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Review

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Neural mechanisms underlying upright bipedal gait: role of cortico-brainstem-spinal pathways involved in posture-gait control

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Abstract

Bipedal gait involves moving the body while maintaining an upright posture under gravity. Throughout vertebrate evolution and postnatal development, humans acquired antigravity functions that allow one to achieve biped gait. While walking, our attention is focused on purposeful, intentional movements such as dexterous arm-hand finger movements or searching for the target. On the other hand, postural control comes to our awareness only when we need to alter gait patterns, such as facing demanding conditions. Nonetheless, our body and brain control gait so as not to fall by anticipatorily adjusting posture that optimally achieves multi-tasks consisting of purposeful movements and walking. Accordingly, we have developed the working hypothesis that postural control is achieved by plans and programs that accomplish purposeful actions. Key questions to verify this hypothesis are (1) how higher brain functions brought about by evolution enabled us to acquire a bipedal standing posture that resists gravity and (2) how the frontal cortex, the most developed neocortical area, enabled us to acquire multi-tasks consisting of gait and intentional movements. We postulate that the frontoparietal networks that contribute to planning and programming based on cognitive information and corticofugal pathways that issue command signals to the subcortical structures, particularly the brainstem and spinal cord in which core systems of posture and gait

control exist, play central roles in solving these questions. These mechanisms may be declined in older adults and impaired in patients with degenerative neurological disorders, resulting in posture-gait disturbance such as freezing of gait (FOG) and falling.

Keywords: Vertebrate evolution, postnatal development, aging, gait and posture, cerebral cortex, cortico-brainstem projections, neurodegenerative disorders, gait disturbance

INTRODUCTION

The secret of human mental abilities lies in the enlargement and species-specific elaboration of the neocortex during evolution [Figure 1A][1,2]. Human bipedal gait is a product of vertebrate evolution, which is also the process of the acquisition of anti-gravitational ability associated with the development of the circulatory system[3], the musculoskeletal system[4,5], and the central nervous system. The remarkably developed human brain has advanced higher brain functions such as cognition, learning, and memory. This also allows us to acquire upright posture and biped gait in addition to mastering body-limb-hand-finger movements, leading to diversity in behaviors [Figure 1B][6]. However, aging declines circulatory and musculoskeletal systems' functions, in addition to the higher brain function, which disturbs postural control and gait pattern [Figure 1B]. Older adults often exhibit bending the neck, waist, and legs forward with decreases in walking speed accompanying postural instability, leading to "falls". Daily falls in older adults aged 60 and over rapidly increase[7]. Notably, the posture-gait capability is more severely disturbed by brain disorders such as frontal lobe syndromes, Parkinson's disease (PD), spinocerebellar degeneration (SCD), Alzheimer's disease (AD), and progressive supranuclear palsy (PSP).

Bipedal gait satisfies the following conditions: maintaining an upright posture and moving the body from one place to another. Gait behaviors accompany multi-tasks, such as thinking, talking to others, operating mobile phones, and changing the direction and walking pattern from routine to intentional. Considering that all actions are preceded and accompanied by the suitable posture for the purposeful movements[8,9], postural adjustment requires not only compensating (or correcting) postural fluctuations against changes in the environment but also preparing the posture optimal for the action in advance. Such an anticipatory postural adjustment (APA) requires a higher brain function involving the cerebral cortex, basal ganglia, and cerebellum, acting on the fundamental posture-gait control mechanism in the brainstem and spinal cord[10].

In this review, we first consider the higher brain functions, mainly operating at the cerebral cortex, which may contribute to the acquisition of biped gait with upright posture based on vertebrate evolution and human development and deterioration of bipedalism. Next, we outline the brainstem-spinal cord mechanisms of posture-gait control and suggest the critical involvement of the cortico-brainstem pathways in bipedal gait. Here, we present a working hypothesis of how the information generated by the higher cortical function acts on core systems of posture and gait control in the brainstem and spinal cord (cortico-brainstem-spinal system) so that bipedal posture-gait control is achieved. Finally, we propose pathophysiological mechanisms of posture-gait disturbances caused by the dysfunction of these systems.

EVOLUTION, DEVELOPMENT AND DETERIORATION OF POSTURE AND LOCOMOTION

Evolution and development of posture and locomotion in vertebrates

Fishes swim, reptiles crawl, mammals like cats and dogs walk on four limbs, and humans walk on two legs. While the locomotor pattern differs in these vertebrates, neural mechanisms involved in locomotion have been substantially maintained throughout vertebrate evolution[11]. The "core locomotor system" common to all vertebrates is composed of the subthalamic (diencephalic) and mesencephalic locomotor regions

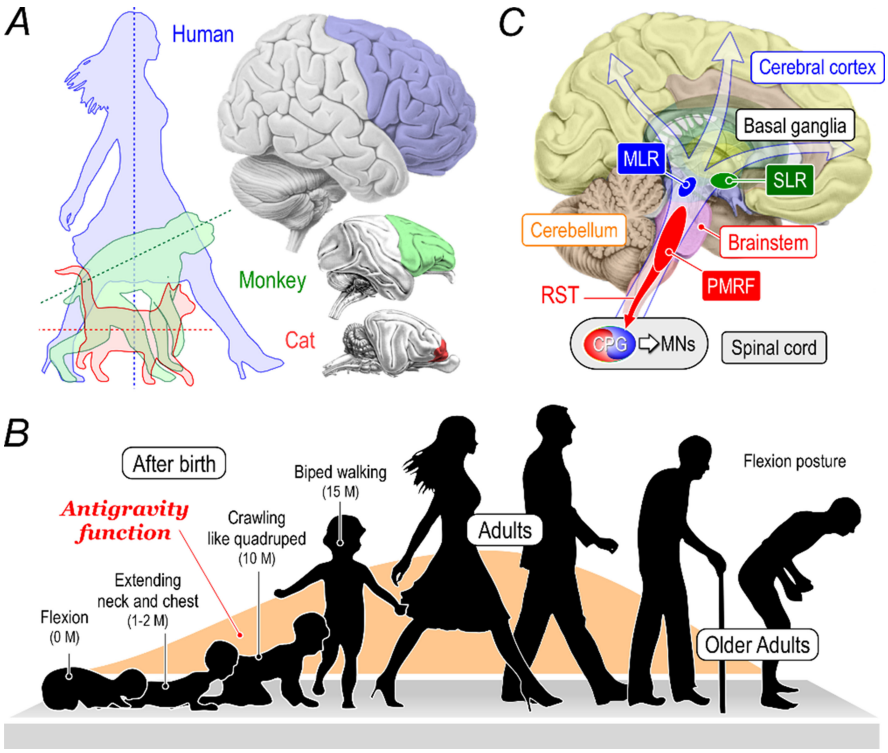

Figure 1. Evolution and development of humans. (A) Evolutional changes in posture and brain in mammals, such as cats, monkeys, and humans. Through vertebrate evolution, the body axis of animals such as cats (red), monkeys (green), and humans (blue) changed from horizontal to vertical, and the frontal lobe area in each animal's cerebral cortex expanded considerably; (B) Changes in posture and gait with postnatal development and aging of humans. The antigravity function, indicated by the orange color, is facilitated by postnatal development, but declines due to aging. While humans exhibit a flexion posture immediately after birth, their antigravity ability develops over time. Specifically, at 1-2 months, the baby extends its neck and chest, and at around ten months, it begins to crawl. Then, at approximately 15 months, the baby starts to walk upright on two legs. Human antigravity capacity reaches its peak during adulthood. However, antigravity capacity declines with age, manifesting as a decreased walking speed and a flexed posture in old adults; (C) An open arrow indicates that postnatal brain maturation progresses from the lower to the upper brain areas. Specifically, spinal reflex neural circuits, including the CPGs, can be functional at birth. Then, the neural networks between the brainstem and spinal cord, including the PMRF and the RST, are maturated. The upper brainstem includes neural structures involved in innate motor functions such as swallowing, vocalization, and excretion, in addition to those contributing to the automatic posture-gait control, including the MLR and SLR. Maturation further progresses to involve the subcortical structures (the basal ganglia, limbic system, and thalamus), cerebellum, and cerebral cortical structures, operating higher brain functions. CPGs: Central pattern generators; PMRF: pontomedullary reticular formation; RST: reticulospinal tract; MLR: midbrain (mesencephalic) locomotor region; SLR: subthalamic (diencephalic) locomotor region; MNs: motoneurons.

(SLR/MLR) from which locomotor signals descend through the reticulospinal tract (RST) to drive the central pattern generators (CPGs) in the spinal cord[11,12] [Figure 1C]. The basal ganglia (BG) primarily regulate the core system in fish and reptiles. In mammals, the cerebral cortex contributes to the control of the core system in addition to the BG, and it places the BG under its regulation[13].

The postural control system has preserved mechanisms common to all vertebrates throughout evolution but dramatically developed the mechanism against environmental changes. For example, eye-head-neck coordination that links saccades with the behavioral orientation is held throughout the vertebrates. Depending on visual information from the retina, the superior colliculus (SC) elicits saccadic eye movements to the target via the pontine gaze center (PGC). The output of the SC further produces head-neck movements coordinating with the saccade via the tectospinal tract (TST)[14]. Even the fish, the brainstem and cerebellum possess vestibulo-ocular reflex, which integrates gaze and neck movements in response to vestibular sensation[15]. Subsequently, the vestibulospinal reflex that regulates body equilibrium

has rapidly developed since reptiles, in which more opportunities to live on the ground where a gravitational influence increases. In mammals on the ground, mechanisms of controlling postural muscle tone and regulating body equilibrium further evolved to cope with the load through their movements. Changes in musculoskeletal systems, particularly seen in the pelvis, accompany evolutional changes in posture. As a result, the body axis altered from horizontal to vertical [Figure 1A]. The human body alignment, where the head is placed directly above the center of gravity, can be the most rational posture with optimal energy consumption in a gravitational condition[16].

Before birth, humans experience the vertebrate's evolutional processes in the mother's womb. Stereotypical patterns of movements, such as eye movement, swallowing, excretion, and flexion-extension of limbs, develop in the womb and are completed after birth. After birth, humans experience the development of postural control and voluntary movement while resisting gravity [Figure 1B]. The baby, immediately after delivery, is in a flexed posture. Still, the neck and chest are extended at 1 to 2 months of age. By developing muscle strength in the upper and lower limbs and trunk, they crawl like quadrupeds at around 10 months. By approximately 15 months, they can walk on two legs. During this period, neural maturation begins in the spinal cord, progresses to the brain stem, diencephalon, and cerebral cortex [Figure 1C], and allows us to obtain postural control mechanisms such as extending the body, supporting loads, and regulating body balance against environmental changes. Therefore, the evolution of vertebrates and the postnatal development of humans have made it possible to acquire antigravity function, leading to a bipedal gait with an upright posture. On the other hand, floppy infant syndrome children in the neonatal and early infant periods have a problem with the acquisition of antigravity function due to hypotonia. The neuromuscular etiology is vast, encompassing primary muscular dystrophies, chromosome abnormalities, neuropathies, and inborn errors of metabolism[17]. As postural muscle tone is integrated into functional terms by a complex physiological network involving the brain, spinal cord, and muscle spindle neural circuits[18,19], the proper functioning of the postural muscle tone control mechanisms ensures posture and movement development after birth.

Basic brain networks in posture and gait control

Figure 2A shows our current interpretation of brain networks involved in posture and gait control in humans. We are usually unaware of rhythmic limb movements and postural adjustment while walking on flat paths. Such automatic gait control is achieved by subcortical networks (core locomotor system), primarily in the brainstem and spinal cord[11,12]. Sensory information from the surroundings alters attentional, emotional, and cognitive states [Figure 2B]. Walking on narrow winding paths requires attentive and cognitive information processing to associate accurate leg movements with postural control by integrating cortical and subcortical networks. When facing danger, the networks adopt escaping, one of the emotional behaviors, or active avoidance, the most elaborating behavior[7]. The BG and cerebellum act on the cerebral cortex, limbic system, and brainstem, enabling context-dependent goal-directed gait behaviors[7,11]. Neurons containing various neurotransmitters, such as acetylcholine (ACh), dopamine (DA), serotonin (5-hydroxytryptamine) (5-HT), and noradrenaline (NA) exist in the brainstem [Figure 2B]. They play a crucial role in maintaining whole brain activities, such as behavioral expression, cognitive functions including learning and memory formation, and homeostatic processes of awake-sleep states and feeding in addition to posture and gait through their broad projections to the cortical and subcortical structures.

Structural deterioration of the brain by aging

Aging declines the antigravity function of the brain, musculoskeletal system, and circulatory system. Brain aging begins in the middle of life, accelerates with age, and affects anything from the genetic and cellular to the network levels, leading to progressive cognitive decline. Brain aging is morphologically characterized by a decrease in volume, thinning in cortical grey matter with degradation of white matter, loss of gyrification,

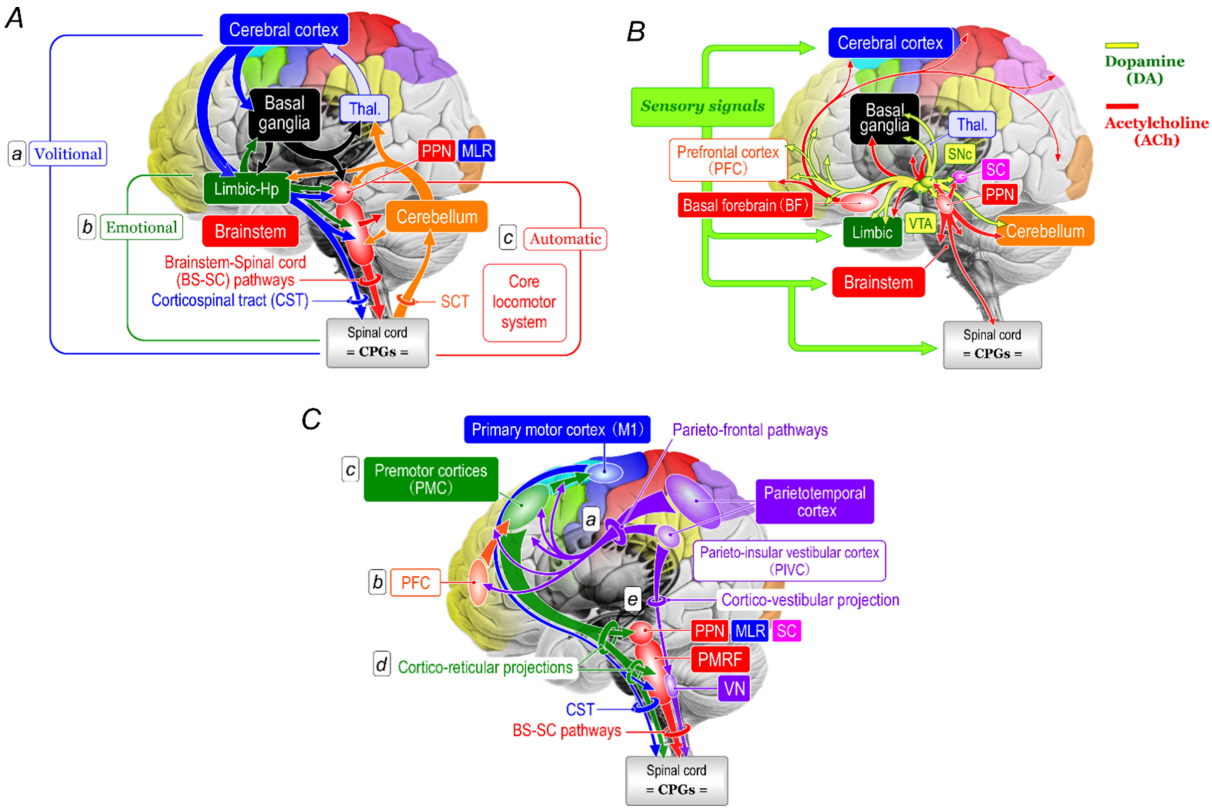

Figure 2. Neural bases of posture-gait control. (A) Basic signal flows in motor control. Locomotor behaviors are composed of volitional (a), emotional (b), and automatic (c) processes. Whether volitional or emotional, the automatic process by the core locomotor system in the brainstem and spinal cord is required. On the other hand, interaction between the volitional (intentional) and emotional processes is essential in selecting either active avoidance or escaping, such as when facing danger; (B) Role of sensory signals and neurotransmitters. Signals from visual, vestibular, auditory, somatosensory (proprioceptive), and visceral sensations act on various sites in the brain. Signals in these sensory systems acting on the brainstem and spinal cord contribute to the modulation of automatic posture-gait control. On the other hand, those acting on the limbic system and cerebral cortex modulate emotional and volitional processes of posture-gait control, respectively. DA neurons in the SNc project to the basal ganglia. Those in the VTA project to the prefrontal cortex and the limbic regions. DA neurons also project to the SC, PPN, and cerebellum. Cholinergic (ACh) BF neurons innervate to broader regions of the cerebral cortex. PPN-ACh project to the thalamus (Thal.), basal ganglia, brainstem, cerebellum, and spinal cord. Accordingly, each neurotransmitter's action alters the activity of the automatic, emotional, and volitional posture-gait control systems. In addition, the cholinergic projections to the thalamic nuclei regulate arousal levels and sensory processing as one of the ascending reticular activation systems; (C) Hypothetical neural mechanisms that are essential for bipedal posture-gait control. Parieto-frontal pathways (a) send cognitive information to the PFC (b) and PMC (c). The cortico-brainstem projection from the PMC to the posture-gait relating areas in the midbrain (PPN, MLR, and SC) and the PMRF (cortico-reticular projection) (d) and that from the parietotemporal cortex, such as the PIVC to the VN (cortico-vestibular projection; e) contribute to the biped posture-gait control. Please look at the text for a detailed explanation. DA: Dopaminergic; SNc: substantia nigra pars compacta; VTA: ventral tegmental area; SC: superior colliculus; PPN: pedunculopontine nucleus; ACh: acetylcholine; BF: basal forebrain; PFC: prefrontal cortex; PMC: premotor cortices; MLR: midbrain (mesencephalic) locomotor region; SC: superior colliculus; PMRF: pontomedullary reticular formation; PIVC: perieto-insular vestibular cortex; VN: vestibular nuclei.

and enlargement of ventricles. The volume decreases by aging at around 5% per decade after 40 years of age and the rate of decline rapidly increases after 70 years old[20]. The volume in the frontal and temporal lobes reduced more than that in the occipital and parietal lobes[21]. Pathological brain aging is associated with the shrinking of neurons, dendrites degeneration, demyelination, microglia activation, white matter lesions, small vessel damage, and low metabolisms[22].

Degenerative substances accumulate and deposit by aging. They are α-synuclein that forms Lewy bodies (LB) and extracellular amyloid-β (Aβ) deposition and intracellular neurofibrillary tangles (NTF)

accompanied by hyperphosphorylated tau protein[23]. LB accumulate in various brain regions. It first appears in the visceral nervous system, then spreads to the olfactory bulb, spinal cord, medulla-pons-midbrain, diencephalon, and finally to the entire cerebral cortex[24]. Interestingly, the progression of LB pathology is like the human brain maturation process [Figure 1C]. LB pathology leads to aging-related neurological disorders called synucleinopathy including PD, multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). Aβ plaques and NTF are hallmark features of AD[25,26].

Neurons containing DA, 5-HT, NA, and ACh possess multiple channels that tightly guard their steady firing. They also broadly arborize their axons and terminals to maintain stable excitability of broad brain areas. As they already exist in lower vertebrate, their axonal arborization has been hugely expanded, accompanied by evolutional enlargement of the brain, particularly its forebrain [Figure 2B]. Because of the higher energy consumption due to the above morphological and electrophysiological properties, they are more vulnerable than other neuronal groups to aging[7,27]. The degeneration of these neuronal groups evokes the core motor disturbances of PD and AD[28-30]. The evolutional brain enlargement led to the ironic result of making it susceptible to aging and degeneration[7].

HYPOTHESIS ON THE MECHANISMS THAT DEVELOPED BIPED POSTURE-GAIT CONTROL IN HUMANS

Based on the concept that the core system for controlling posture and locomotion has been conserved throughout vertebrate evolution, we constructed the following working hypothesis by hybridizing the research findings on posture and locomotion in quadrupedal animals (mostly in cats) with those on higher brain functions relating to the eye, digit, hand and upper limb movements in primates and humans. Therefore, this hypothesis has concerns. For example, the role of cortico-brainstem projections in posture-gait control is primarily based on current findings on upper limb/hand control. While this may be justified, it is necessary to consider that posture-gait control and hand-arm movement control are fundamentally different forms of motor behavior, so they are subject to different control mechanisms. This is the first concern. The second problem is that the working hypothesis may be criticized as speculative, as only some experimental findings involve bipedal posture-gait control by the higher brain functions. Given the potential incompleteness and the likelihood of criticism, we recognize the need for further research to complete this working hypothesis. Nonetheless, we decided to present this hypothesis from a neurophysiological perspective on how humans acquired bipedal posture-gait control. While little research is currently on higher brain functions during bipedal walking in primates or humans, certain percentages of reticulospinal and vestibulospinal neurons, which are significant elements of the brainstem-spinal cord, send axons and terminals in each segment from the cervical to the lumbosacral cord. This indicates that the activity of these descending neurons contributing to upper limb/hand movements also affects the trunk and leg movement control. The implications of this are that the cortico-brainstem projections that control voluntary eye, digit, hand, and upper limb movements are, to a greater or lesser extent, also involved in postural control during standing and walking. This is the presumption that has led us to formulate the following working hypothesis. We believe that this hypothesis is significant in understanding the evolutional process of acquiring bipedal gait, crucially advancing our understanding of neurophysiology and evolutionary biology. More importantly, it provides a potential avenue for understanding and addressing the mechanism by which age-related brain degenerative diseases impair bipedal posture-gait control, a pressing issue in our aging population.

Evolved from quadruped to biped, upper limbs are liberated from locomotion, enabling humans to perform various tasks, such as skillful hand-digit movements and talking to others while walking. Because every movement is preceded by postural control that is optimized for that movement, the postural control system

inevitably enables the prediction of postural disturbances caused by multitasking and ensures postural stability throughout the task. This must fulfill the conditions of completing the intended action and maintaining a stable posture to avoid falls during gait. This multitasking capability demands cognitive function that facilitates highly organized motor programming and translates it into intentional posture-gait behaviors. Considering that the frontal lobe has evolved with bipedalism, the highly developed corticofugal fibers, particularly from the frontal lobe to the brainstem, where the core locomotor systems exist, can play a crucial role in establishing biped gait behaviors. In other words, the central concept of this working hypothesis is that the development of the frontal lobe has promoted the acquisition of neural mechanisms of postural control that enable dexterous movements and multitasking. While we must recognize the importance of developing subcortical function, such as played by the basal ganglia and cerebellum, this paper primarily focuses on the functional organization of cortico-brainstem systems in biped posture-gait control.

Our hypothesis is schematically illustrated in Figure 2C. One cannot help but think that the multitasking motor program includes a forward model of postural control that is optimized to the biped gait while accompanying other tasks. The frontal lobe, which is the most developed in humans, receives cognitive information on the body and space from the parietotemporal cortex via parieto-frontal pathways [Figure 2C(a)]. Then, the prefrontal cortex (PFC) formulates goal-directed behavioral plans [Figure 2C(b)]. According to the behavioral purpose, premotor cortices (PMC) construct motor programs consisting of subprograms of actions, including switching and sequence of each movement paradigm [Figure 2C(c)]. The PMC has abundant corticofugal projection fibers to posture-gait-related areas in the brainstem [Figure 2C(d)], especially the pontomedullary reticular formation (PMRF). Similarly, the parieto-insular vestibular cortex (PIVC), a part of the parietotemporal cortex, has projections to the vestibular nuclei (VN), allowing us to maintain an upright posture according to the sense of verticality [Figure 2C(e)]. Here, we emphasize the importance of these cortico-brainstem projection systems as the critical substrates that enable biped posture-gait control while multitasking. In the following, we describe this hypothesis's content and discuss how posture-gait control is disturbed by impairing corticofugal projections to the brainstem.

BASIC NEURAL MECHANISMS OF POSTURE-GAIT CONTROL

Before considering the role of cortico-brainstem projection systems, we describe core posture-gait control systems in the brainstem and spinal cord. The following summarizes our current understanding of findings in clinical and animal studies [Figure 3].

Mesopontine tegmentum

The mesopontine tegmentum includes functionally critical regions involved in the control of posture and locomotion[11,12,31]. One is the MLR [Figure 3A(a)], and another is the muscle tone inhibitory region corresponding to the PPN [Figure 3A(b)]. Mesopontine tegmental neurons display various transmitter phenotypes, such as glutamatergic (Glu), cholinergic, GABAergic, and peptidergic[32,33]. The cat experiments showed that the MLR corresponded to the cuneiform nucleus (CNF) and included the dorsal part of the PPN[31,34]. Studies of experiments in rodents, cats, and monkeys suggest that Glu neurons[31,34-38] in this area evoke locomotion by consecutively activating brainstem descending pathways and spinal locomotor networks[11,12,39].

The function of the PPN-ACh neurons may be state-dependent[31,40,41]. During wakefulness, they contribute to the control of postural muscle tone and locomotor rhythm. On the other hand, they are involved in muscular atonia during REM sleep. There are reciprocal connections between the PPN-ACh neurons and monoamine neurons, such as NA, 5-HT, and DA neurons, at the mesopontine tegmentum[42-45]. Because

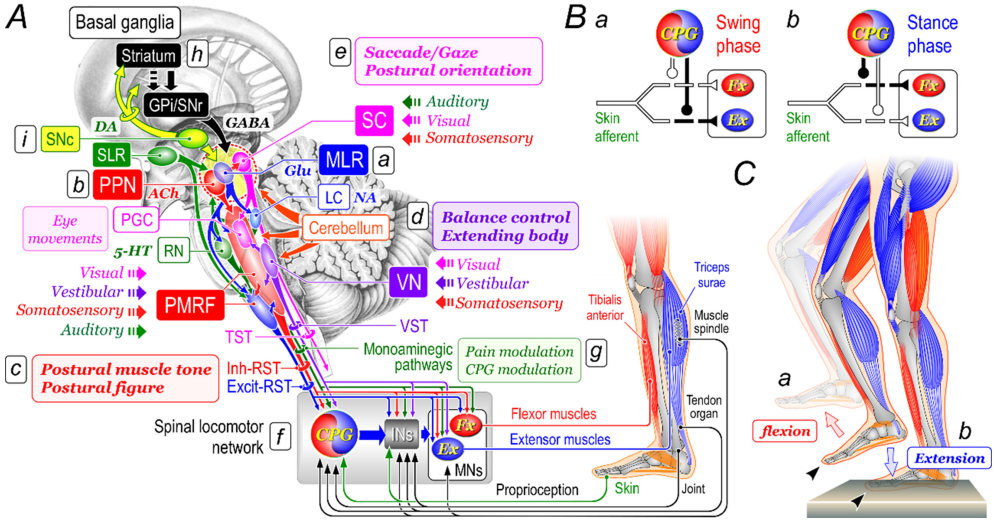

Figure 3. Control of posture and gait by the brainstem and spinal cord. (A) The functional organization of the core posture-gait control system. The red dashed line encircles crucial structures in the mesopontine tegmentum in posture-gait control. They are the PPN, MLR, and SC. (a) Signals from the MLR activate both the excitatory RST (Exit-RST) and inhibitory RST (Inh-RST) in addition to monoaminergic pathways including the NA coerulospinal tract from the LC and serotonergic (5-HT) raphespinal tract from the RN; (b) PPN-ACh neurons activate the Inh-RST descending from the PMRF; (c) The balance between inhibitory and excitatory RSTs' activities regulates postural muscle tone. RST also contributes to the alignment of the trunk and upper and lower limbs, as represented by the tonic neck reflex, which generates the so-called postural figures; (d) The VST from the VN contributes to balance control and extending the body; (e) The tectospinal tract from the SC is involved in gazing (saccade) by acting to the PGC in the paramedian pontine reticular formation. Various sensory inputs acting on the PMRF, VN, and SC evoke postural reactions (postural reflexes); (f) Supraspinal inputs to the spinal locomotor network, including the CPGs, generate locomotor rhythm, regulate locomotor pattern, and activate motoneurons innervating extensor (Ex) and flexor (Fx) muscles to elicit locomotion. Proprioceptive sensation from muscle spindles, tendon organs, joints, and skin modulates locomotion by acting on the locomotor network; (g) Monoaminergic pathways from the LC and RN contribute to modulating pain sensation and CPG activity; (h-i) Nigrostriatal DA projection (i) modulates activity of the intrinsic basal ganglia pathways (h) to alter GABAergic output from the internal segment of the GPi and SNr. GABAergic output from GPi/SNr to SC, MLR, and PPN modulates saccade, locomotion, and postural muscle tone, respectively; (B) Effects of skin afferent depend on step cycles. (a) During the swing phase, CPGs' output facilitates the skin afferent's transmission to flexor motoneurons and inhibits it to extensor motoneurons; (b) During the stance (support) phase, CPGs' output facilitates the skin afferent's transmission to extensor motoneurons and inhibits it to flexor motoneurons; (C) Stumble-corrective reaction. Stimuli to toe, indicated by filled arrows, during the stance phase, elicits leg flexion (a) but facilitates the extension of the leg, i.e., presses foot sole firmly against the grand during stance phase (b). PPN: Pedunculopontine tegmental nucleus; MLR: mesencephalic (midbrain) locomotor region; SC: superior colliculus; RST: reticulospinal tract; NA: noradrenaline; LC: locus coeruleus; 5-HT: serotonin (5-hydroxytryptamine); RN: raphe nuclei; ACh: acetylcholine; PMRF: pontomedullary reticular formation; VST: vestibulospinal tract; VN: vestibular nuclei; PGC: pontine gaze center; CPGs: central pattern generators; LC: locus coeruleus; DA: dopamine; GPi: globus pallidus; SNr: substantia nigra pars reticulata; INs: interneurons.

ACh, NA, and 5-HT neurons exhibit state-dependent firing alteration[40,41], the cholinergic-monoaminergic reciprocity can be involved in the state-dependent modification of the cortical and subcortical activities. The PPN/MLR areas in humans also contribute to gait initiation, as evidenced by imaging and lesion studies[46,47]. In addition, the PPN/MLR area is a target of deep brain stimulation (DBS) for surgical therapeutics of posture-gait disturbance in PD patients[48,49].

Brainstem and descending pathways to spinal cord

Four descending pathways contribute to postural control: the RST, vestibulospinal tract (VST), TST, and monoaminergic pathways[50,51]. The RST arises from the bilateral PMRF and innervates whole spinal segments from the cervical to the sacral cords to modulate neuronal activities in each segment. One of the roles of the RST is to control the level of postural muscle tone by modulating the degree of co-contraction of extensor and flexor muscles to maintain joint stiffness so that body weight is supported while standing and moving [Figure 3A(c)]. The RST functionally consists of excitatory and inhibitory RST[31], facilitating and

attenuating muscle co-contraction. The balanced activity of the two tracts regulates the joint stiffness. In the cat, MLR-Glu neurons [Figure 3A(a)] recruit excitatory and inhibitory RST neurons during locomotion. However, PPN-ACh neurons [Figure 3A(b)] excite the inhibitory RST to reduce the activity of interneurons and motoneurons in the spinal cord, leading to muscle tone suppression[31,51,52]. On the other hand, monoaminergic pathways, including the coerulospinal tract from the locus coeruleus (LC) and raphespinal tract from the raphe nuclei (RN), attenuate and facilitate the actions of inhibitory and excitatory RSTs, respectively[53,54].

In response to the changes in vestibular sensation, the medial VST arising from the medial VN regulates eye position and the lateral VST descending from the lateral VN regulates postural equilibrium[50,55] [Figure 3A(d)]. The medial VST controls neck extensor muscle contractions together with eye position. The lateral VST contracts antigravity (extensor) muscles from the neck to the leg and relaxes antagonistic (flexor) muscles of the ipsilateral side, extending the whole body when activated bilaterally [Figure 3A(d)]. Recent bipedal human simulation studies suggested the importance of the cooperation of the RST and VST in maintaining an upright standing posture[56,57].

The SC has a retinotopic map in its superficial layer and somatosensory and auditory maps in the deep layer[58,59]. The SC, thus, converts these sensations into signals that evoke saccades. The signals further evoke the head and body posture orientation accompanying the saccade via the TST and tecto-RST [Figure 3A(e)][58,59]. Because signals from the SC and VN act on the PMRF[60,61], the RST primarily contributes to the postural control against changes in any sensations.

The locomotor network in the spinal cord

There is no doubt that CPGs also exist in humans[62,63]. However, the detailed organization of the locomotor network in the spinal cord in humans has yet to be examined. Therefore, we describe the findings obtained in cats, assuming that the fundamental organization of the locomotor network is expected to be common to humans and cats[11,12]. Functionally, the spinal locomotor network exhibits three layers of organization [Figure 3A(f)]. The first layer has CPGs, consisting of a particular group of the interneuronal network that generates temporospatial patterns of rhythmic locomotor activity[11,12]. The CPGs transfer the rhythmic activity to the layer of interneurons which shape the rhythmic locomotor patterns into templates of each muscle's contractions[11,12,64]. This group likely includes reciprocal Ia interneurons, Ib interneurons, and Renshaw cells[11,12]. Signals of the second layer interneurons are finally sent to the target motoneurons, the third layer, innervating limb muscles[11,12]. The lamina VIII interneurons project to the contralateral side and contribute to alternating left-right limb movements[65,66]. Sensory afferents affect the spinal locomotor network in a step-cycle-dependent manner[11,12]. For example, while group Ib afferents elicit leg flexion during the swing phase, those facilitate leg extension to increase the duration and strength of the support during the stance phase. This is a "reflex reversal" phenomenon. Skin afferents also have a powerful influence on the spinal locomotor network[67]. They are essential in detecting obstacles and correct steps to avoid them when skin afferents from the paw are activated during the swing phase ("stumble-corrective reaction")[67,68] [Figure 3B(a) and C(a)]. However, activation of the paw afferents during the stance phase oppositely excites extensor muscle contractions to reinforce the ongoing extension [Figures 3B(b) and C(b)]. These step cycle-dependent reflex modifications assist in stabilizing posture during locomotion. Activities of the spinal locomotor network are also sent to the supraspinal structures via ascending tracts, such as the spinocerebellar tract (SCT) [Figure 2A] and spinoreticular tract so that the supraspinal motor centers monitor any events in the spinal cord[11,12].

Locomotor commands from the PPN/MLR activate RST to affect all layers of the spinal locomotor network[11,12,31,69], resulting in simultaneous control of locomotor rhythm, pattern, and postural muscle tone[31]. Output from the MLR also activates descending monoaminergic pathways from the RN and LC[39,69], which release 5-HT and NA in the spinal cord. These neurotransmitters increase the excitability of CPGs and modulate sensory processing, mainly suppressing nociception, at the dorsal horn [Figure 3A(g)][70,71].

POSTURE-GAIT CONTROL BY THE HIGHER BRAIN FUNCTION

Human gait is realized by motor programs to maintain an upright posture in response to behavioral plans and changes in the external environment. Multitasking, such as thinking and handling a mobile phone while walking, requires the more sophisticated the action plan and motor program, the more complex the behavior, and the more refined the movement. Therefore, to successfully achieve postural control that satisfies these requirements while walking, each cerebral cortical region that generates cognitive information, action plans, motor programs, *etc*., acts on the postural-related areas of the brainstem so that cortico-brainstem projection regulates biped gait.

Cognitive information processing in the parietal and temporal cortices

Signals in the somatosensory, visual, and vestibular sensation systems are integrated at the parietotemporal cortex, where cognitive information on self and surroundings is produced [Figure 4A(a)][72-74]. This process is critical to maintaining self-consciousness, including the sense of postural verticality[75,76], which is a three-dimensional perception of body schema[77-79]. Spatial cognitive information is conveyed to the frontal lobe via the parieto-prefrontal ("where") and the parieto-premotor ("how") pathways. The former acts on the lateral PFC to promote spatial working memory [Figure 4A(b)]. The latter acts on the PMC to facilitate visually guided movements, such as affordance [Figure 4A(c)].

The ventral occipitotemporal pathway ("What" pathway) concerns visual identification and pattern discrimination of objects [Figure 4A(d)]. Together with semantic auditory information of the temporal lobe, the semantic visual information is transferred to the hippocampus and amygdala. Via the parieto-medial temporal pathway [Figure 4B(a)], the temporospatial visual information is sent to the limbic regions, where the information is emotionally evaluated in the amygdala and memorized in the hippocampus to be used for learning and behavioral navigation[73]. The lateral PFC receives assigned signals of emotional valence to the sensory information via the cingulate-prefrontal pathway[80] [Figure 4B(b)] and the information encoding and retrieving long-term memory via the limbic-prefrontal pathway [Figure 4B(c)] for generating working memory[81].

Frontal cortical presentation of behavior expression

We adjust our daily actions by detecting environmental changes and focusing on information relevant to our goals. This cognitive capability is a hallmark of executive functions[82,83], in which the frontal cortex plays a crucial role.

The PFC

The PFC, which constitutes the core of executive functions, is divided into the lateral, medial, and orbital PFC. The PFC communicates with posterior cortical areas to obtain information concerning the inside and outside of the body. Then, the PFC achieves desired goal-directed behaviors, which consist of complex processes such as orientation and attention, decision making, generation of working memory, planning the action sequence including task switching, personality, and emotionality[82,84-86]. The PMC then generates motor plans and programs to execute the desired movement via corticofugal pathways to subcortical structures.

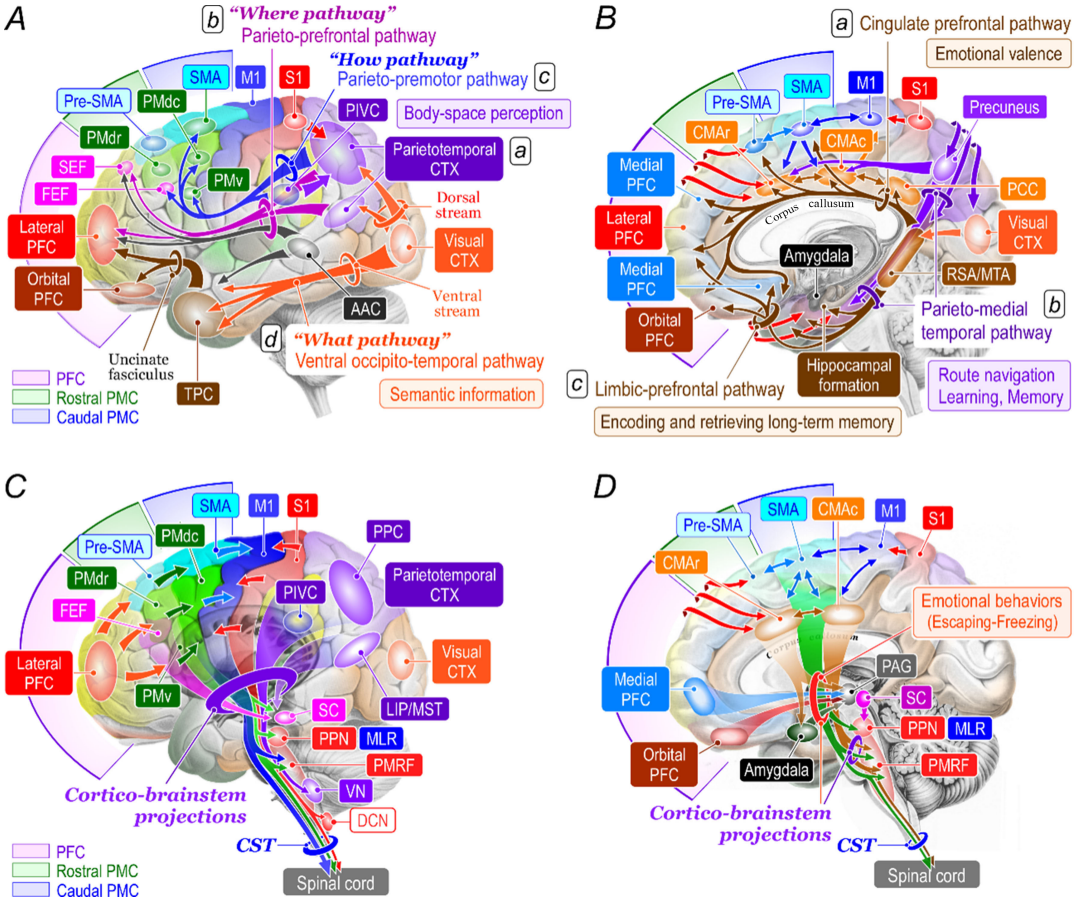

Figure 4. Afferents to (A and B) and efferents from (C and D) the frontal cortex. (A) The lateral view of the cortico-cortical networks. (a) Parietotemporal cortex contributes to generating body and space perception; (b) The parieto-prefrontal pathway (Where pathway) transfers perceptive information of self-body and surroundings to promote spatial working memory in the PFC; (c) The parieto-premotor pathway (How pathway) contributes to visually-guided movement control by the PMC; (d) The ventral occipito-temporal pathway (What pathway) conveys semantic information, such as those concerning pattern discrimination and the visual identification of objects; (B) The medial view of the cortico-cortical networks. (a) The cingulate-prefrontal pathway is involved in assigning emotional valence to sensory information; (b) The parieto-medial temporal pathway contributes to spatial route navigation, route learning, and long-term spatial memory; (c) The limbic-prefrontal pathway contributes to encoding and retrieving long-term memory; (C) The lateral view of the cortico-cortical and corticofugal projections. Intra-cortical connections exist among the PFC and rostral and caudal PMC. Signals in the PFC proceed to the primary motor cortex (M1) via the rostral and caudal PMC. The rostral PMC has projections to the brainstem. The caudal PMC and M1 have projections to the brainstem and spinal cord. The primary sensory cortex (S1) has projections to the DCN and dorsal horn of the spinal cord. Cortico-brainstem projections also arise from the PPC, PIVC, LIP, and MST; (D) The medial view of the corticofugal projections to the brainstem and spinal cord. The PAG receives projections from the medial and orbital PFC. The CMAr directly and indirectly connects to the PAG and SC via the amygdala. These corticofugal PAG-SC afferents may contribute to emotional behaviors, such as escaping and freezing. PFC: Prefrontal cortex; PMC: premotor cortices; DCN: dorsal column nuclei; PPC: posterior parietal cortex; PIVC: parieto-insular vestibular cortex; LIP: lateral intraparietal area; MST: middle superior temporal visual area; PAG: periaqueductal grey; CMAr: cingulate motor area; SC: superior colliculus; AAC: auditory association cortex; CMAr and CMAc: rostral and caudal regions of the cingulate motor area; FEF: frontal eye field; PMdr and PMdc: rostral and caudal regions of the dorsal premotor areas; PMv: ventral premotor area; pre-SMA: pre-supplementary motor area; MTA: medial temporal cortical areas; SEF: supplementary eye field; SMA: supplementary motor area; PCC: posterior cingulate cortex; RSA: retrosplenial cortex; TPC: temporopolar cortex.

The lateral PFC receives exteroceptive and interoceptive information from the posterior cortical regions to produce the global plan of the goal-directed behavior and decide whether to put the plan into action [Figure 4A and B]. The lateral PFC activates the cascade of projections reaching the caudal PMC and the primary motor cortex (M1) via synaptic linkages in the rostral PMC [Figure 4C].

Orbital and medial PFC connect with the hypothalamus and mesencephalic periaqueductal grey (PAG) in addition to the BG and amygdala to constitute a part of the emotional motor system[87,88] [Figure 4D]. The medial PFC projection to the lateral PAG elicits fight-and-flight reactions with accelerated sympathetic activities. By contrast, the orbital PFC pathway to the ventrolateral PAG produces quiescence (freezing) with reduced sympathetic responses[89,90]. The orbital PFC receives olfactory, gustatory, autonomic, visual, and somatosensory afferents[91]. While the lateral part of the orbital PFC facilitates the sensory information into the reward value of positive reinforcement, the medial part of the orbital PFC evaluates them into negative reinforcement, such as punishment[92].

The premotor cortex

The premotor cortex (PMC) uses information through the "how pathway" [Figure 4A(c)] to develop plans and programs to achieve the goal-directed behaviors indicated by PFC's signals. Plans and programs are translated into motor command signals from the PMC and M1 to the brainstem and spinal cord. The PMC is structurally and functionally divided into the rostral and caudal regions.

The rostral PMC primarily receives signals from the lateral PFC[72] and contributes to cognitive motor control processes, such as selecting potential actions, sequencing movements, initiating action, motor learning, and motivation[93-95]. The rostral PMC corresponds to the supplementary eye field (SEF), frontal eye field (FEF), anterior part of the dorsal premotor area (PMd), pre-supplementary motor area (pre-SMA), and rostral cingulate motor area (CMA). Rostral PMC neurons project to the brainstem [Figure 4C and D]. The caudal PMC receives cognitive information of the body and space via "how pathway"[73]. The caudal PMC includes the supplementary motor area (SMA), the caudal part of the PMd, and the ventral premotor area (PMv). The caudal PMC exhibits a somatotopic representation, while not as clear as the M1[96]. Roughly, the PMv relates to the upper extremities, caudal PMd to the upper and lower extremities, and the SMA is primarily associated with the whole body (the face, hand, arm, trunk, and legs)[97]. The caudal PMC sends numerous bundles of fibers projecting to the brainstem and spinal cord [Figure 4C and D]. While the rostral and caudal PMCs play separate roles, they have abundant interconnected fibers[98], indicating that they may share common information to contribute to common tasks.

Figure 5 shows the inputs and outputs of each area in the frontal lobe, along with their roles. Information from the parietal, temporal, and occipital lobes is collected in the PFC, where goal-directed behaviors are planned [Figure 5A]. The pre-SMA and SMA are critically involved in multitask motor programming, such as controlling the onset, sequence of multiple movements, and switching from automatic routine to intentional and vice versa [Figure 5B][82,93,99-102]. The SMA is also involved in language function[103,104]. Because these areas receive information on space and agency from the parietal cortex[74,105,106] [Figure 5C], they enable generating postural control programs optimal to the action sequences while spatially monitoring one's movements [Figure 5B].

The PMd and PMv are primarily involved in visually-guided movements [Figure 5B]. Specifically, the PMv contributes to preshaping the hand and digits to manipulate objects by collating the motor signals with its three-dimensional information from the intraparietal sulcus (AIP)[72], implicated the PMv-AIP circuit in the affordance of reaching and grasping[107]. The PMd may preferentially contribute to body and proximal limb movements, such as orienting body-arm activities while selecting and coding object locations[108]. Further, the PMd may control visually guided gait modification by drawing precise foot trajectories to avoid obstacles and accurate foot placement. The right PMd activity was enhanced during visually-guided paradoxical gait in PD patients[109].

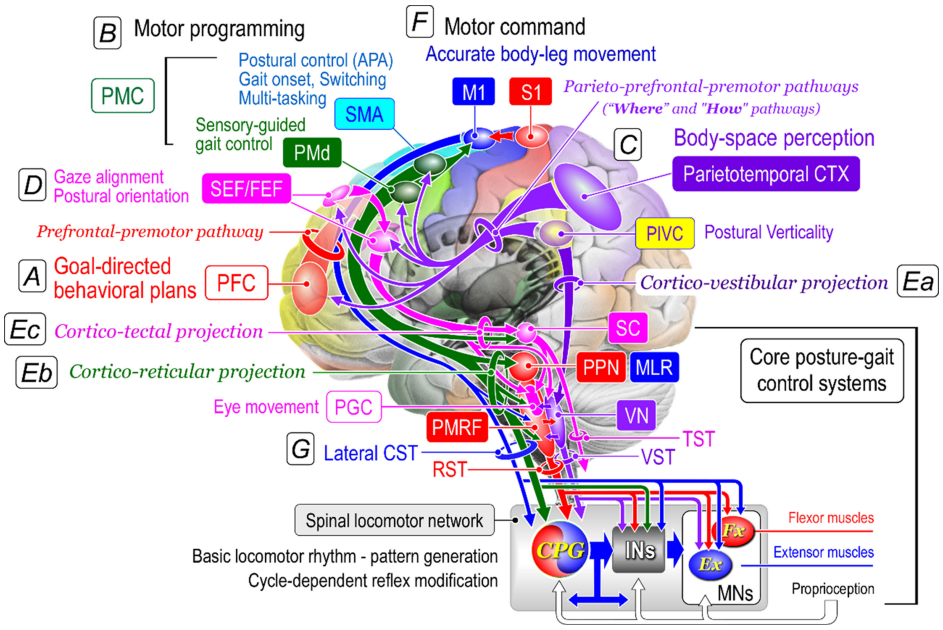

Figure 5. Summary of the cortico-brainstem-spinal cord system involved in bipedal posture-gait control. (A) The PFC is involved in the planning of goal-directed behaviors. The planning signals are issued via the where and how pathways to eye movement-related areas, such as the SEF and FEF, and PMC, including the PMd and SMA, respectively; (B) The PMC contributes to motor programming; (C). The parietotemporal cortex integrates sensory signals to generate "self-body and space perception." This cognitive information is carried via the parietal-prefrontal (where) and parieto-premotor (how) pathways; (D) The SEF and FEF (eye movement-related areas) contribute to gaze alignment and postural orientation; (E) The corticofugal projections, such as the cortico-vestibular (Ea), cortico-reticular (Eb), and cortico-tectal projections, to the posture-gait-related areas in the brainstem, activate brainstem-spinal cord pathways (RST, TST, and VST) to achieve biped posture-gait control; (F and G) The primary motor cortex (M1) (F) issues motor commands to the brainstem and spinal cord via the lateral CST. Please look at the text for detailed explanations. PFC: Prefrontal cortex; SEF: supplementary eye field; FEF: frontal eye field; PMC: premotor cortices; PMd: dorsal premotor area; SMA: supplementary motor area; RST: reticulospinal tract; TST: tectospinal tract; VST: vestibulospinal tract; CST: corticospinal tract.

One realigns the gaze with a saccade to the travel path direction before starting to walk. The head-body reorientation follows this gaze realignment[110,111]. Therefore, cognitive visuomotor eye movements and postural orientation anticipate gait modification[112,113]. The SEF and FEF are primarily involved in this purpose [Figure 5D] according to the signal issued from the prefrontal eye field at the caudal end of the lateral PFC. By representing gaze movements, the SEF participates in deciding the context-dependent action selection that optimally meets the demands of the goal-directed behavior[114-116].

Possible roles of corticofugal projections to the brainstem and spinal cord in the bipedal posture-gait control

Upright (vertical) posture

Appropriate body-space perception enables one to maintain an upright posture. The parietotemporal cortex is critical to the perception of agency, including body schema, sense of agency, and sense of ownership, in addition to the sense of postural verticality[74-78] [Figure 5C]. Because the vestibular sensation always refers to gravity, this is superior to any other sensation to maintain posture[76,77]. Different from other special sensations, the primary vestibular cortex does not exist. Signals in the vestibular system reach the PMC (SMA/PMd), primary sensory cortex (S1), and PIVC via the posterior thalamus. PIVC is the most crucial area of interest, as this region is connected with other vestibular-related cortical areas and has descending projections to the vestibular nuclei[117-120]. Accordingly, corticofugal pathways from the PIVC [cortico-vestibular projection; Figure 5E(a)] and PMC [the cortico-reticular projection; Figure 5E(b)] may contribute to upright posture by recruiting the action of the VST and RST.

Gaze alignment and postural orientation

When one starts walking or changes route direction, one shifts gaze and then turns the body to the target direction (posture orientation). The SEF uses the spatial information [Figure 5C] via the "where pathway" to generate the "gaze alignment and postural orientation" program [Figure 5D]. This program acts on the SC via the corticotectal projection from the FEF [Figure 5E(c)]. In addition to the SEF, the monkey's SMA and PMd have corticotectal projections to the SC, indicating that gaze alignment and postural orientation induced by corticotectal projections are one of the postural control programs of purposeful movement[121,122]. Then, the SC transfers signals to the PGC to facilitate the attention to the target by gazing with postural orientation[59,82] [Figure 3A(c)], leading to the postural set. Further, the FEF regulates vestibulo-ocular reflex, which contributes to stabilizing eye position caused by head movements, via the corticofugal projection to the medial VN. Other eye fields in the parietal [lateral intraparietal area (LIP)] and temporal [middle superior temporal visual area (MST)] cortices [Figure 4C] participate in the pursuit of eye movements by acting on the dorsolateral pontine tegmentum and SC[123-125]. All these eye fields are interconnected. Moreover, feedback signals from the BG and cerebellum regulate the activity of these eye movement networks in the cerebral cortex and brainstem.

Regulation of postural muscle tone and APA

Based on the behavioral plan emitted by the PFC [Figure 5A] and the perceptive information from the parietotemporal cortex [Figure 5C] via the "how pathway", the SMA and PMA generate programs of voluntary movement[72,73,82,93,99,102,126,127] [Figure 5B]. This may consist of a purposeful dexterous movement program, such as sophisticated hand-digits action and precisely controlled leg-foot placement, and a posture control program to achieve multitasking[93,98,102,109]. Postural control programs in the SMA/PMA may induce APA[128,129] by activating cortico-reticular projections[130-136] [Figure 5E(b)] and the RST[31,66,137] [Figure 3B].

Next, the dexterous movement program is transmitted to the M1 [Figure 5F], where motor commands drive the lateral corticospinal tract (CST) [Figure 5G] to evoke accurate body-leg movements. The SMA and the PIVC share cognitive bodily information[117]. The former may maintain load bearing via the cortico-reticular projection [Figure 5E(b)] and the RST. The latter may extend body, maintain upright posture, and control balance via the cortico-vestibular projection [Figure 5E(a)] and the VST. During multitasking, activities of the pre-SMA and SMA are increased by signals through the "how pathway"[93,102]. Accordingly, cortico-brainstem projections [Figure 5E(a-c)] may allow one to achieve any movements, including multitasking, while walking.

Cooperation of cortico-reticulospinal and corticospinal pathways

The caudal PMC and M1 have contralaterally descending fibers via the lateral CST [Figure 5G]. A proportion of M1 neurons have monosynaptic connections with spinal motoneurons. Such cortico-motoneuronal (C-M) connections exist only in humans and some groups of non-human primates, to subserve skilled dexterous movements[6,138,139]. There are also disynaptic corticospinal pathways to forelimb motoneurons from the medial (CMA/SMA) and lateral (PMd/ PMv) PMC and an area 5 of the parietal cortex[139] [Figure 3C and D].

The role of CST neurons in posture-gait control has yet to be examined. Based on the consideration by Strick *et al.* about the function of CST neurons in the control of hand-digit movements, they may play distinct roles in different areas of posture and gait control[6]. For example, the PMd may contribute to the increase in visually-guided gait skills, such as drawing accurate leg trajectories and precise foot placement, and the CMA and SMA may be involved in expanded cognitive posture-gait control, such as gait initiation, route selection, and gait pattern switching. Abundant cortico-reticular fibers from the SMA and PMd to the

PMRF [Figure 5E(b)][130-136], including the PPN/MLR area[140], have connections to forelimb and hindlimb motoneurons via the RST fibers[31,66,137]. These PMC regions, therefore, have parallel and disynaptic connections to motoneurons via parallel direct (corticospinal) and indirect (cortico-reticulospinal) pathways to distal muscles[137]. These parallel pathways are critical, particularly when switching gait patterns. Specifically, the cortico-reticulospinal projection provokes APA to optimize gait alternation with appropriate trunk-leg alignments. The CST achieves accurate foot trajectory and placement. Notably, both descending pathways' signals are integrated with kinesthetic afferent signals at the spinal interneurons, including the CPGs [Figure 3A]. When these processes are impaired, one may lose smoothly changing gait patterns, leading to freezing or falling.

Involvement of emotional system, BG, and cerebellum in posture-gait control

When one faces danger while walking, there is a need to switch gait patterns from routine to intentional abruptly. Such a gait pattern alteration requires rapid anticipation and compensation of posture-gait control. The frontal cortex contributes to this task by using its networks with other cortical areas and subcortical structures such as the BG, limbic areas, cerebellum, and brainstem. These networks enable error detection, switching, and selecting behaviors either proactively by monitoring a contextual cue or retroactively based on error feedback[82,83,141-146]. Declines in executive function disturb these network functions, resulting in posture-gait deficiencies such as hesitation and freezing.

Contribution of the emotional system to the escaping behaviors

Normal subjects usually protect themselves from potentially dangerous situations through escape or active avoidance[7]. However, patients with frontal lobe syndrome and PD exhibit freezing or start hesitation (difficulty in initiation of walking)[147,148]. The midbrain PAG and SC are essential areas for defense and escape [Figure 4D]; their outputs elicit either freezing or flight behaviors accompanied by proptosis, urination, and defecation. However, substantial differences exist. The PAG is primarily involved in such emotional motor behaviors[88]. On the other side, SC increases the alertness of prey species that are exposed to nearby predators[149,150].

Corticofugal projections to the PAG and SC are thus involved in defense and escape behaviors [Figure 4D]. The output from the orbital and medial PFC to the PAG elicits freezing and escaping, respectively[89,90]. The rostral CMA directly connects with the PAG and SC[151] and indirectly via the amygdala and insula[152,153]. The amygdala encodes the environmental context[154], context-dependent fear response, negative affective states, and fear memory consolidation[146,155,156]. Then, it quickly decides whether to retreat, hide, or escape in an emergency[157]. The basolateral part of the amygdala may filter sensory information into decision variables and send them to these cortical areas so that one can select appropriate actions or modify ongoing activities[146].

Contribution of the BG and DA system to the posture-gait control

The BG receives frontal cortical inputs primarily at the striatum. Intrinsic BG circuits, including hyper-direct, direct, and indirect pathways, then convert them into inhibitory outputs from the internal segment of the globus pallidus and substantia nigra pars reticulata (GPi/SNr) [Figure 3A(h)][158]. The output nuclei use GABA as a neurotransmitter. The output of the BG regulates the frontal cortex activity via the thalamus. These neural networks between the cerebral cortex and BG are called cortico-BG loops[159,160], by which the BG contribute to cognitive posture-gait control [Figure 2A]. The BG output directly acts on posture-gait-related areas in the midbrain [Figure 3A(h)]. Specifically, the SNr-SC projection inhibits saccade[14,161] to regulate gazing and orienting posture. The SNr-PPN/MLR projections reduce the activity of the inhibitory RST and locomotor system[34,162]. Accordingly, excessive BG output in PD patients may disturb posture-gait control by affecting cortical and brainstem activities.

The PFC, limbic system, and BG receive the midbrain DA projections. The substantia nigra pars compacta (SNc) has a nigrostriatal DA projection and regulates BG-related motor functions[163-165]. The higher DA release in the striatum decreases the BG output, increasing cortical and brainstem activities to facilitate motor activities. The DA neurons in the SNc also project to the PPN, SC, and cerebellum to modulate posture and gait by directly affecting the core locomotor system's activity[42,45,166] [Figure 2B]. On the other hand, DA neurons in the ventral tegmental area (VTA) project to the PFC (the mesocortical projection) and to the limbic region (the mesolimbic projection, Figure 2B). The former contributes to executive functions, thought, and motivation. The latter involves emotional expression and memory consolidation[127,163-165]. Essentially, DA systems enable one to acquire behaviors accompanying the maximum reward by facilitating plasticity in the associated neural networks[167]. This allows us to obtain reward-oriented reinforcement learning, which may lead to context-dependent posture-gait automatization, the basis of habitualization.

Cerebellar posture-gait control by performance monitoring

The cerebellum primarily contributes to the automatic posture-gait control in a sensory-dependent manner. Using proprioceptive, visual, and vestibular signals in addition to feedback from the spinal cord via the SCT [Figure 2A], the cerebellum monitors the present status based on the internal model[144]. The medial part of the cerebellum receives corticofugal signals, including motor programs and commands, as an efference copy via mossy fiber systems. These signals are integrated at the medial cerebellum, which puts them into signals to adjust gait patterns. Then, they are sent to the brainstem and the motor cortex via the thalamus (motor loops of the cerebellum)[168,169]. On the other hand, the cognitive loop composed of the lateral PFC and the lateral cerebellum contributes to intentional posture-gait control, such as in situations demanding stealthy steps[142,170]. Specifically, the lateral PFC issues instruction via climbing fibers to evoke complex spikes in Purkinje cells in the lateral cerebellar cortex. Complex spikes modulate the motor loop's activity to minimize errors and adapt gait patterns to the given environment. The cerebellum then updates internal models to meet new paradigms, which is an error-based motor learning process[126,170,171].

The concept of the cerebellar internal model places the cerebellum at the interface between motor behavior and cognition, ascribing a critical role in monitoring the performance of diverse cognitive and emotional functions as bases of adaptive behaviors. They are performance-related feedback, error detection, suppression of conflicting response tendencies, allocation of attentional resources, and regulation of emotional responses to specific outcomes such as rewards or punishments[144].

POSSIBLE PATHOPHYSIOLOGICAL MECHANISMS OF POSTURE-GAIT DISTURBANCES WITH REFERENCE TO CORTICO-BRAINSTEM-SPINAL CORD SYSTEMS

The role of cognitive functions in posture-gait control in the elderly subject

Gait velocity is normally 1.1-1.3 m/s. However, it starts to decrease between 60 and 70 years old, even for cognitively normal older individuals[172,173]. As one age, the gait function becomes increasingly reliant on neural systems, including cognitive processes[174,175]. As cognition declines, gait velocity decreases, variability increases, and the ability to multitask during walking is impaired[176]. Approximately 35% of older individuals exhibit abnormal gait with losing automaticity[177]. Further, older adults adopt a slower, more conservative obstacle-avoiding strategy by forward flexion posture with hip flexion to adjust their foot trajectory and placement, indicating that older adults come into contact with obstacles more often than younger people[178]. The decline of posture-gait functions accompanies sensory disruption of visual, vestibular, and proprioceptive components[179] and prolonged APA[180], leading to unstable posture when attentional demand is required. Therefore, gait impairment is a higher risk of developing cognitive

decline[181-183], such as mild cognitive impairments (MCI) and AD[176,184,185]. Motoric cognitive risk syndrome, which has been recently proposed, is a predementia condition featuring subjective cognitive impairment with motor disturbances such as a slow gait, falls, disability, and abnormal movements. The pathological basis relates to frontal lobe damage, particularly in the premotor and pre-frontal cortices, with cholinergic dysfunction. This syndrome is related to diabetes, hypertension, stroke, obesity, depression, smoking, low education, and a sedentary lifestyle[186].

Disturbances in executive cortical function

Posture-gait control requires predicting changes in body-environment interaction induced by one's movements[8,9]. This prediction requires executive function and attention in the frontal lobe, relying on cognitive information via pathways from the occipital-parietal-temporal cortices[72] [Figure 4A and B]. Evidence that damage in any frontal[187], parietal[188,189], and temporal[190] cortices elicits posture-gait disturbance strongly suggests that the intercortical network plays a crucial role in the executive function for controlling posture and gait, and the disruption of this network elicits freezing. The following studies on AD may also validate this consideration. While the clinical phenotypes of AD are strikingly heterogeneous, reflecting the various pathologies with the differences in the cortical distribution of NFT and Aβ plaques[25,26], typical AD is characterized by medial temporal lobe atrophy[191,192]. However, AD features motor symptoms manifested as gait dysfunction[176,185,193]. Moreover, even early-stage AD patients exhibited gait impairments when completing tasks with a greater cognitive load[193].

The frontal cortex is critically involved in behavioral alterations, such as proactive (medial PFC and ACC) and retroactive (pre-SMA) behavioral switching[82,84], the configuration of switched behaviors (lateral PFC), and the selection and dual tasking achievement (pre-SMA and SMA)[93,102]. Frontal cortical dysfunction may, thus, make it challenging to alter posture-gait patterns demanding intentional control, such as starting walking, turning, narrow doorway passing, and obstacle negotiation. Frontal lobe gait disturbances may account for 30% of posture-gait abnormalities in older adults. Symptoms are primarily common to PD, such as delayed gait initiation, decreased gait speed, wide stance, plantar solid contact, and FOG. The impact of dual tasks on gait and cognitive testing on executive function and attention was more disturbed in patients with FOG than those without FOG[194,195]. The interpretation that FOG relates to conflict processing and task switching[196-200] can be plausible. The impairment in psychological functions also results in FOG accompanied by fear of falling[53,201].

Dysfunction of the PFC-PAG pathway may cause freezing[202-204]. While the PFC receives numerous efferent fibers from the cingulate cortex in addition to the occipital, parietal, and temporal cortices [Figure 4A and B], they preferentially act on the orbital PFC if the medial PFC is disturbed. Then, the orbital PFC-PAG pathway [Figure 4D] is facilitated, leading to freezing. Alternatively, dysfunction of the medial PFC may elicit freezing due to either the failure to issue internal cues to prompt alternating the strategy against the external conditions or insufficient PFC command transfer to the PMC to produce motor programs. Because the PFC receives DA from the ventral tegmental area (VTA) of the midbrain[163] and ACh from the basal forebrain[205] [Figure 2B], the PFC dysfunction is also induced by a reduced supply of these neurotransmitters. Dysfunction of the above cortical regions by focal lesions or insufficient ACh and DA supply may disturb the evasion system's function, making it hard to choose either escape or active avoidance. Additionally, failure in planning and programming and maladaptive emotional changes may result in the inability to make decisions to exhibit anxiety and unexplained panic[7]. The alternative interpretation is that the changes in emotional valence to sensory stimuli in the amygdala (fall anxiety) and cognitive load in the hippocampus (memory of falling) may reduce the weight of the relevant decision variables forward to the frontal cortex, leading to freezing.

Disturbances in cortico-brainstem pathways

Because cortical output is sent to subcortical structures to express executive functions, lesions in the corticofugal pathways disturb posture-gait control. The cortico-reticular projection from the SMA [Figure 5D] contributes to upright posture, APA, maintenance of postural muscle tone to withstand antigravity loads, and task switching [Figures 4 and 5C]. The damage in the SMA and its cortico-reticular pathway may, thus, impair posture-gait control, such as postural instability, reduced activity in the trunk and proximal muscles, and delayed walking recovery[206-209]. In contrast, when the damage of this projection was minor, the recovery of bipedal gait, as well as hand-finger movement dexterity, was relatively fast[134,210].

Upright posture is impaired to exhibit lateral leaning or lateral flexion posture in pathological conditions such as "pusher syndrome" by lesions affecting PIVC and posterior thalamus after stroke[211] and "Pisa syndrome" in advanced PD[212,213]. Perception of subjective postural verticality may be disturbed by insufficient PIVC activity[76,118] [Figures 2C(e) and 5E], leading to the imbalance in the left and right cortico-vestibular pathways to elicit Pisa syndrome and pusher syndrome. A recent study showed restoring the injured vestibular-PIVC connections leads to the recovery of pusher syndrome in a stroke patient[210,214]. Supine positioning alleviates the symptoms, while they worsen during standing and walking[215]. These findings suggest that the mismatch between proprioception, visual sensation, and vestibular gravitation may underlie these postural disturbances[76,117,213,216]. Alternatively, symmetry in pallidal output in PD may elicit an imbalance of the thalamocortical processing of vestibular gravitation[217,218], as vestibular sensation signals also reach the PMC where major cortico-reticular fibers arise. Dysregulation of cholinergic actions at cortical and subcortical structures may also be possible in the background[212,213,219].

When the lesion is subcortical, both neurons and fibers of passage are damaged. For example, PSP pathologically exhibits four-repeat tauopathy associated with neuronal loss and gliosis in gray and white matter[220,221]. The tauopathy broadly extends to the cortical and subcortical regions to disrupt cortical connections with subcortical and brainstem structures. Patients with PSP are clinically characterized by early postural instability and falls, vertical supranuclear gaze palsy, parkinsonism with poor response to levodopa, pseudobulbar palsy, and cognitive impairment with predominant frontal executive dysfunction. The gaze deficits concern vertical saccades, vergence impairment, and the disturbed modulation of the linear vestibulo-ocular reflex for viewing distance, leading to abnormal visuospatial cognition[222,223]. Fibers involved in these functions passing through the midbrain tegmentum, including the pretectal area, are severely degenerated. This region also contains fibers connecting the cerebral cortex, BG, and cerebellum with the brainstem, involving gaze control (SC) and posture-gait control (PPN/MLR). In addition, PPN-ACh neurons, which control the activity of the RST and thalamus via their descending and ascending fibers[224], are heavily degenerated[225]. Accordingly, severe damage to the responsible region may cause muscle tone abnormality, postural instability, gait disturbance, and gaze disability. Taken with the prominent early feature of falls, Chen *et al.* suggest that PSP impairs a recently evolved neural system concerned with biped gait in upright posture and frequent gaze shifts between the distant environment and proximate hands[222].

LB pathology leads to a broad range of aging-related neurodegenerative disorders called synucleinopathy, which includes PD, MSA, DLB, and REM sleep behavior disorder (RBD)[226]. Posture-gait disturbances depend on the spread of LB pathology. They are complexified by the combination of cortical executive dysfunction, dysregulation of the execution and switching of automatic movements by the basal ganglia and cerebellum, psychological factors such as fear of falling involving the limbic system, and abnormalities in postural reflexes, muscle tone, and rhythmic limb movements controlled by the brainstem and spinal cord.

Dysfunction of the brainstem and spinal cord

PD is clinically characterized by various motor deficits, such as hypokinesia, resting tremors with 3-5 Hz, muscular rigidity, impairment of postural reflexes, extreme antero-flexion posture, and gait disturbances, including FOG and turning disability[227,228]. While the primary cause is the degeneration of the midbrain DA neurons[7,226], the appearance and expansion of LB pathology strongly modifies symptoms[7,24,226]. In addition to the degeneration of DA neurons, the LB pathology impairs neurons containing ACh, monoamines, glutamine, peptide, and GABA in the brainstem. Impairment of the PPN-ACh neurons is one of the major pathological features of PD, and it relates to the higher incidence of RBD and posture-gait disturbances[229-231]. Further, the damage in monoamine neurons may disturb cholinergic-monoaminergic interaction that regulates posture-gait control and awake-sleep cycles[31,54]. Because MLR-Glu neurons contribute to the initiation of locomotion, the impairment of ACh and Glu neurons in the PPN/MLR area can be the significant pathophysiological basis of posture-gait disturbance.

The dysregulation of the brainstem-spinal cord pathways may be closely related to postural disturbances in PD[213]. For example, dysfunction of the RST may result in muscular rigidity characterized by excessive muscle co-contractions. Specifically, impairment of PPN-ACh neurons may reduce inhibitory RST's activity, which, in turn, facilitates excitatory RST's activity, leading to enhancement of muscle co-contractions. Leg muscle co-contraction is more potent in PD patients during standing and walking than in healthy subjects[232]. This becomes more pronounced with the severity of the disease[233]. Because PD patients become further incapable of anticipatory and compensatory postural responses as the disease progresses[233], dysfunction of the RST not only dysregulates muscle tone but impairs these postural responses.

Dysfunction of the vestibulospinal systems in PD may impair upright posture and vestibular-related postural reflexes[234-237]. Specifically, impairment of the medial VST may reduce neck extensor muscle contractions, resulting in neck bending. Bilateral damages in the lateral VST may decrease contractions of the neck, trunk, and legs, leading to antero-flexion posture. Because noradrenergic LC neurons and serotonergic RN neurons are also degenerated in PD, reduced monoamine supply at the spinal dorsal horn may increase nociceptive afferent signals [Figure 2B(e)], leading to a lower threshold in pain sensation[237,238]. This may facilitate flexion reflex pathways in the spinal cord[239] to further increase flexor muscle contractions, enhancing flexion posture. Besides the LB pathology, the activity of the SC neurons can be suppressed by pathologically increased BG inhibitory effects[240] [Figure 2B]. This may disturb saccade and the following postural orientating responses.

Severe damage in the spinal cord by LB pathology may lead to dysfunction of the spinal locomotor network [Figure 3A(d)]. For example, enhanced muscle co-contractions (muscular rigidity) in PD may increase signals in group Ib muscle afferents and flexion reflex afferents from foot sole and leg joints. Moreover, impairment of the monoaminergic pathways may neither maintain CPGs' activity nor block nociception, disturbing gait rhythmicity and enhancing flexion reflexes [Figure 3A(e)]. These abnormalities may lead to mis-integrating signals from the supraspinal sources, sensory afferents, and CPGs. Notably, increased activity in Ib afferents and skin afferents during the stance phase possibly disturbs switching stance-swing phases. These afferent signals increase during the stance phase, where the reflex reversal can be further enhanced, leading to small stride walking accompanied by lengthening the stance phase and shortening the swing phase.

CONCLUSION

Antigravity function acquired during human postnatal development allows us to control bipedal posture and gait. The antigravity capability involves the development of both the cognitive function of the temporoparietal cortex that enables gravity-related postural control and the motor programming of the motor-related areas in the frontal cortex that allows APA for multitasking during gait. The abundant projections from each cortical area to posture-related regions in the brainstem, such as the PMRF, VN, and SC, enable the strong postural controllability of bipedalism. The cortico-reticular, cortico-tectal, and cortico-vestibular projections may contribute to maintaining postural muscle tone, regulating balance by extending the body, and postural orientation with gazing, respectively. We conclude that the impairment of the cortico-brainstem projection function underlies posture-gait disturbances due to aging and brain degenerative diseases.

DECLARATIONS

Authors' contributions

Wrote the whole manuscript: Takakusaki K
Made substantial contributions to the conception and design of this article: Noguchi T, Chiba R, Ota J
Assisted material preparation: Takahashi M, Kaminishi K, Fukuyama S
All authors discussed the contents and reviewed the article.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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