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**Transcranial Direct Current Stimulation (tDCS) to Improve Lower Limb Motor Recovery  
Following Stroke: A Review and Study Proposal**

A Thesis Presented

by

Jessica Fantz-Sands

To the Keck Science Department

of

Claremont McKenna, Scripps, and Pitzer Colleges

In Partial Fulfillment of

The Degree of Bachelor of Arts

Senior Thesis in Neuroscience

December 12, 2022

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## **Abstract**

Strokes are the result of restricted blood flow to particular areas of the brain classified by their cause. The neural damage they cause are of growing concern as the number of young adults experiencing strokes has increased by 11% in the last decade. Following stroke, there is an imbalance of inhibitory and excitatory neuronal activity, and disruption of neural networks. These changes lead to neuronal death and loss of synaptic connections that, depending on which part of the brain is affected, result in behavioral deficits such as weakness, limb hemiparesis, and loss of coordination, as well as speech and cognitive impairments. However, this loss of function can be partly recovered due to neuroplastic processes. Non-invasive brain stimulation (NIBS) is an approach that involves implanting electrodes into targeted areas of the brain which are connected to an implantable pulse generator on the skin that delivers chronic electric pulse. There are different forms of stimulation, but one with some established success in improving upper and lower limb mobility, as well as some cognitive symptoms, is transcranial direct current stimulation (tDCS). For the treatment of stroke, tDCS aims to increase excitability of the lesioned areas to improve contralesional mobility. While past research has focused on stimulating well established motor regions, such as the cerebellum, motor cortex, and basal ganglia, sensory systems also play a key role in sending information through the ascending dorsal column medial lemniscal pathway, posterior and anterior spinocerebellar tracts, and spinoreticular tracts. Here is a review of the current research on the integration of sensory and motor information in order to carry out desired movement, a discussion about how these networks are being targeted by tDCS after stroke to help patients regain lower limb movement, and finally, a proposed study in which improvements in balance, gait, and postural stability after anodal tDCS continue up to a year post-treatment in chronic ischemic stroke patients.

# 1. What do we know about the neural systems for voluntary control of movement?

## 1.1 Neuroanatomy and Neural Pathways of Voluntary Motor Control

Non-invasive brain stimulation (NIBS) is an approach that involves implanting electrodes into targeted areas of the brain which are connected to an implantable pulse generator on the skin that delivers chronic electric pulse. There are different form of stimulation including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), transcranial alternating current (tACS), transcranial random noise stimulation (tRNS), cerebellar intermittent theta-burst stimulation (CRB-iTBS), and variations and combinations of these stimulation methods. For the treatment of stroke, each form of stimulation aims to increase the excitability of the lesioned areas to improve contralesional mobility. Of particular research interest is in stimulating the cerebellum, motor cortex (M1), and basal ganglia due their major roles in maintaining balance, posture, coordination, and voluntary movement. However, less associated regions have also been implicated including, the hippocampus and inferior parietal cortex (Surgent et al., 2019).

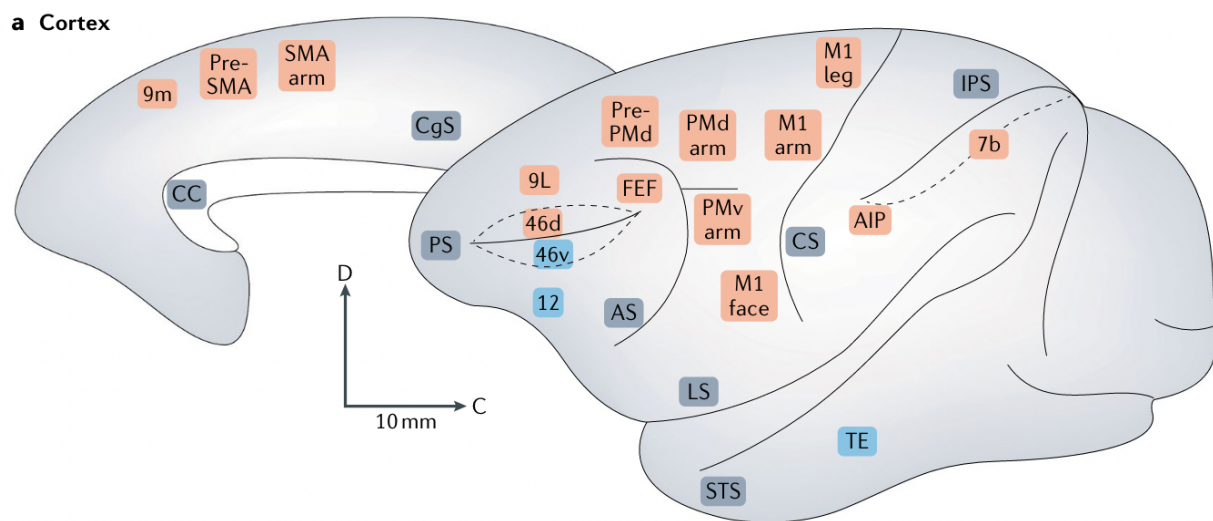
Surgent et al. (2019) originally found 71 regions within a review of brain correlates for postural balance, but was able to dwindle them down to the cerebellum, basal ganglia, thalamus, hippocampus, inferior parietal cortex, and frontal lobe regions after frequency of implication of each region was assessed. In clinical populations, the cerebellum and brainstem were the most frequently investigated, and within the cerebellum/brainstem findings, the cerebellar gray matter accounted for over half of the findings. The superior cerebellar peduncle (SCP) accounted for 10.1% of the brainstem/cerebellar findings with higher white matter integrity (as indexed by DTI measures of higher FA and lower MD) being associated with better balance in assessment studies. Following the brainstem/cerebellar region, the frontal region had the most findings with a total of 44 findings from 13 studies. The inferior orbitofrontal cortex, primary motor cortex, superior frontal gyrus, and supplementary motor areas each accounted for 11.9% of the findings in the frontal region. Temporal regions were implicated in over half of the balance studies with 28 findings from 11 studies (33% of papers). This was largely due to the hippocampus, which accounted for 46.4% of the temporal region findings. Increased hippocampal gray matter volume was associated with better balance. The middle temporal gyrus accounted for an additional 17.8% of the findings in the temporal lobe. Individuals with expert balance showed increased gray matter volume in the middle temporal gyrus, while typically developing individuals showed gray matter volume decreases during balance training that correlated positively with balance improvement. Subcortical regions were implicated in 9 studies included in this review (24% of studies) with 24 findings. The basal ganglia and thalamus each accounted for over 20% of the subcortical findings and the nucleus accumbens each accounted for 12.5%. The majority of findings in the basal ganglia came from balance assessment studies. Reduced size and the presence of white matter hyperintensities in the basal ganglia were associated with poorer

balance ability. The gray matter volume in the basal ganglia, specifically the putamen, was seen to decrease over the course of balance training in typically developing individuals. Findings in the thalamus accounted for 20.8% of the total findings in the subcortical regions and all stemmed from balance assessment studies. Gray matter volume in the thalamus was increased in individuals with exceptional balance and conversely decreased in individuals with balance impairments. Nineteen findings across nine studies (24% of studies) were attributed to structures within the occipital region. Similar to the frontal regions, there were no structures within the occipital region that showed significant and distinct contributions to balance ability or improvement. The parietal regions had only 18 findings in 7 studies (18% of studies). However, the inferior parietal cortex accounted for one-third of the findings in the parietal regions, potentially making it a critical region for understanding the neural mechanisms associated with balance. Typically developing individuals show decreased white matter integrity in this region over the course of balance training. The corpus callosum, insular regions and ventricles/paraventricular regions were all implicated in balance less than six times and in fewer than five studies indicating that while they may play a supportive role in balance, they likely are not the most critical underlying components of balance in the brain.

Although it is unsurprising that the cerebellum was the most implicated region involved in balance, given the widely accepted role of the cerebellum in motor coordination and planning, the degree to which the cerebellum was implicated above all other structures clearly demonstrates its importance specifically to balance. The relatively high implication of the superior cerebellar peduncle (SCP) is also unsurprising, as it is known to transmit motor coordination information from the cerebellum to cortical areas. Thus, it is logical that reduced white matter integrity, in the form of low FA and high MD, was consistently associated with poorer balance in individuals with balance disorders. Unlike regions such as the cerebellum, the hippocampus is not often thought to be at the forefront of balance or motor functions. However, the present results suggest that the hippocampus may play a key role in balance. The hippocampus and parahippocampus may be involved in the encoding or retrieval of spatial information, likely needed for successful balance. It is possible that tracks leading toward and away from the hippocampal regions are also involved in balance and have yet to be explored or reported. The basal ganglia are another known hub of motor function and therefore are highly implicated in balance disorders. Similar to the basal ganglia, the thalamus is thought to play a key role in balance as well as several other sensory-motor functions. Its role in motor ability has been documented through lesion studies of thalamic nuclei and correspondence with movement deficits. As the inferior parietal cortex is involved in a wide range of functions including perception, planning, and interpretation of sensory information, its role in balance is likely one of higher order motor integration and planning rather than motor execution.

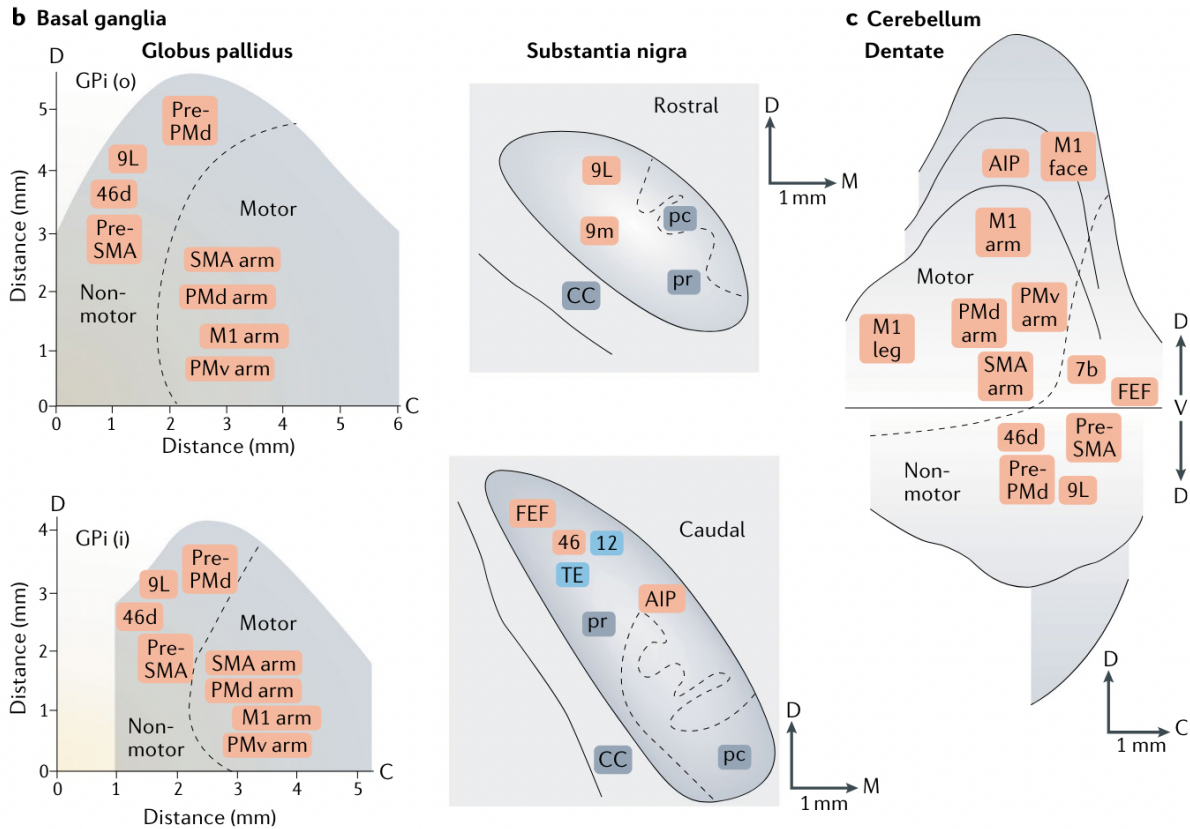
The communication network between the basal ganglia, cerebellum, and cerebral cortex is key to proper motor functioning. Recent studies using non-human primate models found the basal

ganglia and cerebellum to be interconnected at the subcortical level. The subthalamic nucleus in the basal ganglia was the source of a dense disynaptic projection to the cerebellar cortex, and the dentate nucleus in the cerebellum was the source of a dense disynaptic projection to the striatum. This forms an integrated network between the basal ganglia, the cerebellum, and the cerebral cortex (Figure 1). Topographical organization makes it so the motor, cognitive and affective territories of each node in the network are interconnected (Figure 2). This explains how synaptic modifications or abnormal activity at one node can have network-wide effects (Bostan and Strick, 2018).



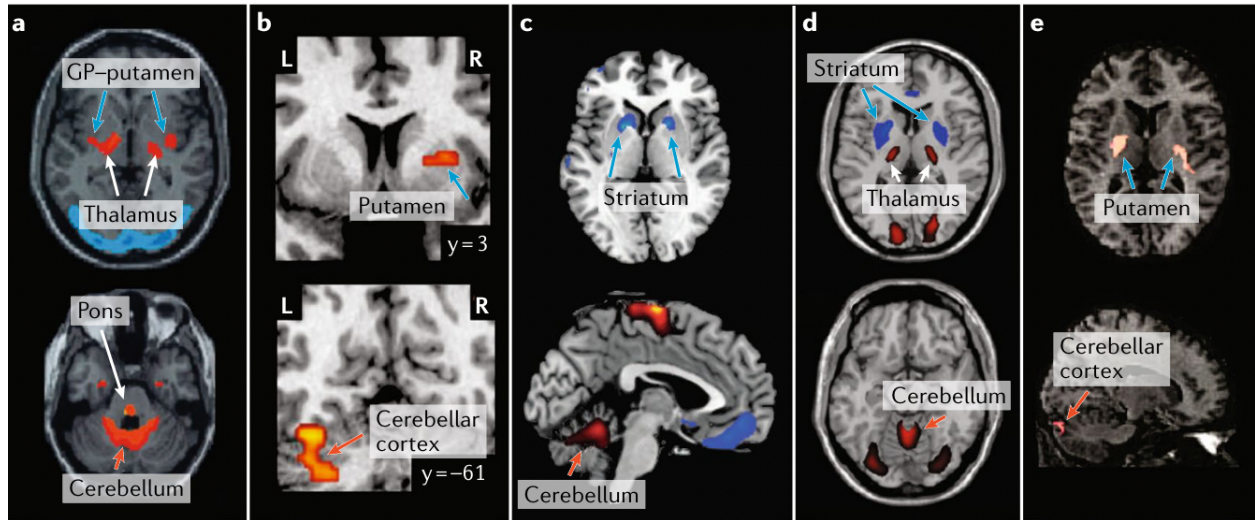
**Figure 1.** The cortical targets of basal ganglia and cerebellar outputs are indicated on medial and lateral views of the *Cebus* monkey brain. Dashed line is the division between motor and non-motor areas of the internal segment of the globus pallidus (GPi) and the dentate nucleus. The orange labels indicate areas of the cerebral cortex that are the targets of both basal ganglia and cerebellar outputs, whereas blue labels indicate areas of the cerebral cortex that are the targets of basal ganglia, but not cerebellar output. The numbers refer to cytoarchitectonic areas. From Bostan AC, Strick PL (2018) The basal ganglia and the cerebellum: nodes in an integrated network. *Nat Rev Neurosci* 19:338–350.



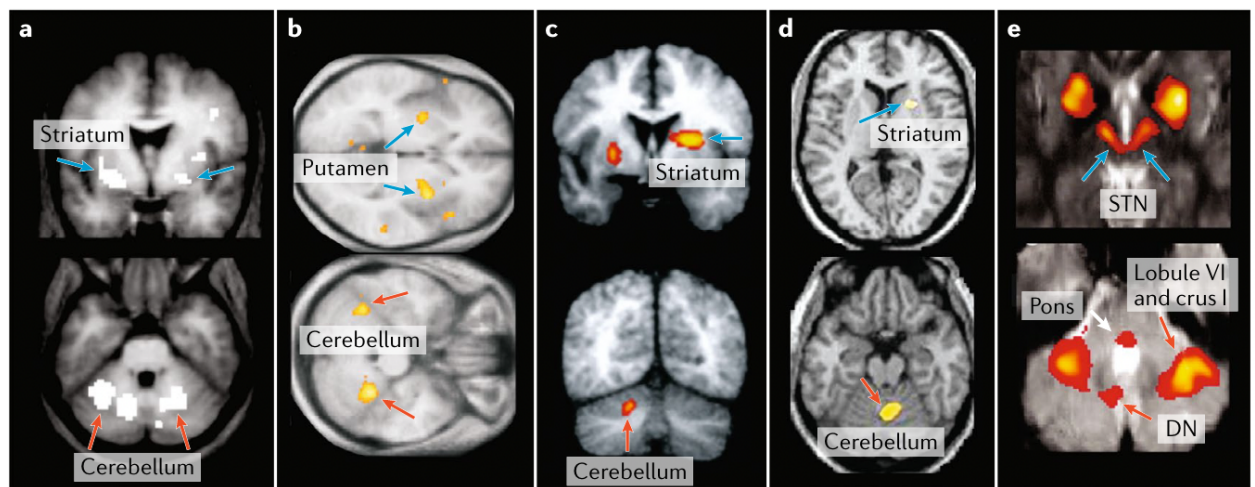


**Figure 2. b)** Summary maps of topography in the basal ganglia and **c)** cerebellar output nuclei on the basis of their cortical targets in the *Cebus* monkey. The division between motor and non-motor areas of the internal segment of the globus pallidus (GPI) and the dentate nucleus is indicated by the dashed lines. In all panels, orange labels indicate areas of the cerebral cortex that are the targets of both basal ganglia and cerebellar outputs, whereas blue labels indicate areas of the cerebral cortex that are the targets of basal ganglia, but not cerebellar output. The numbers refer to cytoarchitectonic areas. From Bostan AC, Strick PL (2018) The basal ganglia and the cerebellum: nodes in an integrated network. *Nat Rev Neurosci* 19:338–350.

Neuroimaging studies in humans also show interactions between the cerebellum and the basal ganglia, in particular, abnormal structure, connectivity and activity in both the basal ganglia and the cerebellum have been reported in several debilitating disorders. Comparing Figure 3 and Figure 4, there is evidence that these pathways may mediate meaningful interactions between cortico–basal ganglia and cortico–cerebellar circuits in health and disease. These observations provide support for the concept that the basal ganglia, the cerebellum and the cerebral cortex are nodes in an interconnected network that operates over multiple functional domains. Findings from neuroimaging studies in healthy individuals have shown co-activations in the basal ganglia and cerebellum in various tasks. These examples include evidence that the cerebellum is involved in functions that are usually associated with the basal ganglia (Figure 4 a and b), and an example of basal ganglia activation in a task that is often considered to rely exclusively on the cerebellum (Figure 4d).



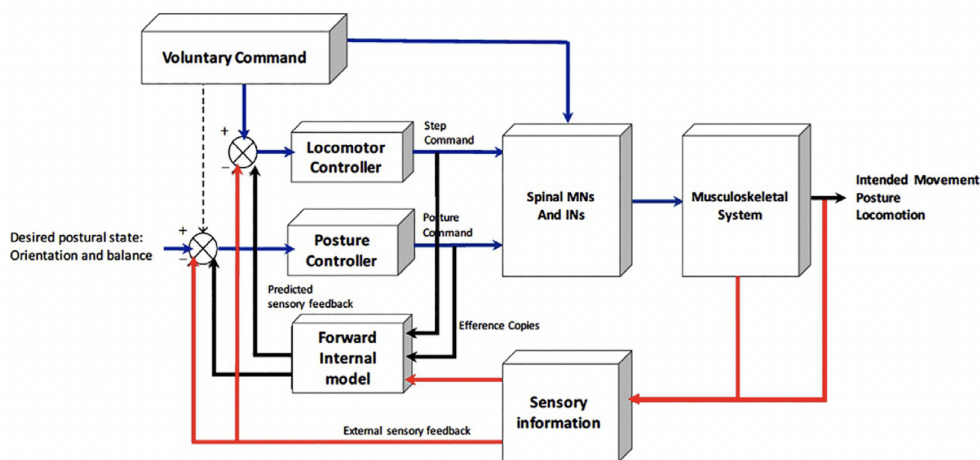
**Figure 3.** Neuroimaging evidence for basal ganglia and cerebellar interactions in disease. **a)** Parkinson disease (PD) **b)** Obsessive-compulsive disorder (OCD) **c)** Tourette syndrome (TS) **d)** Huntington disease (HD) gene carriers **e)** Non-manifesting carriers of dystonia associated mutations in torsin 1A (TOR1A; also known as DYT1). From Bostan AC, Strick PL (2018) The basal ganglia and the cerebellum: nodes in an integrated network. *Nat Rev Neurosci* 19:338–350.



**Figure 4.** Neuroimaging evidence for basal ganglia and cerebellar interactions in normal function. **a)** Temporal difference prediction error during appetitive conditioning with a pleasant taste reward and **b)** during higher-order aversive conditioning. **c)** Movement vigor associated with regional cerebral blood flow increases in regions of both the basal ganglia (putamen and globus pallidus) and the cerebellum. **d)** Sensorimotor adaptation associated with increased activity in both the basal ganglia and the cerebellum. **e)** Early stages of sequence learning are associated with activation of both the subthalamic nucleus (STN) and the cerebellum. Orange arrows in this figure point to activation sites in the cerebellum and blue arrows point to activation sites in the basal ganglia. From Bostan AC, Strick PL (2018) The basal ganglia and the cerebellum: nodes in an integrated network. *Nat Rev Neurosci* 19:338–350.

Production of voluntary movement involves more than the main motor regions previously discussed as sensory information is needed to help orient one's body in the environment.

Locomotion systems can be organized to fulfill the five goals of maintaining vertical support, maintaining balance, providing appropriate postural stability, controlling foot trajectory, and attenuating the transmission of accelerations to the head in order to stabilize the visual and vestibular apparatus. Mackinnon's (2018) generalized model of the components required for anticipatory and reactive control of balance, support, and postural stability emphasizes that motor commands that act upon the musculoskeletal system must be coupled with commands to locomotor and postural control centers (Figure 5). Sensory feedback from self-generated or imposed movement can modulate central motor, locomotor, and postural commands based on the difference between the sensed and desired outcome of movement. Core components for accomplishing the five aforementioned goals include input from sensory systems (visual, vestibular, and somatosensory systems) to provide feedback about the location and movement of objects in the external environment, orientation and motion of the head in space, and the relative position and motion of the body segments, higher-order supraspinal centers that plan, initiate, and execute movement based on goals, reward, and multisensory input, and lower-order subcortical centers (brainstem nuclei and spinal cord) that integrate motor commands with multisensory feedback to ensure the volitional and automatic actions are coupled to appropriate postural adjustments.

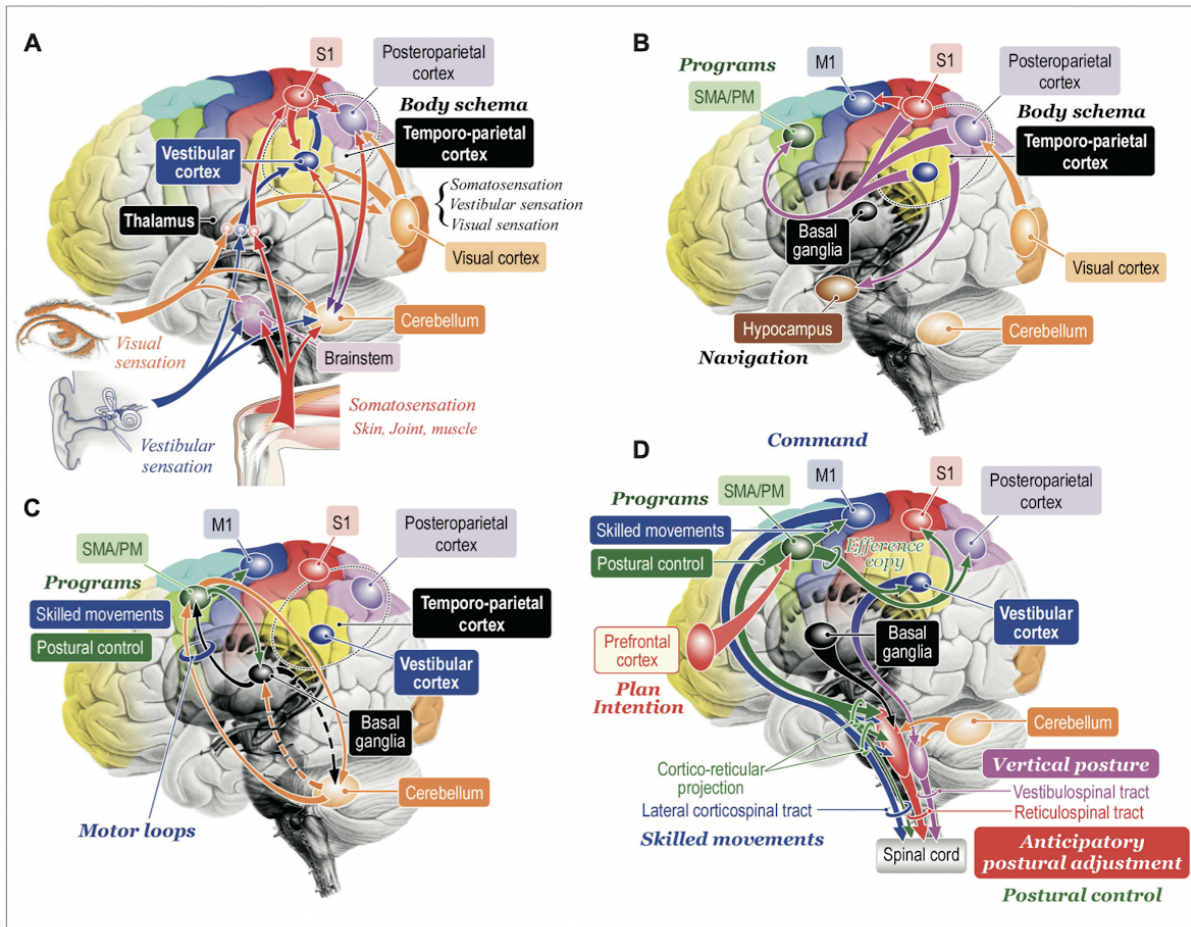


**Figure 5.** General model of posture, locomotion, and voluntary movement control with an emphasis on the conjunction of sensory networks and motor networks to produce fluid movement. From MacKinnon CD (2018) Chapter 1 - Sensorimotor anatomy of gait, balance, and falls. In: Handbook of Clinical Neurology (Day BL, Lord SR, eds), pp 3–26 Balance, Gait, and Falls.

Other authors and researchers such as Haaland et al. (2017) concur that neural control of movement also relies extensively on cognitive mechanisms, and multiple intracortical as well as cortico-subcortical loops support such an interaction. Functional neuroimaging of healthy individuals has shown that greater sequence complexity is associated with activity in a larger number of brain regions, including parietal (inferior and superior) and frontal (lateral and medial premotor, dorsolateral prefrontal) lobes. This has been interpreted as reflecting a greater

contribution of cognitive functions such as planning and working memory, as well as organization, selection, and retrieval of responses commonly ascribed to these regions.

Takakusaki (2017) has hypothesized the cognitive process of postural control into four steps: cognition of bodily information, transmission of bodily information, motor programming, and postural control by corticofugal projections to the brainstem and spinal cord (Figure 6).



**Figure 6.** Hypothesis of cognitive process of posture-gait control. **A) Cognition of bodily information.** Sensory signals flowing into the central nervous system converge to the brainstem, cerebellum, thalamus, and cerebral cortex. At the level of cerebral cortex, signals from the visual cortex, vestibular cortex and primary sensory cortex (S1) is integrated and internal model of self-body, such as body schema and verticality can be constructed at the temporoparietal cortex including the vestibular cortex and posteroparietal cortex. Reciprocal connection between the temporoparietal cortex and cerebellum may contribute to this process. **B) Transmission of bodily information.** The bodily information is then transmitted to the supplementary motor area (SMA) and premotor area (PM) where the information can be utilized as materials to produce motor programs. Similarly, the information is transferred to the hippocampus and is used to navigate further behaviors. **C) Motor programming.** The motor cortical areas closely cooperate with the basal ganglia and cerebellum so that appropriate motor programs are constructed. **D) Postural control by corticofugal projections to the brainstem and spinal cord.** The bodily information generated at the vestibular cortex may be utilized for sustenance of vertical posture via cortico-vestibular and vestibulospinal tract. Signals from the prefrontal cortex including plans and intentions may trigger to run motor programs in the

SMA/PM, which may include those for purposeful movements and associating postural control. The postural control program may be utilized to generate anticipatory postural adjustment via cortico-reticular and reticulospinal tract. Then motor programs are sent to the M1 so that goal-directed purposeful skilled movements can be achieved. From Takakusaki K (2017) Functional Neuroanatomy for Posture and Gait Control. J Mov Disord 10:1–17.

### 1.1.1. Neural Pathways of Sensorimotor Systems

#### 1.1.1.1. Sensorimotor Postural Control

The visual, vestibular, and somatosensory systems provide sensory feedback information to the nervous system that is then used to establish an internal schema of the orientation and motion of the body and its relationship to the external environment. However, each sensory modality does not function independently. Instead, there is extensive convergence and integration of multisensory input, at multiple levels of the neuraxis, on to regions that receive motor (or locomotor) commands and project to motor and premotor neurons in the spinal cord (Bronstein, 2016). Convergence is beneficial because it allows for the modulation of output depending upon the reliability and salience of each input and the goals of the intended movement.

#### 1.1.1.2. Proprioceptive Receptors

Proprioception is a major way in which humans sense their environment. It refers to the unconscious processing of sensory information pertaining to body or limb position and motion in space that is derived from receptors in the muscles, tendons, and joint capsules (Konczak et al., 2009). Proprioceptive and cutaneous receptors are used to convey to the nervous system information about the relative locations, orientations, and rate of movement of the body segments and their relationship to the base of support.

Muscle spindles embedded in skeletal muscles provide signals encoding muscle length and rate of muscle stretch. This feedback modulates muscle activity and informs the nervous system of the relative position and motion of the joint. Fast-conducting afferent feedback from muscle spindles plays a critical role in reactive postural control (stretch reflexes), regulating the stiffness of the joint, providing kinesthetic sense, and has a strong influence on the phase and pattern of locomotion. Kinesthesia is the term used to describe the conscious awareness of the body or limb position in space (MacKinnon, 2018).

Golgi tendon organs (GTOs) are mechanoreceptors that provide output encoding the level of tensile load applied to the tendon. For this reason, GTOs, particularly those in the lower limb extensors, are critical for sensing the forces exerted to resist imposed loads or the force of gravity acting on the body and regulating extensor activity required for maintaining vertical support and postural stability. Cutaneous receptors of the feet provide feedback about the distribution of pressure beneath the foot (base of support), the direction, level, and rate of load bearing (pressure), and the compliance and geometry of the support surface. Four receptor structures of

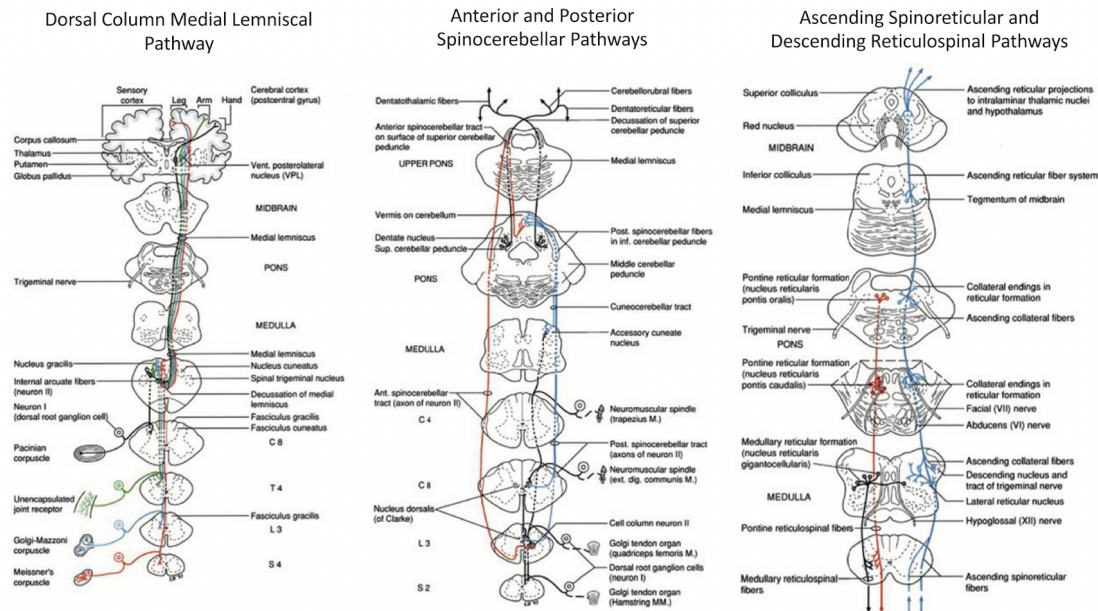
the glabrous skin provide this information: Merkel discs, Meissner corpuscles, Pacinian corpuscles, and Ruffini endings.

### 1.1.1.3. Sensorimotor Ascending Pathways

The main pathway of transmission of proprioceptive and exteroceptive information is via the dorsal column medial lemniscal pathway, posterior and anterior spinocerebellar tracts, and spinoreticular tracts (Figure 7).

## SENSORIMOTOR ANATOMY OF GAIT, BALANCE, AND FALLS

9



**Figure 7.** Primary ascending sensory pathways that contribute to the control of posture, balance, and locomotion. From MacKinnon CD (2018) Chapter 1 - Sensorimotor anatomy of gait, balance, and falls. In: Handbook of Clinical Neurology (Day BL, Lord SR, eds), pp 3–26 Balance, Gait, and Falls.

Based on Carpenter (1991), the fastest-conducting pathway conveying proprioceptive and cutaneous signals is via the dorsal column medial lemniscal pathway. Branches of the muscles, spindle Ia and II afferents, and cutaneous and joint receptor axons travel via the ipsilateral posterior white columns, synapse on to internal arcuate fibers in the nucleus gracilis or cuneatus at the level of the medulla, decussate, then travel via the medial lemniscus to the somatosensory region of the contralateral thalamus. Thalamocortical projections from muscle spindle afferents mainly target Brodmann’s area 3a of the primary somatosensory cortex, near the base of the central sulcus, while cutaneous afferents project to area 3b of the primary sensorimotor cortex.

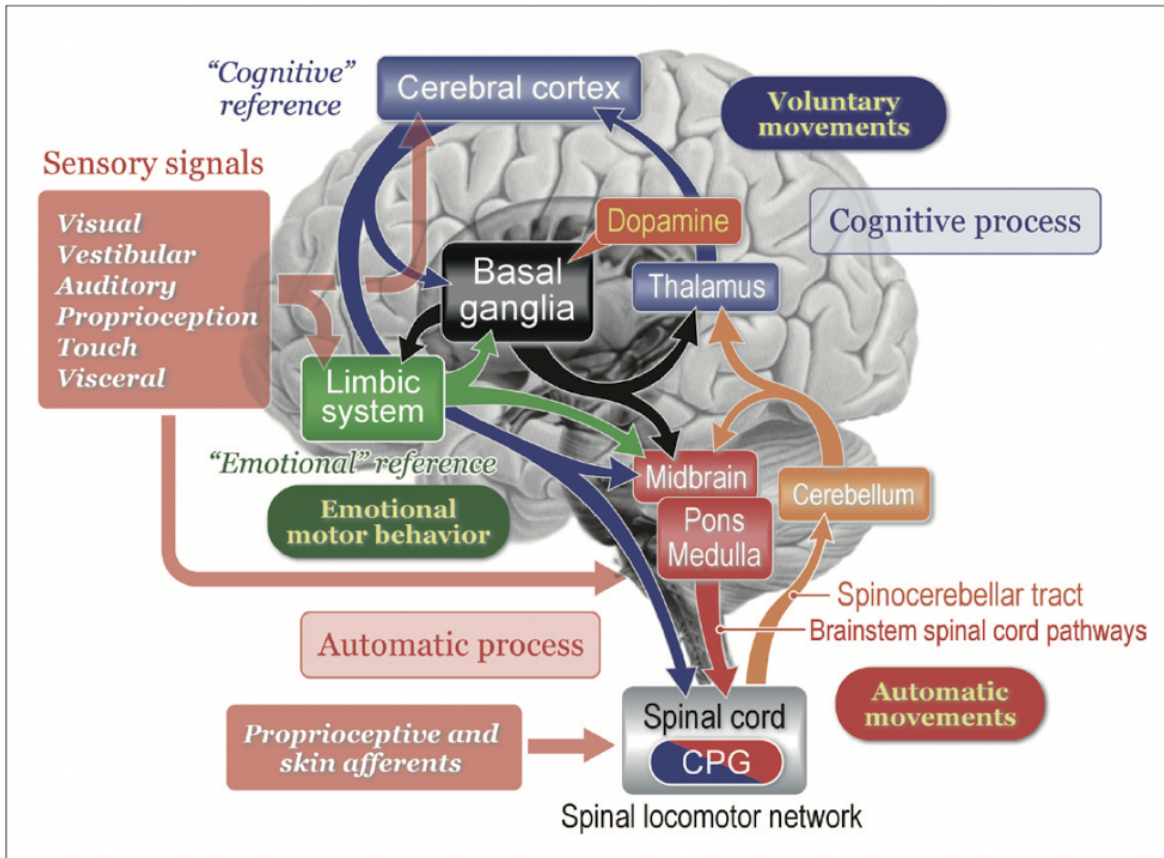
Both the posterior and anterior spinocerebellar tracts are specialized for the transmission of proprioceptive and exteroceptive signals from the lower limb to the cerebellum. The anterior spinocerebellar tract is composed of axons originating from Rexed’s laminae V–VII (Carpenter, 1991). Cells of the anterior tract receive convergent input from proprioceptive and cutaneous

afferents, and they receive collateral projections from descending pathways including the corticospinal and vestibulospinal systems, thus providing supraspinal modulation of ascending activity according to task and postural demands. Axons of the anterior tract immediately cross at the level of the spinal cord through anterior commissural fibers and ascend contralaterally along the anterolateral funiculus, through the superior cerebellar peduncle, and terminate in the contralateral or ipsilateral anterior cerebellar vermis (lobules I–IV). Collaterals of these fibers terminate on regions of the dorsal and medial accessory olivary nuclei. The posterior spinocerebellar tract is derived from large cells of the dorsal nucleus of Clarke. Ascending fibers from the dorsal nucleus ascend ipsilaterally via the posterolateral region of the lateral funiculus, through the inferior cerebellar peduncle, and terminate as mossy fibers in rostral and caudal portions of the vermis (lobule I–IV, pyramus and paramedian lobule; the paleocerebellum). The dorsal nucleus of Clarke is not present above the level of C8. For this reason, some uncrossed Ia and Ib afferent fibers terminate on to cells of the accessory cuneate nucleus in the medulla and ascend via the cuneocerebellar tract to lobule V of the cerebellar cortex.

Axons from proprioceptive (Ia, II, and Ib) afferents synapse onto cells in the posterior horn that give rise to the spinoreticular tract (Carpenter, 1991). These fibers ascend predominantly via the anterolateral portion of the ipsilateral spinal cord then send extensive collaterals that terminate across the extent of the pontomedullary reticular formation, including the nucleus reticularis pontis caudalis and oralis and nucleus reticularis gigantocellularis; regions with reticulospinal neurons that contribute to the control of anticipatory and reactive postural adjustments, locomotion, and postural tone.

### 1.2.2. Integration of Sensory Information in the Brain

Sensory systems send information from their respective receptors through the ascending pathways of dorsal column medial lemniscal pathway, posterior and anterior spinocerebellar tracts, and spinoreticular tracts. They then become integrated in the motor cortices, basal ganglia, and cerebellum and motor information is sent down the lateral and anterior corticospinal tracts, vestibulospinal tract, and the reticulospinal tract (Figure 8).



**Figure 8.** Multisensory signals from the visual, vestibular, auditory somatosensory (proprioceptive), and visceral receptors act on various sites in the central nervous system are sent to and work in combination with the basal ganglia, cerebellum, and cerebral cortex of the brain to produce voluntary movement. From Takakusaki K (2017) Functional Neuroanatomy for Posture and Gait Control. J Mov Disord 10:1–17.

### 1.2.3. Neural Pathways of Voluntary Motor Systems

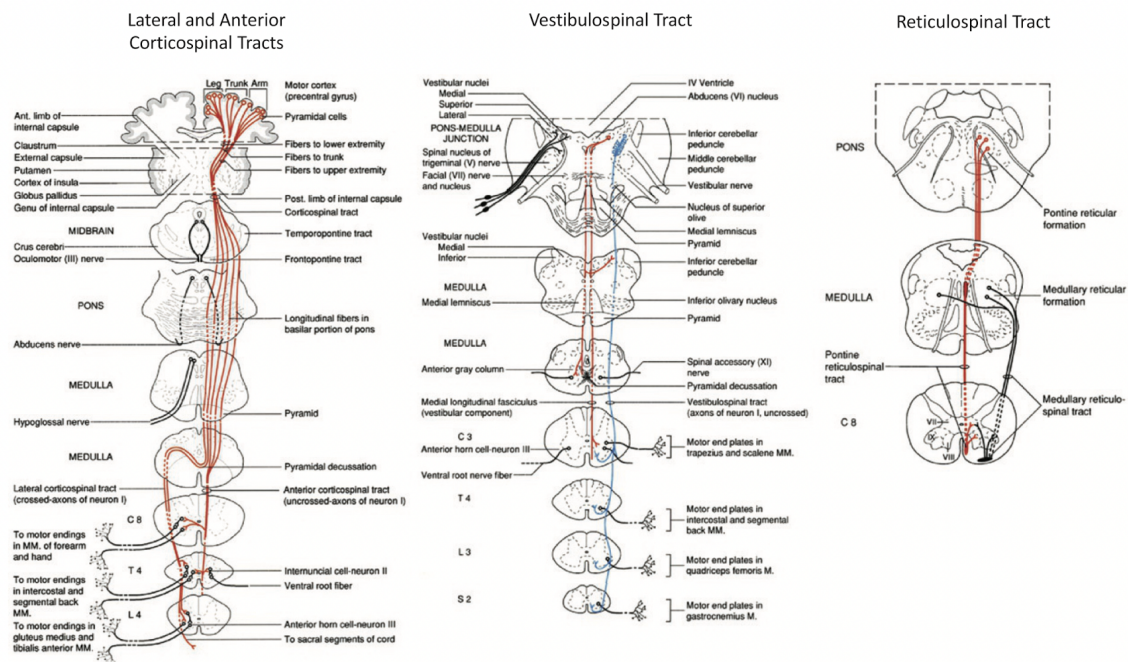
Frontal regions of the cortex, including the prefrontal, premotor, and primary motor cortex, are critical for the selection, planning, initiation, and execution of intended movements. However, as previously described, movements initiated by motor cortical commands must be coupled with postural and locomotor controllers to ensure that postural disturbances generated by movement are anticipated and corrected immediately prior to, or during, the intended action (MacKinnon, 2018). Accordingly, motor and premotor cortical areas have direct projections to the vestibular nuclei, mesencephalic locomotor region (MLR), pontomedullary reticular formation, and intermediate zones of the spinal cord. The midbrain locomotor region (MLR) includes the cuneiform nucleus (CNF) and the pedunculopontine tegmental nucleus (PPN) with room to debate exact location. The vestibular nuclei receive extensive projections from primary motor, premotor and supplementary motor areas, and primary somatosensory sensory areas. Similarly, the pontomedullary reticular formation receives direct projections from primary motor, premotor, and supplementary motor areas.



Similarly, Takakusaki (2017) reviewed the neuroanatomy relevant to posture and gait control, and found that the automatic process of gait, which is steady-state stepping movements associating with postural reflexes including head-eye coordination accompanied by appropriate alignment of body segments and optimal level of postural muscle tone, is mediated by the descending pathways from the brainstem to the spinal cord. Most prominently, reticulospinal pathways arising from the lateral part of the mesopontine tegmentum and spinal locomotor network contribute to this process. Additionally, walking in unfamiliar circumstances requires a cognitive process of postural control, which depends on knowledge of self-body, such as body motion in space and body schema. Next, cognitive information is produced at the temporoparietal association cortex, and is fundamental to sustenance of vertical posture and construction of motor programs. The programs in the motor cortical areas run to execute anticipatory postural adjustment that is optimal for achievement of goal-directed movements. Finally, the basal ganglia and cerebellum may affect both the automatic and cognitive processes of posture-gait control through reciprocal connections with the brainstem and cerebral cortex, respectively.

### 1.2.3.1. Motor Descending Pathways

The three primary descending pathways to produce motor movement are the corticospinal, vestibulospinal, and reticulospinal tracts (Figure 9).



**Figure 9.** Primary descending motor pathways that contribute to the control of posture, balance, and locomotion. From MacKinnon CD (2018) Chapter 1 - Sensorimotor anatomy of gait, balance, and falls. In: Handbook of Clinical Neurology (Day BL, Lord SR, eds), pp 3–26 Balance, Gait, and Falls.

Internally generated movements are selected in prefrontal regions of the cortex, including the dorsolateral prefrontal and presupplementary motor areas, then prepared in mesial premotor regions of Brodmann's area 6, including the supplementary and cingulate motor areas. Each of the motor and premotor regions (premotor cortex, supplementary motor cortex, cingulate motor cortex) sends extensive projections to the spinal cord via the corticospinal tract.

The lateral vestibulospinal tract is the largest of the two tracts and is primarily composed of axons from neurons in the lateral vestibular nucleus (Dieter's nucleus) with some contribution from the descending (inferior) nucleus. The fibers descend ipsilaterally in the ventrolateral columns and have branches that innervate multiple levels of the spinal cord, thus providing the capacity to modulate spinal motoneuron activity across segments. The primary sites of termination of vestibulospinal projections are on interneurons in Rexed's laminae VII and VIII, thus this pathway indirectly influences spinal motoneuron activity via di- or polysynaptic connections (Carpenter, 1991).

The pontomedullary reticular formation and reticulospinal tract is a major descending system for the control of movement and a critical hub for sensorimotor integration that allows the nervous system to appropriately couple voluntary actions with posture and locomotion. This system has been shown to play a prominent role in: (1) anticipatory and reactive postural adjustments; (2) control of locomotor intensity and mode (walking vs. running); and (3) regulation of muscle tone (Takakusaki, 2017). The reticulospinal tract, in conjunction with the vestibulospinal tract, comprises the medial descending motor system (Lawrence and Kuypers, 1968).

## 2. Types of Stroke and how they affect motor systems

Strokes are typically differentiated by their etiologies or the damage they can cause in the brain. The main two categories and most common strokes are Ischemic and Hemorrhagic strokes. Ischemic strokes make up about 90% of strokes while Haemorrhagic strokes make up only 10%.

### 2.1. Ischemic Strokes

#### 2.1.1. Definition/Cause of Ischemic Strokes

A cerebral infarction is the primary lesion of an ischemic stroke. When there is inadequate supply of blood to cerebral tissue, there is a reversible loss of tissue function and, in time, infarction with loss of neurons and supportive structures. Ischemia sets off a cascade of events that begins with loss of electrical function and progresses to disturbance of membrane function with calcium influx leading to calcium-dependent excitotoxicity, generation of reactive oxygen species, and ultimately destruction of cell membranes and lysis of cells. The progression of cerebral tissue to irreversible infarction, depends on the magnitude of the drop in cerebral blood flow and the duration of this drop. With a fall of cerebral blood flow by approximately 50%, patients remain asymptomatic. With a further fall, reversible neuronal dysfunction occurs, leading to ischemic symptoms, typically deficits of function corresponding to the location of the ischemia. If flow is restored rapidly enough, neuronal function returns without infarction and the patient is said to have had a transient ischemic attack. If low flow causing ischemia lasts long enough, irreversible tissue injury occurs, leading to the pathophysiologic events described for cerebral infarction or ischemic stroke. Infarction may occur within minutes in the core of the lesion, and it may occur much later in the periphery of the lesion (Feske, 2021).

#### 2.1.2. Subtypes/Classification of Ischemic Strokes

There are multiple systems to classify the subtypes of ischemic stroke in order to better predict, prevent, and rehabilitate based on etiology. These systems include, TOAST, an updated TOAST (SSS-TOAST), a computerized version of the updated TOAST (Causative Classification System, CCS) all modified TOAST systems based on language and cultural population, and ASCO/ASCOD classifications (Radu et al., 2017). In addition there is the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank and the Oxfordshire Community Stroke Project (OCSP) (Amarenco et al., 2009). TOAST was originally created by Adams et al. (1993) and is the most widely used classification system and maintains five subtypes of ischemic stroke, even in updated and modified versions, based on causation. The five subtypes are large artery atherosclerosis, cardioembolism (or cardio-aortic embolism), small vessel occlusion (or small artery disease), stroke of other determined cause, and stroke of undetermined cause.

### 2.1.2.1. Large Artery Atherosclerosis

Large-artery atherosclerosis is defined as >50% stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis (cortical or cerebellar dysfunction; no lacunar syndrome; cortical, cerebellar, brain stem or subcortical infarct >1.5 cm (15 mm); stenosis of extracranial internal carotid artery; no other abnormalities on tests). There should be no cardiac source of embolism, nor subcortical or brainstem infarct <1.5 cm (15mm) (Amarenco et al., 2009). Large vessel atherosclerotic disease, most commonly in the proximal cervical internal carotid arteries, but often more distally in the internal carotid arteries, in the aorta, the vertebral and basilar arteries, or intracranially, may cause strokes. Arterial dissection of the internal carotid or vertebral arteries is the next most common cause of large vessel disease, particularly in younger patients with no other risk-factor (Feske, 2021).

### 2.1.1.2. Cardioembolism/Cardio-aortic embolism

Embolism is the most common mechanism of stroke. The great majority of emboli are blood clots generated from the heart (cardioembolism) due to cardiac disease (Feske, 2021). High-risk factors are having a mechanical prosthetic valve, mitral stenosis with atrial fibrillation (AF), AF other than lone AF, left atrial/atrial appendage thrombus, sick sinus syndrome, recent myocardial infarction (<4 weeks), left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, and infective endocarditis. Medium risk factors include mitral valve prolapse, mitral annulus calcification, mitral stenosis without AF, left atrial turbulence (smoke), atrial septal aneurysm, patent foramen ovale, atrial flutter, lone AF, bioprosthetic cardiac valve, nonbacterial thrombotic endocarditis, congestive heart failure, hypokinetic left ventricular segment, and myocardial infarction >4 weeks and <6 months (Amarenco et al., 2009). Right-to-left shunting most commonly from patent foramen ovale or from congenital heart disease may lead to paradoxical embolism from the venous circulation. Artery-to-artery embolism occurs when thrombus, usually in association with atherosclerotic plaque or at sites of arterial dissection, is dislodged from large vessel walls to flow distally and lodge in smaller downstream vessels. Some diseases that compromise the integrity of connective tissues and lead to dissection are Fibromuscular dysplasia, Marfan syndrome, vascular Ehlers-Danlos syndrome, Loeys-Dietz syndrome, arterial tortuosity syndrome, Moyamoya disease and moyamoya syndrome, and Large vessel vasculitis (Feske, 2021).

### 2.1.1.3. Small Vessel Occlusion/Small Artery Disease

This is one of the traditional clinical lacunar syndromes and there is no evidence of cerebral cortical dysfunction. There is generally a history of diabetes or hypertension to support the diagnosis. The CT/MRI examination should be normal, or there will be a relevant brain stem or subcortical hemispheric lesion with a diameter of <1.5 cm (Amarenco et al., 2009). Small vessel disease typically causes small deep strokes. Ischemia extends around occluded distal arteries to create lacunar strokes. Small penetrating arteries, most vulnerable to the effects of chronic hypertension and other risk factors, are most commonly affected. Lacunar infarction at common

sites may cause recognizable clinical presentations: posterior limb (pure motor hemiplegia and ataxic hemiparesis) and genu (clumsy hand-dysarthria) of the internal capsule, the basis pontis (pure motor hemiplegia and clumsy hand-dysarthria), the thalamus (pure hemisensory), and the cerebellum. Other sites of deep white matter infarction may cause symptoms referable to their locations (Feske, 2021).

#### 2.1.1.4. Stroke of other determined cause

In these stroke cases, there is usually mixed causation, and causes include nonatherosclerotic vasculopathies, hypercoagulable states, hematologic disorders, and cardiac source of embolism or large artery atherosclerosis should be excluded (Amarenco et al., 2009).

#### 2.1.1.5. Stroke of undetermined cause

Similarly to the previous subtype, stroke of other determined cause, two or more causes are thought to be involved (Amarenco et al., 2009).

#### 2.1.3. Diagnosing Strokes

Noncontrast head computed tomography (CT) is, in most institutions, the first study of choice. The CT is reviewed with special attention to a possible hemorrhage or other alternative non-stroke diagnosis that might explain the presentation, signs of infarction, and evidence of the site of vascular occlusion. Early signs of infarction include insular ribbon sign, which is the loss of gray-white differentiation due to decreased density in gray matter structures such as the insular cortex, or loss of the deep gray (loss of putaminal definition). Given time, sulcal effacement due to tissue swelling, other signs of mass effect, and frank hypodensity can be seen. Magnetic resonance imaging (MRI) is more sensitive for the early identification of acute ischemic stroke, but it is not commonly used in initial assessment because it is less widely available and takes longer to complete. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences are nearly 100% sensitive in identifying acute infarction. MR angiography (MRA) can demonstrate flow or stenosis or occlusion in the arteries of the chest, neck, and head (Feske, 2021).

## 2.2. Hemorrhagic Strokes

### 2.2.1. Definition/Cause of Hemorrhagic Strokes

Nontraumatic intracerebral hemorrhage (ICH) is a subgroup of acute stroke with varying manifestations, including primary intraparenchymal hematoma, intraventricular hemorrhage (IVH), and subarachnoid hemorrhage. It can be from primary causes, or secondary causes that include cerebral venous thrombosis (CVT), rupture of congenital vascular malformations or dural arteriovenous fistulae (dAVF), central nervous system (CNS) vasculopathy/vasculitis (Montaño et al., 2021).

### 2.2.2. Subtypes/Classifications of Hemorrhagic Strokes

Intracerebral hemorrhage may be due to either primary or secondary causes. The most common underlying etiologies depend on several demographic features, including sex, age, race, and socioeconomic status. Below the age of 40, the most common causes of ICH are vascular malformations, cerebral venous thrombosis, sympathomimetic drug use, eclampsia, hypertension, and cryptogenicity (Ruiz-Sandoval et al., 2006).

### 3. How is electrical stimulation used in stroke motor movement rehabilitation?

#### 3.1. Non-Invasive Brain Stimulation (NIBS)

Brain oscillations are rhythmic patterns of neuronal firing generated by the synchronized interaction of neuronal assemblies. These ranges are defined as: delta (1–3 Hz), theta (3–7 Hz), alpha (8–12 Hz), beta (13–25 Hz), and gamma (25–100 Hz). Electrophysiological techniques have revealed distinct behavioral regimes for each oscillatory frequency during both wakefulness and sleep. Delta oscillations have inhibitory functions that are important for cognitive processing, particularly filtering out unnecessary and distracting stimuli. Theta oscillations are largely thought to be involved in spatial learning and memory, but are also involved in non-spatial working memory tasks where the “gating” of oscillations increases synchrony across multiple cortical brain regions. Mental imagery increases cross-regional synchronization of theta and alpha oscillations. Local increases of alpha synchronization are found during the suppression of stimuli, causing individuals to selectively attend to other stimuli modalities, whereas long-range increases of alpha synchronization enhance information transfer between lower and higher order regions, improving sensory integration. Beta oscillations are prominent during wakefulness and are involved in maintaining neuronal equilibrium, working memory, sensory information integration, and voluntary movement control. Gamma oscillations are involved in working memory, sensory and visual responses, and long-term plasticity changes such as the strengthening of synapses.

Following stroke, on a circuit and interhemispheric level, there is an imbalance of inhibitory and excitatory neuronal activity, and disruption of neural networks. These changes lead to neuronal death and loss of synaptic connections that, depending on which part of the brain is affected, result in behavioral deficits such as weakness, limb hemiparesis, and loss of coordination, as well as speech and cognitive impairments. However, this loss of function can be partly recovered due to neuroplastic processes, including the rewiring of neural connections and compensation from other brain regions. Brain stimulation methods, both invasive and non-invasive have shown promising results, but their effects which range from the molecular to the behavioral level, remain poorly understood. In this review they attend to recent advances in stroke recovery related to changes in brain oscillations. Evoked neural oscillations have recently shown an ability to restore and maintain intrinsic homeostatic processes in the brain and could be rapidly deployed during emergency care or shortly after admission into the clinic, making them a promising, non-invasive therapeutic option (Storch et al., 2021).

##### 3.1.1 Transcranial Direct Current Stimulation (tDCS)

tDCS uses low-intensity electrical current flowing unidirectionally from one electrode to the other. The flow of electrons creates a region under the anode where neuronal activity is facilitated and a region under the cathode where activity is inhibited through modifications of transmembrane neuronal potentials and cortical excitability (Gabriel Tortella et al., 2015).

Anodal tDCS over the target brain area and the cathode placed over the contralateral region, has proved effective in improving both upper and lower limb impairments in stroke patients, as well as anxiety and depressive symptoms (Gowan and Hordacre, 2020). Beta coherence between the ipsilesional motor cortex and other brain regions increased in stroke patients who received cathodal tDCS over the contralesional primary motor cortex in the first 4 weeks after stroke, and this increase correlated with improved motor function (Nicolo et al., 2018). However, this coherence has not been shown when using CRB-iTMS. Anodal tDCS over the ipsilesional primary motor cortex has also been associated with increased alpha coherence, which is thought to be involved in neuroplastic changes and corticospinal excitability (Hordacre et al., 2018).

### 3.1.2. Transcranial Alternating Current Stimulation (tACS)

tACS is another transcranial electrical stimulation technique that applies oscillatory electrical stimulation which overrides endogenous rhythmic cortical activities during cognitive processes. Studies using tACS have already shown increases in cerebral blood flow in both hemispheres and lowered resistance in the intracranial vascular bed in patients during the acute phase to 3 months after stroke. Have also shown network integration and segregation in both motor-related regions and on a whole-brain level after 10 and 20 Hz tACS stimulation (Storch et al., 2021).

### 3.1.3. Transcranial Magnetic Stimulation (TMS)

TMS uses a magnetic field to induce electric fields in cortical tissue. Electric current flows through a coil generating a magnetic field, that then flows to the neural tissue and generates another electric field. Repetitive TMS (rTMS) is used in therapeutic interventions and involves long periods of stimulation that are made up of short bursts of pulses. rTMS can either be low frequency (<5 Hz), which causes inhibition, or high frequency stimulation (>5 Hz) which leads to excitation (Storch et al., 2021).

### 3.1.4. Technical Guides to NIBS tools

A technical guide to tDCS, and related non-invasive brain stimulation tools was written by Woods et al. (2016) and covers preparation of preparing and placing electrodes, considerations for stimulating one hemisphere versus the whole brain, monitoring for adverse effects, and its practical use in combination with EEG. Additionally, there is a more basic beginner's guide to creating a tDCS study protocol by Thair et al. (2017), which goes over different variables that should be considered in the implementation of a study.

### 3.1.5. Clinical Utility of NIBS

Clinical utility of NIBS techniques in combination with EEG to treat psychiatric and neurological disorders was written by Tremblay et al. (2019). However, this review focuses primarily on TMS-EEG, little is written on tDCS, tACS, or other variations of NIBS.



### 3.1.5.1. Safety Considerations

Low intensity transcranial electrical stimulation (TES) in humans, encompassing transcranial direct current (tDCS), appears to be safe. No serious adverse events (SAEs) have been reported so far in over 18,000 sessions administered to healthy subjects, neurological and psychiatric patients, as summarized here. Moderate adverse events (AEs), as defined by the necessity to intervene, are rare, and include skin burns with tDCS due to suboptimal electrode-skin contact. Very rarely mania or hypomania was induced in patients with depression (11 documented cases), yet a causal relationship is difficult to prove because of the low incidence rate and limited numbers of subjects in controlled trials. Mild AEs (MAEs) include headache and fatigue following stimulation as well as prickling and burning sensations occurring during tDCS at peak-to-baseline intensities of 1–2 mA and during tACS at higher peak-to-peak intensities above 2 mA. Safety is established for low-intensity ‘conventional’ TES defined as <4 mA, up to 60 min duration per day. Animal studies and modeling evidence indicate that brain injury could occur at predicted current densities in the brain of 6.3–13 A/m<sup>2</sup> that are over an order of magnitude above those produced by tDCS in humans. Using AC stimulation fewer AEs were reported compared to DC (Antal et al., 2017).

### 3.2. Current Research on NIBS focusing on tDCS

Much of NIBS research on stroke recovery has been on finding the most suitable neuromodulatory technique for motor recovery. Generally, seeking to use one of the previously explained techniques in combination with a physical therapy to uncover the quickest and most efficient recovery time. tDCS has been found to have an array of effectiveness across multiple measures of motor recovery. The following are some recent studies following lower limb recovery using tDCS post-stroke.

A random-effects meta-analysis indicated that tDCS alone (SMD =0.44; 95%CI = 0.69/0.19; p<0.001) and combined with another intervention (SMD = 0.31; 95%CI=0.51/ 0.11; p= 0.002) improved balance in adults with neurological disorders (small to moderate effect sizes). Balance improvements were evidenced regardless of the number of sessions and targeted area (Beretta et al., 2022).

A total of 145 studies were found, of which 10 (n = 246) met the inclusion criteria and included in this paper. The present meta-analysis showed that active tDCS have beneficial effects on timed up and go test (TUGT) [mean difference (MD): 0.35; 95% confidence interval (CI): 0.11 to 0.58] and Functional Ambulation Category (FAC) (MD: -2.54; 95% CI: -3.93 to -1.15) in stroke patients. However, the results were not significant on the berg balance scale (BBS) (MD: -0.20; 95% CI: -1.44 to 1.04), lower extremity subscale of Fugl-Meyer Assessment (FMA-LE) (MD: -0.43; 95% CI: -1.70 to 0.84), 10-m walk test (10 MWT) (MD: -0.93; 95% CI: -2.68 to 0.82) and 6-min walking test (6 MWT) (MD: -2.55; 95% CI: -18.34 to 13.23). It was revealed that

tDCS might be an effective option for restoring walking independence and functional ambulation for stroke patients in this systematic review and meta-analysis (Dong et al., 2021).

The meta-analysis of primary outcomes revealed that active tDCS had no better effect than sham on walking speed [ $n = 7$ , standardized mean difference (SMD) = 0.189,  $P = 0.252$ ] and 6-minute walking distance ( $n = 3$ , SMD = 0.209,  $P = 0.453$ ). Among the secondary outcomes, significant positive effects were found on functional ambulation category (FAC) ( $n = 5$ , SMD = 0.542,  $P = 0.008$ ), Rivermead Mobility Index ( $n = 3$ , SMD = 0.699,  $P = 0.008$ ), and timed up and go test (TUG) ( $n = 5$ , SMD = 0.676,  $P = 0.001$ ), whereas non-significant positive effects were found on Tinetti test ( $n = 3$ , SMD = 0.441,  $P = 0.062$ ) and Berg Balance Scale ( $n = 2$ , SMD = 0.408,  $P = 0.177$ ). In subgroup analyses, anodal tDCS had significant positive effects on FAC ( $n = 4$ , SMD = 0.611,  $P = 0.005$ ) and dual-hemispheric tDCS on TUG ( $n = 2$ , SMD = 1.090,  $P = 0.000$ ). The results provide up-to-date evidence of variable effects of tDCS on walking and functional mobility after stroke (Tien et al., 2020).

A total of 24 studies were finally included in this review, totaling  $n = 651$  subjects. Detailed analyses revealed  $n = 4$  (17%) studies with large effect sizes ( $\geq 0.8$ ),  $n = 6$  (25%) studies with medium ones ( $\geq 0.5$ ), and  $n = 6$  (25%) studies yielding low effects sizes ( $\leq 0.2$ ). Statistically significant negative correlations ( $\rho = -0.65$ ,  $p = 0.04$ ) and differences ( $p = 0.03$ ) argued in favor of tDCS interventions in the sub-acute phase. Finally, significant differences ( $p = 0.03$ ) were argued in favor of a bifocal stimulation montage (anodal M1 ipsilesional and cathodal M1 contralesional) with respect to anodal ipsilesional M1. This systematic review highlights the potential of tDCS to contribute to gait recovery following stroke, although also the urgent need to improve current stimulation strategies and subject-customized interventions considering stroke severity, type or time-course, and the use of network-based multifocal stimulation approaches guided by computational biophysical modeling (Corominas-Teruel et al., 2022).

In Koganemaru et al. (2019), each patient received oscillatory transcranial direct current stimulation over the affected M1 foot area and sham stimulation during treadmill gait. The brain stimulation was synchronized with individual gait rhythm, and the electrical current peaks reached immediately before initiation of the swing phase of the paretic lower limb. Ankle dorsiflexion was assisted by electrical neuromuscular stimulation in both real and sham conditions. In a single intervention, the speed of self-paced gait was significantly increased after oscillatory transcranial direct current stimulation, but not after sham stimulation (paired  $t$  test,  $P=0.009$ ). After the intervention was administered repeatedly, self and maximally paced gait speed and timed up and go test performance were significantly improved (self-paced:  $F(1,21)=8.91$ ,  $P=0.007$ , maximally paced:  $F(1,21)=7.09$ ,  $P=0.015$  and timed up and go test:  $F(1,21)=12.27$ ,  $P=0.002$ ), along with improved balance function and increased joint flexion of the paretic limbs during gait. These findings suggest that rhythmic brain stimulation

synchronized with gait rhythm might be a promising approach to induce gait recovery in poststroke patients.

The effect of ctDCS was tested during three static positions, namely, eyes open, eyes closed, and in a tandem position. No effects of ctDCS on standing balance performance were found in the first two positions for patients nor in control subjects. In the tandem stance position, a significant decrease in four separate CoP parameters and in the CoP comp-score was found, suggesting an improvement in standing balance performance in the stroke patients after contra-lesional anodal stimulation. In healthy controls, no effect of ctDCS was found in the tandem stance position (Zandvliet et al., 2018).

25 appropriate studies (including 657 stroke subjects) were found. The data indicates that non-invasive brain stimulation/spinal cord stimulation is effective in supporting recovery. The effects are inhomogeneous across studies: (1) transcranial/trans-spinal direct current/alternating current stimulation induce greater effects than repetitive transcranial magnetic stimulation, and (2) bilateral application of non-invasive brain stimulation is superior to unilateral stimulation. The current evidence encourages further research and suggests that more individualized approaches are necessary for increasing effect sizes in stroke patients (Veldema and Gharabaghi, 2022).

Single-pulse transcranial magnetic stimulation was used to quantify change in corticospinal excitability following tDCS. At the beginning of each session, functional connectivity was estimated using the debiased-weighted phase lag index from EEG recordings at rest. Magnetic resonance imaging identified lesion location and lesion volume. Partial least squares regression identified models of functional connectivity which maximally accounted for variance in anodal tDCS responses. Stronger connectivity of a network with a seed approximating the stimulated ipsilesional motor cortex, and clusters of electrodes approximating the ipsilesional parietal cortex and contralesional frontotemporal cortex in the alpha band (8–13 Hz) was strongly associated with a greater increase of corticospinal excitability following anodal tDCS. This association was not observed following sham stimulation. Addition of a structural measure(s) of injury (lesion volume) provided an improved model fit for connectivity between the seed electrode and ipsilesional parietal cortex, but not the contralesional frontotemporal cortex. tDCS has potential to greatly assist stroke rehabilitation and functional connectivity appears a robust and specific biomarker of response which may assist clinical translation of this therapy (Hordacre et al., 2018).

The purpose of this double-blinded, sham-controlled study was to examine the acute effects of anodal tDCS over the lesioned motor cortex leg area with concurrent limits of stability training on postural control in individuals with chronic post-stroke hemiparesis. Ten individuals with chronic post-stroke hemiparesis received two sessions of either anodal or sham tDCS stimulation

over the lesioned leg region of the motor cortex while undergoing 20 min of postural training, separated by 14 days. Before and immediately after 20 min of tDCS, the 10 m walk test, the Berg Balance Scale, and dynamic posturography assessments were performed. After a single session of anodal tDCS with concurrent postural training, no changes in clinical measures of balance and walking, assessed using the Berg Balance Scale and 10 m walk test were observed. For dynamic posturography assessments, participants demonstrated improvements in adaptation responses to toes-up and toes-down perturbations, regardless of the condition of tDCS they received. Additionally, improved performance in the shifting center of gravity was observed during anodal tDCS. Multiple sessions of tDCS stimulation may be needed to improve functional measures of postural control and walking (Liang et al., 2020).

Kang et al.'s (2020) systematic review and meta-analysis investigated the effects of rTMS and tDCS on functional balance and postural control in patients with stroke. tDCS did not show any significant therapeutic effects. However, findings regarding the potential treatment effects of NIBS interventions on the functional activities of the lower extremities are limited. Despite the therapeutic effects on functional balance and postural control collapsed across the rTMS and tDCS interventions, the moderator-variable analysis identified a significant overall effect size for the rTMS protocols. The different treatment effects between the rTMS and tDCS were consistent with previous meta-analytic findings that rTMS combined with movement training significantly improved gait speed in patients with stroke whereas tDCS combined with movement training did not enhance gait speed. Vaz et al., (2019) suggested the lower rate of tDCS treatment effects on lower limb function may be related to low-intensity stimulation (1-1.5mA), and this may be insufficient to trigger the deep structures that modulate the brain activations related to the lower leg muscles. In this meta-analysis, although low levels of stimulation intensity (1-1.5mA) were used in 3 out of 9 tDCS studies, the 3 comparisons did not necessarily indicate lower treatment effects. No related significant relationship was observed for the number of sessions of tDCS and greater improvements in functional balance and postural control post-stroke. This result is consistent with a prior meta-analysis that failed to identify any significant immediate treatment effects using multiple tDCS sessions on upper limb recovery (Tedesco Triccas et al., 2016). It should be taken into consideration that the methodological differences between rTMS and tDCS protocols (studies explored various brain regions including M1, SMA, and cerebellum) may additionally have influenced the treatment effects on functional balance and postural control post-stroke (Kang et al., 2020).

A growing concern is tDCS's ability to stimulate deeper brain regions, as this may be the reason no significant improvement was seen in this meta-analysis. tDCS needs to find a way to deal with the functional and anatomical limitations of the leg area of the M1. Given the region of leg representations in the motor areas on the medial wall of the hemisphere within the longitudinal fissure, NIBS techniques for functional balance and postural control rehabilitation need to be more precise and in-depth regarding the triggering of exact lower limb cortical motor areas. For

rTMS, the double-cone coil and H-coil are presumably more effective for stimulating deeper brain areas (depth of the stimulated structure: 3-4cm by double-cone coil and 4-6 cm by H-coil) than the conventional figure-of-8 coil rTMS technique. For tDCS, high-definition tDCS targeting a focal area using specialized small electrodes are potentially more beneficial than conventional tDCS using relatively wide electrodes because this technique may stimulate specific targeted cortical as well as deep brain structures (Caparelli-Daquer et al., 2012).

Preliminary evidence from both healthy adults and stroke survivors indicates that tDCS is a promising intervention to support recovery of lower limb function. Studies provide some indication of both behavioral and physiological changes in brain activity following tDCS. However, much work still remains to be performed to demonstrate the clinical potential of this neuromodulatory intervention. Future studies should consider treatment targets based on individual lesion characteristics, stage of recovery (acute vs. chronic), and residual white matter integrity while accounting for known determinants and biomarkers of tDCS response (Gowan and Hordacre, 2020), efficacy, time per stimulation session, and more.

## 4. Research Proposal

### 4.1. Introduction

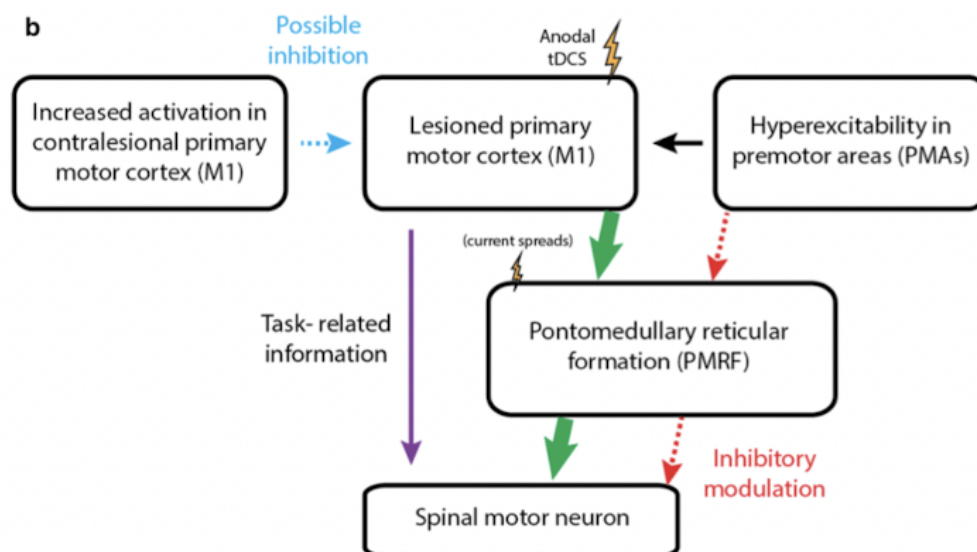
The prevalence of strokes is on the rise in young adults and the current therapies have left about 38% of stroke survivors non-ambulatory 6 months post-stroke and 80% unable to successfully maintain balance and postural control, leaving them more susceptible to falling, rehospitalization, decreased quality of life, and unable to live independently (Geurts et al., 2005; Kollen et al., 2006; Tyson et al., 2006; Batchelor et al., 2015). Non-invasive brain stimulation is of growing interest due to research showing its ability to alleviate symptoms of neurological, mental, and substance abuse disorders (Boes et al., 2018; Beretta et al., 2022). Of the different variations, tDCS has shown to improve mobility in both upper and lower extremities in post-stroke patients as well as alleviate more affective symptoms, such as depression and anxiety (Gowan and Hordacre, 2020). The stimulation aims to increase the excitability of the lesioned areas to improve contralesional mobility (Surgent et al., 2019). tDCS has shown to improve balance, postural stability and gait in acute and chronic post-stroke stages, in some instances within four weeks of treatment (Nicolo et al., 2018; Zandvliet et al., 2018; Liang et al., 2020; Tien et al., 2020; Corominas-Teruel et al., 2022). However, much is needed to be explored in tDCS research to determine the methodology that is the most efficient and effective in the long-term, including single session duration, frequency of sessions, total duration of therapy, use on stroke subtypes and severity, lesion location, electrode placements, and the best time to introduce therapy following a stroke to produce long-term mobility.

A modeling study in which the researchers developed anatomical models of ischemic stroke regions from 10 cm<sup>3</sup> to 50 cm<sup>3</sup> to mimic an acute and chronic ischemic stroke patient, and used electric montages to compare tDCS electric field intensity distributions, has found that chronic ischemic stroke patients that undergo tDCS therapy receive the greatest benefit compared to stroke patients in the acute post-stroke stage since contrasts in the tissue conductivity of the chronic model resulted in a higher electric field induced around the lesion volume, which could stimulate the remaining healthy tissue in the area (Manoli et al., 2017). Additionally, current research lacks longitudinal studies on the long-term effects of non-invasive brain stimulation techniques. A recent study on acute stroke patients followed their mobility improvements (on the Wolf Motor Function Test (Wolf et al., 2001), the Semmes Weinstein Monofilament Test (Weinstein, 1993), the Upper Extremity section (UEFM), the Lower Extremity section (LEFM) and the Somatosensory section of the Fugl-Meyer Test (Fugl-Meyer et al., 1975), the Tardieu Spasticity Scale (Ansari et al., 2008), the Stroke Impact Scale (Lin et al., 2010), the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) and the Barthel Index (Shah et al., 1989)) through one month of anodal tDCS therapy, and followed up with the same assessments three months, six months, and one year after completing the therapy. The study found improvement in balance, gait, and lower limb movements up to a year after completion of the therapy (Bornheim et al., 2020).

Due to the possibility of tDCS being more effective on chronic stroke patients and a lack of research into the long-term effects of NIBS, this study aims to use the protocol created by Bornheim et al. (2020) to compare motor control of lower limb movements of chronic stroke patients following a four week anodal tDCS therapy and following their progress the third month, sixth month, and one year after completion of the therapy. Additionally, this study will use a sham tDCS condition as a comparison to true tDCS to assess whether any improvements can be attributed to tDCS or due to natural reshaping due to neuroplasticity. Although this study is based on Bornheim et al. (2020), it will differ in some of the assessments that will be used. The mentioned study has multiple upper extremity measures, whereas this study will focus on lower extremity mobility. Instead of using the Wolf Motor Function Test (Wolf et al., 2001), the Semmes Weinstein Monofilament Test (Weinstein, 1993), the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) and the Barthel Index (Shah et al., 1989), this study will use the Berg Balance Scale (Berg et al., 1992) and the Falls Efficacy Scale (Tinetti et al., 1990). The study will maintain the the Lower Extremity section (LEFM) of the Fugl-Meyer Test (Fugl-Meyer et al., 1975), and the Stroke Impact Scale (Lin et al., 2010). Based on Manoli et al. (2017), the first hypothesis is that chronic stroke patients will score statistically significantly higher in all assessments following initial use of tDCS compared to the sham tDCS, and using Bornheim et al. (2020) it can be further hypothesized that effects will continue up to a year following completion of tDCS therapy, which will be reflected in increased scores in assessments.

#### 4.2. Methods

This study will combine previously published protocols regarding the use of tDCS on acute stroke patients and chronic stroke patients. There are multiple forms of tDCS, each with contradicting results about their efficacy. One analysis has shown both cathodal tDCS over the contralesional hemisphere and bilateral tDCS induce greater improvement in balance, gait, and lower limb movements parameters in stroke patients (Veldema and Gharabaghi, 2022), yet another that had hypothesized cathodal tDCS to perform better than anodal tDCS, found anodal tDCS over M1 to offer a new neuromodulatory target to remediate the imbalance in neuronal excitability between PMAs and subcortical brainstem level, which in turn improve the posture and movement planning, preparation, and execution in individuals with stroke (Yang et al., 2021). Anodal tDCS is when the anode is placed over the motor cortical area to be stimulated, and the cathode above the contralateral eye, tDCS (thus termed anodal) increases cortical excitability. Conversely, when the cathode is placed over the motor cortical area to be stimulated, and the anode above the contralateral eye, cortical excitability is reduced. Following Yang et al. (2021), anodal tDCS over the ipsilesional M1 and the cathode over the contralateral supraorbital ridge. The mechanism by which anodal tDCS promotes balance, postural stability, and movement planning can be found in Figure 10.



**Figure 10.** Application of anodal tDCS over the contralesional stroke patients' M1 facilitates the subcortical PMRF via the cortico-reticular drive (green arrow) or via direct excitations caused by applied current, promoting postural stability and movement planning. Yang C, Gad A, Creath RA, Magder L, Rogers MW, Waller SM (2021) Effects of transcranial direct current stimulation (tDCS) on posture, movement planning, and execution during standing voluntary reach following stroke. *J Neuroeng Rehabil* 18:5.

Outcome measures will be the Berg Balance Scale (Berg et al., 1992), Falls Efficacy Scale (Tinetti et al., 1990), Lower Extremity section (LEFM) of the Fugl-Meyer Test (Fugl-Meyer et al., 1975), and the Stroke Impact Scale (Lin et al., 2010). Assessments will be completed prior to either therapy condition, and repeated following each period of interest after beginning therapy (1 week, 2 weeks, 3 weeks, 4 weeks, 3 months, 6 months, 1 year).

#### 4.2.1. Participants

Participants will be recruited from rehabilitation and physical therapy offices. Once potential patients have been identified, researchers will approach them to provide information about the study, both in verbal and written form, only after the patient has indicated interest in participating. Bornheim et al. (2020) initially had 50 participants but four dropped out before final analysis, yielding a dropout rate of 8%. Meta analyses on the use of tDCS has shown inconsistent effect sizes, ranging from low to high (Kang et al., 2020; Tien et al., 2020; Chow et al., 2022). Hence, this study will use a moderate effect size of 0.6. With 80% power (20% Type II Error), setting the standard deviation to 1, setting a two-sided statistical significance to  $p < 0.05$  (5% Type I Error), making the standard  $z$ -alpha/2 score is 1.96 and the standard  $z$ -beta score is 0.84, 88 participants are needed. Correcting for the 8% dropout rate, 96 participants are needed. With 96 total participants, 48 will be assigned to the sham tDCS condition and 48 will be assigned to undergo the real tDCS.



In order to be included participants must be at least 18 years old and have had an ischemic stroke at least six months prior, with hemiparesis following unilateral hemispheric cerebral lesions. They also need to be able to understand and follow instructions (cannot have aphasia), and be able to consent to the procedures. Participants will be excluded from initial participation if they have any recent surgical history, have an unconfirmed lesion, suffered a Hemorrhagic stroke, suffered a Transient Ischemic Attack, over the age of 80, have a pacemaker, have chronic use of alcohol or drugs, or have a progressive/neurological disorder (Geiger et al., 2017; Bornheim et al., 2020). Participants will be excluded from the study at any point if they experience adverse to severe side effects from tDCS, have another stroke, or die for unrelated reasons. Use of human participants will be approved by the IRB at the location of the study. Demographic information will be recorded and presented.

#### 4.2.2. Procedure

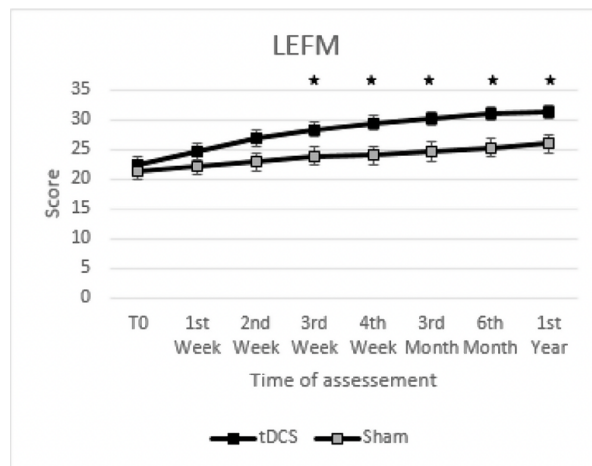
Following Bornheim et al. 's (2020) procedure, patients will be randomly assigned to either anodal tDCS or sham tDCS. The electrodes, both 25 cm<sup>2</sup>, placed on a participant's head with the anode placed over the primary motor cortex of the lesioned side and the cathode over the contralesional eye (C3/Fp2 or C4/Fp1) (the 10/20 EEG system is the most frequently used in stroke research. The electrodes were attached using a neoprene EEG cap, to deliver either a continuous current or no current and at a rate of 5 times per week for 4 weeks. tDCS will last 20 min at 1 mA, with a 15 s ramp up and ramp down. Sham tDCS will consist of a 15 s ramp up followed by a 15 s ramp down of the current. This method has been shown to be efficient for blinding patients (Gandiga et al., 2006). Prior to their first therapy session, participants will undergo the Berg Balance Scale (Berg et al., 1992), Falls Efficacy Scale (Tinetti et al., 1990), Lower Extremity section (LEFM) of the Fugl-Meyer Test (Fugl-Meyer et al., 1975), and the Stroke Impact Scale (Lin et al., 2010) to establish a point to begin comparison. Assessments will be completed following each of the predetermined periods of interest. Adverse effects will be systematically measured by a questionnaire resembling that of Brunoni et al., (2011).

#### 4.2.3. Analytic Approach

The Shapiro-Wilk test will be used to test normality. To compare the groups for baseline homogeneity and throughout the different evaluations, the Student *t*-test will be used. A two-way ANOVA will be applied to all outcome measures (LEFM of the Fugl Meyer, SIS, BBS, and FES). Assuming the assumption of homogeneity is not violated, Tukey post-hoc multiple comparisons tests will be carried out, which will reveal any significant differences across the time periods of interest. If the assumption of homogeneity is violated, the Games-Howell comparisons will be completed. Data will be presented as mean  $\pm$  standard deviation. Cohen's *d* will be used to estimate the effect size of treatment. Statistical significance was accepted at  $p < 0.05$ . SPSS software will be used for statistical analysis.

### 4.3. Anticipated Results

This study will investigate two hypotheses. The first hypothesis is that the stroke patients will score statistically significantly higher in all assessments following initial use of tDCS compared to the sham tDCS. The second hypothesis is that there will be continued improvement up to a year following the completion of the treatment. Each two-way ANOVA should yield statistically relevant results. For example, a two-way ANOVA will be performed to analyze the effect of sham tDCS and anodal tDCS on score on the Fugl-Meyer Lower Extremity scale. A two-way ANOVA should reveal that there is a statistically significant interaction between the effects of sham tDCS and anodal tDCS ( $F(df \text{ interaction}, df \text{ within}) = F\text{-value}, p < 0.05$ ). Simple main effects analysis will show that sham tDCS does not have a statistically significant effect on the score of the Fugl-Meyer Lower Extremity Scale of chronic stroke patients ( $p > 0.05$ ). Simple main effects analysis will show that the anodal tDCS does have a statistically significant effect on the score of the Fugl-Meyer Lower Extremity Scale of chronic stroke patients ( $p < 0.05$ ). This trend should be consistent across all two-way ANOVAs for BBS, FES, and SIS assessments. An example of plotted data is in Figure 11.



**Figure 11.** Example of predicted results using the Fugl-Meyer Lower Extremity assessment. From Bornheim S, Croisier J-L, Maquet P, Kaux J-F (2020) Transcranial direct current stimulation associated with physical-therapy in acute stroke patients - A randomized, triple blind, sham-controlled study. *Brain Stimulation* 13:329–336.

There should be an overall trend of improvement over time, and significantly more improvement, reflected in better scores, in chronic stroke patients that are exposed to real anodal tDCS. However, due to the mixed results on the success of anodal tDCS there may be some assessments that do not show improvement to a statistically significant degree (Yang et al., 2021; Veldema and Gharabaghi, 2022).

### 4.4. Discussion

This study should show that anodal tDCS is beneficial due to its long-term effects on balance, postural control, and gait. It has now been shown to be an effective therapy in both acute and

chronic stroke. The mechanism is likely that the application of anodal tDCS over the contralesional stroke patients' M1 facilitates the subcortical PMRF via the cortico-reticular drive, or via direct excitations caused by applied current, promoting postural stability and movement planning. Much remains to be learned, including the most effective duration for single session stimulation, electrode placement, frequency of sessions, total duration of therapy, use on stroke subtypes and severity, lesion location, electrode placements, and the best time to introduce therapy following a stroke to produce long-term mobility. Any one of these unknowns could skew future results. Future studies should continue analyzing long-term use and effects of tDCS to determine if and at what point tDCS is no longer effective in improving mobility in both upper and lower limbs. Additionally, researchers should compare data from acute and chronic patients in the long-term to examine the efficacy at different stages of stroke recovery, and if tDCS should be introduced as a therapy in a later stage rather than the acute phase.

## References

- Carpenter MB (1991). Core text of neuroanatomy, fourth edition, Williams & Wilkins, Baltimore.
- Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG (2009) Classification of Stroke Subtypes. *CEB* 27:493–501.
- Ansari NN, Naghdi S, Hasson S, Azarsa MH, Azarnia S (2008) The Modified Tardieu Scale for the measurement of elbow flexor spasticity in adult patients with hemiplegia. *Brain Injury* 22:1007–1012.
- Antal A et al. (2017) Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology* 128:1774–1809.
- Batchelor FA, Williams SB, Wijeratne T, Said CM, Petty S (2015) Balance and Gait Impairment in Transient Ischemic Attack and Minor Stroke. *Journal of Stroke and Cerebrovascular Diseases* 24:2291–2297.
- Beretta VS, Santos PCR, Orcioli-Silva D, Zampier VC, Vitória R, Gobbi LTB (2022) Transcranial direct current stimulation for balance rehabilitation in neurological disorders: A systematic review and meta-analysis. *Ageing Research Reviews* 81:101736.
- Berg KO, Wood-Dauphinee SL, Williams JI, Maki B (1992) Measuring balance in the elderly: validation of an instrument. *Can J Public Health* 83 Suppl 2:S7-11.
- Boes AD, Kelly MS, Trapp NT, Stern AP, Press DZ, Pascual-Leone A (2018) Noninvasive Brain Stimulation: Challenges and Opportunities for a New Clinical Specialty. *JNP* 30:173–179.
- Bornheim S, Croisier J-L, Maquet P, Kaux J-F (2020) Transcranial direct current stimulation associated with physical-therapy in acute stroke patients - A randomized, triple blind, sham-controlled study. *Brain Stimulation* 13:329–336.
- Bostan AC, Strick PL (2018) The basal ganglia and the cerebellum: nodes in an integrated network. *Nat Rev Neurosci* 19:338–350.
- Bronstein AM (2016) Chapter 4 - Multisensory integration in balance control. In: *Handbook of Clinical Neurology* (Furman JM, Lempert T, eds), pp 57–66 Neuro-Otology. Elsevier. Available at: <https://www.sciencedirect.com/science/article/pii/B9780444634375000042> [Accessed November 20, 2022].
- Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F (2011) A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology* 14:1133–1145.
- Carpenter MB (1991). Core text of neuroanatomy, fourth edition, Williams & Wilkins, Baltimore.
- Caparelli-Daquer EM, Zimmermann TJ, Mooshagian E, Parra LC, Rice JK, Datta A, Bikson M, Wassermann EM (2012) A pilot study on effects of 4×1 High-Definition tDCS on motor cortex excitability. In: 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, pp 735–738.
- Chow A-MD, Shin J, Wang H, Kellawan JM, Pereira HM (2022) Influence of Transcranial Direct Current Stimulation Dosage and Associated Therapy on Motor Recovery Post-stroke: A Systematic Review and Meta-Analysis. *Front Aging Neurosci* 14:821915.
- Corominas-Teruel X, Mozo RMSS, Simó MF, Colomina Fosch MT, Valero-Cabré A (2022) Transcranial direct current stimulation for gait recovery following stroke: A systematic review of current literature and beyond. *Front Neurol* 13:953939.
- Feske SK (2021) Ischemic Stroke. *The American Journal of Medicine* 134:1457–1464.
- Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S (1975) The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med* 7:13–31.
- Gabriel Tortella RC, O GD, Urso JB, Bora Muszkat B de SPJ, Brunoni R (2015) Transcranial direct current stimulation in psychiatric disorders. *World Journal of Psychiatry* 5:88–102.
- Gandiga PC, Hummel FC, Cohen LG (2006) Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology* 117:845–850.

- Geiger M, Supiot A, Zory R, Aegerter P, Pradon D, Roche N (2017) The effect of transcranial direct current stimulation (tDCS) on locomotion and balance in patients with chronic stroke: study protocol for a randomised controlled trial. *Trials* 18:492.
- Geurts ACH, de Haart M, van Nes IJW, Duysens J (2005) A review of standing balance recovery from stroke. *Gait & Posture* 22:267–281.
- Gowan S, Hordacre B (2020) Transcranial Direct Current Stimulation to Facilitate Lower Limb Recovery Following Stroke: Current Evidence and Future Directions. *Brain Sci* 10:310.
- Haaland KY, Dum RP, Mutha PK, Strick PL, Tröster AI (2017) The Neuropsychology of Movement and Movement Disorders: Neuroanatomical and Cognitive Considerations. *Journal of the International Neuropsychological Society* 23:768–777.
- Hordacre B, Moezzi B, Ridding MC (2018) Neuroplasticity and network connectivity of the motor cortex following stroke: A transcranial direct current stimulation study. *Hum Brain Mapp* 39:3326–3339.
- Kang N, Lee RD, Lee JH, Hwang MH (2020) Functional Balance and Postural Control Improvements in Patients With Stroke After Noninvasive Brain Stimulation: A Meta-analysis. *Archives of Physical Medicine and Rehabilitation* 101:141–153.
- Koganemaru S, Kitatani R, Fukushima-Maeda A, Mikami Y, Okita Y, Matsushashi M, Ohata K, Kansaku K, Mima T (2019) Gait-Synchronized Rhythmic Brain Stimulation Improves Poststroke Gait Disturbance. *Stroke* 50:3205–3212.
- Kollen B, Kwakkel G, Lindeman E (2006) Longitudinal robustness of variables predicting independent gait following severe middle cerebral artery stroke: a prospective cohort study. *Clin Rehabil* 20:262–268.
- Konczak J, Corcos DM, Horak F, Poizner H, Shapiro M, Tuite P, Volkmann J, Maschke M (2009) Proprioception and Motor Control in Parkinson's Disease. *Journal of Motor Behavior* 41:543–552.
- LAWRENCE DG, KUYPERS HGJM (1968) THE FUNCTIONAL ORGANIZATION OF THE MOTOR SYSTEM IN THE MONKEY I: I. THE EFFECTS OF BILATERAL PYRAMIDAL LESIONS. *Brain* 91:1–14.
- Liang JN, Ubalde L, Jacklin J, Hobson P, Wright-Avila S, Lee Y-J (2020) Immediate Effects of Anodal Transcranial Direct Current Stimulation on Postural Stability Using Computerized Dynamic Posturography in People With Chronic Post-stroke Hemiparesis. *Frontiers in Human Neuroscience* 14 Available at: <https://www.frontiersin.org/articles/10.3389/fnhum.2020.00341> [Accessed December 11, 2022].
- Lin K-C, Fu T, Wu C-Y, Hsieh Y-W, Chen C-L, Lee P-C (2010) Psychometric comparisons of the Stroke Impact Scale 3.0 and Stroke-Specific Quality of Life Scale. *Qual Life Res* 19:435–443.
- MacKinnon CD (2018) Chapter 1 - Sensorimotor anatomy of gait, balance, and falls. In: *Handbook of Clinical Neurology* (Day BL, Lord SR, eds), pp 3–26 Balance, Gait, and Falls. Elsevier. Available at: <https://www.sciencedirect.com/science/article/pii/B978044463916500001X> [Accessed November 4, 2022].
- Manoli Z, Parazzini M, Ravazzani P, Samaras T (2017) The electric field distributions in anatomical head models during transcranial direct current stimulation for post-stroke rehabilitation. *Medical Physics* 44:262–271.
- Montaño A, Hanley DF, Hemphill JC (2021) Chapter 13 - Hemorrhagic stroke. In: *Handbook of Clinical Neurology* (Hettis SW, Cooke DL, eds), pp 229–248 Interventional Neuroradiology. Elsevier. Available at: <https://www.sciencedirect.com/science/article/pii/B9780444640345000195> [Accessed November 8, 2022].
- Nicolo P, Magnin C, Pedrazzini E, Plomp G, Mottaz A, Schnider A, Guggisberg AG (2018) Comparison of Neuroplastic Responses to Cathodal Transcranial Direct Current Stimulation and Continuous Theta Burst Stimulation in Subacute Stroke. *Archives of Physical Medicine and Rehabilitation* 99:862-872.e1.
- Radu RA, Terecoasă EO, Băjenaru OA, Tiu C (2017) Etiologic classification of ischemic stroke: Where do we stand? *Clinical Neurology and Neurosurgery* 159:93–106.

- Shah S, Vanclay F, Cooper B (1989) Improving the sensitivity of the Barthel Index for stroke rehabilitation. *Journal of Clinical Epidemiology* 42:703–709.
- Storch S, Samantzis M, Balbi M (2021) Driving Oscillatory Dynamics: Neuromodulation for Recovery After Stroke. *Frontiers in Systems Neuroscience* 15 Available at: <https://www.frontiersin.org/articles/10.3389/fnsys.2021.712664> [Accessed September 16, 2022].
- Surgent OJ, Dadalko OI, Pickett KA, Travers BG (2019) Balance and the brain: A review of structural brain correlates of postural balance and balance training in humans. *Gait & Posture* 71:245–252.
- Takakusaki K (2017) Functional Neuroanatomy for Posture and Gait Control. *J Mov Disord* 10:1–17.
- Tedesco Triccas L, BurrIDGE JH, Hughes AM, Pickering RM, Desikan M, Rothwell JC, Verheyden G (2016) Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis. *Clinical Neurophysiology* 127:946–955.
- Thair H, Holloway AL, Newport R, Smith AD (2017) Transcranial Direct Current Stimulation (tDCS): A Beginner’s Guide for Design and Implementation. *Frontiers in Neuroscience* 11 Available at: <https://www.frontiersin.org/articles/10.3389/fnins.2017.00641> [Accessed December 11, 2022].
- Tien H-H, Liu W-Y, Chen Y-L, Wu Y-C, Lien H-Y (2020) Transcranial direct current stimulation for improving ambulation after stroke: a systematic review and meta-analysis. *Int J Rehabil Res* 43:299–309.
- Tinetti ME, Richman D, Powell L (1990) Falls efficacy as a measure of fear of falling. *J Gerontol* 45:P239-243.
- Tremblay S et al. (2019) Clinical utility and prospective of TMS–EEG. *Clinical Neurophysiology* 130:802–844.
- Tyson SF, Hanley M, Chillala J, Selley A, Tallis RC (2006) Balance Disability After Stroke. *Physical Therapy* 86:30–38.
- Vaz PG, Salazar AP da S, Stein C, Marchese RR, Lukrafka JL, Plentz RDM, Pagnussat AS (2019) Noninvasive brain stimulation combined with other therapies improves gait speed after stroke: a systematic review and meta-analysis. *Topics in Stroke Rehabilitation* 26:201–213.
- Veldema J, Gharabaghi A (2022) Non-invasive brain stimulation for improving gait, balance, and lower limbs motor function in stroke. *Journal of NeuroEngineering and Rehabilitation* 19:84.
- Weinstein S (1993) Fifty years of somatosensory research: from the Semmes-Weinstein monofilaments to the Weinstein Enhanced Sensory Test. *J Hand Ther* 6:11–22; discussion 50.
- Wolf SL, Catlin PA, Ellis M, Archer AL, Morgan B, Piacentino A (2001) Assessing Wolf Motor Function Test as Outcome Measure for Research in Patients After Stroke. *Stroke* 32:1635–1639.
- Woods AJ et al. (2016) A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology* 127:1031–1048.
- Yang C, Gad A, Creath RA, Magder L, Rogers MW, Waller SM (2021) Effects of transcranial direct current stimulation (tDCS) on posture, movement planning, and execution during standing voluntary reach following stroke. *J Neuroeng Rehabil* 18:5.
- Zandvliet SB, Meskers CGM, Kwakkel G, van Wegen EEH (2018) Short-Term Effects of Cerebellar tDCS on Standing Balance Performance in Patients with Chronic Stroke and Healthy Age-Matched Elderly. *Cerebellum* 17:575–589.
- Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica* 67:361–370.