Introduction

Until very recently, the adult brain was considered immutable, and the notion of neurogenesis in the adult brain was regarded as far-fetched. In the last 2 decades, it is clear that the central nervous system is plastic that, it changes as a result of experience, and that neurogenesis occurs in the adult brain at discrete locations. These paradigm shifts have fueled the notion that brain function can be modulated to improve neurologic recovery and aid in rehabilitation ***(Ming and Song, 2005).***

Because neuromodulators can transform the intrinsic firing properties of circuit neurons and alter effective synaptic strength, neuromodulatory techniques (as transcranial direct current stimulation tDCS) reconfigure neuronal circuits often massively, altering their output ***(Eva Marder, 2012).***

Most reports in the 1950s focused on positive phenomena that were elicited by brain stimulation ***(Hassler et al., 1960).*** And so, the idea of treating neurologic disorders with chronic stimulation began to emerge in the 1960s, but stimulation was largely used for targeting surgical lesions rather than neurological degenerative lesions ***(Bergstrom et al., 1966).***

Since the discovery of transcranial direct current stimulation (tDCS) - a non-invasive brain stimulator - years ago, interest in tDCS has grown exponentially. A noninvasive stimulation technique that induces robust excitability changes within the stimulated cortex, tDCS is increasingly being used in a wide range of neurological and psychiatric disorders ***(Stagg and Nitsche, 2011).***

Clinical therapy using tDCS may be the most promising therapeutic application specially that there have been therapeutic effects shown in clinical trials involving diseases like Parkinson's disease ***(Boggio et al., 2006).***

Postural instability and gait disturbance are universal features of advanced disease in Parkinson's disease (PD), but may be an important early sign in patients with progressive supranuclear palsy (PSP) or multiple system atrophy (MSA). Even before falls develop, patients often describe a loss of confidence on their feet, and a feeling of imbalance. Speed of walking is slowed, and this may be one of the first signs of Parkinsonism noticeable to others ***(David et al., 2013).***

Gait and balance disorders in hypokinetic gait disorders are usually multifactorial in origin and require a comprehensive assessment to determine contributing factors and targeted interventions. Early identification of

gait and balance disorders and appropriate intervention may prevent dysfunction and loss of independence. Patients with gait disorders can be rehabilitated through clinical treatment, exercise, and few other rehabilitation systems through neuromodulation ***(Gschwind et al., 2010).***

The motor loop –which originates from the motor cortices, namely, the primary motor cortex, supplementary motor area (SMA), and lateral premotor cortex, and projects to the somatomotor region of the basal ganglia- plays an important role in controlling voluntary movement. Dysfunction of the basal ganglia-thalamo-SMA loop results in gait disturbance in Parkinson's disease and vascular Parkinsonism. The dysfunction of the SMA loop could be compensated for by the activation of the lateral premotor cortex, the function of which appears to be preserved under appropriate external stimuli in such patients ***(Iseki and Hanakawa, 2010).***

There is mounting evidence for the efficacy of non-invasive brain stimulation in various areas of physical and rehabilitation medicine. These findings are therefore encouraging further studies testing novel parameters of stimulation that might find better approaches for the clinical use of non-invasive brain stimulation in combination with ordinary gait training to achieve the maximum outcome.

So, the aim of our work was to evaluate the role of Anodal transcranial direct current stimulation (tDCS) on lateral premotor cortex (Cz) in the rehabilitation of different hypo kinetic gait disorders in comparison to standard gait rehabilitation.

Gait Control in Normal and in Hypokinetic Gait Disorders

Human gait is defined as bipedal, biphasic forward propulsion of center of gravity of human body, with alternate movements of different segments of the body with least expenditure of energy ***(Inman et al., 2006).***

Gait cycle

Each gait cycle is divided into two phases: stance and swing ***(Figure 1).***

Stance stands for the whole period during which the foot is on the ground, it is also known as "support phase" or "contact phase", and lasts from initial contact to toe off. It is subdivided into: loading response, mid-stance, terminal stance, and pre-swing ***(Ashutosh et al., 2011).***

Swing stands for the time the foot is in the air for limb advancement, and it begins as the foot is lifted from the floor (toe-off), to the next initial contact. It is subdivided into: initial swing, mid-swing, and terminal swing ***(Ashutosh et al., 2011) (Figure 2).***

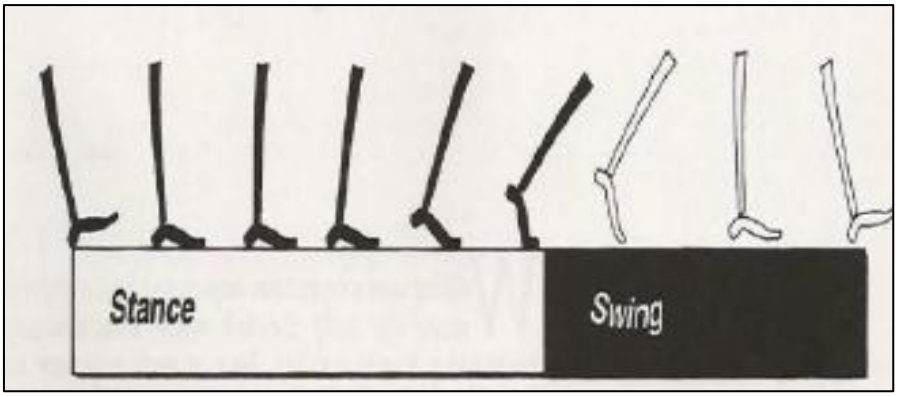


Figure (1): The two phases of gait cycle

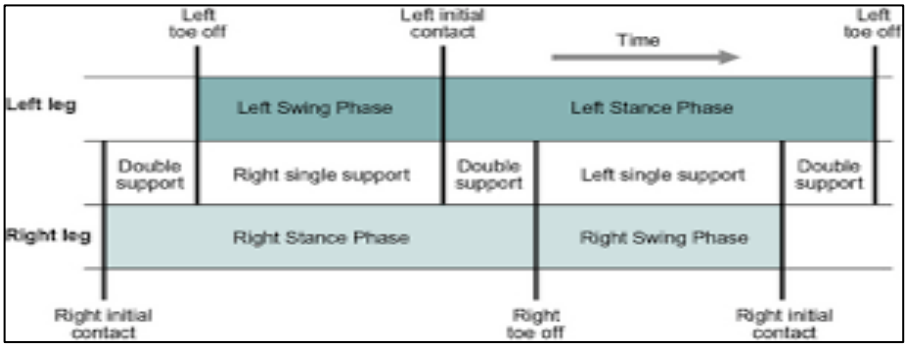


Figure (2): The usage of two legs within the gait cycle

The duration of a complete gait cycle is known as the cycle time, which is divided into stance time and swing time. And they are further subdivided into seven periods, four of which occur in the stance phase, and three in the swing phase ***(Table 1, Figure 3).***

Table (1): The seven periods of a complete gait cycle:

Stance phase periods	Swing phase periods
Initial contact	Toe off
Opposite toe off	Feet adjacent
Heel rise	Tibia vertical
Opposite initial contact	

(Ashutosh et al., 2011)

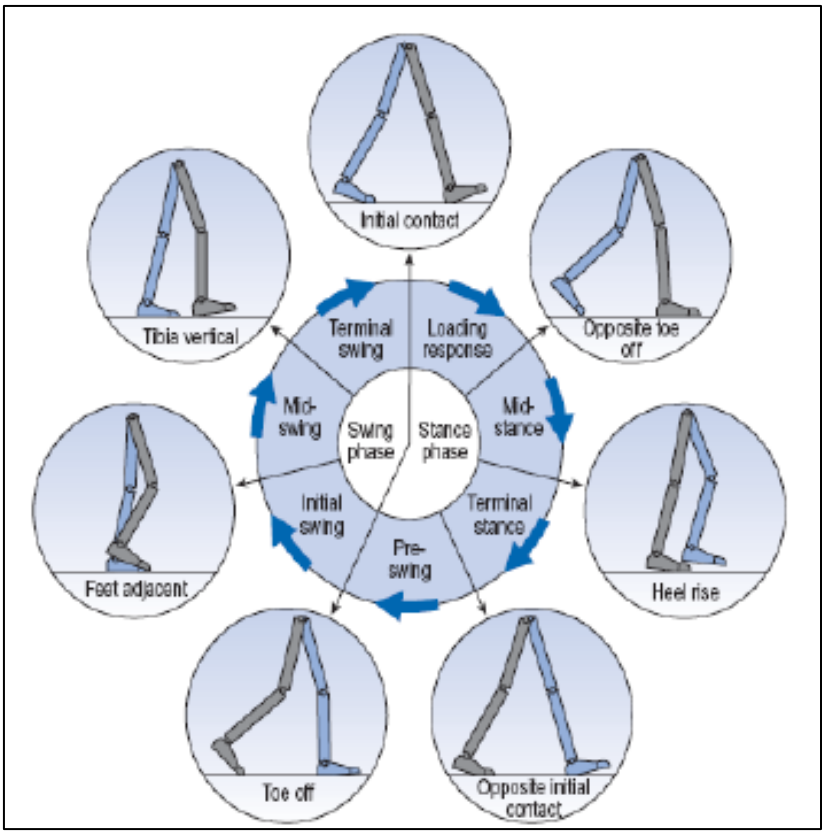


Figure (3): Gait cycle seven periods

Gait in Healthy Individuals

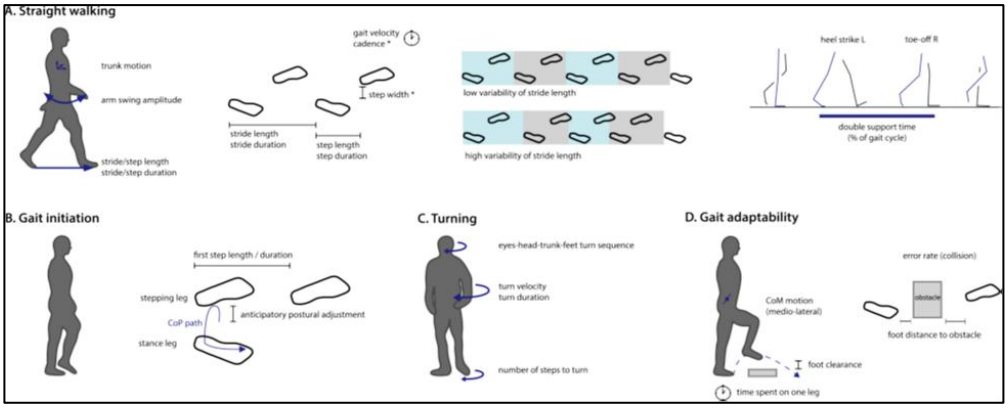
Gait has multiple components, each of which requires varying degrees of cognitive, and therefore, cortical control ***(Figure 4).*** The first, and least cognitive (or most automatic) component, is *straight walking* over a flat surface. It requires only minimal attention in healthy young adults. The main parameters for straight walking reflect speed (gait speed, step or stride time, cadence), amplitude (step or stride length, arm swing), regularity of movement (step-to-step variability, step width variability), and control of balance (step width, trunk motion) ***(Dubost et al., 2006).***

A second component, *initiation of gait*, involves more cortical control than straight walking as it generates goal-directed movements. Gait initiation consists of a postural weight shift forward and toward the stance leg in order to unload the stepping leg, which is defined as the anticipatory postural adjustment (APA). Following the APA, the foot pushes off and moves forward to execute the first step. Relevant parameters for gait initiation include the duration and amplitude of the APA, push-off forces, first step length and latency of foot-off ***(Patel et al., 2014).***

A third component is *turning,* which requires even more cognitive control to modify the gait pattern, execute an asymmetrical stepping pattern, and regulate dynamic

balance ***(Dibilio et al., 2016)***. In daily life, people make as many as 80-100 turns each hour, and patients with Parkinson's disease make just as many turns as control subjects ***(Mancini et al., 2015).*** The stepping pattern during turning involves asymmetric rotation of the foot in space and of the upper body over the leg on the ground. Healthy adults turn by first turning their eyes, then head towards the new direction, followed by the trunk, pelvis and legs ***(Patla et al., 1999).*** The number of steps taken to complete the turn, speed of turning, dynamic postural stability (i.e. relation of the body center of mass (CoM) to the edge of foot support) and coordination of head-trunk-feet motion are used to quantify turning ***(Mellone et al., 2016).***

A fourth component is the *ability to adjust gait to negotiate environmental hazards*, such as irregular surfaces and crowded spaces. This form of gait is highly dependent on cognitive control to plan, make judgments, and inhibit actions ***(Weerdesteyn et al., 2003; Smulders et al., 2012).*** Adaptability of gait is tested using obstacle avoidance paradigms, in which the subjects walk while stepping over or around obstacles. Typical outcome measures of gait adaptability using obstacle avoidance are success rates, clearance of the obstacles (distance between foot and obstacle), and stability during obstacle crossing ***(Hegeman et al., 2012).***



COP: center of pressure, COM: center of mass ***(Smulders et al., 2016)***

Figure (4): Different components of walking in everyday life and related objective outcome measures

The Neural Control of Movement

To control movement, humans ought to have full control on their posture as well as their gait. And since locomotion is important in humans' adaptive survival, its neural control involves wide range of interconnected circuitry across multiple levels of the nervous system, including the spinal cord, brainstem, basal ganglia, cerebellum, thalamus, and cerebral cortex ***(Takakusaki, 2008).***

I) Postural control

Postural control is a complex function that evolved mainly in humans. Maintaining stable position and posture is essential to the stability of axial body segments during the execution of different activities as voluntary movements

(arms or whole-body movements) as well as during different postures (sitting and standing). These activities may be further complicated by various environmental conditions such as in the case of uneven ground, climbing stairs, and carrying heavy objects ***(Amblard et al., 1985).***

Amblard and colleagues (1985) suggested the existence of a dual postural control system, part of which deals with body orientation with respect to gravity, and part deals with body stabilization. The first system allows a proper arrangement of body segments (i.e. erect axial segments aligned with gravitational coordinates and limbs positioned in such a way that the involvement of the muscles for joint stabilization is minimized). The second system, body stabilization, is aimed at maintaining the center of the body mass within the limits imposed by the base of support (equilibrium). These two postural control systems most likely interact, providing a stable physical basis for perception and action ***(Vaugoyeau & Azulay, 2010).***

Horak and colleagues (1992) found that to organize a given movement, the central nervous system (CNS) has to coordinate the control of body stabilization and body orientation. In order to achieve this complicated organization, the CNS relies on three main distinct processes:

1) *Sensory organization:*

In which one or more of the orientation senses (somatosensory, visual and vestibular) are involved and integrated for erect postural control ***(Vaugoyeau et al., 2007).***

2) *Postural adjustment*:

In order to maintain balance, there are two types of postural responses, feedback and feedforward. The type of response activated depends on the postural task. Feedback postural responses are activated when subjects were submitted to unexpected disturbances of balance by means of controlled destabilizations ***(Leonard et al., 2009).*** Spinal cord produces the lowest level of this neural feedback in the form of local reflexes ***(Nashner, 1977).***

The second and most important level of feedback is mid-brain. The brainstem serves as a relay and integration center, receiving and sending great numbers of sensory and motor command signals, and responsible for much more complex movements, mostly of an automatic nature. Thus, it modulates the behavior of lower level reflexes, and is itself modulated by the higher levels ***(Bouisset & Zattara, 1987)***.

The cerebral cortex and related structures generate highly complex movements, mostly of a voluntary nature.

In this case, postural adjustments occur prior to movement onset, to prevent the center of mass from shifting outside the base of support. To ensure a controlled transition from one postural configuration to another, these adjustments of posture must be planned by the central nervous system (CNS) in advance, and a feed forward mode of neural control sends commands to both focal and postural muscles to initiate and stabilize posture ***(Commissaris et al., 2001).***

3) The background tone of the muscles "postural tone":

Which is subconscious tonic activation of skeletal muscles that is necessary to maintain the relative positions of body segments and to prevent the body from collapsing against gravity. Thus, its modulation can provide the body with both mechanical and operational flexibility for different types of movements ***(Cacciatore et al., 2010).***

II) Gait control

The coordination of limb rhythmic activities is one of the main features of locomotion ***(Dietz, 2002).*** Locomotor activity is driven by particular neural circuits called central pattern generators, they are located in the upper (cervical) and lower (thoracolumbar) spinal cord, to organize lower and upper limb movement respectively ***(Grillner, 1981),*** and in medulla and pons of the brainstem to ensure flexible and dynamic control over the relatively automatic neural reflexes of the spinal cord ***(MacKay-Lyons, 2002).***

Neural activity in these central pattern generators leads to coordinated firing of the circuitry present in spinal segments, leading to a wider range of potential movement patterns that are more easily manipulated in response to behavioral contingencies. For example, the mesencephalic locomotor region (MLR) of the brainstem is mainly involved in the production of movement, whereas the dorsal pedunculopontine nucleus (PPNd) is associated with the abrupt cessation of movement ***(Maloney et al., 2000)***.

Moreover, the spinal cord circuits are coordinated by long propriospinal neurons, which couple the cervical and lumbar enlargements by functional, and task dependent gating of neuronal pathways to stabilize the body during walking ***(Dietz & Michel, 2009),*** and this coupling of the neuronal circuits is under supraspinal control ***(Wannier et al., 2001)***.

The cerebellum also plays an important role in the dynamic coordination of muscle movements, although the precise functional importance of the cerebellum is still a matter of study ***(Ito, 2008)***.

The cerebral cortex appears to offer a wide variety of behavioral pattern. There is emerging evidence to suggest that the cortex and cerebellum work together to create a spectrum of behavioral capacities ***(Doya, 2000; Balsters & Ramnani, 2011).***

The aforementioned neural systems offer a great deal of behavioral flexibility in response to changing

environmental contingency. However, they are effectively useless unless coupled with a system that affords control over their output. The basal ganglia nuclei, which consist of a series of highly interconnected nuclei in the telencephalon are ideally placed to execute this function ***(Shergill et al., 2013)***.

At rest, the main output structures of the basal ganglia (the globus pallidus internus [GPi] and the substantia nigra pars reticularis [SNr]) provide tonic GABAergic inhibitory tone over the brainstem structures that control gait (such as the mesencephalic locomotor region (MLR) and dorsal pedunculopontine nucleus (PPNd) and the motor thalamus, effectively constraining information flow in the spinal cord and cortex, respectively. During activity, cortical input to the basal ganglia can either relieve (via the striatum) or facilitate (via the sub-thalamic nucleus [STN]) this inhibitory output. This allows flexible and volitional control over motor outputs. To effectively mediate complex and rapidly changing external environments, a neural system controlling motor function also requires timely and appropriate feedback from the sensory environment surrounding the organism via sensory systems (visual, auditory, and somatosensory receptors) ***(Shergill et al., 2013) (Figure 5).***