements are somatotopically represented, and in →area PMv. Dysfunction of the mirror neuron system has been implicated in autism (Aziz-Zadeh and Ivry 2009; Hauser and Wood 2010; Iacoboni 2009; Iriki 2006; Rizzolatti et al. 2014).

Area 12 and area 46 in prefrontal cortex (PFC) of macaques are sources of cortico-cortical and cortico-tectal projections. These areas project to area AIP and area PFG, suggesting that the PFC sends information about grasp goals to the parietal areas and thereby selects between different affordances constructed in these areas based on visual and other information (Gerbella et al. 2017). Projections from area 12 and area 46 to the →superior colliculus (SC) and mesencephalic reticular formation could represent a descending motor pathway for

controlling proximo-distal arm synergies and conveying information related to hand action goals, object identity and selection, and information from memory related to behavioral goals and rules (Borra et al. 2014).

Primary Motor Cortex (Area F1, Area M1). The hand field of area F1 receives projections from several premotor and somatosensory parietal areas and, in higher primates, controls dexterous hand movements via partly monosynaptic connections to →skeleto-motoneurons, i.e., →cortico-motoneuronal connections (Borra et al. 2017; Isa 2019; Lemon 2008). Besides, in humans, cortico-motoneuronal cells also connect to skeleto-motoneurons innervating arm, back and leg muscles and are active in uncomplicated locomotion and even hopping (Nielsen 2016). Cortico-motoneuronal cells projecting to hand muscles are active during →skilled hand and digit movements, and a precision grip but not a power grip (Lemon 2008, 2019; Muir and Lemon 1983). Discharge activity of neurons in macaque area F1 during a precision grip is linearly correlated with muscle activity measured by →electromyography (EMG) of the hand and forearm muscles and by kinematic variables (Townsend et al. 2006; Grafton 2010).

Secondary Somatosensory Cortex (S2, SII) in macaques contributes sensory information about objects to grasp. It contains cells that respond to visual stimuli, somatosensory stimuli which represent physical object properties such as texture, slippiness, weight etc, and to active hand and mouth movements (Gerbella et al. 2017).

Reticular Formation (RF). Cells in the →ponto-medullary RF of macaques discharge during fine finger movements. In a study involving two monkeys, index finger flexion-extension to track a visual target on a computer screen resulted in discharge activity in the ipsilateral RF. The ponto-medullary RF may thus contribute to hand control via the →reticulo-spinal tract, previously thought to mainly mediate gross movements such as postural adjustments and locomotion (Brownstone and Chopek 2018; Soteropoulos et al. 2012).

Proprio-spinal C3-C4 Neurons. Rodents and carnivores have no direct cortico-motoneuronal connections which could contribute to dexterous paw movements. In cats, proprio-spinal neurons at cervical levels C3-C4 contribute to reaching, whereas spinal interneurons with a broader rostro-caudal distribution are involved in grasping. In higher non-human primates (e.g., macaques), various lesions at different sites from →motor cortex to spinal cord suggest that proprio-spinal C3-C4 neurons are involved in the control of reach and precision grip. The C3-C4 neurons project to forelimb →motoneurons at level C6-Th1 and receive motor commands from cortico-, rubro-, reticulo- and →tecto-spinal tracts (→cortico-bulbo-spinal system) (Isa 2019). They also receive positive and →negative feedback from forelimb sensory afferents. Negative feedback appears significant in target reaching, since elimination renders the movement →hypermetric, i.e., movement that exceeds the intended goal (Alstermark et al. 1986). Proprio-spinal C3-C4 neurons also project to the cerebellum via the →lateral reticular nucleus (LRN). This signal pathway may provide an →efference copy that updates the cortical command network during reaching, because genetic elimination or optogenetic activation of →V2a interneurons in the pathway in mice disrupts reaching movement kinematics (Alstermark and Isa 2012; Azim and Alstermark 2015). Proprio-spinal C3-C4 neurons may be partly responsible for the recovery

of precision grip after lesions of direct cortico-motoneuronal projections in the lateral →cortico-spinal tract (CST) (Isa 2019; Nishimura and Isa 2012). A more extensive and diverse efferent-copy system is found in the mouse cervical and rostral thoracic spinal cord, where premotor interneurons projecting to forelimb motoneurons send collaterals to the ipsilateral LRN and to most →cranial motor nuclei both ipsi- and contralaterally, as well as to the external cuneate nucleus (ECN) (Pivetta et al. 2014).

A cervical proprio-spinal system in humans has also been demonstrated in humans, evidenced by responses elicited in upper limb motoneurons by →transcranial magnetic stimulation (TMS) over the motor cortex. Forelimb responses to graded TMS suggest the involvement of a network of inhibitory spinal premotor interneurons, distinct from segmental interneurons and located rostral to spinal motoneurons (Pierrot-Deseilligny 1996; Pierrot-Deseilligny and Marchand-Pauvert 2002).

26.2.6.2 Grasp-related Cortical Regions Revealed by Functional Imaging

→Functional magnetic resonance imaging (FMRI) in humans as well as in behaving monkeys has revealed a number of cortical regions involved in object manipulation, grasping and reaching (Schneider and Hermsdörfer 2016), some of which are briefly described here. They illustrate certain aspects of grasping, reaching and learning of related motor skills that occur in defined cortical regions.

For example, the transport component of a reaching movement activates the superior parieto-occipital cortex (SPOC) and rostral superior parietal lobule (SPL), while the grip component activates the anterior intraparietal sulcus and the left PMv as well as somatosensory areas. Integration of the two components into a reach-to-grasp movement activates the PMd and →supplementary motor area (SMA), indicating that they play important roles in coordinating reach-to-grasp movements (Cavina-Pratesi et al. 2010).

In humans, Area aIPS, the putative human equivalent of monkey area AIP (area hAIP) (Borra et al. 2017; Kastner et al. 2017) is activated more strongly during object grasping and tool use than during reaching, irrespective of hand trajectory. Significant activation of aIPS occurs during precision but not whole-hand grips, irrespective of object size. It is also activated by tactile manipulation of objects and while observing hand movements made by other subjects (Borra et al. 2017; Castiello and Begliomini 2008). An area in the caudal intraparietal sulcus (cIPS) is thought to be involved in finger and hand manipulation of objects. More superior and medial SPL areas appear necessary for grasping adjustments (Vingerhoets 2014).

The most likely human homologue of monkey area F5 is →Brodmann´s area 44, the caudal part of Broca´s region (Binkofski and Buccino 2006; Fadiga and Craighero 2006; Vingerhoets 2014). Activation of area 44 occurs during preparation and execution of complex finger/hand movements and manipulation of complex objects, as well as during observation of hand and finger movements, imaging hand actions, mental hand rotation, observing and naming tools and →learning novel visuo-motor associations and motor sequences (Binkofski and Buccino 2006).

Activation of primary motor cortex (area F1, area M1) during reach-to-grasp tasks appears to be modulated by the degree of congruence between grasp type and object size. A similar pattern is found in PMd (Castiello and Begliomini 2008).

26.2.6.3 Effects of Cortical Lesions on Grasping Movements

Lesions of the two action-related fronto-parietal pathways produce dissociable deficits. In monkeys, area V6A lesion produces misreaching and deficits in wrist orientation and grasping movements (Borra et al. 2017). In humans, lesions of the dorso-medial pathway coursing through the SPL evoke →optic ataxia; a lack of muscle control or coordination of voluntary movements, while lesions of the (left) dorso-lateral pathway coursing through the inferior parietal lobule (IPL) cause →apraxia; difficulty with programming the motor movements, especially in the use of familiar tools (Binkofski and Buxbaum 2013).

Transient inactivation of area AIP or area F5 in monkeys produces deficits or failure of visually guided hand shaping that precedes object grasping (Borra et al. 2017). In humans, transcranial magnetic stimulation (TMS) of area aIPS (area hAIP) disrupts adjustments of hand preshaping when object orientation suddenly changes and impairs reactive on-line adjustment of grip force, and TMS over PMv interferes with the predictive scaling of precision grip force (Borra et al. 2017; Culham and Valyear 2006; Dafotakis et al. 2008).

Lesions of primary motor cortex (area F1, area M1) or its descending output result in contralateral weakness, which may or may not be associated with →spasticity. After recovery from the initial →paresis, fractionated finger movements remain impaired or impossible. Along with the disrupture of alternating finger movements, there is deterioration of manual skill (Halsband and Freund 1990). →Voluntary movements of an individual finger elicit unintentional movements of others, but synergistic movements in a power grip remain intact. The cortico-spinal tract (CST), containing direct cortico-motobneuronal fibers, is thus crucially involved in organizing individuated finger movements (Castiello and Begliomini 2008; Isa 2019; Schieber et al. 2009). It must be emphasized that CST lesions affect a number of descending pathways and induce compensatory effects in other pathways (Lemon 2008).

26.2.7 Sensory Updates and Corrections in Grasping

Anterior intraparietal sulcus (aIPS) in humans is involved in dynamic goal-dependent updating of reach-to-grasp movements. In particular, area aIPS is thought to perform rapid comparisons between sensory inputs and current motor commands, to provide error signals that downstream structures can use for corrective actions (Tunik et al. 2005).

26.2.7.1 Differential Effects of Vision on Grasping

Hand-shaping during a reach-to-grasp movement is not altered when vision is occluded during the reach. Thus, continuous visual feedback of the hand and or object is not needed for proper hand pre-shaping. Memory suffices, although the presence or absence of vision

before movement onset influences grasp kinematics (Winges et al. 2003).

If reach-to-grasp movements are perturbed after movement start due to changes in target location or size or shape, they are corrected at short latency, in ways depending on the precise nature of the visual perturbation. The gain of the changes in the digits' movements towards their planned contact points depends on the reliability of the visual information about the individual digits (Smeets et al. 2019).

In precise grip-force control, the frequency of visual feedback is important for processing visuo-motor information in the parietal cortex, premotor cortex and cerebellum. Human brain imaging studies have shown that frequent (25 Hz) visual feedback activates the lateral cerebellum, whereas the anterior intermediate cerebellum is active throughout. The parietal and premotor cortices are active during frequent visual feedback. The premotor cortices are activated by infrequent feedback as well, although with differences between hemispheric sides. This suggests that different brain regions are differentially involved in visuo-motor processing, depending on the frequency of intermittent visual feedback (Vaillancourt et al. 2006).

26.2.7.2 Effects of Tactile Feedback on Grasping

Tactile information is useful for two functions: corrections and updating of internal models. If the initial estimates of object properties prove wrong, they can be rapidly updated by sensory feedback, which initiates learned corrective responses and updates the internal representation of object properties in memory (Flanagan et al. 2006; Nowak et al. 2013; O ´Shea and Redmond 2021).

Corrections can be notably fast. As early as 34 ms after contact of the object during a precision grip, EMG activity →reflexly increases in a number of intrinsic and extrinsic hand muscles, probably via both spinal and supraspinal pathways. Feedback from small regions of the fingertip influences not only prehensile muscles, but also from muscles of the whole arm which provides stabilization (Collins et al. 1999). Small frictional slips, probably signaled by rapidly adapting type-I (RAI) afferents, trigger phase-dependent corrective actions leading to an update of the grip force-to-load force ratios (Johansson and Flanagan 2009).

Elimination of tactile sensory feedback, by anesthesia or due to →peripheral neuropathy or lesions of the finger area of cortical area S1, disrupts grip force control with no evidence of adaptation. People with impaired finger sensibility show clumsiness in gripping and holding objects, often dropping them or crushing them if they are fragile, and in loss of sensitively while manipulating them. The deficit is compensated for by substantial increases in dynamic and static grip forces (Witney et al. 2004). Such increases also occur in patients suffering from →stroke, →amyotrophic lateral sclerosis (ALS), cerebellar disorders, →basal ganglia disorders, and →writer´s cramp, probably as a default strategy after loss of precise control (Johansson and Flanagan 2009). Chronically →de-afferented subjects are also unable to predictively adjust their grip forces adequately to the prevailing circumstances (Nowak et al. 2013). The inferior parietal cortex appears to play an important role in detecting mismatches between predicted and actual object weight (Johansson and Flanagan 2009). A hemispheric asymmetry is suggested by various lines of evidence indicating that the right hemisphere

(for the left hand) tends to dominate in touch-related guidance for reaching and grasping, while the left hemisphere (for the right hand) is superior in visually guided reaching and grasping (Stone and Gonzalez 2015).

26.2.8 Tool Use

Many animals use simple objects to extend their physical capabilities (Johnson-Frey 2004). Even birds use sticks to search for worms or pebbles to open nuts or shells. Non-human primates raised in a laboratory can learn to use tools in ways never seen in the wild. (Macellino et al. 2012), but only humans have established a culture that is built on the fabrication and use of complicated tools (Maravita and Romano 2018). This requires two basic faculties: abstract, conceptual knowledge of the relation between tool and function, and motor skills for manipulating tools (Buxbaum 2017; Imamizu and Kawato 2012; Reynaud et al. 2016).

Skilled use of tools changes the body schema, expands the peri-personal space and activates distributed brain structures with a strong left-hemispheric lateralization (Lewis 2006; Imamizu and Kawato 2012; Kastner et al. 2017; Maravita and Romano 2018; Martel et al. 2106; Reynaud et al. 2016; Vingerhoets 2014). The left inferior parietal cortex is thought to be important for understanding tool use (Maravita and Romano 2018; Reynaud et al. 2016). Hand-with-tool movements differentially activate areas in parietal and occipito-parietal regions that appear specifically tool- or hand-related or related to the action. The left anterior supra-marginal gyrus (aSMG) is devoted to tool use in humans but not in non-human primates, and to imitation learning. Its damage results in →ideomotor apraxia (Borra et al. 2017). While the human area AIP (area hAIP) is activated by the tool being grasped, the left aSMG is activated by observing a tool being moved to achieve a goal (Orban and Caruana 2014). Some areas in the intraparietal sulcus (IPS) and premotor cortex (area PMd and area PMv) may be concerned with the movement goal (Gallivan et al. 2013). Cerebellar activation tends to be distributed predominantly in the anterior cerebellar lobe, the precise loci being dependent on the types of tool used and the activities evoked by peripheral sensory feedback. On the other hand, when subjects imagine using tools without actually doing so, activation tends to be located more laterally in the posterior lobe (Imamizu and Kawato 2012).

26.3 Organization of Manipulative Movements

Pure manipulation is often performed by many animal species to explore and recognize objects (Errante et al. 2021).

When macaques spontaneously manipulate small objects, most of the time is spent with an object in front of the chest or the mouth. After reaching to grasp an object, it is almost immediately brought in front of the chest or mouth for further manipulation. The hand is usually in a grip posture near the mouth or in various complex postures in central space, involving the forearm and wrist, independent of the fingers. These prototypical responses have been replicated by electrical microstimulation of different zones of the motor cortex with a prescribed sequence, which caused monkeys to perform a repertoire of movements that occur during spontaneous grasping and manipulation (Graziano et al.

2002).

Manipulation and fine-tuning of arm, hand and finger movements engage the primary motor cortex (area F1, area M1), possibly aided by →area VIP and area F4 (Johnson-Frey 2003). Primary motor cortex is particularly well suited for controlling manipulation. It receives strong projections from the post-central somatosensory areas (S1 and PE) and has a high proportion of neurons with small tactile receptive fields on the fingers that are responsive to passive and active finger movements. A large proportion of giant Betz pyramidal cells are involved, well as cells with monosynaptic connections to motoneurons innervating finger, hand and wrist muscles (Graziano et al. 2002). In addition, the primary motor cortex polysynaptically modulates proximal muscles to provide postural support and flexibility for basic motor patterns (Kurtzer et al. 2005).

Functions of monkey area F1 and area M1 are supported by the dorsal cingulate motor area (CMAd), which corresponds to the caudal cingulate zone (CCZ) in humans (Picard and Strick 2001). The CCZ is activated during simple motor tasks, such as finger movements and other manual tasks (Romanelli et al. 2005).

Lateral premotor and supplementary motor areas are also activated during fractionated finger movements in humans, but more strongly during shoulder movements, indicating a coordinated action of diverse systems involved in voluntary movements (Colebatch et al. 1991). In addition to various cerebro-cortical areas, and in close interaction with them, the basal ganglia and cerebellum contribute to object manipulation (Errante et al. 2021).

26.4 Bimanual Interactions

Natural two-handed manipulation of objects consists of a complex and coordinated blend of symmetric and asymmetric movement elements (Swinnen 2002). Often, one hand assumes the role of the prime actor, while the other takes over a supportive, postural role. It has been suggested that there is a division of labor between networks in the two cerebral hemispheres during the performance of bimanual tasks. The dominant hemisphere is thought to control movement trajectories and dynamics performed with the dominant hand, while the non-dominant hemisphere stabilizes the object against loads by controlling the position of the non-dominant hand (Sainburg 2005).

Cerebro-cortical motor areas interact via inter-hemispheric connections through the →corpus callosum. Damage to the corpus callosum, in particular the posterior portion, can lead to loss of forceful inter-hemispheric inhibition and to disinhibition of common excitatory inputs to both motor cortices. Nonetheless, →split-brain patients are able to perform bilaterally asymmetric movements in an essentially independent way (Oliveira and Ivry 2008).

Brain imaging in humans has shown that when two hands are engaged in independent tasks, the premotor (SMA, cingulate and lateral premotor areas), parietal cortex and cerebellum are activated more strongly and extensively than during one-handed tasks. Bimanual object-manipulation activates a dorsal fronto-parietal network biased to the left side and bilateral occipito-temporal cortex. Activation of medial premotor areas depends on the choice of left or

right hand rather than on grip type, i.e., unimanual or bimanual. Monkey primary motor cortex (area F1, area M1) contains neurons that are tuned for ipsilateral, contralateral or bilateral arm movements (Theorin and Johansson 2007).

In humans, during the planning phase of reaches or grasps, many fronto-parietal areas are active for contralateral actions, but several areas in PPC, premotor cortex, dorso-lateral prefrontal cortex (DLPFC), →pre-supplementary motor area (pre-SMA, area F6) and primary motor cortex also encode ipsilateral actions (Gallivan et al. 2013). Moreover, there are many crossed influences at the segmental spinal level. Spinal reflex pathways on one side are modulated by movements of the other side by a number of mechanisms, including →presynaptic inhibition and reciprocal Ia inhibition (Carson 2005). Such cross-influences are flexible and can be plastically moulded by training and →motor learning (Swinnen and Wenderoth 2004).

26.5 Eye-Hand Coordination

Many hand actions that are controlled visually require coordinated eye movements (Battaglia-Mayer 2018). In many cases, eye and hand movements mutually influence each other (Pelisson and Prablanc 2009; Soechting 2009). For instance, when a subject rapidly points to an extra-foveal stationary target, central movement commands are sent simultaneously to eye, head and arm/trunk muscles. However, the eyes move before the head and the head moves before the arm and trunk. The foveal signal, eye-movement signals and an efference copy result in an update of hand movement (Battaglia-Mayer and Carminiti 2009; Battaglia-Mayer et al. 2003; Pélisson and Prablanc 2009; Soechting 2009). During target tracking, gaze is intermittently fixated at task-relevant points in a coordinated sequence. Since gaze and hand movements appear to be driven by common signals, they influence each other´s motions Thus, when gaze deviates from its normal sequence, reaching for and manipulating objects are degraded. These findings support the notion that at least some of the neural substrates underlying target tracking are shared by the two systems (Battaglia-Mayer et al. 2003; Crawford et al. 2004; Engel and Soechting 2003; Pelisson and Prablanc 2009).

Eye-hand coordination is organized, depending on motor task, by flexible distributed neural networks involving areas in the frontal and parietal cortices and →sub-cortical structures. This distributed system consists of populations of cells that encode eye and/or hand position signals and embedded eye and/or hand movement-related domains, with different degrees of eye or hand dominance. Eye-dominant domains predominate caudally in posterior parietal cortex (PPC) and rostrally in frontal areas, and smoothly transgress into hand-dominant domains rostrally in PCC and caudally in frontal areas (Battaglia-Mayer 2018). →Area F4d and →area F5p cooperate in controlling forelimb and eye movements, most efficiently in the execution and completion of coordinated eye-hand movements for reaching and grasping under visual guidance (Kurata 2018). In monkeys trained to perform movements with the hand, eye or both together towards visuomotor targets, neurons showing activity during coordinated hand and eye movements occurred most frequently in PMv between the →frontal eye field (FEF) and primary motor cortex (area F1, area M1) (Kurata 2017).

Projections from the the hand-eye cortical network to intermediate and deep layers of the ipsilateral superior colliculus (SC) control →micro-saccades and downward gaze shifts. The SC contains arm-movement-related neurons and cells modulated by hand contact with the target. These projections are hypothesized to convey information about possibilities for grasping actions and hand-action goals to the SC. The SC uses the information to control gaze and reaching movements, organize eye-hand coordination, and to contribute to proximal-distal arm synergies (Battaglia-Mayer 2018; Borra et al. 2014; Brochier and Umiltà 2007; Caminiti et al. 2015; Castiello and Begliomini 2008; Grafton 2010; Vesia and Crawford 2012). Hand-related information is conveyed via the mesencephalic reticular formation to pre-motoneurons and motoneurons in the spinal cord (Battaglia-Mayer 2018).

26.6 Role of the Basal Ganglia in Arm and Hand Movements

Different basal ganglia nuclei have been hypothesized to have differential functions (Desmurget and Turner 2008; Desrochers et al. 2016; Turner and Desmurget 2010). For example, the more anteriorly located basal ganglia nuclei have been implicated in planning and selection of precision grip force, while more posteriorly situated nuclei might be concerned with the dynamic control of grip force amplitude and rate of force change (Prodoehl et al. 2009; Wasson et al. 2010).

26.6.1 Movement Disturbances Linked to Basal Ganglia Disorders, Lesions and Depressant Neurochemicals

The belief that the basal ganglia have important roles in motor control of arm, hand and trunk movements, including those involved with grasping and manipulation of objects, is based on the clinical history of motor-related →degenerative diseases involving the basal ganglia, such as →Parkinson´s disease, →Huntington´s disease, →dystonia, →Tourette syndrome. In monkeys, approaches to test the involvement of the basal ganglia in arm, hand and trunk movemets have been to place lesions in specific regions of the basal ganglia, or to reversibly inactivate local excitatory →synaptic transmission with depressant neurochemicals.

Chemical inactivation of the middle-posterior →putamen in monkeys disrupts well-learned sequences of movements, whereas inactivation of the anterior →caudate nucleus and putamen impairs learning of novel sequential movements (Tanji 2001). Inactivation of the →globus pallidus internus (GPi) region by →muscimol, a $GABA_A$ receptor →agonist, impairs visually guided out-and-in reaching movements to different targets, as evidenced by decreased peak velocity and →acceleration and by →hypometric and →bradykinesic outward reaching. Focal lesions of the posterior motor basal ganglia also produce bradykinesia, hypometria, and reduction in the rate of force change. The results suggest that the basal ganglia regulate motor effort and energy expenditure (Desmurget and Turner 2008; Turner and Desmurget 2010).

26.6.2 Major Movement Disorders and Grasping in Parkinson´s Disease

The basal ganglia (BG) are the most seriously affected brain areas in Parkinson's Disease (PD). The primary symptoms of PD, bradykinesia, →rigidity and →tremor, result from greatly reduced activity of →dopamine-secreting cells in the →substantia nigra pars compacta (SNc). Grasping is also impaired, evidenced by increased peak and variability of grip forces, deficits in releasing objects, and deranged temporal coupling between grip and load forces (Prodoehl et a. 2009). Parkinsonian patients also suffer from sensory impairments. In particular, processing and utilization of proprioceptive information and the integration of different types of sensory inputs to guide movement are disrupted (Conte et al. 2013; Konczak et al. 2009; Rinalduzzi et al. 2015).

Approximately fifty percent of Parkinsonian patients show a →resting tremor at 3-5 Hz and →postural tremor at 4-8 Hz, in the fingers, hands, legs, trunk, neck, lips, tongue, and eyelids. Parkinson´s disease affects not only the basal ganglia, but also other sub-cortical as well as cortical structures, particularly at later stages. The cerebellum, which is bidirectionally connected to the basal ganglia, shows abnormal and rhythmic activity (Bostan and Strick 2018).

26.6.3 Neuronal Discharges in the Basal Ganglia

Regions in globus pallidus internus (GPi) that project via the ventro-lateral →thalamus to the arm representation in area F1 (area M1) contain neurons that discharge in relation to arm movements (Middleton and Strick 2000). Few →substantia nigra pars reticularis (SNr) neurons are active in visually directed reaching and if so, mostly prior to movement onset (Desmurget and Turner 2008).

26.7 Role of the Cerebellum in Arm and Hand Movements

The cerebellar role in arm and hand movements can be divided into immediate (on-line) functions and error correction, as well as in adaptation and learning (Bloedel and Bracha 2009). It has been proposed that once a potential action is selected by cortico-basal ganglia-cortical circuits, the cerebellar on-line function amplifies and fine-tunes the selected motor pattern. The selected primary movements and corrections are amplified by positive feedback through cortico-pontine nuclei-cerebellar nuclei-cortical loops, then held in check and sculpted by inhibitory loops that incorporate→Purkinje cell actions (Houk et al. 2007).

Cerebellar lesions produce significant motor disturbances that affect arm and hand movements, such as those involved in reaching (Therrien and Bastian 2015). In cats, inactivation of the →nucleus interpositus impairs inter-segmental dynamics in the forearm during reaching. In monkeys, it causes intense →action tremor (3-5 Hz) of the arm during reaching (Thach et al. 1992). Genetic manipulation and ablation experiments in mice identified a subset of →glutamatergic neurons in the nucleus interpositus which give rise to nucleo-cortical →mossy fibers that preferentially target a specific forelimb-related region of the cerebellar cortex and primarily project to a restricted region of the motor thalamus

connected to the caudal forelimb area of the motor cortex. Ablation by diphtheria toxin and optogenetic stimulation disrupted skilled reach-to-grasp movements and locomotion by altering limb positioning, movement and timing (Low et al. 2018).

In monkeys, inactivation of the dentate nucleus produces deficits of reaching and grasping, with excessive changes of shoulder and elbow angles resulting in overshoot beyond the target, and incoordination of finger movements leading to clumsiness when manipulating small objects (Thach et al. 1992). Dentate cooling produces errors in the rate, extent and force of movement, and muscimol injections increase errors in executing learned movement sequences (Tanji 2001). In trained baboons, tracking of a visual target with hands and eyes deteriorates substantially (Vercher and Gauthier 1988).

Damage to the lateral cerebellum in humans produces symptoms that are more pronounced in the upper than the lower leg. Errors in direction and deviations from the intended course accompany reaching movements. The velocity profile is often irregular, with an →intention tremor that increases in amplitude as the intended object is approached. Human subjects with cerebellar damage are also impaired in their ability to predictively adjust grip force to changing object loads, and they tend to exert too much force (Nowak et al. 2007). In addition, reaction to load perturbation is delayed, suggesting that cerebellar transmission is impaired. (Serrien and Wiesendanger 1999). Temporary disruption of cerebellar function in healthy subjects by repeated transcranial magnetic stimulation (TMS) disturbs goal-directed arm movements, indicating that the cerebellum predicts the arm´s mechanical state during movement from a history of motor commands (Shadmehr et al. 2010). During target-tracking tasks, disturbed eye and hand movements mutually interact with each other, making things worse during coordinated eye-hand movements (van Donkelaar and Lee 1994). There are several probable sites of interaction, including the dentate nucleus (MacKay 1988), where lesioning temporally uncouples manual and oculomotor outputs (Vercher and Gauthier 1988).

Large firing rate variations are seen in mossy fibers and →climbing fibers, Purkinje cells, interpositus neurons when monkeys palpated an object or made adjustments for accuracy during precision grips (Stein and Glickstein 1992).

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27

Sensory-motor Learning

CONTENTS

Abstract

• This chapter provides an overview of types of motor learning that support hand and arm movements, and regions of the central nervous system (CNS) that enable them.

• There are two broad categories of motor learning: motor adaptation, the fast return of motor behavior to baseline after perturbations; and motor learning, practice-related performance improvement.

• Two types of hand-arm motor adaptation have been analyzed in depth and described in detail in man and non-human primates: adaptations on a relatively fast time scale to perturbations that alter the relation between visual input and motor action, and slower adaptations to the dynamics of a subject´s body and its environment.

• Multiple CNS systems are involved in hand and arm motor adaptation, skill acquisition and motor sequence learning; but any one structure may perform several functions, including learning of different motor skills.

• Prefrontal cortex, supplementary motor cortex, premotor cortex and anterior cingulate cortex make individual contributions, or in concert, to: visual-motor adaptation, to complex, temporally ordered sequences of motor acts, to changing loads and to adjustments in kinematics.

• Various lines of evidence have implicated the basal ganglia in motor-skill learning such as acquisition of serial movements associated with hand and arm movements.

• The cerebellum plays an important role in visuo-motor adaptation during hand-arm target tracking, including error correction and representation of kinematics and kinetics.

27.1 Introduction

The sheer complexity of the body and its environment and their diverse interrelations require that movements be learned, adapted or →optimized for new conditions. →Motor learning ranges from low-level calibration of movements to high-level decisions about how to act in novel situations (Krakauer et al. 2019) and requires various forms of →attention (Song 2019). The processes can be classified into two broad categories. One type, →motor adaptation, refers to the fast return of motor behavior to baseline performance level after perturbation. Examples are adaptation of the vestibulo-ocular reflex (VOR adaptation), adaptation of movements to altered visuo-motor associations; and adaptation of movements to altered dynamics. Another type, →motor-skill learning, involves practice-related and experience-dependent improvements in motor performance. Improving motor performance often entails reducing the variability of successive actions, for instance in learning to play tennis or the piano to some perfection or learning movement sequences (Dhawale et al. 2017; Diedrichsen and Kornysheva 2015; Krakauer et al. 2019; Shmuelof and Krakauer 2011).

The following description of →sensory-motor learning focusses on movements of the hands and arms. It begins with a general overview of types of motor learning that enable body-environment interactions and different types of learning. It then describes regions of the →central nervous system (CNS) that support sensory-motor learning.

27.2 Adaptation to Altered Visuo-motor Associations

Movements may be perturbed by altering the relation between visual input and motor action, for example by displacing the visual world by means of glass prisms (Fleury et al. 2019; Petitet e al. 2018) or by rotating the computer mouse-cursor relation or the latter´s gain (Krakauer et al. 2019). Under prism exposure, the subject at first incorrectly reaches in the direction of a visual target, but soon compensates for aiming errors. After removal of the prisms, aiming errors occur initially in the opposite direction, but are quickly compensated for. As a test for adaptation to visuo-motor rotations, the direction of cursor motion on a screen is changed relative to the hand that moves the cursor. Movements initially start in the wrong direction, but adapt over subsequent trials so that the aiming error declines. After removal of the rotation, opposite movement errors occur initially and then decline. After this fast re-adaptation, longer-lasting effects (`savings´) remain, such as recall, i.e., →memory of previous successful actions, and faster re-learning, i.e., greater sensitivity to errors possibly due to consolidation (Krakauer et al. 2019).

The after-effects have been interpreted as the persistence of an altered →forward internal model, whose adaptation (updating) is driven by →prediction errors between the desired and actual movement consequences (Della-Maggiore et al. 2014; Mutha et al. 2012; Popa and Ebner 2019; Popa et al. 2019; Schultz and Dickenson 2000; Yavari et al. 2013). This `implicit´ adaptation is commonly thought to be performed by the →cerebellum. This does not mean, however, that adaptation is based only on a single mechanism. Instead, there is evidence that multiple, qualitatively different processes occur during adaptation, including →cognitive strategies and processes, the relative contributions of the different processes depending on various factors (McDougle et al. 2016). Contributions may also be made by

→reinforcement learning, in which adaptation is driven by the →reward prediction error signaled by →midbrain →dopaminergic neurons (Krakauer et al. 2019; Mutha et al. 2012; Schultz 2015, 2019; but see Garr 2019). These processes probably involve the →prefrontal cortex (PFC) and →basal ganglia (Taylor and Ivry 2014).

In right-handed subjects, the left and right arms show differences in adaptation. Right arm movements tend to be straighter, smoother and →energetically more efficient, and the left arm is more accurate and precise in attaining the desired end-point, particularly in response to perturbations during the ongoing movement. This difference has been attributed to functional lateralization of the →cerebral hemispheres**,** the left hemisphere being stronger in predicting movement direction and dynamics, while the right hemisphere is better at sensory feedback-dependent position accuracy (Mutha et al. 2012).

27.3 Adaptation to Altered Dynamics

The dynamics of a subject's body and its environment change over the course of →ontogenetic development, after →muscle fatigue and injury, during movement itself, and due to changing dynamic demands imposed by various imposed loads and objects (Krakauer et al. 2019; Shadmehr 2017). For example, human subjects with →large-fiber sensory neuropathy who lack proprioceptive feedback commit reaching errors because they can no longer adapt to movement-dependent →torques resulting from inter-segmental dynamics, whereas they are able to learn spatial transformations needed for mirror drawing (Ghez and Sainburg 1995).

Coriolis Forces. Another example of adaptive sensory-motor learning is a compensatory response to the Coriolis effect, whereby a →mass moving in a rotating system experiences a force (the →coriolis force) acting perpendicular to the direction of motion and to the axis of rotation. When a subject´s trunk is rotated, centrifugal reaching and other movements generate coriolis forces. During passive rotation, Coriolis forces disrupt movement trajectory and end-point accuracy, which is compensated for within about 20 repeated trials. Initially after terminating rotation, movement paths are mirror images of the initial rotatory mis-reaches, indicating that there is a temporary persistence of a new internal representation of the body-world relationship, which subsides within a few reaches. Very large Coriolis forces during voluntary turns and while reaching for an object occur, without increasing movement errors. This indicates that feed-forward anticipatory processes compensate for the effects of self-generated coriolis forces on movement trajectory, and suggests that torso velocity is accurately predicted during natural turns (Lackner and DiZio 2005a,b). The vestibulo-ocular reflex (VOR) appears to play an important role in the control of arm movements during body movements (Blouin et al. 2015).

Changing External Loads. Suddenly added force fields that perturb the reaching movements initially cause aiming errors that decline with continuing practice (force-field adaptation). After removal of the force field, opposite errors (after-effects) occur initially and then decline. Despite successful re-adaptation, a memory trace of the adaptation process remains, as evidenced by faster learning rates with renewed adaptation. Adaptation of reaching movements to altered dynamics involves a decline in →skeletal muscle activity,

with co-activation of agonist and antagonist muscles and with decreased metabolic →power. Changes in metabolic power far outlast those in muscle activity (Huang et al. 2012).

Adaptation to new loads and re-adaptation to the old ones argue for the development of →internal models that anticipate the disturbing forces (Shadmehr 2017). The new internal models are limited to a region surrounding that part of space where the perturbation has been applied. The development of internal models involves memory consolidation, which takes at least 4-6 hours, and is not dependent on practice. The models are enhanced over time without further training. Their anatomical substrates are distributed throughout the CNS (Bizzi and Mussa-Ivaldi 1998; Krakauer and Shadmehr 2006).

Predictable and Unpredictable Loads. Adaptation to predictable changes in load differs from adaptation to unpredictable loads. When subjects are requested to make individual joint or reaching movements and are confronted with randomly changing loads, they learn to plan their actual movement on the basis of weighted averages of their performance over past experiences. The same applies to →precision grips in a series, in which object properties vary randomly. In this case, the anticipatory modulation of grip force depends on the weighted average of the object´s properties as experienced over the previous grips (Davidson and Wolpert 2003). However, when loads change systematically, reaching and grasping movements differ. Grip force is correctly adjusted to the next larger weight in a series of gradually increasing weights; by contrast, when reaching in a series of increasing force perturbations, the expectation of the next larger perturbation amplitude is based on the average amplitude within the previous few trials. Results such as these indicate that prior experience and the effect of environment variability are reasons for differences in expectation during lifting and reaching and not from extrapolation to the future (Mawase and Karniel 2012).

The strategy used by subjects also depends on perturbation predictability. When subjects are requested to reach in a predictable force field, they learn to apply the compensatory forces. Early on, arm →stiffness is high and then declines. With unpredictable loads, however, arm stiffness may be maintained by co-contraction of many muscles or may be high in the direction of the expected perturbations (Davidson and Wolpert 2003; Soechting and Flanders 2008). Little is known concerning the manner by which forward →motor commands are altered to improve motor skills while optimizing stability, accuracy, speed and efficiency. It seems likely that sensory feedback is involved (Diedrichsen and Kornysheva 2015; Franklin et al. 2008; Makino et al. 2016).

27.4 CNS Regions Involved in Sensory-motor Learning

During adaptation of reaching to new environmental conditions, the kinematics and kinetics (dynamics) of movements change. →Psychophysical studies suggest that new kinematics are learned from errors in the extent of movement and direction in an extrinsic →frame of reference. New kinematics also evolve from proprioceptive errors in the intrinsic reference frame that are independent of each other and probably require separate internal models (Krakauer et al. 1999).

Cerebro-cortical and →sub-cortical neurons that contribute to the preparation and execution of reaching movements also need to adapt. In general, many CNS systems are involved in motor control, motor adaptation, →skill aquisition and motor →sequence learning. Brain imaging and electrophysiological recordings have revealed activity changes in regions from the prefrontal cortex (PFC), via the →premotor cortex, →primary motor cortex (area F1, area M1) and →parietal cortex to the →basal ganglia and cerebellum (Desrochers et al. 2016; Diedrichsen and Kornysheva 2015; Hardwick et al. 2013; Hikosaka et al. 2002; Krakauer et al. 2019; Krakauer and Mazzoni 2011; Li et al. 2001; Lohse et al. 2014; Makino et al. 2016; Penhune and Steele 2012).

Sensory-motor learning involves →perceptual learning, which encompasses changes in the detection, discrimination or categorization of sensory stimuli, and in the response properties of individual and populations of neurons in sensory regions and networks (Makino et al. 2016; McGann 2015).

Alterations occur in the perceived position of the limb, in →visual motion perception and auditory localization. Conversely, force-field learning induces changes in somatosensory evoked potentials and in functional connectivity between →secondary somatosensory cortex (S2, SII), →supplementary motor area (SMA) and →ventro-lateral premotor cortex (PMv) (Ostry and Gribble 2016).

Many CNS structures that are involved in motor control are also concerned with motor learning. Any one structure may perform several functions, including learning of different motor skills, and these systems may use different forms of learning. For example, the →cerebral cortex, cerebellum and basal ganglia, which are reciprocally connected with each other, have been suggested to use →unsupervised learning, →supervised learning and reinforcement learning, respectively (Bostan and Strick 2018; Doya 2000; Raymond and Medina 2018), but they must cooperate (Caligiore et al. 2019).

27.4.1 Alterations in Brain Activity During Sensory-motor Learning

Many human brain imaging studies have been conducted to reveal changes in brain activity during motor learning and have come up with somewhat variable results that probably depend on different experimental paradigms and methods. In humans studied with neuroimaging, the →dorso-lateral prefrontal cortex (DLPFC) and the →pre-supplementary motor area (pre-SMA) were activated during early learning, while the →intraparietal sulcus (IPS) and the posterior-medial portion of the parietal cortex were active later during learning. Explicit learning with awareness of performance is associated with activation of the prefrontal cortex (PFC) and pre-SMA, but not the sensory-motor cortex (Hikosaka et al. 2002).

During early *visuo-motor adaptation*, improvements in performance are associated with enhanced bilateral activity in the prefrontal cortex (PFC), →frontal eye fields (FEFs) and areas of the visual →dorsal stream. At later learning stages, these improvements are associated with decreased activity in these regions**,** and activity shifts to left (contralateral) sensory-motor cortex, left →cingulate motor cortex, left →posterior parietal cortex (PPC) and anterior

cerebellum (Della-Maggiore et al. 2014).

Motor-skill learning evolves through an initial fast phase with large gains and a subsequent slow phase with smaller gains, the durations depending on the difficulty of the skill to be learned. In humans, the fast phase of learning sequential motor tasks is associated with decreasing activation in the dorso-lateral prefrontal cortex (DLPFC), primary motor cortex (M1) and pre-supplementary motor area (pre-SMA), but increasing activation in the premotor cortex, supplementary motor area (SMA), parietal regions, →striatum of the basal ganglia and the cerebellum (Dayan and Cohen 2011).

The interactions between the different brain regions during motor-skill learning are not well understood. In one model (Hikosaka et al. 2002), two loops are supposed to learn in parallel the spatial and motor features of sequences. The spatial coordinates are learnt within a circuit between fronto-parietal associative areas, the striatum and the cerebellum. The motor coordinates are learnt in a circuit between area M1, the sensory-motor striatum and the cerebellum. Transformations between the two coordinate systems depend on the SMA, pre-SMA and premotor cortices. Additionally, fast motor skill learning requires heightened attention which is reflected in increased functional connectivity between the DLPFC and premotor cortex (Dayan and Cohen 2011).

Progress in motor-skill learning from the early fast to the late slow phases and throughout the latter reflects an increase in automaticity and is associated with increasing activation in area M1, →primary somatosensory cortex (S1, SI), SMA and →putamen, as well as decreasing activation in the cerebellum, as well as with a shift in →functional magnetic resonance imaging (fMRI) activation from associative to sensory-motor striatum (Dayan and Cohen 2011).

27.4.2 Cerebral Cortex

Attempts at elucidating the role of cerebral cortex in motor adaptation have as yet not come up with a clear and coherent picture (Krakauer et al. 2019). In particular, the hypothesis that the cerebral cortex uses an unsupervised learning scheme and thus does not need an error signal to drive plasticity is still debated.

27.4.2.1 Parietal Cortex

Brain imaging in humans showed that execution errors committed during visuo-motor and force-field perturbations co-activated regions in anterior parietal cortex and in the cerebellum, making these areas possible sites of plastic changes in internal models for reaching. By contrast, target errors resulting from sudden target displacements during reaching activated the posterior →superior parietal lobule (SPL) and the →striatum of the basal ganglia (Diedrichsen et al. 2005).

Primary Somatosensory Cortex (S1, SI). In a mouse model, photo-inhibition of primary somatosensory cortex (S1) was applied to study forelimb adaptation to force-field perturbations. The inhibition of S1 abolished the ability to update subsequent motor

commands needed to reduce →motor errors (Mathis et al. 2017).

Posterior Parietal Cortex (PPC). Focal stroke in the left PPC disrupts adaptation (Mutha et al. 2012). →Transcranial magnetic stimulation (TMS) disrupting the PPC during adaptation to a →viscous force field has no effect on the early phase of adaptation but keeps errors high in the late phase (Della-Maggiore et al. 2004). PPC activation is increased during the late rather than the initial phase of adaptation to visuo-motor rotation as shown by →positron emission tomography (PET). Increased PPC activation during adaptation to a force-field occurred late, after the initial learning period (Krakauer et al. 2019).

27.4.2.2 Premotor Cortex

In humans who were pointing at visual targets and adapting to *prism goggles*, transient inactivation of the human dorso-lateral premotor area (PMd) by transcranial magnetic stimulation (TMS) reduced the rate of adaptation and the shift in perceived arm position, but only if there was continuous vision of the arm throughout the movement, suggesting that area PMd contributes to the generation of visually based on-line error corrections (Lee and van Donkelaar 2006).

In monkeys, prism adaptation is impaired by inactivation of the ventral part of the premotor cortex (→area PMv) but not the dorsal part (area PMd) (Kurata and Hoshi 1999). In response to various kinds of visuo-motor alterations, neurons in the monkey caudal area PMd changed the magnitude of activity modulation, about half of the cells showing increases and the other decreases. The same scenario was revealed in →SMA neurons (Wise et al. 1998). Similarly, each individual neuron in the premotor cortex and area F1 showed an increased discharge in its →preferred direction and a decreased rate in the opposite direction so that the average ensemble activity did not change (Inoue et al. 2016).

While learning the new kinematics in response to visuo-motor rotations, changes in firing characteristics appear earlier in monkey SMA than in primary motor cortex (area F1, area M1). Neuronal changes in SMA are correlated with the early rapid phase of learning, while changes in area F1 appear later during the phase of slower learning (Lalazar and Vaadia 2008).

In monkeys adapting to an external perturbing *force field*, neurons in SMA shift their preferred direction in the direction of the external force during adaptation to the force field and back in the opposite direction during re-adaptation to the non-perturbed state, which suggests they contibute to the modification of internal models (Padoa-Schioppa et al. 2004).

In *sequence learning*, responses in areas SMA and pre-SMA appear closely related to the temporal representation of the sequences (Desrochers et al. 2016). Pre-SMA neurons encode rank order, i.e., the specified position of a movement within a sequence, while SMA neurons encode the transition from one to the next movement. The order sensitivity is stronger in pre-SMA, which is active during the explicit learning of new sequences, and thereafter only during the first movement of a sequence. Sequence learning in SMA and in pre-SMA is evidently GABA-ergic-modulated, since local injection of →muscimol in the pre-SMA of monkeys (Nakamura et al. 1999) leads to selective deficits in learning new sequences. The

→anterior cingulate cortex (ACC) may also contribute to learning of new sequences (Hikosaka et al. 2002; Ashe et al. 2006).

27.4.2.3 Primary Motor Cortex

During arm-reaching movements, the discharge of motor cortical cells is related to diverse movement variables, such as direction, force, speed or amplitude. These variables change during perturbations and must be corrected by modified neural activity during learning. The adaptations of discharge have been interpreted as reflecting the internal model that handles the physics of body and environment (Li et al. 2001; Shadmehr 2017).

Cells in primary motor cortex (area F1) changed the magnitude of activity modulation in response to various kinds of visuo-motor alterations, with increases and decreases being approximately equal (Wise et al. 1998). Electrode recordings in monkeys suggest that area F1 may be involved in building internal models of changing loads during reaching. For example in one study (Gribble and Scott 2002), cells in area F1 of monkeys trained to reach for targets under different velocity-dependent forces applied to the shoulder and/or elbow exhibited discharge patterns that depended on loading conditions. Some area F1 cells responded to both shoulder and elbow loads, indicating a single internal model for sub-loads as well as their combinations. Moreover, one sub-group of cells exhibited a rapid increase in activity, while another sub-group exhibited a gradual slow decrease (Mandelblat-Cerf et al. 2011; Richardson et al. 2008). These findings support the concept that cells in M1 are organized in a highly structured manner to represent different components of learned motor tasks involved in reaching.

In monkeys trained to make arm reaches to a visual target and to adapt to a force field perpendicular to the trained direction, the firing rates of a large sub-population of neurons in area F1 and premotor cortex (PM) was consistently modulated depending on the distance of their preferred direction from the initially learned movement direction. The newly acquired activity showed maximal increases in directions that opposed the perturbing force and decreases in opposite directions. Consequently, the combined neuronal activity of a population of cells generated an adapted vector. The findings suggested that the new combined activation of neuronal ensembles could underlie the change in the internal model of movement dynamics (Arce et al. 2010).

Whereas brain imaging in humans has not revealed error coding in primary motor cortex (area M1) and premotor cortex (PM), electrode recordings in monkeys suggest that the two regions encode information on end-point errors in reaching (Inoue et al. 2016). Evidently, individual neurons encode error information with increased discharge in a preferred direction and a decreased rate in the opposite direction, such that the average ensemble activity does not change (Inoue et al. 2016).

A proposed circuit by which the cerebral →motor cortex utilizes error signals for adaptation during reaching connects the cerebral cortex to the cerebellar cortex via the →nucleus ruber and →inferior olive (IO). In the anterior and posterior lobules of the cerebellum, the end-point error is encoded by complex spikes in →Purkinje cells (PCs), where plastic processes

lead to adaptation. The error-driven adaptive plasticity has a feedback connection to the motor cortex via the →thalamus. Motor-cortical error signals might also induce plasticity in local circuits of the primary motor cortex where plastic mechanisms are available (Inoue et al. 2016).

Mechanisms of Cerebro-Cortical Plasticity. An abundance of mechanisms may underlie cortical plasticity, from →synaptic plasticity to structural changes. The term `synaptic plasticity´ refers to changes in →synaptic transmission strength without changes in circuit wiring. `Structural plasticity´ refers to changes in →synapse numbers, synaptic connectivity patterns, dendritic spines, →dendritic and →axonal branching patterns, axonal fiber densities, and neuronal cell numbers (Butz et al. 2009; Dayan and Cohen 2011).

Intense motor training can change the →somatotopic →motor map in area F1 (area M1), such that representation of body parts involved in trained movements is slowly enlarged. Local changes in synaptic efficacy in area F1 (area M1) accompany motor learning. Re-organization of the motor map in area F1 (area M1) also occurs after injury. Attendant structural changes include increased →gray matter density, growth of dendritic spines and axon collaterals and changes in →white matter, e.g., increases in →meylination (Dayan and Cohen 2011). In humans, intense visuo-motor adaptation is associated with increased gray matter concentration over the hand area of contralateral area M1. Analogous results have been reported in rodents and non-human →primates (Luft and Buitrago 2005; Makino et al. 2016; Matsuzaka et al. 2007; Monfils et al. 2005; Penhune and Steele 2012; Papale and Hooks 2018; Peters et al. 2017; Schieber 2009).

Similar structural changes that accompany learning motor tasks occur in other brain regions (Della-Maggiore et al. 2014). In macaque monkeys, learning to use a rake to retrieve food →rewards is associated with increases in gray matter in the superior temporal sulcus (STS), secondary somatosensory cortex (S2, SII) and intraparietal sulcus (IPS), most significantly in the right hemisphere, as well as with bilateral increases of white matter in lobule 5 of the cerebellar hemisphere (Quallo et al. 2009).

In rat primary motor cortex, excitatory synapses operated by →α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA) receptors and →N-methyl-D-aspartate (NMDA) receptors were strengthened, and presynaptic →glutamate release was increased two days after motor training. Moreover, neuronal excitability is also altered by long-term changes in neuron properties such as →resting membrane potential, →action potential →threshold, and →afterhyperpolarization (AHP). Potentially, these changes could be supported by extracellular increase in →acetylcholine concentration after training (Kida and Mitsushima 2018).

Learning processes in the motor cortex are modulated by →monoamines (dopamine, →noradrenaline, →serotonin (5-HT), →histamine) as well as acetylcholine. The modulatation of motor cortical plasticity by monoamines suggests major roles in the acquisition of new motor skills. Acetylcholine modulates the re-organization of cortical maps following motor training (Vitrac and Benoit-Marand 2017), and enhances neuronal excitability by reducing AHP amplitude (Kida and Mitsushima 2018).

27.4.3 Cerebellum

There is evidence obtained from various species that the cerebellum estimates the sensory consequences of motor commands by use of a forward internal model that enables predictive control and requires updating to adjust for persistent sensory errors that result from perturbations (Ishikawa et al. 2016; Krakauer and Mazzoni 2011; Popa and Ebner 2019; Shmuelof and Krakauer 2011; Sokolov et al. 2017; Taylor and Ivry 2014).

Brain imaging showed that the arm area of cerebellar lobules V and VI encodes somatosensory prediction errors in reaching (Schlerf et al. 2012). Neurophysiological findings in monkeys confirm the presence of error signals in Purkinje cell discharge during movement, both in →simple-spike (SS) discharge and →climbing-fiber (CS) discharge. Furthermore, at the population level, SS and CS Purkinje cell firing contains both predictions about upcoming movements and sensory feedback of the movement consequences (Popa et al. 2019).

Patients with cerebellar degeneration exhibit deficits in visuo-motor adaptation, force-field adaptation, saccadic adaptation, locomotor adaptation and speech adaptation (Krakauer et al. 2019; Rabe et al. 2009; Therrien and Bastian 2015). Some patients may use a conscious strategy to quickly counter visuo-motor rotation (Taylor and Ivry 2014).

Brain imaging in healthy humans during learning visuo-motor rotations indicates that errors in visually guided tracking are correlated with increased activity in large cerebellar areas, which decrease in the course of adaptation. By contrast, activity not related to errors increases initially and remains high during adaptation (Imamizu and Kawato 2012).

The lateral cerebellum is activated when learning to deal with the complex dynamics of objects. The loci which are activated after visuo-motor rotation learning and after *altered dynamics learning* differ from each other, indicating that kinematics and kinetics are represented, processed and learned independently (Imamizu and Kawato 2012). This is corroborated by neuropsychological findings in cerebellar patients, in whom atrophy of the intermediate and lateral zones of the anterior lobe correlates with deficits in adaptation to altered force fields. Atrophy of the intermediate zone of the posterior lobe on the other hand correlates with impaired adaptation to altered visuo-motor associations (Rabe et al. 2009).

Brain imaging of humans with cerebellar disorders also indicates that, within the anterior cerebellar arm area, a more anterior part including lobules IV and V is related to force-field adaptation. A more posterior part of lobule VI, extending into lobule V, is associated with visuo-motor adaptation, and the postero-lateral cerebellum may contribute to both tasks (Donchin et al. 2012).

Cerebellar activity associated with motor learning appears to be related to error computation, but how the error signal is processed is not established. One hypothesis is that it is transferred to the posterior parietal cortex (PPC), where adaptation takes place (Mutha et al. 2012; Shadmehr et al. 2010; Taylor and Ivry 2014).

Mechanisms of Plasticity. The way the cerebellum is involved in learning and memory of motor skills is still not clear. An influential older theory is the classical →Albus-Marr-Ito hypothesis, a form of supervised learning, which proposes that motor errors are signaled by →climbing fibers from the inferior olive to the Purkinje cells (PCs) (Raymond and Medina 2018). Evidence which supports the hypothesis is that CF activity induces →long-term depression (LTD) at parallel fiber-to-Purkinje cell synapses, which alters the simple-spike (SS) responses to →mossy fiber inputs (Ito 2013). In the meantime, however, a multitude of different suggestions have emerged that many different forms of synaptic and non-synaptic plasticity, acting at various sites, can control multiple types of learning behavior. The various hypotheses contradict each other as to the mechanisms underlying cerebellar learning and await reconciliation and unification (De Zeeuw 2021).

When monkeys learn to oppose altered loads in a wrist flexion-extension task, Purkinje cell (PC) complex-spike (CS) discharge changes, firing preferentially during adaptation to the new load; and when monkeys learn new gains of reaching to targets, complex spikes appear to encode a speed error (Lalazar and Vaadia 2008).

Although climbing fiber (CF) activity is modulated with motor errors in many eye, limb and locomotor movements, it is often not obviously related to the degree, direction and precision of the error, nor to motor adaptation. Errror signals might also be encoded in Purkinje cell simple-spike (SS) discharge because in a reaching paradigm, adaptation to mechanical perturbations was shown to align with widespread changes in SS firing. The sensitivity and timing of the discharge that encoded position and velocity changed throughout learning. The changes were independent of climbing-fiber (CF) firing, indicating that the latter is unnecessary for adaptation. It has been proposed that SS firing patterns induce updating of a cerebellar forward internal model (Popa and Ebner 2019).

In mice, →granule cells, which provide the parallel-fiber input to Purkinje cells, also convey diverse signals about experience and expectations of rewards, while the climbing fibers convey instructive reward prediction errors. The cerebellum is thus integrated in an extended reward processing network of →neocortical, basal ganglia and →ventral tegmental area (VTA) regions which are also involved in reward-dependent learning (Wagner and Luo 2020).

There are many forms of cerebellar synaptic plasticity, such as long-term depression (LTD) and →long-term potentiation (LTP) at various excitatory and inhibitory synapses and neurons in other parts of the cerebellum and in →deep cerebellar nuclei. Studies continue to reveal how multiple forms of plasticity contribute to motor learning adaptation in the cerebellum (D´Angelo et al. 2016; Gao et al. 2012; Hirano 2018; Mapelli et al. 2015).

Structural changes may assist in adaptation. In humans, the rate of adaptation to new visuo-motor associations is correlated with changes in white-matter structure in the lateral posterior cerebellum and the superior cerebellar peduncle connecting the cerebellum to the motor and premotor cortex (Della-Maggiore et al. 2009). Animal experiments have also yielded evidence for structural changes at parallel fiber-to-Purkinje cell synapses after motor-skill learning (Nishiyama 2014).

27.4.4 Basal Ganglia

Human brain imaging demonstrates that the basal ganglia are activated during the early but less during the late phase of visuo-motor and force-field adaptation. This observation is consistent with findings in both →Huntington's disease and →Parkinson's disease patients (Grillner et al. 2020), who show normal early adaptation to visuo-motor and force-field perturbations, with diverse deficits in later phases. This suggests that the basal ganglia are not involved in implicit adaptation but with more cognitive components potentially related to reward-based reinforcement learning (Krakauer et al. 2019). The required reward prediction error is possibly conveyed by nigro-striatal fibers from midbrain dopaminergic neurons (but see Garr 2019).

Various lines of evidence have implicated the basal ganglia (BG) in motor-skill learning such as acquisition of serial movements (Boraud et al. 2018; Dayan and Cohen 2011; Desrochers et al. 2016; Garr 2019; Graybiel and Grafton 2015; Grillner et al. 2020; Penhune and Steele 2012). For example, mice that have learned rapid action sequences exhibit basal-ganglia neuronal activity consistent with complex movement integration. The basal-ganglia →direct pathway and →indirect pathway were found to be simultaneously active during sequence initiation, but pathways differed in discharge responsiveness during sequence performance. Some basal-ganglia neurons exhibited discharge properties in association with start/stop signal sequence discrimination, while others displayed either sustained or inhibited activity throughout the execution of an entire sequence (Jin et al. 2014).

In monkeys, transient chemical inactivation of the anterior →caudate nucleus and putamen impairs learning of novel sequential movements, whereas inactivation of the middle-posterior putamen disrupts the execution of well-learned sequences. In human brain imaging, the anterior striatum and →globus pallidus are active during the learning of novel motor sequences, whereas the posterior putamen is more active during execution of pre-learned sequences. Pallidotomy in Parkinsonian patients impairs the ability to learn new motor sequences, but not the ability to perform overlearned skills, such as daily routines (Hikosaka et al. 2002; Tanji 2001; Turner and Desmurget 2010).

The striatum, in conjunction with dopaminergic modulation, is involved in the learning of action selection, although details are not well understood (Surmeier et al. 2011). The dorsal striatum, in particular, has also been implicated in the learning and memory of stimulus-response associations or →habits (Packard and Knowlton 2002).

Mechanisms of Plasticity. Synaptic plasticity including long-term potentiation (LTP) and long-term depression (LTD) is present in several basal ganglia nuclei (Cerovic et al. 2013; Di Filippo et al. 2009; Grillner et al. 2020). In these processes, intracellular calcium (Ca^{2+}) concentrations appear not to be the dominating factor, while →endocannabinoids and dopamine importantly modulate synaptic plasticity (Cerovic et al. 2013; Wickens 2009). →Cannabinoid CB1 receptors are required for several forms of striatal synaptic plasticity (Goodman and Packard 2015). The nigro-striatal dopamine system appears necessary for both the learning and execution of sequential tasks (Turner and Desmurget 2010). Single-cell recording from basal ganglia (BG) neurons and inactivation protocols support two hypotheses: (1) The basal ganglia modulate movement vigor linked to context-specific cost/reward functions. (2) The basal ganglia contribute to motor learning by adjusting the

strength of cortico-striatal →synapses, guided by the midbrain dopaminergic neurons that provide reward prediction errors (Bamford et al. 2018; Schultz 2015, 2019). Dopamine has differential effects on the D1-mediated direct pathway and D2-mediated indirect pathway. In situations in which postsynaptic NMDA receptors are activated and presynaptic firing precedes postsynaptic firing and dopamine release quickly follows presynaptic firing, postsynaptic D1 receptor activation induces long-term potentiation (LTP), while dopamine absence leads to long-term depression (LTD). By contrast, during postsynaptic D2 receptor activation, synchronous cortico-striatal pre- and postsynaptic activation results in LTD (Garr 2019). In the mouse, activation of D1 dopamine receptors in the direct pathway and inactivation of D2 dopamine receptors in the indirect pathway control reward learning and avoidance learning, respectively (Hikida et al. 2016). However, the opposite-function model of direct and indirect pathways as outlined above is a simplification (Garr 2019).

27.4.5 Spinal Cord

Spinal-cord circuits change with age thoughout life in an activity-dependent fashion, during ontogenetic development and during skill acquisition. Spinal plasticity has been investigated most thoroughly in nociceptive pathways in the →dorsal horn and in relation to recovery from →spinal cord injury (Christiansen et al. 2017; Grau 2014; Wolpaw 2006).

Changes after Spinal Cord Injury (SCI). Injury to the spinal cord, often accompanied by →spasticity, can alter several functions, from spinal reflexes to locomotor pattern generation, depending on the severity of SCI (Christiansen et al. 2017; Gossard et al. 2015). The spinal cord is capable of motor learning by relearning kinematics and kinetics.

The mechanisms underlying and supporting recovery from spinal cord injury are manifold, including locomotor training, axon →sprouting of remaining nerve fibers, and circuit reorganization. Neurons within the lumbosacral spinal cord can adapt when isolated from the brain by thoracic transection (Rossignol and Frigon 2011; Taccola et al. 2018).

Plasticity of Spinal Reflexes. Various spinal reflexes change gain after training in paradigms that involve long-term physical exercise, such as professional ballet dancing (Christiansen et al. 2017; Wolpaw 2006). Pavlovian conditioning and →operant conditioning of →H-reflexes, as well, as show →habituation and →sensitization (Grau 2014; Thompson and Wolpaw 2014). Operant conditioning (OC) can increase or decrease the size of H-reflexes based on reward exerted by the →cortico-spinal tract (SCT). OC might encompass a hierarchy of plastic steps: First, the inferior olive (IO) determines whether a reward occurs. Mossy fibers then convey an →efference copy of the cortico-spinal tract (CST) to Purkinje cells via parallel fibers. The conjunction of these two signals changes the plasticity of Purkinje cells, whose projections to the sensory-motor cortex change CST excitability and reduce excitability of H-reflexes in a manner that increases the probability of reward. Cellular mechanisms during down-conditioning of the H-reflex include elevations in →motoneuron firing threshold, increases in the number of →ventral-horn GABAergic →interneurons and their synapses on motoneurons, and changes in →motor-unit properties (Chen et al. 2016; Thompson and Wolpaw 2014).

Motor Sequence Learning. Spinal plasticity during adaptation or motor-skill learning is more difficult to demonstrate. In healthy young humans learning sequential finger movements, functional magnetic resonance imaging (fMRI) reveals learning-related changes in activity in the C6–C8 spinal segments that is independent of activity in supraspinal sensory-motor structures. In the course of motor-sequence learning, the initial linear relationship between the sensory-motor cortex and the spinal cord gradually fades away, whereas connectivity between spinal activity and the anterior cerebellum increases in strength. These findings indicate that the spinal cord contributes to the learning process in a way distinct from the brain (Vahdat et al. 2015). The precise neurophysiological mechanisms underlying the spinal processes have still to be elucidated in full. So far, it has been demonstrated that motor sequence learning in healthy humans decreases the size of the H-reflex in flexor carpi radialis muscle, possibly by an altered descending effect on →presynaptic inhibition of group Ia afferents from muscle spindles (Lungu et al. 2010).

A recent model based on principles of cerebellar learning suggests that spinal motor learning involves circuits built of group Ia afferents, motoneurons and Renhaw cells (Brownstone et al. 2015; Windhorst 2007). These neuronal elements interact in regulating the properties of spinal circuits. For example, in genetically modified mice, deficient Renshaw cells increased their excitability, while motoneurons showed lower input resistance, received spontaneous inhibitory synaptic inputs and had an increased number of proprioceptive glutamatergic synapses on their soma and proximal →dendrites. These changes probably acted as compensatory adaptations so as to prevent alterations of drug-induced fictive locomotion in neonatal mice or changes in gait, motor coordination or grip force in adult mice (Enjin et al. 2017). The precise mechanisms underlying these adaptations remain to be elucidated.

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*Glossary entries list the chapters in which the keywords (in **bold letters**) occur. These are underlined for better identification. Horizontal arrows before the underlined notions indicate glossary entries giving definitions and providing more information.*

Glossary

Ia – see group Ia afferent

Ib – see group Ib afferent

II – see group II afferent

III – see →group III afferent

IV – see →group IV afferent

5-HT receptor – see →receptor and Chap 5

5-hydroxytryptophan (**5-HTP**) – precursor of →serotonin (5-HT)

A5-A7 cell groups – (`A´ for aminergic); these groups give rise to →spinally descending →noradrenergic fibers; A5 and A6 constitute the →locus coeruleus; see Chaps 4, 5

A band (in →skeletal muscle) – see Chap 17

Abducens motoneuron (nerve, nucleus) – *nervus (nucleus) abducens:* →cranial nerve VI; see Chap 16

Aβ fiber– designates →axon of →β-motoneuron or sensory group II afferent; see Chap 4

Absolute disparity (d_{abs}) – angular separation of an image point in one eye with respect to the →fovea (α) minus that in the other eye (β), hence α−β. Absolute disparity carries information about an object point´s depth relative to the point of fixation, depends on the vergence angle and can thus be used to locate objects in 3D space and to drive vergence eye movements; see Chap 14

Acceleration – In physics, acceleration (a vector) denotes the time-derivative of the velocity (a vector) of a specific particle. For a material body consisting of many particles, each particle is subject to an acceleration vector making up an acceleration field at each instant of time; see Chaps 1, 4, 8, 10, 15, 19, 20, 21, 25, 26

Accessory olfactory bulb (AOB) – see Chap 3

Accessory olfactory system – see Chap 3

Accessory optic system (AOS) – →sub-cortical visual pathway that is responsible for the analysis of optic flow resulting from self-motion; see Chaps 10, 14

Accommodation – This term has at least two different meanings in neuroscience. First, it refers to the effect of slow and long-lasting →depolarization of the membrane potential (→resting membrane potential), which entails an inactivation of the sodium (Na^+) channels and hence inability to generate →action potentials. Second, it denotes the increase in the refractive power of the lens of the eye.

Accommodation (of the eye lens) – increase in the refractive power of the lens of the eye; see Chaps 13, 15, 16

Accommodation reflex – see →reflex and Chap 13

Acetic acid – see Chap 2

Acetylcholine (ACh) – classical →neurotransmitter released from autonomic (→autonomic nervous system) →preganglionic neuron terminals, at →synapses of autonomic ganglia, at somatic →motoneuron terminals (at the →neuromuscular junction and the recurrent →axon collaterals), and at various other central synapses; see Chaps 2, 3, 10, 17, 18, 27

Acetylcholine receptor (AChR) – see →receptor and Chap 17

Achilles tendon reflex – →tendon reflex elicited by a brief tap on the Achilles tendon; see →reflex and Chaps 1, 9, 17, 20

Achilles tendon – see →tendon reflex and Chaps 1, 17

ACh – →acetylcholine

AChR – →acetylcholine →receptor

Acid-base balance – see Chaps 2, 4

Acidosis – state characterized by acidic pH (high H^+ concentration); see Chap 17

Acid-sensing ion channels (ASICs) are amiloride-sensitive Na^+-permeable →ion channels activated by protons; they belong to the family of degenerin/epithelial sodium (Na^+) channels (DEG/ENaC) and occur in at least eight different ASIC subunits (including ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, ASIC4, ASIC5) encoded by five genes (ASIC1-ASIC5). ASICs are

widely but differentially expressed in the →peripheral nervous system (PNS) and →central nervous system (CNS). They detect tissue →acidosis occurring in tissue injury, →inflammation, →ischemia, →stroke, tumors as well as →muscle fatigue. They thus play an important role in →nociception and also in proprioception, probably in peripheral sensory endings such as the muscle spindle primary endings. Centrally, they occur as postsynaptic receptors activated by protons co-released with →glutamate at glutamatergic synapses; (ii) as modulators of →synaptic transmission at glutamatergic synapses and →GABAergic synapses; (iii) in →synaptic plasticity, →memory and →learning; see Chaps 2, 4, 6, 8

Acoustic cues – see Chap 12

Acoustic flow – see Chap 12

Acoustic trauma – see Chap 11

Acquired immuno-deficiency syndrome (AIDS) – see Chap 17

Across-fiber (across-neuron) pattern code or ensemble or population code – hypothesis stating that neural information is represented by spatio-temporal patterns of activity of populations of nerve fibers and central →neurons rather than in the activity of individual neurons. For example, since the three types of retinal cone photoreceptors respond broadly, albeit differentially, to overlapping ranges of light wavelengths, any individual wavelength is represented by a specific ratio of activities across the different cone types; see Chaps 2, 13

Actin – see Chaps 8, 10, 11, 17, 18, 19

Action map – see Chap 25

Action potential – Long-distance communication along nerve fibers (→axons) and skeletal →muscle fibers employs action potentials as signals, which have various shapes. Most are pulses (also called *impulses* or *spikes*) of fairly short duration, on the order of 1-3 ms except for those in heart or smooth muscle cells. In a usually non-active cell, a spike evolves from a →resting membrane potential of about -50 to -90 mV (inside negative), →depolarizes at a steep rate and reaches a peak, and rapidily repolarizes back to the resting potential. A delayed depolarization or protracted →afterhyperpolarization (AHP) may follow; in most chapters

Action potentials in central neurons – →Neurons of the mammalian →central nervous system (CNS) express complex repertoires of →ion channels and firing behaviors based thereupon. Individual neurons typically express several sub-types of voltage-gated sodium (Na^+) channels, potassium (K^+) channels and calcium (Ca^{2+}) channels (→voltage-gated ion channels) that enable production of diverse →action potential shapes and firing patterns. Action potential amplitude, shape and firing rate are particularly important at presynaptic →axon terminals, where they determine – via the amount of presynaptic Ca^{2+} influx – the amount of released →neurotransmitter.

Action potential propagation – Mode of →action potential spread along nerve or →muscle fibers occurs automatically due to →electrotonic spread of local membrane potential changes (→resting membrane potential). – Action potential propagation along smooth →axons or muscle fibers occurs continuously. The conduction velocity is related to the square root of the fiber diameter. One means of increasing the conduction velocity is to increase the fiber diameter. – Action potential propagation along →myelinated axons enables faster propagation based on the →myelin sheath. When a node of Ranvier is →depolarized during an →action potential, local circuit currents depolarize the next one ahead, without the internodal region (between adjacent nodes of Ranvier) needing discharging. The excitation thus skips from node to node by→saltatory conduction. The conduction velocity is determined by a number of factors, but largely by the internode length, which is approximately proportional to the fiber diameter; see Chaps 17, 18

Action selection – see Chaps 1, 16, 23, 24, 25, 26, 27

Action sequence – see Chaps 1, 27

Action tremor (also called kinetic →tremor) occurs during muscle actions (e.g., outstretched arm or movements) and subsides at rest, in distinction to →resting tremor in →Parkinson´s disease. It occurs in a variety of diseases, e.g., →cerebellar damage. Some action tremors are exaggerated forms of (`enhanced´) physiological tremor, e.g., during states with hyper-adrenergic (→adrenaline) drive (excitement, nervousness, pharmacological treatment with agents augmenting adrenergic drive), and possibly involve oscillations in the →stretch reflex (→intention tremor); see Chaps 23, 26

Active listening – see Chap 12

Active touch – see Chap 7

Actomyosin – see actin and myosin and Chap 17

Acupuncture – see Chap 4

Acute pain – transient pain acutely associated with a →noxious stimulus; see Chaps 4, 5

Adaptation (to light) – see Chap 13

Adaptation (of membrane potential or neural discharge or neural system response to a maintained stimulus) – see →resting membrane potential and most chapters

Adaptation (of neural system or response to changed conditions) – in most chapters

Adductor femoris muscle – see Chap 17

Aδ afferent – see →group III afferent

Adenosine – purine nucleoside that forms →adenosine triphosphate (ATP), adenosine diphosphate (ADP) and →cyclic adenosine monophosphate (cAMP). ATP is built from two ADP molecules; and during cellular activity, free adenosine is released and transported out of cells. Adenosine acts upon different receptors (→purinergic receptors), some (A1 and A3) having inhibitory and some (A2a and A2b) excitatory effects; see Chaps 3, 4

Adenosine diphosphate (ADP) – see →adenosine and Chap 17

Adenosine triphosphate (ATP) – high-→energy compound used by cells predominantly for metabolic purposes, e.g., for energizing muscle contraction. But it also acts as →neurotransmitter in the →spinal →dorsal horn. In the superficial dorsal horn, ATP mediates excitatory postsynaptic responses in →nociceptive transmission, and in the deep dorsal horn it mediates transmission of innocuous primary afferent inputs. Extracellular conversion of ATP to →adenosine mediates inhibitory postsynaptic responses from Pacinian corpuscle afferents; see Chaps 2, 4, 5, 6, 17

ADP – **a**denosine **di**phosphate – see →adenosine and Chap 17

Adrenal gland – located above each kidney, consisting of the →adrenal medulla and the surrounding adrenal cortex; see Chap 5

Adrenal medulla – interior part of the →adrenal gland, containing cell groups that are modified →postganglionic →neurons that are innervated by →preganglionic fibers of the →sympathetic division of the →autonomic nervous system (ANS); upon →stress exposure (e.g., exercise, threats), adrenal cells release →catechoamines (→adrenaline, →noradrenaline and small amounts of →dopamine), thereby affecting →energy disposure, heart rate, blood pressure, and metabolism; see Chap 13

Adrenaline – also called epinephrine: →catecholamine released as a →neurotransmitter from →neurons in the →central nervous system (CNS) and as a →hormone from chromaffine cells in the →adrenal medulla. Adrenaline increases metabolic and cardiovascular activities during →stress. Its cellular actions are mediated via cell-membrane-bound →G-protein-coupled receptors; see Chap 13

Adrenoceptors – group of →G protein-coupled receptors for many →catecholamines like →adrenaline and →noradrenaline produced by the body; prevalent in the →sympathetic nervous system. The main sub-types are α1, α2, β1, β2 and β3 and may occur as auto- or heteroreceptors modulating transmitter release; also →receptors for many medications; see Chap 5

Aerobic condition – condition in the presence of oxygen; see Chap 17

Affect, affecive – →hedonic quality of pleasure or displeasure. Affect-related regions are spread across the brain; see Chaps 2, 3, 4, 5, 7, 10, 12, 20, 23

Affective touch – also pleasant touch or sensual touch; see Chaps 4, 6, 7

Affordances – opportunities for action or motor possibilities that an animal´s environment or a specific object offers depending on the animal´s motor capabilities. Affordances may be divided into stable and variable ones. Stable affordances are based on object knowledge and previous experiences. Variable affordances change with changes in object size, orientation etc.; see Chap 24, 25, 26

Afterhyperpolarization (AHP) – In mammalian central →neurons, afterhyperpolarizations following the →repolarization phase of the →action potential are complex. They may show different phases: fast, medium and slow. The contributing potassium (K^+) channels include →BK (`big´ $K^+$) and →SK (`slow´ K^+) channels and Kv7 channels mediating the →M-current. BK-channel-mediated afterhyperpolarizations are usually brief, while SK-channel-mediated ones can last up to seconds (Bean 2007). Na^+-activated K^+ channels (K(Na) channels) may contribute to slow afterhyperpolarization after repetitive discharge (firing); see Chaps 18, 22

Aggression, aggressive – see Chaps 3, 25

Agnosia – inability to →recognize objects or their properties. *Visual agnosias* come in various specific forms, for example, →color agnosia (achromatopsia), motion agnosia (→akinetopsia), generalized object agnosia, agnosia for faces (prosopagnosia), agnosia for depth. There is also a tactile agnosia called →astereognosia; see Chap 12

Agonist (→motoneuron, muscle) – see Chaps 9, 15, 19, 20, 22, 27

Agonist (pharmacological) – ligand that binds to a specific cellular →receptor and triggers a response in the cell; see →receptor agonist and Chaps 2, 4, 5, 14, 22, 26

Akinesia – lack or poverty of movement, resulting from an inability to initiate or change motor activity and thus movements easily and rapidly; →hypokinesia and →bradykinesia (slowness of movement) denote lesser degrees of impairment, for example in →Parkinson´s disease; see Chap 23

Akinetopsia – motion →agnosia, motion →perception disorder: lack of →visual motion perception resulting from →cerebral cortical damage. Deficient motion perception may manifest in various forms. Some patients perceive objects in discrete positions at subsequent moments as if the world appeared intermittently illuminated by a strobe light. Others are unable to perceive radial motion (optic flow), which normally occurs when one moves through an environment, and thus be compromised when navigating through cluttered environments. Still others are not able to discriminate speeds of motion or extract discontinuities from motion, although higher-level motion perception of heading in an environment, or radial and rotational motion may be intact. Akinetopsia can also be evoked in normal subjects by temporarily inactivating – by →transcortical magnetic stimulation – the primary visual cortex (→striate cortex, area V1) and a particular pre-striate →cortical area; see Chap 14

Albus-Marr-Ito hypothesis – this hypothesis propounds that →climbing fibers from the →inferior olive (IO) provide feedback of →motor errors; climbing fibers induce complex spikes in →Purkinje cells and →plastic changes in →synaptic transmission at parallel fiber-to-Purkinje cell →synapses, which alters the→ simple-spike (SS) responses to →mossy fiber inputs; see Chaps 15, 27

Alcoholic peripheral neuropathy – see Chap 5

Alcoholism – see Chap 20

Alert, alertness – ability to direct and sustain →attention; reflects cerebro-cortical activation and is modulated by →sleep/wake regulatory mechanisms; see →arousal and Chaps 1, 5, 6, 7, 10, 11, 13, 14, 16, 19, 23

Alkaloids – are naturally occurring (organic), nitrogen-containing and often bitter-tasting and poisonous substances; see Chap 2

Allocentric cues (in navigation) denote local and distal environmental cues used for navigation. Local cues include odors on the ground. Distal cues are principally visual and provide information about the distance to →landmarks and spatial arrangement among landmarks. Allocentric cues are typically contrasted with →idiothetic cues; see Chap 25

Allocentric frame of reference – reference frame fixed to objects, locations or reference directions in the 3D scene outside the subject´s body, such as a mountain or an individual object; the existence of allocentric reference frames has been debated, it has been argued that they can be linked to →egocentric frames of reference; see Chaps 23, 24

Allodynia – pain or unpleasant sensation in response to a non-→noxious stimulus, e.g., a tactile stimulus (mechanical allodynia or tactile allodynia) or mild change in temperature (usually cold) stimulus (cold allodynia); see Chaps 4, 5, 7

α–rigidity – see Chaps 19, 26

α-Amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA) – amino acid derivative that binds to the AMPA-type →glutamate ionotropic receptor; see Chaps 3, 11, 27

α-γ-Co-activation – simultaneous activation of →α-motoneurons and →γ-motoneurons; see Chap 9

α-Motoneurons – large →motoneurons with →axons in nerve-fiber group Aα and innervating skeletal →muscle fibers only; see Chaps 4, 8, 9, 18, 19, 20, 22, 23

Amacrine cell (in retina) – see Chap 13

Amiloride – directly blocks the →epithelial sodium channel (ENaC); see Chap 2

Amiloride-sensitive Na^+ channel – see Chap 2

Amino acid – see Chaps 2, 3, 5

AMPA receptor – →α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid receptor for →glutamate ; see →glutamate receptors and Chaps 3, 10, 11, 27

Amphibia – see Chaps 15, 18, 22

Amplitude modulation (AM) – see Chaps 11, 12, 23

Amplitude spectrum – see Chap 12

Ampulla (in vestibular organ) – see Chap 10

Amyotrophic lateral sclerosis (ALS) – also called *Lou Gehrig's disease*; fatal →degenerative disorder resulting from progressive degeneration of cerebro-cortical →neurons giving rise to →cortico-spinal fibers and →motoneurons in →brainstem and →spinal cord; see Chap 26

Amygdala – heterogeneous nuclear complex embedded deep within the rostral pole of the cerebral temporal lobe. The amygdala attach →emotional significance to sensory stimuli, and are involved in associated →learning and expression of conditioned responses. The basolateral portion receives inputs from all sensory modalities and conveys this information to the central nucleus that projects to the →hypothalamus and →brainstem to initiate autonomic (→autonomic nervous system), →endocrine, and motor responses associated with emotion; see Chaps 2, 3, 4, 5, 12, 13, 14, 23

Anaerobic condition – condition in the absence of oxygen; see Chaps 17, 18

Analgesia – lack of pain sensation in response to a stimulus that would normally be perceived as painful; see Chaps 4, 5, 7

Anandamide – N-arachidonylethanolamine; see →arachidonic acid, →endocannabinoids and Chap 2

Androstadienone – androsta-4,16-dien-3-one, endogenous steroid supposed to have a pheromone-like effect in humans; see Chap 3

Androstenone – the first mammalian steroidal pheromone to be identified; see Chap 3

Anemic decerebration – see Chap 19

Anencephalic – without →encephalon; see Chap 22

Anesthesia – see Chaps 7, 9, 20, 26

Anesthesia dolorosa – see Chap 5

Angina pectoris – see Chap 4

Ankle joint – see Chaps 1, 17, 19, 20, 21, 22

Ankle strategy – see Chap 20

Anoctamid – see Chap 4

Antagonist (→motoneuron, muscle) – see Chaps 9, 15, 17, 19, 20, 21, 22, 23, 27

Antagonist (pharmacological) – ligand that binds to a specific cellular →receptor, thereby blocking the binding of an →agonist and its effect on the cell; see Chaps 2, 3, 5, 10, 22

Anterior cingulate cortex (ACC) (in →cerebral cortex) – anterior area of the →cingulate cortex (gyrus) with connections to the →prefrontal cortex (PFC), →amygdala, →thalamus, and →striatum (→basal ganglia), inputs from nociceptive pathways and →orbitofrontal cortex (OFC) and outputs to the →cortico-spinal tract (CST). The ACC contributes to behavioral drive, →emotion, and regulation of →affective behavior; see Chaps 2, 4, 5, 7, 10, 12, 16, 20, 27

Anterior insular (cortex) (in→cerebral cortex) – see →insula and Chaps 2, 3 4, 5, 7

Anterior intraparietal sulcus (aIPS) (in→cerebral cortex) – see →**i**ntra**p**arietal **s**ulcus, →parietal cortex and Chap 26

Anterior olfactory nucleus (AON) – see Chap 3

Anterior parietal cortex (APC) (in→cerebral cortex) – cerebro-cortical region posterior to the central sulcus, containing the →primary somatosensory cortex (S1, SI); see →parietal cortex (lobe) and Chaps 7, 10, 27

Anterior piriform cortex (in→cerebral cortex) – see Chap 3

Anterior supra-marginal gyrus (aSMG) (in→cerebral cortex) – see →supra-marginal (SMG) and Chaps 7, 26

Anterior ventral cochlear nucleus (AVCN) – see →ventral cochlear nucleus and Chap 12

Antero-lateral belt (AL) (in auditory →cerebral cortex) – see Chap 12

Anterior lateral motor cortex (ALM) (in the mouse) – see Chap 24

Antero-lateral system – see Chap 7

Anticipatory grip adjustment – see Chap 26

Anticipatory postural adjustment – unconscious movements aimed at counterbalancing the →balance perturbation caused by a primary movement, e.g., by initiating the displacement of the body →center of mass (COM) when starting gait or performing whole-body reaching movements; see Chaps 1, 20, 21, 24, 25, 26

Antidromic – →action potential propagation in the direction opposite to the naturally occurring direction; see Chap 5, 18, 19

Anti-nociception – see Chap 5

Anti-saccade – see saccade and Chap 16

Anuran - see Chap 14

Anxiety – see Chaps 4, 5, 20

Aperture problem – see Chaps. 7, 14

Aponeurosis – flat tendon sheet; see Chaps 8, 17

Appetitive behavior – Behavior related to appetite, →energy balance and feeding. The lateral hypothalamus contains →neuron groups with →orexin as →neurotransmitter, controlling appetite, energy balance and →vigilance states. Orexinergic projections target →brainstem areas and have been implicated in feeding and appetitive behaviors, with projections to the →mesencephalic locomotor region (MRL) facilitating locomotion; see Chap 23

Apraxia – disorder of →learned movements without sensory loss, muscle weakness, incoordination, intellectual deterioration or lack of comprehension. Different forms of apraxia are distinguished according to different body parts and functions affected; see Chap 25, 26

Arachidonic acid – important lipid compound formed from cell membrane phospholipids and serving as precursor for various mediators such as →eicosanoids (→prostaglandins, leukotrienes etc.) or the →endocannabinoid →receptor ligand →anandamide (N-arachidonylethanolamine); see Chaps 4, 5, 19

Arcuate sulcus (AS) – see Chaps 16, 25

Area (in →cerebral cortex) **–** The →cerebral cortex in →primates is divided into a large number of areas (about 180 per hemisphere in humans) based on criteria such as cyto- and myelo-architecture, and/or chemo-architecture, →topographic organization, input-output connections (including intra-cortical and →sub-cortical connections), electrophysiological properties of →neurons and deficits resulting from local lesions or deactivation. →Brodmann ´s (1909) classification of human →cortical areas is based on cyto- and myelo-architecture. Von Bonin and Bailey´s (1947) classification for monkeys is cruder than Brodmann´s (1909) and names areas first according to their location in one of the major lobes (F, frontal; P, parietal; O, occipital; T, temporal). The subsequent letter has no specific significance, but is one of the initial alphabetic characters. This scheme has been refined and led to further differentiations including, for example, anatomical designations such as `a´ for anterior, `c´ for caudal etc. For instance, `PGa´ denotes the anterior portion of →area PG (area `G´ in the →parietal cortex (lobe)), which is situated rostral to the lateral fissure (→Sylvian fissure) close to its posterior end. Some areas are simply designated according to their form or anatomical location, e.g.,

area AIP = anterior intraparietal, or according to their function, e.g., →primary motor cortex (area M1, area F1). Unfortunately, these diverse nomenclatures are often used interchangeably, such that, e.g., →Brodmann´s area 17 = →striate cortex = primary visual cortex = area V1, or Brodmann´s area 4 = area M1 = area F1. A limited list of →cortical areas without too many specifications is presented under `Area…´; see Chaps 2, 3, 4, 7, 10, 11, 12, 14, 15, 16, 23, 24, 25, 26

Area 1 – part of →primary somatosensory cortex (S1, SI); see Chaps 2, 7, 8

Area 2 – part of →primary somatosensory cortex (S1, SI); see Chaps 2, 7, 8, 10

Area 3 – →Brodmann´s area 3; see Chaps 2, 14

Area 3a – part of →primary somatosensory cortex (S1, SI); see Chaps 7, 8, 10, 14

Area 3b – part of →primary somatosensory cortex (S1, SI); see Chaps 7, 8

Area 4 – →Brodmann´s area 4 (in humans) = →primary motor cortex = area M1 = area F1 (in monkeys); see Chaps 7, 8, 14

Area 5 – according to →Brodmann part of →posterior parietal cortex (PPC), now divided into several sub-areas: PE, PEci (cingulate PE), PEc (caudal PE), PEip (intraparietal PE, also called PEa, anterior PE), area MIP (medial intraparietal), medial part of →area VIP (ventral intraparietal); see Chaps 7, 23, 25

Area 5d – see Chap 24

Area 6 – →Brodmann´s area 6; see Chaps 7, 10, 16

Area 7 is composed of area 7a, area 7b, area 7m; see Chaps 7, 10, 16

Area 7a – composed of →area PG and →area Opt; see Chaps 14, 16, 25

Area 7b – also called rostral →inferior parietal lobule (rIPL), composed of area PF and area PFG; see Chap 7

Area 7m – (also called →area PGm) corresponding to →precuneus in humans; see →eye fields and Chaps 16, 25

Area 8 – →Brodmann´s area 8; see Chaps 14, 20

Area 8B – situated between →Brodmann´s area 6 and area 8; see Chap 16

Area 9 – →Brodmann´s area 9; see Chaps 16, 20

Area 10 – →Brodmann´s area 10; see Chap 4

Area 12 – →Brodmann´s area 12; see Chaps 12, 25, 26

Area 17 – →Brodmann´s area 17 (in humans), also primary visual cortex, area striata (→striate cortex), area V1 (in monkeys); see Chap 14

Area 22 – →Brodmann´s area 22; see Chap 12

Area 23 – →Brodmann´s area 23; see Chap 23

Area 29 – →Brodmann´s area 29; see Chap 23

Area 30 – →Brodmann´s area 30; see Chap 23

Area 31 – →Brodmann´s area 31; see Chap 23

Area 39 – →Brodmann´s area 39; see Chap 10

Area 40 – →Brodmann´s area 40; see Chap 10

Area 41 – →Brodmann´s area 41; see →area A1 and Chap 12

Area 42 – →Brodmann´s area 42; see Chap12

Area 44 – →Brodmann´s area 44; see →premotor cortex and Chaps 12, 26

Area 45 – →Brodmann´s area 45; see Chaps 12, 16

Area 45A – see Chap 16

Area 45B – see Chap 16

Area 46 – →Brodmann´s area 46; see Chaps 14, 16, 25, 26

Area A1 – primary auditory area (in→cerebral cortex). In humans, the →primary auditory cortex (A1) is situated in →Brodmann´s areas 41 and 42 in the superior temporal gyrus (Heschl´s gyrus) and is organized tonotopically; see Chap 12

Area AIP (**a**nterior **i**ntra**p**arietal) – see Chaps 14, 24, 25, 26

Area AIT (**a**nterior **i**nfero-**t**emporal) – see Chap 14

Area CIP (**c**audal **i**ntra**p**arietal) – represents information about 3D aspects of objects; see Chap 14, 19

Area cIPS (**c**audal →**i**ntra**p**arietal **s**ulcus) – see Chap 14

Area CIT (central **i**nfero-**t**emporal**)** – see Chap 14

Area F1 – →primary motor cortex (= area M1 = →Brodmann´s area 4); see Chap 24, 25, 26, 27

Area F2 = area PMdc, **d**orso-lateral →**p**remotor **c**ortex, **c**audal portion (part of →Brodmann´s area 6); see Chaps 14, 25, 26

Area F2vr – **v**entro-**r**ostral sector of →area F2; see Chap 26

Area F3 – →supplementary motor area (SMA) (postero-medial part of →Brodmann´s area 6); see Chaps 24, 25

Area F4 belongs to the ventro-lateral →premotor cortex (→area PMv) and lies on a dorsal convexity immediately rostral to the →primary motor cortex (M1). It can be divided into dorsal and ventral sub-regions, F4d and F4v, which are involved in forelimb and orofacial movements, respectively; see Chaps 14, 25, 26

Area F4d – see Chap 26

Area F4v – see →area F4

Area F5 belongs to the ventro-lateral →premotor cortex →(area PMv) and can be divided into several sub-areas; see Chaps 14, 25, 26

Area F5d – dorsal →area F5; see Chap 26

Area F6 – →pre-supplementary motor area (pre-SMA) (antero-mesial part of →Brodmann´s area 6); see Chaps 24, 25, 26

Area F7 – rostral portion of dorso-lateral →premotor cortex (area PMd) (part of →Brodmann´s area 6); receives projections from the →prefrontal cortex (PFC), including frontal eye field (FEF), →dorso-lateral prefrontal cortex (DLPFC), and →orbito-frontal cortex(OFC). Area F7 has no direct connections to the →primary motor cortex (area M1, area F1), projects to motor nuclei of the →brainstem; see Chaps 14, 26

Area FST (**f**loor of **s**uperior **t**emporal sulcus) (in→cerebral cortex) – see Chap 14

Area hAIP – **h**uman equivalent of monkey area AIP; see Chap 26

Area Id – dysgranular →insula; see Chap 26

Area LIP (**l**ateral **i**ntra**p**arietal) – also called the parietal eye field (PEF); see →eye fields and Chaps 16, 24, 25

Area M1 (Area F1) – →primary motor cortex, area 4 according to Brodmann; see Chaps 24, 25, 26, 27

Area MIP (**m**edial **i**ntra**p**arietal) – see →area 5 and Chaps 24, 25

Area MST (**m**edial **s**uperior **t**emporal) – represents a large part of the →visual field, is activated by →visual motion, in particular by self-motion; see →eye fields and Chaps 7, 10, 14, 15, 16, 25

Area MSTd (**m**edial **s**uperior **t**emporal, **d**orsal) – see Chaps 14, 16

Area MSTl (**m**edial **s**uperior **t**emporal, **l**ateral) – see Chap 16

Area MT (**m**iddle **t**emporal) – also referred to as area V5; represents the central part of the contralateral →visual field, is organized →retinotopically and involved in the analysis of motion; see Chaps 7, 13, 14, 15, 16

Area Opt – see Chap 25

Area PE – see →area 5 and Chap 25

Area PEa (anterior area PE) – see →area 5 and Chap 25

Area PEc (caudal area PE) – see →area 5 and Chap 25

Area PEip (**i**ntra**p**arietal sector of area PE) – also called area PEa; see →area 5 and Chap 25

Area PFG – appears involved in the control of hand actions; also contains *parietal mirror →neurons*; see Chaps 25, 26

Area PG – part of →area 7a; situated rostral to lateral fissure (→Sylvian fissure) close to its posterior end; see Chap 25

Area PITd (**p**osterior **i**nfero**t**emporal, **d**orsal) – see Chap 14

Area PMd – **d**orso-lateral →premotor cortex; see Chaps 25, 26, 27

Area PMdc = →area F2 – dorso-lateral →premotor cortex, caudal portion

Area PMdr = →area F7 – dorso-lateral →premotor cortex, rostral portion

Area PMv – **v**entro-lateral →premotor cortex. The PMv is divided into sub-regions (→area F4 and →area F5) that form an integrated system supposedly involved in functions from →decision making to eye-hand coordination; see Chaps 26, 27

Area postrema – trigger zone for emesis (`vomiting center´) located dorsal to the →nucleus of the solitary tract (NTS) on the dorsal surface of the →medulla oblongata at the caudal end of the fourth ventricle; see Chap 2

Area S1 (SI) – see →primary somatosensory cortex (S1, SI) and Chaps 4, 26

Area STP – →**s**uperior **t**emporal **p**olysensory area; see Chaps 7, 14

Area STPa – **s**uperior **t**emporal **p**olysensory, **a**nterior; see Chap 14

Area TE – Temporal area TE occupies the →inferior temporal (IT) cortex caudal to the superior temporal sulcus (STS) and anterior to the middle temporal sulcus. Area TE is divided on the basis of cytoarchitecture, myeloarchitecture, and afferent input into area TEa (anterior portion of TE), area TEm (medial portion of TE), TE3, TE2 and TE1; see Chap 14

Area TEa – see Chap 26

Area TEm – see Chap 26

Area TEO – **te**mporo-**o**ccipital, posterior inferior temporal (IT) area (interposed between →area TE anteriorly and (occipital) area V4 posteriorly, corresponding roughly to area PITv and area VOT; see Chap 14

Area V1 – see primary visual cortex (area V1) and Chaps 13, 14, 15, 16, 26

Area V2 – see Chaps 13, 14, 15, 16

Area V3 – see Chaps 13, 14, 15, 16

Area V3A – in the macaque, part of the →neurons are activated by motion of simple visual stimuli, in part in a direction-→sensitive way; stronger activation by motion in humans; see Chaps 13, 14, 16

Area V4 – see Chaps 13, 14, 16

Area V5 – also called →area MT; see Chaps 13

Area V6 – visual area, →retinotopically organized, representing the entire contralateral hemifield and →sensitive to →visual motion; part of monkey parieto-occipital area PO; may be homologous to human posterior superior parieto-occipital cortex (SPOC); presumably plays a role in the visual →recognition of object motion and self-motion; see Chaps 7, 14

Area V6A – part of monkey parieto-occipital area PO; may be homologous to human anterior superior parieto-occipital cortex (SPOC); plays a role in arm/hand/finger movements; see Chaps 14, 16, 24, 25, 26

Area VIP (**v**entral **i**ntra**p**arietal) – area in the →posterior parietal cortex (PPC) with multiple sensory inputs (visual, auditory, vestibular and tactile); human area VIP contains a somatosensory face map aligned with a near-face visual space map; see →area 5 and Chaps 10 , 14, 16, 24, 25, 26

Arginine – see Chap 2

Arm movement – see Chaps 1, 6, 9, 20, 23, 24, 25, 26, 27

Arousal – involved in wakefulness, awareness, →alertness, →attention, →cognition, →motivation, →emotion, sexual activity, and →stress. Several brain systems evoke waking from →sleep in response to sensory stimuli, generate and maintain wakefulness irrespective of sensory stimuli during the active part of the day, and prolong or enhance arousal in response to specific stimuli. These arousal systems (Jones 2003) consist of →neuron groups in the →brainstem →reticular formation, posterior →hypothalamus, →thalamus and →basal forebrain, and utilize different →neurotransmitters (→acetylcholine, →dopamine, →glutamate, →histamine, →noradrenaline, →orexin/hypocretin, →serotonin (5-HT)). Through ascending projections, these systems stimulate cortical activity; through descending projections to the →spinal cord, they enhance or modulate →muscle tone and activity as well as sensory-motor responsiveness; see Chaps 1, 2, 3, 4, 8, 12, 13, 23

Articulation (of joints) – see Chap 17

Ascorbic acid – see Chap 4

ASIC – →**A**cid-**s**ensing **i**on **c**hannels form a family of three types of →ion channels (ASIC1, ASIC2, ASIC3) and are the mammalian homologs of worm degenerin/epithelial Na^+ channels (DEG/ENaC); see Chaps 4, 6, 8

Aspartate – excitatory →neurotransmitter at excitatory chemical →synapses; see Chaps 2, 5, 10

Astasia – inability to stand; see Chap 23

Asthenia – weakness, lack of force and power; see Chap 23

Astrocytes – are heterogeneous, irregularly, stellate- or spider-shaped cells with many long processes. They are the largest and most numerous (20-40%) →glia cells in the brain and →spinal cord. They have extensive contacts with blood vessels as well as →synapses and →neuronal cell bodies. Under normal conditions, they exert →homeostatic functions [pain suppresssion, water →homeostasis, potassium (K^+) homeostasis, →glutamate homeostasis, structural support for →synapses and regulation of synaptogenesis], but also play a role in neuronal signaling by responding to neuronal →neurotransmitter release and in turn releasing neurotransmitters which modulate neuronal excitability, synchrony and →synaptic transmission. Astrocytes are involved in CNS diseases, including →chronic pain and chronic →itch as well as degenerative, psychiatric and developmental diseases, and gliomas. In →neuropathic pain, `reactive astrocytes´ interact with neurons and →microglia; see Chaps 4,

Ataxia – also *asynergia* or *dyssynergia*: large group of rare neurological disorders, including several forms of inherited ataxias. Ataxia may result from alterations in sensory, →spinal cord, vestibular or →cerebellar systems. Signs include abnormal motor coordination, kinetic →tremor, imbalance, wide-based stance and dysarthria, probems with eye movements, →volitional movements and speech, especially when the movements are produced quickly and require coordination of multiple joints. *Cerebellar ataxia* is characterized by →nystagmus, dysmetria, wide-based gait (→truncal ataxia), poor dexterity in performing rapid alternating movements (→dysdiadochokinesis), and slurred speech (ataxic dysarthria; deficit of speech articulation). Movements exhibit abnormal timing with delayed muscle activations, deranged interplay between agonist and antagonist muscles, and sudden interruptions followed by exaggerated corrections; see Chaps 19, 20, 23

ATP – see →**a**denosine **t**ri**p**hosphate, →adenosine and Chaps 2, 4, 5, 6, 17

ATPase – enzyme splitting →adenosine triphosphate (ATP); see Chaps 4, 17

Atropine – competitive pharmacological →antagonist of →acetylcholine at →muscarinic receptors (at intermediate doses) and at →nicotinic receptors (at high doses); see Chap 10

Attention – allocation of →cognitive capacity to an object or task, so that currently behaviorally significant information is selected and non-significant information suppressed. Attention is commonly divided into various forms depending on conditions. →Bottom-up, *exogenous or involuntary attention* is based on the →salience of sensory stimuli. →Top-down, *endogenous or voluntary attention* is driven goal-directed processes, involving directed selective attention controlled by the brain. It allows visual attention to be shifted to spatial loci (spatial attention*)* or, non-spatially across the →visual field, to particular features such as shape, color, orientation, direction of motion (*feature-based attention)*, or entire objects (*object-based attention)*. *Overt attention* is directed to a goal in conjunction with a motor response, e.g., an eye/head movement (saccade), while *covert attention* is not associated with an overt motor response and is localized away from the direction of gaze; see Chaps 1, 2, 3, 4, 7, 9, 10, 11 ,12, 13, 14, 16, 23, 24, 27

Attention shift – →attention that is switched between tasks that have to be performed simultaneously and processing resources are not able to perform the task in parallel; see Chap 16

Audiogyral illusion – effect of angular →acceleration on sound localization; see →illusion and Chap 10

Audition, auditory – hearing; see Chaps 1, 2, 3, 7, 9, 10, 11, 12, 14, 16, 18, 19, 23, 24, 25, 26, 27

Auditory imagery – see Chap 12

Auditory map – see Chap 12

Auditory object – specific, behaviorally significant →spectro-temporal pattern extracted from the complex mixture of →sounds in the acoustic environment; see Chaps 11, 12

Auditory pathway – see Chap 12

Auditory scene analysis – organization and segregation of acoustic stimuli into biologically significant elements or →auditory objects; see Chaps 11, 12

Auditory threshold – see →threshold (in sensory systems) and Chap 11

Auditory tool network – see Chap 12

Autism – developmental disorder of social interaction and communication, showing restricted and repetitive behavior; see Chap 26

Autonomic nervous system (ANS) – that part of the nervous system that regulates basic internal processes of smooth muscle, cardiac muscle and glands. The executing part of the ANS is divided into a →parasympathetic and a →sympathetic branch (→sympathetic nervous system); see Chaps 2, 3, 4, 5, 10, 19

Aversive conditioning – employment of an unpleasant (e.g., painful) stimulus or punishment to stop an unwanted behavior to be modified or abolished or to induce an aversion against a targeted behavior; see →conditioned taste aversion and Chap 3

Avian – see Chaps 12, 15

Avoidance – see Chaps 1, 2, 3, 4, 7, 20, 22, 23, 25, 27

Awareness – see Chaps 3, 5, 7, 8, 9, 14, 27

Axon – tubular process extending from a →neuron body towards target cells. Axons carry →action potentials from the cell body to the nerve terminal. Depending on their function, axons may have varying diameter and be →myelinated or not; see Chaps 1, 3, 4, 5, 6, 7, 10, 12, 13, 16, 17, 18, 19, 22, 23, 27

Axon conduction velocity – velocity at which an →action potential propagates along an →axon; see Chap 18

Axon reflex – neurally mediated effector response that is brought about by the passage of →action potentials along →axons without traversing a →synapse, except that between the nerve ending and the effector tissue. The best known example is the cutaneous →flare response to irritation or injury. When some axon branches are activated by an irritant stimulus, nerve impulses travel centrally to the branching points and pass →antidromically to the other branches and thus back to the skin, where peri-arteriolar branches of sensory →neurons release vasoactive →neurotransmitters (e.g., →calcitonin-gene-related peptide and →substance P) and thereby cause arteriolar dilatation; see Chaps 4, 5

Baboon – see Chaps 19, 26

Backward walking – see Chaps 1, 21, 22, 23

Bag fiber – →intrafusal muscle fiber in muscle spindle; see Chap 8

Balance – The definition of balance depends on the specific motion task. In *static situations* such as quiet upright stance, balance requires the vertical projection of the body →center of mass (COM) into the →base of support to achieve postural equilibrium and orientation with minimal movement. The base of support describes the possible range of the →center of pressure (COP). Static balance control aligns the body with the direction of →gravity, the support surface and the visual environment. In *dynamic situations* such as locomotion, the term balance often implies robust and safe task execution known as *dynamic balance* control. Under these conditions, the COM may temporarily move out of the base of support, but balance must eventually be restored in time; see Chaps 1, 7, 8, 10, 12, 17, 19, 20, 21, 22, 23, 25

Ball-and-socket joint – see Chap 1, 17

Band-pass filter – filter that attenuates low- and high-frequency components of an input signal below and above a central band of the →spectrum; see Chaps 1, 11, 12, 14

Band-passed noise (BPN) – see Chap 11

Bandwidth – difference between the highest and lowest frequency contained in a signal; see Chaps 11, 12

Barn owl – see Chap 12

Basal forebrain – structures located on the ventral aspect of the →forebrain. These structures include →pre-optic area, anterior →hypothalamus, septal nuclei, →bed nucleus of the stria terminalis, diagonal band of Broca nuclei, substantia innominata including the basal nucleus of Meynert, olfactory tubercle and olfactory cortex, amygdaloid nuclei (→amygdala), →nucleus accumbens (→basal ganglia). More commonly, the basal forebrain is defined as a collection of →cholinergic (→acetylcholine) →neurons that occupy the areas below the lenticular nuclei (`lens shaped´ →putamen and →globus pallidus; →basal ganglia); see Chaps 3, 7, 13, 16, 23

Basal ganglia – The basal ganglia can be roughly divided into three broad `domains´: the dorso-lateral, dorso-medial and ventral basal ganglia. The input stations of the basal ganglia are the →striatum and the →nucleus accumbens, various →thalamic nuclei, the →centro-median (CM) nucleus and parafascicular nucleus and the entire cerebro-cortical mantle. Cerebral inputs arise from →neurons whose →axons remain in the →telencephalon and innervate the striatum. →Pyramidal tract neurons (PTNs) that project to the →brainstem and/or →spinal cord also give off collaterals to more than one basal ganglia region. The major

basal-ganglia outputs originate in the →globus pallidus internus (GPi) and →substantia nigra pars reticularis (SNr), and are routed through the →thalamus back to the →cerebral cortex, with some important outputs targeting →sub-cortical structures. The basal ganglia are implicated in various functions such as →learning, especially of associations between actions and their consequences; →habit formation using →reinforcement learning; computation of movement costs (e.g., control complexity, physical →work, elapsed time) and available →rewards based on previous experience; contribution to →decision making and →action selection; feedforward planning and regulation of intensive movement aspects, such as peak force, velocity, and scaling; on-line feedback control of movement trajectory with correction of →motor errors; organization of rapidly alternating or sequential motor acts; →motor learning, and retention and →recall of well-learned motor skills; see Chaps 2, 3, 4, 5, 7, 9, 10, 12, 14, 16, 20, 22, 23, 24, 25, 26, 27

Basal ganglia disorders – Disturbances and diseases of the →basal ganglia cause a number of syndromes. There are several forms of →hyperkinetic disorders, characterized by involuntary and uncontrollable movement fragments intruding into the normal flow of motor activity. These disorders include: →Huntington´s disease, →dystonia, →Tourette syndrome. A typical →hypokinetic disorder is →Parkinson´s disease, which is characterized by lack or reduction of voluntary movement (→akinesia or →hypokinesia, respectively), and some other symptoms. Most basal ganglia disorders also involve psychic and →cognitive impairments; see Chaps 16, 26

Base of support (BOS) – area(s) of the body in contact with the environment, which area(s) may enable support from `environment reaction´ forces; see Chaps 19, 20, 21

Basilar membrane (BM) – see Chaps 1, 11

Basket cells (in cerebellar cortex) – inhibit →Purkinje cells; see Chap 10

Bat – see Chaps 1, 11, 12, 16

Bed nucleus of the stria terminalis – see Chap 2

Bee – see Chap 1

Behavior, behavioral – almost all chapters

Behavior control column – see Chap 23

Belt (in auditory →cerebral cortex) – see Chap 12

Bereitschaftspotential – readiness potential; see Chap 24

Bernstein´s problem – problem of elimination of →redundant →degrees of freedom (DOFs) during natural movements; see Chap 1

β-motoneurons – relatively large →motoneurons with →axon diameters largely overlapping those of →α-motoneurons and innervate →muscle fibers in →skeletal muscles (extrafusal muscle fibers) and in muscle spindles (→intrafusal muscle fibers); see Chaps 19, 22

Beta oscillation – see →neuronal oscillations and Chap 3

Betz pyramidal cell – see Chap 26

Biceps brachii muscle – see Chaps 1, 9, 17, 18, 25

Biceps femoris muscle – see Chap 21

Binaural – having, or relating to, two ears; see Chaps 12, 20

Binaural integration – see Chap 11

Binocular correspondence – condition in which images from the left and right eyes occupy identical positions on the two retinae; see Chap 14

Binocular disparity – difference in images cast upon the two retinae; necessary and sufficient condition for stereopsis; see Chaps 13, 14, 15, 16

Binocular rivalry – When two different images are projected onto corresponding retinal areas of the two eyes, one image is dominant and the other suppressed in alternation; see Chap 14

Binocular vision – see Chap 14

Biological motion recognition – see →recognition and Chap 14

Biomechanics – mechanics of biological structures and processes and science thereof; see Chaps 1, 19, 20, 21, 22, 25

Biped – meaning "two legs"; see Chaps 19, 20, 21, 23

Bipedal gait – see Chap 21

Bipolar cell (in retina) – see Chap 13

Bird – see Chaps 1, 12, 17, 26

Bitter taste – see Chap 2

Blind, blindness – loss of the ability to see; may be caused by damage to the eye (particularly the retina), →optic nerve, →optic tract, optic radiation (→radiatio optica), brain areas involved in processing visual stimuli or the connections between these areas; see Chaps 7, 14

Blindfolded – see Chaps 7, 9, 12, 20

Blindsight – residual vision following lesions of the optic radiation (→radiatio optica) and/or primary visual cortex (area V1); see Chaps 13, 14

Blind spot – the disc without photoreceptors, where nerve fibers from retinal ganglion cells (RGCs) exit the eye ball and form the →optic nerve; see Chaps 13, 14

Blood-brain barrier – see →area postrema and Chap 2

Blood flow – see Chaps 2, 5, 10, 17

Blood pressure – see Chaps 1, 2, 4, 8, 9, 10

Blood sugar – see Chap 8

Blue-yellow opponency (in retina) – see Chap 13

Bodily self-consciousness includes at least three aspects: *self-identification* (also referred to as →body-ownership): a subject´s feeling that the physical body and its parts belong to himself/herself; self-location: experience of one´s place in space; *first-person perspective*: experience of the position from where a subject perceives the world; see →body-ownership and Chap 10

Body-centered (→frame of reference) – frame of reference centered at the body; see Chap 24

Body geometry – see Chaps 1, 7, 9, 19, 20

Body image – The controversial term `body image´ may be defined as a →perceptual, heterogeneous body representation. It has different aspects: the subject´s perceptual awareness of his/her own body; the subject´s conceptual understanding (including mythical and/or scientific knowledge) of the body; the subject´s →emotional attitude toward his/her own body; see Chaps 1, 20

Body-ownership – also referred to as *self-identification*: a subject´s feeling that the physical body and its parts belong to himself/herself; component of →bodily self-consciousness, complemented by `self-location´ (experience of one´s place in space) and `first-person perspective´ (experience of the position from where a subject perceives the world); see also Chaps 6, 7

Body-part-centered (→frame of reference) – frame of reference centered at a body part; see Chap 25

Body schema – see Chaps 1, 7, 9, 19, 26

Bone – see Chaps 1, 4, 8, 10, 11, 17, 19, 26

Border ownership (in vision) is coded by subsets of →neurons in areas V1, V2 and V4. They encode not only local →contrast borders, but also the side (object) to which the border belongs. This `decision´ is based on signals from far outside the classical →receptive field (RF), indicating that non-classical receptive-field surrounds may contribute to the determination of border ownership and, hence, figure-ground segregation and →depth-ordering; see Chap 14

Bottom-up processing – information processing proceeding in a single direction from sensory input to `higher centers´, without feedback from higher centers; see →top-down processing and Chaps 12, 14, 16

Boundary cells – The term 'boundary cells' includes `boundary vector cells´ and →`border cells´. The discharge of a boundary cell is primarily determined by environmental boundaries such as vertical surfaces ('walls') or drop edges ('cliffs'). A *boundary vector cell* discharges at a preferred distance and direction from an environmental boundary, for example whenever there is a boundary 40 cm to the north of the animal. For a *border cell*, most of its locational firing field occurs adjacent to a boundary; see Chap 23

Brachialis muscle – see Chaps 17, 18

Brachial plexus – see Chap 9

Brachio-radialis brachii muscle – see Chap 1

Bradykinesia – slowness of movement and poverty of normal associated movements, in particular in →Parkinson´s disease; see Chaps 23, 26

Bradykinin – small peptide of the kinin family that excites peripheral nerves and regulates the contraction of blood vessels and fluid transport by epithelia; see Chaps 4, 5, 9, 19

Braille – see Chap 14

Brain-derived neurotrophic factor (BDNF) – belongs to the family of →neurotrophic factors (neurotrophins, Nts); regulates neuronal development, →synaptic transmission, and cellular and →synaptic plasticity; contributes to the formation and maintenance of certain forms of →memory; see Chaps 3, 5

Brain imaging – see Chaps 2, 3, 7, 10, 12, 14, 24, 25, 26, 27

Brainstem – *truncus cerebri*, composed of →n (→mesencephalon), →pons, and →medulla oblongata; see almost all chapters

Brainstem burst generator (in oculomotor control) – see Chap 16

Breathing – see Chaps 1, 17

Broca´s region (→Brodmann´s area 44 and area 45) lies in the inferior frontal gyrus (→opercular part) of the →frontal cortex (lobe) and can be subdivided into more than a dozen areas; it has traditionally been thought to be involved in speech planning but not execution; it has also been implicated in language comprehension, syntactical analysis, mathematical calculation, music processing, pure →memory processes, →binocular disparity, representation of sequential information, grasping and manipulation, and – as part of the human `mirror neuron system´ (mirror neurons) – in understanding the actions of others; see Chap 26

Brodmann´s areas are areas in the human →cerebral cortex (→cortical areas) distinguished from one another by differences in cellular organization (cytoarchitecture) and →white matter patterns (myeloarchitecture); see Chaps 4, 10, 12, 14, 16, 20, 26

Brown-Séquard syndrome – This syndrome is characterized by differential sensory and motor loss resulting from →spinal cord injury. Musculature innervated by →motoneurons below the lesion site becomes →hemiparetic, and vasomotor tone and sweat production are reduced, leading to an initial overwarming, reddening and dryness of the skin. Interruption of the →dorsal columns entails loss of deep kinesthetic and vibration →sensitivity. On the contralateral intact side, pain and temperature sensation are abolished and touch →sensitivity is slightly reduced; see Chap 7

Bug detector – see Chap 13

Build-up neuron (BUN) (in oculomotor control) – also *prelude* →*neuron*; see Chap 16

Burst firing (bursting) – →neuron´s endogenous ability to generate an oscillation of the membrane potential whose successive →depolarizations drive rhythmic bursts of →action potentials. This ability is based on a set of active →voltage-gated ion channels. Endogenous bursters often are also referred to as →pacemaker neurons. Some so-called `conditional bursting neurons´ can only burst in the presence of specific →neuromodulators; see repetitive discharge (firing) and Chaps 2, 3, 5, 8, 9, 10, 13, 16, 18, 22, 23, 25

Bushy cells (in the →ventral cochlear nucleus) – →neurons that receive large →synapses (calyces of Held) from auditory nerve fibers and project to the superior olivary complex (SOC); see Chaps 11, 12

C3-C4 proprio-spinal system – see Chap 23

Ca^{2+} channel – see →calcium (Ca^{2+}) channel and Chap 13

Calcarine fissure (sulcus) – *fissura calcarina*; see Chap 14

Calcitonin-gene-related peptide (CGRP) – co-transmitter derived from the gene encoding calcitonin. It acts on the CGRP →receptor, which belongs to the family of →G-protein-coupled receptors. It is expressed in group Aδ (III) and group C (IV) sensory nerve fibers and acts as pro-→nociceptive →neurotransmitter at central release sites and as pro-→inflammatory mediator at peripheral release sites; see Chaps 4, 5, 10

Calcium (Ca^{2+}) – see Chaps 2, 3, 4, 5, 8, 10, 11, 17, 18, 22, 27

Ca^{2+}-activated Cl^- channel – calcium-activated chloride channel; see Chap 4

Calcium carbonate (calcite) – see Chap 10

Calcium (Ca^{2+}) channel – see Chap 5

Ca^{2+}-dependent K^+ channels – type of →voltage-gated ion channel specific for potassium (K^+) ions, whose opening requires the binding of Ca^{2+} ions to its internal surface; see →afterhyperpolarization (AHP); →BK channels (large-→conductance →Ca^{2+}-dependent K^+ channel; see →afterhyperpolarization (AHP) and →ligand-gated ion channels), SK channels, and Chaps 5, 22

Calyx of Held – see Chap 18

Ca^{2+} pump – see Chap 17

Callosal – refers to the →corpus callosum; see Chap 7

Calmodulin (CaM) – calcium(Ca^{2+})-binding protein that regulates diverse proteins and cellular functions; see Chaps 17, 18

Caloric stimulation (irrigation) - an artificial means of stimulating the vestibular labyrinths (Chap 6). The stimulation is produced by circulating warm (up to 40°C) or cool (down to 0°C) water in the outer ear canal. Besides vertigo, this stimulation induces →nystagmus via the vestibulo-ocular reflex (VOR); see Chap 10

Cannabinoids – group of lipophilic compounds that bind to cannabinoid →G-protein-coupled receptors CB1 and CB2 and certain subsets of →transient receptor potential (TRP) channels; they are classified by their source: herbal (derived from the hemp plant *Cannabis sativa*, marijuana), endogenous (→endocannabinoids produced by animal cells) or synthetic; see Chaps 2, 5, 27

Capsaicin – component of capsicum pepper, active agent in spicy foods; capsaicin acts on the →transient receptor potential (TRP) channel vanilloid subfamily member 1 (→TRPV1); see Chaps 2, 4, 5

Capsule (of joint) – see Chaps 1, 6, 8, 17, 19

Carbon monoxide (CO) – see Chap 3

Carnivore – see Chap 26

Carpometacarpal joint – see Chap 17

Carrageenan – see Chap 4

Cartesian coordinate system – see →coordinate system and Chap 1

Cartilage – see Chaps 1, 17, 21

Cat – see Chaps 1, 5, 7, 8, 10, 12, 16, 17, 18, 19, 20, 21, 22, 23, 25

Catch property (of →skeletal muscle or →motor unit) – rapid increase in force generated by a muscle or motor unit when two →action potentials activating the muscle are closely spaced in time (i.e. a doublet); see Chaps 18, 19

Catecholamines – biological amines derived from the amino acid L-tyrosine, including →adrenaline (epinephrine), →noradrenaline (norepinephrine), →dopamine and →L-DOPA (a precursor of dopamine). Catecholaminergic cell groups and fibers are found widely throughout the nervous system. See →monoamines and Chaps 4, 5

Cation channel – →ion channel permeable to positively charged ions; see Chaps 4, 8, 11

Caudal cingulate zone (CCZ) (in humans) – see →cingulate motor areas and Chap 26

Caudal intraparietal (CIP) area – see Chaps 14, 19

Caudal intraparietal sulcus (cIPS) – see →intraparietal sulcus and Chaps 24, 26

Caudate nucleus – →nucleus caudatus: large cell assembly elongating into a tail and belonging to the →basal ganglia; see Chaps 2, 16, 26, 27

Caudo-medial belt (CM) (in auditory →cerebral cortex) – see Chap 12

Center frequency – see Chaps 11, 12

Center of gravity (COG) – see →center of mass (COM) and Chaps 17, 21, 26

Center of mass (COM) – the point in or near the body where total body →mass is concentrated. COM is also called the center of →gravity, which in a strict sense is not quite correct; see Chaps 1, 19, 20, 21, 23, 24

Center of pressure (COP) – the central point of the distributed pressures exerted by the body on the ground; it varies with time; see Chaps 19, 20, 21, 25

Center-surround organization – Retinal ganglion cells (RGCs), lateral geniculate nucleus (LGN) cells and many visual cortical cells have →receptive fields (RFs) made up of a disk-shaped `center´ and an annular `surround´. The borders between center and surround are defined by different preferences for stimulus →contrast (bright or dark) or sometimes by preferences for stimulus wavelength (color); see Chaps 13, 14

Central fatigue – see →muscle fatigue, neural factors and Chaps 17, 22

Central mesencephalic reticular formation (cMRF) – see →reticular formation (RF) and Chap 16

Central nervous system (CNS) – also called →neuraxis, consisting of the →spinal cord, →brainstem, and →telencephalon; see almost all chapters

Central nucleus of the inferior colliculus (ICC) – see →inferior colliculus and Chap 12

Central pattern generator (CPG) – see Chaps 1, 9, 20, 21, 22, 23

Central sensitization – increased responsiveness of →nociceptive neurons in the →central nervous system (CNS) to their normal or sub-threshold afferent input [→threshold (in sensory systems)]; see Chaps 4, 5

Cerebellar cortex – see →cerebellum and Chaps 10, 15, 16, 23, 26, 27

Cerebellar cortical atrophy – non-hereditary degenerative →ataxia; see →cerebellum and Chap 20

Cerebellar disorders – see →cerebellum and Chaps 20, 26, 27

Cerebellar intermediate hemisphere – see →cerebellum and Chap 23

Cerebellar lateral hemisphere – see →cerebellum and Chap 23

Cerebellar locomotor region (CLR) – see →cerebellum and Chap 23

Cerebellar peduncle – see →cerebellum and Chap 27

Cerebellar vermis – see →cerebellum, →vermis and Chaps 10, 20, 23

Cerebellum – A dorsal, transverse foliated appendage to the →pons. The cerebellar cortex receives three kinds of inputs: (i) →mossy fibers from various sources (sensory signals of various modalities including vestibular and proprioceptive information; →efference copies from motor centers and the →spinal cord); (ii) →climbing fibers (CFs) from the medullary →inferior olive (IO); (iii) →neuromodulatory fibers from →brainstem systems. The only output from the cerebellar cortex originates from the inhibitory →Purkinje cells which target the →vestibular nuclei and →deep cerebellar nuclei [→nucleus fastiguus, →nucleus interpositus (in humans: *nuclei emboliformis et globosus*), and →nucleus dentatus] with further widespread connections. The cerebellum is implicated in a number of functions, including oculomotor control, control of upright stance and locomotion, reaching and grasping and speech, timing and coordination of movement, control of →motor cortex (area F1, area M1) excitability, prediction of sensory consequences of actions, error detection and correction, →motor learning, →classical conditioning (e.g. eyeblink conditioning), and even →emotional, →motivational and →cognitive functions; see almost all chapters

Cerebral achromatopsia – see Chap 14

Cerebral column – group of functionally related →neurons arranged in a vertical cylinder or slice of →cerebral cortex; see Chap 14

Cerebral cortex – The thin sheet of neural tissue on the surface of the →forebrain, containing several layers of nerve cells. The human cortex has a thickness of about 3 mm (0.1 in) and performs a vast array of complex functions; see almost all chapters

Cerebro-cortical – refers to →cerebral cortex; see almost all chapters

Cerebro-olivo-cerebellar (COCP) pathway – see Chap 23

Cervico-ocular reflex – see →reflex and Chaps 9, 16

Cervico-spinal reflex – →reflex activation of body muscles elicited by stimulation of neck →sensory receptors, particularly muscle spindles in deep, inter-vertebral muscles; see →reflex and Chap 20

Chain fiber – →intrafusal muscle fiber in muscle spindle; see Chap 8

Channelopathy – disease resulting from alteration and dysfunction of an →ion channel; see Chap 5

Characteristic frequency – that →sound frequency at which a given auditory →neuron responds best, i.e., at lowest threshold [→threshold (in sensory systems)]; see Chap 11

Chemokines – →cytokines (small secreted proteins) that induce directed chemotaxis in nearby responsive cells (*chemo*-attractant cyto*kines*) through binding to →G-protein-coupled receptors; see Chap 5

Chemo-receptor (chemo-sensor) – chemical sensor, →receptor →sensitive to molecular properties of chemical substances; see Chaps 1, 3

Chemo-sensation, chemo-sensitive – see Chaps 2, 3, 9

Chemotopy – see Chaps 2, 3

Chemotopic map– see Chap 3

Chick – see Chap 22

Chimpanzee – see Chap 2

Chinchilla – see Chap 11

Chloride (Cl^-) – see Chaps 3, 5

Cholecystokinin (CCK) – intestinal peptide →hormone released in response to food entering the intestine. CCK induces gall bladder contractions and secretion of pancreatic enzymes. Within the →central nervous system (CNS), CCK appears to act as a →neuromodulator; see Chaps 2, 5

Cholinergic refers to →acetylcholine and cells producing and secreting acetylcholine as a →neurotransmitter; see Chaps 2, 3, 7, 10, 11, 12, 13, 14, 16, 22, 23

Chopper cell – also called T →stellate, type I multipolar, planar multipolar cell; see Chap 12

Chorda tympani – see Chap 2

Chorea – hyperkinetic disorder (hyperkinesia) characterized by involuntary, non-symmetrical, irregular, brief, rapid, jerky movements of face, head, arms or hands. Grimacing and smacking may be further signs. In mild cases, choreatic movements may be blended into natural movements and can thus be mis-interpreted as gestures of embarrassment. In more severe cases, choreatic movements derange daily life, and may lead to fatigue and exhaustion. →Muscle tone is often reduced (→hypotonia). Chorea is seen in →Huntington´s disease, can be caused by chronic use of →L-DOPA (levodopa) in →Parkinson´s disease, and occurs in the rare condition of Sydenham´s chorea. Chorea may be generalized or localized to one body side (*hemi-chorea*). Choreoathetosis is the term used when the movements have a slower writhing component; see Chap 16

Chronic pain – pain lasting for long time periods exceeding the period of initial tissue damage and its healing. Chronic pain is now recognized as a separate disease caused by many aeteologies, an important mechanism underlying its maintenance being the neuro-→inflammation mediated by →astrocytes. It results from activity-dependent →synaptic plasticity that leads to the →sensitization of →nociceptive networks (increases in excitatory →synaptic transmission and loss of inhibitory synaptic transmission) (→central sensitization); see Chaps 1, 4, 5, 9

Chronic stress – see →stress and Chap 5

Chronic work-related neck pain – see Chap 20

Ciliary body – see Chap 13

Ciliary ganglion – see Chap 13

Ciliary muscle – see Chaps 13, 16

Cingulate cortex (gyrus) (in →cerebral cortex) – *gyrus cinguli*. The →anterior cingulate cortex (ACC) receives inputs from various structures. Inputs from the →orbitofrontal cortex (OFC) may convey information about →reward and non-reward behavioral outcomes. The →posterior cingulate cortex receives inputs conveying spatial and action-related information from →parietal cortical →areas. This constellation may enable the cingulate cortex to learn associations between actions and their outcomes, with outputs from the mid-→cingulate motor areas conveying the results to →premotor →cortical areas; see Chaps 2, 4, 5, 7, 10, 16, 23

Cingulate eye field – see →eye fields and Chap 16

Cingulate motor areas (in →cerebral cortex) are situated in the →cingulate cortex (gyrus) on the medial surface of the hemisphere and include: (i) dorsal cingulate motor area (area CMAd) in monkeys (probably corresponding to the human caudal cingulate zone (CCZ)); ventral cingulate motor area (area CMAv) (probably corresponding to the posterior rostral cingulate zone (RCZp)); (iii) rostral cingulate motor area (area CMAr) (probably corresponding to the anterior rostral cingulate zone (RCZa)). Cingulate motor areas (CMAd, CMAr, CMAv) have been implicated in the preparation and execution of movements. Area CMAr receives task-relevant information from the →prefrontal cortex (PFC), →limbic system, basolateral →amygdala and ventral →striatum, and may thus be involved in →emotional-motor interactions; see Chaps 7, 16, 24

Circadian rhythm – rhythmic variation of many biological variables at a cycle period of circa one day (circa diem), when removed from regular, 24 h daily cycles of the environment, such as light and dark or warm and cold. Internally generated circadian rhythms are synchronized to the exact external daily oscillation by several signals, with light acting as the major signal; see Chap 13

Circumvallate papilla – see Chap 2

Circumventricular organs – see Chap 2

Citric acid – see Chap 2

Clarke´s column – see Chap 19

Classical conditioning (Pavlovian conditioning) – form of associative →learning where two stimuli become associated by repeated coupled presentations. An example is →eyelid conditioning; see Chaps 10, 16

Classical receptive field (CRF) (in vision) – see →receptive field (RF) and Chaps 13, 14

Claustrum – lamina of →gray matter running in parallel to the →putamen (→basal ganglia), with reciprocal connections to ipsi- and contralateral cerebro-cortical areas; see Chap 14

Climbing fibers (CFs) – nerve fibers originating from →neurons in the →inferior olive (IO) and projecting to the →cerebellum; one olivo-cerebellar →axon splits into several branches, each coiling around and climbing up the →dendrites of one →Purkinje cell of the cerebellar cortex; olivo-cerebellar axons also project to the →deep cerebellar nuclei and the →synapses from →mossy fibers to →granule cells; see Chaps 10, 15, 16, 23, 24, 26, 27

Clitoris – see Chap 6

Closed loop – In engineering, `closed loop´ is used in the context of a closed-loop control system whose output variable is to behave in a desired way. Such an arrangement consists of the physical →plant to be controlled, sensors measuring the plant output, actuators used to steer the plant and a control law governing the actuators. The control law transforms commands representing the desired system behavior and feedback signals (from the sensors) representing the actual system behavior into signals steering the actuator, which act on the plant; see Chaps 1, 5, 16

Cochlea – see Chaps 1, 10, 11, 12

Cochlear nucleus – composed of the →anterior ventral cochlear nucleus (AVCN) and the posterior ventral cochlear nucleus (PVCN); see Chaps 11, 12

Cochleotopy (cochleotopic) – also called *tonotopy* (→tonotopic mapping); see Chap 12

Cockroach – see Chap 17

Cognition, cognitive – The term is used differently in different disciplines. In neuroscience, it refers to mental processes including →attention, awareness, →perception, →decision making, →learning, →memory, problem solving, reasoning, thinking; see Chaps 1, 2, 3, 4, 5, 7, 10, 14, 16, 19, 20, 21, 23, 24, 27

Coincidence detector – →neuron with a high →sensitivity to simultaneously arriving inputs, the probability of a spike discharge rising with the synchronicity of inputs; see Chap 3

Cold allodynia – see Chaps 4, 5

Cold receptor – see →receptor cell and **Chap 1**

Collagen – glycoproteins that are the main proteins of connective tissue (cartilage, ligaments, tendons, bone and teeth); see Chaps 6, 17

Colliculi – The term usually refers to the →mesencephalic colliculi, consisting of the →superior colliculus (SC) and →inferior colliculus (IC) and collectively building the quadrigeminal plate or tectum mesencephali; see Chaps 12, 19

Colliculus superior (SC) – →colliculi, →superior colliculus; see →colliculi and Chap 16

Color constancy – phenomenon that the color of a surface is →perceived fairly much the same irrespective of the actual illumination that significantly influences the wavelength composition of the light reflected from the surface; see Chap 14

Color contrast – enhancement of one color (e.g., red) when surrounded by its opponent (e.g., green); see Chaps 13, 14

Color opponency – see Chap 13

Color vision – see Chaps 13, 14

Commissural interneuron – see Chaps 22, 23

Common fate – see →Gestalt principles and Chap 14

Complex cell (in primary visual cortex, area V1)) – type of →neuron exhibiting particular →receptive field (RF) structure and physiological properties; see Chap 14

Complex regional pain syndrome (CRPS) – →chronic pain usually affecting a limb after trauma or injury and having inflammatory and neuropathic components; see Chap 4

Complex spike (CS) (of →cerebellar →Purkinje cell) – see Chaps 10, 15, 16, 23, 27

Compression non-linearity – see Chaps 8, 11

Concentric contraction – →skeletal muscle contraction with shortening; see Chap 18

Conditioned taste aversion – particular paradigm of →aversive conditioning or conditioned →learning, in which a subject learns to avoid a taste stimulus (conditioned sensory stimulus) that is paired with visceral malaise (unconditioned stimulus); as a consequence of conditioned taste aversions, the →hedonic value (→hedonics; →taste hedonics) of the conditioned taste becomes →aversive and disliked; see Chap 2

Conductance (electrical) – measure of the ability of an electric circuit to conduct electricity, reciprocal of electrical resistance; see Chaps 2, 3, 4, 11, 13

Conduction velocity (of →action potential propagation) – see Chaps 8, 18

Cone photoreceptor – see →receptor cell and Chaps 1, 13, 16

Conjugate eye movement – see Chaps 15, 16

Consonant – see Chap 11

Con-specific – member of the same species; see Chaps 3, 7, 11, 12

Con-specific call – see Chap 11

Constant error (in pointing/reaching) – see Chap 24

Contour – see Chaps 7, 13, 14

Contour completion – see Chap 14

Contraction time (of →skeletal muscle) – see Chap 18

Contrast (in sensory systems) – measure of relative stimulus →intensity at some point in relation to the average (background) intensity level *I* in its surroundings, usually expressed as $\Delta I/I$; see Chaps 3, 11, 13, 14, 16

Contraversive – directed toward the contralateral side; see Chaps 15, 16

Convergence (of eye movements) – see Chaps 13, 14, 15, 16

Coordinate system – a system to assign numbers (coordinates) to objects or locations in space with respect to some →frame of reference; see Chaps 1, 12, 15, 16, 24

Coordinate transformation – conversion of a signal from one →frame of reference into another; see Chaps 1, 7, 16, 24, 25

Core (in auditory cortex) – see Chap 12

Coriolis force – velocity-dependent force imposed on objects when they move in relation to a rotating environment; see Chaps 1, 27

Cornea – see Chap 13

Corollary discharge – term introduced by Roger Sperry (1950), often used synonymously with von Holst and Mittelstaedt´s (1950) →efference copy; see Chap 1

Corpus callosum – largest commissure of the (human) brain, connecting the two hemispheres; see Chaps 7, 13, 26

Correction saccade – see saccade and Chaps 15, 16

Cortex – The term cortex has various meanings. Most often it is used to refer to →cerebral cortex. However, not only the →cerebrum has a cortex, but also the →cerebellum, as well as the kidney and →adrenal gland.

Cortical area – see →area (in →cerebral cortex) and Chaps 2,3, 4, 7, 10, 12, 13, 14, 15, 16, 20, 23, 24, 25, 26

Cortico-bulbo-spinal system – The rostral →premotor cortical areas (F6, F7) strongly project to various →brainstem nuclei, the major target being the magnocellular reticular nucleus in the →reticular formation. These nuclei in turn give rise to the medial descending system, which terminates on →spinal →interneurons, long proprio-spinal neurons, commissural interneurons and →motoneurons predominantly innervating proximal limb and axial (trunk) muscles. Together with other ventro-medial pathways, this bilaterally organized cortico-→reticulo-spinal system is involved in body and head orientation, the postural stabilization and coordination of body and limbs in preparation for and during voluntary limb movements (e.g., target reaching), and in their visual guidance. In cats and non-human →primates, the cortex projects to the →nucleus ruber in the →n, which gives rise to the →rubro-spinal tract that descends, together with the lateral →cortico-spinal tract (CST), in the contralateral dorso-lateral →funiculus. The cortico-rubro-spinal system is →somatotopically organized. see Chaps 23, 26

Cortico-bulbar tract – tract of nerve fibers originating from →neurons in the →cerebral cortex and targeting neurons in the →brainstem; see Chap 23

Cortico-motoneuronal cell – →neuron in the →cerebral cortex, whose descending →axon collaterals make monosyaptic connections to →skeleto-motoneurons; these connections are absent in non-→primates and vary in extent in primates. They are most numerous in the great apes and humans. In humans, they connect to skeleto-motoneurons innervating arm, back and leg muscles; see Chap 26

Cortico-spinal tract (CST) – The cortico-spinal system originates from pyramidal cells of the →cerebral cortex including all →premotor areas, →primary somatosensory cortex (S1, SI), →posterior parietal cortex (PPC), and the parietal →operculum, and projects all along the →spinal cord in a ventral and a lateral portion. Most of the cortico-spinal fibers originating in the →primary motor cortex (area F1, area M1) cross to the contralateral side (about 75% in the →pyramids and 15% in the spinal cord), the rest (roughly 10%) remains uncrossed and innervate proximal shoulder →motoneurons. While the proportion of cortico-spinal fibers in the human →capsula interna and even the cerebral peduncle is small, their influence on motor control of the hand is disproportionately strong and important for dexterity, although non-monosynaptic cortico-motoneuronal connections via cervical segmental →interneurons and →proprio-spinal C3-C4 →neurons play a role as well. Many cortico-spinal tract fibers also send collaterals to →brainstem structures, including the magnocellular →nucleus ruber, from which fibers join direct cortico-spinal fibers in the lateral descending system. Since the

cortico-spinal tract fibers also branch to the spinal →dorsal column nuclei and the →dorsal-horn laminae, they influence sensory information transmission, presumably related to →nociceptive, somatosensory, →reflex, →autonomic and somatic motor functions; see Chaps 3, 5, 7, 19, 20, 22, 23, 26, 27

Corticotropin-releasing factor (CRF) or hormone (CRH) – see Chap 10

Cosine gain rule – see Chap 10

Cranial nerves – nerves originating in the →brainstem, with the exception of the first and second cranial nerves, which are no true peripheral nerves but fiber tracts of the brain. Cranial nerves include: I, n. opticus; II, n. olfactorius; III, n. oculomotorius; IV, n. trochlearis; V, n. →trigeminus; VI, n. abducens; VII, n. facialis; VIII, n. acustico-vestibularis; IX, n. glossopharyngeus; X, n. vagus; XI, n. accesssorius; XII, n. hypoglossus; see Chaps 2, 10, 11, 15

Crawling – see Chap 22

Creatine – see Chap 16

Creatine phosphate (CrP) – see Chap 17

Cribriform plate – see Chap 3

Crista ampullaris – see Chap 10

Cross-bridge (in →skeletal muscle) – see Chaps 8, 17, 18, 19

Cross-bridge cycling – see Chaps 17, 18

Crossed extension reflex – see →reflex and Chaps 1, 20

Cross-modal – see Chaps 2, 3, 7, 12, 14

Crustacean – see Chaps 1, 3

Cuneate nucleus – see Chap 7

Cupula (in inner ear) **–** see Chap 10

Current (electrical) – see Chaps 3, 8, 10, 17, 18, 20, 22

Cutaneous mechano-receptors – →sensory receptors →sensitive to mechanical stimuli hitting the skin; see →receptor cell and Chaps 1, 6, 7, 8, 9, 19, 20, 22

Cutaneous pain – pain originating in the skin; see Chap 4

Cutaneous receptive field – →receptive field (RF) of a →cutaneous mechano-receptor**;** see Chap 6

Cutaneous receptors – see →receptor cell and Chaps 1, 6, 20, 22

Cutaneous reflexes – →reflex motor actions to a stimulus hitting the skin; see →reflex and Chap 22

Cyclic adenosine monophosphate (cAMP) – 3-5-cyclic adenosine monophosphate is formed from →adenosine triphosphate (ATP). It acts as a second messenger for intracellular →signal transduction of some `first messengers´, e.g., →hormones and →neurotransmitters, or sensory messages such as odorants; see →adenosine and Chap 3

Cyclic guanosine monophosphate (cGMP) is an intracellular second messenger formed from guanosine triphosphate (GTP); see Chaps 3, 5

Cycling (bicyle) – see Chap 17

Cytochrome oxidase (CO) – oxidative enzyme of the mitochondrial respiratory chain, which is present in →neurons and whose intensity correlates with neuronal activity; see Chap 14

Cytokine – The term `cytokine´ was formerly used to refer to proteins, such as interleukins and →tumor necrosis factor-α (TNF-α), released from →immune cells (lymphocytes, →macrophages/→microglia and polymorphs; →leukocytes) and modulating the behavior of other blood and non-blood cells in response to injury, infection and →inflammation. In neurobiology, the term is now used to refer to all low-molecular-weight messengers for inter-cellular communication and may, for example, encompass →neurotrophic factors [→neurotrophic factors (neurotrophins, NTs)], prostaglandin E_2 (PGE_2) and →adrenaline. Cytokines exert their biological effect by interacting with →metabotropic receptors (metaboreceptors). Some cytokines have pro-inflammatory effects [interleukin-1 (IL-1), IL-6 and tumor necrosis factor], others have anti-inflammatory effects [e.g., IL-10, transforming →growth factor β1 (TGF-β1)]; see Chaps 4, 5, 17

De-afferentation – interruption and loss of afferent sensory input to the →central nervous system (CNS); see Chaps 5, 19, 22, 25, 26

Deafness – see Chap 11

DeciBel – dimensionless value corresponding to ten times the logarithm (base 10) of the ratio of two intensities, two powers, or two →energies, and to 20 times the logarithm of the ratio of two pressures (for →sound pressures); see Chap 11

Decision making – Decisions can made on the basis of a gut feeling, →memory of what worked last time or careful planning. Different decisions are dissociable behaviorally and are carried out by distinct brain systems because they have different computational demands.

Decisions to strive at or avoid a goal depend on several factors. The current internal state (drives) and external situation must be →recognized. The chosen goals, items or goods must be evaluated as to their availability and desirability. The available behavioral options must be evaluated as to the benefits (utility, value), such as the quality, quantity and probability of →rewards or punishments to be expected, the time already spent and the time remaining towards the reward acquisition, and the required effort (cost) and risk involved in attaining the goal. Estimates of utility or value are continuously updated by →learning associations between expected and actual outcome (e.g., by →reinforcement learning), which requires →memory. A favorable action option must be selected, and a re-evaluation may be performed after its outcome; see Chaps 1, 4, 7, 12, 16, 23, 24, 25

Deep cerebellar nuclei – output stages of the →cerebellum, including →nucleus fastiguus, →nucleus interpositus, →nucleus dentatus; conceptually, →vestibular nuclei receiving direct →Purkinje cell outputs belong to cerebellar output nuclei but are usually not considered anatomical parts of the cerebellum; see Chaps 10, 23, 27

Deep pain – see Chap 4

Defense, defensive behavior – →aversive or escape behavior, normally associated with walking, running, leaping, galloping or →freezing; see Chaps 1, 3, 7, 23, 25

DEG/ENaC – **deg**enerin/**e**pithelial **Na**$^+$ **c**hannel; see →ASIC and Chap 4

Degenerative diseases originate from a loss of neural tissue (e.g., →Alzheimer's disease, →cerebellar degenerations, →Parkinson´s disease); see Chaps 5, 13,16, 26

Degenerin/epithelial Na$^+$ channel (DEG/ENaC) – see →ASIC and Chap 4

Degrees of freedom (DOFs) – number of variables (coordinates) needed to describe a process, such as a body´s motion in space. The DOFs of a system of rigid segments are obtained by the general relationship: DOFs = (number of generalized coordinates) – (number of constraints); see Chaps 1, 17, 21, 22, 25, 26

Delay-line hypothesis – see →Jeffress model and Chap 12

Deltoid muscle – see Chap 18

Demyelination – loss of existing →myelin sheaths of nerve fibers, which may be caused by many processes; see Chap 5

Dendrites – branched processes of a →neuron, through which information is carried from →synaptic sites towards the cell body or soma; see Chaps 3, 4, 5, 27

Dentate nucleus – see →nucleus dentatus and Chaps 10, 23, 24, 26

Depolarization – change in membrane potential (→resting membrane potential) towards more positive values on the intracellular side. A depolarization exceeding a →threshold elicit →action potentials [→threshold (of action potential)]. In many cases, depolarizations are generated by the influx of sodium (Na^+) ions through voltage-gated Na^+ channels, but can also be caused by the influx of calcium (Ca^{2+}) ions; see Chaps 1, 2, 3, 4, 5, 8, 10, 11, 17, 18, 22

Depression (mood) – see Chaps 4, 5

Depth interval – interval in depth between surfaces or objects; see Chap 14

Depth-ordering – neural process of computing the depth arrangement of visible surfaces; see Chap 14

Depth perception – see Chaps 14, 25

Dermatome – the skin region supplied by the paired →dorsal root nerves from one →spinal segment; see Chap 7

Descending vestibular nucleus (DVN) – see Chap 10

De-sensitization – see Chaps 3, 9

Dexterity, dexterous – ability to use the hand skilfully in performing difficult actions; see Chaps 1, 25, 26

dI1 interneurons represent one of six identified, embryologically early, dorsally derived populations of →spinal →interneurons (dI1– dI6). They form three →spino-cerebellar tracts (SCTs) that transmit sensory feedback to the →cerebellum. In cervico-thoracic segments, dI1 interneurons form the →rostral spino-cerebellar tract (RSCT). In thoraco-lumbo-sacral segments, dI1 interneurons build two clusters that form the →dorsal spino-cerebellar tract (DSCT) and the →ventral spino-cerebellar tract (vSCT). The SCTs convey sensory information from muscle afferents and to a lesser degree, from low-threshold mechano-receptors (LTMRs) to the cerebellum; see Chap 7

dI3 interneurons represent one of six identified, embryologically early, dorsally derived populations of →spinal →interneurons (dI1– dI6). dI3 interneurons are primarily located in laminae V-VII. dI3 interneurons receive primary afferent (predominantly group Aβ cutaneous) inputs, send out ipsilateral projections, are predominantly →glutamatergic and directly excite →α–motoneurons; dI3 interneurons thus disynaptically link cutaneous afferents (conveying touch) with motoneurons; see Chap 7

dI4 interneurons represent one of six identified, embryologically early, dorsally derived populations of →spinal →interneurons (dI1– dI6). They give rise to →GABAergic interneurons mediating →presynaptic inhibition; see Chaps 7, 19

dI6 interneurons reside in laminae VII/VIII of the mouse →spinal cord. One inhibitory subset sends axons to ipsilateral and contralateral targets, including →motoneurons (MNs) and possibly Renshaw cells as well as →cholinergic neurons (possibly $V0_C$ interneurons). Another inhibitory subset sends commissural axons to targets in close proximity to commissural neurons in the intermediate →gray matter, but not to motoneurons. Both subsets fire rhythmically during fictive locomotion, and their ablation causes defects in left-right alternation; see Chap 22

Diabetic neuropathy – a specific form of →peripheral neuropathy resulting from diabetes mellitus; see Chaps 4, 5, 20

Diagonal band of Broca – see →basal forebrain and Chaps 2, 3

Diaphragm – see →rapid-eye-movement (REM) sleep and Chap 8

Dichromacy, dichromatopsia – see Chap 13

Diencephalic locomotor region (DLR) – see Chap 23

Diencephalon – consists of four parts: epithalamus (with →habenulae and epiphysis or →pineal gland), dorsal →thalamus, subthalamus (with →subthalamic nucleus (STN) and →globus pallidus as parts of the →basal ganglia), →hypothalamus (with *neurohypophysis*; →pituitary gland); see Chaps 5, 16, 22

Diffuse noxious inhibitory control (DNIC) – see Chap 4

Digastric muscle – see Chap 8

Dihydropyridine receptor (DHPR) – see Chap 17

Dilator pupillae (of the iris) – see Chap 13

Diplopia – double vision; see Chap 14

Direction disparity – see Chap 14

Direct pathway (in →basal ganglia) – pathway from →cerebral cortex via →striatum to →substantia nigra pasr reticularis (SNr); see Chaps 16, 23, 27

Disparity (in vision) – see →binocular disparity and Chaps 14, 15, 16

Disparity limit of fusion (in vision) – see Chap 14

Dog – see Chaps 1, 20, 22

Dopamine (DA) – multi-functional endogenous →catecholamine found in several ‚sub-cortical regions of the brain. Widely distributed dopamine systems originate in the →n →substantia nigra pars compacta (SNc) and the →ventral tegmental area (VTA). This system is involved in functions related to sensory →salience, →motivation, →reward, mood and →habit formation. Dopamine acts via five →G-protein-coupled →receptors, two of which activate (D1, D5) and three of which (D2, D3, D4) reduce →cyclic adenosine monophosphate (cAMP); see Chaps 2, 3, 5, 7, 10**,** 12, 13, 14, 16, 20, 22, 23, 26, 27

Doppler effect – As a →sound source emitting a periodic sound approaches an observer, the duration of successive periods of the ongoing sound wave decreases, thereby increasing perceived pitch over time. Conversely, as a sound source moves away from the observer, the duration of the successive periods of the sound wave increases, thereby decreasing perceived pitch; see Chap 12

Dorsal cingulate motor area (CMAd) – see →cingulate motor areas and Chap 26

Dorsal cochlear nucleus – nucleus cochlearis dorsalis; see Chap 12

Dorsal columns – The dorsal columns comprise two bundles of nerve fibers on each dorsal side of the →spinal cord. These fibers conduct signals predominantly from →mechano-receptors in skin and deep body tissues to the →dorsal column nuclei; see Chaps 4, 7

Dorsal column nuclei (DCN) – nuclear complex near the spino-medullary junction of the →central nervous system (CNS), made up of the nucleus cuneatus (cuneate nucleus) and →nucleus gracilis (gracile nucleus), which receive ascending somatosensory inputs via the →dorsal columns and descending modulating inputs from higher structures; see Chaps 4, 7, 12

Dorsal horn – dorsal extension of the →spinal →gray matter; see Chap 4, 5, 7, 20, 22, 27

Dorsal paraflocculus (DPFL) – see Chap 15

Dorsal root (or posterior root) – afferent sensory root of a →spinal nerve. →Axons in the dorsal root convey somatosensory and viscero-sensory information into the →spinal cord and brain from the periphery; see Chaps 5, 7, 9

Dorsal-root ganglion (DRG) – →neuron assembly integrated in the →spinal →dorsal root, contains cell bodies of sensory afferent nerve fibers; see Chaps 4, 5, 6

Dorsal-root reflex (DRR) – →action potential conducted →antidromically on the afferent sensory →axon when primary afferent terminals reach firing→threshold [→threshold (of action potential)] due to →primary afferent depolarization (PAD); see Chap 5

Dorsal spino-cerebellar tract (DSCT) – tract of nerve fibers originating in the →spinal cord (Clarke´s column and dorsal horn) and targeting →neurons in the →cerebellum; see Chaps 7, 8, 9, 19, 23

Dorsal stream (in auditory processing) – `where´ stream for sound localization; see Chap 12

Dorsal visual stream (in visual processing) – `where´ stream, `how stream´, `vision-for-action´ stream: involved in organization and visual guidance of motor actions in space; and Chaps 13, 14, 27

Dorsal tegmental field (DTF) – see →tegmentum and Chap 23

Dorso-lateral pontine nucleus (DLPN) – see Chap 15

Dorso-lateral prefrontal cortex (DLPFC) – part of the →prefrontal cortex (PFC); is assumed to be involved in →attention and →working memory; contains the prefrontal eye field (PFEF) in the posterior part of area 46; see →prefrontal cortex (PFC), →eye fields and Chaps 4, 12, 13, 14, 16, 26, 27

Dorso-lateral premotor area (PMd) – see →premotor cortex and Chaps 7, 12, 16, 24, 25, 26, 27

Dorso-lateral striatum – see →striatum and Chap 23

Dorso-medial striatum – see →striatum and Chap 23

Dorsal reticular nucleus (DRT) – see reticular nuclei and Chaps 4, 5

Double-opponent cell – see Chap 14

Duplicity theory of vision – see Chap 13

Duty cycle – see Chap 21

Duplex theory of cutanous surface roughness →perception – see Chap 7

Dynamics – see Chaps 1, 15, 16, 23, 24, 25, 26, 27

Dynamic equilibrium – see Chap 19

Dynamic fusimotor activation, neuron – see →motoneurons and Chaps 8, 22

Dynamic stereopsis – see Chap 14

Dynorphin – class of →opioid peptides; see Chap 16

Dystonia – heterogeneous group of diseases featuring disturbances of normal →muscle tone distributions, with involuntary, sustained or repetitive contractions of opposing muscles leading to grotesque twisted postures and movements. Dystonia can be focal or multi-focal, affecting multiple body parts. It can be evoked by repetitive motor actions, e.g. playing a musical instrument or typing and then lead to →writer´s cramp; see Chap 26

Ear – see Chaps 11, 12

Eardrum – tympanic membrane; see Chaps 11, 12

Earth vertical – see →graviception and Chaps 1, 19, 20

Eccentric contraction – muscle contraction during lengthening; see Chaps 8, 18, 19

Echolocation – see Chap 12

Ectopic discharge – spontaneous →action potential discharge activity that can occur at different sites along →axons away from the normal site of impulse generation; see Chap 5

Edibility, edible – see Chaps 1, 2

Edinger-Westphal nucleus – see Chaps 13, 16

Effector selection – see Chap 24

Efference copy – copy of a →motor command; element of the re-afference principle; see Chaps 1, 9, 10, 15, 16, 20, 23, 25, 26, 27

Efferent vestibular nucleus (EVN) – origin in the →brainstem of the efferent →cholinergic (→nicotinergic and →muscarinergic) innervation of vestibular sensory neurons. The vestibular efferents project ipsilaterally, contralaterally or sometimes bilaterally to synapse on the primary afferents of Type I hair cells and directly on Type II hair cells; see Chap 10

Efficient code – theoretical model of sensory coding based on information theory. The efficient coding hypothesis posits that sensory systems are communication channels in which neuronal →action potential production aims to maximize available channel capacity by minimizing the redundancy between representational neuronal units; see Chaps 11, 13

Egocentric frame of reference – →frame or reference centered on the body (→body-centered) or body parts such as the retina (→retinotopic, →eye-centered or gaze-centered), head (→head-centered auditory system), shoulder (→shoulder-centered) or hand (→hand-centered); see Chaps 1, 14, 24

Elastic, elasticity – property of a solid material that, when deformed by an external force, recovers its original shape after force removal; see Chaps 1, 6, 8, 9, 15, 16, 17, 18, 20, 21, 22

Electro-acupuncture – see Chap 4

Electrocorticographic (EcoG) recording – electrical recording using electrodes placed on the surface of the →cerebral cortex; see Chap 25

Electroencephalogram, electroencephalophy (EEG) – recording of electrical brain activity from the human (or animal) scalp or cortex; see Chaps 7, 14, 18, 20, 23, 24, 25

Electro-magnetic (senses) – see Chap 1

Electromyogram, electromyography (EMG) – recording of the electrical activity of →skeletal muscle by means of electrodes either overlying (on the skin) a muscle or inserted into the muscle; see Chaps 1, 17, 19, 20, 21, 22, 23, 25, 26

Electrotonic spread – see Chap 8

Emesis – vomiting; see Chap 2

Emetic chemotaxic center – see Chap 2

Emotion – the brain´s reaction to an important environmental object or event, having three components: emotional experience or feelings; emotional communication (→vocalizations, facial expressions, gestures); physiological and behavioral responses typically mediated by the →autonomic nervous system and →sub-cortical brain structures; emotions include sadness, happiness, fear, anger and disgust; see Chaps 1, 2, 3, 4, 5, 7, 9, 10, 11, 12, 13, 14, 16, 20, 23, 26

Endocannabinoids (eBCs) – →cannabinoids produced endogenously by animal cells. The best characterized eBCs to date are N-arachidonyl-ethanol-amine (→anandamide) and 2-arachidonoyl-glycerol (derived from →arachidonic acid). The *eBC system* (eBCs, their →receptors CB1 and CB2, and eBC-synthesizing and -degrading enzymes) is widely distributed throughout the nervous system and has been implicated in processes of neurogenesis and neuroprotection, anti-excitotoxicity, appetite regulation, feeding behavior and emesis (vomiting), anti-→inflammation, anti-→nociception, sensory →perception, motor control and coordination, →reward, addiction, mood enhancement and anxiety reduction, →cognition, →learning and →memory; CB1 receptors are located primarily at presynaptic sites, while CB2 receptors are located preferentially (not exclusively), on →immune cells; see Chaps 2, 3, 5, 22, 27

Endocrine – referring to internal secretion, e.g., release and transport of →hormones from glands into the blood and the effects of hormones on specific target organs; see Chaps 4, 10, 17

Endogenous opioid receptors are expressed throughout the body, including the →peripheral nervous system and the →central nervous system (CNS), and modulate various neuronal circuits and functions, among which are the ascending →nociceptive systems; see →opioids and Chap 5

Endolymph – fluid within the membranous labyrinth, similar to intracellular fluids with a high potassium (K^+) and low sodium (Na^+) content; see Chaps 10, 11

Endorphins – *endo*genous substances [e.g., β-endorphin, met-enkephalin (→enkephalins)] chemically similar to opiate drugs (→opioids). Endorphins modulate pain →perception and coping with acute →stress.

Endothelins – three vasoactive peptides (21 amino acids), involved in the regulation of vascular and bronchiolar tone and the control of natrium (Na^+) excretion by the kidney; see Chap 4

Endurance – fatigue resistance; see Chap 18

Energy – ability of one system (body, molecule, atom) to do →work (product of force and distance) on another system. There are different sorts of energy: chemical, heat, nuclear, radiant, electrical, magnetic, mechanical (→kinetic energy and →potential energy); they are measured in different units but can be converted into each other; see Chaps 1, 2, 8, 11, 15, 16, 17, 18, 19, 21, 23, 27

Energy consumption – see →energy and Chap 21

Energy expenditure – see →energy and Chaps, 1, 18, 21, 23, 26

Energy recovery – see →energy and Chap 21

Enkephalins – two closely related penta-peptides (methionine enkephalin and leucine enkephalin) with opiate-like qualities, present in the brain, →spinal cord and other parts of the body. They may act as →neuromodulators, in some cases producing →analgesic and sedative actions or affecting mood and →motivation; see Chap 16

Ensemble code – see →across-fiber (across-neuron) pattern code or population code and Chaps 9, 11

Enteroception, enteroceptive – Enteroceptive →receptors and →senses receive stimuli arising within the body and comprise proprioception and various other senses, such as deep thermo-sensibility and pain; see →receptor cell and Chap 6

Entorhinal cortex (in→cerebral cortex) – The entorhinal cortex (→Brodmann´s area 28) occupies a large anterior part of the →hippocampal gyrus and receives inputs from many different brain areas, including the olfactory bulb and →piriform cortex, temporal cortex and →prefrontal cortex (PFC), →amygdala, and →hippocampus, and innervates mainly the →hippocampal complex and the allocortex. Functionally, the entorhinal cortex plays, with the hippocampus, important roles in navigation, →memory and pathological disorders, notably temporal lobe →epilepsy; see Chaps 3, 5, 10, 14, 23

Ephaptic – see Chap 3

Epidermis – see Chaps 6, 7

Epiglottis – see Chap 2

Epilepsies – diverse group of neurological disorders characterized by recurrent, chronic abnormalities in electrical brain activity and ensuing changes in various functions. Epilepsies can result from various brain lesions and many systemic diseases, or be idiopathic if no organic cause can be found. Each episode is called a →seizure and can go along with motor phenomena (*convulsive seizure*) or sensory, →cognitive or →emotional phenomena; see Chap 4

Epithelial Na^+ channel (ENaC) – see →acid-sensing ion channels (ASICs) and Chaps 2, 4, 8

Equilibrium – see Chaps 1, 10, 19, 20, 22, 23, 26

Equivalent motor act – see motor equivalence and Chap 1

Erector spinae muscles – see Chap 21

Ergoreceptor – see →receptor cell and Chap 4

Error correction – see Chaps 1, 23, 25, 26, 27

Error detection – see Chaps 15, 23

Error signal – see Chaps 15, 16, 23, 26, 27

Eucalyptol – see Chap 4

Event-related potential – summed electrical response of many →neurons recorded by surface electrodes and evoked by an event; see Chap 7

Ewe – see Chap 3

Ex-afference – see Chaps 1, 10, 12, 23

Excitation-contraction coupling (ECC) (in →skeletal muscle) – see Chaps 15, 17, 18

Excitatory burst neuron (**EBN)** (in oculomotor control) – see Chap 16

Excitatory downward burst neuron ($DMLB_e$) (in oculomotor control) – see Chap 16

Excitatory postsynaptic current (EPSC) – see Chap 23

Excitatory postsynaptic potential (EPSP) – increase in postsynaptic membrane potential (→resting membrane potential) caused by the flow of positively charged ions into the postsynaptic cell elicited by the action of a →neurotransmitter released from a presynaptic terminal; see →postsynaptic potential and Chaps 5, 10, 13, 18, 22

Excitatory upward burst neurons ($UMLB_e$) (in oculomotor control) – see Chap 16

Executive control – see Chaps 4, 14, 24

Expectation – see Chaps 1, 2, 3, 4, 5, 10, 11, 12, 14, 16, 21, 22, 23, 25, 27

Explicit learning – →intentional remembrance of information at a certain conscious level, such as learning of historical events, phone numbers, etc.; see Chap 27

Exploratory behavior – see Chap 23

Express saccade – see saccade and Chap 16

Extensor digitorum longus (EDL) muscle – see Chap 22

Extensor digitorum brevis – see Chap 19

External auditory meatus – auditory canal; see Chap 11

External cuneate nucleus – nucleus cuneatus externus; see Chap 26

External nucleus of the inferior colliculus (ICX) – see →inferior colliculus and Chap 12

External plexiform layer (in the main olfactory bulb) – see Chap 3

Exteroception, exteroceptive – Exteroceptive →receptors and →senses receive stimuli from the world external to the body and comprise gustation (taste) and olfaction (smell), audition (hearing), and vision; see →receptor cell and Chaps 6, 23

Extracellular matrix (ECM) (of →skeletal muscle) – see Chap 17

Extrafusal muscle fibers – skeletal →muscle fibers outside →intrafusal muscle fibers; see →β-motoneurons and Chap 9

Extraocular motoneuron – see Chaps 15, 16

Extraocular muscle – see Chaps 8, 10, 15, 16, 18, 20

Extra-personal space – see Chap 26

Extra-retinal signals – non-visual signals encoding the position of the eyes in orbit; see Chap 16

Extra-striate – (synonym pre-striate) refers to cerebro-cortical regions outside the →striate cortex (area striata; primary visual cortex, area V1); see Chaps 13, 14, 16, 25

Extra-striate body area (EBA) (in →cerebral cortex) – see Chap 14

Extrinsic coordinate system – see Chap 1

Eye – see Chaps 1, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 23, 25, 26, 27

Eyeball – see Chaps 15, 16

Eye-centered (→frame of reference) – set of axes for defining the location of an object with the eyes as reference points; see →egocentric (→frame of reference) and Chaps 1, 16, 23, 24, 25

Eye fields (in →cerebral cortex) – network of multiple regions that contribute to the initiation and control of eye movements, including: prefrontal eye field (PFEF, located in the posterior part of →Brodmann´s area 46 of the →dorso-lateral prefrontal cortex, DLPFC), cingulate eye field, frontal eye field (FEF), premotor eye field, supplementary eye field (SEF), parietal eye field (PEF, corresponding to →area LIP), middle superior temporal area (→area MST), →area 7m (→precuneus in humans); see Chap 16

Eye-hand coordination – see Chaps 16, 24, 25, 26

Eye-head coordination – see Chap 16

Eye movement – see Chaps 1, 9, 10, 12, 13, 14, 15, 16, 20, 23, 24, 25, 26

Face – see Chaps 2, 3, 7, 9, 12, 14, 25

Face perception – see Chap 14

Face recognition – see →recognition and Chap 14

Facial nerve – *nervus facialis*, →cranial nerve VII; see Chap 2

Fascia – see Chap 17

Fast adapting type-I (FAI) receptor – also rapidly adapting type-I (RAI) receptor; see →receptor cell and Chaps 6, 7

Fast adapting type-II (FAII) receptor – also rapidly adapting type-II (RAII) receptor; see →receptor cell and Chaps 6, 7

Fastigial nucleus – →nucleus fastiguus; see Chaps 10, 16, 20, 23, 24

Far space – see Chap 1

Fastigial long-lead burst (FaLLB) neuron (in oculomotor control) – see Chap 16

Fastigial oculomotor region (FOR) – see Chap 16

Fear – see Chaps 2, 4, 5, 14, 16, 20, 21, 23

Fear conditioning – form of →classical conditioning, in which an animal or human →learns the relationship between →aversive events and the environmental stimuli predicting such events. The animal learns to express fear and to elicit a →defense reaction to an initially neutral stimulus (the conditioned stimulus, such as a tone), after it has been associated or paired with a →noxious stimulus (the unconditioned stimulus, e.g., an electrical shock); see Chaps 2, 3

Fear of falling – see Chap 20

Feature extraction – process underlying the detection of specific stimulus features; see Chaps 6, 13

Feature grouping – see Chap 14

Feedback – see →feedback systems and almost all chapters

Feedback system – generally made up of a →plant (sub-system to be controlled), a controller and feedback pathway(s) carrying signals about the plant output to the controller. →Negative feedback control systems are regulatory systems that maintain or controllably change certain variables. In the first case, any disturbance in the system is brought back to the desired level or reference value (set point). In the second case, the reference value changes and the plant output follows the reference; see Chaps 1, 16, 19, 22

Feedforward – see →feedforward control and Chaps 1, 2, 3, 13, 14, 18, 20, 23

Feedforward control – direct control of some variable without the use of feedback. In the context of motor control, feedforward often refers to the advance influence that the nervous system exerts on some characteristics of motor actions, before these are started or accomplished; see Chap 16

Feedforward system – see Chap 1

F-type motoneuron, motor unit – see →motor unit and Chap 18

FF-type motoneuron, motor unit – see →motor unit and Chap 18

Ferret – see Chaps 12, 23

Fever – see Chap 4

Fictive locomotion – see Chaps 22, 23, 27

Fictive scratching – see scratch and Chap 22

Fight or flight – The fight-or-flight response is the reaction of an animal to a threat or strong →emotion (acute →stress), consisting of a motor behavior accompanied and sustained by a generalized activation of the →sympathetic nervous system including the release of →adrenaline and →noradrenaline from the →adrenal medulla into the blood and of noradrenaline secreted from →sympathetic nerve terminals causing increased blood pressure and cardiac output, relaxation of bronchial, intestinal and many other smooth muscles, mydriasis, and metabolic changes that increase levels of blood glucose and free fatty acids; see →stress and Chaps 1, 4, 5, 8, 10, 22, 23

Figure-ground segregation – see Chap 14

Filiform papilla – see Chap 2

Filling-in (in →perception) – see Chaps 14, 15

Finger movement – see Chaps 1, 7, 9, 12, 16, 22, 26, 27

First (fast) pain – see Chap 4

Fish – see Chaps 1, 17

Fitts´ law – speed-accuracy trade-off; see Chap 25

Fixation (of gaze) – epoch between saccades; see Chaps 9, 12, 14, 15, 16, 23, 25, 26

Fixational eye movement – continuous small eye movements occurring during fixation; see Chap 15

Fixation neuron (in oculomotor control) – also tectal pause neuron; see Chap 16

Flagella – see Chap 1

Flamingo – see Chap 19

Flavor – unified →perceptual experience of a food that arises from the integrated sensory signals of several sensory modalities, such as taste, olfaction, oral somato-sensation (tactile, temperature, and texture) and oral →nociception (pain); see Chaps 2, 3

Flexion reflex – also called *flexor reflex* or withdrawal reflex: →reflex contraction of limb flexor muscles (with concurrent inhibition of antagonist extensor muscles) evoked by a →noxious stimulus, mediated by oligosynaptic →interneuronal pathways in the →spinal cord and withdrawing the limb from the stimulus; see →reflex and Chaps 1, 4, 22

Flexor digitorum brevis muscle – see Chap 20

Flexor digitorum longus muscle – see Chaps 18, 19, 22

Flexor carpi radialis muscle – see Chap 27

Flexor hallucis longus – see Chap 19

Flocculus – see Chaps 10, 15, 16

Floccular complex (lobe) – also flocculo-nodular lobe: flocculus plus ventral paraflocculus (of →cerebellum); see Chaps 15, 20

Flocculus-target neuron (FTN) (in oculomotor control) – see Chap 15

Flutter (sensation, stimulus) – see Chaps 6, 7

Flying – see Chap 1

Foliate papilla – see Chap 2

Follow-up servo hypothesis – see Chap 22

Foraging – see Chap 23

Force feedback – see Chaps 19, 22

Force-field adaptation – see Chap 27

Force-velocity relation – see Chaps 15, 18

Forebrain – →telencephalon plus →diencephalon, brain rostral to the →mesencephalon (→n); see Chaps 2, 3, 5, 8, 9, 12, 22, 23

Forel´s field – see Chap 16

Forward (direct) dynamics – see Chap 1

Forward internal model – Representation of the predictable relationship between the input and output of a system, thus providing an estimation of a new state or outcome given an input. Forward models are typically adaptive, updated by experience. In sensory-motor systems, a forward →internal model is assumed to predict the sensory consequences of →motor commands by integrating →efference copies of motor signals with current sensory signals; an extension of this model is its →plasticity in response to output errors; forward internal models may also serve other functions, such as filtering sensory signals, enhancing or attenuating information for the control of movements, and cancelling the sensory effects of self-generated movements to enhance more important sensory inputs; see →predictive internal model and Chaps 1, 25, 27

Forward walking – see Chaps 1, 21, 22

Fourier transform – mathematical operation that decomposes a time-varying continuous signal (represented in the `time domain´) into the frequency components it is composed of

(thus producing a `frequency-domain´ representation). This frequency-domain representation consists of a sum (integral) of sinusoidal components, each component being defined by a frequency, a magnitude and a starting phase term; see Chap 11

Fovea (centralis) – depression in the posterior retina of ca. 1.5 mm diameter, locus of highest →visual acuity; see Chaps 13, 14, 15, 16, 25, 26

Frame of reference – reference frame: rigid system of coordinate axes with respect to which spatial locations and motions of objects are defined. As to their point of origin, reference frames are defined relative to the subject, →egocentric, or relative to something other than the subject, →allocentric. Specifically, the subject-centered reference frame can be sub-divided into →eye-centered (gaze-centered), →head-centered, →body-centered or body-part-centered reference frames. The allocentric reference frame includes object- or environment-relative frameworks; see Chaps 1, 7, 12, 14, 16, 23, 24, 25, 27

Frequency-band discrimination – see Chap 12

Free nerve ending – see Chaps 1, 4, 5, 6, 8, 9

Free radical – see Chap 5

Freezing – one of the main →defensive reactions to threat across species; form of behavioral inhibition that, if unsuccessful, may prepare for action (→fight or flight); during freezing, the →sympathetic and →parasympathetic systems are activated, such that the latter dominates; parasympathetic dominance has been associated with a net heart-rate deceleration or a reduced heart-rate acceleration, altered respiration rates and →vocalizations; in rodents, freezing depends on inhibitory projections from the →amygdala to the →peri-aqueductal gray (PAG); similar brain regions may be involved in humans; see Chaps 3, 5

Frequency modulation (FM) – see Chaps 11, 12

Frequency-response area (FRA) – see Chap 11, 12

Friction – see Chaps 1, 6, 7, 25, 26

Frog – see Chaps 1, 11, 13, 17

Frontal cortex (lobe) – part of the →forebrain anterior to the central sulcus and lateral fissure (→Sylvian fissure). The frontal cortex is divided into the →agranular cortex (lacking granular layer 4) primarily devoted to motor functions, and prefrontal or granular regions devoted to →cognitive functions. →Prefrontal cortex (PFC) is made up of many areas with different structures and functions. The agranular frontal cortex is divided into the →primary motor cortex (area M1, area F1), and →premotor areas; see Chaps 1, 7, 10, 12, 14, 16, 24

Frontal eye field (FEF) (in →cerebral cortex) – in monkeys located in area 8, in human in area 6; see →eye fields and Chaps 10, 12, 16, 26, 27

Frontal pursuit area (FPA) – see →FEFsem and Chap 16

Fructose – see Chap 2

F-type motoneuron, motor unit – see →motor unit and Chap 18

FF-type motoneuron, motor unit – see →motor unit and Chap 18

Functional electrical stimulation (FES) – see Chap 17

Functional magnetic resonance imaging (fMRI) – special form of magnetic resonance imaging, which indirectly assesses changes in →neuronal brain activation by monitoring hemodynamic changes (in blood flow and oxygenation); see Chaps 7, 12, 14, 18, 20, 26, 27

Functional near-infrared spectroscopy (fNIRS) – non-invasive brain imaging technique that uses non-ionizing laser light in the range of red to near-infrared to detect changes in cerebral blood oxygenation; see Chap 20

Fungiform papilla – see Chap 2

Funiculus – long bundle of nerve fibers, primarily in the →spinal cord; see Chaps 7, 23

Fused contraction (of →skeletal muscle) – see Chap 18

Fusiform body area (FBA) – see Chap 14

Fusiform face area – see Chap 14

Fusiform gyrus (in→cerebral cortex) – *gyrus fusiformis*; see Chap 14

Fusimotor – refers to fusimotor neurons innervating →intrafusal muscle fibers and the effects of their activation on muscle spindle discharge; see Chaps 1, 8, 9,19, 22, 24

GABA – →γ-amino-butyric acid; see Chaps 2, 3, 5, 7, 10, 16, 19, 23, 25, 27

$GABA_A$ receptor – →receptor binding →**γ-a**mino-**b**utyric **a**cid (GABA) and associated with a →ligand-gated ion channel. Upon binding of GABA to the receptor, the →ion channel opens to enable the influx of anions [chloride (Cl^-) ions] into the receptor-bearing cell. This reduces the ability of excitatory inputs to the →neuron to generate an →action potential; see Chaps 2, 3, 7, 9, 26

$GABA_B$ receptor – →receptor binding →**γ-a**mino-**b**utyric **a**cid (GABA), consisting of two sub-units, both →G-protein-coupled receptors, which mediate the slow and prolonged physiological effects of the inhibitory →neurotransmitter GABA, for example in →presynaptic inhibition; $GABA_B$ receptors are expressed in almost all neurons at pre- or postsynaptic sites throughout the nervous system; see Chaps 2, 4, 5

Gait – see Chaps 1, 19, 20, 21, 22, 27

Gait akinesia – see →akinesia and Chap 23

Gait ataxia – see →ataxia and Chap 23

Gait bradykinesia – see →bradykinesia and Chap 23

Gait disorder – see →Huntington´s disease, →Parkinson´s disease, →spasticity, and Chap 23

Gait initiation – see Chap 21

Gait stabilization – see Chap 21

Gait termination – see Chap 21

Galanin – peptide found in →pre-optic area →neurons of the →forebrain and involved in →sleep regulation; see Chap 2

Gallop – see Chaps 19, 21, 22, 23

Galvanic vestibular stimulation usually refers to electrical stimulation of the vestibular labyrinth, which is performed by using constant-amplitude, long-duration pulses of current or continuous currents applied through electrodes on the mastoid bone(s); see →caloric stimulation and Chaps 20, 25

γ-Amino-butyric acid (GABA) – major inhibitory →neurotransmitter in the adult brain; see Chaps 2, 3, 10 16

γ-Motoneurons – small →motoneurons with →axons in group Aγ which innervate →intrafusal muscle fibers in muscle spindles; see Chaps 9, 18, 19, 21, 22

γ_d – dynamic gamma motor axon; see Chap 8

γ_s – static gamma motor axon; see Chap 8

Gamma rhythm – see →neuronal oscillations and Chap 3

γ–rigidity – see Chap 19

Ganglion (*pl.* ganglia) – assembly (accumulation) of →neuronal cell bodies; see →basal ganglia, →dorsal-root ganglion (DRG) ; see Chaps 3, 5,10, 13,

Ganglion cell (in retina) – see Chap 13

Gastrin releasing peptide (GRP) – see Chap 5

Gastrocnemius motor unit– see Chap18

Gastrocnemius muscle – see Chaps 17, 18, 19, 20, 22

Gaze – see Chaps 1, 10, 12, 14, 15, 16, 26

Gaze-centered (→frame of reference) – see Chap 16

Gaze holding – see Chaps 15, 16

Gaze-paretic nystagmus – →nystagmus developing during eccentric gaze; see Chap 15

Gaze shift(ing) – see Chaps 15, 16, 19, 26

Gaze stabilization – see Chaps 10, 15, 16, 20

Gene, genetic – in many chapters

General visceral afferent (GVA) – see Chap 4

Gestalt principles – →perceptual grouping principles that help organize individual stimuli (elements) into forms or shapes of objects. see Chaps 7, 11, 14

Glabrous skin – skin surface devoid of hair, e.g., palm surface of the hand and plantar surface of the foot; see Chaps 4, 6, 7

Glia cell – class of non-→neuronal cells in the →central nervous system (CNS), including →astrocytes, oligodendrocytes, and →microglia; see Chap 5

Glia cell-derived neurotrophic factor (GDNF) – see →neurotrophic factors (neurotrophins, NTs) and Chap 4

Globus pallidus – ventro-medial part of →basal ganglia, consisting of the external (lateral) and internal (medial) segments; see Chaps 2, 16, 23, 27

Globus pallidus externus (GPe) – lateral (external) segment of →globus pallidus (→basal ganglia); see Chap 16

Globus pallidus internus (GPi) – medial (internal) segment of →globus pallidus (→basal ganglia); see Chaps 16, 25, 26

Glomerulus (in olfactory bulb) – see Chap 3

Glossopharyngeal nerve – →cranial nerve IX; see Chaps 2, 4

Glucagon – peptide →hormone secreted by A-cells of the pancreatic islets of Langerhans and in the stomach; see Chap 2

Glucagon-like peptide-1 (GLP-1) – GLP-1 stimulates →insulin secretion from B cells of the pancreatic islets of Langerhans; see Chap 2

Glucocorticoids (glucocorticosteroids) – steroid →hormones secreted from the adrenal cortex of the →adrenal gland upon →stress exposure, injury and disease, with cortisol in humans and corticosterone in rodents being of major importance. They exert a wide range of actions throughout the brain and body with potent effects on, e.g., →energy metabolism, →immune system and →cognition. Elevated glucocorticoid concentrations induce structural →plasticity in neurons, →Schwann cells, →microglia, oligodendrocytes, and →astrocytes. They also change the release and re-uptake of →glutamate;.see Chap 5

Glucose – see Chaps 2, 3, 4, 17

Glucose transporter type 4 (GLUT4) – see Chap 2

Glutamate, glutamatergic – also referred to as *glutamic acid*: key molecule in cellular metabolism and main excitatory →neurotransmitter of the →central nervous system (CNS); see Chaps 2, 3, 4, 5, 7, 8, 10, 11, 16, 18, 19, 22, 23, 26, 27

Glutamate receptors – glutamatergic receptors: ligand-gated →receptors for the major excitatory →neurotransmitter →glutamate, which acts on two general classes of receptors: →metabotropic receptors (metaboreceptors), which are →G-protein-coupled receptors, and ionotropic receptors, which are →ion channels. The most important ionotropic glutamatergic receptors are distinguished by the actions of glutamate →agonists: →N-methyl-D-aspartate (NMDA) and non-NMDA receptors including →α-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA) and →kainate receptors. Glutamate receptors play important roles in →synaptic transmission, →synaptic plasticity, →learning, →memory and →ontogenetic development. In excess, glutamate triggers excitotoxicity, causing →neuron and →glia cell death; see Chaps 2, 5, 8, 10, 14

Gluteus medius muscle – see Chap 21

Glycine, glycinergic – belongs to the amino acid family of classical →neurotransmitters. It has an inhibitory effect in the →spinal cord, →medulla oblongata, and retina. Glycine binds to glycine →receptors, which leads to the influx of chloride (Cl^-) into the postsynaptic cell and inhibition. Glycine also binds to a site on →N-methyl-D-aspartatic acid (NMDA) channels, which increases the →conductance of this channel; see Chaps 5, 10, 19, 20, 23

Glycogen – polysaccharide of glucose, which serves as an →energy store in liver, muscles, brain and other tissues; see Chaps 17, 18

Glycogenolysis – breakdown of →glycogen into glucose-1-phosphate; see Chap 17

Glycolysis – cascade of biochemical reactions converting glucose into pyruvate; see Chaps 17, 18

Goat – see Chap 15

Golgi cells (in cerebellar cortex) – influence signal transmission from →mossy fibers to →granule cells; see →cerebellum and Chap 10

Golgi tendon organ (GTO) – see Chaps 1, 6, 8, 9, 15, 19, 20, 22, 23, 25

Golgi tendon organ-like ending – see Chap 8

Good continuation – see →Gestalt principles and Chap 14

G-protein-coupled receptors – also called *seven transmembrane →receptors (7TM receptors, heptahelical receptors):* large protein family of receptors that sense inter-cellular messages (→hormones, →neurotransmitters) or sensory signals (odorants and pheromones or photons) outside the cell and activate →signal transduction pathways inside the cell, which ultimately lead to cellular responses; see Chaps 2, 3, 4, 5

Granular frontal opercular area (GrFO) – see Chap 26

Granule cells (in cerebellar cortex) – receive excitatory inputs from various sources via →mossy fibers and distribute their outputs to the other →cerebellar cortical →neurons. A granule cell has 4–5 →dendrites that, within glomeruli, are innervated by different mossy fibers and, within the →vestibulo-cerebellum, by →unipolar brush cells (UBCs). A granule cell has a single →axon that ascends into the glomerular layer and branches into a parallel fiber, which runs along a folium through the perpendicularly staggered dendritic trees of →Purkinje cell and other cells; see →cerebellum and Chaps 10, 23, 27

Granule cell (in olfactory bulb) **–** see Chap 3

Grapheme-color synesthesia – see →synesthesia and Chap 14

Grasping – see Chaps 1, 3, 6, 7, 9, 10, 13, 14, 16, 19, 23, 24, 25, 26, 27

Graviception – sensory processes that contribute to the neural representation of the direction of the →gravity vector with respect to an organism and of motion of the organism with respect to the gravity vector; see Chap 1

Graviceptors – →sensory receptors contributing to →graviception. The major contributor is the vestibular system (Chap 6); see →receptor cell and Chaps 1, 19, 23

Gravity, gravitational – attractive force acting between →masses, such as the pull exerted by the earth on other masses; see Chaps 1, 6, 8, 9, 10, 15, 17, 18, 19, 20, 21, 22, 23, 25, 26

Gray matter – →neuraxis structures consisting predominantly of nerve cell bodies, →dendrites and →synapses, together with glial cells; see Chaps 5, 7, 8, 20, 22, 27

Grid cell – para-hippocampal →neuron that fires whenever the animal is located at one of the vertices of a periodic triangular array tessellating the entire extent of an explored space; grid cells are thought to provide a coordinate frame to →cognitive maps, and to support →path integration using self-motion cues, but they are also influenced by allothetic cues such as boundaries; see Chaps 10, 23

Grip – see Chaps 25, 26

Grip aperture – see Chap 26

Grip force – see Chaps 1, 6, 7, 20,25, 26, 27

Grip prototype – see Chap 26

Grip stability – see Chap 26

Ground reaction forces – forces arising in the area of contact between the body and environment, e.g., between the foot and the ground or between the hand and a stable object or surface; see Chaps 19, 20, 21

Group I – group Ia and group Ib – see Chaps 8, 22

Group Ia afferent – see Chaps 1, 7, 8, 9, 19, 20, 22, 23, 24, 27

Group Ia EPSP – →excitatory postsynaptic potential elicited by group Ia afferent(s) in postsynaptic →neuron; see Chap 18

Group Ib afferent – nerve fiber from Golgi tendon organ; see Chaps 8, 19, 22, 23

Group II (Aß) afferent – nerve fiber from muscle spindle secondary endings or other →receptor cells; see Chaps 4, 5, 6, 7, 8, 9, 19, 20, 22, 23

Group III (Aδ) afferent – also Aδ afferent, (thinly →myelinated) afferent nerve fiber originating from free nerve ending and in part from paciniform ending. Group III afferents are sensitive to chemical, thermal and mechanical stimuli. They are more mechano-sensitive than group IV afferents during →skeletal muscle contraction, force production, dynamic/static muscle stretch and local intramuscular pressure; see Chaps 4, 5, 6, 8, 9, 19

Group IV (C) afferent – also group C, (un-→myelinated) afferent nerve fiber originating from free nerve ending. Group IV afferents are sensitive to chemical, thermal and mechanical stimuli. Muscle group IV afferents are more metabo-sensitive than group III afferents because their activation usually starts after a delay during prolonged muscle contraction and continues to discharge until the withdrawal of muscle metabolites; see Chaps 4, 5, 6, 8, 9, 17, 19

Group Aα (β) efferent – see →motoneurons

Group Aβ afferent – group II afferent

Group Aδ (III) afferent – group III afferent

Group Aγ efferent – from →γ-motoneuron ito innervate →intrafusal muscle fibers of muscle spindles

Group C afferent – →group IV

Growth factors – broad term encompassing molecules that promote cell division, differentiation, migration or survival. Two important growth factors in the nervous system are nerve growth factor (NGF) and →brain-derived neurotrophic factor (BDNF) (→neurotrophic factors (neurotrophins, Nts); see Chaps 4, 5

Guillain-Barré syndrome (GBS) – acute →inflammatory neuropathy of unknown cause. The majority of cases occur after a viral or bacterial infection. It is almost certainly an immune-mediated disorder, in which the →immune system becomes sensitized to unique proteins on the →myelin sheath and attacks them as if they were foreign to the body, causing →inflammation and destruction; see Chap 17

Guinea pig – see Chap 12

Gustation, gustatory – →sense of taste; see Chaps 2,14

Gustatory cortex – see Chap 2

Gustatory imagery – ability to generate →percept-like gustatory experiences without gustatory stimulation by retrieval of information from →memory; see →mental imagery and Chap 2

Gustatory system – see Chaps 2, 3

Gyri temporales transversales (Heschl) – see Chap 12

Gyrus angularis (in→cerebral cortex) – →angular gyrus, curves around the posterior end of the superior temporal sulcus (STS); see Chap 25

Haarscheibe – see Chap 6

Habenulae (Hb) –a bilateral pair of small nuclei at the posterior end of and above the →thalamus. It has been implicated in →endocrine functions, ingestion, mating, olfaction, in pain modulation and →analgesia, in →affective, →motivational, →cognitive and →reward functions, and in decisions between approach or avoidance; see Chap 5

Habit – daily or routine activities triggered by appropriate events occurring in particular contexts; habits are acquired for adaptation to the environment, mainly using →learned stimulus-response associations; see Chaps 2, 16, 27

Habituation – reversible decline in behavioral and physiological responses to the repeated exposure of a specific sensory stimulus; see Chaps 1, 27

Hagfish – see Chap 2

Hair cells – sensory cells serving as mechano-electrical transducers of the vestibular (Chap 6), auditory, and lateral-line systems of all vertebrate species. When their `hairs´ (stereocilia or stiff →microvilli) are deflected, they produce →receptor potentials which →synaptically stimulate the generation of spikes in afferent →neurons; see Chaps 1, 10, 11

Hairy skin – see Chaps 6, 7

Half-center – see Chap 22

Hamstring muscles – →skeletal muscles on the back side of the thigh, including hip extensors and knee flexors (semimembranosus, semitendinosus, biceps femoris); see Chaps 17, 19, 22

Hamster – see Chap 3

Hand-centered (→frame of reference) – set of axes for defining the location of an object with the hand as reference point; see →egocentric, →frame of reference and Chaps 1, 24

Handedness – differences in sensory-motor abilities of the two arms/hands; see Chap 24

Hand movement – see Chaps 1, 7, 12, 16, 23, 24, 25, 26

Hand muscle – see Chaps 8, 18, 25, 26

Hand shape – see Chap 26

Haptic(s) – →perception of combined tactile and kinesthetic inputs during object manipulation (active touch): sensory experience of the environment (mediated by →mechano-receptors in skin, muscles, tendons and joints) through active exploration or manipulation, typically with the hands; see Chaps 1, 6, 7, 14, 20, 24, 26

Hb9 – see Chap 22

HCl – hydrochloric acid; see Chap 2

HCN channels – see →**h**yperpolarization-activated **c**yclic **n**ucleotide-gated channels

HCN2 channel – see Chap 5

Head burst neuron (in oculomotor control) – see Chap 16

Head-centered (→frame of reference) – set of axes for defining the location of an object with the head as reference point; see →egocentric, →frame of reference and Chaps 1, 10, 12, 15, 24, 25

Head direction cell (HD cell) – →neuron that discharges whenever the animal's head faces a particular direction relative to the environment in the horizontal plane, found in para-hippocampal areas and other brain regions regions; see Chap 23

Heading – see Chaps 10, 14, 16, 23

Head movement – see Chaps 1, 10, 12, 14, 15, 16, 20

Hearing (audition) – see Chaps 1, 3, 7, 9, 10, 11, 12

Hearing loss – see Chap 11

Heart rate – see Chaps 4, 9, 10

Hebbian learning – type of associative →learning, based on the idea that simultaneous activation of presynaptic and postsynaptic cells increases the synaptic strength between those cells; may be the →neuronal basis of →unsupervised learning; see Chap 7

Hedonic map– see Chap 3

Hedonics – pleasantness or unpleasantness of feelings accompanying sensations; see Chaps 2, 3, 4

Helicotrema – see Chap 11

Hemispatial neglect – acquired lack of conscious experience of half-space; neglect has been most intensively studied in the visual modality, but also occurs in the chemical, tactile and auditory modalities, separately or concurrently; see Chaps 16, 25

Herpes simplex encephalitis – see Chap 4

Herpes zoster (shingles, zoster, zona) results from re-activation of an infection with varicella zoster virus, which is dormant (latent) in cells of a →dorsal-root ganglion or in the →ganglion semilunare (ganglion Gasseri) of the →trigeminal nerve. The earliest symptoms include headache, fever and malaise, commonly followed by a painful skin rash with blisters in the related skin area. Pain is often described as →itching, tingling, aching, numbing, burning, stinging or throbbing, can be interspersed with quick jabs of agonizing pain, and includes hyperesthesia (over-→sensitivity) or →paresthesia ("pins and needles"); see Chap 4

Heschl´s gyrus – gyri temporales transversales; see Chap 12

Heterogenic reflex – see →reflex and Chap 19

High-frequency fatigue – special form of →muscle fatigue; see Chap 17

High-threshold mechanical (HTM) nociceptor – →nociceptor activated by strong mechanical stimuli; see Chap 4

Hindbrain – composed of →pons, →cerebellum and →medulla oblongata; see Chaps 2, 11

Hinge joint – see Chaps 1, 17

Hip abductor muscle – see Chaps 20, 21

Hip adductor muscle – see Chap 21

Hippocampal complex (in→cerebral cortex) – composed of →hippocampal formation [→hippocampus proper (cornu ammonis), dentate gyrus, subiculum] and para-hippocampal gyrus (→entorhinal cortex, →perirhinal cortex, and para-hippocampal cortex); see Chap 14

Hippocampal formation (in→cerebral cortex) – composed of →hippocampus proper (cornu ammonis), dentate gyrus and subiculum; see Chaps 14, 23

Hippocampus (*cornu ammonis*) (in→cerebral cortex) – evolutionarily old structure with the shape of a seahorse located in the →medial temporal lobe of the brain; involved in →endocrine functions, →memory consolidation, spatial →cognition and navigation; see Chaps 2, 3, 4, 5, 10, 12, 14, 23

Hip strategy – see Chap 20

Histamine – amine →neurotransmitter and →neuromodulator. Histaminergic cells are located in the tubero-mammillary nucleus of the posterior →hypothalamus and distribute →axons widely throughout the →central nervous system (CNS). They are active only during waking and modulate wakefulness, the sleep-wake cycle, thermo- and immuno-regulation, appetite, food intake, →energy balance, →attention, →arousal, →emotion, anxiety, →learning and →memory. Histamine is also an →inflammatory mediator, mostly generated and stored in →mast cells and upon release eliciting pain and →itch by exciting un-myelinated group C (IV) sensory fibers; see Chaps 4, 9, 10, 13, 16, 27

Homeostasis – self-regulating processes by which an organism maintains the stability of its internal milieu while adjusting to changing external conditions. Rather than being static, these dynamic processes are dynamic and can change internal conditions as required to survive external challenges Homeostatic regulation results from the complex interaction of multiple →feedback systems that can be modified by higher control centers; see Chaps 4, 17

Homunculus – see Chap 7

Hook bundle of Russell – see Chap 23

Hopping – see Chaps 17, 22, 23, 26

Horizontal cell (in retina) – see Chaps 13, 14

Horizontal disparity – see Chap 14

H-reflex – Hoffmann-reflex: short-latency connections from group Ia muscle spindle afferents to →motoneurons can be tested by selectively stimulating the group Ia afferents electrically, which leads to excitation of the motoneurons and an →electromyogram (EMG) volley in the associated muscle(s); see →reflex and Chaps 19, 22, 27

Hormone – molecule that is transported in the blood, reaches a specific target organ, where it binds to specific →receptors, and may influence →ontogenetic development, metabolism or behavior; see Chaps 1, 2, 3, 4

Horopter – see Chap 14

Horse – see Chap 20

Human MT complex (→hMT+) – human homologue of macaque →area MT); see Chap 7

Human sensory and autonomic neuropathy type IV – see Chap 4

Hunger – see Chaps 1, 2, 3, 23

Huntington´s disease (HD) – progressive, ultimately fatal, autosomal dominant, →degenerative disorder showing a gradual atrophy of →neurons in the →cerebral cortex, →hippocampus, but mainly the →striatum (→basal ganglia). Clinically, it presents with progressive movement disturbances (including →chorea, →dystonia, →athetosis, →bradykinesia, →rigidity) and by →cognitive and psychiatric symptoms (aggression, anxiety, depression, dementia, hallucinations); see Chaps 16, 26, 27

Hyperalgesia – hyper-→sensitivity to →noxious stimuli; see Chaps 4, 5

Hyper-direct pathway (in →basal ganglia) – pathway from →cerebral cortex via →subthalamic nucleus (STN) to →substantia nigra pars reticularis (SNr); see Chap 16

Hypermetria – →dysmetric disturbance usually seen in cerebellar disorders and characterized by overshooting of an intended target; see Chap 26

Hyperpolarization, hyperpolarized – change in cell →resting membrane potential to more negative values inside, making the →neuron less excitable; see Chaps 4, 5, 10, 11, 13, 18, 22

Hyperpolarization-activated cyclic nucleotide-regulated (HCN) channels – slowly activated by membrane →hyperpolarization and by intracellular →cAMP or →cGMP, and give rise to →depolarizing inward ionic currents termed →I_h, I_f. They are widely distributed in various excitable cells including →central nervous system (CNS) →neurons, taste buds and retinal photoreceptors. They are involved in a range of functions, including the setting of →resting membrane potential, input →conductance and length constants (→electrotonic spread), dendritic integration, cardiac and neuronal →pacemaker activity, and the regulation of presynaptic release of →neurotransmitter; see Chaps 3, 4, 5

Hypertonic saline – see Chaps 4, 19

Hypokinesia – reduction and paucity of movement, impaired movement initiation, most often in →Parkinson´s disease; see Chap 23

Hypometria – →dysmetric disturbance usually seen in cerebellar disorders and characterized by undershooting of an intended target during a saccade or a limb movement towards that target; see Chaps 16, 26

Hyporeflexia – diminution of →reflexes; see →reflex and Chap 23

Hypothalamus – →diencephalic structure in the →basal forebrain, consisting of several nuclei that are critical for integrated autonomic (→autonomic nervous system) and →endocrine responses, for →homeostasis and adaptation to internal or external stimuli, regulation of metabolism and body temperature, feeding behavior, reproductive behavior, control of →arousal, regulation of →sleep/wake cycles, →stress response, etc.; see Chaps 2, 3, 4, 5, 10, 12, 13, 22, 23

Hypotonia – diminished →muscle tone occurring in: →spinal cord injury (acute phase), →motoneuron disease, peripheral nerve disease, →neuromuscular junction disorders, myopathies (muscle diseases). Hypotonia also occurs in →Huntington´s disease (HD) and cerebellar disorders; see Chap 23

Hypoxia – reduced availability and tissue concentration of oxygen; see Chaps 3, 18

Hysteresis (of →skeletal muscle) – see Chaps 9, 18

H zone (in →skeletal muscle) – see Chap 17

I band (in →skeletal muscle) – see Chap 17

Ibotenic acid – →glutamate receptor →agonist; see Chap 14

Idiothetic cues (in navigation) – cues relating to an animal's self-motion, enabling updating of heading and position and supporting →path integration; idiothetic cues are provided by proprioceptive and vestibular signals and by efferent copies of →motor commands; many

researchers consider use of visual and optic flow as idiothetic processing, supporting path integration; idiothetic cues are typically contrasted with →allocentric cues; see Chap 23

Iliopsoas muscle – see Chap 22

Illusion, illusory – non-veridical →percept, contradicting the concept of `naïve´ realism that percepts faithfully reflect sensory stimuli; see Chaps 7, 9, 10, 12, 14, 19, 20, 25, 26

Illusory contour – also *subjective contour*: visual contour that is →perceived in the absence of any physical edge in the image; see →illusion and Chap 14

Imitation learning – see Chaps 26

Immediate-early gene – genes activated transiently and rapidly in response to a wide range of cellular signals; see Chap 9

Immune response – see Chap 4

Immune system – collection of body structures defending the body against endogenous factors or hostile exogenous agents, such as invading micro-organisms. *Innate immunity* attacks the hostile agents indifferentially without necessarily recognizing them and is carried by natural killer cells, basophils, →phagocytic cells including →macrophages (→leukocytes). *Adaptive immunity* learns to →recognize the hostile agents and is carried by T and B lymphocytes (→leukocytes); see Chaps 2, 4, 5

Indirect pathway (in →basal ganglia) – pathway from →cerebral cortex via →striatum to →substantia nigra pars reticularis (SNr) through globus pallidus externus (GPe) and/or →subthalamic nucleus (STN); see Chaps 16, 23, 27

Indole – see Chap 3

Inertia (in mechanics) – property of matter or a body to resist any change in its motion, formalized as the proportionality constant relating the force (or →torque) needed to →accelerate the body to the resulting acceleration; see Chaps 1, 9, 10, 15, 17, 19, 20, 26

Inertial anisotropy – see Chap 1

Inferior colliculus (IC) – →mesencephalic processing station in the auditory pathways. The IC also receives →multi-sensory signals related to somato-sensation, vision, eye position and movement, as well as behavioral context, these signals possibly being significant for the localization of →sound sources, →attention to →salient stimuli, distinction of environmental from self-generated sounds (e.g., →vocalization, respiration, mastication), and the →perception and generation of vocal communication sounds; see Chaps 11, 12

Inferior frontal gyrus (IFG) (in→cerebral cortex) – see Chaps 3, 12, 14

Inferior oblique eye muscle – see Chaps 15, 16

Inferior olive (IO), inferior olivary complex – folded gray mass in the →medulla oblongata, consisting of a principal nucleus and dorsal and medial accessory nuclei. IO →neurons are electrotonically coupled via →gap junctions. They send olivo-cerebellar fibers to the →deep cerebellar nuclei (which return GABA-mediated inhibition to IO neurons), to →synapses from →mossy fibers to →granule cells, and →climbing fibers to →Purkinje cells of the cerebellar cortex. IO neurons receive inputs from many regions including the →cerebral cortex, various →cranial nerve nuclei, and the →spinal cord; see →cerebellum and Chaps 10, 12, 16, 23, 27

Inferior parietal lobule (IPL) (in→cerebral cortex) – In humans, the IPL is the inferior part of the lateral →posterior parietal cortex (PPC) (below the →intraparietal sulcus, IPS) and consists of two cytoarchitectonically different regions which roughly correspond to the →supra-marginal gyrus (SMG) [→Brodmann area (BA) 40] and the →angular gyrus (BA 39). The macaque IPL is cytoarchitectonically different and has a different organization. The monkey IPL contains: (i) →area PF; (ii) →area PFG; (iii) →area PG (together with area Opt constituting →area 7a); (iv) area AIP (**a**nterior **i**ntra**p**arietal); (v) →area LIP (**l**ateral **i**ntra**p**arietal); (vi) →area CIP (**c**audal **i**ntra**p**arietal); (vii) →area VIP (**v**entral **i**ntra**p**arietal, lateral part). The IPL receives somatosensory afferents and massive visual inputs, and projects to ventro-lateral →premotor cortex (area PMv, area F4 and area F5) and to →prefrontal cortex (PFC); see Chaps 3, 7, 10, 12, 16, 25, 26

Inferior rectus eye muscle – see Chaps 15, 16

Inferior temporal (IT) cortex – see Chaps 14, 26

Inferior temporal gyrus– see Chap 12

Inflammation – first immune response to irritation or infection, characterized by: redness (rubor), heat (calor), swelling (tumor), pain (dolor) and dysfunction of the organs involved (functio laesa); see Chaps 2, 4, 5, 9, 17, 19

Inflammatory mediators – soluble, diffusible molecules acting as messengers locally and more distally at the site of tissue damage and infection; see Chaps 4, 5, 9

Inflammatory pain – pain associated with tissue damage and →inflammation; see Chaps 4, 5

Inflammatory soup – see Chap 4

Inhibitory burst neuron (**IBN)** (in oculomotor control) – see Chap 16

Inhibitory upward burst neuron (UMLB$_i$) (in oculomotor control) – see Chap 16

Inhibitory vertical burst neuron (in oculomotor control) – see Chap 16

Inner ear – see Chaps 1, 10, 11

Inner hair cells (IHCs) in inner ear – see Chaps 11, 12

Inner plexiform layer (of the retina) – see Chap 13

Inorganic phosphate (P_i) – see Chap 17

Inositol-1,4,5-trisphosphate (IP_3) – see Chap 3

Inositol-1,4,5-trisphosphate receptor (IP3R) – see →receptor andChap 17

Insect – see Chap 23

Insula, insular cortex, Island of Reil – region of the →cerebral cortex located within the lateral fissure (→Sylvian fissure) and covered by parts of the →frontal cortex (lobe) and temporal cortex. The insula is involved in representing taste, pain and temperature sensations, in viscero-sensory, viscero-motor and →enteroceptive functions, →emotions, and language. It receives inputs from the →thalamus and connects with the →orbito-frontal cortex, →amygdala, →hypothalamus, and →brainstem autonomic nuclei (→autonomic nervous system); see Chaps 2, 3, 4, 5, 7, 10, 12, 14, 25, 26

Insular cortex – see →insula and Chaps 4,5,7,12, 25

Insulin – →hormone produced and secreted by B cells of the pancreatic islets of Langerhans; see Chaps 2, 3

Intensity, intensity coding (of sensory stimuli) – The quantitative static relationships between sensory stimulus intensity and amplitude of the →receptor potential or discharge rate in following →neurons may take different forms in different sensory systems. In many mechano-sensory systems, it is close to linear, while in other systems it is often non-linear, e.g., logarithmic. This diversity is related to the range of stimulus intensities encountered in different systems. As a gross rule, linear relationships prevail where stimulus range is relatively limited, and non-linear mappings occur in systems where stimulus intensity can vary over many orders of magnitude, such as in the auditory and visual systems; see Chaps 2, 3, 4,5, 6, 7, 9, 11, 12, 13, 16, 17, 18, 20 23

Intention – representational states that bridge the gap between deliberation and action′; willed action involves the intention to act; see Chaps 1, 14, 26

Intention tremor – →action tremor that occurs during intended movements, in particular of high precision, primarily in patients with essential →tremor or cerebellar disorders. For instance, when a →cerebellar patient makes an arm movement towards a target, the arm starts oscillating, with the oscillatory amplitude increasing with approach to the target; see Chap 26

Interaction forces – see Chaps 1, 17, 20

Interaural distance – see Chap 12

Interaural level difference (ILD) – see Chap 12

Interaural time difference (ITD) – see Chap 12

Interception (movement) – see Chaps 1, 25

Intercostal muscle – see Chap 8

Interleukin – pro-→inflammatory →cytokine; see Chap 5

Inter-limb coordination – see Chaps 9, 22, 23

Internal model – conceptual scheme derived from engineering concepts. In neuroscience, the term means, broadly and generally, that the →central nervous system (CNS) possesses sub-systems that mimic the input-output behaviors of natural systems. See →forward internal model, →inverse internal model and Chaps 1, 7, 10, 12, 15, 19, 25, 26, 27

Internal model of gravity – neural representation of →gravity, which helps anticipate the motion of a free falling object and the visual →perception of the →allocentric vertical; see Chaps 1, 25

Interneuron – →neuron whose cell body and →axon terminations are in the same nucleus or restricted region of the →central nervous system (CNS); see Chaps 1, 3, 4, 5, 7, 8, 10, 13, 15, 16, 17, 19, 20, 22, 23, 24, 25, 26, 27

Interposed (interpositus) nucleus – →nucleus interpositus; see Chaps 16, 23

Interpositus neuron – →neuron in →nucleus interpositus; see Chaps 16, 23,26

Inter-segmental coordination – see Chap 21

Inter-segmental interaction – see →interaction forces, interaction →torques and Chaps 1, 8, 19, 21, 24

Interstitial nucleus of Cajal (INC) – see Chaps 15, 16

Intrafusal muscle fiber – specialized →muscle fiber within the spindle-like capsule of a muscle spindle; see Chaps 8, 9, 18, 22

Intralaminar nuclei (of →thalamus) – group of dorsal nuclei between fiber laminae; see Chaps 4, 7

Intraparietal sulcus (IPS) – sulcus intraparietalis, between the →inferior parietal lobule (IPL) and →superior parietal lobule (SPL) of the →posterior parietal cortex (PPC); see Chaps 7, 14, 16, 24, 25, 26, 27

Intrinsic coordinate system – see →coordinate system and Chap 1

Invariance (or constancy) in →perception – In sensory systems, invariance denotes the fact that some properties of the perception or neural representation of objects remain invariant under varying conditions; see →perceptual constancy (or invariance) and Chaps 3, 12, 14

Inverse dynamics – see Chaps 1, 14

Inverse internal model – In neuroscience, an inverse →internal model denotes a control mechanism that computes those control signals needed to realize a desired state of an effector (i.e., limb or eye); see Chap 1

Inverse myotatic reflex – see →reflex and Chap 19

Invertebrate – see Chaps 10, 18, 22, 24

Inverted pendulum – see Chap 19

Ion channels – proteins which span the cell membrane and have pores that can be opened by transmembrane →voltage changes (→voltage-gated ion channels) or by binding of a →neurotransmitter (→ligand-gated ion channels). Ion channels, which are selective for sodium (Na^+) or calcium (Ca^{2+}) ions, cause excitation, while ion channels with selectivity for potassium (K^+) or chloride (Cl^-) usually cause inhibition of cells. Ion channels are often multimeric and regulated by a wide variety of mechanisms (e.g., ligand-binding, voltage changes, →phosphorylation); see Chaps 1, 2, 4, 5, 6, 8, 11, 13, 17, 22

Ipsiversive – directed toward the ipsilateral side; see Chap 16

Iris – see Chap 13

Ischemia/ischemic – reduced bloodflow to a tissue resulting from constriction or obstruction of blood vessels, which may lead to →stroke and other insults; see Chaps 4, 5

Iso-frequency strip – see Chap 12

Isometric (contraction) – see Chaps 8, 17, 18, 21

Isotonic (contraction) – see Chap 18

Itch – unpleasant sensation on the skin produced by various stimuli and conditions and eliciting a strong urge to scratch; see Chaps 1, 4, 5

Itch circuit – see Chap 4

Jaw elevator muscle – see Chap 8

Jeffress model – delay line hypothesis on the detection of interaural time differences (ITD) for sound localization as it might be realized in barn owls. The Jeffress model posits a matrix of →coincidence detectors and delay lines. Each →neuron in an iso-frequency layer is tuned to a different ITD by virtue of differences in →axonal conduction delay from the ear. Owing to the relatively high-frequency tuning of binaural neurons in the barn owl, neurons are sharply tuned for ITDs relatively to the width of the head. The lateral position of a sound source is read out as the position within the matrix that is maximally active – a form of local coding. Neurons in each brain hemisphere are tuned to different lateral positions in contralateral space; see Chap 12

Joint afferent – see Chaps 4, 8, 9, 19

Joint angle – see Chaps 1, 6, 7, 8, 9,17,19, 20, 21, 25, 26

Joint capsule – see Chaps 1, 8, 9, 17, 19

Joint position sense – see Chap 9

Joint receptor – see →receptor cell and Chaps 1, 8, 9, 19, 20, 22, 24

Joint torque – see Chaps 1, 8, 19, 25, 26

Jumping – see Chaps 1, 19, 23

K^+ channel – potassium channel; see Chap 2

Kainate (KA) – pharmacological →agonist to non-→NMDA →glutamate receptors; see →receptor and Chaps 5, 10, 11

Kangaroo – see Chap 17

KCNK potassium channel – see Chap 4

Keratinocyte – cell of the epidermis producing keratine; see Chap 6

Kinase – see Chap 3

Kinematic(s) – see Chaps 1, 3, 9, 17, 19, 20, 21, 22, 23, 24, 25, 26, 27

Kinematic-to-kinetic transformation – see Chaps 1, 25

Kinematic trajectory planning in joint-angle space –target-directed reaching/pointing movements that are planned in joint-angle space. The →central nervous system (CNS) first transforms the extrinsic target position into the arm/hand posture (set of joint angles) required

to attain the target and then computes the joint-angle trajectories moving the limb from the initial into the final posture; see Chap 25

Kinematic trajectory planning in task space – Correlated changes in joint angles during movements that correspond to kinematic synergies; see Chap 25

Kinesthesia, kinesthetic – see Chaps 1, 8, 9, 10, 24, 26

Kinesthetic illusion – see →illusion and Chap 19

Kinetic energy (in mechanics) – →energy inherent in motion: one-half the product of the →mass of a particle or body times the square of its speed; see Chap 21

Kinetic, kinetics – see Chaps 1, 9, 19, 21, 25, 26, 27

Kinetic planning in joint-torque space – When the →central nervous system (CNS) plans target-directed movements in kinematic coordinates, it performs complex kinematic-to-kinetic transformations. In addition to →torques securing equilibrium, a linear synergy is produced; see Chap 25

Kinocilium – see Chap 10

Kölliker-Fuse nucleus – see Chap 22

Koniocellular (K) cells (in →primates) – small cells in the lateral geniculate nucleus (LGN); see Chaps 13

Labeled-line code – also *dedicated-line code*; in this code, neural information is envisaged to be coded in the activities of →neurons →sensitive to modalities and sub-modalities, place etc.; see Chaps 2, 3, 4, 11, 13

Labyrinth (in inner ear) – see Chaps 10, 20, 23

Labyrinthectomy – partial or total destruction of the membranous labyrinth of the inner ear by surgical or pharmacological means (e.g., ototoxic drugs destroying the →hair cells); see Chap 20

Lactacidosis (lactic acidosis) – →acidosis due to extrusion of lactic acid from hyperactive skeletal →muscle fibers; see Chap 17

Lactate – salt or ester of lactic acid; see Chap 17

Lactic acid – see Chaps 4, 17, 19

Lamprey – see Chap 22

Landmark – environmental cue used by animals to navigate. Landmarks have stable spatial relations to a goal location; see Chap 23

Landmark navigation (or piloting) – see Chap 23

Large-fiber sensory neuropathy – degeneration of the thick →myelinated afferent nerve fibers carrying tactile information and proprioceptive information (from muscles and joints) with preserved temperature and pain sensation; see Chaps 9, 27

Larynx, laryngeal – see Chap 2

Laryngeal muscle – see Chap 8

Latch neuron (in oculomotor control) – see Chap 16

Lateral gastrocnemius muscle – see Chaps 19, 22

Lateral geniculate nucleus (LGN) – see Chaps 13, 14

Lateral hypothalamus – see Chaps 2, 23

Lateral inhibition – see Chaps 3, 7

Lateral intraparietal (LIP) area – represents information about 2D aspects of objects; has many →neurons with bi- of trimodal responses to auditory, visual and/or somatosensory stimuli; may also be implicated in spatial →attention, →decision making, categorization and →working memory; see →area LIP and Chaps 16, 24, 25

Lateral lemniscus – lemniscus lateralis; nerve fiber tract (and associated nuclei) carrying sensory information from cochlear nucleus to →inferior colliculus. In mammals, the lateral lemniscus is predominantly an auditory pathway; see Chap 12

Lateral occipital complex (LOC) (in→cerebral cortex) – together with the fusiform gyrus possible human homologue of the monkey →inferior temporal (IT) cortex; see Chaps 7, 14

Lateral olfactory tract (LOT) – see Chap 3

Lateral preoptic area – see Chap 2

Lateral rectus eye muscle – see Chaps 15, 16

Lateral reticular nucleus (LRN) – pre-→cerebellar →brainstem nucleus that receives signals from the →cerebral cortex and →spinal cord and sends →mossy fibers to the →cerebellum; see reticular nuclei and Chaps 5, 7, 26

Lateral sulcus – lateral (Sylvian) fissure; see Chap 12

Lateral superior olive (LSO) – see Chap 12

Lateral vestibular nucleus (LVN) of Deiters – see Chaps 10, 20

Law of specific sense energies – see Chap 1

L-DOPA – 3,4-**d**ihydr**o**xy-**p**henyl**a**lanin, precursor of →dopamine and →noradrenaline, the latter being the precursor of →adrenaline. L-DOPA (levodopa) is used in the pharmacological treatment of →Parkinson´s disease; see →monoamines and Chaps 20, 22

Leaky integration/integrator (in oculomotor control) – see Chap 15

Learning – Very generally, learning may be defined as the process(es) of acquiring new information, knowledge, behavior or skill, outlasting the inducing events and linked to experience-dependent neural →plasticity; in almost all chapters

Length-tension relation (of →skeletal muscle) – see Chaps 15, 18, 22

Lens (of the eye) – see Chaps 13, 15, 16

Leptin – →hormone released from fat cells and involved in the regulation of appetite, →energy expenditure and metabolism; see Chap 2

Levodopa – →L-DOPA

Ligament – see Chaps 1, 8, 9, 17, 19

Ligament receptor – see →receptor cell and Chaps 1, 8, 9

Ligand-gated ion channel – →ion channel that bears extracellular ligand-binding sites which, upon binding of →neurotransmitter, modulate the opening or closing of the channel; see Chap 4

Limb-centered (→frame of reference) – frame of reference centered at a limb; see Chaps 24, 25

Limbic system – involved in the genesis of →affects, →emotions and emotional responses. Consists of a collection of extensively interconnected →central nervous system (CNS) regions stretching from the →forebrain to the →spinal cord and including the medial →prefrontal cortex (PFC), →anterior cingulate cortex (ACC), →insula, →hippocampal formation, →amygdala, →nucleus accumbens (*limbic →striatum*; →basal ganglia), anterior and medio-dorsal →thalamus, →habenulae, anterior →hypothalamus, →peri-aqueductal gray (PAD), →basal forebrain →cholinergic (→acetylcholine) and →brainstem →monoaminergic systems (e.g., →dopaminergic cell groups, →serotonergic →raphé nuclei, →noradrenergic →locus coeruleus); see Chaps 1, 2, 3, 12, 14, 16, 23, 26

Linear synergy – see →synergy and Chap 25

Lingual gyrus (in →cerebral cortex) – see Chap 14

Lipocalin – see Chap 3

Lizard – see Chap 11

Load compensation – change in active muscle force evoked by a change in loading of a muscle or body segment; see Chap 22

Load force – see Chaps 6, 20, 26

Load receptor – sensory →receptor cell →sensitive to mechanical load; see Chaps 19, 22, 23

Local distortion (in pointing/reaching) – see Chap 24

Local field potentials (LFPs) represent extracellularly recorded →voltage fluctuations of a local →neuronal population; see Chap 3

Locomotion – in the majority of chapters

Locomotor adaptation – see Chaps 23, 27

Locomotor body schema – see Chap 1

Locomotor drive potential (LDP) – see Chap 22

Locomotor frame of reference – →frame of reference with reference axes defined as instantaneous heading and its normal in the horizontal ground plane; see Chap 23

Locomotor training – see Chap 27

Locus coeruleus (LC) – →monoaminergic cell groups A5 and A6 in the rostral →pons of animals and humans. LC →neurons synthesize →noradrenaline and send highly diffuse projections throughout the →neuraxis where they release noradrenaline as a →neurotransmitter and →neuromodulator. LC neurons control →sleep and wakefulnes, discharge during waking and →arousal, thereby elevating both cerebro-cortical activation and behavioral arousal with motor activity and →muscle tone. During waking, LC neurons influence various behaviors, modulate sensory signal processing at several levels (sensory →salience including pain), →attention and →memory, →decision making and →learning by influencing several forms of activity-dependent →synaptic plasticity. By direct projections onto the →preganglionic neurons in the →spinal cord, they also excite the peripheral →sympathetic system to support motor activity by appropriate physiological adjustments; see Chaps 2, 3, 4, 5, 7, 10, 13, 15, 19, 20, 22, 23

Long-latency stretch reflex – motor response of longer than →spinal →stretch reflex latency to an unexpected mechanical perturbation probably routed, at least partially, through the →primary motor cortex (M1, MI); it shows some characteristics of voluntary responses: modulation by subject intent and task goals, `knowledge´ of the physical properties of the arm and environment, flexible routing of sensory information across the musculature; see →reflex and Chap 25

Long-lead burst neuron (LLBN) (in oculomotor control) – see Chap 16

Long-term depression (LTD) – physiological mechanism of →learning manifest as the reduction of →synaptic transmission between two →neurons, typically resulting from a strong excitatory input. LTD was first described in the →hippocampus, but has been shown to exist widely throughout the brain. In the cerebellar cortex, LTD of parallel fiber synapses onto →Purkinje cells is triggered by powerful →climbing fiber input; see Chaps 5, 10, 15, 27

Long-term memory refers to information derived from life-long experience or to the system(s) storing such information; see Chaps 7, 14, 25

Long-term potentiation (LTP) – enhancement of →synaptic transmission between two →neurons that occurs following application of a series of high-frequency electrical stimuli to the afferent fibers of the presynaptic →neuron. LTP is believed to underlie several functions during →ontogenetic development and experience-dependent →plasticity, including →explicit (explanatory) and →implicit (procedural) →learning and →memory. LTP is influenced by →neuromodulators such as →acetylcholine, →dopamine, →adrenaline and →serotonin (5-HT); see Chaps 5, 10, 15, 27

Loudness – subjective →intensity or `magnitude´ of a →sound; see Chaps 11,12

Low-frequency fatigue – special form of →muscle fatigue; see Chap 17

Low-pass filter – filter passing only low-frequency components in the →spectrum composing its input signals; see Chap 18

Low-threshold mechano-receptor (LTMR) – see Chaps 5, 7, 19

Lugaro cell – inhibitory →interneuron in the →cerebellum with a high sensitivity to →serotonin (5-HT); see Chap 10

Luteinizing hormone (LH) – see Chap 3

Lymphocyte – see →leukocytes and Chap 5

Macaque – see Chaps 2, 3, 6, 7, 9, 10, 12, 14, 15, 16, 19, 20, 25, 26, 27

Macrophages – resident innate immune cells, including →microglia in the →central nervous system (CNS). Infection, injury or other disturbance of the tissue can activate macrophages to

eliminate damaged tissue, infected cells or tumor cells, to increase the secretion of →inflammatory mediators and cytotoxic substances, and to activate the adaptive immune response; see →immune system, →leukocytes and Chaps 4, 5

Macular degeneration – see Chap 13

Macula sacculi – see sacculus and Chap 10

Macula utriculi – see Chap 10

Magnesium (Mg^{2+}) – see Chaps 4, 5, 17

Magnetoencephalography (MEG) – group of non-contact, non-invasive brain imaging techniques for detecting the magnetic field generated by the electrical brain activity; see Chaps 4, 7

Magnet reaction – see Chap 20

Magnocellular (M) cell – large cell in lateral geniculate nucleus (LGN); see Chap 13

Main olfactory bulb (MOB) – see Chap 3

Main olfactory epithelium (MOE) – see Chap 3

Main olfactory system – see Chap 3

Male effect – see Chap 3

Mammal – see Chaps 2, 3, 4, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 21, 22

Mammillary body (nuclei) – located in the medial zone of the →hypothalamus; see Chap 23

Manipulation – see Chaps 1, 4, 6, 7, 9, 14, 16, 24, 25, 26

Marmoset – see Chaps 12, 13

Mass (in mechanics) – quantitative measure of a body´s →inertia, i.e., its resistance to →acceleration; see Chaps 1, 9, 15, 19, 20, 21, 25, 26, 27

Mast cells – resident →leukocytes with numerous cytoplasmic granules containing →histamine, →bradykinin, →prostaglandins, etc. Upon mast cell activation, these substances are released and exert effects such as vasodilation, smooth muscle contraction, activation of →nociceptors. Activated mast cells can also secrete →cytokines. Mast cell activation plays a role in →stress-associated pain and neuro-→inflammation; see Chap 5

Mastication – see Chaps 2, 6

Mate – see Chaps 1, 11, 12

McGurk effect – modulation of the →perception of an acoustic speech signal by simultaneous observation of lip movements; see Chap 12

M-currents (M for →muscarine) flow through *M-channels* which are non-inactivating, voltage-sensitive potassium (K^+) channels. Without →acetylcholine, M-channels open at →resting membrane potential and diminish excitability; see Chap 10

Mecamylamine – →antagonist of →nicotinic receptors; see Chap 22

Mechanical allodynia – see →allodynia and Chaps 4, 5

Mechanical nociceptor – →nociceptor activated by mechanical stimuli; see Chaps 4, 5

Mechano-electrical transduction (MET) – transformation of force into →receptor potentials in →receptor cells mediated by the opening of different types of mechano-sensitive ion channels, including TREK/TRAAK K2P channels, Piezo1/2, TMEM63/OSCA, and TMC1/2. Mechano-electrical →transduction is important in hearing, →balance, touch and proprioception and is also implicated in the →autonomic regulation of blood pressure and breathing; see Chaps 6, 10, 11

Mechano-heat nociceptor – →nociceptor activated by mechanical and heat stimuli; see Chap 4

Mechano-receptors – →sensory receptors responsive to mechanical stimuli. There are →cutaneous mechano-receptors of different sorts, and deep mechano-receptors in the bodily interior, e.g., proprioceptors, such as muscle spindles, Golgi tendon organs, joint receptors, ligament receptors, various other mechanically →sensitive receptors in internal organs; →hair cells in the →vestibular apparatus and cochlea of the inner ear; see →receptor cell and Chaps 1, 4, 5, 6, 7, 8, 9, 19, 20, 22

Medial frontal gyrus – *gyrus frontalis medius*, in humans large gyrus in the lateral frontal lobe rostral to the pre-central gyrus (PCG) between the inferior frontal gyrus (IFG) and the superior frontal gyrus; see Chap 12

Medial gastrocnemius muscle – see Chaps 17, 18, 19, 22

Medial geniculate body (complex) – see →thalamus and Chap 12

Medial lemniscus – see Chap 7

Medial longitudinal fascicle (MLF) – nerve fiber bundle running rostro-caudally in the →brainstem; see Chap 16

Medial occipital cortex (MOC) – see Chap 7

Medial parietal region (MPR) (in →cerebral cortex) – see Chap 23

Medial plantar nerve – see Chap 22

Medial rectus eye muscle – see Chaps 15, 16

Medial superior olive (MSO) – see Chap 12

Medial superior temporal (MST) area – see →area MST and Chaps 7, 10, 14, 25

Medial temporal cortex (lobe) – part of the temporal cortex that includes →hippocampal complex (→hippocampus proper, dentate gyrus, subiculum, and →entorhinal cortex, →perirhinal cortex and para-hippocampal cortex) and is related to different →memory functions; see Chap 14

Medial vestibular nucleus (MVN) of Schwalbe – see Chaps 10, 15, 16, 20

Median eminence – see Chap 2

Medium-lead burst neuron (MLBN) (in oculomotor control) – see Chap 16

Medulla oblongata – most caudal part of the →hindbrain and →brainstem, just rostral to the →spinal cord; see Chaps 2, 7, 15, 16, 23

Medullary reticular formation (MRF) – →reticular formation in the →medullar oblongata; see Chap 25

Meissner corpuscle – see Chaps 1, 6, 7

Melanopsin – see Chap 13

Melatonin – N-acetyl-5-methoxytryptamine, also called →pineal or darkness →hormone, is derived from tryptophan via →serotonin (5-HT). Melatonin is primarily synthesized in and secreted by the →pineal body (gland) during the dark phase of the day and is involved in the regulation of the →circadian rhythm; see Chap 13

Membrane potential – see →resting membrane potential and Chaps 4, 10, 11, 13, 17, 18

Memory – ability to acquire, represent, maintain and →recall various types of information. See →long-term memory, →procedural memory, →short-term memory and Chaps 1, 2, 3, 4, 6, 7, 10, 11, 12, 14, 15, 16, 23, 24, 26, 27

Memory-guided saccade – see saccade and Chap 16

Median nerve – see Chap 7

Meniscus – see Chaps 8, 9

Mental imagery – ability to generate →percept-like experiences without sensory inputs by retrieval of information from →memory; see Chap 7

Menthol – secondary terpene alcohol, occurring in different forms; *l*-menthol is isolated from *Menta arvensis*, has a peppermint flavor and appears to cool mouth and skin; see Chaps 2, 4

Merkel cell (disk) – see Chaps 6 , 7

Merkel-neurite complex – see Chap 6

Merkel touch spot – see Chap 6

Mesencephalic, mesencephalon – refers to the most rostral part of the →brainstem; see Chaps 2, 3, 5, 16, 19

Mesencephalic locomotor region (MLR) – collection of cell groups organized into nuclei; cell groups include →glutamatergic, GABAergic, →cholinergic or peptidergic, which have differential effects, glutamatergic cells facilitating locomotion and GABAergic cells stopping it; see Chaps 22, 23

Mesencephalic reticular formation (MRF) – see →reticular formation and Chaps 16, 26

Metabotropic glutamate receptor – see →receptor and Chaps 5, 10

Metabotropic receptor (**metaboreceptor**) – The binding of a →hormone or →neurotransmitter (excitatory neurotransmitters such as →glutamate or inhibitory transmitters such as GABA) to metabotropic receptors (metaboreceptors) activates or inhibits intracellular biochemical processes, causing relatively long-lasting changes in the activity of →voltage-gated ion channels; see →receptor and Chaps 2, 3, 4

Metazoa – multi-cellular organisms; see Chap 1

Microelectrode – see Chap 2

Microglia – brain-resident →immune cells that, normally at rest, can be activated by injury or illness to serve as antigen-presenting cells and phagocytes; they also produce →cytokines and →neurotrophins; see Chap 5

Micro-gravity – weightlessness or reduced →gravity (relative to superficial terrestrial conditions) during orbital flight in space; see Chaps 9, 19

Micro-movement (of eyes) – see Chap 15

Micro-neurography – recording of electrical signals from nerve fibers in awake human subjects by insertion of an insulated tungsten microelectrode through the skin into an accessible peripheral or →cranial nerve; see Chaps 9, 20

Micro-saccade – largest and fastest fixational eye movement; see saccade and Chaps 15, 26

Micro-stimulation – low-→intensity electrical stimulation of a brain region through a microelectrode; see Chaps 9, 14, 16, 25

Microvilli – small cellular processes on the receptive surface of sensory cells, such as gustatory cells or olfactory cells, or Merkel cells; see Chaps 3, 11

Midbrain – mesencephalon: most rostral part of the →brainstem; see Chaps 2, 4, 5, 10, 12, 13, 16, 19, 20, 23, 25, 27

Middle ear – see Chaps 11, 12

Midget bipolar cell (in retina) – see Chap 13

Midget ganglion cell (in retina) – see Chap 13

Mid-posterior intraparietal sulcus (mIPS) – putative homologue of monkey area MIP (**m**edial **i**ntraparietal); see →intraparietal sulcus (IPS) and Chap 25

Migraine – common, paroxysmal, complex brain disorder. The central symptom is a usually unilateral, moderate to severe, pulsating headache, often associated with other symptoms, such as nausea, vomiting, photophobia (fear of light) and phonophobia (fear of →sound); see Chap 14

Mirror drawing – see Chap 27

Mirror image allodynia – →allodynia occurring not only at the site of injury and →inflammation, but also at the corresponding site on the contralateral side; see Chap 5

Mirror neuron – see Chaps 12, 25, 26

Mirror neuron system – see Chap 26

Mitochondrial dysfunction – see Chap 5

Mitochondrial myopathies – muscle diseases that result from defects in the mitochondrial respiratory chain, leading to diminution of →energy production and consequently to cramps, myalgia (muscle pain), recurrent *myoglobinuria* (excretion of →myoglobin via urine), and exercise intolerance or weakness, which in extraocular muscles entails ptosis (drooping of eyelids) and progressive external →ophthalmoplegia (Chap 9); see Chap 17

Mitral/tufted cell (in olfactory bulb) – see Chap 3

M-line (in →skeletal muscle) – see Chap 17

Modality (of →senses) – see Chaps 1, 2, 4, 5, 7, 9, 12, 14, 16, 19, 20, 22, 24, 26

Modiolus – see Chap 11

Moment arm – see Chap 17

Momentum (in mechanics) – product of body´s →mass and velocity; see Chap 21

Monaural – related to one ear; see Chap 12

Monaural nucleus of the lateral lemniscus (NLL) – see Chap 12

Monkey – see Chaps 2, 7, 9, 10, 12, 13, 14, 15, 16, 20, 23, 24, 25, 26, 27

Monoamines – Brain monoamines act as →synaptic →neurotransmitters and are classified as →catecholamines or indolamines, depending on whether they derive from phenylalanine or tryptophan, respectively. The catecholamines →dopamine, →adrenaline (epinephrine) and →noradrenaline (norepinephrine) derive from L-tyrosine. Adrenaline is synthesized from noradrenaline in a restricted group of →neurons in the →brainstem. The indolamine →serotonin (5-HT) is synthetized from L-tryptophan. Specific brain monoamines function in many aspects of behavior ranging from motor control to →emotional and →cognitive processes. Monoamine neurotransmitters act via specific postsynaptic →receptor sub-types; monoamines are mediators of →arousal, →attention and →motivation, and exert influences on →learning processes; see Chaps 10, 22, 27

Monocular cues – see Chap 14

Mood – see Chaps 3, 4, 12, 13, 14

Mossy fibers carry most inputs from the →brainstem or →spinal cord to the →cerebellum and terminate in the →granule cell layer of the cerebellar cortex; see Chaps 10, 15, 16, 23, 26, 27

Motion after-effect – visual →illusion produced by adaptation to a stimulus moving in one direction for a long time. On subsequent viewing of a stationary surround, this surround appears to move in the opposite direction; for example, when first looking into a waterfall for some time and then looking onto the rocks beside it, the rocks appear to move upwards; see Chap 14

Motion in depth – see Chap 14

Motion parallax – When an observer moves past a scene and fixates an object at middle distance, farther objects move slowly in the same and closer objects fast in the opposite direction. This cue can provide a strong impression of depth; see Chap 14

Motion perception – see Chaps 7, 16, 27

Motion sickness – *kinetosis:* A prerequisite for developing motion sickness is the exposure to a real or →illusory motion stimulus. Motion sickness is characterized by combinations of symptoms like drowsiness, dizziness, discomfort, malaise, stomach awareness, nausea, vomiting, repetitive yawning, bradycardia, arterial hypotension, pallor, sweating, headache, and apathy; see Chap 10

Motivation – inferred internal state variable that precedes, instigates and invigorates goal-directed behaviors. There are two forms, →drive and *incentive motivation*. Drive states are assumed to reflect internal states such as thirst and hunger. Reduction of a specific drive state by consumption of food or water reduces motivation to seek these stimuli. Incentive-motivational states are triggered by environmental stimuli that the animal tends to approach and work for. Incentive stimuli may be seen as →rewards and provide →reinforcement to repeat action patterns that bring the organism into contact with these natural stimuli. In part, incentive motivation depends on →dopamine; see Chaps 1, 2, 3, 4, 6, 7, 10, 12, 16, 19, 23, 24

Motoneurons – There are several classes of motoneurons. Autonomic motoneurons (→autonomic nervous system) innervate smooth muscle cells in heart and arteries and glands. Somatic motoneurons innervate →muscle fibers. For extraocular muscles, there are two types of motoneurons innervating different types of muscle fibers. For →skeletal muscles, motoneurons can be classified into →skeleto-motoneurons (→α-motoneurons and →β-motoneurons) innervating skeletal muscle fibers and fusi-motoneurons (β-motoneurons and γ-motoneurons) innervating muscle fibers in muscle spindles. β-Motoneurons thus innervate both types of muscle fiber; in the majority of chapters

Motoneuron (motor) nucleus or pool – group of →motoneurons innervating a macroscopic →skeletal muscle; see Chaps 1, 15, 17, 18, 19, 20, 22

Motor adaptation – fast return of motor behavior to baseline performance level after perturbation (changing own-body or environmental properties); see Chaps 1, 23, 27

Motor axon – →axon of a →motoneuron; see Chaps 8, 13, 17, 18, 22

Motor command – signal issued by high-level central motor structures and carried to executive lower-level structures (e.g., →motoneurons in the →brainstem or →spinal cord) by →neurons of descending systems, e.g., →cortico-spinal tract (CST) neurons; see Chaps 1, 9, 10, 15, 16, 20, 22, 23, 24, 25, 26, 27

Motor cortex (in →cerebral cortex) – The term has historically has been used to refer to →primary motor cortex (area M1, area F1). This term is now used in a wider sense to refer collectively to primary and →secondary motor areas of the →frontal cortex (lobe); see Chaps 5, 7, 9, 12, 14, 19, 20, 23, 24, 25, 26, 27

Motor endplate (MEP) – also →neuromuscular junction: →synaptic connection between a motor axon and skeletal →muscle fiber; see Chap 17

Motor error – difference between the desired motor goal and actual motor behavior; such errors may arise from unpredictable changes in target location (target errors), or from mis-calibration of →internal models (execution errors). The latter in turn may be due to mis-calibration of kinematics (e.g., when prisms alter visual feedback) or to mis-calibration of kinetics (dynamics) (e.g.. when a force field alters limb dynamics); see Chaps 16, 24, 25, 27

Motor imagery – motor example of →mental imagery; mental simulation or rehearsal of a particular movement without its actual execution; see Chap 25

Motor learning – process of adapting motor behavior to new conditions or of acquiring new motor skills, so that individual or sequential movements become performed effortlessly through repeated practice and interactions with the environment. It involves adaptive modifications of the spatio-temporal structure of movements, forming new or adjusting existing sensory-motor transformations and forming new movement sequences; see →motor-skill learning and Chaps 1, 10, 15, 20, 23, 25, 26, 27

Motor map – →topographically organized representation of →skeletal muscles or movements in →central nervous system (CNS) structures; see Chaps 12, 16, 27

Motor-related cortical potential (MRCP) – see Chap 24

Motor skill – see Chaps 6, 26, 27

Motor-skill learning – also called procedural learning: →learning of a sensory-motor task by practice or experience, such as riding a bike or playing the piano; acquisition of new combinations of movements that lead to new capacities for goal-directed action or improvement of motor performance above baseline levels in terms of accuracy, consistency, smoothness and speed. Motor-skill learning is based on changes in →neuronal circuitry, such as changes in circuit connectivity, →synaptic strength, and neuronal excitability; see Chaps 1, 27

Motor unit – complex of a →skeleto-motoneuron and the group of skeletal →muscle fibers it innervates; a motor unit constitutes the smallest unit of motor control; see Chaps 8, 17, 18, 19, 20, 26

Motor unit action potential (MUAP) – extracellular potential recorded upon nearly simultaneous excitation of all the skeletal →muscle fibers in a single →motor unit; see Chap 17

Motor unit classification – in cat muscles, motor units can be roughly classified into different groups with different properties: *S,* slow-twitch, fatigue-resistant; *FR*, fast-twitch, fatigue-resistant; *F(int)*, fast-twitch, intermediate fatiguability; *FF*, fast-twitch, fatiguable; see Chap 18

Mouse, mice – see Chaps 3, 4, 5, 6, 7, 8, 10, 13, 15, 19, 20, 22, 23, 24, 26, 27

Mouth – see Chaps 1, 2, 7, 12, 14, 25, 26

Movement field –see Chap 16

Movement sense (sensation) – see Chap 9

Movement sequence – see Chaps 1, 25, 26, 27

Multi-modal refers to more than one sensory modality (Chap 1) and is often used synonymously with →multi-sensory; see Chaps 1, 3, 4, 9, 10, 12, 16, 20, 23, 25

Multi-modal integration – see →multi-sensory integration and Chap 1

Multiple sclerosis (**MS)** - group of **i**diopathic →**i**nflammatory →**d**emyelinating **d**iseases (IIDDs) of the →central nervous system (CNS). Typically, its course starts as a series of relapses and remissions, but transcends into a progressive form resulting from accumulation of permanent damage. The cause remains unknown. Viral and auto-→immune etiologies have been postulated. Genetic and environmental factors contribute to MS. Early symptoms may include optic neuritis, diplopia (double vision), numbness and/or →paresthesia, mono- or paraparesis, →ataxia, and bladder-control problems. Other symptoms include increasing →spasticity, with abnormalities in gait, dysarthria (deficit of speech articulation), vertigo, incoordination and other →cerebellar problems, depression, →emotional lability, fatigue and pain. Pathologically, MS is characterized by the presence of areas of →demyelination and perivascular →inflammation in the brain →white matter. Loss of →neurons and →axons adds to the pathology; see Chaps 4, 17

Multi-sensory integration (interaction) – neural integration or combination of information from more than one sensory modality, such as gustation and olfaction, touch, audition, vision, but also pain, proprioception, vestibular →sense, leading to more complex neural representations of various entities; often used synonymously with →multi-modal integration; see Chaps 1, 2, 3, 9, 10, 16, 19, 20, 26

Multi-sensory map – see Chap 7

Muscarine – pharmacological →agonist of →acetylcholine at →muscarinic receptors, contained in the mushroom *amanita muscaria*; see Chaps 2, 10

Muscarinic receptors – →G-protein-coupled receptors for →acetylcholine and →muscarine; they can be blocked by →atropine, →scopolamine and related →antagonists; see Chap 10

Muscimol – pharmacological →agonist of →γ-amino-butyric acid (GABA); see Chaps 23, 26, 27

Muscle (skeletal) – in the majority of chapters

Muscle compartment – see Chaps 8, 15, 17

Muscle fatigue – loss of force-generating capacity (relative to maximal capacity) during prolonged muscle activation, due to peripheral factors (→muscle fatigue, peripheral factors) or to neural factors (→muscle fatigue, neural factors); see Chaps 1, 4, 8, 9, 17, 18, 19, 20, 22, 27

Muscle fatigue, neural factors – Muscle fatigue must dealt with by the nervous system while generating posture and movement. The reduction in force-generating capacity induces changes in →skeletal muscle and all levels of the →central nervous system (CNS). Processes in the CNS are subsumed under central fatigue, denoting a failure of the CNS to drive →skeleto-motoneurons (→motoneurons) maximally. The mechanisms underlying the decline in maximal force capacity depend on the details of the task being performed; see Chaps 17, 18, 22

Muscle fatigue, peripheral factors – see Chap 17

Muscle fiber (in extraocular muscle and →skeletal muscle) – multi-cellular syncytia, may have a thousand or more nuclei; see Chaps 1, 8, 9, 15, 17, 18, 19

Muscle plasticity – see Chap 18

Muscle space – see Chap 1

Muscle spindle – see Chaps 1, 7, 8, 9, 15, 18, 19, 20, 21, 22, 23, 24, 25, 27

Muscle tone – resistance of a relaxed muscle to passive stretching; see Chaps 1, 19, 20, 22, 23

Muscle torque – product of muscle force and muscle moment arm; see →torque and Chaps 1, 15, 20, 21, 25

Muscle unit – that group of skeletal →muscle fibers innervated by a single →skeleto-motoneuron, i.e., the muscle part of a →motor unit; see Chaps 17, 18

Muscle vibration – see Chaps 8, 9, 10, 19, 20, 25

Muscular dystrophies – large group of inherited heterogeneous myopathies, characterized by progressive muscle weakness and wasting, and including four major forms: Duchenne muscular dystrophy, fascio-scapulo-humeral muscular dystrophy, →myotonic dystrophy and limb-girdle muscular dystrophy; see Chap 17

Musculotopic map – ordered →somatotopic map between the locations of →motoneurons in the →spinal cord or →brainstem and the peripheral locations of the innervated muscles in the body; see Chap 17

Music – see Chaps 1, 4, 9, 11, 12, 14, 24

Mutual excitation – see Chap 22

Mutual inhibition – see Chap 3

Myasthenia gravis (MG) – heterogeneous neuromuscular disease. The most frequent form is an acquired auto-immune disease with failure of →neuromuscular transmission. Auto-immune MG results from antibodies against the →nicotinic acetylcholine receptor (AChR) and sometimes other postsynaptic →neuromuscular junction antigens, leading to decreased concentrations of AChRs and damage to the neuromuscular junction. The main features are changeable pathological fatiguability and characteristic fluctuating weakness, most commonly in muscles of the head, neck, and upper extremities (*generalized MG*). In 15% of patients, only extraocular muscles are affected with variable ptosis (drooping of eyelids), squint and double vision (*ocular MG*); see Chap 17

Mydriasis – pupil dilation; see Chap 13

Myelinated – surrounded by →myelin; see Chaps 2, 3, 4 5,.6, 7, 17, 18, 19

Myelin sheath – A myelin sheath is built by repetitively wrapping the cell membranes of a →Schwann cell [in the →peripheral nervous system (PNS)] or oligodendrocyte [in the →central nervous system (CNS)] around an →axon, in which process the cytoplasm is squeezed out. A stretch of axon 0.5 to 2 mm length becomes covered by a multi-layered stack of membranes, adjacent stretches being separated by gaps of 1-2 μm. These gaps are called nodes of Ranvier and the stretches in between internodes. Myelin sheaths form insulators around an axon; see Chaps 2, 3, 4

Myocardial infarction – see Chap 4

Myocyte – muscle cell; see Chap 17

Myoclonus – involuntary, abrupt jerks of limbs or trunk, which may occur spontaneously at rest, in response to sensory stimuli, with voluntary movements or during →rapid-eye-movement (REM) sleep. Myoclonus also occurs in a variety of generalized metabolic and neurological disorders; see Chap 12

Myofascial force transmission – see Chap 17

Myofibril – see Chap 17

Myofilament – see Chap 17

Myoglobin – oxygen (O_2) carrier in skeletal →muscle fibers; see Chap 18

Myokine – see Chap 17

Myosin – see Chaps 8, 10, 11, 17, 18, 19

Myosin isoform – see Chap 18

Myosin light chain kinase (MLCK) – see Chap 18

Myotendinous junction – connection between skeletal →muscle fibers and tendon fibers, such that fingerlike extensions of the sarcolemma at the ends of muscle fibers interdigitate with similar extensions of the connective tissue of the tendon; see Chaps 8, 15

Myotonic dystrophy – group of hereditary →skeletal muscle diseases which may be so mild as to show almost no symptoms or so severe as to start early in life. Characteristic symptoms include weakness in cranial and limb muscles, myotonia (impairment of muscle relaxation after strong voluntary contraction or electrical stimulation) and often cataracts, baldness and testicular atrophy in men; see Chap 17

Na^+K^+-ATPase – The Na^+K^+-ATPase (also called the *cellular sodium pump*) maintains the high Na^+ and K^+ gradient across the cell membrane by transporting three Na^+ ions out of and two K^+ ions into the cell, using the →energy of →ATP hydrolysis (electrogenic transport). The Na^+K^+-ATPase activity is enhanced by muscle excitation, raised intracellular Na^+ concentration, β-→adrenergic stimulation and raised temperature, and is selectively inhibited by cardiac glycosides; see Chap 17

Natural scene (in vision) – see Chap 14

Natural sound – see Chaps 11, 12

Navigation – see Chaps 1, 3, 10, 12, 14, 22, 23

Navigational strategy – see Chap 23

Near-response neuron – →n →neuron with an activity pattern related to horizontal vergence eye movement and lens →accommodation; see Chap 16

Near trias – see Chap 16

Nebulin – protein in →skeletal muscle; see Chap 17

Neck muscle – see Chaps 8, 9, 10, 16, 19, 20

Neck muscle vibration – see Chaps 10, 19, 20

Neck movement – see Chaps 12, 23

Negative feedback – control mechanism to regulate a system´s constant or time-variable output variable according to some desired reference value. →Closed-loop control implies that the system´s output variable is measured, fed back to a controller that compares the system´s output variable with the desired reference value, the difference then being used to determine

the system´s input signal. Negative feedback control implies that a given change in the output variable is counteracted by appropriate changes in the input signal, computed by the controller; see Chaps 3, 13, 16, 26

Neocortex (in →cerebral cortex) – also called isocortex: evolutionarily most recent part of the vertebrate →forebrain. It has six layers (laminas) and →neuron types assembling into repetitive circuits; see Chaps 14, 19

Neophobia – fear of the new; see Chap 2

Nerve growth factor (NGF) – see →growth factors and →neurotrophic factors (neurotrophins, NTs); see Chaps 4, 5

Neuralgia – sharp, paroxysmal pain along a nerve; see Chap 4

Neural integrator (in oculomotor control) – see Chaps 15, 16

Neuronal oscillations – Synchronized oscillatory states in brain →neuronal networks that commonly occur in different frequency bands: *delta (δ) rhythm (0.5-4 Hz)*; *theta (θ) rhythm (4-9 Hz)*; *alpha (α) rhythm (8-14 Hz)*; *beta (β) rhythm (14-30 Hz)* and *gamma (γ) rhythm (30-100 Hz)*. Oscillations play important roles in →sleep-wakefulness, →arousal, →attention, →memory, consciousness, feature binding in sensory processing, sensory and motor processes as well as in pathological processes, such as →Parkinson´s disease (and psychiatric diseases such as →schizophrenia and →autism. The origins of oscillations and their synchronization are manifold. *Activity of individual →pacemaker neurons* based on intrinsic membrane properties. *Variously interconnected networks* of neurons, including inhibitory circuits, that may produce oscillatory global activity patterns under appropriate conditions of excitatory background and connectivity. *Combinations* of the two preceding possibilities in which inter-connected pacemaker neurons become synchronized or otherwise correlated; See Chaps 12, 22

Neuraxis – →central nervous system (CNS), from the →spinal cord (medulla spinalis) to the →cerebrum; see Chaps 1, 6, 17, 19, 25

Neuro-endocrine axis – structural and functional basis for interactions between brain, →hormones and glands, comprising three pathways and their feedback mechanisms: hypothalamic-pituitary-adrenal (HPA) axis from the →hypothalamus via the anterior lobe of the →pituitary gland to the adrenal cortex; hypothalamic-pituitary-thyroid (HPT) axis from the hypothalamus to the thyroid gland; hypothalamic-pituitary-gonadal (HPG) axis, involving the male or female gonads; see Chap 10

Neurogenic inflammation – effects of the local release from afferent nerve terminals of →inflammatory mediators such as →substance P and →calcitonin-gene-related peptide (CGRP); see Chaps 4, 5

Neuroimaging – see Chaps 3, 4, 7, 12, 14, 18, 20, 23, 27

Neurokinins (NKs) – see →tachykinins and Chap 5

Neuromodulation – actions altering the intrinsic properties of →neurons and →synapses; see →neuromodulators and Chaps 2, 3, 7, 12, 13, 14, 16

Neuromodulators – chemical compounds released by →neurons that modulate the activity of targeted cells. Neuromodulators are typically amines or peptides that can →phosphorylate →ion channels, alter second messenger pathways and intracellular calcium (Ca^{2+}) concentrations. These modulatory effects change ion channel properties, which in turn lead to the alteration of neuronal discharge patterns They can also enhance or decrease the efficiency of excitatory or inhibitory →synapses mediated by classical →neurotransmitters such as →glutamate or GABA; see Chaps 4, 5, 10, 16, 22

Neuromuscular compartment – see Chap 17

Neuromuscular junction – also called *nerve-muscle junction* or *motor endplate*: →synaptic enlargement formed by a motor axon terminal where it contacts a skeletal →muscle fiber, plus the complex postsynaptic specialization in the muscle fiber immediately beneath it. Normally there is only one such junction per muscle fiber. The neuromuscular junction is a classical chemical →synapse, where →acetylcholine (ACh) is released presynaptically and binds to postsynaptic acetylcholine receptors (AchRs); see →receptor and Chaps 17, 18

Neuromuscular transmission – cascade of events at the →neuromuscular junction leading to transfer of excitation from the presynaptic motor nerve terminal to the skeletal →muscle fiber; see Chap 17

Neuron – excitable nerve cell, possessing specialized membrane structures with →ion channels and →receptors for various compounds (ligands), second messengers, etc. Neurons are able to produce and conduct →action potentials, and are usually integrated in elaborate neuronal networks through →axons and →dendrites; throughout chapters

Neuronopathy – see Chap 7

Neuropathic itch – see Chap 4

Neuropathic pain – describes pain states resulting from lesions to peripheral nerves, →spinal cord and brain, as well as from neuropathies associated with disease states such as diabetes, human immunodeficiency virus/AIDS, →herpes zoster, →multiple sclerosis, cancer, and chemotherapy; see Chaps 4, 5, 7

Neuropeptides – short-chain peptides with multifarious actions, some functioning as →neurotransmitters, →neuromodulators and others functioning as →hormones. See Chaps 2, 4, 10

Neuropeptide Y (NPY) – peptide →neuromodulator involved in the regulation of feeding and →circadian rhythm; see Chaps 2, 4

Neuroplasticity – see →plasticity and Chap 5

Neuropsychology – see Chaps 9, 27

Neurotransmitters – briefly, *transmitters*: small molecules that mediate →synaptic transmission at chemical synapses. They are synthetized in →neurons and stored in →synaptic vesicles in presynaptic terminals and released upon →action potential invasion of the terminals, after which they bind to →receptors of an effector cell. This binding can lead to excitatory or inhibitory actions of the target cell. →Glutamate is the most prominent excitatory neurotransmitter, whereas GABA (→γ-amino-butyric acid) is the most important inhibitory transmitter; see Chaps 1, 2, 4, 5, 10, 11, 16, 22

Neurotrophic factors (neurotrophins, NTs) – group of proteins enhancing the growth and ensuring the survival of →neurons during →ontogenetic development and regeneration after damage. Among NTs are nerve growth factor (NGF), glia cell-derived neurotrophic factor (GDNF), →brain-derived neurotrophic factor (BDNF), NT-3, NT-4/5 and NT-6 (existing only in teleost fish); see Chaps 3, 5, 9

Neutrophils (granulocytes) – short-lived →leukocytes with poly-morphic nuclei, continuously generated from myeloid precursors in the bone marrow. They are elements of the innate →immune system essential to fight micro-organisms and clear cellular debris. They are activated by bacterial and tissue-damage products, such as →cytokines, damage-associated molecular patterns (DAMPs), and →growth factors. When activated, neutrophils produce cytokines, →chemokines, →acetylcholine and →catecholamines and thus interact with nerve cells. Neutrophils contribute to →inflammatory and →neuropathic pain; see →leukocytes and Chaps 4, 5

Newborn stepping – see Chap 22

New-World monkey – see Chap 13

Nicotine – pharmacological →agonist of →acetylcholine at →nicotinic receptors; see →receptor and Chap 10

Nicotinic receptors – →ligand-gated ion channels for →acetylcholine and its →agonist →nicotine; see →receptor and Chap 10, 22

Nigro-striatal projection – →dopaminergic projection from the →n →ventral tegmental area (VTA) (→tegmentum) and the →substantia nigra pars compacta (SNc) to the →striatum of the →basal ganglia; see →basal ganglia, →dopamine and Chap 27

Nipple – see Chap 6

Nitric oxide (NO) – diffusible gas that is produced in cells possessing the enzyme NO synthase which breaks down L-arginine to L-citrulline; NO easily permeates cell membranes and plays a role in inter-cellular communication; see Chaps 3, 5, 10, 17

NMDA receptors (NMDARs) – see Chaps 2, 3, 5, 10, 27

N-methyl-D-aspartate (NMDA) – amino acid derivative that acts as a pharmacological →agonist of and thereby characterizes a particular type of →glutamate receptor; see →receptor and Chaps 2, 3, 5, 11, 19, 22, 27

Nocebo – opposite to →placebo; see Chap 5

Nociception, nociceptive – detection, by sub-populations of peripheral nerve fibers, of intense chemical, mechanical and/or thermal stimuli that may be harmful to the body; see Chaps 1, 2, 4, 5, 6, 7, 8, 14, 20, 22, 27

Nociceptive afferents – see Chaps 4, 19

Nociceptive neuron – peripheral or central →neuron capable of encoding →noxious stimuli; see Chaps 4, 5

Nociceptive pathways – see Chaps 4, 5, 27

Nociceptive-specific neuron (NS neuron) – see Chap 4

Nociceptors – →sensory receptors capable of →transducing and encoding →noxious stimuli; see →receptor cell and Chaps 1, 2, 4, 5

Noise can be random or deterministic and, when superimposed on the signal of interest, may distort this signal; see Chaps 1, 3, 7, 11, 12, 19

Noradrenaline (NA) – also called norepinephrine: →catecholamine that is widely distributed throughout the →central nervous system (CNS) and is also present in →sympathetic adrenergic →neurons and the →adrenal gland; see Chaps 2, 3, 5, 10, 20, 22, 27

Norepinephrine (NE) – also called →noradrenaline (NA); see Chap 10

Nostril – see Chap 3

Novelty (detection) – see Chaps 2, 6

Noxious stimulus – actually or potentially tissue-damaging stimuli including excessive temperature, mechnical stimulation and chemicals; see Chaps 1, 4, 5, 7, 9, 20, 22, 23

Nucleus accumbens – ventro-medial input station of the →basal ganglia, with sub-territories including a core and a shell. The nucleus accumbens has widespread connections to cerebro-cortical and →brainstem regions, including the →prefrontal cortex (PFC), →anterior cingulate cortex (ACC), →habenulae, →thalamus, →amygdala, →hippocampus, ventral →pallidum (of the basal ganglia), lateral hypothalamus, ventral →mesencephalon, →periaqueductal gray (PAG). It plays roles in addiction, →reward, →motivational and →emotional processing, pleasure and pain (→analgesia); see Chaps 2, 4, 5, 12, 16, 23

Nucleus basalis – see Chap 12

Nucleus caudatus – caudate nucleus: large cell assembly elongating into a tail and belonging to the →basal ganglia; see Chaps 16, 23

Nucleus centralis lateralis (CL) of the →thalamus – see Chap 7

Nucleus cuneiformis – see Chap 23

Nucleus dentatus – dentate nucleus: most lateral of the →deep cerebellar nuclei, with inputs from motor, premotor, prefrontal and visual cerebro-cortical regions, and output to →thalamus, parvocellular →nucleus ruber, →nucleus reticularis tegmenti pontis (NRTP) (→tegmentum), →inferior olive (IO); see →cerebellum and Chaps 10, 23, 25

Nucleus fastiguus – fastigial nucleus: most medial of the →deep cerebellar nuclei, with inputs from →vestibular nuclei, →lateral reticular nucleus (LRN), →spino-cerebellar tracts, and outputs to →thalamus, lateral and descending vestibular nuclei, →nucleus reticularis tegmenti pontis (NRTP) (→tegmentum), nucleus praepositus hypoglossi (NPH), →n reticular →gray matter, →inferior olive (IO), contralateral →spinal →motoneurons; see →cerebellum and Chaps 10, 23, 24

Nucleus intercalatus – see Chap 10

Nucleus interpositus – interposed nucleus (in humans: nucleus globosus and nucleus emboliformis): one of the →deep cerebellar nuclei, interposed between →nucleus fastiguus and →nucleus dentatus, with inputs from somatosensory →receptors in the limbs via →spino-cerebellar tracts and from →motor cortex, and outputs to →thalamus, magnocellular →nucleus ruber (small in humans), →nucleus reticularis tegmenti pontis (NRTP) (→tegmentum), →inferior olive (IO), →spinal →gray matter; see →cerebellum and Chaps 10, 23, 25, 26

Nucleus of the brachium of the inferior colliculus (nBIC) – see →inferior colliculus and Chap 12

Nucleus of the lateral lemniscus – see →lateral lemniscus and Chap 12

Nucleus of the solitary tract (NST) – nucleus tractus solitarii. The NST is a nucleus in the dorso-medial →medulla oblongata and constitutes the first relay station for taste and general visceral afferents. The NST conveys this information to all central autonomic regions (→autonomic nervous system), both directly and via the →parabrachial nucleus (PBN), and is critically involved in all medullary →reflexes controlling cardio-vascular, respiratory, and gastro-intestinal functions; see Chap 10

Nucleus paragigantocellularis dorsalis (PGD) – see Chap 16

Nucleus praepositus hypoglossi (NPH) – see Chaps 15, 16

Nucleus praepositus hypoglossi-medial vestibular nucleus region (NPH-MVN) – see Chap 16

Nucleus reticularis tegmenti pontis (NRTP) – large reticular nucleus in the pontine →reticular formation. NRTP projects to the →cerebellum and receives substantial feedback from the →deep cerebellar nuclei as well as inputs from cerebro-cortical and higher-level →sub-cortical structures; see →tegmentum and Chap 16

Nucleus ruber – *rubral or* red nucleus: reddish-looking nucleus located in the →n, has a magnocellular and a parvocellular part. The nucleus receives inputs from the →cerebral cortex and, more importantly, from the →nucleus interpositus. It sends outputs to the →spinal cord, the pre-cerebellar →lateral reticular nucleus, →inferior olive, vestibular complex, facial nucleus, sensory →trigeminal nuclei, and cuneate nuclei; see Chaps 5, 19, 20, 23, 25, 27

Nucleus tractus solitarii (NTS) – see →nucleus of the solitary tract and Chaps 2, 4

Nucleus ventralis postero-inferior (VPI) of →thalamus – see Chap 7

Nutrient – see Chaps 2, 3, 18

Nystagmus – rhythmic movement of the eyes, usually consisting of a rapid or saccadic movement in one direction and a slower, smooth movement in the opposite direction; see Chaps 9, 15, 16

Object-centered (→frame of reference) – frame of reference centered at an object; see Chap 24

Object constancy – see Chap 1

Obscurin – protein in →skeletal muscle; see Chap 17

Obstacle avoidance – see Chap 23

Occipital cortex (lobe) – posterior part of the →cerebral cortex; see Chaps 7, 14

Occipital gyrus (in →cerebral cortex) – see Chap 14

Occlusion (of visual objects) – see Chap 14

Octopus cells of the posterior →ventral cochlear nucleus (PVCN) receive small auditory nerve terminals and project to the ventral nucleus of the →lateral lemniscus; see Chaps 11, 12

Ocular dominance – dominance of visual inputs from one eye in influencing the response of a given →neuron in the visual pathway or the →perception of a scene; see Chap 14

Ocular-dominance column – see →ocular dominance and Chap 14

Ocular drift – see Chap 15

Ocular following response (OFR) – →reflexive smooth tracking eye movement in response to sudden, rapid, large-field stimulus motion; see Chaps 15, 16

Ocular tremor – see →tremor and Chap 15

Oculogravic illusion – →illusion caused by linear →acceleration/deceleration resulting in apparent movement of the →visual field; see →illusion and Chap 10

Oculogyral illusion – apparent motion of an object that is fixed in relation to an observer whose semicircular canals have been stimulated by rotational motion; see →illusion and Chap 10

Oculomotor – motor control of eye movements; see Chaps 1, 10, 12, 13, 14, 15, 16, 23, 26

Oculomotor cerebellum – includes dorsal →vermis (lobules VI and VII) and the →nucleus fastigius as well as the ansiform lobe (crus I and II); is concerned with saccades, smooth pursuit eye movements and vergence eye movements; see →cerebellum and Chap 15

Oculomotor nerve – nervus oculomotorius; →cranial nerve III, see Chap 15

Oculomotor nucleus – nucleus oculomotorius; see Chap 16

Oculomotor vermis – lobules VIc and VII of the posterior cerebellar vermis involved in oculomotor control, especially of saccades and smooth pursuit eye movements; see Chap 16

Odor – see Chaps 1, 2, 3, 4, 23

Odorant – see Chaps 1, 3

Odorant receptor (OR) – see →receptor and Chap 3

Odorant receptor protein – see Chap 3

Odor field – see Chap 3

Odor object – see Chap 3

Oesophagus – see Chap 2

Olivo-cerebellar pathway – connection from the →inferior olive (IO) to cerebellar cortex and deep nuclei; see →cerebellum and Chap 8

Old-World monkey – see Chap 13

Olfaction, olfactory – →sense of smell; see Chaps 1, 2, 3, 11, 14, 23, 26

Olfactory binding protein (OBP) – see Chap 3

Olfactory bulb (OB) – see Chap 3

Olfactory cortex (in →cerebral cortex) – see Chaps 2, 3

Olfactory epithelium – see Chap 3

Olfactory imagery – ability to generate →percept-like olfactory experiences without olfactory stimulation by retrieval of information from →memory; see →mental imagery and Chap 3

Olfactory learning – see Chap 3

Olfactory nerve – see Chap 3

Olfactory perception – see →perception and Chap 3

Olfactory receptor protein – see →receptor and Chap 3

Olfactory receptor (sensory) neuron (ORN) – see →receptor cell and Chaps 3, 11

Olfactory tract – tractus olfactorius; see Chap 3

Olfactory tubercle (OT) – see →basal forebrain and Chaps 3, 23

Omnipause neuron (OPN) (in oculomotor control) – see Chap 16

One glomerulus-one receptor hypothesis (in olfaction) – see Chap 3

Ontogenesis, ontogenetic – refers to the biological development of an individual animal; see Chaps 1, 3, 7, 11, 12, 15, 18, 22, 27

Operant conditioning – also called *instrumental conditioning* or instrumental →learning: type of associative learning denoting the process by which a subject learns to associate behaviors with their consequences, desirable or →aversive; see Chap 27

Operculum (in →cerebral cortex) – part of the posterior portion of the inferior frontal gyrus of the →frontal cortex (lobe); see Chaps 2, 4, 7

Opioids comprise opiate →alkaloids and endogenous opioid peptides (β-→endorphins, →enkephalins, dynorphins) interacting with the three opioid →receptor sub-types (μ, δ, κ). Opioid receptors are expressed throughout the body, including the →peripheral nervous system and the →central nervous system (CNS). In the latter, opioid receptors are expressed in the →cerebral cortex, →striatum, →thalamus, →hypothalamus, →amygdala, rostral ventral →medulla oblongata, →peri-aqueductal gray (PAG), superficial laminae of the →spinal →dorsal horn, →dorsal-root ganglia (DRG); opioid receptors are also expressed in

peripheral →nociceptive →neurons; in addition to roles in nociception, opioids have effects on neurogenesis, →affect, mood, →emotions, →reward, →stress-related behaviors, →learning and →memory; see Chaps 4, 5, 7, 10, 20

Opsin – see Chap 13

Optic ataxia – inability to properly direct the eyes or an arm to a target and to adequately position and open hand and fingers for grasping. The deficit is most severe for objects in the peripheral field of vision. Nonetheless, it is a deficit in motor control and not in →perception. Lesions confined to the right →posterior parietal cortex (PPC) lead to mis-reaching with one or both hands in the contralateral →visual field (*field effect*), while left parietal lesions entail mis-reaching with the right hand in both ipsi- and contralateral visual fields (*hand effect*). This syndrome is commonly associated with damage to foci in the medial occipito-parietal junction (mOPJ), superior occipital gyrus, →intraparietal sulcus (IPS), →superior parietal lobule (SPL) (particularly in the left hemisphere), or →inferior parietal lobule (IPL) (particularly in the right hemisphere), and at times with lesions of the →frontal cortex (lobe) and →corpus callosum; see Chaps 25, 26

Optic blur – see Chap 16

Optic chiasm – union of the →optic nerves (*nervi optici*) to give rise to the →optic tracts (*tractus optici*); see Chap 13

Optic flow – see Chaps 10, 12, 14, 15, 16, 20, 23, 25

Optic nerve – nerve emerging from an eyeball and comprising the →axons of the retinal ganglion cells; see Chap 13

Optic tract – tractus opticus; emerges from the →optic chiasm and projects to the lateral geniculate nucleus (LGN); see Chap 13

Optimal Feedback Control – see Chap 25

Optimization – mechanism or algorithm to achieve a particular goal by minimizing, maximizing or optimizing a specific cost function; see Chaps 1, 3, 4, 18, 25, 26, 27

Optokinetic – see Chaps 10, 15, 20

Optokinetic after-nystagmus (OKAN) – see Chap 15

Optokinetic nystagmus (OKN) – involuntary tracking eye movement elicited by large-field visual stimulus motion. Smooth tracking in the direction of stimulus motion (slow phase) alternates with fast backward saccades (quick phases) to reset the eyes; see Chap 15

Optokinetic reflex or response (OKR) – see →reflex and Chaps 14, 15, 16

Orai1 Ca^{2+} permeable channel – see Chap 17

Orbito-frontal cortex (OFC) (in →cerebral cortex) – part of the →prefrontal cortex (PFC) facing the ocular orbits. The OFC is differentiated by inputs and functions. It receives afferents from gustatory, somatosensory, auditory, visual and visceral sources. It is assumed to serve several and complex functions, including →multi-sensory integration, →hedonic evaluation of current sensory stimuli, →reward evaluation, the generation of outcome expectations (predictions) based on the comparison between previous action experiences and predicted outcomes (which requires →learning and →memory), decisions between behavioral choices (→decision making), and goal-directed learning and behavior; see Chaps 2, 3, 5, 7, 12, 13, 14

Orexin/hypocretin – Orexins (OxA and OxB) or hypocretins are two excitatory →neuropeptides binding to two →receptors (Ox1 and Ox2). They are produced by cell groups in the lateral hypothalamus/perifornical area and are distributed by ascending and descending fibers throughout the →neuraxis including the →motor cortex, →basal ganglia, →cerebellum, →brainstem and →spinal cord. They modulate central motor structures involved in locomotion so that their loss may cause motor deficits, but their precise functions are mostly unknown. Orexins also influence →cognition, →arousal, →reward seeking, feeding, →endocrine and visceral functions, regulation of →sleep/wakefulness, →energy →homeostasis, sensory modulation, →stress and pain processing, →learning and →memory; see Chaps 5, 10, 23

Organ of Corti – see Chap 11

Orientation constancy – see Chap 14

Orientation selectivity (specificity) – see Chaps 7, 13, 14

Orienting behavior, movement, reflex – Orienting behavior aims at optimally perceiving significant environmental events and at efficiently organizing a suitable motor response comprising coordinated movements of body parts, such as eyes, head and trunk. If these events are particularly intense or previously unexperienced, orienting is `→reflexive´. It starts with generalized→arousal. Orienting is also easily induced by events signalling a potential danger or a positive →reinforcement; see Chaps 3, 4, 12, 16, 23

Orthodromic action potential propagation – propagation of →action potentials in the direction that is naturally taken in vivo; see Chap 5

Osmolarity – see Chaps 1, 4

Osmoreceptor – see →receptor cell and Chap 4

Ossicle – `little bone´; see Chap 11

Oto-acoustic emission – see Chap 11

Otocone – see Chap 10

Otolith (organ) – see Chaps 1, 9, 10, 15, 20

Ototoxic drug – see Chap 12

Outer ear – see Chaps 11, 12

Outer hair cell (OHC) (in inner ear) – see Chaps 11, 12

Outer plexiform layer (in retina) – see Chap 13

Oval window – see Chap 11

Ovarian cycle – see Chap 3

Ovulation – see Chap 3

Owl – see Chap 12

Oxidative enzyme – see Chap 18

Oxidative stress – see Chap 5

Oxygen (O_2) – see Chaps 3, 4, 5, 12, 17, 18

Oxytocin is a nona-peptide →hormone primarily synthetized within the paraventricular and supra-optic nuclei of the →hypothalamus and secreted into the bloodstream by the neurophypophysis and involved in labor during birth, lactation, and sexual and maternal behavior; in the →central nervous system (CNS), oxytocin also acts as →neurotransmitter or →neuromodulator in the →hippocampus, →nucleus accumbens, →amygdala and hypothalamus. Oxytocin enhances neural plasticity at synaptic and cellular levels in various brain regions. Oxytocin receptors (Oxtrs) are expressed differentially, being high in the visual pathways of →primates, in the auditory system of birds, and in the main olfactory bulb (MOB) in mice;.see Chaps 5, 7

Pacemaker neuron – →neuron firing spontaneous regular series of →actions potentials; see →burst firing (bursting) and Chap 22

Pacini(an) corpuscle – see Chaps 1, 6, 7, 8, 22

Paciniform ending – see Chaps 4, 8

Pain – see Chaps 1, 4, 5, 7, 8, 9, 10, 11, 13,18, 20

Pain matrix – see Chap 4

Pain memory – see Chaps 4, 5

Pain modulation – see Chaps 4, 5

Palate – see Chap 2

Paleo-cortex (in →cerebral cortex) – see Chap 3

Palisade ending – see Chap 15

Pallidum – short for →globus pallidus; see →basal ganglia and Chap 23

Pallidotomy – destruction of the →globus pallidus; see Chap 27

Parabrachial nucleus (PBN) – In rodents, the PBN is located in the →brainstem and composed of ten sub-nuclei distributed over three main regions: the ventral region (also known as the Kölliker-Fuse nucleus), the medial region and the dorso-lateral region. It is a sensory relay receiving many →enteroceptive and →exteroceptive inputs relevant to taste, ingestive behavior, pain, respiration, blood pressure, water balance, and thermo-regulation; see Chaps 2, 4, 13

Paracrine signal – signal produced by a cell to influence nearby cells; see Chap 4

Paraflocculus – see Chaps 15, 16

Paragigantocellular nucleus – see Chap 23

Parallel fiber (in cerebellar cortex) – see →cerebellum and Chaps 10, 15, 27

Paralysis – severe loss of motor strength, which can result from damage to inputs to, or output from, →motoneurons. Motoneuron paralysis may involve individual muscles and show muscle atrophy and →hypotonia, fasciculations (visible, rapid flickerings caused by synchronous repetitive twitch contractions of all skeletal →muscle fibers in a →motor unit) and →fibrillations, and lack of →tendon reflexes. Lesions of descending tracts impinging on motoneurons usually entail paralysis of diffusely distributed muscles, fasciculations, little muscle atrophy, →spasticity, and →Babinski sign (reflex); see Chaps 9, 18, 22, 23

Paramecium – see Chap 1

Paramedian pontine reticular formation (PPRF) – see →reticular formation and Chap 16

Paraplegia – bilateral loss of motor strength of the lower body, most often resulting from damage to the →spinal cord, →spinal roots or peripheral nerves; see Chap 17

Parasol ganglion cell (in retina) – see Chap 13

Parasolitary nucleus (Psol) – see Chap 10

Paraspinal muscles – see Chap 20

Parasubiculum – see Chap 23

Parasympathetic (nervous system) – part of the →autonomic nervous system, originating in specific →cranial nerve nuclei and sacral →spinal cord segments. The parasympathetic system innervates organs such as the sphincter pupillae and ciliary body in the eye, secretory glands producing fluid, and it enhances the motility of stomach and distal colon, bladder, etc.; see Chaps 13, 16

Paravermis, paravermal – regions of the →cerebellum lateral to the →vermis; see Chap 23

Paresis – weakness of a muscle or muscles resulting from disease of the muscle(s), →motoneurons, or the efferent motor nerve fibers; see Chaps 23, 26

Paresthesia – abnormal sensory experiences, e.g., numbness, pins-and-needles sensations and tingling, occurring spontaneously or with some sensory →peripheral neuropathies; see Chap 4

Parietal cortex (lobe) – part of the →cerebral cortex, extending from the central sulcus to the parieto-occipital sulcus (POS); see Chaps 7, 9, 10, 12, 14, 16, 23, 24, 25, 26, 27

Parietal eye field (PEF) (in →cerebral cortex) – corresponds to →area LIP; see →eye fields and Chap 16

Parietal opercular cortex (in →cerebral cortex) – see Chap 7

Parietal reach region (PRR) (in →cerebral cortex) – includes area MIP, area PEa (area PEip) and →area V6A; has many →neurons with bi- of trimodal responses to auditory, visual and/or somatosensory stimuli; see Chaps 16, 24, 25

Parietal ventral area (PV) (in →cerebral cortex) – see Chap 7

Parieto-insular vestibular cortex (PIVC) (in →cerebral cortex) – see Chap 10

Parkinson´s disease (PD) –→hypokinetic disorder characterized by muscle →rigidity; →akinesia or →hypokinesia; →bradykinesia and a variety of autonomic, →cognitive, sensory (→nociceptive, thermo-sensory, tactile, proprioceptive), and mood disturbances. The causes of PD are ill defined. It is generally assumed that the basic initial defect in idiopathic Parkinson´s disease is the degeneration of →n →dopaminergic cells, in particular in the →substantia nigra pars compacta (SNc); recently, genetic factors have been implicated in the pathogenesis; see Chaps 4, 9, 17, 20, 23, 26

Parvalbumin – see Chaps 5, 17, 18

Parvocellular (P) cell (in lateral geniculate nucleus, LGN) – see Chap 13

Patella reflex – →tendon reflex elicited by a brief tap on the patella tendon; see →reflex and Chap 20

Path integration – also called *dead reckoning*; Path integration is a self-motion-based estimation of current position and heading, computed from the effects of the subject's own movements since the last-known position and heading; see Chaps 10, 23

Pavlovian conditioning – see →classical conditioning and Chap 27

pCO_2 – see Chap 1

Pectoralis muscle – see Chap 17

Pedunculo-pontine nucleus (PPN) – functionally and neurochemically heterogeneous nucleus with →cholinergic, GABAergic and →glutamatergic →neuron groups; receives inputs from the →cerebral cortex and →basal ganglia, sends outputs to the basal ganglia, →cerebellum, →brainstem and →spinal cord; is involved in →arousal, →cognitive processes (→attention, →motivation, →learning and →memory), →sleep control, regulation of motor control (locomotion, posture and gaze) and →muscle tone; see Chap 23

Penis – see Chap 6

Peptide, peptidergic – see Chaps 2, 4, 5, 10, 16, 17, 18

Percept, perception – conscious sensory experience that is also determined by →cognitive processes (e.g., →attention, →memory); in most chapters

Perceptual completion – see →Gestalt principles and Chap 7

Perceptual constancy (or invariance) – tendency of →perceiving sensory stimuli as about the same despite changing contexts. For example, in con-specific call →recognition, it is necessary to recognize a call type and its meaning despite large variations in →pitch, amplitude and other parameters that vary with the emitter´s identity and mood, and with →noise background. And in vision, objects and scenes can be perceived as invariant in size, shape, lightness, color, etc., despite variations arising from varying viewing distance, viewing angle or illumination, etc.; see Chaps 3, 12

Perceptual invariance – see →perceptual constancy (or invariance) and Chap 12

Perceptual learning – experience-dependent improvement of →perceptual performance, such as the detection, discrimination or categorization of sensory stimuli; involves changes in the response properties of individual and populations of →neurons; see Chaps 12, 27

Performance monitoring – see Chap 16

Peri-aqueductal gray (PAG) – →midbrain mass of →gray matter surrounding the aqueduct of Sylvius. The PAG is composed of longitudinal cell columns with somewhat specialized functions. It is an important node in →arousal and defence systems for survival, and is involved in organizing active or passive coping strategies in response to escapable or inescapable threats or →stressors, respectively. Depending on the strength of the threat, organized reactions include →fight or flight, →freezing, playing dead, with associated motor and autonomic (cardio-vascular and respiratory) responses as well as →opioid or non-opioid-mediated analgesia. The PAG also has roles in reproductive and maternal behaviors. It receives ascending sensory inputs from →nociceptive and thermo-sensitive fibers of the spino-thalamic tract, descending inputs from the →prefrontal cortex, →amygdala and →hypothalamus, and sends descending outputs to the →pons, →cerebellum, →medulla oblongata and →spinal cord; see Chaps 4, 5, 7

Periglomerular cell (in olfactory bulb) – see Chap 3

Perilymph – fluid inside the bony labyrinth surrounding the membranous labyrinth; it is similar to cerebro-spinal fluid (CSF) with a high sodium (Na^+) concentration and low potassium (K^+) concentration; see Chaps 10, 11

Peri-personal space – see Chaps 1, 12, 14, 25, 26

Peripheral nervous system (PNS) – nervous structures (mostly nerves) outside the →central nervous system (CNS), not including the enteric nervous system (in the guts); see Chap 4

Peripheral neuropathies – acute or chronic diseases of peripheral nerves, frequently affecting both motor and sensory fibers. Affliction of motor fibers entails muscle weakness and reduction or loss of →tendon reflexes. Affliction of sensory fibers may produce varying symptoms including →paresthesias, impairment of cutaneous pain and temperature sensations with risk of injuries, and varied impairment of cutaneous mechanical sensation and proprioception. Most strongly involved are often peripheral body parts, leading to the so-called glove-and-stocking pattern. There is a specific form of →large-fiber sensory neuropathy; see Chaps 5, 20, 26

Peripheral sensitization – see Chaps 4, 5

Perirhinal cortex (in →cerebral cortex) – lies, in →primates, on the ventral surface of the temporal lobe and contributes to →perception, →recognition →memory, identification of objects (by associating different features) and associating different objects and abstractions; see Chap 14

Peroneus brevis muscle – see Chaps 17, 19

Peroneus longus muscle – see Chaps 17, 19

Peroneus muscles – see Chap 19

Persistent inward currents (PICs) – PICs, for example in →skeleto-motoneurons, are mainly carried by voltage-dependent slow-activating L-type Ca^{2+} and fast-activating Na^+ currents in →dendrites and are strongly modulated by descending diffuse →noradrenergic and →serotonergic inputs. PICs can amplify →synaptic inputs; see Chap 22

Persistent Na^+ current (I_{naP}) – one of the →persistent inward currents (PICs); →tetrodotoxin (TTX)-sensitive, voltage-gated Na^+ currents, which flow at membrane potentials (→resting membrane potential) between –65 and –40 mV; they thus significantly influence the rate and pattern of →neuronal discharge; see repetitive discharge (firing) and Chap 22

pH – see Chaps 1, 2, 4

Phantom limb – see Chap 9

Phantom pain – see Chap 5

Pharynx, pharyngeal – see Chap 2

Phase disparity – see Chap 14

Pheromone – see Chap 3

Phocomelic – see Chap 9

Phon – see Chap 11

Phosphor (P_i), phosporylation – see Chaps 17, 18

Photon – see Chaps 13, 15

Photopic – daylight conditions or vision; see Chap 13

Photopigment – see Chap 13

Photoreceptor – →receptor cell and specialized for light; see Chaps 1, 11, 13, 15, 16

Phylogeny, phylogenetic – evolutionary development or history of living organisms; see Chaps 1, 10, 14, 23

Physical exercise – see Chaps 4, 8, 18, 27

Physiological pain – see Chap 4

Picrotoxin – pharmacological →antagonist of →γ-amino-butyric acid (GABA) at the →$GABA_A$ receptor; see →synapses and Chap 3

Piezo2 (channels) – mechano-sensitive ion channels, →depolarizing non-selective cation channels, highly expressed in low-threshold →mechano-receptors (large-diameter →dorsal-root ganglion neurons) that innervate the skin, in Merkel cells (tactile epithelial cells) and in muscle spindles. Piezo2 is responsible for light touch sensation and involved in mechanical allodynia. Piezo2 channels are also found in vagal sensory neurons innervating the airway. Together with Piezo1 channels, Piezo2 channels act in the baroreceptors of the aorta and carotid sinus. Activation of mechano-sensitive →ion channels by force is direct, causing a change in membrane potential and eliciting biochemical responses; see →mechano-electrical transduction (MET) and Chaps 4, 6, 8

Pig – see Chap 3

Piloting – also called landmark navigation; see Chap 23

Pinna – see Chaps 11, 16

Pineal body (gland) – also called *epiphysis*, of pine cone shape, →endocrine gland located in the →diencephalon, and synthesizing and releasing the →hormone →melatonin, which is involved in the regulation of various processes (e.g., →circadian rhythms, →sleep and reproduction); see Chap 13

Pinkus-Iggo receptor – see →receptor cell and Chap 6

Pinocchio illusion – see →illusion and Chaps 7, 9

Piriform cortex (in →cerebral cortex) – three-layered paleo-cortex (old cortex); see Chap 3

Pitch – Pitch →perception is important for speech and music perception and for →auditory object →recognition in a complex acoustic environment. Pitch is the percept that allows →sounds to be ordered on a musical scale from low to high defined by its fundamental frequency, and is closely associated with the perception of harmonically structured or periodic sounds. An important phenomenon is the percept of the *missing fundamental:* When the harmonics of a fundamental frequency are presented together, the pitch is still perceived as matching the fundamental frequency even if the fundamental frequency component is missing; see Chaps 7, 11, 12

spatial contexts ('remapping'); see Chaps 10, 23

Place code – see Chap 16

Place field – see Chap 23

Place principle – see Chap 11

Place areas (in →cerebral cortex) **–** see Chap 14

Placebo – treatment by means of drugs, devices or other means with no intrinsic physiological or pharmacological effect used to reduce pain sensation; see Chap 5

Place cell – →hippocampal pyramidal →neuron that discharges in one or more restricted regions of space. An individual place cell fires differently, often unpredictably, in different spatial contexts ('remapping'); see Chaps 10, 23

Planar co-variation – see Chap 21

Planning (of movements) – see Chaps 1, 7, 12, 16, 20, 23, 24, 25, 26

Plant – In engineering parlance, the plant denotes the sub-system to be controlled by a controller. Examples are industrial robotic manipulators, airplanes, hands, legs, torso, eyes. Very generally, the skeleto-muscular system can be defined as the plant to be controlled by the nervous system; see Chaps 15, 16

Plantaris muscle – see Chaps 17, 22

Planum temporale (in→cerebral cortex) – large region covering the superior temporal plane posterior to Heschl´s gyrus; see Chap 12

Plasticity – ability of the neuro-muscular and →central nervous system (CNS) to change its structure (circuits, networks, wiring), neural representations (e.g., →motor maps and →sensory maps), and functional organization (e.g., by changes in →synaptic transmission), according to previous experience, altered behavioral demands, or following changes in peripheral conditions or damage; throughout chapters

Plateau potential – sustained membrane potential →depolarization relative to the →resting membrane potential, the depolarization usually being caused and maintained by →persistent inward currents (PICs) [e.g. →persistent Na^+ current, low-voltage-activated Ca^{2+} currents (LVA I_{Ca}), etc.], whose onset and termination are usually triggered by excitatory and inhibitory →synaptic inputs. Except by synaptically mediated →hyperpolarization, the plateau potential can also be terminated by intrinsic mechanisms, such as persistent Ca^{2+} influx activating →Ca^{2+}-dependent K^+ channels and a consequent outward current [$I_{K(Ca)}$]; see Chaps 5, 22

Pleasant touch – also affective touch or sensual touch; see Chaps 1, 4, 7

pO_2 – see Chap 1

Pointing (movement) – see Chaps 1, 16, 24, 25, 26, 27

Polar coordinates – see Chap 1

Polymodal nociceptive neuron – see Chap 4

Polymodal receptor – →receptor cell (e.g., →nociceptor), which responds to more than one modality or sub-modality (quality), e.g., to pressure, temperature and/or some chemical substances. Polymodality is also a feature of central →neurons; see Chaps 1, 4

Pons, pontine – part of the →hindbrain and →brainstem between →mesencephalon and →medulla oblongata; see Chaps 2, 5, 7, 14, 15, 16, 23, 26

Pontine nuclei – see Chaps 7, 16, 23, 26

Pontine reticular formation (PRF) – see →reticular formation and Chap 23

Ponto-geniculo-occipital (PGO) spikes – see →rapid-eye-movement (REM) sleep

Ponto-medullary reticular formation (PMRF) – →reticular formation in the →pons and →medulla oblongata; see Chap 20

Population code – see →across-fiber (across-neuron) pattern code or ensemble code and Chaps 6, 9, 12

Position disparity – see Chap 14

Position invariance, tolerance – see Chap 14

Position sense – see Chaps 7, 8, 9

Position-vestibular-pause (PVP) cell (in oculomotor control) – see Chap 15

Positive force feedback – see Chap 22

Positron emission tomography (PET) – imaging technique suited to quantitatively evaluate biochemical and physiological processes in vivo, by using radio-pharmaceuticals labeled with short-lived positron-emitting radio-nuclides; see Chaps 7, 20, 27

Post-central gyrus (in→cerebral cortex) – gyrus post-centralis; gyrus of the →parietal cortex (lobe), lying just posterior and parallel to the central sulcus; see Chap 7

Posterior cingulate cortex (PCC) (in →cerebral cortex) – receives inputs conveying spatial and action-related information from →parietal cortical →areas and sends outputs to the →hippocampal complex, it may be involved in →memory; see →cingulate cortex (gyrus) and Chaps 2, 23

Posterior hypothalamic/subthalamic locomotor region (SLR) – see Chap 23

Posterior parietal cortex (PPC) (in →cerebral cortex) – The PPC is part of the →parietal cortex (lobe) and is situated between the →somatosensory cortical areas and the occipital visual areas; it is strategically favorably located to integrate auditory, visual and somatosensory spatial information and to transform this information into different →frames of reference in regard to eyes, body and the exterior world; see Chaps 1, 4, 7, 10, 12, 14, 16, 23, 24, 25, 26, 27

Posterior piriform cortex (in →cerebral cortex) – see Chap 3

Posterior ventral cochlear nucleus (PVCN) – see Chap 12

Posterior ventro-medial thalamic nucleus (VMpo) – see Chap 7

Postganglionic usually refers to peripheral →axons of →neuron somata located in autonomic →ganglia (→autonomic nervous system); see Chap 5

Post-rotatory sensation – see Chap 10

Post-rotatory vestibular nystagmus – see Chap 15

Postsynaptic dorsal-column neuron, projection – see Chaps 4, 7

Postsynaptic potential (PSP) – change in →resting membrane potential elicited in a postsynaptic cell by activation of a presynaptic input; see →synapse and Chaps 5,19

Post-tetanic potentiation (of muscle contraction) – see Chap 18

Postural adjustment – see Chaps 1, 19, 20, 24, 25, 26

Postural body schema – see Chaps 1, 19

Postural equilibrium – also →balance; see Chaps 1, 19, 20, 24

Postural instability – see Chap 20

Postural muscle – see Chaps 9, 20, 23

Postural orientation – see Chaps 1, 19

Postural reaction – see Chaps 10, 20

Postural schema – see Chaps 1, 7

Postural strategy – see Chap 20

Postural tremors may arise when a body part is kept in a constant position; see →tremor and Chap 26

Postural sway – see Chaps 7, 12, 19, 20

Posture – often used interchangeably with →balance; in most chapters

Potassium (K^+) – see Chaps 4, 8, 9, 10, 17, 19, 22

Potassium-chloride exporter KCC2 – see Chap 5

Potassium (K^+) channel – see Chaps 2, 5, 6, 17

Potential energy – →energy due to position or configuration; see Chaps 17, 21

Potentiation – the response of a system to a combination of two or more inputs is larger than the sum of the responses to each input alone; potentiation may manifest in various systems and forms, e.g., in →skeletal muscle, and at →synapses as →long-term potentiation (LTP); see Chap 18

Power – scalar quantity (with magnitude but without direction) expressing the amount of →energy produced per unit time or the time rate of doing →work; it is often given in units of watt (1 joule of work per second); see Chaps 3, 11, 17, 18, 22, 23, 27

Power grip – usually involves extended contact between the grasped object and a larger part of the hand such as the palm and/or multiple palmar finger surfaces; see Chaps 3, 26

Pre-central – rostral to the central sulcus; see Chap 23

Pre-central gyrus (PCG) (in →cerebral cortex) – *gyrus praecentralis*; gyrus of the →frontal cortex (lobe) in the →cerebral cortex, lying just in front of and parallel to the central sulcus, see Chap 12

Pre-central sulcus (PCS) (in→cerebral cortex) – see Chap 12

Pre-cerebellar long-lead burst neuron (PCLLBN) (in oculomotor control) – see →cerebellum and Chap 16

Precision grip – grip formed when grasping an object with the distal tips of digits. Usually refers to grasping with the tips of the thumb and index finger on either side of an object; see Chaps 3, 6, 7, 26, 27

Precuneus (PCu) (in→cerebral cortex) – part of the medial →parietal cortex (lobe) of nearly square shape in humans; in macaques, it contains area PEc and →area 7m; see →eye fields and Chaps 4, 16, 25

Predator - see Chaps 1, 3, 11, 12, 14, 23

Prediction error – Signal arising from the mismatch between the expected sensory consequences of a stimulus or movement and the actual sensory input; see →reinforcement learning and Chaps 1, 10, 12, 27

Predictive internal models – forward →internal models that can be used for: estimation of future states of the motor system and consequences of motor actions; generation of sensory error signals (difference between predicted sensory feedback and actual feedback) that can

guide adaptation and →learning of internal models; anticipation and cancellation of sensory consequences of self-generated movements (this is the basis of the re-afference principle); estimation of the properties of external objects to be dealt with; mental practice of movements to be →learned; see →internal model and Chaps 1, 20

Preferred direction (of a →neuron) – modulation of the neuronal response as function of the direction of motion of a stimulus or background, or of a movement; see Chaps 9, 13, 15, 16, 27

Prefrontal cortex (PFC) (in →cerebral cortex) – that part of the →frontal cortex (lobe) anterior to the →premotor cortex. The prefrontal cortex is grossly divided into the →dorso-lateral prefrontal cortex (DLPFC), ventro-lateral prefrontal cortex (VLPFC), medial prefrontal cortex (on the medial surface of the hemisphere), and the →orbito-frontal cortex (facing the eye orbits). It has been assigned several functions, differentiated according to area. Generally, functions include →cognitive (executive) control over the organization of thought, →memory and action in accordance with internal goals maintenance of task sets and the encoding, representation and storage of knowledge about the consequences of behaviors in complex situations). PFC functions are modulated by inputs from ascending, interacting →cholinergic, →dopaminergic, →noradrenergic and →serotonergic systems; see Chaps 2, 4, 5, 7, 12, 14, 20, 23, 24, 26, 27

Prefrontal eye field (PFEF) (in→cerebral cortex) – see →eye fields and Chap 16

Preganglionic neurons innervate autonomic →ganglia (→autonomic nervous system) and arise in the →spinal cord and the →brainstem where they are arranged in columns and nuclei; see Chaps 4, 13, 16

Prehension – taking hold, e.g., grasping with the hand; see Chaps 25, 26

Prelude neuron (in oculomotor control) – see Chap 16

Pre-mammillary (or sub-thalamic) cat – see Chap 23

Premotor cortex (in→cerebral cortex) in monkeys corresponds to →Brodmann´s area 6 in humans, is located rostral to the →primary motor cortex (area F1, area M1) and contains →secondary motor areas of the →cerebral cortex. Premotor cortex is composed of three main sections: the dorso-lateral (PMd), ventro-lateral (PMv) areas on the lateral surface of the hemisphere, and areas on the medial surface of the hemisphere; see Chaps 7, 12, 14, 24, 25, 26, 27

Premotor ear-eye field (PEEF) (in→cerebral cortex) – see →eye fields and Chap 16

Pre-optic area – area in the →basal forebrain, rostral to the →hypothalamus and lateral to the third ventricle (widening of brain tissue amid the →diencephalon filled with cerebro-spinal fluid (CSF)), plays a role in thermo-regulation, thirst, gonadotropin secretion, male sexual behavior, offspring care and locomotion; see Chap 23

Presbyacusis – see Chap 11

Presso-receptor – see →receptor cell and Chap 1

Pre-supplementary motor area (pre-SMA) (in→cerebral cortex) – →area F6 (antero-mesial part of →Brodmann´s area 6); densely connected with →prefrontal cortex (PFC) (including area 46, frontal eye field (FEF) and →orbito-frontal cortex), rostral →cingulate area 24c, dorsal and ventral →premotor hand/arm fields, and medial →parietal cortical areas; has no direct connections to the →primary motor cortex (area M1, area F1), projects to motor nuclei of the →brainstem; supposed to be involved in higher-order aspects of motor control, such as updating of motor plans, selection of effector-independent actions, organization and →learning of complex motor sequences, control of interval timing, and performance monitoring; contains →neurons with discharge related to reaching and grasping movements; see Chaps 12, 24, 26, 27

Presynaptic inhibition - decreases the efficacy of →synaptic transmission by acting on the presynaptic terminal without altering postsynaptic membrane →conductances directly; see Chaps 1, 3, 4, 5, 7, 19, 22, 25, 26, 27

Pretectum – part of the →midbrain (→mesencephalon) ventral to the tectum mesencephali; see Chaps 13, 16

Prey - see Chaps 1, 3, 11, 12, 14, 17

Primary afferent depolarization (PAD) – prolonged reduction of membrane potential (→resting membrane potential) in afferent nerve fiber terminals, usually produced by →presynaptic inhibition; see Chaps 5, 22

Primary auditory cortex (A1) (in →cerebral cortex) – see →area A1 and Chaps 12, 14

Primary hyperalgesia – increased pain →perception in area of injury or exposure to →noxious stimulus; see →hyperalgesia and Chap 5

Primary motor cortex (in→cerebral cortex) – area M1, area F1 (in monkeys), →Brodmann´s area 4 (in humans) has a high density of giant pyramidal (Betz) cells. Area M1 is strongly and reciprocally connected with area 3a and area 3b in the →primary somatosensory cortex (S1, SI). All three are organized →topographically and maintain corresponding connections. →Neurons in layers II and III connect area F1 with other →cortical areas, e.g., in →premotor cortex, →cingulate cortex and somatosensory cortex, while neurons in layer V project to extra-cortical regions, such as the →basal ganglia, →cerebellum (via pontine nuclei), ponto-medullary →reticular formation, →nucleus ruber, and/or the →spinal cord; see Chaps 7, 8, 12, 16, 20, 23, 24, 25, 26, 27

Primary olfactory cortex (in→cerebral cortex) – see Chaps 2, 3

Primary receptor system – see →receptor cell and Chap 1

Primary sensory ending (of muscle spindle) – see Chap 8

Primary somatosensory cortex (S1, SI) (in→cerebral cortex) – S1 comprises four cytoarchitectonic regions, →areas 3a, 3b, 1 and 2, located in the anterior portion of the →parietal cortex (lobe); see Chaps 2, 4, 5, 6, 7, 9, 23, 24, 25, 27

Primary visual cortex (in→cerebral cortex) = →Brodmann´s area 17 = →striate cortex (area striata) = area V1; see Chaps 3, 10, 13, 14, 16, 19, 26

Primate – Primates are a group of about 200 mammals characterized by forward-looking eyes, laminated lateral geniculate nucleus (LGN), expanded visually related brain areas, grasping hindfeet with abductable toes, thumb opposability, grasping hand, enlarged →frontal cortex (lobe); in most chapters

Principal sensory trigeminal nucleus – see Chap 7

Principal sulcus (PS) – see Chap 25

Prism adaptation – see Chap 27

Projection neurons have relatively long →axons which leave a circumscribed local neuronal circuit (e.g., nucleus), in distinction to →interneurons; see Chaps 4, 5, 7, 10, 13, 23

Proprioception, proprioceptive, proprioceptor – in most chapters

Proprioceptive map – see Chap 1

Propriogyral illusions – Vibrating postural muscles of subjects standing in the dark can elicit illusions of visual target motion and of continuous body tilt and rotation; see →illusion and Chap 9

Proprio-spinal connection, fiber, interneuron – see Chaps 19, 22, 26

Proprio-spinal C3-C4 neuron – see Chaps 23, 26

Prostaglandins – →hormone-like substances derived from →arachidonic acid; see Chaps 4, 5, 9

Prostaglandin E2 (PGE2) – see Chap 5

Proton (H^+) – see Chaps 2, 5, 17

Pruriceptor – →itch-detecting →receptor cell; see Chap 4

Pruritogen – substance eliciting →itch; see Chap 4

Psychogenic pain – see Chap 4

Psychophysics – field of experimental psychology that deals with the quantitative measure of sensory →perception. It describes the relationship between physical stimuli and the perceptions they evoke; see Chaps 14, 24, 27

Pulfrich effect – When one watches a pendulum swinging in a frontal plane with both eyes open and unimpeded, the pendulum is perceived as swinging in this plane. However, when one eye is covered by a dark transparent glass, the pendulum is perceived as swinging also in depth, i.e, in an ellipse with the short axis in anterior-posterior direction. This effect is interpreted as resulting from the slower processing of light falling into the darkened eye. Such difference in processing latencies may also occur in various diseases of the ocular system and central visual pathways; see Chap 14

Pulvinar – largest nucleus of the human →thalamus, posterior, medial and dorsal to the lateral geniculate nucleus (LGN); reciprocally connected with much of the →cerebral cortex as well as with →sub-cortical structures such as the →superior colliculus (SC). It integrates visual and motor information, this integration possibly enabling a distinction between changes in the visual environment caused by external sources versus self-generated →visual motion (caused by eye movements or locomotion). The pulvinar is also concerned with →salience and involved in selective →attention; see Chaps 13, 14

Pupil – see Chaps 13, 15, 16

Pupillary light reflex – constriction of the pupils in response to increased light falling onto the retina; see →reflex and Chap 13

Purines – include →adenosine and →adenosine triphosphate (ATP); see Chap 5

Purinergic receptors (purinoceptors) – cell membrane →receptors in →neuronal and →glia cells. P2 purinoceptors are grouped into two families. P2X receptors (7 types: P2X1-P2X7) are ionotropic receptors and bind →adenosine triphosphate (ATP). P2Y receptors (8 types: P2Y1, 2, 4, 6, 11, 12, 13, 14) are →metabotropic receptors (metaboreceptors) (→G-protein-coupled receptors), and bind nucleotides which are released from neurons and non-excitable cells; see Chaps 2, 3, 4, 5

Purkinje cell (PC) – large GABAergic cell in the cerebellar cortex, possessing 2-3 complex, sheath-like →dendrites and an →axon projecting to →deep cerebellar nuclei or →vestibular nuclei; see →cerebellum and Chaps 10, 15, 16, 23, 24, 25, 27

Pursuit eye movement – see Chaps 10, 14, 15, 16

Putamen – part of the →basal ganglia; putamen and →nucleus caudatus together form the →striatum (corpus striatum); see Chaps 4, 9, 12, 16, 23, 26, 27

Pyramidal cell, neuron – see Chaps 3, 23, 26

Pyramidal tract – large nerve-fiber bundle running through the pyramids in the →medulla oblongata. Most of these fibers originate in the →cerebral cortex and terminate in the →spinal cord and thus make up the →cortico-spinal tract (CST); see Chaps 20, 23

Pyramidal tract neuron (PTN) – cerebro-cortical →neuron sending a descending →axon through the →pyramid. These neurons send axons to the →spinal cord, but also collaterals to sub-cortical structures such as the →nucleus ruber and the pontine nuclei, the latter connections providing an →efference copy to the →cerebellum. see Chaps 20, 23, 24

Pyridoxine (vitamin B6) intoxication results from excessive intake of vitamin B6 and may lead to chronic sensory →polyneuropathy, characterized by numbness, tingling and pain in the extremities, as well as sensory →ataxia; see Chaps 20, 22

Pyruvate – see →glycolysis and Chap 17

Quadriceps femoris muscle – see Chaps 17, 19, 20, 22

Quadruped – see Chaps 1, 7, 19, 20, 21, 22, 23

Quadrupedal gait – see Chap 21

Quality (sub-modality) (of →senses) – see Chaps 1, 2, 3, 7, 11, 12, 16

Quinine – see Chaps 2, 3

Rabbit – see Chaps 3, 8, 13, 20, 22, 23

Raphé nuclei – The raphé nuclei are cell assemblies in the center and most medial portion of the →brainstem →reticular formation. Their widespread projections have vast impacts upon the →central nervous system (CNS). Many (though not most) of the →neurons in the nuclei are →serotonergic; see Chaps 3, 7, 10, 13, 22, 23

Raphé-spinal tract – see Chap 19

Rapid eye movement (REM) – see Chap 16

Rapidly adapting type-I (RAI) cutaneous afferent – also **f**ast **a**dapting type-**I** (FAI) cutaneous afferent; see Chaps 6, 7, 26

Rapidly adapting type-II (RAII) cutaneous afferent – also **f**ast **a**dapting type-**II** (FAII) cutaneous afferent; see Chaps 6, 7

Rat – see Chaps 2, 3, 4, 5, 20, 25, 27

Rate coding – coding by a →neuron of the →intensity (strength) of an input signal in terms of an output defined by the spike firing rate; see Chap 3

Reaching movement – see Chaps 1, 3, 7, 9, 10, 13, 14, 16, 20, 23, 24, 25, 26, 27

Reach-to-grasp movement – see Chaps 3, 14, 24, 25, 26

Reach-to-grasp postural strategy – rapid reaching/grasping for stable support in response to a postural perturbation; see Chap 20

Reaction time – time from stimulus onset to reaction onset; see Chaps 7, 14, 16, 24

Reactive nitrogen species (RNS) – see Chap 5, 17

Reactive oxygen species (ROS) – see Chaps 5, 17

Readiness potential (RP) – see →Bereitschaftspotential and Chap 24

Re-afference – see Chaps 1, 10, 23

Re-afference principle – see Chap 1

Rebound potentiation (RP) – see Chap 10

Recall – ability to →recognize a stimulus or event experienced in the past and to retrieve spatio-temporal details of the context; see Chaps 3, 14

Receptive field (RF) – area, quality and functional structure of the sensory environment that a given →neuron responds to; see Chaps 4, 5, 6, 7, 9, 12, 13, 14, 16, 20, 23, 24, 25, 26

Receptor (pharmacological) – see Chaps 2, 3, 4, 5, 6, 7, 9, 10, 11, 16, 17, 19, 22, 23, 26, 27

Receptor cell – see →sensory receptor and Chaps 1, 2, 3, 6, 7, 11

Receptor agonist – molecule that binds to a particular pharmacologically defined →receptor and mimics the effects of endogenous signaling compounds, such as →neurotransmitters, →neuromodulators and →hormones; see →agonist and Chaps 4, 22

Receptor current – In a specialized →sensory receptor cell, a physico-chemical stimulus evokes a trans-membrane current by opening or closing of specific →ion channels in the →receptor membrane, which entails and →receptor potential; see Chap 10

Receptor membrane – specialized region of a →sensory receptor cell, where a physico-chemical stimulus is converted, by a specific process called →sensory transduction, into →receptor current and →receptor potential; see Chaps 1, 2

Receptor potential – change in membrane potential that occurs in the peripheral end of a sensory afferent fiber due to →transduction of a stimulus into ion flux; see →receptor current and Chaps 3,4, 8, 11

Reciprocal inhibition – see Chaps 19, 20, 22

Reciprocal Ia inhibition – see Chaps 19, 22, 26

Reciprocal Ia inhibitory interneuron – see Chaps 19, 22, 25

Recognition – realization that a specific object or event has been experienced or encountered before; see Chaps 1, 2, 3, 4, 7, 11, 12, 13, 14, 16, 18, 19, 24

Recovery (from →muscle fatigue) – see Chap 17

Recovery (from nervous tissue damage) – see Chap 22

Recruitment (of →motor units) – see Chaps 18, 22

Recruitment coding – see Chap 3

Recruitment gradation (of muscle force) – see Chap 18

Rectus femoris muscle (of quadriceps femoris) – see Chap 21

Recurrent excitation – see Chap 22

Recurrent facilitation – see Chap 19

Recurrent facilitatory postsynaptic potentials (RFPSPs) – see Chap 19

Recurrent inhibition – basic type of postsynaptic inhibition exerted by →neuronal circuits present throughout the nervous system; see Chaps 3, 7, 19, 20, 22

Red-green opponency – see Chap 13

Red nucleus – also rubral nucleus, →nucleus ruber; see →nucleus ruber and Chaps 10, 23, 25

Redundancy – excess of →degrees of freedom (DOFs) within a system over the number of constraints imposed; see Chaps 1, 25

Reference frame – see →frame of reference and Chaps 1, 7, 10, 12, 14, 15, 16, 20, 23, 24, 25

Referred pain – see Chap 4

Reflex – appropriate behavioral and →motoneuron response closely coupled to a sensory input of some sort; throughout chapters

Reflexive saccade – see →reflex, saccade and and Chap 16

Reinforcement – central concept in →operant conditioning (also called *instrumental conditioning*); see →reinforcement learning – type of →learning, in which the learning process is driven by positive reinforcement (→reward) or negative reinforcement (punishment), such that the system tries to maximize the sum of total future rewards and minimize punishments; see Chaps 2, 4, 16

Reinforcement learning – type of →learning, in which the learning process is driven by the difference between the predicted value of future →reward and the ultimate reward attained (positive →reinforcement) or between the predicted punishment and ultimate punishment suffered (negative reinforcement), i.e., by the →reward prediction error, such that the system tries to maximize the sum of total future rewards and minimize punishments. This type of learning requires three pieces of information: signals representing the context in which an action takes place; a signal representing the action that is being taken (possibly provided by an →efference copy of the →motor command); and a signal representing the outcome of that action;.see Chap 4, 16, 27

Re-innervation – return of lost nerve fibers to a cell, tissue, organ; see Chaps 18, 22

Relative disparity (d_{rel}) – difference between two →absolute disparities of two points. Hence, with the absolute disparity of one point being $\alpha_1-\beta_1$ and that of the other point being $\alpha_2-\beta_2$, the relative disparity is $(\alpha_1-\beta_1) - (\alpha_2-\beta_2)$. It is independent of vergence angle and can be used to extract information about the relative depth of object points enabling 3D shape →recognition, reaching and grasping; see Chap 14

Renshaw cell – see Chaps 19, 22, 25, 27

Repolarization – change in membrane potential towards →resting membrane potential; see Chap 22

Reproductive behavior – see Chaps 3, 23

Resonance theory (in hearing) – see Chap 11

Respiration – see Chaps 2, 3, 10

Resting membrane potential – membrane potential in excitable cells in the absence of excitatory or inhibitory inputs; see Chaps 17, 18, 22, 27

Resting tremors – →tremors present at rest; they usually abate during voluntary movements. Resting tremor is a symptom of patients suffering from →Parkinson´s disease, but may be absent. It occurs mostly in the distal extremities (e.g., hand) at a frequency between 4 and 8 Hz. It may also occur in other diseases, such as severe essential tremor; see Chap 26

Reticular activating system (RAS) – see Chap 23

Reticular formation (RF) – diffusely organized area that forms the central core of the →brainstem and is composed of several nuclei or cell clusters sending separate descending fiber bundles into the →spinal cord (→reticulo-spinal tract). The RF contains different neural types including →monoaminergic, →cholinergic, GABAergic, →glycinergic and →glutamatergic →neurons, with glutamatergic reticulo-spinal neurons forming the key descending output. The RF maintains vegetative functions (e.g., cardio-vascular, micturition), coordinates motor functions (vomiting, →muscle tone, →reflexes, posture, escape, rhythmic motor patterns such as breathing, locomotion, reaching and grasping), and is involved in →thalamo-cortical and cerebro-cortical activation important for →attention, wakefulness, and →sleep; see Chaps 4, 10, 14, 16, 19, 23, 25, 26

Reticular nuclei – see Chap 23

Reticular thalamic nucleus – see reticular nuclei and Chap 12

Reticulo-spinal long-lead burst neuron (RSLLBN) (in oculomotor control) – see Chap 16

Reticulo-spinal tract (RST) – tract of nerve fibers originating in the ponto-medullary →reticular formation (PMRF) and targeting →neurons in the →spinal cord. The RST is part of the →cortico-bulbo-spinal system and receives inputs from cerebro-cortical motor and premotor regions, →cerebellar →nucleus fastiguus, →vestibular nuclei, the →mesencephalic locomotor region (MLR), and spino-reticular projections of cutaneous and muscle afferents**.** Many RST neurons innervate both cervical and lumbar segments with diffuse projection patterns. Some RST neurons have axons that cross the midline at the cervical or lumbar levels and innervate the →gray matter of both sides. In addition, RST axons also terminate on commissural interneurons. RST neurons have both excitatory and inhibitory effects on flexor and extensor forelimb and hindlimb motoneurons, predominantly via →interneurons in Rexed ´s laminae VII and VIII. The RST may be comprised of several parallel pathways with distinct functions such as mediating locomotion, →startle responses, postural stability and →autonomic functions; see Chaps 19, 20, 22, 23, 25, 26

Retina – see Chaps 1, 3, 13, 14, 15, 16, 19, 20, 25

Retino-centric (→frame of reference) – also oculo-centric or →eye-centered reference frame specifying the location of a visual target with respect to the position of the eyes in space, and moving with the eye; see Chaps 1, 12

Retinal ganglion cell (RGC) – see Chap 13

Retinal slip – motion of the visual image across the retina; see Chap 15

Retinitis pigmentosa – designates a group of hereditary or mutation-induced eye diseases leading to degeneration of the retina with deposits of pigment; see Chap 13

Retinotopic, retinotopy – orderly projection between the retina and a central visual area, in which near-neighborhood relationships are maintained; that is, nearby cells in the retina project to nearby cells in the central area, thus maintaining the relative →topographic organization of visual space in the central area; see Chaps 13, 14, 16, 25

Retro-splenial cortex (RSC) (in →cerebral cortex) – see Chaps 10, 14, 23

Reverse transduction – transformation of an electrical signal into a mechanical output; see Chap 11

Reward - the →hedonic →affect of pleasure (`liking´), the →motivation to obain the reward (`wanting´) and reward-related →learning. A presumed reward circuitry in the brain consists of several nodes and connections, including →dopamine neurons in the →ventral tegmental area (VTA), with two projection target: the ventral striatum and the →prefrontal cortex. Hypothetically, the →neocortex sends reward-related information to the →cerebellum which in turn, via several output pathways from the →deep cerebellar nuclei, may influence widespread reward circuitry, including the striatum and the →prefrontal cortex (via the →thalamus) as well as (via monosynaptic connections) the VTA dopamine neurons; see Chaps 1, 2, 3, 5, 10, 12, 14, 15, 16, 23, 24, 27

Reward prediction error – difference between actual and predicted →reward, supposed to be calculated by →brainstem →dopamine →neurons; see →prediction error, →reinforcement learning and Chaps 16, 27

Rheobase – magnitude of a rectangular →depolarizing current necessary to elicit an →action potential; see Chap 18

Rhesus monkey – see Chaps 12, 16

Rhinotopic map – see Chap 3

Rhizotomy – severance of →spinal roots; see Chap 9

Rhodopsin – see Chaps 3, 13

Rigidity –muscles are in maintained contraction and produce a constant elevated resistance to passive stretch. For example, in →Parkinson´s disease, there is a `lead-pipe´ (plastic) increase in →muscle tone and resistance to lengthening, in both flexor and extensor muscles, but most pronounced in muscles maintaining a flexed position. It is easily detectable in large muscles, but also present in smaller muscles of the face, tongue and larynx; see Chaps 19, 26

Robot, robotics – see Chaps 1,23

Rodent – see Chaps 2, 3, 5, 6, 7, 13, 22, 23, 24, 25, 26, 27

Rod photoreceptor – see →receptor cell and Chap 13

RORα interneuron – retinoic acid receptor-related orphan receptor α →interneuron; see Chaps 7, 23

RORβ orphan nuclear receptor – retinoic acid receptor-related orphan receptor ß; see Chaps 19, 22

Rostral core auditory area (R) – see Chaps 12

Rostral field – see Chap 12

Rostral temporal field (RT), (in auditory →cerebral cortex) – see Chap 12

Rostral interstitial nucleus of the medial longitudinal fascicle (riMLF) – The riMLF borders caudally with a second interstitial nucleus of the →medial longitudinal fascicle (MLF), the interstitial nucleus of Cajal (INC); see Chap 16

Rostral spino-cerebellar tract (RSCT) – tract of nerve fibers originating in the →spinal cord and targeting →neurons in the →cerebellum; see Chap 7

Rostral ventro-medial medulla (RVM) – comprised of →neurons in the nucleus raphé magnus (→raphé nuclei), nucleus reticularis gigantocellularis (pars alpha) and nucleus paragigantocellularis lateralis; the RVM appears to be the final relay in descending pain modulation, sending projections via the dorso-lateral funiculus to the trigeminal nucleus caudalis and the →spinal →dorsal horn; see Chaps 4, 5

Rotatory vestibulo-ocular reflex (RVOR) – see →reflex, vestibuilo-ocular reflex and Chap 15

Rubral nucleus – red nucleus; see →nucleus ruber and Chap 23

Rubro-spinal tract (RuST) – Tract of nerve fibers originating in the →nucleus ruber in a →somatotopically ordered manner, in that neurons projecting to the cervical, thoracic and lumbar →spinal cord are separated in the nucleus. The fibers project to Rexed´s laminae V-VII in the contralateral spinal cord, housing →interneurons that also receive primary afferents from →skeletal muscles and other sources. The RuST predominantly facilitates flexor and inhibiting extensor →motoneurons and is involved in fine and strong movements; see Chaps 19, 20, 22, 23

Ruffini corpuscle, ending – see Chaps 6, 22

Ruffini-like ending – see Chap 8

Running – see Chaps 8, 14, 17, 18, 19, 21, 22, 23

Ryanodine receptor (RyR1) – see Chap 17

Saccade, saccadic eye movement – see Chaps 12,14, 15, 16, 23, 24, 25, 26

Saccade adaptation – see Chaps 16, 27

Saccade-related burst neuron – see Chap 16

Saccade-vergence interaction – see Chap 16

Saccadic gain adaptation – see Chap 16

Saccadic suppression – see Chaps 15, 16

Sacculus, saccule (in inner ear) – one of two otolith organs that sense →gravity and linear →acceleration; see Chaps 10, 15

Saddle joint – see Chap 17

Safety stance – see Chap 19

Salamander – see Chap 13

Salience, saliency – distinctiveness, conspicuity or degree of popping out of a stimulus or stimulus attribute, which may elicit →arousal, →alertness or →attention; see Chaps 14, 15, 16

Saliency map – see Chap 16

Saliency network – see Chap 4

Salt – see Chap 2

Salty taste – see Chap 2

Sarcolemma – cell membrane of the →muscle fiber; see Chaps 17, 18

Sarcomere – see Chaps 17, 18

Sarcoplasm – intracellular milieu within a →muscle fiber; see Chaps 17, 18

Sarcoplasmic reticulum (SR) – see Chap 17

Satiety – see Chaps 2, 3

Scala media (in cochlea) – see Chap 11

Scala tympani (in cochlea) – see Chap 11

Scala vestibuli (in cochlea) – see Chap 11

Scarpa´s ganglion – see →ganglion and Chap 10

Scopolamine [L(-)-hyoscine] – →antagonist at →muscarinic receptors for →acetylcholine, dampening motor activity, promoting →sleep; used as drug against motion sickness (kinetosis); see Chap 10

Scotopic – night condition or vision; see Chap 13

Scratch, scratchng – see Chaps 1, 4, 23

Scratch reflex – see →reflex and Chap 1, 9

Secondary hyperalgesia – increased pain →perception in the region surrounding the area exposed to a →noxious stimulus;see →hyperalgesia and Chap 5

Secondary olfactory cortex (in →cerebral cortex) – see Chap 2

Secondary receptor system – see →receptor cell and Chaps 1, 2

Secondary sensory ending (in muscle spindle) – see Chap 8

Secondary somatosensory cortex (S2, SII) (in →cerebral cortex) – also called parietal →operculum, higher-order cerebro-cortical sensory area, located within the depths of the lateral sulcus; hypothetically involved in tactile object recognition and →memory, interpersonal touch, tactile expectancies about the contact with objects, movement execution (e.g., grasping), observation of actions; see Chaps 4, 7, 25, 26, 27

Secondary taste cortex (in →cerebral cortex) – see taste and Chap 2

Second (slow) pain – see Chap 4

Self-motion – see Chaps 7, 10, 11, 12, 14, 15, 23, 25

Self-motion perception – see Chaps 10, 12, 14

Semicircular canal – see Chaps 1, 10, 15, 16, 19, 20

Semitendinosus muscle – see Chap 22

Sensation – see Chaps 1, 2, 4, 5, 6, 7, 9, 10, 11, 12, 13, 15, 20, 23

Sense of effort – see Chaps 8, 9

Sense of muscle force – see Chaps 8, 9

Sense of object heaviness – see Chap 9

Senses – classification – Senses can be classified according to several criteria. One classification is according to the nature of the stimuli activating →sensory receptors: electromagnetic (light), mechanical (touch, →sounds etc.), chemical (concentration of substances), temperature (heat and cold), etc.; see Chaps

Sensitivity (of →sensory receptors or other →neurons) – defined by two variables: →threshold (in sensory systems) and steepness (gain) of the relationship between stimulus →intensity and receptor response magnitude. Corresponding definitions hold for central →neurons; in most chapters

Sensitization – increased responsiveness of →neurons to sensory stimuli. This may lead to behavioral changes, such as an increase in →arousal and an enhancement of →reflexes. Sensitization is typically strong to →noxious or fear-evoking stimuli and represents a type of non-associative →learning; see Chaps 1, 3, 4, 5, 9, 27

Sensory map – →topographically ordered representation of sensory signals in a central structure; sensory maps occur in several modalities (see, e.g., chemotopy, cochleotopy, →retinotopy, →somatotopy); see Chaps 7, 16

Sensory-motor cortex (in →cerebral cortex) – see Chaps 23, 27

Sensory-motor learning – improvement in an organism´s ability to interact with the environment by selective extraction and efficient processing of sensory signals to generate an appropriate motor response; see Chaps 1, 27

Sensory-motor transformation – see Chaps 1, 4, 14, 15, 16, 19, 23, 24, 25

Sensory neuropathies – diseases of peripheral sensory nerve fibers, either alone (*pure sensory neuropathies*) or in combination with motor nerve fibers (→peripheral neuropathies). The former may involve all types of sensory fibers (*pan-sensory*); thick sensory fibers (→large-fiber sensory neuropathies); small sensory fibers; see Chap 9

Sensory partitioning – see Chap 8

Sensory receptors - respond to physico-chemical sensory stimuli in the external or internal environment. Receptors initiate a →sensory transduction process by producing graded →receptor potentials, which elicit →action potentials that are conducted along afferent nerve fibers to →central nervous system (CNS) structures; see →receptor cell and Chaps 1, 2, 5, 7, 8, 9, 11, 19, 20, 22

Sensory-sensory transformation – see Chap 1

Sensory system – see Chaps 1, 3, 11, 12, 15, 16, 23

Sensory threshold – see →threshold (in sensory systems) and Chap 20

Sensory transduction – process by which, in a →sensory receptor cell, a physico-chemical sensory stimulus is converted into the opening or closing of →ion channels; see Chaps 1, 2, 4, 6, 8, 10, 11, 13

Sensual touch – also affective touch or pleasant touch; see Chap 1

Sequence learning – specific type of →motor-skill learning: →learning of a series of multiple discrete movement elements towards a goal, like learning to play a musical instrument or learning to play tennis. In sequence learning, cerebro-cortical motor areas, →prefrontal cortex (PFC) and →sub-cortical structures, particularly the →basal ganglia, are of major importance; see Chap 27

Serotonin – 5-hydroxytryptamine (5-HT). →Monoamine that is common in the →central nervous system (CNS) and →peripheral nervous system (PNS) and the →immune system, is synthesized from L-tryptophan and can be converted to →melatonin. Clusters of serotonergic →neurons (B1 to B9) are located in the →raphé nuclei and parapyramidal region of the →brainstem and project widely throughout the CNS. At least 14 →receptor subtypes for serotonin are known. Serotonin contributes to a vast array of functions such as embryogenesis, gastrointestinal motility, peripheral and central vascular tone, →endocrine and →circadian rhythms, regulation of →sleep rhythm and body temperature, →arousal, anxiety, mood, →emotions, →cognition, appetite, feeding, aggressiveness, social interactions, sexual and reproductive activity, impulsive/compulsive behavior, behavioral flexibility, motor functions, →learning and →memory, processing of expected and received →rewards, →nociception (→analgesia) and motor tone. Outside the CNS, serotonin is present in immune cells [e.g., lymphocytes and monocytes (→leukocytes), and →macrophages] and platelets; see Chaps 2, 3, 4, 5, 6, 9, 10, 19, 22, 27

Servo-assistance hypothesis – see Chap 22

Servo control – control of a variable by a →feedback system which minimizes the error between the desired and actual values of the controlled variable; see Chap 22

Sex, sexual – see Chaps 3, 4, 5, 11, 12, 14, 17

Shark – see Chap 1

Sheep – see Chaps 3, 15

Short-axon cell (SAC; in main olfactory bulb) – see Chap 3

Short-term memory – temporary storage and management of information necessary to conduct →learning and →cognitive tasks; see Chaps 3, 7, 14

Shoulder-centered (→frame of reference) – set of axes for defining the location of an object with a shoulder as reference point; see →egocentric, →frame of reference and Chaps 1, 24

Shox2 – see Chap 22

Sickness response – see Chap 4

Signal-to-noise ratio (SNR) – Measurements of physico-chemical variables (signals of interest) contain an added component of →noise, derived from the measuring device, the physical properties of the processes involved, or biological sources (e.g., the statistical nature of →neuronal activity). The SNR is defined as the ratio between the →power of the signal of interest and the noise accompanying it, and is usually expressed in logarithms of this ratio, a unit known as Bell, or in units of one-tenth of a Bell, the →decibel (dB); see Chaps 3, 11, 13

Signal transduction – processes by which organisms →transduce sensory messages (photons, odorants, pheromones) or inter-cellular messages (e.g., →hormones, →neurotransmitters) into intracellular modifications in order to modify the cellular response; see Chap 5

Silent synapse – →synapse between two →neurons, at which a presynaptic →action potential normally fails to elicit a detectable postsynaptic response, such a response being elicitable (unmasked) under certain conditions, however; see Chap 5

Simple cell (in primary visual cortex, area V1) – see Chap 14

Simple spike (SS) (of →Purkinje cells) – SS activity encodes the kinematics and errors of movements; osee Chaps 10, 15, 25

Single-opponent cells – see Chap 14

Size-contrast illusion – see →contrast, →illusion and Chap 26

Size principle (of →motor unit recruitment) – see Chap 18

Skeletal muscle – If healthy, skeletal muscle provides for mobility underlying posture, respiration, eating, reproduction, and for appropriate function of the senses including taste, vision, and hearing. Skeletal muscle also plays roles in temperature regulation and metabolism, e.g., by regulating whole-body protein and glucose metabolism. Muscle mass is highly →plastic, adapting during growth and disease and to physiological demands; see Chaps 1, 4, 5, 7, 8, 9, 10, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27

Skeleto-motoneuron – →motoneuron that innervates skeletal →muscle fibers, either without (→α-motoneurons) or with (→β-motoneurons) simultaneously innervating muscle fibers in muscle spindles (→intrafusal muscle fibers); see Chaps 1, 8, 17, 18, 19, 21, 22, 23, 26

Skeleton, skeletal – see Chaps 1, 17

Skill – adaptive behavior acquired through practice; see Chaps 1, 6, 14, 19, 23, 24, 25, 26, 27

Skilled locomotion – see Chap 23

Skin – see Chaps 1, 3, 4, 5, 6, 7, 8, 9, 14, 19, 20, 25, 26

Sleep – state of rest characterized by behavioral quiescence and decreased responsiveness to environmental stimuli. Mammals show two types of sleep: →rapid-eye-movement (REM) sleep and non-REM sleep; see Chaps 3, 5, 13, 22

Sleep-wake cycle – see →sleep and Chaps 20, 23

Sliding filament theory (in muscle contraction) – see Chap 17

Slowly activating K^+ current (I_A) – see Chap 22

Slowly adapting type-I (SAI) receptor or cutaneous afferent – see →receptor cell and Chaps 6, 7

Slowly adapting type-II (SAII) receptor or cutaneous afferent – see →receptor cell and Chap 6

Slow-wave sleep (SWS) – component of mammalian non-REM sleep accompanied by high-amplitude →electroencephalogram (EEG) activity in the 0.3–4 Hz frequency range (also known as delta waves; →neuronal oscillations); see →sleep and Chap 5

Small bistratified ganglion cell (in retina) – see Chap 13

Small stratified (blue-on) ganglion cell (in retina) – see Chap 13

Smell – see Chaps 1, 2, 3, 14

Smooth pursuit eye movement – slow eye movement tracking a moving visual stimulus; see Chaps 10, 15, 16

Smooth vergence eye movement – see Chap 16

Snake – see Chaps 1, 3

Sniff(ing) – see Chap 3

Social communication – see Chaps 6, 7, 12, 14

Sodium (Na^+) – see Chaps 2, 4, 8, 17, 22

Sodium (Na^+) channel – see Chap 17

Sodium/glucose cotransporter 1 (SGLT1) – see Chap 2

Soleus muscle – see Chaps 17, 18, 19, 20, 21, 22

Somatic pain – see Chap 4

Somatogravic illusion – vestibular illusion during high →accelerations/decelerations under reduced visual information; see →illusion and Chap 10

Somatosensory body schema – see Chap 9

Somatosensory cortex (in →cerebral cortex) – →primary somatosensory cortex (S1, SI) plus →secondary somatosensory cortex (S2, SII); see Chap.7

Somatosensory map – see Chaps 12, 16

Somatosensory neglect – see Chap 25

Somatosensory pathways originate in →enteroceptive [proprioceptive, visceral and autonomic (→autonomic nervous system)] and →exteroceptive (cutaneous) →receptors and their associated afferent pathways that transmit information about the body to the →spinal cord, →medulla oblongata and to brain structures including the →cerebellum, parabrachial nucleus (PBN), →thalamus and →cerebral cortex; see Chap 7

Somatosensory receptive field – see →receptive field and Chap 9

Somatostatin – peptide →hormone that inhibits the release of →growth hormone from the pituitary gland; it also affects cell proliferation and →synaptic transmission; it is also produced by primary afferents and →dorsal horn interneurons and has an pro-→nociceptive effect; see Chap 4

Somatotopy, somatotopic – differential CNS representation of functions of different body (soma) parts; somatotopic organization exists in motor and sensory systems; see Chaps 4, 5, 6, 7, 8, 12, 16**,** 17, 25, 26, 27

Sound – oscillation in pressure or particle displacement in a medium with →inertia; see Chaps 1, 2, 3, 7, 10, 11, 14, 16, 26

Sound localization – see Chaps 11, 12

Sound pressure – increment in static pressure in a medium, through which a sound wave propagates; see Chaps 11

Sound pressure level – →sound pressure relative to a basic pressure of 20 μPa (micropascal), expressed as logarithmic →decibel level; see Chap 12

Sour taste – see Chap 2

Spasticity – The signs and symptoms of human spasticity are: hypertonia; increase in short-latency →stretch reflexes with enhanced →tendon reflexes and →clonus; loss of →long-latency stretch reflexes; →paresis; movement disorders including gait disorders; synkinesia (co-contraction of normally independently controlled muscles); lack of dexterity; contractures; deterioration of muscle properties such as muscle atrophy and enhanced →muscle fatiguability; autonomic →hyperreflexia (→autonomic nervous system); see Chaps 19, 26, 27

Spastic locomotion – see Chap 23

Spatial attention – →attention directed towards spatial locations; see Chap 7

Spatial constancy – the brain has mechanisms to keep spatial representations of the world as constant as possible during eye, head and body movements in order to ensure stable spatial →perception, stable spatial awareness and accurate guidance of movements; see Chaps 1, 14, 16

Spatial frequency tuning (of cerebro-cortical visual →neurons) – see Chap 14

Spatial map – see Chaps 10, 12, 23

Spatial memory – see Chaps 10, 14, 16, 23

Spatial orientation – an organism´s →sense of body orientation and movement (self-motion) relative to the environment, about which inputs from the →somatosensory, vestibular and visual systems provide critical information; see Chaps 6, 10, 14, 19, 23

Spatial remapping or updating – updating of the spatial representation of an external object within an intrinsic →frame of reference to compensate for passively induced or self-generated motion; see Chap 16

Spatial stability – see Chaps 1, 14

Spatio-temporal transformation – see Chaps 10, 16

Spectrum (in acoustics) – distribution of →sound-wave →energy over a given range of frequencies; see Chaps 1, 11, 12

Spectrum (in vision) - distribution of light →power over a given range of frequencies; see Chap 14

Speech – see Chaps 1, 6, 10, 11, 12, 17, 23, 24, 27

Speed-accuracy trade-off (Fitts´ law) – see Chaps 25, 26

Speed cell – →neuron whose discharge rate is robustly correlated, typically positively and linearly, with the running speed of the animal. Speed cells are thought to provide input to →grid cells to support →path integration; see Chap 23

Spherical coordinate system – →coordinate system in terms of distance, azimuth and elevation; see Chap 24

Sphincter pupillae – *constrictor iris*; see Chap 13

Spike train – series of spikes (or →action potentials); see Chap 11

Spinal cord – *medulla spinalis*: lower-most part of the →neuraxis caudal to the →brainstem; a cross-section shows butterfly-shaped central →gray matter surrounded by →white matter containing long, mostly →myelinated →axons; the gray matter is divided into laminae designated by Roman numbers; see Chaps 1, 4, 5, 7, 8, 9, 10, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27

Spinal cord injury – may result from a sharp penetrating force, contusion or compression, or from infarction by vascular insult. The pathological changes occur in phases. Minutes to weeks after the initial primary injury, the secondary injury includes vascular changes, free radical formation and lipid peroxidation, ionic imbalances of calcium (Ca^{2+}), potassium (K^{+}) and sodium (Na^{+}), apoptosis (programmed cell death), and →inflammatory responses. Days to years after the primary injury, the chronic phase includes dissolution of →gray matter, →demyelination, deposition of connective tissue, and the formation of a →glia scar, which acts as a physical barrier for regrowth of severed →axons; see Chaps 4, 5, 17, 27

Spinalization – severence of the →spinal cord; see Chaps 21, 22, 23

Spinal root – nerve fiber bundle connecting the →spinal cord to the periphery in a segmental fashion; there are →dorsal roots and →ventral roots; see Chaps 5, 7

Spino-cerebellar tracts – nervous fiber bundles (tracts) ascending from the →spinal cord to the →cerebellum; see Chaps 7, 23

Spino-cervical tract – see Chaps 4, 7

Spino-cervico-thalamic tract – see Chap 7

Spino-olivo-cerebellar (SOCP) pathway – see Chap 23

Spino-reticulo-cerebellar tract (SRCT) – see →spinal cord, →reticular formation, →cerebellum and Chaps 8, 23

Spino-thalamic tract (STT) – see Chaps 4, 5

Split-belt treadmill – see Chaps 21, 22, 23

Sprinting – see Chap 19

Sprouting – growth and branching of injured →axons (axon regeneration) or the collateral branching of uninjured axons to form new →synaptic connections, resulting in anatomical reorganization of →neuronal circuitry, often in unordered form because it usually lacks target specificity. Sprouting can occur at peripheral injury level or in the →dorsal root and →central nervous system (CNS); see Chaps 5, 27

Squirrel monkey – see Chaps 12, 15

Stance – see stance phase (during locomotion), quiet upright stance and Chaps 1, 10, 12, 17, 19, 20, 21, 23

Stance phase (in terrestrial locomotion) – see Chaps 9, 17, 19, 20, 21, 22, 23

Stance-to-swing transition – see Chaps 22

Stapedius muscle – see Chaps 11, 12

Stapes – see Chap 11

Startle response – fastest involuntary motor reaction to an unexpected sudden sensory input of different modality (e.g., acoustic, tactile, visual stimuli or activation of the vestibular system by unexpected vertical drops of the body); mediated by the activation of →multi-modal →reticulo-spinal tract →neurons in the ponto-medullary →reticular formation (PMRF) and consisting of a generalized flexion response which progresses rostro-caudally; see Chaps 11, 12, 20, 21

Static equilibrium – see Chap 19

Static fusimotor activation, neuron – see fusimotor neuron and Chaps 8, 22

Steady state – also equilibrium state: unchanging state of a system; see Chaps 3, 11

Steering – see Chaps 1, 22

Stellate cells (in cerebellar cortex) – inhibit →Purkinje cells; see →cerebellum and Chap 10

Stellate cells (in the ventral →cochlear nucleus) – also called type I multipolar, planar multipolar or →chopper cells: →neuron type in the →brainstem cochlear nucleus that receives auditory nerve terminals and projects to the →inferior colliculus or to the contralateral cochlear nucleus; probably involved in →pitch →perception; see Chaps 11, 12

Step cycle – see Chaps 17, 19, 21, 22, 23

Step length – see Chaps 1, 21, 23

Stepping strategy – see Chap 20

Stereocilium (of auditory hair cell) – see Chap 11

Stereocilium (of vestibular hair cell) – see Chaps 10

Stereo-correspondence problem – see Chap 14

Stereoacuity – see Chap 14

Stereopsis, stereoscopic – see Chaps 14, 15, 16

Stiffness – ratio of unit change in force (df) over unit change in length (dl), or (local) slope of the force-length curve of a structure (df/dl); see Chaps 1, 8, 17, 18, 19, 20, 21, 22, 24, 27

Stiffness regulation – see Chap 19

Stork – see Chap 19

Stride length – see Chaps 21

Stress (in psycho-physiology) – most generally defined as a condition or stimulus that challenges →homeostasis; see Chaps 4, 5, 8, 12

Stress-induced analgesia – see →analgesia and Chaps 4, 5

Stress-induced hyperalgesia/allodynia – see →allodynia, →hyperalgesia, →analgesia and Chap 5

Stressor – stimulus or event eliciting →stress; see Chap 4

Stress response – see Chaps 4, 10

Stretch reflex – excitatory response of a muscle (or muscle group) to stretch, usually consisting of multiple components of short, medium and long latency, which are mediated by different →spinal and supraspinal pathways; see →reflex and Chaps 1, 15, 19, 20, 22

Striate cortex (area) (in →cerebral cortex) – area striata: primary visual cortex, area V1 = (in humans) →Brodmann´s area 17 = (in monkeys) area V1; see Chaps 10, 13, 14

Striated muscle – see Chap 8

Striatum – input station of the →basal ganglia, comprised of →nucleus caudatus and →putamen; see Chaps 2, 3, 5, 7, 14, 16, 23, 27

Stroke – acute and focal neurological consequences of disturbances of brain circulation, resulting from brain hemorrhage (due to rupture of a vessel), arterial occlusion (closure of an artery due to embolus or thrombosis), or venous closure; see Chaps 4, 17, 26

S-type motor unit – see Chap 18

Subiculum (in →cerebral cortex) – see →hippocampal formation and Chap 23

Sub-cortical – refers to structures lying below the →cerebral cortex or processes taking place there; see Chaps 2, 3, 4, 7, 12, 13, 14, 15, 16, 23, 24, 25, 26, 27

Subfornical organ – see Chap 2

Subjective postural vertical (SPV) – see Chap 19

Subjective visual vertical (SVV) – see Chap 19

Subjective vertical – see Chap 19

Sub-modalities (qualities) (of →senses) – see Chaps 1, 2, 7, 9, 14

Substance P (SP) – member of a group of peptides known as neurokinins or →tachykinins. SP is an 11-amino acid →neuropeptide and works as a →neurotransmitter, →neuromodulator or →inflammatory mediator in peripheral tissues and in various brain, →brainstem and →spinal cord regions. Mammalian SP has roles in pain, inflammation, cancer, depressive disorders, →immune system, gut function, hematopoiesis, sensory processing, and →hormone regulation. SP is released from →nociceptors to increase pain →sensitivity in the periphery and through its actions in the spinal →dorsal horn. It also appears to promote anti-→nociceptive effects. SP is also expressed by a variety of non-neuronal cell types such as →immune cells (e.g., T cells, tissue-resident →macrophages, dendritic cells and eosinophils, →microglia). SP triggers pro-inflammatory →cytokine release resulting in inflammation, vasodilation and plasma extravasation. SP preferentially activates the neurokinin-1 →receptor (NK1R); see Chaps 4, 5, 10, 16

Substantia gelatinosa (Rolandi) – see Chap 4

Substantia nigra (SN) – bilateral structure located in the →n; see →basal ganglia, →substantia nigra pars compacta (SNc), →substantia nigra pars reticulata (SNr) and Chaps 16, 23

Substantia nigra pars compacta (SNc) – part of the bilateral →substantia nigra (SN) located in the →n; →dopaminergic →neurons in the SNc project to the →striatum (→basal ganglia) and to other →forebrain structures; see Chaps 16, 23

Substantia nigra pars reticularis (SNr) – part of the bilateral →substantia nigra (SN) located in the →n; the SNr and →globus pallidus internus (GPi) form the major output station of the →basal ganglia; see Chaps 16, 23, 26

Subthalamic locomotor region (SLR) – see Chap 23

Subthalamic nucleus (STN) – *nucleus subthalamicus*; belongs to the →basal ganglia; see Chaps 16, 23

Sucrose – see Chap 2

Sugar – see Chap 2

Superficial peroneal nerve – see Chap 22

Superficial radial nerve – see Chap 22

Superior cervical ganglion – →*ganglion cervicale superius*: collection of →neurons of the →sympathetic nervous system; see Chap 13

Superior colliculus (SC) – resides on the dorsal roof of the →n and consists of seven alternating fibrous and cellular layers. It receives direct projections from retinal ganglion cells and conveys information to area V1 through the dorsal lateral geniculate nucleus (dLGN) and to →extra-striate areas through the →pulvinar. It contains cells that respond to visual stimuli at defined locations in the contralateral visual hemi-field. Subsets of cells in the deeper layers respond to visual, auditory or somatosensory stimuli; see Chaps 3, 4, 12, 13, 14, 15, 16, 23, 25, 26

Superior oblique eye muscle – see Chaps 15, 16

Superior olivary complex (SOC) – see Chaps 11, 12

Superior parietal lobule (SPL) (in →cerebral cortex) – In macaques, the SPL is divided into areas PE, PEa, PEc and MIP; area PEc and →area 7m form the anterior and central parts of the →precuneus. In humans, the lateral SPL consists of two cytoarchitectonically different regions, the anterior →Brodmann´s →area 5 and the larger posterior Brodmann →area 7; the SPL extends into the precuneus (with a similar subdivision) on the medial hemisphere surface; SPL receives main inputs from the →primary somatosensory cortex (S1, SI) and some visual areas, and sends outputs primarily to →primary motor cortex (area M1, area F1, area 4) and dorso-lateral premotor area (PMd) (→premotor cortex); see Chaps 7, 14, 16, 25, 26, 27

Superior parieto-occipital cortex (SPOC) (in →cerebral cortex) – see Chap 26

Superior rectus eye muscle – see Chaps 15, 16

Superior temporal gyrus (STG) (in→cerebral cortex) – Heschl´s gyrus; see Chaps 12, 20

Superior temporal polysensory area (STP) (in →cerebral cortex) – see Chaps 7, 12, 14

Superior temporal sulcus (STS) – see Chaps 7, 12, 14, 27

Superior vestibular nucleus (SVN) of Bechterev – see Chap 10

Supervised learning– a desired target is specified internally, by higher-level goals, or externally by the environment, e.g., during imitation learning. The discrepancy between desired output and actual output is used as an error signal that is used to instruct the →learning process; see Chap 27

Supplementary eye field (SEF) (in →cerebral cortex) – part of →area F7; see →eye fields and Chaps 10, 16

Supplementary motor area (SMA) (in →cerebral cortex) – →somatotopically organized, postero-mesial part of →Brodmann´s area 6, also called →area F3 in monkeys, has connections with post-central areas S1 and 5, with cingulate area 24d, the →primary motor cortex (area M1, area F1), →premotor areas F2 and F4, the →spinal cord, →brainstem nuclei, and ipsi- and contralateral →cortical areas; tightly involved in movement generation and control; see area F3 and Chaps 7, 12, 16, 20, 23, 24, 26, 27

Supra-chiasmatic nucleus (SCN) – nucleus of the →hypothalamus, situated above the →optic chiasm, site of the primary circadian oscillator in mammals (→circadian rhythm); see Chap 13

Supra-marginal gyrus (**SMG)** (in→cerebral cortex) – curves around the end of the lateral fissure; see Chaps 7, 20

Sural nerve – see Chap 22

Surface fill-in (in vision) – see Chap 14

Sweet taste – see Chap 2

Sympathetically mediated pain – see Chap 5

Sympathetic nervous system (SNS) – branch of the →autonomic nervous system ANS), which arises from →preganglionic neurons in the →brainstem and the thoraco-lumbar segments of the →spinal cord; sympathetic activity leads to increased →arousal, increased →muscle tone and pain suppression, increased heart rate and cardiac output, increased arterial pressure, inhibition of digestive function and increased respiration, which increase perfusion of active tissues; see Chaps 4, 5, 8, 13

Synapse (synaptic) – structural specialization connecting a presynaptic with a postsynaptic cell and transmits signals between →neurons and other cell types. The modes of signal transmission may be electrical and/or chemical, which often functionally interact with each other; in almost all chapters

Synaptic efficacy – see →synapse and Chaps 7, 19, 22, 27

Synaptic plasticity – phenomenon at the core of most hypotheses of →neuronal development, neuronal circuit reorganization, →learning and →memory. Synaptic efficacy

can be increased or decreased in an activity-dependent manner. Synaptic plasticity is influenced by various →neuromodulators, including →dopamine, →acetylcholine, →noradrenaline and →serotonin (5-HT); see →synapse, activity-dependent synaptic plasticity and Chaps 3, 5, 7, 10, 15,, 27

Synaptic transmission – transmission at →synapses, mediated by electrical currents (electrical synapse) or →neurotransmitters (→synapses); see Chaps 1, 2, 3, 5, 10, 11, 15, 19, 26, 27

Synaptic vesicle – small organelle in a presynaptic terminal at →synapses. It accumulates and stores →neurotransmitters and →neuromodulators, and releases these substances into the synaptic cleft (cleft between the presynaptic →axon ending and postsynaptic cell) by a calcium (Ca^{2+})-dependent exocytosis; see Chaps 17, 18

Synergistic (→motoneuron, muscle) – see Chaps 4, 15, 16, 19, 20, 22, 23, 26

Synergy – In motor control, the term "synergy" is used in many ways and thus difficult to define strictly; alternative terms have also been used: primitive, coordinative structure, mode, module, concinnity, coalition. Broadly speaking, it can be seen as an organizational principle that unites multiple elements into groups such that they can be controlled and directed as a single variable or combined in flexible arrangements. The term synergy is applied at different levels: coordinated movements (kinematic synergies), muscle activation patterns (muscle sysnergies) and underlying neural circuits. It has been discussed controversially whether muscle synergies are organized by the →central nervous system (CNS) to reduce the →degrees of freedom (DOGs) of movements; see Chaps14, 20, 25

Synesthesia – union of →senses; condition in which stimulation in one sensory modality elicits involuntary sensation in another modality; it is rare in adults (1:2,000) and six times more prevalent in women than men, may follow an X-linked dominant inheritance pattern; see Chap 14

Syringomyelia – syndrome generated by fluid-filled caves in the →spinal cord or →medulla oblongata (*syringobulbia*) resulting from trauma or degeneration of circumscribed →glia cell tumors (gliosis spinalis). The most frequent site is the cervical spinal cord, leading to characteristic motor and sensory deficits and vasomotor and trophic disturbances; see Chap 7

Swimming – see Chaps 1, 22

Swing phase (in terrestrial locomotion) – see Chaps 21, 22, 23

Swing-to-stance transition (in terrestrial locomotion) – see Chap 22

T1R receptor – taste receptor of four types: T1R1, T1R2, T1R3, T1R4; see →receptor and Chap 2

T2R receptor – →G-protein-coupled receptors (GPCR) taste →receptor that detects bitter taste ligands; see →receptor and Chap 2

TACAN – see Chap 4

Tactile – see Chaps 1, 2, 3, 4, 5, 6, 7, 9, 12, 14, 16, 19, 20, 23, 24, 25, 26

Tactile acuity – degree of resolution of spatial aspects of tactile →perception, such as the discrimination of two (or more) stimulated points as separate or of the orientation of a spatial grating imposed on the skin; see Chaps 6, 7

Tactile allodynia – see →allodynia and Chap 5

Tactile flutter/vibration sensation – see Chap 7

Tactile memory – see Chap 7

Tactile motion perception – see Chap 7

Tactile object – see Chaps 6, 7

Tactile object discrimination – see Chap 7

Tactile object identification – see Chap 7

Tactile object recognition – see Chap 7

Tactile receptive field – see →receptive field (RF) and Chaps 7, 24, 25, 26

Tactile size constancy – see Chap 7

Tadpole – see Chap 22

Tail flick – see Chap 5

Tannic acid – member of a widely distributed and chemically diverse group of tannins used to tan raw hides into leather; tannic acid occurs in oak gall-nuts; see Chap 2

Targeting saccade – see saccade and Chap 16

Task selection – see Chap 1

Tastant – see Chap 2

Taste – gustation; see Chaps 1, 2, 3, 4, 26

Taste bud – see Chap 2

Taste coding – see Chap 2

Taste hedonics – refers to palatability; see →hedonics and Chap 2

Taste memory – see Chap 2

Taste memory trace (TMT) – see Chap 2

Taste neophobia – fear of novel tastes; see Chap 2

Taste quality – see Chap 2

Taste receptor cell – see →receptor cell and Chap 2

Taste thalamus – ventro-posterior medial (VPM) nucleus of →thalamus

Taurine – amino acid and glia-transmitter; see and Chap 10

Tectal long-lead burst neuron (TLLBN) (in oculomotor control) – see Chap 16

Tectal pause neuron (TPN) (in oculomotor control) – also fixation neuron; see Chap 16

Tectorial membrane – see Chap 11

Tecto-spinal tract – originates in the →mesencephalon (→n) and projects to laminae VI-VIII of the cervical →spinal cord; it is involved in head and neck motor control; see Chaps 23, 26

Tegmentum – tissue layer within the →brainstem situated ventral to the inner liquor space and containing →cranial nerve nuclei; see Chap 23

Temperature (sense) – see Chaps 1, 2, 3, 4, 5, 6, 7, 10, 13, 14, 17, 18

Temporal coding hypothesis – see Chap 2

Temporal cortex (lobe) – see Chaps 12, 14, 23

Temporo-parietal junction (TPJ) – cerebro-cortical region in humans consisting of the posterior superior temporal gyrus (pSTG), →angular gyrus, →supra-marginal gyrus (SMG), →inferior parietal lobule (IPL), parietal →operculum and posterior →insula; see Chaps 17, 14, 25

Tendon – see Chaps 1, 6, 8, 9, 17, 18, 19, 21, 26

Tendon reflex – →reflexive muscle contraction elicited by a brief tap on a muscle tendon. This phasic reflex is used to test the excitability of the →spinal cord, which may be decreased (e.g., in cerebellar disorders: →hyporeflexia) or increased (e.g., in →spasticity: →hyperreflexia; see →reflex and Chap 1

Tendon vibration – see Chaps 8, 9, 19, 20, 25

Tensor tympani muscle – see Chap 12

Terrestrial locomotion – see Chaps 1, 21, 22, 23

Tertiary olfactory cortex (in →cerebral cortex) → – see Chap 2

Tertiary receptor system – see →receptor cell and Chap 1

Tertiary sensory system – see Chap 1

Tetanic contraction or tetanus (in muscle contraction) – mechanical contractile response of →skeletal muscle to a train of closely spaced electrical stimuli applied to the muscle itself (direct muscle stimulation) or to the innervating muscle nerve (indirect muscle stimulation); see Chap 18

Tetanic force or tension – see Chap 18

Tetrapod – vertebrate with four feet, e.g., amphibian, reptile or mammal; see Chaps 1, 26

Tetrodotoxin (TTX) – toxin derived from bacteria and concentrated in certain organs of puffer fish (fugu) and other fishes. Tetrodotoxin is a very potent blocker of most voltage-gated Na^+ channels; see Chap 5

Thalamic reticular nucleus (TRN) – thin shell of inhibitory neurons between →thalamus and →cerebral cortex. Different segments are associated with different thalamic nuclei and their corresponding →cortical areas. The visual segment of TRN has two parts. The lateral part receives →topographically organized excitatory inputs from the lateral geniculate nucleus (LGN) and primary visual cortex (area V1) and sends inhibitory feedback to the LGN; it additionally receives inputs from the →orbito-frontal cortex (OFC) and →dorso-lateral prefrontal cortex (DLPFC), probably mediating →attentional modulation, from the →amygdala, possibly mediating →emotional modulation, and from the →basal forebrain and →brainstem. The medial TRN part is associated with the →pulvinar and various regions of →extra-striate visual cortex; see reticular nuclei and Chap 13

Thalamus – The thalamus forms the larger dorsal sub-division of the →diencephalon located medially to the →capsula interna and →nucleus caudatus. It is a large mass of →gray matter made up of a multitude of nuclei, through which sensory information is relayed and processed on its way to the →cerebral cortex; the thalamus also transmits and processes information from the →basal ganglia and →cerebellum; see Chaps 2, 3, 4, 5, 7, 10, 12, 13, 16, 23, 24, 26, 27

Thermo-reception, thermo-receptive, thermo-receptor – detection and →perception of temperature changes (typically perceived as coolness, coldness, warmth or heat); see →receptor cell and Chaps 2, 4, 6

Thermo-sensation – see Chaps 4, 9

Theta oscillation – see →neuronal oscillations and Chap 3

Thixotropy – motion-dependent →viscosity, such as seen in paint, which becomes less viscous upon stirring; in physiology, thixotropy refers to the fact that a muscle´s passive mechanical properties depend on its previous history of contraction and length changes; see Chap 9

Three-neuron arc – circuit in vestibulo-ocular reflex (VOR); see Chaps 1, 15

Threshold (of →action potential) – membrane potential (→resting membrane potential) at which the fast rising phase (upstroke) of the action potential takes off; see Chaps 4, 5, 7, 18, 22, 27

Threshold (in sensory systems) – *Sensory thresholds* for stimuli (S) are distinguished into absolute and relative or difference thresholds, and so are the respective →sensitivities. The absolute threshold is defined as the minimum stimulus →intensity evoking a recognizable response in the →sensory receptor, a central →neuron or →perception. Many →receptor systems are exquisitely sensitive to adequate stimulus. The *relative threshold* or *difference threshold* is defined as the just-noticeable difference in a stimulus variable. This difference is taken relative to the starting intensity; see Chaps 3, 4, 5, 6, 7, 8, 9, 11, 15, 19, 20, 22, 23, 25

Thyroid gland – see Chap 3

Tibialis anterior (TA) muscle thyroid gland s 19, 20, 21, 22

Tibialis posterior muscle – see Chaps 17, 19

Tibial nerve – see Chap 22

Tickling – see Chap 7

Timbre – →sound quality determined by its →spectral or temporal envelope; see Chap 12

Time constant – time required for a system´s response to a step input to attain 1/e of its final value; see Chaps 10, 11, 15, 18

Tinnitus – see Chaps 11, 12

Tissue oxygenation – see Chap 4

Titin – protein in →skeletal muscle; see Chaps 17, 18

Titubation – see Chap 20

Tone (in audition) – see Chaps 1, 7, 11, 12

Tongue – see Chaps 2, 6, 26

Tonic vibration reflex – sustained contraction of a →skeletal muscle subjected to vibration. Muscle spindle →receptors detect low–amplitude vibrations (as low as few μm) and excite homonymous →skeleto-motoneurons via a →reflex arc that includes one or few →synapses; see →reflex and Chap 9

Tonotopic map – orderly mapping of tone frequencies onto the cochlea or onto spatial arrangements of groups of auditory cells; see Chaps 11, 12

Tool (use) – see Chaps 1, 9, 12, 24, 25, 26

Top-down (processing) – information flow from `higher´ to `lower´ →neuronal centers; top-down influences on lower-level processing may exert effects of →attention, behavioral context, expectation, →perceptual task, →working memory, and previous experience; see →bottom-up processing and Chaps 1, 2, 5, 7, 12, 14, 16

Topographic, topography – preservation of relative ordering (neighborhood relationships) of →neurons in between two regions by ordered neuronal connections; see Chaps 1, 2, 3, 4, 7, 12, 13, 14, 16, 23, 25

Torque – product of a force (a vector) and its perpendicular distance to a point of turning; see Chaps 1, 8, 15, 17, 19, 20, 21, 25, 26, 27

Torsional eye movement – rotation of the eye about the line of sight; see Chap 15

Touch – see Chaps 1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 14, 19, 20, 22, 23, 25, 26

Touch-induced analgesia – see →analgesia and Chap 4

Tourette syndrome – inherited disorder of pre-pubertal onset, characterized by often irrepressible, only temporarily suppressable tics: multiple brief muscular spasms (*convulsive tics*) in the face, neck and shoulder; repetitive, stereotyped, strongly →emotional gestures or →vocalizations (e.g., *vocal tics*, such as grunts and barking →sounds); behavioral abnormalities (obscene utterances). The Tourette syndrome often co-occurs with →attention-deficit/hyperactivity disorder (ADHD) (→attentional deficits), obsessive-compulsive disorder, and a range of other mood and anxiety disorders. The syndrome possibly results from dysfunctions of the ventral →basal ganglia; see Chap 26

Train nystagmus – see →nystagmus and Chap 15

Transcortical reflex – see →reflex and Chaps 15, 22, 25

Transcranial magnetic stimulation (TMS) – non-invasive, nearly painless method of activating human cerebro-cortical →neurons by applying a magnetic pulse over the scalp. TMS allows functional mapping of the human brain and generation of transient functional lesions; see Chaps 7, 14, 23, 24, 25, 26, 27

Transcutaneous electrical nerve stimulation (TENS) – procedure used to reduce pain sensation by electrically stimulating nerve fibers by means of overlying cutaneous surface electrodes; see Chap 4

Transducer, transduction – device viz. process that converts a physico-chemical quantity such as temperature, pressure or substance concentration into an electrical signal; used for both technical devices and →sensory receptors; see Chaps 1, 3, 4, 6, 10, 13, 15

Transient achromatopsia – see Chap 14

Transient receptor potential (TRP) channels. In mammals, more than 25 distinct TRP channels have been described. They fall into seven sub-families: TRPA for `ankyrin´ (TRPA1), TRPC for `canonical´ (TRPC1-7), TRPM for `melastatin´ (TRPM1-8), TRPML for `mucolipin´ (TRPML1-3), TPRN for `NomPC´, TRPP for `polycystin´ (TRPP2, TRPP3, TRPP5), →TRPV for `vanilloid´ (TRPV1-6). TRPs display a variety of activation mechanisms and sensitivities. Subsets of TRP channels are modulated by →cannabinoids. TRP channels are involved in the →transduction of numerous chemical and physical stimuli including temperature, pressure, osmo-sensation, pH, taste, smell, →nociception (pain), hearing, and vision. Other TRP channels are essential for calcium (Ca^{2+}) and magnesium (Mg^{2+}) →homeostasis. Many diseases involve TRP channel dysfunction, including →neuropathic pain, →inflammation, and respiratory disorders; see Chaps 2, 4, 5, 6, 8, 17

Translational vestibulo-ocular reflex (TVOR) – The translational or linear vestibulo-ocular reflex (TVOR, LVOR) is the compensatory eye movement generated in response to a linear displacement of the head; see →reflex and Chap 15

Transverse tubule – T-tubule in skeletal →muscle fiber; see Chap 17

TREK-1 – also called *KCNK-2*: member of the two-pore potassium (K^+) channel family, heat-→sensitive; see Chap 4

Tremor – rhythmical oscillations of body parts (usually distal limbs, head, tongue or jaw, rarely trunk), which occur in a variety of forms, from physiological to pathological types; see Chaps 15, 18, 19, 22, 26

Triceps brachii muscle – see Chap 25

Triceps surae muscle – comprises gastrocnemius medialis, gastrocnemius lateralis and soleus muscles; see Chaps 17, 19, 20, 22

Trichromacy, trichromatic – see Chap 13

Trigeminus, trigeminal – refers to the →trigeminal nerve [fifth →cranial nerve (V) with three main peripheral branches] and nucleus; see Chaps 2, 3, 4, 5, 12

Trigeminal nerve – fifth →cranial nerve (V) that provides the somatosensory innervation of the oral region and face, and the motor innervations to most of the muscles of mastication (chewing); see Chaps 2, 7

Trigeminal nucleus – see Chap 4

Trigger neuron (in oculomotor control) – trigger long-lead burst neuron; see Chap 16

Trochlear nerve – *nervus trochlearis*: →cranial nerve IV; see Chap 15

Tropomyosin – see Chap 17

Tropomyosine receptor kinase A (TrkA) – for nerve growth factor (NGF); see →growth factors, →neurotrophic factors (neurotrophins) and Chap 4

Tropomyosine receptor kinase B (TrkB) – for →brain-derived neurotrophic factor (BDNF) and neurotrophin-4/5 (NT-4/5); see →growth factors, →neurotrophic factors (neurotrophins), and Chaps 5

Troponin – see Chap 17, 18

Trot, trotting – see Chaps 21, 22, 23

TRP ankyrin 1 (TRPA1) channel, receptor – member of the→**t**ransient **r**eceptor **p**otential (TRP) channel family, expressed in a sub-population of small-diameter →neurons in →dorsal root, →trigeminal and nodose ganglia; can be activated by a large range of agents including →inflammatory mediators causing pain, such as →bradykinin and →adenosine triphosphate (ATP); see Chap 4

TRPM2 channel, receptor – member of the→**t**ransient **r**eceptor **p**otential (TRP) channel family; see Chap 4

TRPM3 channel, receptor – member of the→**t**ransient **r**eceptor **p**otential (TRP) channel family, expressed in a subset of →neurons in →dorsal root and →trigeminal ganglia and activated by heat and neurosteroid pregnenolone sulfate in pain responses; see Chap 4

TRPM8 channel, receptor – member of the→**t**ransient **r**eceptor **p**otential (TRP) channel family, widely expressed in small-diameter →neurons in →dorsal root and →trigeminal ganglia and activated by cool to cold temperatures and cooling agents such as →menthol and eucalyptol; see Chap 4

TRPV channel, receptor – **v**anilloid →**t**ransient **r**eceptor **p**otential (TRP) channel family; →sensitive to various tissue-damaging stimuli and mediating pain; their activation increases intracellular Ca^{2+} concentration and may induce →long-term potentiation (LTP) and →long-term depression (LTD) involved in pain →memory; see Chap 4

TRPV1 channel, receptor – gated by →capsaicin, heat, low pH, voltage change, and activated or sensitized by agents associated with →inflammation and tissue damage, such as →bradykinin, →prostaglandins, →adenosine triphosphate (ATP), and many others; see Chaps 4, 5

TRPV2 channel, receptor – member of the→**t**ransient **r**eceptor **p**otential (TRP) channel family; see Chap 4

TRPV3 channel, receptor – member of the→**t**ransient **r**eceptor **p**otential (TRP) channel family, richly expressed in →keratinocytes, potential epidermal contributor to pain and (chronic) →itch; see Chap 4

TRPV4 channel, receptor – member of the→**t**ransient **r**eceptor **p**otential (TRP) channel family richly expressed in →keratinocytes, potential epidermal contributor to pain and →itch; see Chap 4

Tubero-mamillary nucleus (of →hypothalamus) – see Chap 13

Tufted cell (in olfactory bulb) – see Chap 3

Tumor necrosis factor-α (TNF-α) – potent paracrine and →endocrine mediator of →inflammatory and →immune system functions. TNF-α is secreted by activated monocytes and →macrophages, →astrocytes, B lymphocytes, T lymphocytes and fibroblasts (→leukocytes); TNF-α modulates differentiation and growth activities, provides a rapid form of host defense against infection, but is cytotoxic in excess.; see Chap 5

Turtle – see Chaps 1, 22

Twitch – short for twitch contraction, upon single activation, of a →skeletal muscle or group thereof, a →motor unit or group thereof, or a →muscle fiber or group thereof; see Chaps 17, 18

Twitch contraction – see →twitch and Chaps 8, 15, 17, 18

Twitch fiber – refers to a →muscle fiber that, upon single activation, responds with a →twitch contraction; see Chaps 8, 15, 17

Twitch force or tension – maximal force attained by the →twitch; see Chap 18

Two-handed manipulation – see Chap 26

Two-point discrimination (in cutaneous mechano-sensation) **–** ability to discriminate two neighboring stimuli contacting the skin as separate; see Chaps 6, 7, 9

Two-tone interaction – see Chap 12

Two-tone suppression – see Chap 11

Tympanic membrane – eardrum; see Chaps 1, 11

Type 1 muscle fiber – see Chap 18

Type 2A muscle fiber – see Chap 18

Type 2B muscle fiber – see Chap 18

Type 2X muscle fiber – see Chap 18

Type I hair cell (in peripheral vestibular system) – see Chap 10

Type II hair cell (in peripheral vestibular system) – see Chap 10

Type I cell (in taste buds) – see Chap 2

Type II cell (in taste buds) – see Chap 2

Type III cell (in taste buds) – see Chap 2

Ulnar nerve – see Chap 9

Umami receptor – see →receptor cell and Chap 2

Umami taste – see Chap 2

Unfused contraction – see Chap 18

Unipolar brush cell (UBC) – excitatory →glutamatergic →interneuron in the →vestibulo-cerebellar cortex, including the →vermis and the flocculo-nodular lobe, i.e., regions involved in sensorimotor processes that regulate body, head and eye position, A UBC has a short →dendrite whose brush forms →synaptic contact with a single →mossy fiber terminal, and an →axon that branches locally in the granular layer to form glomeruli together with mossy fibers, →granule cells and other UBCs. This arrangement is thought to generate a feed-forward amplification of single mossy fiber signals; see Chap 10

Unsupervised learning (in →motor learning) – In un-supervised →learning (→neural networks), the environment provides neither a desired target nor →reward or punishment. An example is →Hebbian learning. This type of externally unguided learning does not guarantee that the learned internal representation be useful for →decision making and control; see →supervised learning; see Chap 27

Upright stance – see Chaps 1, 10, 12, 19, 20, 21, 22, 23

Utriculus, utricle – see Chaps 10, 15

Uvula-nodulus (of →cerebellum) – see Chap 10

V0, V1, V2, V3 – groups of →interneurons in the mouse ventral →spinal cord, classified according to their origin in progenitor domains aligned in dorso-ventral direction along the midline and showing different genetic and molecular characteristics; see Chap 22

V0 Interneurons are located in lamina VIII of the postnatal →spinal cord. They can be divided into a dorsal inhibitory sub-population ($V0_D$) and a ventral excitatory sub-population ($V0_V$), both responsible for coordinating left-right alternation in locomotion, the dorsal subset at slow locomotor speeds and the ventral subset at higher speed; a small fraction of these cells, the →cholinergic $V0_C$ interneuron sub-population, acts to control the input/output gain of →α-motoneurons; see Chap 22

$V0_C$ Interneuron – →cholinergic →V0 interneurons; see Chaps 7, 20, 22, 23

V1 Interneurons are primarily located in lamina VII/IX of the →spinal cord, mostly inhibitory and include Renshaw cells, reciprocal Ia inhibitory interneurons (which derive from yet another progenitor domain) and a diversity of others, and are involved in flexor-extensor alternation and in regulating locomotor speed; see Chap 22

V2 Interneurons come in three sub-populations: excitatory V2a neurons, inhibitory V2b and V2c. Both the V2a and V2b cells project exclusively to the ipsilateral side. V2a interneurons display diverse projection patterns to $V0_V$, α-motoneurons and the central pattern generator (CPG). Despite their ipsilateral axonal projections, V2a interneurons help maintain left-right alternation at high speeds. Together with V1 cells, V2b interneurons secure the flexor-extensor alternation.

V3 Interneurons are widely distributed in the →spinal cord and have complex connectivities. They are excitatory cells with primarily commissural projections, but also ipsilateral connections between two groups of ventro-medial and ventro-lateral V3 →interneurons and α-MNs, which in turn recurrently excite the V3 cells. Subgroups of V3 interneurons also contact Renshaw cells, reciprocal Ia inhibitory interneurons, as well as V2b cells and other, unidentified, commissural neurons. V3 interneurons are thought to balance locomotor output across the midline and thus to help maintain a stable and robust locomotor pattern; see Chap 22

Vagal, vagus nerve – →cranial nerve X; see Chaps 2, 4

Variable error (in pointing/reaching) – see Chap 24

Vascular organ of lamina terminalis – see Chap 2

Vasoactive intestinal protein (VIP) – vasodilator peptide, widely distributed throughout the nervous system. VIP exerts many biological effects, such as smooth muscle relaxation, fluid secretion from the pancreas and inhibition of gastric acid secretion, and is a

→neurotransmitter in →atropine-resistant →parasympathetic vasodilatation within the salivary glands. In the →supra-chiasmatic nuclei (SCN) of the →hypothalamus, VIP is crucially involved in communication among individual SCN oscillator cells and in synchronizing the timing of SCN function with the light-dark cycle; see Chap 3

Vasopressin (VP) – also called arginine vasopressin (AVP) and anti-diuretic hormone (ADH): peptide →hormone synthesized and released by →neurons in the paraventricular nucleus (PVN), and →supra-chiasmatic nuclei (SCN) of the →hypothalamus, has anti-diuretic and vasopressor actions and many effects in the brain; see Chap 3

Vastus lateralis muscle – see Chap 21

Vection – →illusory self-motion occurring when a stationary observer is presented with global, large-scale, dynamically changing tactile, auditory or visual environments that consequently elicit a strong, illusory sensation of physical self-motion through space, like in the train illusion; see Chaps 7, 12, 20

Vector decomposition – see Chap 16

Velocity memory – see →velocity storage and Chap 16

Velocity profile (of pointing/reaching hand movements) – see Chaps 16, 25, 26

Velocity storage – central vestibular mechanism that stores incoming velocity information about eye, head and body movement; velocity storage is suggested by the fact that the angular velocity estimate of the CNS (as expressed by →reflexive eye movements and →perceptual measures) outlasts the angular velocity signal provided by afferents from the semicircular canals; see Chap 16

Ventral basal banglia – see → basal ganglia and Chaps 16, 23

Ventral cochlear nucleus – nucleus cochlearis ventralis: part of the →cochlear nucleus; see Chap 12

Ventral horn – ventral extension of the →spinal →gray matter; see Chaps 4, 7, 17, 18, 22

Ventral intraparietal area – →area VIP, has many →neurons with bi- of trimodal responses to auditory, visual and/or somatosensory stimuli; see →area 5, →area VIP, →inferior parietal lobule (IPL), →superior parietal lobule (SPL) and Chaps 10, 14, 16, 19, 24, 25, 26

Ventral lateral nucleus (of →thalamus) – motor nucleus of thalamus; see Chap 4

Ventro-medial medullary reticular formation (v-MRF) – see →reticular formation and Chap 23

Ventral paraflocculus (VPFL) (of →cerebellum) – see Chap 15

Ventral posterior (VP) nucleus (of →thalamus) – see Chap 4

Ventral posterior inferior (VPI) nucleus (of →thalamus) – see Chap 4

Ventral root (of →spinal nerve) – bundle of efferent nerve fibers exiting the →spinal cord and targeting peripheral structures; see Chaps 18, 22

Ventral somatosensory area (VS) (in →cerebral cortex) – see Chap 7

Ventral somatosensory pathway – see Chap 7

Ventral spino-cerebellar tract (VSCT) – tract of nerve fibers originating in the →spinal cord and targeting →neurons in the →cerebellum; see Chaps 7, 19, 23

Ventral stream (in auditory processing) – `what´ stream for →sound characterization, identification and discrimination; see Chap 12

Ventral stream (in visual processing) – see →ventral visual stream and Chap 14

Ventral tegmental area (VTA) or field (VTF) – The VTA and →substantia nigra pars compacta (SNc) are the sources of →dopaminergic projections to the →striatum of the →basal ganglia and to →limbic →forebrain areas. Dopaminergic VTA →neurons fire prior to behaviors triggered by sensory stimuli predicting →reward and; their firing scales with the magnitude and unpredicitability of received rewards, consistent with roles in →learned appetitive behaviors and in positive →reinforcement; see →tegmentum and Chaps 23, 27

Ventral visual stream (in visual processing) – `what´ stream for visual →recognition of shape and color and object identification; see Chap 14

Ventro-basal complex (of →thalamus) – see Chap 7

Ventro-lateral medulla (VLM) – see Chap 5

Ventro-lateral prefrontal cortex (VLPFC) (in →cerebral cortex) – see →prefrontal cortex (PFC) and Chaps 12, 26

Ventro-lateral premotor cortex (PMv) (in →cerebral cortex) – PMv is divided into area F4 and area F5. Area F4 lies immediately rostral to →primary motor cortex (area F1, area M1) and is further divided into dorsal and ventral sub-regions F4d and F4v involved in forelimb and oro-facial movements, respectively. Area F5 is divided into F5a (lateral to F5p), F5c (rostral to area F4) and F5p (rostral to area F4). F5p contains `mirror →neurons´ and together with F4d controls forelimb and eye movements. F5a and F5c are hierarchically higher and involved in →decision making; see →premotor cortex and Chaps 7, 12, 24, 26, 27

Ventro-medial medullary reticular formation (v-MRF) – see →reticular formation and Chap 23

Ventro-posterior lateral nucleus (VPL) (of →thalamus) – see Chaps 5, 7

Ventro-posterior medial nucleus parvocellular part (VPMpc) (of →thalamus) – `taste thalamus´; see Chap 2

Vergence (of line of sight) – rotations of the two eyes in opposite directions; see Chaps 15, 16, 25

Vergence eye movements – see Chaps 14, 15, 16

Vermis (of →cerebellum) – see Chaps 10, 16, 20, 23

Vertebrate – in almost all chapters **Vertical disparity** – see Chap 14

Vestibular – see Chaps 1, 10, 11, 12, 14, 15, 16, 19, 20, 21, 23, 25

Vestibular apparatus – The peripheral vestibular apparatus in the inner ear detects head acceleration changes in various directions and converts these changes into neural signals, which are used to →reflexively regulate physiological functions, including body stability (vestibulo-spinal reflex), ocular movements (vestibulo-ocular reflex), →sympathetic nerve activity, arterial blood pressure, food intake, and body temperature; see Chaps 1, 10, 15, 19

Vestibular cerebellum – see Chap 10

Vestibular cingulate area – see Chap 10

Vestibular compensation – see Chap 10

Vestibular complex – see Chaps 10, 19

Vestibular cortex (in →cerebral cortex) – see Chaps 10, 25

Vestibular efferent – see Chap 10

Vestibular nuclear complex – see Chap 10

1**Vestibular nuclei** – usually divided into four nuclei: inferior, lateral, medial, and superior; they receive differential inputs from the peripheral vestibular system in the inner ear, as well as from various other sources, including visual inputs, neck and limb proprioceptive inputs, →motor cortex and other →cortical areas, →hypothalamus, pre-cerebellar →lateral reticular nucleus (LRN), →cerebellum (→vestibulo-cerebellum and →nucleus fastiguus), →nucleus ruber, →reticular formation (RF), →locus coeruleus. Except for the lateral vestibular nucleus, the vestibular nuclei are interconnected through ipsilateral intrinsic pathways and by commissural projections from the contralateral side; see Chaps 1, 10, 15, 16, 19, 20, 23

Vestibular plasticity – see Chap 10

Vestibular primary afferent – see Chap 10

Vestibular receptor – see →receptor cell and Chap 10

Vestibular reflex – see →reflex and Chaps 10, 15

Vestibular system – see Chaps 1, 15, 19, 23

Vestibulo-cerebellar lesion – see Chap 20

Vestibulo-cerebellum – includes flocculus, paraflocculus, nodulus, ovula, →oculomotor vermis. The flocculus/paraflocculus (floccular complex) is involved in high-frequency (brief) vestibular responses, sustained smooth pursuit eye movements, and gaze holding; the nodulus/ventral uvula in low-frequency (sustained) vestibular responses, and the dorsal oculomotor vermis and the posterior portion of the fastigial nucleus (the fastigial oculomotor region) for saccades and smooth pursuit initiation. See also →cerebellum and Chaps 10, 15

Vestibulo-ocular reflex (VOR) – see →reflex and Chaps 1, 10, 15, 16, 27

Vestibulo-spinal reflex – see →reflex and Chaps 10, 20

Vestibulo-spinal tracts (VST) – tracts of nerve fibers originating in the →vestibular nuclei and targeting →neurons in the →spinal cord. The medial vestibulo-spinal tract (MVST) originates in the rostral portion of the descending vestibular nucleus (DVN) as well as the adjacent areas of the medial vestibular nucleus (MVN, Schwalbe) and lateral vestibular nucleus (LVN, Deiters) and exerts main influences on upper-body muscles (particularly neck musculature), with a small fraction providing inputs to segments containing forelimb →motoneurons. The lateral vestibulo-spinal tract (LVST) originates mainly from the lateral vestibular nucleus, with some contribution from the descending nucleus, extends all along the spinal cord and provides extensive inputs to segments containing motoneurons that innervate forelimb and hindlimb muscles. The LVST terminates in Rexed´s laminae VII and VIII and contacts mainly premotor →interneurons, with weak monosynaptic connections to hindlimb motoneurons. Among the interneurons are Renshaw cells, reciprocal Ia inhibitory interneurons, propriospinal interneurons and commissural interneurons. The lateral VST has excitatory effects on extensor motoneurons, with some inhibitory effects on flexor motoneurons; see Chaps 7, 19, 20, 22, 23

Vibration sense – see Chap 7

Vibrotaction – ability to detect and estimate the properties (e.g., amplitude and frequency) of vibration; see Chap 7

Vigilance – ability to sustain the level of →attention required to perform a task; see Chap 10

Viscera, visceral – see Chaps 2, 4, 12, 19, 21

Visco-elastic – refers to combined →viscous and →elastic properties of a material; see Chaps 1, 6, 9, 19, 22

Viscosity, viscous – resistance to flow generated by a gas or liquid when subjected to shear stress; see Chaps 1, 2, 10, 11, 15, 21, 27

Vision, visual – in almost all chapters

Visual acuity – ability to perceive static spatial detail; varies by orders of magnitude across species; see Chaps 13, 14, 15, 16

Visual amnesia – see Chap 14

Visual attention – see →attention and Chap 14

Visual constancy – visual stability; see Chaps 10, 16

Visual cortex (in →cerebral cortex) – see Chaps 7, 10, 13, 14, 16, 20, 23

Visual fading – perfect retinal stabilization leads to image fading due to →neuronal adaptation; see Chap 15

Visual field – field of view: total area in which the external world can be seen; see Chaps 11, 13, 14, 15, 16, 19, 25

Visual hemifield – see Chap 14

Visual imagery – ability to generate →percept-like images without retinal inputs by retrieval of pictorial information from →memory; see →mental imagery and Chap 14

Visual map – see Chaps 12, 14, 16

Visual motion (detection, perception, processing) occurs in various forms with different underlying mechanisms. A first distinction can be drawn between local image (object) motion and larger-scale global image motion caused, e.g., by self-motion. Local motion can deal with animate or inanimate object motion, the first including con-specifics (members of the same species) or non-con-specifics (e.g., predators, prey, neutral objects). Global motion occurs during eye-, head- and whole body movements, locomotion, navigation etc.. These different forms bear different biological significance and use different neural mechanims; see Chaps 7, 10, 15, 16, 19, 20, 25, 27

Visual receptive field – area of the retina, in which changes in luminance influence the activity of a single →neuron; see →receptive field and Chaps 9, 13, 14, 24, 25 **Visual receptive field** – area of the retina, in which changes in luminance influence the activity of a

Visual receptor, sense – see →receptor cell and →senses and Chap1, 20

Visual search – see Chaps 13, 14, 16

Visual system – see Chaps 3, 7, 10, 12, 13, 14, 15, 23

Visual temporal Sylvian area (VTS) (in →cerebral cortex) – see Chap 10

Visuo-motor coordination – see Chaps 1, 24

Visuo-motor mapping – see Chap 24

Visuo-motor rotation – see Chap 27

Vocalization – utterance of various →sounds; complex behavior engaging respiratory movements, laryngeal and supra-laryneal (articulatory) activity and requiring extensive coordination of different neural structures; see Chaps 4, 11, 12, 16

Volition – will. There are many different usages of the term: The `will´ is the decision whether to act at all; →intention; initiation of action; inhibition and executive control of action; sense of agency; see Chaps 21, 23

Voluntariness, voluntary – from Latin *voluntas*: will, desire, →intention; see →volition and Chaps 1, 3, 9, 10, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27

Volley principle – see Chap 11

Voltage-gated Ca^{2+} channels – see →voltage-gated ion channels and Chaps 2, 5, 8, 17

Voltage-gated Ca^{2+} current – see →voltage-gated ion channels and Chap 22

Voltage-gated ion channels – transmembrane proteins building aqueous pores that are more or less selective for sodium (Na^+), calcium (Ca^{2+}), potassium (K^+) or chloride (Cl^-) ions, and open in response to mechanical gates which are sensitive to membrane potential changes (→resting membrane potential); see Chap 5

Vomeronasal class 1 receptor (V1R) – see →receptor and Chap 3

Vomeronasal class 2 receptor (V2R) – see →receptor and Chap 3

Vomeronasal organ (VNO) – *Jacobson´s organ*; see Chap 3

VOR adaptation – adaptation of the vestibulo-ocular reflex (VOR) gain; see Chaps 15, 27

Vowel – see Chap 11

Walk, walking – see Chaps 1, 7, 14, 17, 18, 19, 20, 21, 22, 23

Warm receptor – see →receptor cell and Chap 1

Wavelength (of tone or light) – see Chaps 7, 13, 14

Weber-Fechner law – see Chap 11

Wernicke´s area (in →cerebral cortex) – auditory comprehension center; see Chap 12

Whiplash-associated disorder (WAD) – complex syndrome resulting from fast whip-like neck movements producing abrupt →accelerations and decelerations of the head relative to the body with compressions or torsions of the cervical spine. The consequent bone or soft-tissue injuries may lead to acute pain and →chronic pain (including local mechanical →hyperalgesia) and multifarious other dysfunctions, such as →muscle fatigue, muscle →stiffness, temporo-mandibular dysfunctions, sensory and motor deficits, →cognitive impairments, anxiety, distress, depression, and →sleep disturbances; see Chap 20

Whisker – see Chaps 6, 16

White matter – substance in the →neuraxis appearing white (relative to →gray matter) due to a considerable proportion of →myelinated →axons; see Chap 27

White noise – random →noise, whose →spectrum is flat, i.e., its amplitude is the same at all frequencies; see Chap 11

Wide-dynamic-range (WDR) cell – see Chaps 4, 5, 7

Wiping reflex – see →reflex and Chap 1

Withdrawal reflex – see →reflex and →flexion reflex and Chaps 1, 4, 5, 20

Work – In mechanics, `work´ is defined as the amount of →energy transferred from one system to another or, more precisely, as the time integral of the force component (force is a vector) in the direction of the material body moved times the distance moved by the point of force application. More generally, `work´ is also used to describe the transfer of electrical or osmotic energy; see Chap 21

Working memory – short-term storage of information needed for →perception, reasoning, problem solving, language and motor planning; see Chaps 3, 7, 14, 16, 25, 26

Writer´s cramp – chronic work-related disorder. The clinical findings include cramps, spasms, trembling, →muscle fatigue, loss of power, pain in the thumb and forefinger, abnormal →sensitivity to cold and touch, swelling of the wrist and hand, and radiation of discomfort up the limb. The symptoms need not be confined to the hand, but may extend to the forearm and shoulder, neck and sometimes the whole body. Writer´s cramp is now classified as a focal →dystonia, with abnormal sensory-motor integration and changes in neural activity at many levels of the nervous system; see Chap 26

Xenopus – see Chap 22

Yank – first derivative of force with respect to time; see Chaps 18, 20

Zero-gravity – see →gravity and Chap 1

Z-line or Z-disk (in →skeletal muscle) – see Chap 17