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Neurobiological Basis of Controlling Posture and Locomotion

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Abstract

Posture and movements are our only physical means of interacting with the environment. Because we express our thoughts and emotions through posture and movements, they indicate our will or intensions. Locomotion is representative of purposeful goal-directed behaviors that are initiated by signals arising from either volitional processing in the cerebral cortex or emotional processing in the limbic system. Regardless of whether the locomotion is volitional or emotional, it is accompanied by automatically controlled movement processes such as the adjustment of postural muscle tone and rhythmic limb movements that are unconsciously executed. Sensori-motor integration at the level of the brainstem and spinal cord play major roles in this automatic control. Signals processed in the basal ganglia and the cerebellum act on the cerebral cortex, the limbic system, and the brainstem so that locomotor behaviors are appropriately and precisely regulated depending on the behavioral context. The purpose of this review is to describe how purposeful locomotor behaviors are initiated, executed, and regulated so as to enable locomotive subjects to interact with and adapt to the environment.

Keywords: Locomotor region, Central pattern generator, Postural muscle tone, Parkinson's disease, Cerebellar gait ataxia

Lists of abbreviations in text
ARAS; Ascending reticular activating system
PPN; Pedunculopontine tegmental nucleus
MLR; Midbrain or mesencephalic locomotor region
SLR; Subthalamic locomotor region
CLR; Cerebellar locomotor region
CNF; Cuneiform nucleus
MRF; Medullary reticular formation
LC; Locus coeruleus
RN; Raphe nuclei
PRF; Pontine reticular formation
CPG; Central pattern generator
M1; Primary motor cortex
SMA; Supplementary motor area
S1; Somatosensory cortex
PMd; Dorsal premotor cortex

1. INTRODUCTION

Granit [16] stated “a scientific term motor control implies the knowledge of what is being controlled, how the process is organized, and what purpose it serves”. Brooks [5] declared “the term motor control refers to the study of posture and movements and also the functions of mind and body that govern posture and movements”. Posture and movements are our only physical means of interacting with the environment. Because we express our thoughts and emotions through posture and movements, they indicate our intensions, often revealingly so in our ubiquitous body language. Therefore, the brain links willed and unwilled actions in the control of motor performance. Programs of voluntary movements can already include programs of postural control that accompanies the voluntary movement processes. The predictive actions of postural programs utilize the brainstem, cerebellum, basal ganglia, and cerebral cortex, whose influences are brought to bear through the descending systems. Although postures and movements can be assumed consciously or as automatic adjustments, postural control is brought about by plans and programs that assemble task-related automatic adjustment of movements and posture [6]. The subject of motor control is of prime interest to physiologists, psychologists, and robotics engineers alike. How we can improve impaired performance is of central concern to the clinical neurological sciences and their associated specialties, to orthopedic surgery, to physical medicine and rehabilitation, and directly to the allied health professions, particularly occupational and physical therapy.

This review particularly explores the control of two aspects of motor performance: posture and locomotion. I have attempted to describe and sketch the basic design of the postural and locomotor control mechanisms how these structures interact one another to perform goal-directed adaptive behaviors.

2. BASIC FRAMEWORK OF LOCOMOTOR BEHAVIORS

This section begins with some major landmarks to facilitate the reader’s understanding of an overall impression. Here I would like to identify the general features of the landscape without obscuring it with too much detail. All statements and diagrams are therefore purposefully oversimplified. Moreover, when findings are generally established, diagrams are illustrated on human brain schema to facilitate readers’ understanding (Figs. 2, 4, 7, 10-11, 13-16). However, some diagrams are illustrated on cat brain schema because findings were obtained from cat experiments, but not yet sufficiently determined in higher primates (Figs. 3, 5, 6, 8-9).

2.1. Evolution and Development of the Brain, Body and Movements

MacLean [34] described the human forebrain as having expanded to its great size while retaining the features of three basic formations that reflected ancestral commonalities with reptiles, early mammals (paleomammalian), and late mammals (neomammalian) in its evolution (Fig.1). Radically different in their chemistry and structure and in an evolutionary sense countless generations

apart, the three formations constitute an amalgamation of three brains in one, a triune brain. This situation suggests that motor functions as well as psychobiological functions depend on an evolutionary linkup of structures underlying three quite different mentalities. The deep layer, which corresponds largely to the reptilian brain, is composed of the brainstem and spinal cord that play essential roles that are essential for survival. It contains an autonomic nervous system and a basic locomotor system, which enables crawling by wiggling the trunk associated with alternating limb movements. In the middle layer, the limbic cortex is further developed. Early mammals such as cats and dogs have this layer, and their quadrupedal (four-legged) locomotion is closely linked with various emotional responses that are determined by the limbic cortex. The surface or outer layer is the neocortex that governs higher brain functions such as reasoning, thinking, conceptualizing, intellection, and creating. Development of the neocortex gave rise to capabilities of precise hand-finger movements in addition to bipedal gait.

These phylogenic features of motor function are essentially observed during human development after birth. We are born with only rudimentary motor abilities; the rest have to be learned by active practice during infancy, childhood, and thereafter. Within approximately one year after birth, we achieve bipedal gait after acquisition of the capabilities of crawling and quadrupedal locomotion. Therefore, development ~~of~~ after birth requires sensori-motor integration for adaptable postural control, including the development of musculoskeletal structures and postural muscle tone of antigravity muscles, and the learning of various postural reflexes, a collective name for a large number of reflexes that preserve the body's posture [6].

Studies in the field of motor control generally assume the following issues: (1) Basic mechanisms of locomotor control, as well as autonomic functions, which are essential for surviving, are located in the brainstem and spinal cord [5, 10, 13, 17, 28, 48, 61]. (2) Locomotion comprises variations of emotional and volitional behaviors [18, 50, 58, 67, 72, 80, 86]. (3) The development of the cerebral cortex plays a key role in exquisite hand movement and bipedal gait. [15]. (4) Appropriate embodiment, or musculoskeletal body structure, is required for subjects to respond to environmental circumstances so as to achieve adaptable motor behaviors [71].

2.2. Importance of Inner States of before Initiation of Movements

As all motor behaviors are greatly affected by the organism's inner states, such as arousal levels and emotional states, understanding these inner states, before initiation of movements, is quite important. Arousal is maintained by the activity of the ascending reticular activating system (ARAS) arising from the brainstem reticular formation, one of the oldest parts of the brain (Fig.2A). Sustained signals from the ARAS to both the subcortical structures and the cerebral cortex via the non-specific thalamic nuclei maintain the background excitability of these structures so that the appropriate arousal level is maintained. Attention and expectation of reward also have large effects on the performance of goal-directed movements. The pedunculopontine tegmental nucleus (PPN), a part of the ARAS,

modulates the activity of the dopaminergic system through cholinergic and glutamatergic projections (Fig.2B) [85]. The dopaminergic neurons operate as a "reward system" via projections to the limbic system, basal ganglia, and prefrontal cortex [65]. The dopaminergic projections to the limbic system (in particular the amygdala) and to the basal ganglia nuclei alter emotional states and motor functions, respectively [22, 65, 72]. Moreover, those to the prefrontal cortex may affect attentive states [22-23, 65]. Accordingly, the ARAS plays a crucial role in the modulation of inner states that govern arousal levels, emotion and attention.

Sensory information has multifaceted functions, and it is essential to understand both the specific and general roles of sensory information (Fig.2C). For example, special sensations such as visual, auditory and olfactory signals activate visual, auditory and olfactory cortices, respectively, and give rise to information concerning what the object is, what the sound is, and what the smell is. However, prior to these cognitive processes, each sensory signal activates arousal levels from "relax" to "alert" and alters emotional states concerned with whether the sensation is "pleasant or unpleasant" and "favorite or unfavorite". The activations of sensory cortices are specific functions, and the activations of arousal and emotional states are the general roles of sensory information. The latter process often elicits emotional behaviors in addition to arousal or alerting responses without any involvements of cognitive processing. Because most sensory signals are conveyed to the brainstem, hypothalamus, and the limbic system, as well as the cerebral cortex, via the thalamus, one should note the importance of sensory signals that affect the arousal level, emotional state, and attentive or cognitive processing through the activation of the brainstem (reticular formation), the limbic-hypothalamic systems and the cerebral cortex, respectively. Both specific and general information generated by sensory signals may be integrated at the level of the cerebral cortex and give rise to "orientation", which is a function of *"self-consciousness"* involving awareness of three dimensions: time (what time do I have), place (where I am) and person (who I am). I consider orientation to be the basis of *"self-reference"*. Because disturbances of orientation (disorientation) result from lesions of the brainstem and the subcortical and cortical structures of the cerebral hemispheres in human, they are considered to act together in maintaining awareness and its sub-function, orientation.

2.3. Framework of Motor Control in General

Classical lesion studies in cats demonstrated that different areas in the subcortical forebrain structures are involved in the different types of locomotor behaviors [87-88]. After ablation of a large part of the striatum (a shaded area in Fig.3A), external stimuli led the cats to follow any object that moved, a phenomenon Denny-Brown [10] referred to as a "visually-determined cortical automatism". On the other hand, after removal of the cerebral cortex with preservation of the bilateral striatum (Fig.3B), the cats were hyper-responsive to external stimuli or changes in external circumstances so that the cats represented variety of emotional reactions [88]. Removal of both the cerebral cortex and the

striatum (the thalamus and hypothalamus were preserved) resulted in the cats walking incessantly, even though they did not attend to any environmental stimuli [87]. These findings suggest that cognitive and bodily functions are essential for the animal to adapt to external conditions. Adaptive capabilities are achieved mostly through motor behaviors that depend on factors such as the intention and the emotional state of individuals.

Based on the results of our recent studies [72, 80, 82] as well as those of previous works [17, 48, 61], our current perception of the neuronal pathways involved in motor control is illustrated in Fig.4. Locomotor behaviors require the recruitment of the activities of the entire nervous system as well as those of the musculoskeletal system. Sensory signals, derived from both external stimuli and internal visceral information, can further be used, and may have the following dual functions (Fig.4A). One is to generate cognitive cortical processing that is utilized for working memory and to guide future behavior. Another may affect the emotional and arousal states. Accordingly, animals initiate movements depending on either a *"volitional or cognitive motor reference"* (Fig.4Aa) or an *"emotional motor reference"* (Fig.4Ab) [72]. Consequently, goal-directed locomotor behaviors require the activation of the following three processes: (1) The "*initiation processes*" are derived from volitionally-elicited commands arising from the cerebral cortex and emotionally-triggered commands arising from the limbic- hypothalamus system. (2) Regardless of whether the locomotion is volitional or emotional, it is accompanied by movement processes that are automatically controlled by the "*execution processes*" in the brainstem and spinal cord, which include a locomotor rhythm generating system and muscle tone control systems (Fig.4B). (3) The "*regulation processes*" are driven by neural circuits involving the cerebral cortex, basal ganglia and cerebellum (Fig.4C).

3. BASIC LOCOMOTOR EXECUTION PROCESSES

For execution of locomotion, postural alteration is also required to generate rhythmic limb movements. This is achieved by integrative actions between "postural control systems" and "the locomotor (rhythm generating) system". The integrative actions operate at the levels of both the brainstem and spinal cord. Appropriate postural control requires the following three conditions: (1) development of postural muscle tone that is adequate enough to support body weight and maintain posture against gravity, (2) postural reflexes that sustain body equilibrium in response to environmental changes, and (3) acquisition of sensory information, including vestibular, visual, auditory, proprioceptive, and skin sensations. In addition to the above conditions, locomotor control at least requires the mechanisms of rhythm generation and dynamic postural equilibrium that enables to shift one's body forward.

3.1. Locomotor Regions

Locomotion-evoking regions have been identified in many animal species. Locomotor-related areas in the cat are illustrated in Fig.5A. These are the midbrain or mesencephalic locomotor region (MLR), the subthalamic locomotor region (SLR), and the cerebellar locomotor region (CLR). The

PPN also contributes to the modulation of postural muscle tone and locomotion [82].

The cat MLR is located in the lateral part of the midbrain (Fig.5A). When cats were decerebrated at the precollicular-postmammillary level (x in Fig.5A), the mesencephalic cats maintained a reflex standing posture (Fig.5Ba) due to decerebrate rigidity, characterized by tonic contractions of the hindlimb extensor muscles (Fig.5Ca). Repetitive electrical stimulation (10-50 μA and 20-50 Hz) of the MLR first increased the level of muscle tone (downward arrowhead in Fig.5Cb) and then initiated locomotion (Fig.5Bb, 5Cb), indicating that signals from the MLR may activate both the "*locomotor (rhythm generating) system*" and "*muscle tone excitatory system*" (Fig.5A). The locomotor-evoking sites in the cat midbrain, indicated by blue circles in Fig.5E, are mainly distributed to the area corresponding to the cuneiform nucleus (CNF) and vicinity in the dorsal part of the PPN. There are two major pathways descending from the MLR. One is via the medial medullary reticulospinal neurons descending in the ventrolateral funiculus and the other is via the pontomedullary locomotor strip descending in the dorsolateral funiculus. Both pathways activate the locomotor central pattern generator (CPG) in the spinal cord (see refs. [80, 82]). It was reported that patients with lesions in this area due to micro-infarction exhibited astasia, locomotor deficits, and gait ataxia with no signs of paralysis [21, 37]. Recently it was shown that combined deep brain stimulation of the dorsolateral midbrain and the subthalamic nucleus restored bipedal gait in patients with severe Parkinson's disease [69].

When decerebration was made at the precollicular-premammilary level (y in Fig.5A), the resulting subthalamic cats exhibited spontaneous locomotion on a moving treadmill (Fig.5Da). Thus, neurons responsible for evoking spontaneous locomotion appear to be located in the region between these two decerebrate levels, referred to as the SLR, which corresponds to the lateral hypothalamic area (Fig.5A). In these subthalamic cats, stimulation of the MLR increased locomotion, from that of fast walking to galloping (Fig.5Db). In addition, repetitive stimuli applied to the mid part of the hook bundle in the cerebellar white matter of the decerebrate cats also evoked locomotion on a moving treadmill [49]. This locomotor-evoking region is referred to as the CLR. Because locomotion was not eliminated after destruction of the bilateral MLR in cats with chronically implanted electrodes [49, 61], signals from the SLR and the CLR possibly evoke locomotion by activating the locomotor system arising from reticulospinal neurons in the medullary reticular formation (MRF). Pontomedullary reticulospinal tracts are involved in the activation of spinal rhythm generating systems [11] in addition to the control of postural muscle tone.

3.2. Muscle tone control systems

Muscle tone is regulated by both *excitatory* and *inhibitory* systems (Fig.5A). Muscle tone inhibitory regions are located in the midbrain, pons, and the medulla of the brainstem. As shown in Fig.5, stimulation of the PPN abolished postural muscle tone in the mesencephalic cat (Fig.5Cc) and suppressed spontaneous locomotion in the subthalamic cat (Fig.5Dc). The effective sites (red circles)

were located in the ventrolateral part of the PPN, where cholinergic neurons are abundantly distributed (Fig.5E). Thus, these inhibitory effects are possibly mediated by cholinergic PPN neurons that innervate the "*muscle tone inhibitory system*" (Fig.5A) [73, 74, 80, 86]. Although the neural architecture of the muscle tone inhibitory system is perceived somewhat differently among researchers, it is generally agreed that cholinoceptive pontomedullary reticular formation neurons excite medullary reticulospinal neurons [80, 82]. Stimulation of the dorsal part of the MRF (Fig.6B; red circles) completely abolished postural muscle tone developed in both forelimb and hindlimb extensor muscles (Fig.6Aa). MRF stimulation exerted postsynaptic inhibitory effects on both fore- and hindlimb motoneurons directly or via inhibitory interneurons [7]. The inhibitory reticulospinal tract descends in the bilateral ventrolateral funiculi and suppresses the excitability of α- and γ-motoneurons and interneurons mediating reflex pathways via inhibitory interneurons in Rexed lamina VII [75, 77, 79].

Reticulospinal neurons located in the ventral part of the MRF are possibly involved in muscle tone augmentation. In fact, stimulation of the ventral MRF (open squares in Fig.6B) increased the level of postural muscle tone in the mesencephalic cat (Fig.6Ab). Stimulation of the MRF also induced tegmental reflexes (filled triangles in Fig.6Ac) characterized by fore- and hindlimb flexion on one side and fore- and hindlimb extension on the opposite side [14, 19, 68, 77]. Although the stimulation sites for evoking these effects were intermingled, our studies demonstrated a gross topographical organization (Fig.6B). Namely, sites that decreased (filled circles) and increased muscle tone were roughly distributed in the ventromedial and dorsomedial areas, respectively. Electrical stimuli applied to the lateral and medial areas evoked opposite patterns of tegmental reflexes. Stimulation of the lateral area evoked flexion of fore- and hindlimbs ipsilateral to the stimulus side and extension of contralateral fore- and hindlimbs, while stimulation of the medial area often induced ipsilateral extension and contralateral flexion of fore- and hindlimbs.

In addition to the excitatory reticulospinal tract, monoaminergic descending tracts, such as the coerulospinal, raphespinal, and vestibulospinal tracts also operate as muscle tone excitatory systems. The coerulospinal tract arises from the locus coeruleus (LC) and uses noradrenalin as a transmitter. The raphespinal tract descends from the raphe nuclei (RN) and uses serotonin. There are reciprocal inhibitory interactions between the excitatory and inhibitory systems at the brainstem and spinal cord [80, 82]. The MRF neurons, constituents ~~in~~ of the inhibitory system, inhibit neurons in the LC and the CNF [41]. By contrast, monoaminergic projections from the LC and the RN [24] inhibit the activity of the cholinergic PPN neurons [33, 76, 84] and cholinoceptive pontine reticular formation (PRF) neurons.

Because the reticular formation receives efferents from the cerebral cortex, limbic system, hypothalamus, basal ganglia, and the cerebellum, these structures control postural and locomotor synergies through the descending pontomedullary reticulospinal tracts (Fig.6C). Moreover, various neurotransmitters modulate the activity of reticular formation neurons [80, 82] and control muscle

tone and locomotion. For example, the PRF is one of the major targets of cholinergic and monoaminergic projections [82]. This area receives cholinergic inputs from the PPN and the laterodorsal tegmental nucleus, and monoaminergic inputs from the RN and the LC. In mesencephalic cats, the cholinergic inputs reduced muscle tone and the monoaminergic inputs increased it [76], indicating that muscle tone is under the modulation of cholinergic-monoaminergic reciprocity that plays a key role in the control of vigilance states [59]. Another group of neurons containing orexin, a relatively newly discovered neuropeptide, is located in the lateral hypothalamic area [60, 66]. Orexinergic projections to the brainstem are implicated in feeding or appetitive behaviors [86], and those to the PRF, LC, and the RN also contribute to the control of vigilance states.

3.3. Generation of the Locomotor Rhythm and Pattern in the Spinal Cord and Roles of Sensory Information during Locomotion

Various combinations of spinal reflexes operate during locomotion. A combination of flexion reflex and crossed extension reflex constitutes the basic pattern of locomotor movements. Therefore, interneurons mediating these reflexes undertake major roles in the generation of locomotor rhythm and pattern. Most studies on central pattern generator (CPG) were performed in cats, and current understanding of the spinal locomotor network is shown in Fig.7A [41, 48, 61, 62]. The locomotor CPG is composed of spinal interneuronal networks that generate a detailed locomotor rhythm (Fig.7Aa) regardless of descending or afferent inputs. The rhythmic activities are then translated to second-order interneuronal groups (Fig.7Ab), which may shape “locomotor patterns” of each limb’s movements through their excitatory and inhibitory actions on target motoneurons. Reciprocal Ia interneurons, classical Ib interneurons and Renshaw cells are likely included in these second-order interneuronal groups; they are located in lamina IV-VII of Rexed and project to motoneurons innervating ipsilateral limb motoneurons. In contrast, lamina VIII interneurons project to the contralateral spinal cord and are implicated in the left-right alternations of limb movements during locomotion [40]. The spinal interneurons and motoneurons are excited by descending signals from the cerebral cortex and the brainstem, and are modulated by peripheral sensory afferent signals in a phase dependent manner during locomotion [62]. It should be noted that information concerning “locomotor rhythm and pattern”, which is determined by the interneurons, is then transmitted back to supraspinal structures (Fig.7Ac). Therefore, the brainstem, cerebellum, and the cerebral cortex monitor events in the spinal cord.

If not needed to generate basic locomotor patterns, what then are the roles of sensory information during locomotion? Afferent feedback from proprioceptive and skin receptors plays a crucial role in adapting and modulating the operation of the CPG in the real environment (Fig.7Ad) [62]. Sensory inputs can have global influences in allowing, preventing, or selecting motor patterns. For example, sensory inputs possibly participate in the correct positioning of the feet in uneven terrain or in response to obstacles. They also modify the frequency of the pattern, its intrinsic structure, or the

amplitude of muscle contractions. One immediately realizes the complexity of a situation in which sensory inputs of different modalities must be correctly interpreted while the limbs are continuously changing position during walking. There is thus a need for a great flexibility in the motor responses to sensory inputs during locomotion through dynamic sensorimotor interactions.

Supraspinal structures such as the cerebral cortex and the brainstem modulate the activity of the spinal rhythm generation systems (Fig.7A). In particular, the locomotor system arising from the MLR directly activates the first- and the second-order interneurons to generate locomotor rhythm and alter locomotor pattern [61, 62]. Because both excitatory and inhibitory muscle tone control systems act on interneurons as well as motoneurons (Fig.7B), the muscle tone control systems modulate locomotor rhythm and pattern during locomotion.

4. INITIATION OF LOCOMOTOR BEHAVIORS

There are two sets of behaviors for initiating motor behaviors [18]. One is the volitionally guided behaviors that require *"volitional or cognitive motor references"* (Fig.4Aa), which are produced by cognitive cortical processing utilized for working memory. The other is the emotional motor behaviors that are triggered by *"emotional motor references"* (Fig.4Ab), which are affected by the "emotional and arousal states" of the animal. In this section, we refer mechanisms of emotionally-triggered and volitionally-guided locomotor behaviors. In addition, roles of corticospinal and corticoreticular projections in the volitional locomotor control are discussed.

4.1. Emotional Motor Behaviors

The MLR was initially established as a functional region involved in the initiation of locomotion on the basis of its connections with limbic structures and the basal ganglia [3, 46]. Regardless of the nature of emotional stimuli, they usually elicit alert responses that produce stereotyped movements such as increased postural muscle tone or the locomotion that accompanies autonomic sympathetic responses. The limbic and hypothalamic systems play crucial roles in this process of emotional expression. Sinnamon [67] proposed the following three types of locomotor systems that function in different behavioral or motivational contexts; 1) an appetitive system, 2) a primary defensive system, and 3) an exploratory system.

The above proposition is supported by locomotor behaviors observed in alert animals. In cats with chronically implanted electrodes [50], stimulation of the SLR (the lateral hypothalamic area; Fig.8A) elicited alerting responses followed by exploratory (searching) or defensive behaviors (Fig.8B). Signals from the SLR are mediated by dense fibers in the medial forebrain bundle projecting to the midbrain, including the MLR, the PPN, and the MRF [61]. On the other hand, stimulation of the MLR abruptly elicited machine-like explosive locomotor behaviors (Fig.8C). Neural circuits connecting the nucleus accumbens (the oldest part of the striatum), the hippocampus, and the amygdala, are involved in emotional memory, and projections from the nucleus accumbens to the

MLR may contribute to the expression of exploratory behaviors [45]. Moreover, projections from the lateral and the medial hypothalamic areas to the midbrain (MLR) are thought to operate as defensive and appetitive systems, respectively [18, 28].

The orexin-containing neurons located in the prefornical lateral hypothalamic area (Fig.8D) are considered to control appetite, energy balance, and vigilance states via projections to various areas in the nervous system [60, 64, 66]. It was shown that orexinergic projections to the MLR facilitated the activity of the locomotor system [86], indicating that the hypothalamic orexinergic system contributes to appetitive behaviors depending on energy balance of the animal. However it has not been elucidated whether stimulation of the SLR activates orexinergic neurons in the lateral hypothalamic area.

4.2. Contribution of cerebral cortex to the initiation of volitional and cognitive behaviors

In experiments on cats with implanted electrodes (Fig.9Aa), the majority of motor cortical neurons exhibited simple rhythmic firing in relation to step cycles during steady-state locomotion. But their discharge rates increased considerably when the cats started to walk and had to accurately overcome obstacles (Fig.9Ab) [12]. Thus, commitment of cortical processing seems unnecessary during the automatic execution of locomotion. On the other hand, stepping movements that accompany accurate foot placement resemble the forelimb reaching of higher primates [13, 15]. Such an accurate movement requires visuomotor cognitive processes, which are controlled by neural circuits involving the cerebral cortex, basal ganglia, and cerebellum [43]. Subjects are aware of the locations of obstacles around them, and they can alter their stepping patterns even without available visual information about the location of the obstacles relative to the body. McVea and Pearson [42] reported that perturbing walking cats in a consistent manner evoked lasting changes to the walking pattern that were expressed only in the context in which walking was disturbed. Moreover, cats that had stepped over an obstacle remembered the location of the obstacle and could use working memory to guide stepping. Therefore, sensory inputs that signal context –the surrounding visual and auditory environment– play an important role in shaping the basic pattern of locomotion. Lajoie and Drew [32] observed, after unilateral lesion of area 5 of the posterior parietal cortex (Fig.9B), that cats frequently hit the obstacle as they stepped over it. They also frequently hit the obstacle with their hindlimbs even when the forelimbs negotiated the obstacle successfully. These findings suggest an important role for the posterior parietal cortex in the coordination of the forelimbs and hindlimbs and in the planning and programming of visually guided gait modifications (Fig.9C). Neuroanatomical studies indicate that the posterior parietal cortex sends selected projections to the motor cortical areas from layer III, while those to the lateral cerebellum via the pontine nuclei arise from layer V [2]. Neurons in motor cortical areas 4 and 6 project to spinal cord, and the reticular formation, respectively (Fig.9C) [39].

4.3. Role of Corticospinal and Corticoreticular Projections in the Volitional Locomotor Control

Activities of the cortical motor areas in higher primates have been examined in bipedally

walking monkeys. Microinjections of muscimol, which blocks specific forms of inhibitory neurotransmission, into the hindlimb region of the primary motor cortex (M1) resulted in local paresis of the contralateral hindlimb [54], while those into trunk/hindlimb regions of the supplementary motor area (SMA) did not paralyze limb movement, but disturbed postural control during walking [47]. The M1 and the SMA may, therefore, be involved in limb movements and postural control, respectively, during bipedal locomotion. The SMA sends dense projections to the pontomedullary reticular formation [29], while the M1 projects to the spinal cord. Because patients with damage to the premotor cortices, including the SMA, often exhibit freezing of gait or hesitation of gait initiation, premotor cortices may contribute to programming or planning of locomotion in addition to postural control [58]. The cortico-reticular projections are possibly involved in the postural preparation that precedes gait initiation. Although the PPN receive inputs from the motor cortical areas [38], role of these inputs in the locomotor and postural control has not been established.

Figure 10 summarizes the output from the motor cortical areas to the spinal cord and the brainstem in higher primates. Corticospinal tract neurons arising from the hand and leg regions of M1 descend in the contralateral dorsolateral funiculus of the spinal cord (Fig.10A). Corticospinal neurons in the hand region send their axons to the cervical cord and those in the leg region project to the lumbosacral cord where motoneurons innervating hand and leg muscles are located, respectively. Corticospinal tract neurons in the primary somatosensory cortex also project to the brainstem (dorsal column nuclei) and spinal cord (dorsal horn). Corticospinal tract neurons arising from the primary somatosensory cortex (S1) presynaptically modulates the activity of sensory afferents during movements, so they may contribute to allowing, preventing, and selecting motor patterns. In contrast, a large population of neurons in the leg region of the SMA and the dorsal premotor cortex (PMd) send projections to the pontomedullary reticular formation (corticoreticular projections; Fig.10B). Most reticulospinal neurons project bilaterally to all spinal segments from the cervical to the sacral cord and control motoneurons innervating neck, hand, trunk, and leg muscles. Such longitudinal and bilateral organization of the reticulospinal system is beneficial to control movements of the entire body during locomotion.

A similar organization of the cortico-reticular projections was observed in the cat. When a cat lifts its left or right forelimb, preceding or anticipating postural support is achieved by the other three limbs and the trunk. This postural control requires the recruitment of the enhanced activities of the cat premotor cortices, areas 6aβ and 6aγ, which correspond to the premotor area and the SMA of higher primates, respectively. Corticospinal neurons arise from area 4 in the cat. They descend in the contralateral dorsolateral funiculus and control discrete limb movements. Corticoreticular projections arise largely from areas 6aβ and 6aγ [39]. The pontomedullary reticulospinal tracts descend in the bilateral ventral and ventrolateral funiculi, innervate the entire spinal neuraxis (from cervical to sacral segments), and control trunk and proximal limb muscles. Particularly, neurons in cortical area 6aβ project to the medial part of the reticular formation, while those in area 6aγ project to both the medial

and the lateral areas of the reticular formation. Therefore, the cat premotor cortex may control postural muscle tone and postural figures (tegmental reflexes) via corticoreticular projections. These findings suggest the presence of functional organization in the corticoreticular projections; spread of corticoreticular projections in the dorsoventral and mediolateral directions may be involved in the control of postural muscle tone and postural figures, respectively (Fig.6), so that the cortico-reticular projections have crucial roles in the control of posture during volitionally guided locomotor control.

5. REGULATION OF LOCOMOTION PROCESSES

The basal ganglia and the cerebellum contribute to both the volitional and automatic aspects of locomotion. The current understanding is that neural circuits between the cerebral cortex and the basal ganglia and cerebellar loops are involved in the control of voluntary movements and automatic execution of learned motor plans and programs [23, 36, 43]. Neural circuits between the prefrontal cortex and the caudate nucleus and lateral zone of the cerebellar hemisphere are involved in the regulation of complex, visually guided limb movements and the planning and programming of those movements (cognitive loops) (Figs.11 and 12B). Neural circuits between motor cortical areas and the putamen and the intermediate zone of the cerebellum may contribute to the regulation of voluntary, discrete, ipsilateral limb movements (motor loops) (Fig.11 and 15A). Also the basal ganglia and the cerebellum project to the brainstem, contributing to appropriate regulation of automatic locomotor control. Importantly, the cerebellum receives massive real-time sensory inputs (Fig.4), while the basal ganglia does not receive sensory feedback. The basal ganglia receives “volitional reference” from the cerebral cortex and “emotional reference” from the limbic system (Fig.4). The basal ganglia also receives “reward signals” from the mesencephalic dopaminergic neurons (Fig.2B) [85].

5.1. Basal Ganglia Motor Circuits and the Brainstem-Spinal Cord Motor Systems

During the past decade, the cortico-basal ganglia loop (Fig.11) has come to be recognized as important for the volitional control of movement [1, 9]. When a subject encounters obstacles, each foot must be placed with a high degree of accuracy. The cortico-basal ganglia loop can help serve this purpose. On the other hand, steady-state locomotion can be brought about in the absence of conscious awareness by the basal ganglia outflow to the brainstem [74, 81].

Neural circuits within the basal ganglia are schematically illustrated in Fig.12A. The striatum of the basal ganglia receives excitatory inputs from the cerebral cortex (corticostriatal projections in Fig.11). Output from the basal ganglia is thought to be regulated by hyper-direct, direct, and indirect pathways (Fig.12A). The internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) are output nuclei that inhibit target neurons in the thalamus and brainstem via tonically active GABAergic neurons thus preventing unnecessary movements (Fig.12B) [22]. Signals from the motor cortices first increase the basal ganglia output by activating a hyper-direct pathway from the cerebral cortices to the STN so that the excitability of the target system is further

reduced (Fig.12Ba) [55, 56]. Signals via the direct pathway from the striatum to the GPi/SNr remove this sustained inhibition, thus disinhibiting the target motor systems (Fig.12Bb) [22]. That is, the phasic activity of GABAergic output neurons in the striatum, which are mostly silent, interrupts the tonic GPi/SNr inhibition, thus allowing movements to occur [22]. Finally, signals via the indirect pathway, involving the external segment of the globus pallidus (GPe) and the STN, reestablishes inhibition of the target systems (Fig.12Bc). This sequential information processing enhances the temporal contrast of the excitability of the target motor system; the cerebral cortex and the brainstem. An enhancement of tonic inhibition and a release from inhibition (disinhibition) are key mechanisms of basal ganglia control of movements. The sequential processing ensures that only the selected motor program is initiated, executed, and terminated at the appropriate times, whereas other competing programs are canceled. Nigrostriatal dopaminergic neurons excite direct pathways via D1 receptors but inhibit indirect pathways by acting on D2 receptors. Therefore a decrease in dopamine may facilitate the indirect pathway and suppress the direct pathway, resulting in an increase in GABAergic output from the GPi/SNr.

The above mechanisms may also act on brainstem networks, including the muscle tone control system and locomotor system. Takakusaki et al. [74, 78, 81, 83] demonstrated in the decerebrate cat that the GABAergic basal ganglia output from the SNr to the MLR/PPN controlled locomotion and muscle tone. In the mesencephalic cat, stimulation of the SNr alone did not change muscular activity; however, it did alter MLR-induced locomotion. It reduced the number of step cycles, increased the duration of the stance phase, and disrupted the rhythmic alternation of limb movements. The onset of the locomotion was delayed by SNr stimulation of progressively increasing strength. Moreover stimulation of the SNr attenuated and blocked PPN-induced muscle tone suppression. There is a functional topography in the nigrotegmental projection; medial and lateral SNr projections to the MLR and the PPN control locomotion and muscle tone, respectively [74, 81, 83]. These findings suggest that the basal ganglia-brainstem system (BG-BS system in Fig.11) contributes to the control of postural muscle tone, rhythmic limb movements during walking, and gait initiation.

Thus, these brainstem systems can be coupled with basal ganglia motor circuits in a unified model (Fig.12A). In this combined model, the basal ganglia output controls the MLR for locomotion and the inhibitory region of the PPN for muscle tone. When locomotor movement is in preparation, tonic activity of SNr neurons would continuously inhibit both systems. Once a trigger signal comes in, the hyper-direct pathway would enhance the inhibition. Then the direct pathway would release the activity of these systems, resulting in initiation of locomotion accompanied by a smooth reduction of muscle tone. To terminate locomotion, the direct pathway may inhibit each system, holding up rhythmic movements and increasing the level of muscle tone. A parallel organization of circuits from the SNr to the MLR/PPN would, therefore, be beneficial to regulate the level of muscle tone that accompanies the initiation and termination of locomotion [78].

5.2. Basal Ganglia Control of Movements and Pathophysiology of Parkinson Disease

Based on these considerations, we propose a model for how the basal ganglia integrates the volitional and automatic control of movement (Fig.13A). A cortico-basal ganglia loop is involved in the control of movements that requires volition, cognition, and attention. In contrast, the basal ganglia-brainstem system contributes to the automatic regulation of muscle tone and rhythmic limb movements. The PPN and the pontomedullary reticular formation receive corticofugal inputs mainly from the premotor cortices, including the SMA and the PMd (Fig.10B) [29, 38, 39]. The muscle tone inhibitory system and the locomotor system are consequently under the influence of both a *net* cortical excitation and basal ganglia inhibition. Motor cortical areas receiving basal ganglia outputs use the corticospinal tract to control the velocity and amount of voluntary movement. In contrast, the BG-BS system controls locomotion and muscle tone via the MLR/PPN (Fig. 13A). If this model is correct, how are motor disturbances induced in basal ganglia disorders? Basal ganglia disorders are manifested by an inability to initiate voluntary movements, an inability to suppress involuntary movements, an abnormality in the velocity and amount of movement, and an abnormal muscle tone [57, 63]. Gait failure with postural instability is also a major impediment of Parkinson's disease [20, 51, 53]. Following the model proposed above, and as shown in Fig.13B, GABAergic basal ganglia output is thought to be overactive in Parkinson's disease [1, 9]. The excessive GABAergic inhibition upon thalamocortical neurons decreases the velocity (bradykinesia) and the amount of movement (hypokinesia). The increase in GABAergic inhibition together with a concomitant decrease in cortical excitation to the PPN-influenced muscle tone inhibitory system consequently increases the level of muscle tone (hypertonus). The effect of GABAergic inhibition on the MLR-implicated locomotor system also disturbs gait performance. Additionally, decreased activity of the premotor cortices disturbs the motor programming for precise gait control [20, 58]. Excessive inhibition of the prefrontal and limbic systems reduces the expression of will or intention and emotion. In contrast, following the same model, decreased output from the basal ganglia in Huntington's disease increases the velocity and amount of movements (hyperkinesia) and reduces the level of muscle tone (hypotonus). In summary, the above model (Fig.13A and B) provides a rational explanation of the pathogeneses of basal ganglia disorders such as the hypokinetic-hypertonic syndrome (Parkinsonism) and various hyperkinetic-hypotonic syndromes (Huntington's chorea, ballism, L-DOPA-induced dyskinesia) [81].

Recently, Stefani et al. [69] demonstrated that deep brain stimulation of the mesopontine tegmentum, which possibly included both the PPN and the MLR in addition to the STN, ameliorated and recommenced gait failure and postural instability of Parkinson's disease patients. This important clinical finding substantiated the findings obtained from animal studies [74, 78, 83], and further supports the above hypothesis that the brainstem motor system is strongly inhibited in Parkinson's disease.

5.3. Cerebellar Control of Posture and Locomotion

Generally, the cerebellum contributes to the control of posture (equilibrium and muscle tone) and rhythmic limb movements during locomotion and to visual guided locomotion [52]. There is a functional organization within the cerebellum, and sensory feedback signals play key roles in cerebellar function.

The cerebellum is located dorsal to the brainstem, connected to it by the cerebellar peduncles (Fig.14A). The cerebellum receives massive proprioceptive information via the inferior cerebellar peduncle. Efferents from the brainstem project to the cerebellum via the middle cerebellar peduncle. The superior cerebellar peduncle mainly contains fibers projecting from the cerebellum to the thalamus and the brainstem. The input-output organization of the cerebellum is summarized in Fig.14B and C. There are abundant inputs from primary motor cortex to the medial and intermediate zones of the cerebellum, establishing a somatotopographical representation in the cerebellum. The medial zone (vermis and fastigial nuclei) receives afferent information from primary visual, auditory, vestibular, and somatosensory structures and projects mainly back to the vestibular nuclei and reticular formation of the brainstem and a bit more sparsely to the motor cortical regions via thalamus. The medial zone regulates automatic aspects of controlling posture, equilibrium, and limb movements during locomotion. In addition to efferents from the motor cortex to the medial part of the cerebellum, these massive sensory inputs may trigger locomotion as described in section 3.1. The intermediate zone (intermediate hemisphere and interpositus nuclei) receives most of its afferent information from somatosensory receptors in the limbs and projects both to motor cortical regions via thalamus and to brainstem regions. Control of discrete, ipsilateral limb movements and reflexes is relatively localized to the intermediate zone. The lateral zone of the cerebellum (lateral hemisphere and dentate nuclei) receives afferents from motor, premotor, and prefrontal cortical regions and projects back to them via thalamus [43]. The lateral zone controls complex, visually guided limb movements and the planning of those movements, and may therefore help to control locomotion, particularly when adjustment of the motor output to novel contexts and/or strong visual guidance is required [4, 35].

Basically, the cerebellum operates as a “comparator” for the control of movements (Fig.15A). The spinocerebellum, the medial and intermediate zones of the cerebellum, compares command signals from the cerebral cortex (*internal feed back or efferent copy*) with sensory feedback from the spinal cord (*external feedback or afferent copy*). After comparing these two signals and calculating the difference, the cerebellum sends the “compensated signals” to the cerebral cortex and the brainstem so that “discrete limb movements” and “posture and locomotion”, respectively, can be appropriately altered. If one intends to learn new motor acts, “instruction” signals in the prefrontal cortex activate inferior olivary neurons (Fig.15B). Climbing fibers from the interior olive strongly alter the firing patterns of Purkinje cells from simple spikes to complex spikes by direct synaptic actions, which then changes output from the cerebellum so that activity of the motor cortical neurons can be altered to achieve the required motor action. According to the progress of the learning process,

the occurrence of complex spikes gradually decreases [30, 31]. Such alterations in Purkinje cell firing patterns is induced by synaptic plasticity, so-called long-term depression, which is induced by the simultaneous activation of parallel and climbing fiber synapses on the identical Purkinje cells [26]. It is therefore agreed that long-term depression is the basis of the cerebellar contribution to the motor learning [27]. Because sensory afferents from spinal cord projecting to the inferior olive also modulate the activity of climbing fibers, sensory input may be involved in the motor learning process [89].

5.4. Cerebellar Gait Ataxia

Lesions in the cerebellum, in particular in the medial and intermediate regions, often disturb smooth limb movements and stable posture. Locomotor abnormalities often occur after cerebellar damage and are characterized by a veering, stumbling path, wide base of support, impaired multi-joint coordination, decomposition of joint movements in the leg, and irregular and more variable foot placement. These features of cerebellar gait ataxia were associated with a primary impairment of balance and/or limb coordination [52]. Bipedal human locomotion is less stable than quadrupedal animal locomotion and likely requires additional descending cerebral cortical control. For example, subjects with cerebellar damage lacked foot-placement accuracy when using visual guidance to step on targets during walking [8]. Bipedal locomotion therefore possibly requires additional contributions from the lateral cerebellum that are less critical in quadrupedal locomotion. Cerebellar deficits during human locomotion might also be associated with voluntary, visually guided leg coordination deficits.

6. HOW DOSE THE FOREBRAIN INITIATE, INTEGRATE AND SELECT LOCOMOTOR BEHAVIOR?

Finally, there is a need to discuss how the forebrain initiates, integrates**,** and selects adaptable locomotor behaviors. Emotional locomotor behaviors are enabled by signals from the limbic system to the MLR [67]. However, goal-directed locomotor activities require the activation of non-limbic systems. Neural circuits connecting the cerebral cortex with the basal ganglia and the cerebellum facilitate accurate cognitive operations [43]. Visual sensation is particularly critical for gait modification. For example, the deficiency of parkinsonian gait is dramatically overcome if the floor is grid-patterned, or a transverse-strip is used (Paradoxical gait). Using positron emission tomography, Hanakawa et al. [20] observed that activities of the left parieto-occipital and right prefrontal cortices were increased during paradoxical gait. The results indicated that the circuits are involved in the generation of a *"volitional and cognitive motor reference"*. Although memories of volitional behavior require activity of the non-limbic sensorimotor system, unconscious and motivational limbic influences, such as the *"emotional motor references"*, are needed to enact any motor plans. So that the limbic system can influence the sensorimotor system, an integrated "*gating function*" must operate between the limbic system and non-limbic structures.

Here we refer to a “gating mechanism at the midbrain”. The midbrain receives excitatory inputs from the cerebral cortex and the limbic system, and inhibitory inputs from the basal ganglia (Fig.13A). The basal ganglia also has connections with the cerebral cortex and limbic structures; emotional signals from the limbic-hypothalamus and volitional signals from the cerebral cortex may be modulated by basal ganglia output. Therefore we hypothesize that an increase in basal ganglia output to the limbic system and a decrease in output to the cerebral cortex induce purposeful goal-directed locomotor behaviors depending on the volitional and cognitive motor references (Fig.16A). In contrast, emotional motor references may trigger emotional motor behaviors by an increase in basal ganglia output to the cerebral cortex and a decrease in output to the limbic system (Fig.16B). Consequently, whether the subject expresses volitional or emotional behavior is determined by which of the activities of the above motor references is more dominant, which depend on the internal and external states of the subject. Dopamine may be involved in this determination process, because the dopaminergic projections innervate the prefrontal cortex and the limbic system in addition to the basal ganglia (Figs.2B and 13A). In Parkinson’s disease, activity of the cerebral cortex and the limbic system may be reduced not only by less dopamine effects on these structures, but also by excessive inhibitory effects from the basal ganglia. It follows that both volitional and emotional expressions may be reduced in parkinsonian patients (Fig.13B). Nevertheless, specific sensory signals can elicit sensory-guided movements such as the paradoxical gait ~~as~~ described above. I suppose that the paradoxical motor performance may be induced by the increased activities of cortical and subcortical structures by the sensory signals.

As a consequent, basal ganglia efferents to both the forebrain and the midbrain may have a role in the selection of volitionally-initiated and emotionally-triggered behavior so as to elicit a variety of locomotor behaviors, depending on the behavioral context. Rational gating mechanisms may exist in the forebrain. Nonetheless, it is not yet known how rational and emotional behaviors are selected at the level of the forebrain, between the limbic system and prefrontal cortex, depending on the information of past memory and real time working memory [18]. Finally I would like to mention that in humans, understanding the “gating mechanisms” at the level of the forebrain may require an understanding of the psychological processes of conflict between reason and emotion [72].

7. CONCLUDING THOUGHTS

In this review, many schemas were presented to facilitate a broad range of readers’ interpretation of the neural mechanisms of adaptable motor behaviors. Obviously, some of these schemas are incomplete and over-specified. To test their validity, it is necessary to formulate computational models based on the schemas and simulate the experimental results. Recently, Stuart [71] reviewed the history of integrative and comparative movement neuroscience. This article will provide some insights into how interdisciplinary researches, such as that between the fields of neurobiology (neuroscience) and engineering, should be integrated.

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Figure legends

Figure 1. Diagram of triune development of primate brain modified from MacLean (1985)
The forebrain itself evolves and expands along the lines of three basic formations that reflect ancestral commonalities with replies, early mammals and late mammals. Evolutional changes in posture and movements of animals are recapitulated by developmental changes in posture and movements of humans after birth.

Figure 2. Mechanisms of arousal and attention
A. Ascending reticular activating system (ARAS) arises from the reticular formation and continuously activates background excitability of subcortical and cortical structures via non-specific thalamic nuclei so as to maintain arousal level during wakefulness. B. The pedunculopontine tegmental nucleus (PPN), a part of the ARAS, excites dopaminergic neurons in the *substantia nigra pars compacta* (SNc) and the ventral tegmental nucleus (VTA) through cholinergic (ACh) and glutamatergic (Glu) projections. The dopaminergic neurons, in turn, project to the striatum of the basal ganglia, the limbic system, and the prefrontal cortex, controlling motor function and emotional and attentive states. C. Roles of sensory information. Both special and somatosensory sensations modulate the activity of neurons in the spinal cord, brainstem, limbic-hypothalamic system and the cerebral cortex.

Figure 3. Role of forebrain structures in the expression of locomotor behaviors.
A. Visually-determined cortical automatism was observed in cats following bilateral removal of the caudate nucleus (striatum), a major constituent of the basal ganglia (acaudate cat). B. When cerebral cortex was totally removed (striatal or decorticate cat), cats displayed a variety of emotional behaviors. C. After removal of both the cerebral cortex and the caudate nucleus, the cats walked incessantly regardless of which environmental stimuli were presented. Removed areas are indicated by shade. Abbreviations. Acc, nucleus accumbens; Hypoth., hypothalamus; SN; substantia nigra; Th, thalamus.

Figure 4. Framework of motor control systems
Sensory signals from the external and internal environments may act on the cerebral cortex to generate cognitive processing, and on the limbic system to affect emotional states. A. Movements are initiated depending on either a volitional and cognitive motor reference (a) or an emotional motor reference (b). B. The basic locomotor execution system is located in the brainstem and spinal cord. C. Movements are regulated by neural loops involving the cerebral cortex, basal ganglia, cerebellum, brainstem, and spinal cord. The basal ganglia and the cerebellum play important roles in the regulation of movements.

Figure 5. Locomotor-related areas in the cat
A. Locomotion-related areas are the midbrain or mesencephalic locomotor region (MLR), the subthalamic locomotor region (SLR), the cerebellar locomotor region (CLR), and the pedunculopontine tegmental nucleus (PPN). Decerebration at the precollicular- postmammillary level (x) results in a mesencephalic cat, and at the precollicular- premammillary level (y) in a subthalamic cat. Signals from each region activate the locomotor system and the muscle tone excitatory system to evoke locomotion. Signals from the PPN activate the muscle tone inhibitory system and suppress postural muscle tone. Signals from the motor cortical areas act on neurons in the SLR, the brainstem, and the spinal cord. The motor cortical areas receive efferents from the visual cortex. B. Changes in posture and movements in the decerebrate cat. (a) Reflex standing posture observed in the mesencephalic cat (b) Stimulation of the MLR in the mesencephalic cats evoked locomotion on a treadmill. However, subthalamic cats displayed spontaneous locomotion. (c). Stimulation of the PPN

induced muscle tone suppression in both mesencephalic and the subthalamic cats. C. EMG activities of left (L) and right (R) soleus muscles of the mesencephalic cat. (a) Tonic muscle contractions were observed during reflex standing. (b) Stimulation of the MLR first increased muscle tone (arrowhead) and then evoked locomotion. (c) Tonic EMG activity was completely abolished by stimulating the PPN. D. Soleus EMG activities of the subthalamic cat. (a) Spontaneous locomotion on a treadmill. (b) Stimulation of the MLR altered locomotor patterns from that of fast walking to galloping. (c) The spontaneous locomotion was completely removed by stimulating the PPN. E. A parasagittal plane of the midbrain showing effective stimulus sites for evoking locomotion (blue circles; cuneiform nucleus: CNF) and muscle tone suppression (red circles; PPN) in decerebrate cats.

Figure 6. Effects of electrically stimulating the medullary reticular formation in decerebrate cats.
A. Electromyographic activities were recorded bilaterally from the triceps brachial (forelimb extensor) muscles and soleus (hindlimb extensor) muscles. Repetitive electrical stimulation (50 Hz and 40 μA for 10 seconds) suppressed (a) and increased (b) forelimb and hindlimb extensor muscle tone. The medullary stimulation also induced a tegmental reflex, characterized by activation of the right triceps brachial muscle and ~~a~~ suppression of the right soleus muscle (c). B. Functional topography of the reticular stimulus effects. A total suppression (muscular atonia) or a decrease (hypotonia) in forelimb and hindlimb muscle tone was induced by stimuli applied to the dorsomedial part of the medullary reticular formation (filled circles) corresponding to the nucleus *reticularis gigantocellularis* (NRGc). On the other hand, an increase in muscle tone was induced by stimuli applied to the ventromedial part of the medulla (open squares) corresponding to the nucleus *reticularis mangocellularis* (NRMc). Stimulation of the lateral medulla elicited the tegmental reflex (filled triangles). C. The brainstem reticular formation receives efferent connections from the cerebral cortex, the hypothalamus and limbic system, the basal ganglia, and the cerebellum, all of which are involved in the control of postural muscle tone. Abbreviations; IO, inferior olive; MLF, medial longitudinal fasciculus; NRPv, the nucleus *reticularis parvocellularis*. P, posterior. This figure is modified from Habaguchi et al. [19].

Figure 7. Spinal mechanisms of sensori-motor integration responsible for locomotor movements
A. Spinal interneurons are involved in the generation of locomotor rhythm (a) and pattern formation (b). These signals are then transmitted to spinal motoneurons (E and F) to evoke muscle contraction. The cerebral cortex and the brainstem receive visual, auditory, vestibular somesthetic, and proprioceptive afferents and send descending signals to both the spinal interneurons and the motoneurons. Sensory afferents such as proprioceptive and cutaneous afferents (d) affect the activity of both interneurons and motoneurons. Information from the spinal interneurons is also transmitted to the supraspinal structures via ascending tract neurons (c). B. Descending signals from the MLR excite spinal interneurons to generate locomotor rhythm and pattern. Both excitatory and inhibitory muscle tone control systems act on both interneurons and motoneurons so that both systems modulate the rhythm and pattern of locomotion in addition to controlling the level of postural muscle tone. Abbreviations; CPG, Central pattern generators; E, extensor motoneurons; F; flexor motoneurons; Ia, group Ia muscle afferent; Ib, group Ib muscle afferent; II, group II muscle afferent. This figure is partly modified from Rossignol et al. [62].

Figure 8. Emotional motor behaviors induced by stimulating the SLR and the MLR.
A. Parasagittal plane of the cat brain showing the subthalamic locomotor region (SLR, green) and the midbrain locomotor region (MLR, blue) B. Stimulation of the SLR in chronically implanted cats first induced an alerting response followed by exploratory locomotor behaviors. C. Stimulation of the MLR elicited machine-like explosive locomotor behaviors. D. Orexinergic system. A light

microscopic photograph shows orexin neurons located in the prefornical lateral hypothalamic area. Orexinergic neurons project to most brain areas. B and C are modified from Mori et al. [50].

Figure 9. Cortical control of locomotion
A. Activities of motor cortical neurons during an obstacle avoidance task on a treadmill. (a) Locomotor preparation. (b) From top to bottom, activities of two cortical neurons were simultaneously recorded in the cat primary motor cortex, electromyographic activities of forelimb (CIB) and hindlimb (ST, Srt, and VL) muscles. Firing rates increased when the cat was avoiding the obstacle. (b) is modified from Drew et al. (1996). B. Lesions in the bilateral parietal cortices disturbed the obstacle avoidance task. C. Visuomotor cortical processing may have been mediated by pathways from the visual cortex to the motor cortices (areas 4 and 6) via the parietal cortex (area 5). Abbreviations; CIB, cleidobrachialis; ST, semitendinosus; Srt, sartorius; VL, quadriceps, *vastus lateralis*. This figure is modified from Drew et al. [12].

Figure 10. Organizations of corticospinal (A) and corticoreticular (B) projections
A. Corticospinal neurons arising from the hand (green) and leg (blue) regions of primary motor cortex (M1) descend in the contralateral dorsolateral funiculus of the spinal cord, and control hand motoneurons in the cervical cord and leg motoneurons in the lumbosacral cord, respectively. Neurons in the primary somatosensory cortex (S1; red) also project to the brainstem (dorsal column nuclei) and spinal cord (dorsal horn). B. Corticoreticular projections arise mainly from the supplementary motor area (SMA) and the dorsal premotor cortex (PMd). Most reticulospinal neurons ~~p~~project bilaterally to entire spinal segments from the cervical to the sacral cord and control motoneurons innervating neck, hand, trunk, and leg muscles.

Figure 11. Input-output organizations of the basal ganglia
The basal ganglia (BG) receives inputs from the cerebral cortex (corticostriatal projections) and sends outputs to the cerebral cortex via the thalamus (thalamocortical projections) and to the midbrain of the brainstem. The former constitutes the so-called cortico-basal ganglia loops and the latter the basal ganglia-brainstem (BG-BS) system. There are two major cortico-basal ganglia loops. One is a “motor loop” (blue arrows) between motor cortical areas and the putamen. The other is the “cognitive loop” (green arrows) between prefrontal cortex and the caudate nucleus. Internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) are output nuclei of the basal ganglia. Neurons in these nuclei use GABA as a neurotransmitter and inhibit their target neurons in the thalamus and the midbrain. Outputs from the basal ganglia control the activity of pyramidal neurons in the motor-related areas, which project to the spinal cord via the corticospinal tract and to the reticular formation through the corticoreticular projections. Basal ganglia outputs also affect the activity of midbrain neurons in the MLR and the PPN which project to the spinal cord through the reticulospinal tract neurons in the pontomedullary reticular formation (PMRF). Abbreviations; GABA, gamma-amino butyric acid; VA, ventroanterior nucleus of the thalamus; VL, ventrolateral nucleus of the thalamus.

Figure 12. Possible neural connections between the basal ganglia-thalamocortical loop and the brainstem motor systems.
A. A composite model of basal ganglia motor circuits and brainstem-spinal pathways for controlling locomotion, muscle tone and voluntary movements. (+) indicate excitatory, and (-) inhibitory synaptic connections. B. Basal ganglia modulation of target motor systems. Upper and lower schematic graphs indicate the level of the basal ganglia output and the excitability of target systems, respectively. As basal ganglia output is inhibitory, increased output (a and c) results in decreased excitability of the

target systems, while decreased basal ganglia output allows movements to occur (b). Abbreviations, D1; dopamine 1 receptors, D2; dopamine 2 receptors, DA; dopamine, enk; enkephaline, GABA; gamma-amino butyric acid, glu; glutamate, GPe, external segment of the globus pallidus, GPi; internal segment of the globus pallidus, SC; superior colliculus, SNc, substantia nigra pars compacta; STN, subthalamic nucleus, Sub P; substance P. This figure is modified from Takakusaki et al. [81].

Figure 13. A. Hypothetical model of basal ganglia regulation of motor control. B. Mechanisms of less volitional and emotional behavioral expressions in patients of Parkinson's disease. This figure is modified from Takakusaki et al. [72]

Figure 14. Input-output organizations of the cerebellum
A. Gross anatomy of the cerebellum and related structures. B. Input to the cerebellum. The vermis and intermediate regions of the cerebellum receive inputs from the spinal cord and the trigeminal nucleus. The vermis also receives visual, auditory, and vestibular inputs. The lateral part of the cerebellum receives inputs from the cerebral cortex via the pontine nucleus (corticopontine inputs). The floccules receives inputs from vestibular organs. C. Output from the cerebellar nuclei. Outputs from the floccules control balance (postural equilibrium) and eye movements via the vestibular nuclei. Outputs from the vermis to the brainstem control posture and locomotion via the fastigial nucleus. Outputs from the intermediate region to the motor cortex and the red nucleus contribute to the control of precise limb movements via the interposed nuclei. Outputs from the cerebellar hemisphere to the motor and premotor cortices are involved in motor planning.

Figure 15. Role of neural circuits connecting cerebellum with cerebral cortex, brainstem, and spinal cord.
A. Motor control by the cerebellum. The cerebellum receives internal feedback (copies of motor command; a) from the motor cortex via the pontine nucleus (1) and external, movement-related feedback (sensory feedback; b), from the spinal cord (2). The cerebellum compares these signals (3), calculates the difference between the two signals (3) and sends compensated signals (c) to the brainstem and the cerebral cortex via the ventrolateral nucleus (VL) of the thalamus. Therefore the cerebellum operates as comparator to control movements. B. Motor learning by the cerebellum. Novel instructions to the prefrontal cortex activate inferior olivary neurons, which send projections to the cerebellum via the climbing fibers. Activities of the climbing fibers alter the firing properties of Purkinje cells in the cerebellum, from simple spikes to complex spikes. Motor commands arising from the motor cortices may, in turn, be modulated by the alteration of cerebellar output to the cerebral cortex. Repetition of these processes may finally alter the motor command so as to execute novel motor acts according to the instructions. Firing properties of the Purkinje cells are returned to simple spiking after learning the novel actions.

Figure 16. Hypothetical mechanisms of initiation, integration and selection of locomotor behaviors.
A and B. Mechanisms of volitional and cognitive motor behaviors (A) and emotional motor behaviors (B). This figure is modified from Takakusaki et al. [72].

Figure 1

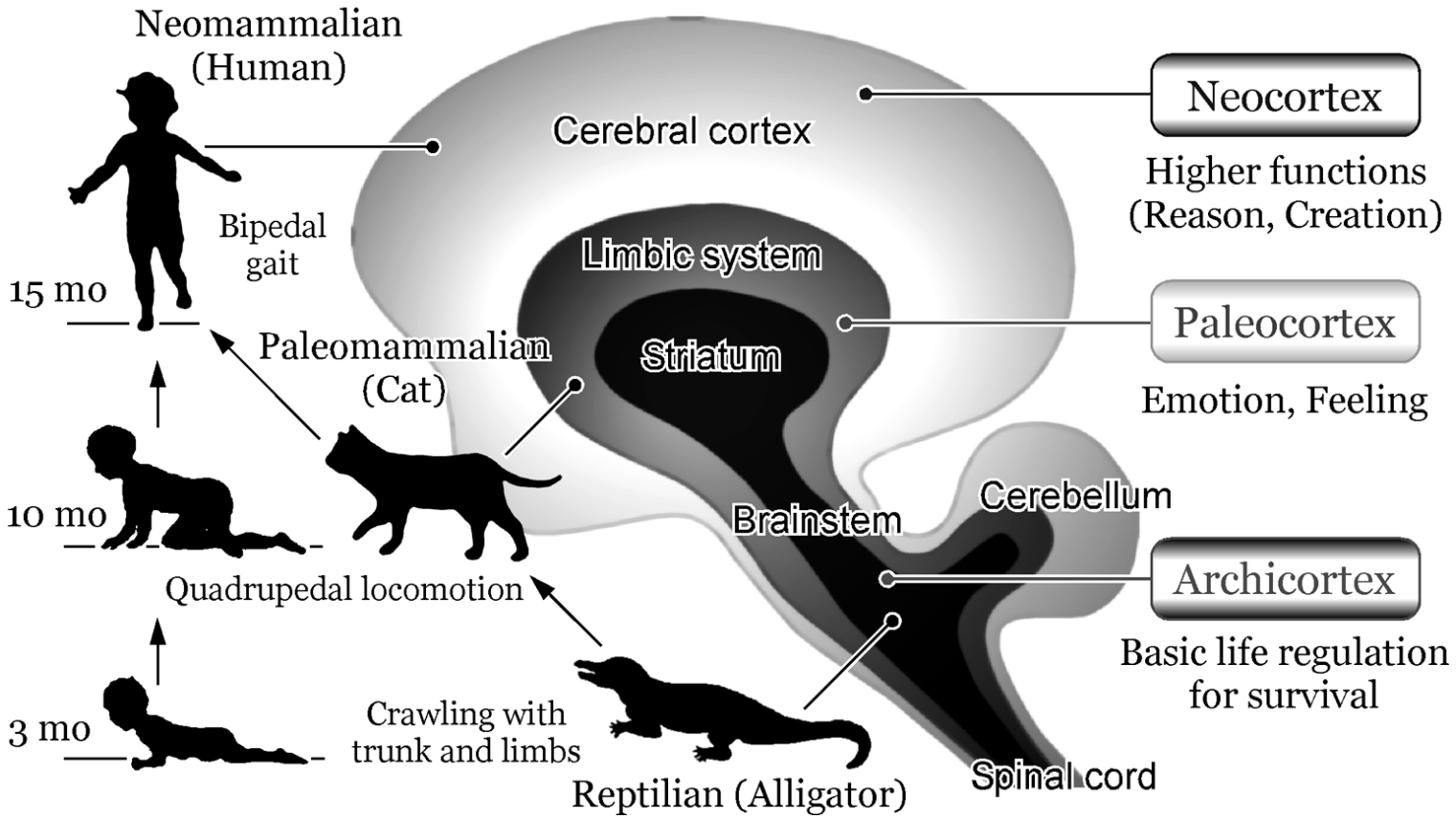
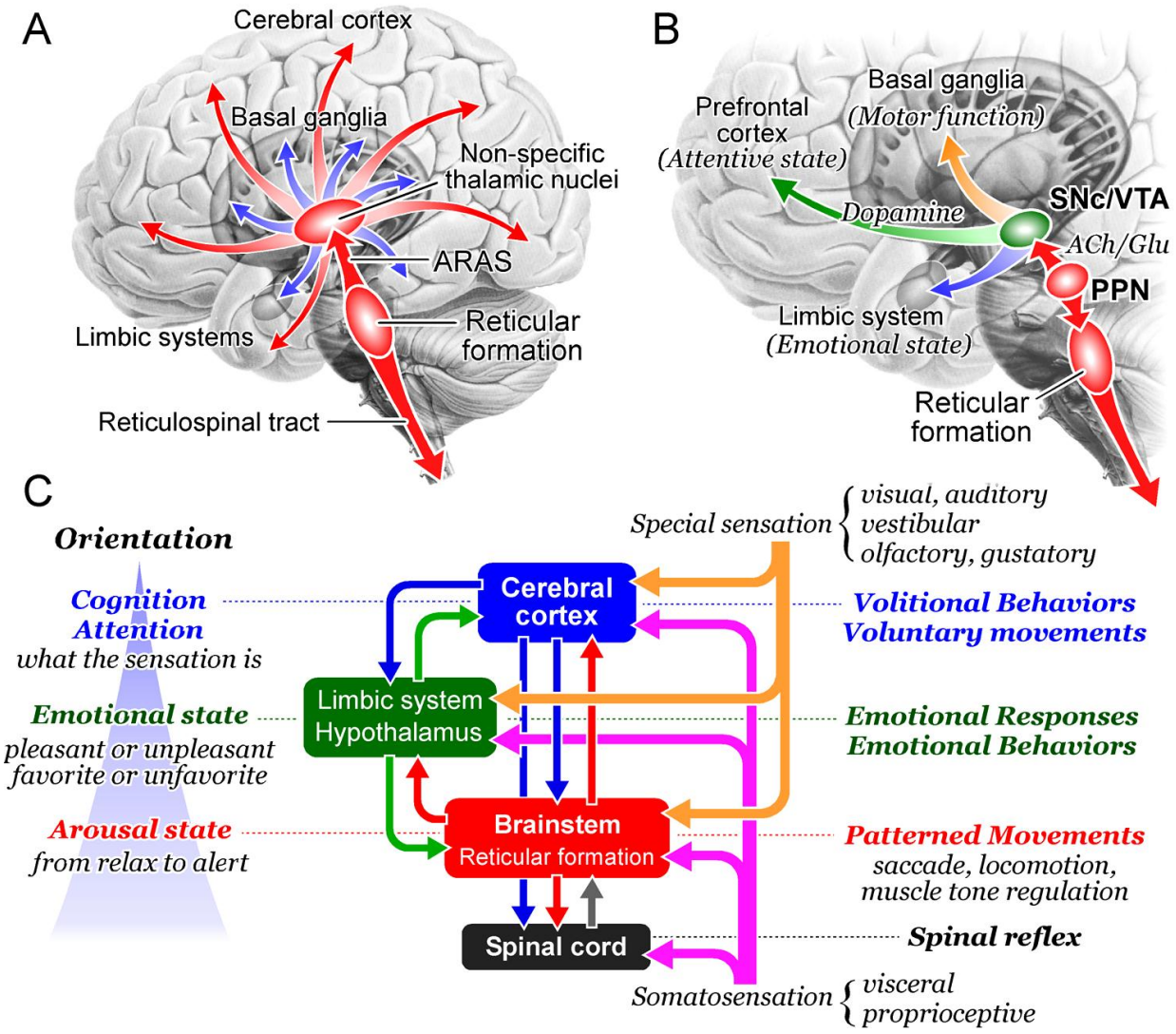

Neomammalian
(Human)
Bipedal
gait
15 mo
Paleomammalian
(Cat)
10 mo
Quadrupedal locomotion
3 mo
Crawling with
trunk and limbs
Reptilian (Alligator)
Cerebral cortex
Limbic system
Striatum
Brainstem
Cerebellum
Spinal cord
Neocortex
Higher functions
(Reason, Creation)
Paleocortex
Emotion, Feeling
Archicortex
Basic life regulation
for survival

Figure 2


A
Cerebral cortex
Basal ganglia
Non-specific thalamic nuclei
ARAS
Reticular formation
Limbic systems
Reticulospinal tract
B
Basal ganglia
(Motor function)
Prefrontal cortex
(Attentive state)
Dopamine
SNc/VTA
ACh/Glu
PPN
Limbic system
(Emotional state)
Reticular formation
C
Orientation
Cognition
Attention
what the sensation is
Emotional state
pleasant or unpleasant
favorite or unfavorite
Arousal state
from relax to alert
Special sensation
visual, auditory
vestibular
olfactory, gustatory
Cerebral cortex
Limbic system
Hypothalamus
Brainstem
Reticular formation
Spinal cord
Volitional Behaviors
Voluntary movements
Emotional Responses
Emotional Behaviors
Patterned Movements
saccade, locomotion,
muscle tone regulation
Spinal reflex
Somatosensation
visceral
proprioceptive

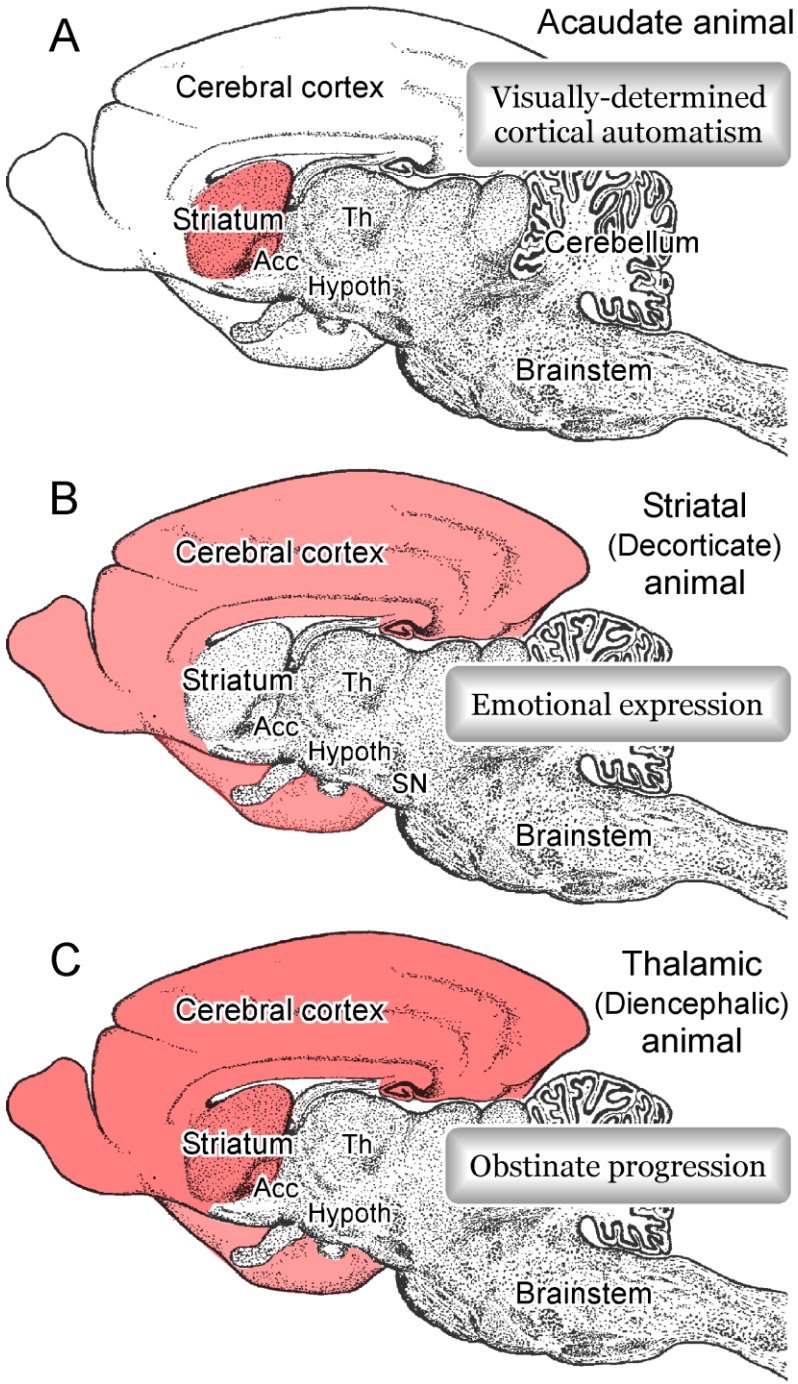

A
Acaudate animal
Cerebral cortex
Visually-determined cortical automatism
Striatum
Th
Cerebellum
Acc
Hypoth
Brainstem
B
Striatal (Decorticate) animal
Cerebral cortex
Striatum
Th
Emotional expression
Acc
Hypoth
SN
Brainstem
C
Thalamic (Diencephalic) animal
Cerebral cortex
Striatum
Th
Obstinate progression
Acc
Hypoth
Brainstem

Figure 3

Figure 4

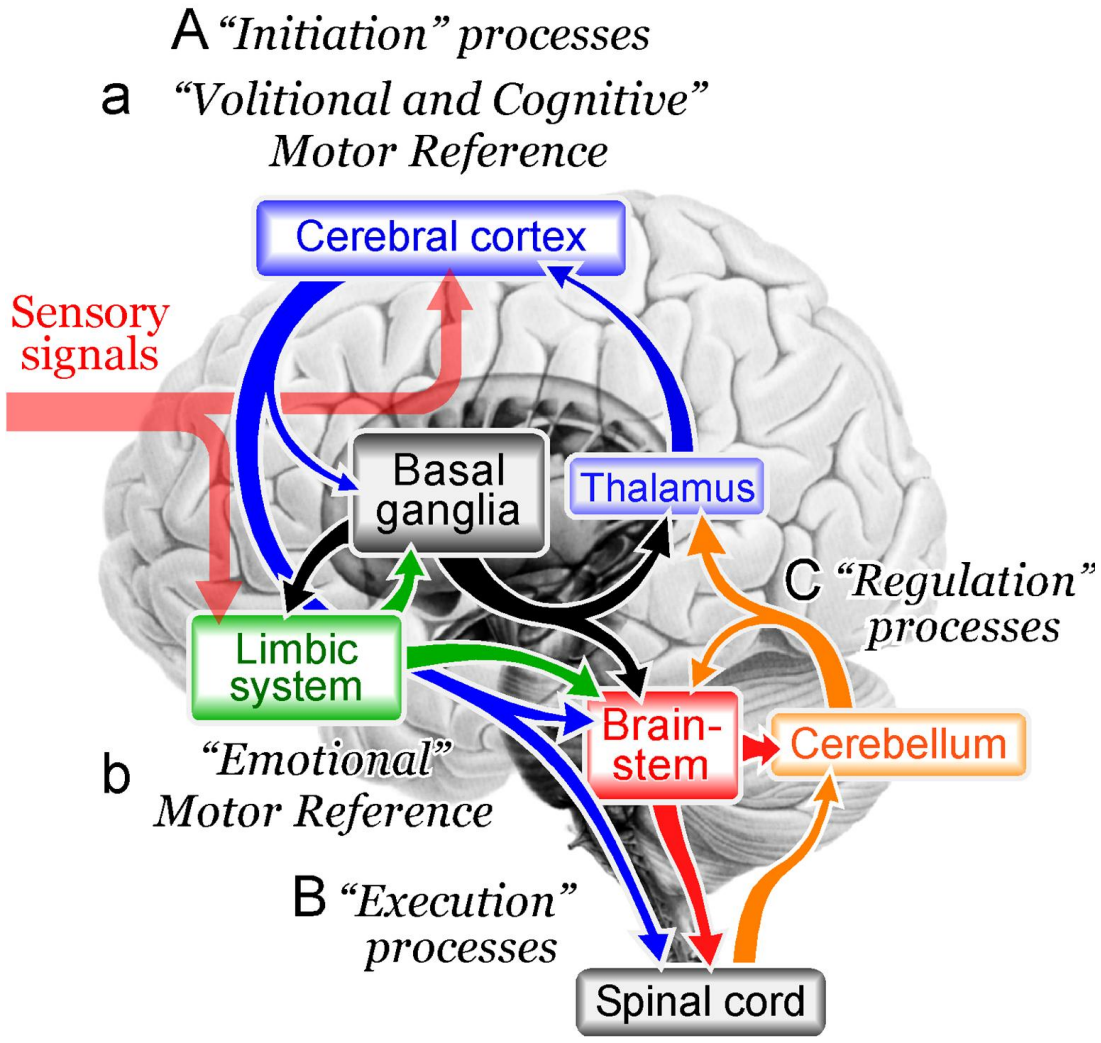

A "Initiation" processes
a "Volitional and Cognitive" Motor Reference
Cerebral cortex
Sensory signals
Basal ganglia
Thalamus
C "Regulation" processes
Limbic system
Brain-stem
Cerebellum
b "Emotional" Motor Reference
B "Execution" processes
Spinal cord

Figure 5

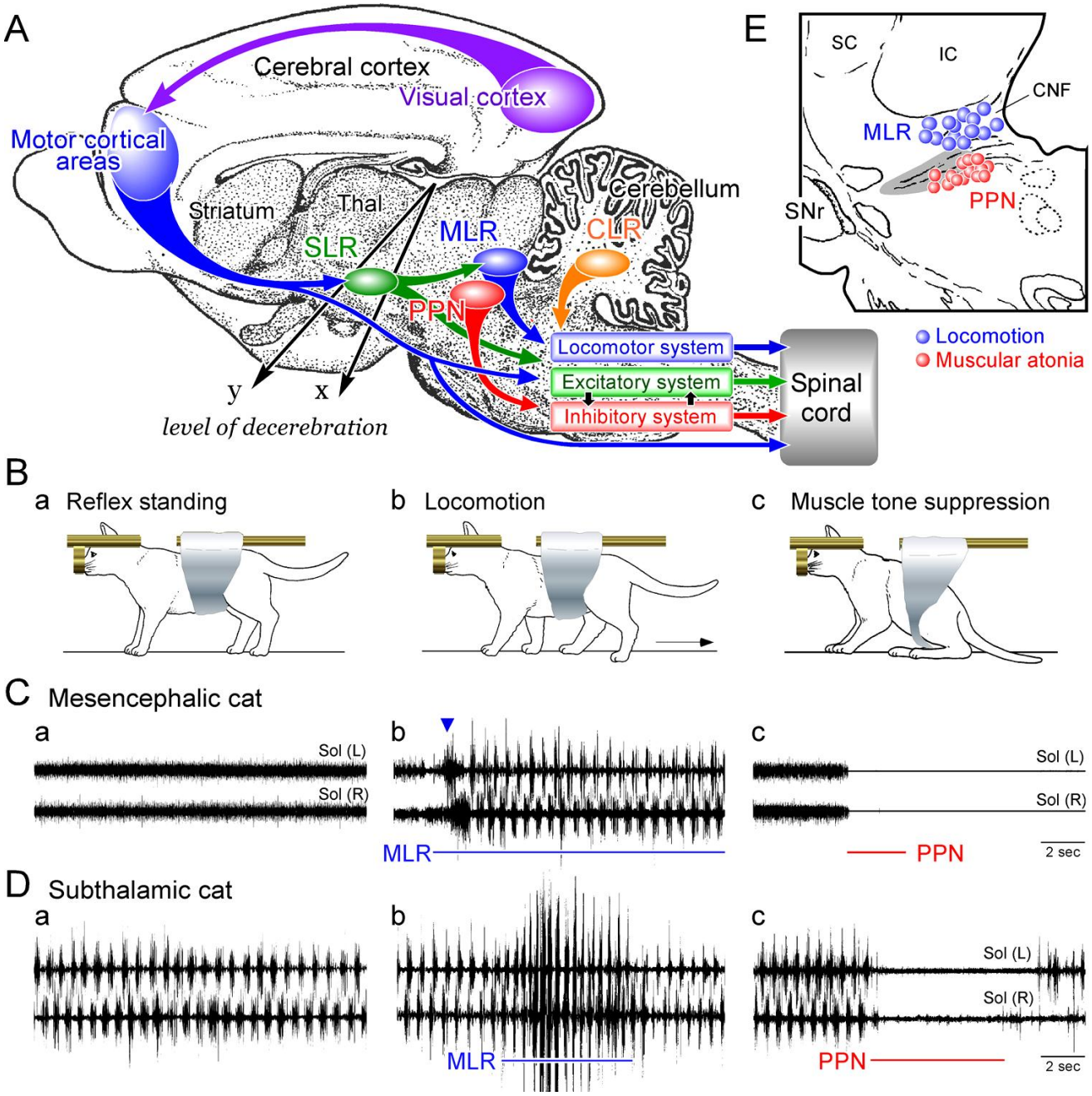

A
Cerebral cortex
Visual cortex
Motor cortical areas
Striatum
Thal
SLR
MLR
CLR
Cerebellum
PPN
Locomotor system
Excitatory system
Inhibitory system
Spinal cord
y
x
level of decerebration
E
SC
IC
CNF
MLR
PPN
SNr
Locomotion
Muscular atonia
B
a Reflex standing
b Locomotion
c Muscle tone suppression
C Mesencephalic cat
a
b
c
Sol (L)
Sol (R)
MLR
PPN
2 sec
D Subthalamic cat
a
b
c
Sol (L)
Sol (R)
MLR
PPN
2 sec

Figure 6

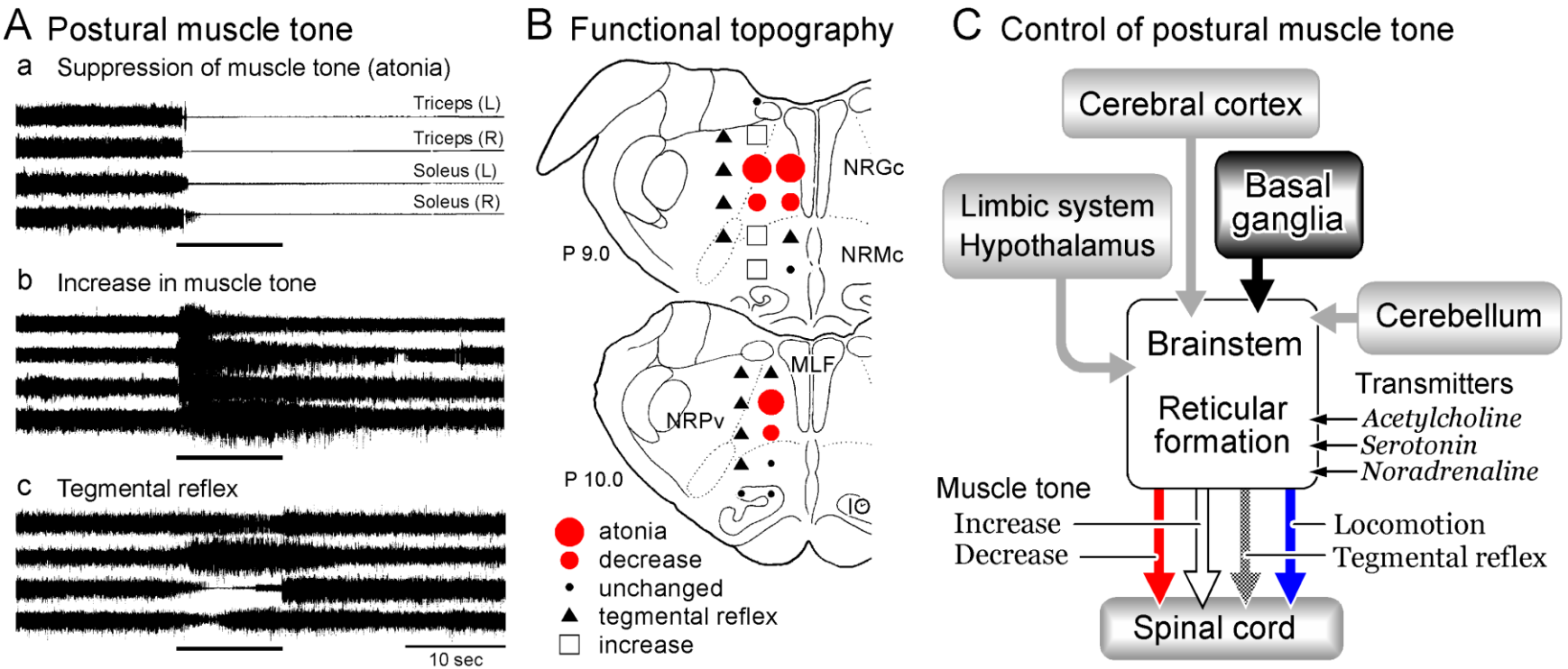

A Postural muscle tone
a Suppression of muscle tone (atonia)
Triceps (L)
Triceps (R)
Soleus (L)
Soleus (R)
b Increase in muscle tone
c Tegmental reflex
10 sec
B Functional topography
NRGc
NRMc
P 9.0
MLF
NRPv
P 10.0
atonia
decrease
unchanged
tegmental reflex
increase
C Control of postural muscle tone
Cerebral cortex
Limbic system
Hypothalamus
Basal ganglia
Cerebellum
Brainstem
Reticular formation
Transmitters
Acetylcholine
Serotonin
Noradrenaline
Muscle tone
Increase
Decrease
Locomotion
Tegmental reflex
Spinal cord

Figure 7

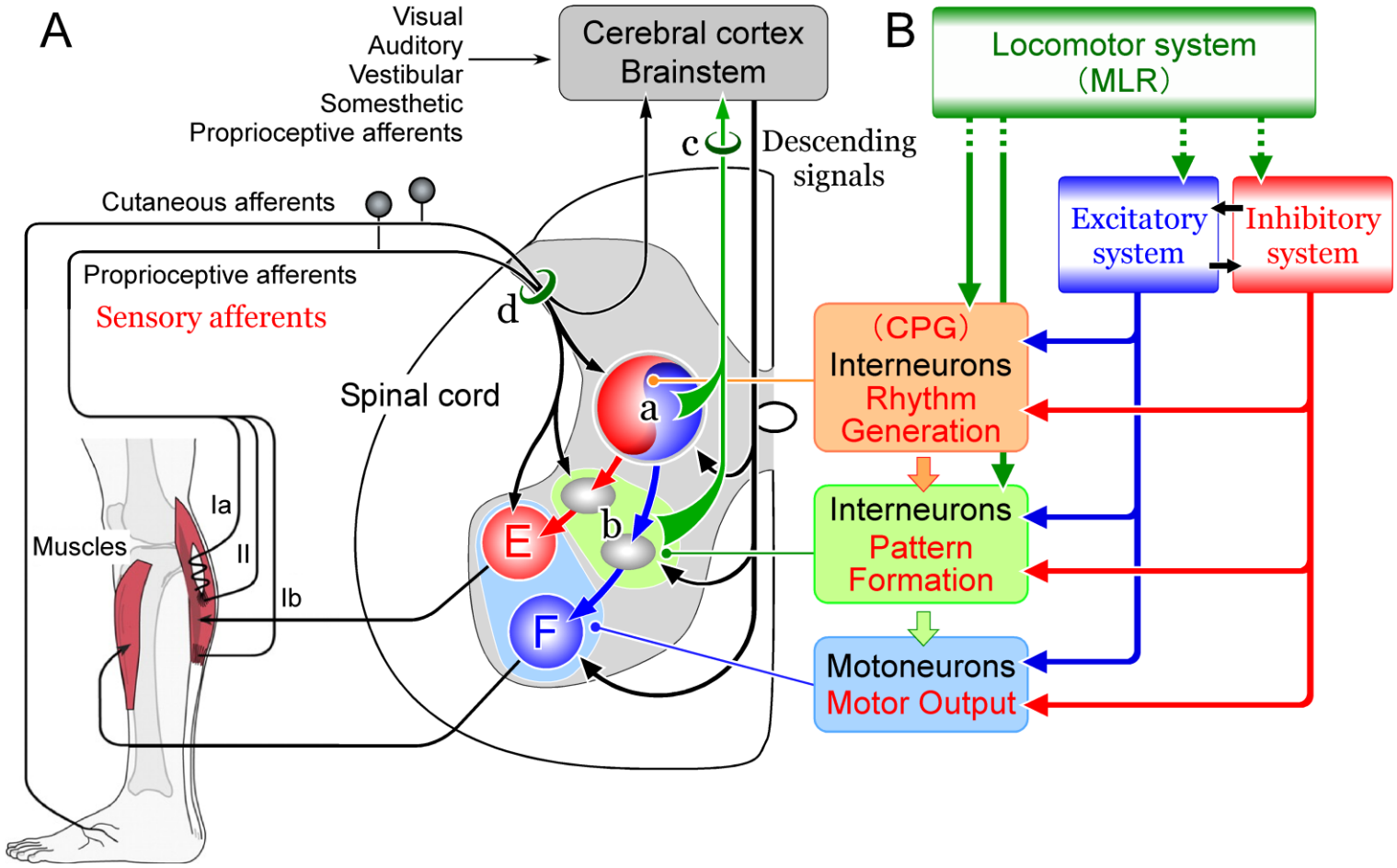

A
Visual
Auditory
Vestibular
Somesthetic
Proprioceptive afferents
Cerebral cortex
Brainstem
c
Descending
signals
Cutaneous afferents
Proprioceptive afferents
Sensory afferents
d
Spinal cord
a
b
E
F
Ia
II
Ib
Muscles
B
Locomotor system
(MLR)
Excitatory
system
Inhibitory
system
(CPG)
Interneurons
Rhythm
Generation
Interneurons
Pattern
Formation
Motoneurons
Motor Output

Figure 8

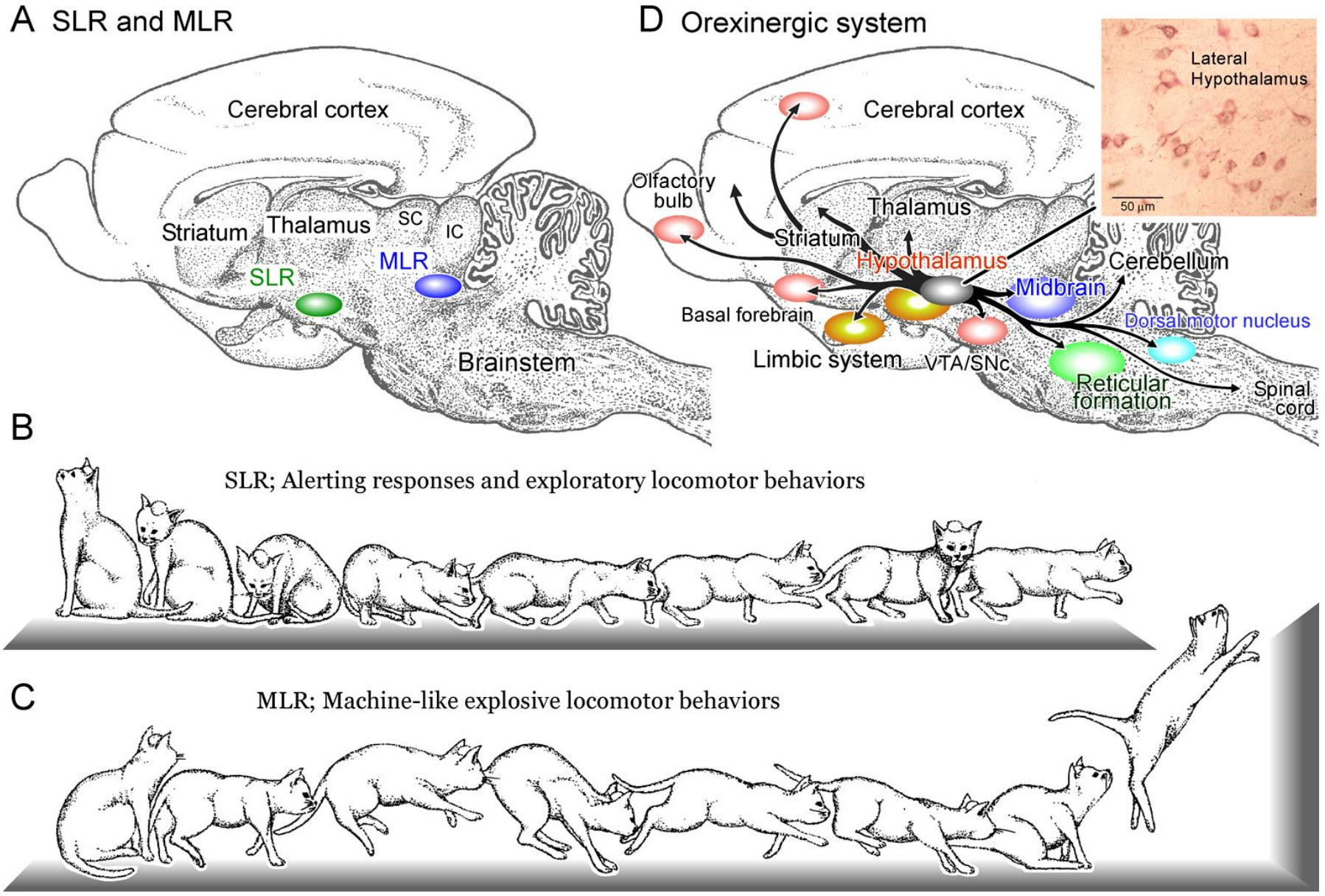

A SLR and MLR
Cerebral cortex
Striatum
Thalamus
SC
IC
MLR
SLR
Brainstem
D Orexinergic system
Lateral Hypothalamus
50 μm
Cerebral cortex
Olfactory bulb
Thalamus
Striatum
Hypothalamus
Cerebellum
Midbrain
Basal forebrain
Dorsal motor nucleus
Limbic system
VTA/SNc
Reticular formation
Spinal cord
B
SLR; Alerting responses and exploratory locomotor behaviors
C
MLR; Machine-like explosive locomotor behaviors

Figure 9

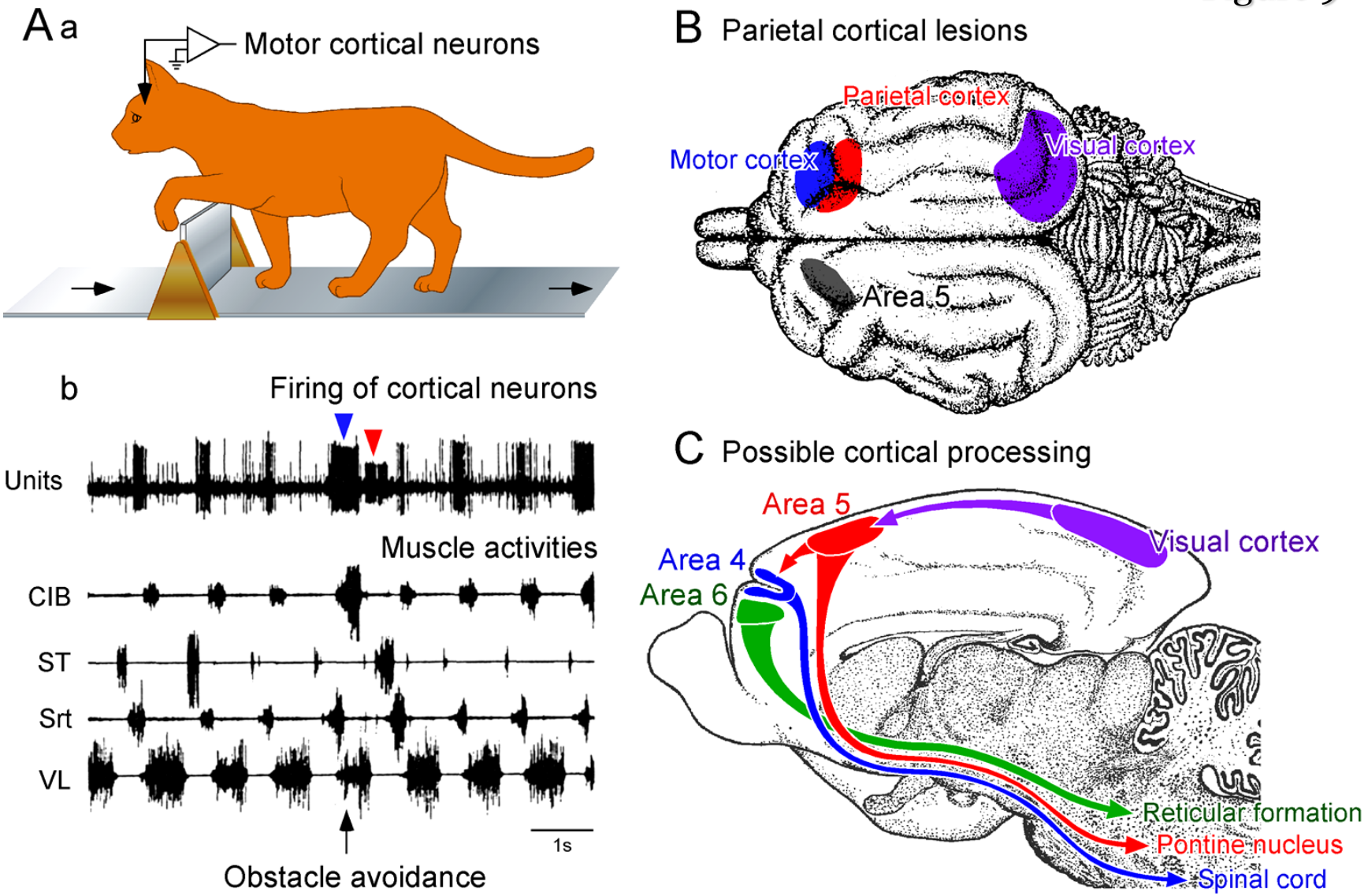

A a
Motor cortical neurons
b
Firing of cortical neurons
Units
Muscle activities
CIB
ST
Srt
VL
1s
Obstacle avoidance
B Parietal cortical lesions
Parietal cortex
Visual cortex
Motor cortex
Area 5
C Possible cortical processing
Area 5
Visual cortex
Area 4
Area 6
Reticular formation
Pontine nucleus
Spinal cord

Figure 10

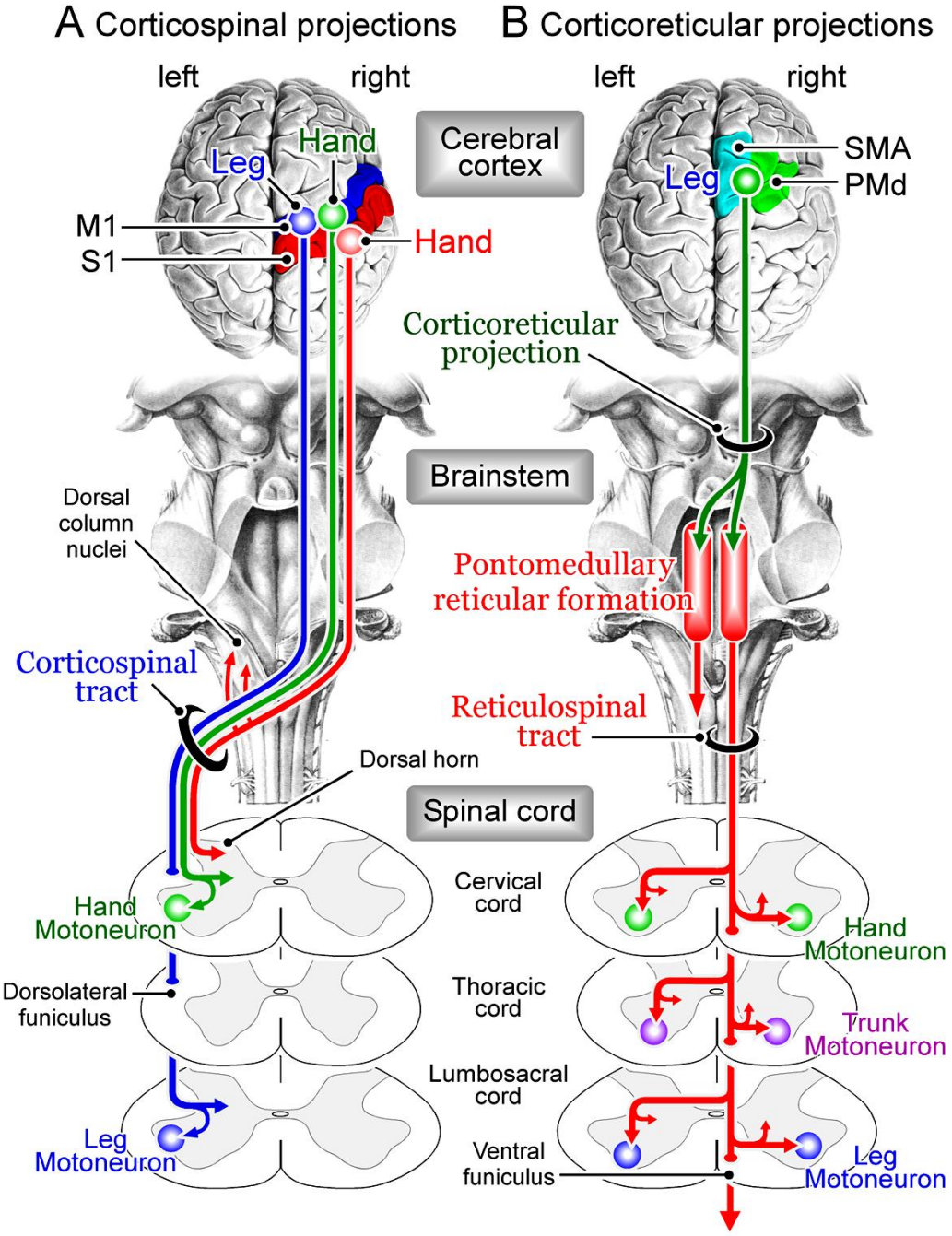

A Corticospinal projections
B Corticoreticular projections
left
right
left
right
Cerebral cortex
Leg
Hand
M1
S1
Hand
SMA
PMd
Leg
Corticoreticular projection
Brainstem
Dorsal column nuclei
Pontomedullary reticular formation
Corticospinal tract
Reticulospinal tract
Dorsal horn
Spinal cord
Cervical cord
Thoracic cord
Lumbosacral cord
Hand Motoneuron
Dorsolateral funiculus
Leg Motoneuron
Ventral funiculus
Hand Motoneuron
Trunk Motoneuron
Leg Motoneuron

Figure 11

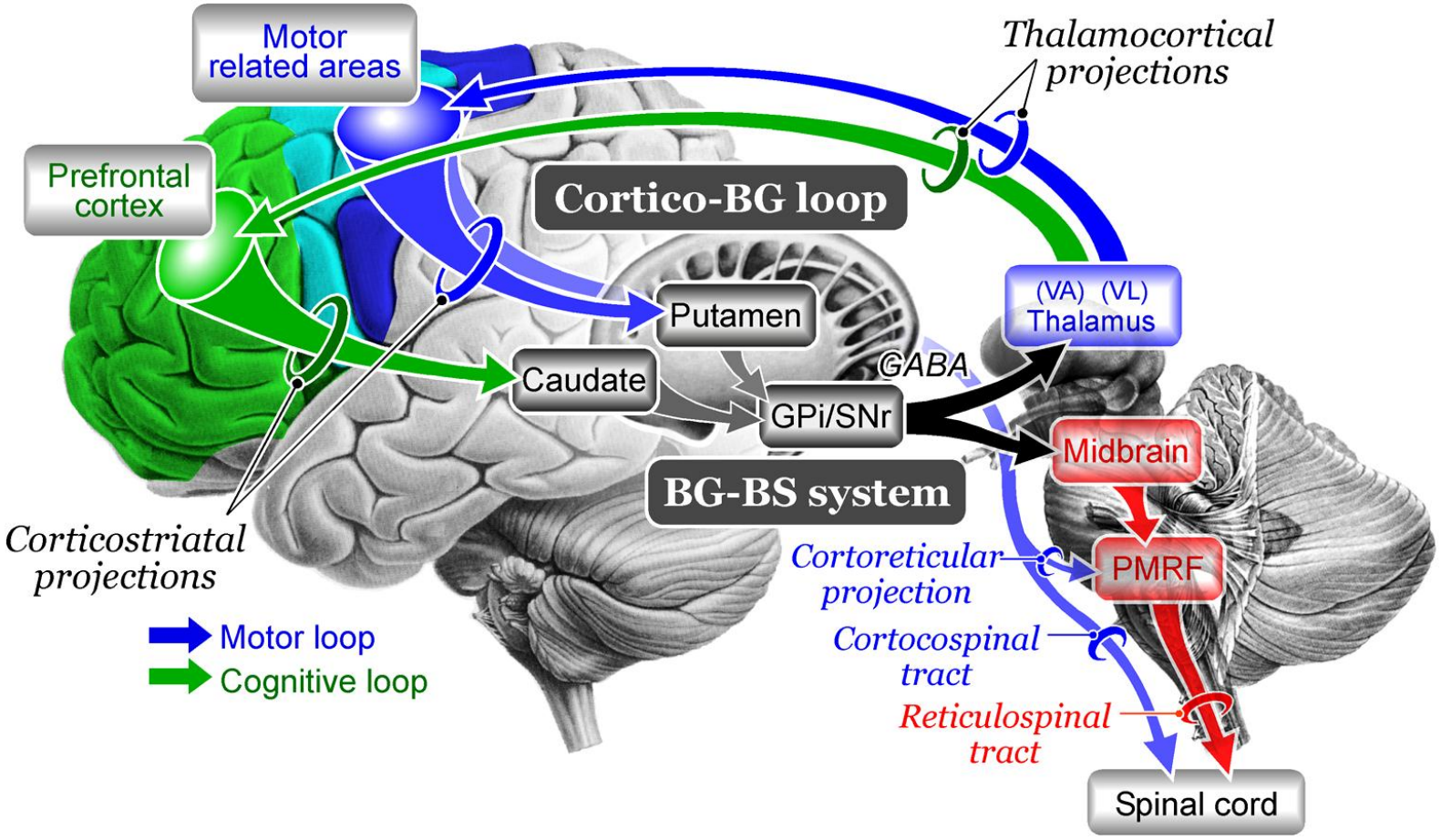

Motor related areas
Prefrontal cortex
Cortico-BG loop
Thalamocortical projections
Putamen
Caudate
GPi/SNr
GABA
(VA) (VL) Thalamus
Midbrain
BG-BS system
Corticostriatal projections
Cortoreticular projection
PMRF
Cortocospinal tract
Reticulospinal tract
Spinal cord
Motor loop
Cognitive loop

Figure 12

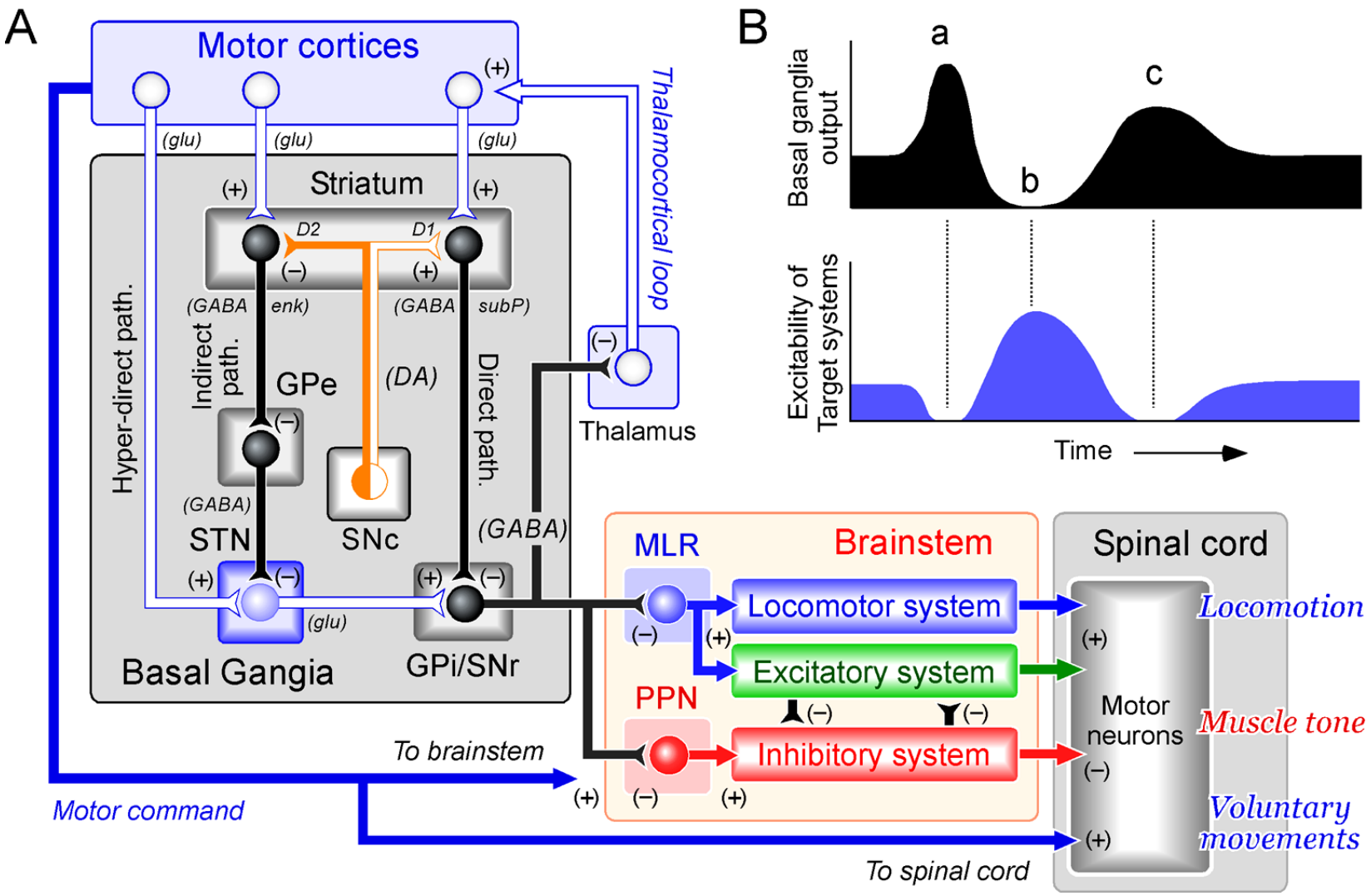

A
Motor cortices
(+)
(glu)
(glu)
(glu)
Thalamocortical loop
Striatum
(+)
(+)
D2
D1
(–)
(+)
(GABA
enk)
(GABA
subP)
Indirect path.
GPe
(DA)
Direct path.
Hyper-direct path.
(–)
Thalamus
(GABA)
STN
SNc
(GABA)
(+)
(–)
(+)
(–)
(glu)
Basal Gangia
GPi/SNr
MLR
Brainstem
Spinal cord
Locomotor system
Excitatory system
PPN
(–)
(–)
Inhibitory system
Motor
neurons
Locomotion
Muscle tone
Voluntary
movements
(+)
(–)
(+)
(–)
(+)
(–)
(+)
To brainstem
Motor command
To spinal cord
B
a
b
c
Basal ganglia
output
Excitability of
Target systems
Time

Figure 13

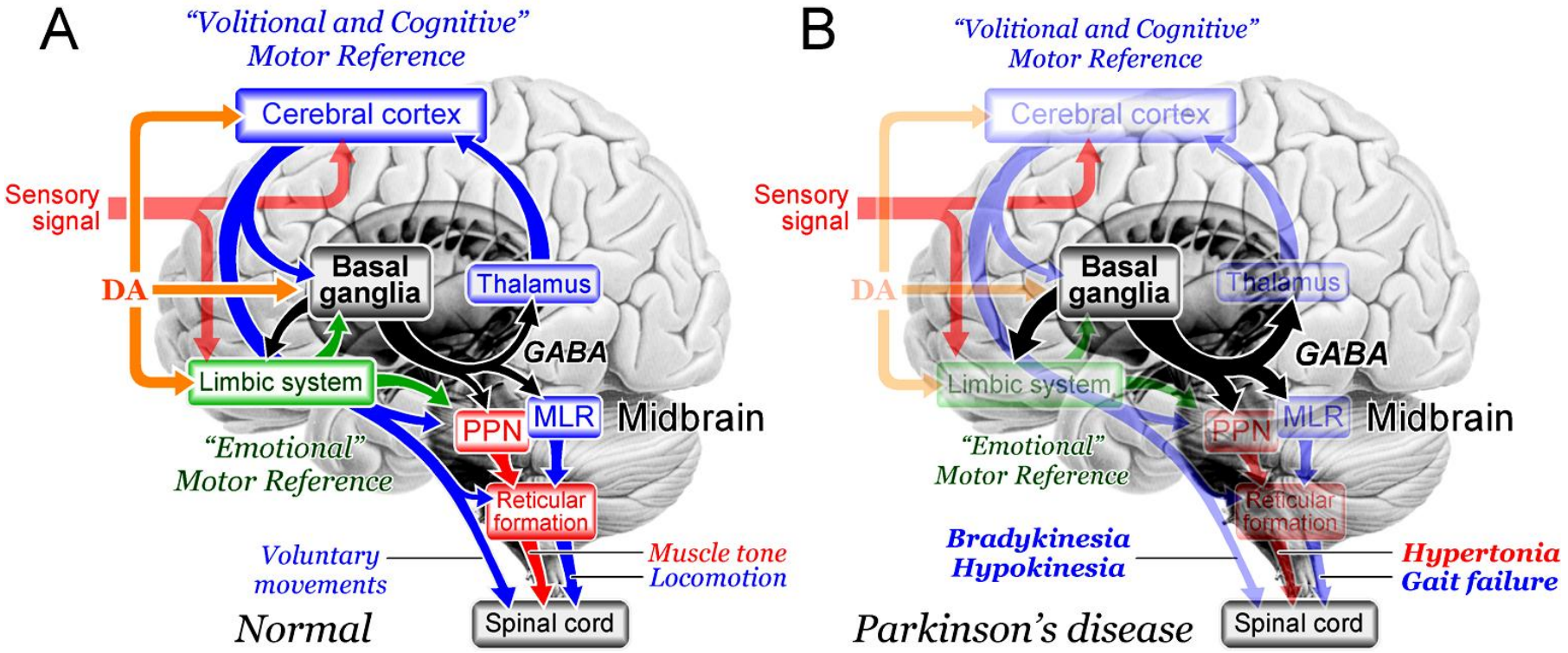

A
"Volitional and Cognitive" Motor Reference
Cerebral cortex
Sensory signal
DA
Basal ganglia
Thalamus
GABA
Limbic system
PPN
MLR
Midbrain
"Emotional" Motor Reference
Reticular formation
Voluntary movements
Muscle tone
Locomotion
Normal
Spinal cord
B
"Volitional and Cognitive" Motor Reference
Cerebral cortex
Sensory signal
DA
Basal ganglia
Thalamus
GABA
Limbic system
PPN
MLR
Midbrain
"Emotional" Motor Reference
Reticular formation
Bradykinesia
Hypokinesia
Hypertonia
Gait failure
Parkinson's disease
Spinal cord

Figure 14

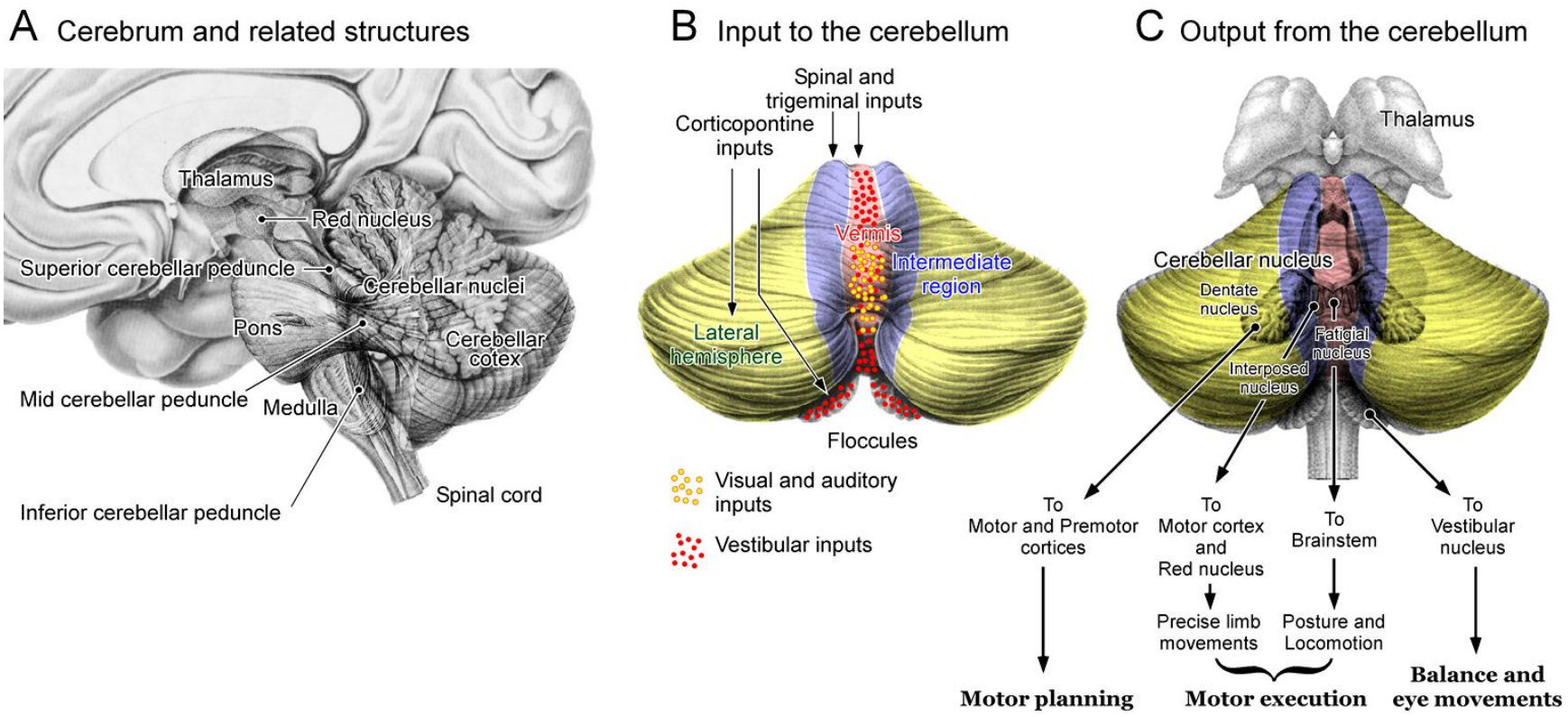

A Cerebrum and related structures
Thalamus
Red nucleus
Superior cerebellar peduncle
Cerebellar nuclei
Pons
Cerebellar cotex
Mid cerebellar peduncle
Medulla
Inferior cerebellar peduncle
Spinal cord
B Input to the cerebellum
Spinal and trigeminal inputs
Corticopontine inputs
Vermis
Intermediate region
Lateral hemisphere
Floccules
Visual and auditory inputs
Vestibular inputs
C Output from the cerebellum
Thalamus
Cerebellar nucleus
Dentate nucleus
Fatigial nucleus
Interposed nucleus
To Motor and Premotor cortices
To Motor cortex and Red nucleus
To Brainstem
To Vestibular nucleus
Precise limb movements
Posture and Locomotion
Motor planning
Motor execution
Balance and eye movements

Figure 15

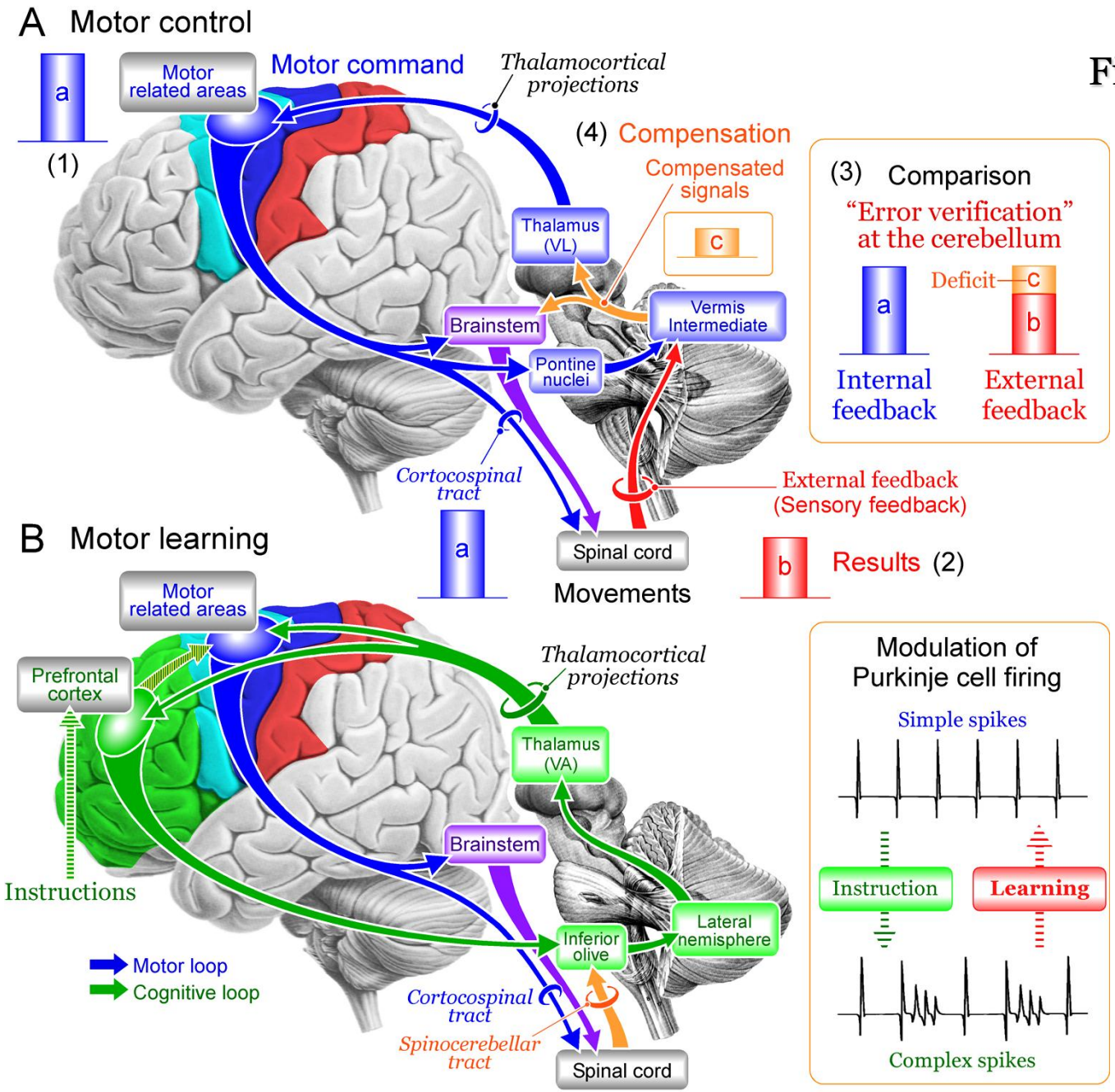
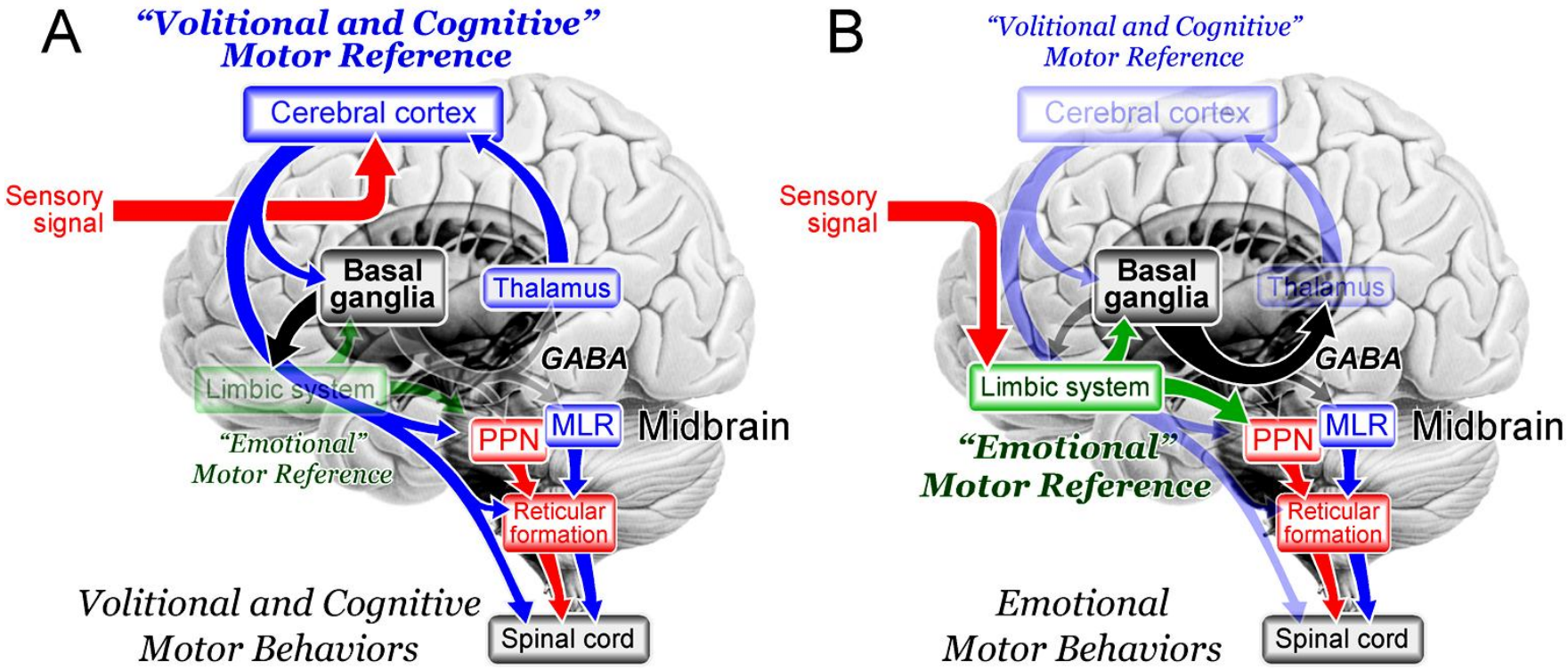

A Motor control
a
(1)
Motor related areas
Motor command
Thalamocortical projections
(4) Compensation
Compensated signals
c
Thalamus (VL)
Brainstem
Vermis Intermediate
Pontine nuclei
Cortocospinal tract
External feedback (Sensory feedback)
Spinal cord
Movements
(3) Comparison
"Error verification" at the cerebellum
a
Deficit
c
b
Internal feedback
External feedback
b
Results (2)
B Motor learning
a
Motor related areas
Prefrontal cortex
Thalamocortical projections
Thalamus (VA)
Brainstem
Instructions
Lateral hemisphere
Inferior olive
Motor loop
Cognitive loop
Cortocospinal tract
Spinocerebellar tract
Spinal cord
Modulation of Purkinje cell firing
Simple spikes
Instruction
Learning
Complex spikes

Figure 16


A
"Volitional and Cognitive" Motor Reference
Cerebral cortex
Sensory signal
Basal ganglia
Thalamus
GABA
Limbic system
"Emotional" Motor Reference
PPN
MLR
Midbrain
Reticular formation
Volitional and Cognitive Motor Behaviors
Spinal cord
B
"Volitional and Cognitive" Motor Reference
Cerebral cortex
Sensory signal
Basal ganglia
Thalamus
GABA
Limbic system
"Emotional" Motor Reference
PPN
MLR
Midbrain
Reticular formation
Emotional Motor Behaviors
Spinal cord