Effects of transcranial direct-current stimulation on gait initiation in people with Parkinson's disease.

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Abstract

Background: Gait initiation is a major issue in Parkinson's disease (PD). Moreover, the effect of current treatment on motor deficits vary alongside individual differences and disease severity. In some cases, postural instability has been documented as a major side-effect and refractory symptom to dopaminergic medication. Despite these shortcomings, research involving other forms of therapy including deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS), has evidenced the improvement of postural deficits in PD. In this regard, there is a strong rational for the modulation of subcortical brain activity via the application of non-invasive transcranial direct current stimulation (tDCS) to interconnected cortical brain structures. ***Purpose:*** Therefore, we sought to determine the effect of tDCS applied to the supplementary motor area (SMA), on gait initiation preparation and performance in PD. ***Methods:*** A within subjects repeated measures quasi-experimental design was used to investigate the effects of a 10-minute sham-controlled tDCS intervention. Clinically diagnosed participants (n=12) with idiopathic PD were tested on medication during two sessions that bookended one week. Those who had previously undergone other forms of brain stimulation, had diabetes, severe freezing of gait, or any other neurological or functional limitations that could interfere with gait initiation were excluded from the study. ***Statistical Analyses/Results:*** Two-way repeated measures ANOVAs with Bonferroni corrections and a post-hoc analyses when appropriate, revealed a significant reduction in the magnitude of center of pressure (CoP) displacement and velocity in the mediolateral (ML) direction following tDCS. ***Conclusions:*** Findings from this study provide insights that may guide scientific research regarding the effects of tDCS on gait initiation among those with PD. Additionally, our work may highlight the importance of ML postural stability for individuals with comorbid and/or pharmacologically induced postural instabilities.

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Chapter I: General Introduction

In response to an ageing population, the global burden of Parkinson's disease has more than doubled in recent times (Dorsey et al., 2018). In Canada, there are an estimated 100,000 or more people living with Parkinson's and about 6,600 new cases diagnosed each year (UCB, 2019). This growing problem is compounded when more than half of these individuals report diminished social experiences, increased personal expenditures, and a lack of independence – relying on family members to adopt caregiving roles as a result of their disease (Wong, Gilmour, & Ramage-Morin, 2014). This highlights an urgency for research that seeks to reduce the overall burden of PD within society.

1 – Introduction

PD is a progressive neurological disorder characterized by the degeneration of dopamine producing cells within the brain. Dopamine acts as a chemical messenger responsible for the upkeep of both cognitive and motor performance (Marti & Tolosa, 2013). For those with PD, these neurons gradually degenerate which reduces levels of dopamine in the brain. This compounding effect jeopardizes the body's cognitive and motor pathways, ultimately contributing to a declining quality of life (Perez-Lloret & Barrantes, 2016).

Primary motor symptoms include tremors (unintentional rhythmic muscle activation), rigidity (muscle stiffness), bradykinesia (slow movements), and postural instability (impaired balance). All of which are consistently recognized across the literature to contribute to cumbersome and ineffective movement and have shown variable response to treatment (Nonnekes et al., 2016). More specifically, Contreras and Grandas (2012) have shown that the variables most associated with falls are ones Tinetti Balance score and Hoehn and Yahr staging. The current treatment for the motor symptoms of PD range from prescription drugs such as

Levodopa to various electric and magnetic brain stimulations which have all upheld relatively ambiguous effects, given the wide range of disease severity and individual differences among those with PD (Nonnekes et al., 2016; Williams & Litvan, 2013).

Gait initiation requires a transition from static (quiet stance) to dynamic (stepping forward) balance that relies on the integration of multiple neuromotor pathways. Therefore, it is a complex multifactorial movement in which proper execution is more difficult than both quiet standing and steady state walking alone. In PD, gait initiation has been documented as one of the most common fall-related activities (Yiou, Caderby, Delafontaine, Fourcade, & Honeine, 2017). The asymmetric nature of this activity combined with deficits in postural stability are factors that could explain the high occurrence of falls during gait initiation (Rigoldi, Galli, Maras, & Riboldazzi, 2016).

Although dopaminergic drugs are the primary treatment option for most, they have also been shown to markedly reduce postural stability during quiet standing and throughout gait. Furthermore, knowledge of their influence on the initiation of voluntary movement among those with PD is limited. Previously, Nantel and Bronte-Stewart (2014) examined the effect of medication and the role of postural instability among those with PD experiencing freezing of gait. Groups of freezers (n=15), non-freezers (n=15) and controls (n=14) were compared both off and on medication. Of all three groups, freezers were found to exhibit significantly greater improvements in Unified Parkinson's Disease Rating Scale (UPDRS) section III Motor Examination scores, as well as the number and duration of freezing episodes despite their longer disease duration. Of this group, 13% appeared to worsen on medication, which seems to emphasize similar paradoxical findings of Espay et al. (2012), in which those with advanced PD also experienced greater disturbances in balance on medication, and therefore may have more

difficulty controlling spatiotemporal gait characteristics. Medication had no effect on stepping in place cycle variability between groups. Altogether, the beneficial effects of medication on UPDRS III, freezing episodes, and stride duration has been suggested to support the selective contribution of dopaminergic pathways in the regulation of such gait parameters. Whereas non-dopaminergic pathways have been suggested to regulate gait symmetry and rhythmicity since these variables appear unresponsive to medication (Nantel & Bronte-Stewart, 2014). While Schaafsma et al. (2003) reported on the positive effects of levodopa on stride-to-stride variability during a walking task, Curtze, Nutt, Carlson-Kuhta, Mancini, and Horak (2015) found no effect of medication on other measures of dynamic stability such as double support time. Curtze et al. (2015) also measured CoP_{ML} and anteroposterior (AP) displacements and velocities during quiet standing and found that Levodopa had diminishing effects on postural stability among those with dyskinesia. Zappia, Montesanti, Colao, and Quattrone (1994) evaluated reaction times (RT) and movement times (MT) following a visual directional-choice task. It was found that MTs improved significantly in response to Levodopa and correlated with disease severity and side-dominance, whereas RTs did not. It has been proposed that RT may be a product of one's attentional, cognitive, and motor capacity, while MT may be a product of one's motor capacity alone (Bloxham, Dick, & Moore, 1987; Hallett & Khoshbin, 1980; Jordan, Sagar, & Cooper, 1992; Kaneoke, Koike, Sakurai, Takahashi, & Watanabe, 1989). Therefore, it appears that specific variables associated with balance (i.e. CoP displacement and velocity) and movement initiation (i.e. RT and MT) are differentially modulated by medication.

Other therapies such as deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS) are much less common and incur their own sets of drawbacks. DBS for example, is an invasive, high-risk surgical

procedure that is only available to a small portion of those with the disease based on several contraindications. Both rTMS and tDCS are much less invasive, portable and readily available in comparison. However, the specific effects of electrical stimulation and their complete therapeutic benefits are not yet well understood. Previous studies have shown promising effects in the application of tDCS on M1 for improvement of gait and motor symptoms, specifically regarding Levodopa induced dyskinesias, RTs, and postural stability. In combination with cued gait training and physical therapy for PD, tDCS application over the lower limb motor area, supplementary motor area, and contralateral DLPFC has shown prolonged improvement in both gait and motor abilities (Lattari et al., 2017; Manenti et al., 2014). This has led to the recent development of evidence-based guidelines on the therapeutic use of tDCS (Lefaucheur et al., 2017). With respect to voluntary movement initiation, (Carlsen, Eagles, & MacKinnon, 2015) examined tDCS relative to a sham stimulation in a sample of 10 and 7 healthy volunteers, respectively. They concluded that cathodal tDCS over the SMA decreased the frequency of movement release following an auditory cue and drove the production of slower RTs, most significantly in the 10 minutes that followed stimulation. Whereas, anodal tDCS only facilitated faster RTs and sham stimulation made no significant difference.

Therefore, the purpose of this study is to examine the effect of anodal tDCS on muscle activation and postural stabilization during gait initiation in medicated participants with PD following a consistent auditory cue. To objectively quantify muscular activity and movement, electromyographic and kinetic measures have been recorded. Variables of interest are RT, MT, postural stability, and muscular activity during gait initiation following each treatment condition (tDCS vs. sham stimulation). Ultimately, the potential findings of such research may not only promote safe and effective movement for those with PD but provide some of the foundation to

future research that could extend the application of tDCS to our ageing demographic and those with other neurological disorders. Additionally, the fact that tDCS application is non-invasive, inexpensive, and has already displayed positive results, strengthens its potential as an alternative therapy that could help reduce some of the mounting stresses among those with PD and within Canadian healthcare (Finès, 2015). Lastly, this research will contribute to a better understanding of the complexities that underlie human locomotion.

2 – Purpose and Research Hypotheses

2.1 – Purpose

The purpose of this study was to evaluate the neuromotor effects of tDCS on gait initiation in people with PD. More specifically, we aimed to determine the effect of tDCS on the APAs pertaining to dynamic postural stability in the ML and AP directions, RT and MT, as well as its effect on the EMG profiles of the tibialis anterior (TA) and medial gastrocnemius (MG) during gait initiation.

2.2 – Research Hypotheses

It is hypothesized that the application of tDCS to the SMA will induce changes to APAs during GI, thereby enhancing:

1) Muscle activity, as measured by duration of TA burst (DoB_{TA}), TA and MG burst amplitude (Amp_{TA}) and (Amp_{MG}), and co-contraction index of TA and MG ($CCI_{TA\text{-}MG}$).
2) Postural stability, as measured by CoP displacement and velocity in both the ML (CoP_{ML}) and AP (CoP_{AP}) directions.
3) Movement efficiency, as measured by RT and MT.

Chapter II: Review of Literature

1– Parkinson's Disease

1.1 – General Motor Deficits

PD-induced motor complications tend to appear and become more noticeable as the disease progresses. The primary motor deficits associated with PD include; tremors (trembling), bradykinesia (slowness of movement), and postural instability (reduced balance and coordination) (Jankovic, 2008). It should also be noted that the symptoms of PD are not limited to this shortened list of motor deficits. The primary focus of this literature review will highlight motor deficits specific to fall reduction in gait initiation such as postural instabilities and bradykinesia.

1.2 – The Dopamine System in PD

PD is a disabling neurological disorder marked by a progressive degeneration of dopamine-producing neurons in the brain, specifically within the nigrostriatal pathways of the basal ganglia (Damier, Hirsch, Agid, & Graybiel, 1999; Guo et al., 2016). Not only is dopamine an important chemical messenger that facilitates synaptic transmission within these regions, but its interaction within the basal ganglia-thalamocortical circuit specifically, plays an integral role in the production and control of movement and posture (Beninger, 1983; Horak, Frank, & Nutt, 1996). In addition, projecting nerve fibers from structures such as the supplementary motor area (SMA) have been linked to movement preparation and initiation (Carlsen et al., 2015). Consequently, people with PD suffer from depleted striatal dopamine among other brain regions, which attributes to gradual cognitive decline accompanied with a wide range of motor deficits including gait initiation (Marti & Tolosa, 2013). With respect to locomotor activity in PD,

previous research has shown that the SMA could serve as a cortical target for intervention through neuromodulation involving tDCS (Costa-Ribeiro et al., 2016).

1.3 – Neurological comparison of Motor Control in Healthy Individuals

Our understanding of the basal ganglia and its involvement with motor control are relatively well established, however recent advancements are reviewed in detail by Simonyan (2019). Within the brain it is thought that there are three main cortical loops that engage with the basal ganglia including the motor, associative, and limbic loops (Simonyan, 2019). Depending on neurological input and desired output, these cortical loops will organize themselves according to parallel-projecting and/or to information convergence hypotheses (Draganski et al., 2008; Percheron & Filion, 1991; Wiesendanger, Clarke, Kraftsik, & Tardif, 2004). If movement facilitation or inhibition is the goal, then synaptic signaling will occur primarily along the motor loop and activate what is known as the direct or indirect pathway respectively (Albin, Young, & Penney, 1989). During movement facilitation for instance, the direct pathways is primarily engaged. A motor input signal is transmitted from the cortex (ex. SMA) to the striatum, at which point dopamine binds with D1-dopamine receptors signaling the inhibition of the internal globus pallidus (GPi) and substantia nigra pars reticulate (SNr) (Simonyan, 2019). The inhibition of GPi and SNr reduces their capacity to inhibit the ever-active thalamus, completing the feedback loop with the motor cortex and signaling movement (Simonyan, 2019). During movement inhibition on the other hand, the indirect pathway is primarily engaged. Synaptic transmission will proceed from the cortex (ex. SMA) to the striatum where dopamine binds with D2-dopamine receptors signaling the inhibition of the external globus pallidus (GPe) (Simonyan, 2019). The inhibition of GPe reduces its capacity to inhibit the ever-active subthalamic nucleus (STN), which in turn, signals the excitation of the GPi and SNr (Simonyan, 2019). At this point, the GPi and SNr. –

which naturally inhibit the thalamus, increase their level of thalamic inhibition leading to reduced cortical excitability, ultimately completing the feedback loop and withholding movement (Simonyan, 2019). Both direct and indirect pathways are typically modulated by the substantia nigra pars compacta (SNc) through the endogenous release of dopamine which may reinforce optimal motor control as electrical impulses travel between brain structures (Simonyan, 2019). Interestingly, this model – which traditionally separates the contributions of each pathway as being distinctly independent of one another, has been challenged in recent times (Simonyan, Cho, Hamzehei Sichani, Rubien-Thomas, & Hallett, 2017; Wu, Richard, & Parent, 2000).

1.4 – Potential Mechanisms of Neuromodulation via tDCS in PD

In PD, it is well known that dopaminergic cell death largely affects motor control and cognitively driven movements such as walking. The degeneration of dopamine producing cells projecting from the substantia nigra pars compacta (SNc) to the striatum, result in impaired dopaminergic pathways (Herz, Eickhoff, Lokkegaard, & Siebner, 2014). With a chemical imbalance of dopamine, the SNc cannot modulate this process and changes in subcortical networks may lead to plastic changes and the development of compensatory pathways in the motor cortex to effectively move (Helmich et al., 2010). Moreover, the fact that many features of gait and cognitive impairment remain unresponsive to levodopa may suggest the involvement of other GABAergic, glutamatergic, adrenergic, serotoninergic, and cholinergic pathways that may equally benefit from tDCS (Lim, Fox, & Lang, 2009). Therefore, interventions that target both the malfunctioning basal ganglia-thalamocortical loop and potential compensatory pathways should be examined (Fregni et al., 2006). Although the underlying mechanisms of tDCS and its interaction with medication is not fully understood (Broeder et al., 2015; Fregni et al., 2006),

there have been several hypothesized processes involved in facilitating desired movement outputs.

First, it is thought that tDCS may have the potential to modulate local cortical excitability and by augmenting or reducing the likelihood of synaptic signaling within cortical structures such as the SMA (Nitsche et al., 2008; Paulus, 2011). Weather exogenous electric current applied superficially to the scalp has a cascading effect on deeper brain structures is still however, a fundamental question that remains largely unanswered (Chen & Chen, 2019). However, secondary to these short-term extracellular polarity specific effects, tDCS has been shown to strengthen long-term potentiation and depression-like effects with respect to synaptic plasticity and task-dependent learning (Jackson et al., 2016; Kronberg, Bridi, Abel, Bikson, & Parra, 2017; Orban de Xivry & Shadmehr, 2014). Although primarily observed in computational and rodent models, both long-term and short-term "boosts" (Kronberg, Rahman, Sharma, Bikson, & Parra, 2019; Podda et al., 2016) are thought to act synergistically with dopamine (Schroll, Vitay, & Hamker, 2014) via the direct, indirect, and/or hyperdirect pathways of the basal ganglia (see Figure 1.) (Chen & Chen, 2019; Fregni et al., 2006; Helmich et al., 2010; Hess, 2013; Nitsche et al., 2006; Polania, Nitsche, & Paulus, 2011). Interestingly, tDCS may be most sensitive to the hyperdirect pathway as the cortico-subthalamo-pallidal circuit bypasses the striatum altogether, which may contribute to faster signal transmission and greater residual effects (Nambu, Tokuno, & Takada, 2002). It may well be the case that tDCS takes effect on other functionally integrated as well as segregated neuronal circuits (Alexander, DeLong, & Strick, 1986; Nitsche et al., 2004; Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010) to regulate the execution and inhibition of movements such as gait initiation (Carlsen et al., 2015; Kaski, Dominguez, Allum, Islam, & Bronstein, 2014). There is also a notion that tDCS might strengthen neurological functioning in

PD by promoting cortical compensation for deficient basal ganglia pathways (Wu et al., 2012). Therefore, with repeated use, tDCS may have the potential to modulate long-term cortical plasticity leading to changes in compensatory and/or adapted motor programs (Broeder et al., 2015).

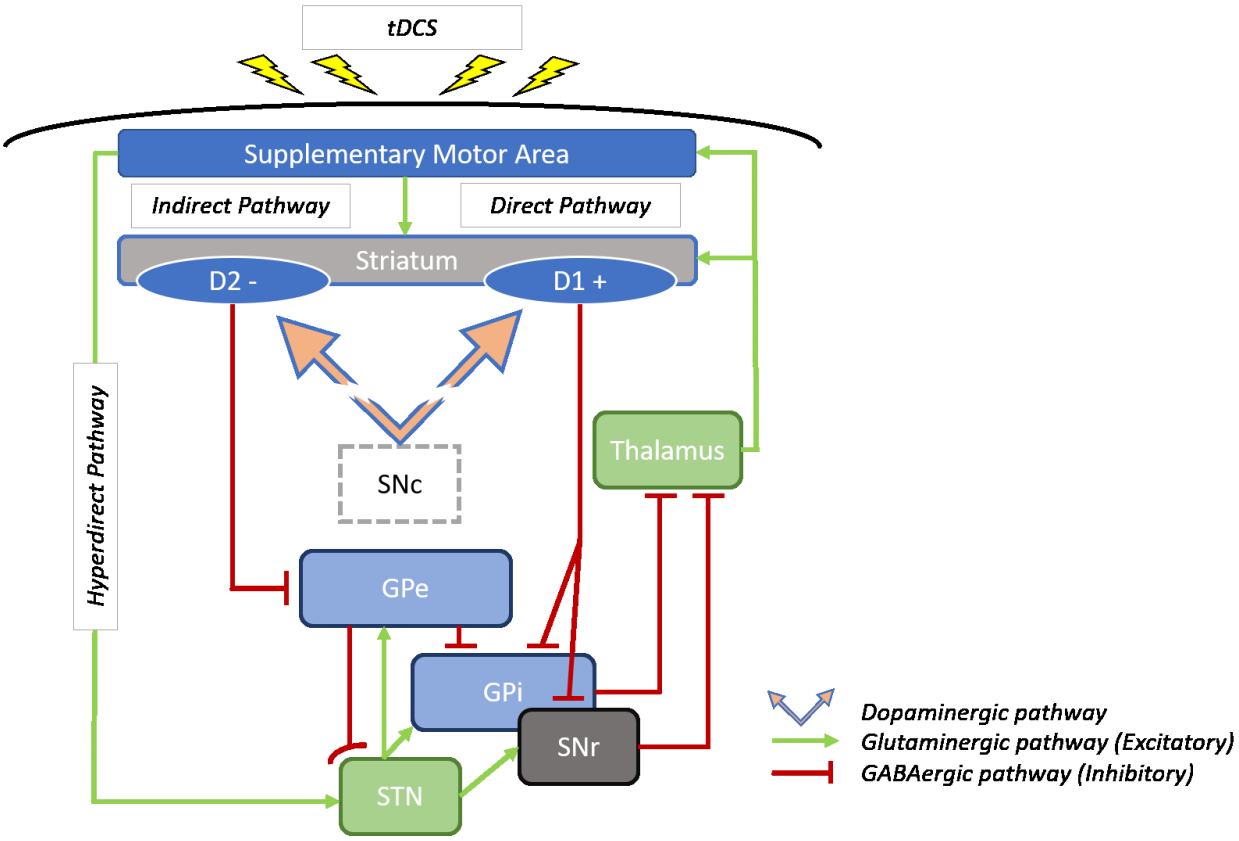

Figure 1. *Schematic representation the possible influence of tDCS on the basal ganglia-thalamocortical circuit in Parkinson's disease, adapted from Hess (2013), Chen and Chen (2019), and Simonyan (2019).*

The application of tDCS is not limited however, to the above mechanisms of action. Several studies including EEG indicate that site specific stimulation may induce oscillatory changes in neuronal activity that are synchronous throughout the brain (Ardolino, Bossi, Barbieri, & Priori, 2005; Lang et al., 2005; Luft, Zioga, & Bhattacharya, 2018; Marshall, Molle, Hallschmid, & Born, 2004). Given the neurological orchestra at play, this observation has not

only led to the use of tDCS in the relief of motor symptoms, but several non-motor symptoms including verbal fluency (Bueno et al., 2019; Pereira et al., 2013). In addition, though most research has focused on the direct synaptic effects of tDCS, other pathophysiological mechanisms have been reported. For example; improved vascular function (Cancel, Arias, Bikson, & Tarbell, 2018; Iyer & Madhavan, 2018; Zaghi et al., 2010), increased endogenous dopamine release (Fukai et al., 2019; Lu et al., 2015; Tanaka et al., 2013), improved glial cell function (Monai et al., 2016), growth (Pelletier et al., 2014), mobility (Keuters et al., 2015), and neurogenesis (Braun et al., 2016; Rueger et al., 2012) has been observed. In this regard, it is extremely important to reiterate that PD is a progressive neurodegenerative disease where small changes in cortical networks result in large-scale pathological complications in which the reorganization of neuronal circuitry is required to accommodate functional impairments (Caproni et al., 2013; Herz et al., 2014). How tDCS might globally affect the unique neurophysiology of PD and therefore gait initiation, may ultimately depend on individual differences in synaptic plasticity (Citri & Malenka, 2008), and brain state (ie. dopamine concentrations) in combination with other factors such as the polarity of electrodes and stimulation site, to name a few (Li, Uehara, & Hanakawa, 2015; Morya et al., 2019). Therefore, the precise mechanisms by which tDCS might directly, or indirectly affect membrane excitability, synaptic transmission, and a multitude of other neurochemical processes throughout the brain remain up for debate. Evidently, more research is needed to elucidate the underlying mechanisms of tDCS and its effect on neuromotor control and gait initiation given the highly integrated and complex nature of the human brain.

2 – Postural Stability in PD and Controls

2.1 – The Functional Role of Posture

When a voluntary movement begins, activation of the muscle groups primarily responsible for the intended action, the so-called prime movers, are not the only electromyography (EMG) detectable events. In fact, prior to the activation of prime movers, excitatory and/or inhibitory effects can be recorded through EMG. It is argued that the functional role of these early detectable EMG events, is the production of postural adjustments that aim to minimize equilibrium disturbances associated with subsequent movements (Massion, Alexandrov, & Frolov, 2004).

Postural adjustments have long been understood to play an important role in execution of deliberate motor commands. In general, these short muscle bursts have important stabilizing functions as they tend to precede, accompany, and follow goal-directed movement and are therefore referred to as anticipatory postural adjustments (APAs), synchronous postural adjustments, and consecutive postural adjustments respectively (Bouisset & Do, 2008). The importance of APAs in maintaining postural stability during gait initiation has equally been argued as both a counter-perturbation that serves to anticipate (or negate) an imminent deliberate postural disturbance, and as a perturbation that provokes (or facilitates) an imminent deliberate postural disturbance (Bouisset & Zattara, 1987). Therefore, APAs can not only counteract postural destabilization during gait initiation, but also encourage it, thereby assisting in the lateral transfer of body weight necessary for effective forward propulsion (Bouisset & Do, 2008).

2.2 – Temporospatial Aspects of Movement and Postural Stability in PD

Effective locomotion requires appropriately scaled movement. In other words, proper stepping relies on the CNS to control movement parameters such as magnitude, direction, speed,

and accuracy. Altered neural pathways in PD make these adjustments particularly challenging. In addition to motor deficits, people with PD are reported to experience problems with internal attentional control (Torres, Heilman, & Poizner, 2011), which may lead to excessive reliance on external cues (ie. visual, auditory, and tactile stimuli) for the proper execution of movement (Majsak, Kaminski, Gentile, & Flanagan, 1998; Nombela, Hughes, Owen, & Grahn, 2013). In this regard, previous research has focused on the attentional control of volitional movement with and without temporospatial constraints. In movements concerning both upper and lower limbs, researchers agree that; as choice complexity increases, movements in those with PD become progressively slower, more variable, and error-prone compared to age-matched controls (Beaulne-Seguin & Nantel, 2016; Bloxham et al., 1987; Sheridan & Flowers, 1990). It remains unclear whether such movement complexities are tied to motor and/or non-motor regions within the brain. Recent research has confirmed that impaired stepping responses in PD such as RT, MT, and movement errors are associated with disease severity and cognitive impairments. Both of which contribute to an increased susceptibility to falling, as confirmed by correlations with UPDRS and Montreal Cognitive Assessment scores respectively (Caetano et al., 2018).

To understand impaired stepping response and reduce the occurrence of falls in PD, (Caetano et al., 2018) studied movement performance during a choice reaction and Stroop stepping test. Participants on medication were required to step with both legs in multiple directions following either congruent or incongruent visual stimuli. In the choice reaction test, PD participants and controls had similar mean performance scores however intra-individual variability was significantly greater in those with PD. Therefore, when responding to congruent stimuli, significant differences were attributed to motor related disease deficits such as bradykinesia (Jankovic, 2008). In the Stroop test however, when responding to incongruent

stimuli, significant differences in both mean response times and intra-individual variability were attributed to non-motor related disease deficits such as impaired attentional control and cognition. Measures of gait adaptability were also recorded in a series of walking tests (Caetano et al., 2018). Compared with controls, those with PD exhibited significantly worse step accuracy, and increased step frequency in response to obstacles appearing at shorter distances.

These findings highlight the modulatory effects of medication and task complexity on the temporospatial aspects of self-generated stepping in PD. Since there was no significant difference in MT between groups under simple conditions in which processes are automatic, it appears that MTs may be regulated through dopaminergic pathways and therefore respond well to medication. Under the same conditions however, intra-individual variability for RT and total response time was significantly larger in the PD group. Taken together, this underscores the modulatory inefficiencies of dopaminergic medication with respect to attentional control and decision-making processes that ultimately dictate RT. Altogether, these findings support an evident need for additive therapeutic modalities that target brain regions specific to attentional control and cognition. The question remains as to what extent these neurological deficiencies will improve in response to non-invasive electrical stimulation of the brain.

2.3 – Postural Stability During Quiet Stance

When considering balance during gait initiation, we must first consider postural control during quiet stance as a fundamental platform from which gait initiation occurs. Static balance during quiet standing depends on the width of the feet (ie. base of support) which acts as a foundation of stability for any and all forthcoming movement. In PD, increased postural sway, especially in the ML direction has largely been associated with falls (Frenklach, Louie, Koop, & Bronte-Stewart, 2009; Matinolli et al., 2007; Mitchell, Collins, De Luca, Burrows, & Lipsitz,

1995). Prior to treatment with dopaminergic medication, people with PD tend to exhibit greater postural sway displacement, velocity, and variability during quite stance than do healthy controls (Schoneburg, Mancini, Horak, & Nutt, 2013). Moreover, following treatments with either medication alone or medication and STN-DBS combined, these postural sway parameters become even further exacerbated (Schoneburg et al., 2013). It is thought that levodopa-induced dyskinesia may be a contributing factor to these reported postural instabilities while on optimally functioning medication(Chung, Lobb, Nutt, McNames, & Horak, 2010). It is only during combined treatment with medication and GPi-DBS that postural sway appears to decrease reaching a level that is comparable with healthy controls (Schoneburg et al., 2013). The transition from a dual legged base of support to a single legged base of support as seen in gait initiation, presents an interesting phase of movement with respect to controlled instability. In this regard ML displacements in CoP are of special interest as this would represent the primary APA control parameter for gait initiation and postural stability.

2.4 – Postural Stability During Gait Initiation

Gait initiation is defined as the transient period between quiet standing and steady-state walking. It is a functional task that is classically used in the literature to investigate how the central nervous system (CNS) controls balance during whole-body movements involving CoP displacement and a changing base of support. It has been suggested that gait initiation is a product of two highly coordinated motor programs that dictate the fluidity of controlled forward propulsion (Brunt et al., 1991)

Delval, Tard, and Defebvre (2014) outlined a stereotypical preparation pattern for gait initiation in healthy subjects. They described the role of APAs as the co-activation of agonist/antagonist muscle groups in preparation for forward movement. In the context of taking a

first step, this involves the co-activation (inhibition) of the MG and (activation) of the TA just prior to foot-off of the swing-leg. This anticipatory muscle synergy is thought to help support the bodies upright position throughout GI. APAs therefore, serve as the primary mechanism in which a mediolateral and posterior shift of the CoP towards the swing leg is generated. Following this, a mediolateral and anterior displacement of the CoP towards the stance-leg is observed. APAs are merely one part of the motor program responsible for postural control, the second part is that which contributes to the localized movement. Bouisset and Do (2008) described this unique motor control pattern in two ways; as one's posturo-kinetic capacity and foco-kinetic capacity respectively. The corresponding localized movement for gait initiation begins with heel-off of the swing leg followed by a lateral CoP displacement towards the stance leg. Immediately thereafter, toe-off is observed, followed by an anterior CoP displacement towards the stance leg.

In terms of APAs among healthy subjects while attempting to clear a forthcoming obstacle, Yiou, Artico, Teyssedre, Labaune, and Fourcade (2016) showed that CoP_{ML} displacement, center of mass (CoM) velocity in ML, and the duration of swing phase during GI, increase with obstacle height, not distance. Conversely, the same measures in the AP direction decrease with obstacle height, not distance. Taken together, these findings denote the adaptability of the CNS to a changing environment given the appropriate sensory information. This would also imply that among healthy individuals, the CNS can scale the spatiotemporal parameters of APAs according to the environment.

Given impaired neurological functioning, gait initiation in PD can be challenging, since a controlled muscular effort is required to move the bodies' CoM away from its stable starting position in which CoM and CoP are aligned. This produces an inherently unstable posture.

Moreover, people with PD are consistently shown to overcompensate for postural asymmetries using abnormal and inefficient movement patterns to gain control over balance (Aruin, 2006; Boonstra, Schouten, van Vugt, Bloem, & van der Kooij, 2014; Djaldetti, Ziv, & Melamed, 2006; Moya, Siqueira, Caffaro, Fu, & Tanaka, 2009). While initiating gait, much like a controlled forward fall, the body leans forward prior to heel-off. It is during this transient phase of movement that people with PD are disadvantaged due to their inability to adequately prepare the anticipatory postural adjustments (Bouisset & Do, 2008) required to accommodate this predominantly ML shift in CoP.

APAs have long been considered a major pathophysiological mechanism underlying impaired gait initiation in PD (Halliday, Winter, Frank, Patla, & Prince, 1998). As the disease progresses, the timing and amplitude of bilateral TA excitation during gait initiation has been shown to degrade, and in some cases, may be absent altogether (Viallet, Gantchev, Aurenty, & Massion, 1996). Consequently, ML and AP ground reaction forces, along with CoP changes that characterize APAs in PD are weaker and slower, with prolonged delays between onset and the first step (Burleigh-Jacobs, Horak, Nutt, & Obeso, 1997; Dibble et al., 2004; Halliday et al., 1998; Krystkowiak et al., 2006). A lack of APAs is reported most frequently in those who display either start hesitation or very slow forward progression (Burleigh-Jacobs et al., 1997). Multiple APAs can also occur and correspond to a subtype of FoG referred to as ‘‘knee trembling’’ (Jacobs, Lou, Kraakevik, & Horak, 2009). In addition, the presence of multiple APAs (measured from repeated CoP shifts) and the absence of adequate postural perturbation (i.e. no CoP shifts towards the swing leg) is more frequently observed in freezers than in non-freezers (Delval et al., 2014). This also lends itself to impaired stepping performance, with a shorter first step length and a lower initial stepping speed among prototypical freezers (Delval et al., 2014). Among those

with untreated early-moderate PD, in which start hesitation may not be clinically detectable, low-magnitude APAs (as measured from peak CoP displacements and accelerations) have also been discerned (Mancini et al., 2011).

Delval et al. (2014) summarized the importance of studying gait initiation in PD with respect to the underlying neurological mechanisms associated with abnormal APAs and subsequent stepping. According to their review, a single person with PD can experience multiple and/or no APAs (both bradykinetic and hypokinetic) from trial to trial. This pattern bodes well with a previously defined dual control model of movement, in which separate neurological circuits are called upon to produce the appropriate APAs necessary for maintaining balance during goal-directed movement (Collins & De Luca, 1993). In addition, Delval et al. (2014) noted the outcome of a study performed by Chastan et al. (2009) in which the effects of bilateral Subthalamic nucleus (STN)-DBS and Substantia nigra (SNr)-DBS were evaluated with respect to APAs and stepping. Results varied such that SNr stimulation appeared to relieve axial motor symptoms of gait and balance, whereas STN stimulation relieved both axial and distal motor symptoms including segmental akinesia, rigidity, and tremors. These findings share a common similarity to those involving the effects of medication, in that the mechanisms of control for gait and posture may involve separate neuronal circuitry (Chastan et al., 2009). The fact that levodopa has been shown to improve some aspects of gait initiation and locomotion in people with off-drug gait impairment may suggest that alterations in basal ganglia output to both the cortex and brainstem has a role in both the triggering of movement initiation and the coupling of posture and locomotion.

A similar multifactorial model of control was suggested by Massion (1992) in which the APA is generated by a circuit that includes the supplementary motor area (SMA) and basal

ganglia, whereas goal-directed movement (i.e. stepping) resides in circuitry involving the dorsolateral premotor cortex (DLPC) and primary motor cortex (M1). Moreover, these pathways are thought to be integrated within the brainstems postural and locomotor centers and that impaired gait initiation may be a result of a breakdown in the coupling of these pathways as well as cholinergic and non-cholinergic systems (Garcia-Rill & Skinner, 1987). For example, the mesencephalic locomotor region is known to share strong ties to the extrapyramidal area and pontomedullary reticular formation, both of which seem to play a role in the pattern generation needed for controlled gait and posture during locomotion (Kim et al., 2017). Furthermore, some brain imaging studies in both PD and the elderly have revealed a lack of automaticity in generating self-triggered movement (Vercruysse et al., 2014; Wu, Hallett, & Chan, 2015). Hypoperfusion of the SMA was observed while participants were shown a walking video and told to imagine themselves performing the task (Wang, Wai, Kuo, Yeh, & Wang, 2008). These results may point towards a visual dependency in PD and the elderly, which also supports the hypothesis that external cues may be used to compensate for deficient internal cueing in those with PD.

Other research by Singer, McIlroy, and Prentice (2014) examined age related changes in ML dynamic stability during step initiation while recognizing the importance of restabilising a line of action between the net ground reaction force and the CoM. Compared to younger adults, older adults appear to exhibit a reduced angle of divergence between these two kinetic components and increased temporal variability during later phases of re-stabilisation. These observations could signify deficits in reactive postural control among the elderly and likewise, may have important implications for those with PD. In a general review that compared the postural stability of healthy young adults, elderly, and people with PD via CoP displacements,

Halliday et al. (1998) showed that CoP displacement and velocity become smaller with age and even smaller with PD and as disease severity increases. Moreover, Beaulne-Seguin and Nantel (2016) examined gait initiation among freezers, non-freezers and controls. They reported the greatest impairment was among freezers who displayed reduced CoP displacement and velocity in ML and AP directions. In comparison, non-freezers only exhibited reduction in ML and AP CoP velocity. Altogether, it appears that in contrast to abnormally large postural sway parameters during quiet stance, people with PD and especially freezers, tend to exhibit a more restrictive postural control strategy as evidenced by CoP displacements directed toward the stance limb, prolonged APAs, and decreased propulsive forces when executing deliberate movements such as gait initiation (Beaulne-Seguin & Nantel, 2016; Burleigh-Jacobs et al., 1997; Crenna, Frigo, Giovannini, & Piccolo, 1990; Ingvarsson, Johnels, & Steg, 1986; Vaugoyeau, Viallet, Mesure, & Massion, 2003). Burleigh-Jacobs et al. (1997) found that people with PD both on and off medication were able to increase APA force and velocity given a cutaneous go signal. A working hypothesis for these observations is that a portion of gait initiation may be controlled by non-dopaminergic pathways or that levodopa does not adequately control posture during this complex movement. In addition, gait initiation may require greater cognitive capacity than both quiet standing and steady state walking, and therefore a neurological overload may reduce the brains compensatory capacity to take over form malfunctioning dopaminergic pathways (Crenna et al., 2006).

3 – Effect of Therapeutic Interventions on Gait and Postural Stability in PD

Currently, there is no universal cure for PD. However, therapeutic modalities including dopaminergic and non-dopaminergic medication, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and a

handful of physical therapy tactics and exercises are often used in hopes of suppressing the debilitating motor and non-motor symptoms that exist with PD. These interventions have their own set of strengths and weaknesses and will be reviewed in the context of gait and postural stability.

3.1 – Dopaminergic Medication (Levodopa)

Levodopa is currently the dominating treatment for PD. However, its long-term use can lead to several complications in the execution of volitional movements (dyskinesia) (Nonnekes et al., 2016). Dopaminergic medication is known to cycle through periods in which said dyskinesia are well moderated (ON-State) and poorly moderated (OFF-State) (Kalia & Lang, 2015). Unfortunately, symptom responsiveness to Levodopa is variable due to disease severity and unique neurological differences among those with PD.

In a study that analyzed 104 participants with PD wearing inertial sensors (Curtze et al., 2015), 35 different balance and gait metrics were collected and compared between those with and without dyskinesias, and healthy controls. Stance, swing, and double support times, as well as the root mean square (RMS) - measure of sway variability, and mean velocity in both the ML and AP directions were identified and appeared to worsen in response to medication. Interestingly, the deleterious effects of Levodopa on postural sway were only present during quiet standing in the subgroup of participants who exhibited dyskinesias, while balance control during gait was unaffected. Further supporting the hypothesis that static and dynamic balance are differentially controlled by the CNS. On the other hand, Levodopa appeared to increase the amplitude of APAs during GI, confirming the results of (Burleigh-Jacobs et al., 1997) who demonstrated that both Levodopa and external cueing can improve force production during self-initiated APAs. In addition to APA enhancement, Levodopa was also found to improve turning

speed and drive a more exaggerated arm swing in the dyskinetic subgroup. Regarding the functional role of Levodopa, these findings suggest its excessive motor disinhibition along with a failure to improve postural control. Taken together, this trade-off might explain the observed association between dyskinesia and self-reported history of falls while on medication.

Furthermore, Smulders, Dale, Carlson-Kuhta, Nutt, and Horak (2016) sought to extend the findings of Burleigh-Jacobs et al. (1997) regarding the influence of dopaminergic pathways on self-generated, but not externally triggered postural adjustments, to several gait parameters. In this review, the effects of different pharmacological interventions on four distinct components of gait; straight walking, gait initiation, turning, and gait adaptability, were summarized. In general, bradykinetic and hypometric spatial characteristics of gait and turning seemed to improve with dopaminergic medication. During gait initiation specifically, Levodopa appeared to increase force production during the push-off phase, which when weak, would normally cause delayed stepping, shorter first step length, and poor spatially scaled APAs, therefore enhancing postural stability. However, with emphasis on temporally scaled APAs, cadence, and double support times, the efficacy of dopaminergic medication has presented with mixed reviews (Burleigh-Jacobs et al., 1997; Horak, Mancini, Carlson-Kuhta, Nutt, & Salarian, 2016; Jacobs, Lou, et al., 2009; Rocchi, Chiari, Cappello, & Horak, 2006; Rosin, Topka, & Dichgans, 1997).

Lastly, it has been proposed that Levodopa negatively affects frontal executive function and can promote freezing of gait in select cases (Espay et al., 2012). In a review by Nonnekes et al. (2016), it was found that the primary symptoms of PD may persist given its long-term use, as those with PD tend to develop a resistance to the drug over time. It was noted however, that postponing Levodopa treatment did not lead to substantial long-term benefits when compared

with early users and may have compromising effects on coordination, balance, and postural stability.

3.2 – Non-dopaminergic Medication

Other antiparkinsonian drugs such as dopamine agonists, catechol-O-methyl transferase inhibitors, monoamine oxidase type B inhibitors, amantadine and other non-dopaminergic agents such as glutaminergic, cholinergic, norepinephrine, methylphenidate and other drugs for co-morbidities have been shown to influence balance and locomotor abilities (Smulders et al., 2016), which suggests that some symptoms of PD may stem from multiple neurological factors not limited to a drastic reduction in dopamine (Fox, 2013). However, the evidence in support of non-dopaminergic medication is somewhat limited. Due to the complex nature of PD there is no straightforward relief mechanism for the growing number of motor deficiencies that persist and worsen as the disease progresses. Thus, additive therapeutic modalities such as DBS and tDCS, in combination with pharmacotherapy should be considered and regarded as a viable solution.

3.3 – Deep Brain Stimulation (DBS)

DBS is a surgical technique in which one or more electrodes attached to leads are implanted in specific regions of the brain. The electrodes are connected to an impulse generator, which delivers electrical stimuli to the surrounding brain tissue and modulates neuronal signaling in targeted regions deep within the brain. Two specific sites in the brain have most commonly been used for DBS therapy in PD: the STN and the internal segment of the globus pallidus. Both are nuclei in the basal ganglia, where much of the degenerative neural change in PD occurs (DBS Study Group, 2001; Okun, 2012). This form of therapy, however, is not without its limitations as there are several adverse effects that must be considered with this highly invasive surgical procedure. Buhmann et al. (2017) conducted a long-term retrospective research study of

123 patients, in which the possible adverse effects of DBS were explored. Over the course of the study (578 participant-years in its entirety), 433 adverse events were recorded in 86.2% of participants. Any serious adverse events that occurred within 4 weeks of surgery were reversible, however, non-reversible adverse events were only observed in those with PD (4.9% of participants). With respect to GPi stimulation, these adverse events included; suicide, weight gain >20 kg, impairment of gait and speech, and cognitive decline. With respect to STN stimulation, these adverse events included; impaired speech or gait, depression, weight gain, cognitive disturbances or urinary incontinence (Buhmann et al., 2017). For this reason, patients must undergo a thorough screening process and continuous post-operative monitoring in order to receive this treatment. In addition to the plethora of adverse effects associated with DBS, a validated set of criteria for optimal delivery, with specific reference to amplitude, frequency, duration, and location of the applied electrical current has not yet been developed.

Research pertaining to the effects of DBS on postural stability and gait is less extensive. Nonetheless, DBS has captured the interest of researchers far and wide, with some promising effects. Nantel, McDonald, and Bronte-Stewart (2012) compared the effects of dopaminergic medication to that of DBS, the neuromotor aspects of postural control in PD were assessed. It was found that dopaminergic medication significantly increased postural sway in the ML direction, while STN-DBS appeared to reverse this deleterious effect (Nantel et al., 2012). Some studies, however, have presented conflicting results regarding the effects of DBS on postural stability. In line with the findings of Curtze et al. (2015) which highlight the negative effects of Levodopa resulting from dyskinesia, St George et al. (2012) determined that functional stability worsened among those who received STN, rather than GPi stimulation. Furthermore, Muniz et al. (2010) evaluated gait initiation in PD after STN-DBS with a 7-year follow-up. Principal

components analysis of APAs during gait initiation using vertical, AP, and ML ground reaction forces revealed a significant difference in APA amplitude for vertical and AP ground reaction forces among those with PD on medication. In the follow-up assessment, all three (vertical, AP, and ML) showed increased standard differences. Therefore, pointing towards a worsening of gait initiation.

Nantel et al. (2012) examined postural stability in 129 participants with PD off and on medication. This procedure was then repeated for a subgroup of 28 participants in which the same measurements were recorded both off and on medication, and before and after STN-DBS. Results from this study clearly indicate that postural sway in quiet stance increases with disease severity, and that medication alone seems to exacerbate its displacement and velocity in the ML direction. Moreover, STN-DBS was found to significantly correct excessive CoP_{ML} velocities induced by medication alone. Other studies have reported large effect sizes when stimulating the bilateral STN via DBS for spatiotemporal gait parameters, such as speed, stride length, cycle time and double support time, while smaller effect sizes were obtained for cadence and stride length when paired with pharmacological treatment (Speciali et al., 2015). Conversely, Krystkowiak et al. (2003) found that STN stimulation provided little benefit for gait velocity and stride length.

Dynamic posturography has been used to examine the specific sensory and motor aspects of postural control in people with PD before and after bilateral STN-DBS. This type of stimulation was shown to significantly improve postural bradykinesia, whereas medication did not (Shivitz, Koop, Fahimi, Heit, & Bronte-Stewart, 2006). Results from Shivitz et al. (2006) further conclude that neither bilateral STN-DBS nor medication appear to influence postural RT. In another study that analyzed the effects of DBS on RT, Klostermann et al. (2010) confirmed

that people with PD off-DBS are generally slower than controls and that bilateral STN-DBS was only effective at improving RTs in a choice response task in which motor programs are generated spontaneously in response to specific stimuli rather than deliberately planned. These findings support the notion that the neuromotor complications involved with postural instability extend to multiple networks, and that while some aspects may be unresponsive to medication, others can be modulated via electrical stimulation of the brain.

3.4 – Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS is a unique therapeutic modality derived from an electric current that runs through a coil of copper wires such that it generates a relatively strong magnetic field. When applied to the scalp it can modulate the neural activity of specific regions within the brain. Through neuroimaging, rTMS has been successfully administered for both PD and depression to induce cortical stimulation of the M1 and left/right prefrontal cortices respectively (Gonzalez-Garcia et al., 2011; Luber et al., 2017). In PD trials, the use of rTMS has translated with both positive and negative effects. On one hand, it has contributed to the improvement of several brain functions related to motor performance, cognition and emotional state (Filipovic, Rothwell, van de Warrenburg, & Bhatia, 2009; Khedr, Farweez, & Islam, 2003; Randver, 2018). Likewise, it has significantly reduced UPDRS III scores related to bradykinesia, muscle rigidity and tremors for those with PD (Siebner, Rossmeier, Mentschel, Peinemann, & Conrad, 2000). On the other hand however, rTMS has been documented to have no influence on these clinical scores, nor on measures of RT, executive function, working memory, or psychomotor speed (Sedlackova, Rektorova, Srovnalova, & Rektor, 2009). In select cases it has caused noticeable worsening of tremor and has even been shown to induced seizures (Boylan, Pullman, Lisanby, Spicknall, & Sackeim, 2001; Wassermann, 2000). Above all, when applied to the SMA of participants with

PD, rTMS has been shown to slow RTs in the preparation phase of complex upper body movements (i.e. spiral drawing), while having no effect on MTs throughout (Boylan et al., 2001).

Despite the scarcity of research on the effects of rTMS as it pertains to gait initiation in PD. It is thought that the SMA plays a large role in the generation of APAs when programming voluntary movements (Bolzoni, Bruttini, Esposti, Castellani, & Cavallari, 2015). For those with PD this malfunctioning brain structure may contribute to diminished, prolonged, and more variable APAs (Rocchi et al., 2006). In turn, this may translate into gait complications such as reduced postural stability and poor muscular coordination. Jacobs, Lou, et al. (2009) therefore, sought to reveal the underlying neurological contributions of the SMA during step initiation using rTMS to test the hypothesis that the SMA is responsible for generating the amplitude and timing of APAs. Having compared the effects of SMA versus dorsolateral premotor cortex stimulation, they determined that the SMA is likely responsible for the timing, but not the amplitude of APAs during gait initiation (Jacobs, Lou, et al., 2009).

rTMS however, as a standalone treatment for hypokinetic gait in PD has variable effects depending on the stimulation parameters (Chen et al., 1997; Hallett, 2007; Karima et al., 2003; Pascual-Leone, Valls-Sole, Brasil-Neto, Cammarota, et al., 1994; Pascual-Leone, Valls-Sole, Brasil-Neto, Cohen, & Hallett, 1994). Therefore, von Papen, Fisse, Sarfeld, Fink, and Nowak (2014) studied the effects of preconditioning rTMS with anodal, cathodal, and sham tDCS on gait kinematics in PD. It was determined that rTMS alone, (rTMS + cathodal tDCS), and (rTMS + sham tDCS) were ineffective, while rTMS preconditioned by anodal tDCS was found to significantly increase step count and step length, however, its affects increased double support times which may be interpreted as destabilizing to posture. In addition, this preconditioning protocol appeared to have some gait enhancing affects as it significantly decreased cadence in

those with PD (von Papen et al., 2014). Since hypokinetic gait in PD is typically characterized by an increase in; number of steps, double support times, and stance phases, along with a decrease in; stride length, cadence, and swing phases, the results of preconditioning rTMS with tDCS may generally be interpreted as mixed.

To date, research detailing the effects of rTMS alone, on postural stability in PD is equally as scarce. Within the literature, there is some data suggesting that cumulative high frequency rTMS over the primary motor cortex lower leg area, may improve FoG-Q, timed Up and Go, and UPDRS-III scores (Kim et al., 2015). However, to our knowledge these findings have not since been replicated. The use of rTMS was extended in a clinical trial by Forogh et al. (2017) to manage the balance impairments acquired by individuals post stroke. In this study (Forogh et al., 2017), static and dynamic balance measures were collected using; a Biodex device (Biodex Medical Systems). Medical Research Council Scale for muscle strength, and a Berg Balance Scale. Static postural stability improved significantly for those in the treatment group compared with a sham group. It remains unclear whether the same balance enhancing properties of rTMS hold true for those with similar neurodegenerative diseases such as PD.

3.5 – Transcranial Direct Current Stimulation (tDCS)

Compared with rTMS, tDCS involves the direct application of a sustained, low electrical current to the scalp, which may be advantageous in reducing the risk of seizures – a known side effect of rTMS among those with implanted metal objects and a past diagnosis of epilepsy (Forogh et al., 2017; Jacobs, Lou, et al., 2009; Zaghi, Heine, & Fregni, 2009). Lately, tDCS has also been recognized as a practical, more cost-effective stimulation technique (Zaghi et al., 2009). Both forms of electrical stimulation have the capability of inducing neurological change with promising motor effects, as they manipulate the balance of ions that surround neural

membranes (Conley et al., 2015). With tDCS, Nitsche and Paulus (2000) discovered that the nature and magnitude of these effects depend on the polarity of stimulation. They observed that cathodal and anodal tDCS promote both hyperpolarization and depolarization respectively. It was made apparent that both types of stimulation appear to differentially regulate the resultant amplitudes of motor-evoked potentials. Specifically, amplitudes increased with anodal tDCS, while they decreased with cathodal tDCS. Furthermore, the effects of polarity specific tDCS were shown to persist up to 5 minutes beyond the stimulation window, therefore extending the longevity of motor enhancements. It was noted however, that a minimum stimulation period of 3 minutes at 1mA (or 5 minutes at 0.6mA) was required to observe this relationship. Albeit, the origin and duration of such after-effects is mostly unknown, but they have been hypothesized to stem from post-tetanic potentiation, short-term potentiation and processes like post-excitatory central inhibition (Nitsche & Paulus, 2000). As tDCS is an emerging therapeutic tool, its ongoing use and long-term effects are much less understood.

Regarding the functional role of tDCS for gait initiation in PD, it is presumed to facilitate the execution of deliberate motor commands, specifically those involved in the generation of proper APAs. In PD, inappropriately timed or absent APAs can result in a significant destabilization to posture and balance (Lu, Amundsen Huffmaster, Tuite, & MacKinnon, 2018). Impairments in the control of APAs have been described in a variety of neurological disorders, such as Parkinson's disease (Rogers et al., 2011), stroke (Aruin, 2006), and hemiparesis (Dumont et al., 2015). Currently, the mechanisms by which the nervous system prepares and integrates APAs with voluntary movements are not well understood. As an alternative approach to rTMS, tDCS interventions have demonstrated both positive and significant results for similar measures

of gait and postural stability among the neurologically impaired (Dumont et al., 2015; Park, Kim, & Song, 2015).

In most research, the effects of anodal tDCS on balance and gait have been assessed relative to sham stimulations. However, in a single 79-year-old participant with moderate PD, tDCS was applied concurrently with tango dancing. This unique therapeutic intervention was observed to significantly increases trunk velocity in both pitch and roll thereby reducing trunk rigidity (Kaski, Allum, Bronstein, & Dominguez, 2014). For the same participant, the effects of tDCS were then isolated to gait metrics alone as it significantly reduced the time taken to complete a 3-meter timed Up & Go task and 6-meter walk (Kaski, Allum, et al., 2014). It has also been observed in a timed Up & Go task that, when applied over the dorsolateral prefrontal cortex (DLPFC), tDCS significantly reduced RTs among those with PD (Manenti et al., 2014)**.** Kaminski et al. (2017) applied tDCS over the M1 leg area of healthy older adults and found that it facilitated the motor learning of a dynamic balance task and that its effects outlasted the stimulation period. The same study group also analyzed the specific relationships between anodal tDCS and similar kinematic variables. In line with their previous research, postural imbalances correlated with higher velocity and acceleration during a dynamic balance task prior to tDCS administration, while smaller velocity and accelerations were observed post tDCS in a group of healthy young participants. Conversely, Kaminski et al. (2017)found that tDCS did not facilitate dynamic balance task learning in healthy older adults. In older adults, tDCS has also been shown to increase dual-task postural sway complexity (Zhou et al., 2015).

For the most effective delivery, Fregni et al. (2006) conducted a study that compared three different applications of tDCS in PD. The first consisted of anodal tDCS on the primary motor cortex (M1), the second consisted of cathodal tDCS on M1, and the third consisted of

anodal tDCS on the DLPFC. They established that a single session of anodal tDCS on M1 significantly improved motor function in a simple RT task, as well as UPDRS scores compared to sham stimulation (Fregni et al., 2006). Another study showed that anodal tDCS placed on M1, significantly reduced the numbers of steps in those with self-reported festination, and the number and duration of FoG episodes in those with self-reported FoG, relative to a sham stimulation (Valentino et al., 2014). In a similar study, Lattari et al. (2017) explored the efficacy of stimulating the left DLPC for balance and functional mobility in PD. Compared to sham stimulation, their results indicated a significant improvement among outcome measures including the Berg Balance Scale, Dynamic Gait Index, and Timed Up and Go (Lattari et al., 2017).

We know that the brainstem and basal ganglia interact because neural imaging studies show that motor programs can be suppressed via tonic inhibition from the basal ganglia as well as excited by direct cortical input (Takakusaki, 2008). One way to test the influence of these cortical areas on postural maintenance and APA production is to up- or down-regulate cortical excitability and observe the effects on the preparation of a voluntary movement (ie. RTs) (Carlsen et al., 2015). There are only a handful of studies that examine the application of tDCS to the M1 leg area. In one instance, Jeffery, Norton, Roy, and Gorassini (2007) demonstrated that 10 minutes of contralateral tDCS delivered at 0.06 mA/cm^2, enhanced cortical excitability in the M1 leg area and lasted up to 60 minutes post stimulation. In another, Foerster, Rezaee, Paulus, Nitsche, and Dutta (2018) found that a small-anode montage with the cathode positioned at T7 (−70 mm, −16 mm, −8 mm) in accordance with the 10–10 system defined in Oostenveld and Praamstra (2001), resulted in the best specificity and excitability. In addition to the M1 leg area, tDCS has been applied to the SMA of healthy volunteers and has had an influence on RTs and

movement preparation strategies when paired with a startling acoustic stimulus (Carlsen, Almeida, & Franks, 2013; Carlsen et al., 2015; Carlsen, Maslovat, & Franks, 2012; Carlsen, Maslovat, Lam, Chua, & Franks, 2011; Maslovat, Carter, Kennefick, & Carlsen, 2014). Most recently, Lu et al. (2018) conducted a pilot study which evaluated the effects of anodal tDCS over the supplementary motor area on gait initiation in PD with freezing of gait and found that it did not significantly improve self-initiated gait. In the same pilot study however, auditory cueing was used to initiate gait prior to the delivery of anodal tDCS and resulted in significant improvements in the amplitude and timing of gait initiation. Therefore, with only a preliminary body of evidence regarding the influence of tDCS on the neuromotor system, and a clear capacity for improved gait initiation, further research is needed to clarify its therapeutic potential with respect to neuromotor rehabilitation in disorders such as PD

Chapter III: Research Article

Can Transcranial Direct Current Stimulation Improve Gait Initiation in Parkinson's Disease?

Highlights: Transcranial direct current stimulation in Parkinson's disease reduces the size and speed of mediolateral anticipatory postural adjustments during cued gait initiation.

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Abstract

Gait initiation is of primary concern in individuals with Parkinson's disease (PD), due to the deficits in both gait and postural stability and their inherent association with falls and fall related injuries. Current treatment options in PD do not seem to adequately relieve these deficits. Transcranial direct current stimulation (tDCS) is a novel therapeutic intervention that may be used to improve stability during gait initiation by modulating neuronal activity, thereby enhancing movement and postural control. The purpose of this study is to evaluate the effect of tDCS on gait initiation in people with PD when on anti-parkinsonian medication. More specifically, it will determine the effect of tDCS on variables pertinent to muscle activity, dynamic postural stability, movement efficiency, and movement variability. Thirteen participants with PD – on dopaminergic medication took part in a within subjects repeated measures experimental design to investigate the effects of a 10-minute sham-controlled tDCS intervention on gait initiation. Two-way repeated measures ANOVAs showed a significant main effect of time for center of pressure (CoP) displacement and velocity in the mediolateral (ML) direction. Post-hoc analysis revealed a significant reduction in the magnitude of both variables following tDCS intervention. No significant effects were seen in the other variables. A significant decrease in CoP_{ML} displacement and velocity could have a major impact on individuals for whom medication does not adequately regulate this aspect of gait initiation. These results will contribute to a better understanding of the effectiveness of non-invasive anodal tDCS as a means of regulating postural stability in the ML direction during gait initiation. At this stage however, more research is required to evaluate the effectiveness of tDCS as an assistive device for fall prevention in PD.

Keywords: Parkinson's Disease, gait initiation, postural stability, transcranial direct current stimulation, supplementary motor area.

1 – Introduction

Parkinson's disease (PD) is a progressive neurological disease characterized by the degeneration of dopamine producing cells within Basal Ganglia (Damier et al., 1999). This leads to motor symptoms such as tremor, rigidity, bradykinesia, and postural instability (Fasano et al., 2018). Each symptom contributes to cumbersome and impaired movement, yet none are more central to falling than postural instability (Schrag, 2002; Schrag, Choudhury, Kaski, & Gallagher, 2015). Approximately 90% of individuals with PD will fall over the course of their lifetime and in severe cases, this can lead to serious medical consequences (Playfer, 2001).

Locomotor activities such as gait initiation – the transient period between quiet standing and steady state walking, represent a major challenge to postural stability (Jian, Winter, Ishac, & Gilchrist, 1993; Yiou et al., 2017). Primed with postural deficits, people with PD may be at an increased risk of falling due to the asymmetric nature of gait initiation which depends on the coordination of ML and AP muscle groups (Winter, 2009). Gait initiation therefore, demands greater neuromotor control (Vaugoyeau et al., 2003; Winter, 2009), making it a more challenging task than both quiet standing and steady state walking alone (Mille et al., 2012; Mille, Simoneau, & Rogers, 2014; Yiou et al., 2017). Together, impaired neuromotor preparation and a lack of postural stability could explain the high occurrence of falls reported during gait initiation among those with PD (Rigoldi et al., 2016).

A key component of gait initiation is anticipatory postural adjustments (APAs). APAs involve a series of muscle activations in the tibialis anterior (TA) and medial gastrocnemius

(MG) that serve to stabilize posture. This muscle synergy causes a change in the ground reaction forces that displace the net CoP beneath the feet posteriorly and laterally (Brunt et al., 1991; Crenna & Frigo, 1991; Lin, Creath, & Rogers, 2016). When it comes to movement preparation in PD, hypometric APAs are frequently reported in untreated PD, as compared to both elderly and healthy age-matched controls (Burleigh-Jacobs et al., 1997; Halliday et al., 1998; Park, Kang, & Horak, 2015; Vaugoyeau et al., 2003). This is in line with observed reductions in both CoP displacement and velocity (Beaulne-Seguin & Nantel, 2016; Halliday et al., 1998), which may compromise postural stability during gait initiation, especially among those who present with a subclass of PD known as Postural Instability Gait Difficulty (PIGD) (Chen et al., 2015). On the other hand, hypermetric postural control – measured during quiet standing, has also been observed in untreated PD (Schoneburg et al., 2013) which may lead to postural instabilities that may be further exacerbated when on medication (Curtze et al., 2015). A common thread pertaining to this dichotomy between hypometric and hypermetric APAs is that participants are rarely screened and grouped based on progressive subtypes of PD (PIGD or Tremor Dominant (TD) (Thenganatt & Jankovic, 2014), making it difficult to interpret the benefits of study results. Therefore, optimal postural stability during gait initiation perhaps necessitates appropriately scaled APAs to accommodate one's individual needs relative to task demands. In other words, for those with PD, ideal APAs might fall within a 'Goldilocks zone' much like those of healthy controls (Martin et al., 2002).

The current treatment options for PD focus on interventions at the cellular level which target motor symptoms through the modification of cortico-basal ganglia-thalamo-cortical loops. The flow of electricity through these complex neuronal circuits has been modeled using direct and indirect pathways, which are highly dependent on the presence of dopamine to maintain a

balanced motor control system. The overall effects of dopamine on these pathways result in direct excitation and indirect inhibition of the cerebral cortex (ex. SMA), which in turn dictates the release and/or retention of motor commands. Given the lack of dopamine in PD, treatments range from dopamine replenishing drugs (ex. Levodopa), to various electric brain stimulations (ex. Transcranial direct current stimulation (tDCS)) (Bikson et al., 2016; Rossi, Hallett, Rossini, Pascual-Leone, & Safety of, 2009) that alternatively, attempt to modulate neuronal activity through putative effects on these dopaminergic pathways.

While some research argues the stabilizing benefits associated with pharmacological treatment (Burleigh-Jacobs et al., 1997; Lewitt, 2008), reports have been mixed, given the wide range of disease severity and individual differences among those with PD (Nomoto et al., 2009; Nonnekes et al., 2016). In addition, dopaminergic drugs have been shown to markedly reduce postural stability during quiet standing and throughout gait (Horak et al., 1996; Nantel et al., 2012; Nardone & Schieppati, 2006). Nonetheless, dopamine plays an important role in the execution of deliberate motor commands and when optimally balanced has been shown to contribute to may interact with tDCS in

Although the effect of tDCS on extracellular dopamine concentration in the brain is unknown (Hess, 2013; Tanaka et al., 2013; Ziomber et al., 2017), tDCS-induced dopamine dependent effects such as increased excitability, plasticity and oscillations (Morya et al., 2019) have been observed in both human and animal models. The hypothesized mechanism underlying these effects stem from the notion that anodal and cathodal stimulation lead to the hyperpolarization and depolarization of neuronal membranes respectively (Creutzfeldt, Fromm, & Kapp, 1962), thus facilitating and/or inhibiting the propagation of action potentials and subsequent release of neurotransmitters throughout the brain. However, despite limited

knowledge surrounding the modulatory effects of tDCS on subcortical networks, Hess (2013) present a rational for its use in PD; stating that tDCS may influence the central nervous system through the induction of extracellular field effects which may prod subthreshold changes in the excitability of cortical projections linked to key subcortical structures such as the basal ganglia.

Regarding the supplementary motor area (SMA) – which is hypoactive in PD (Chen & Chen, 2019; Sabatini et al., 2000) and known to contribute to the preparation, coordination and coupling of muscles associated with voluntary movements (Carlsen et al., 2015; Eccles, 1982; Hayduk-Costa, Drummond, & Carlsen, 2013), a substantial body of research has established its importance during gait initiation (Jacobs, Lou, et al., 2009; Viallet, Massion, Massarino, & Khalil, 1992). Recently it was shown using continuous theta burst transcranial stimulation, that functional inhibition of the SMA reduced APA phase duration, increased muscle co-activation during the execution phase, and decreased the duration of soleus activity during the stance phase of gait initiation among healthy individuals (Richard et al., 2017). Therefore, based on the principle that anodal tDCS may increase neuronal firing rates via subthreshold modulation of local targets such as the SMA (Carlsen et al., 2015; Orban de Xivry & Shadmehr, 2014), then those with PD may benefit from enhanced coupling of movement and posture, ultimately leading to improved stability during gait initiation.

In a recent pilot study, Lu et al. (2018) analyzed the effects of anodal tDCS compared with sham stimulation over the SMA on self-initiated gait in those with PD and observed no significant differences. However, tDCS-induced changes pertaining APAs driven by lower limb muscles have been observed among healthy older adults during movement initiation (Nomura & Kirimoto, 2018). Likewise, it appears that specific variables associated with postural stability (i.e. CoP displacement and velocity) and movement initiation (i.e. reaction time (RT) and

movement time (MT)), which are heavily influenced by tibialis anterior (TA) and medial gastrocnemius (MG) activity, may be differentially affected by medication and brain stimulation among those with PD (Boylan et al., 2001; Lu et al., 2018; Nomura & Kirimoto, 2018; Rowe et al., 2008; Smulders et al., 2016; Szlufik et al., 2018). The main objective of the present study was to evaluate the effects of anodal tDCS on gait initiation in PD. As such, muscle activity, postural control, and movement efficiency were examined. It was hypothesized that 10 minutes of anodal tDCS would increase cortical excitability in the SMA thereby inducing changes to muscle activity, postural stability, movement efficiency.

2 – Methodology

2.1 – Participants

A convenient sample of 12 individuals (11 male and 1 female) with PD were included in this study. Sample size was determined from priori calculation performed in SigmaPlot (SystatSoftware, 2018). To achieve statistical significance; a power threshold of 0.80, alpha of 0.05, and beta of 0.20 were defined. Effect sizes were estimated based on past findings from Nantel and Bronte-Stewart (2014), where significant differences in CoP_{ML} and CoP_{AP} displacement and velocity were observed among freezers (n=15) compared with non-freezers (n=15) and healthy controls (n=14). Participants were excluded from the study if they did not have the ability to walk unaided for 5 meters or if they had any history of additional neurological conditions. Other exclusion criteria included having undergone DBS surgery, previous injury to the lower extremities and episodes of freezing of gait. There were no severe hearing disorders and all visual disorders were minor and corrected for with glasses. All participants were required to sign a consent form approved by the Research Ethics Board of our institution.

2.2 – Clinical Evaluation

Each participant underwent clinical evaluations, which included the Unified Parkinson's Disease Rating Scale Motor Examination (UPDRS III,) (Fahn, Elton, Calne, & Goldstein, 1987) , and the Hoehn and Yahr rating scale (Hoehn & Yahr, 1967).

2.3 – Data Collection

A single-blinded, quasi-experimental crossover study in which participants were unaware of a sham treatment, was used to determine the effects of anodal tDCS on gait initiation in PD. Testing took place on two different days separated by approximately one week to reduce any carryover effects associated with the intervention (Carlsen et al., 2015). On each day, testing consisted of four phases: Familiarization, pretest, intervention (using tDCS or sham – the order of stimulation was randomly selected), and post-test. The total time for each testing session was

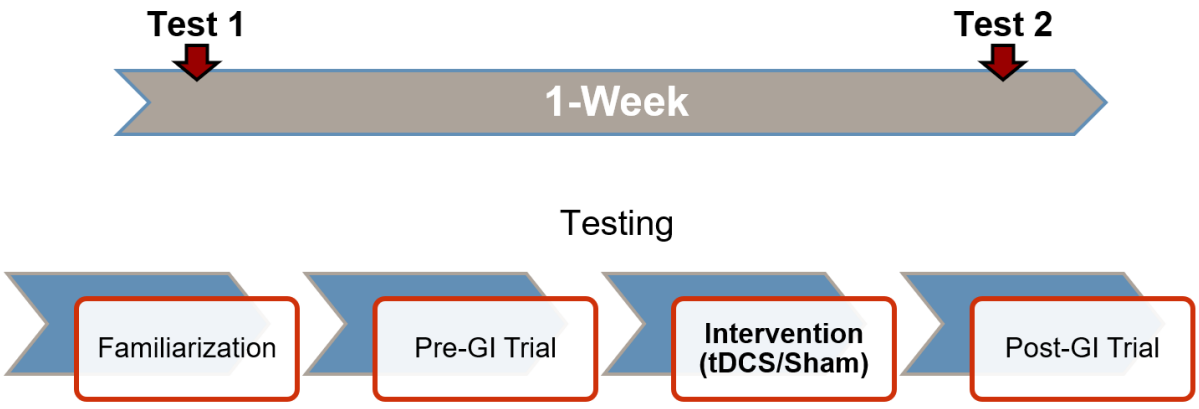

Figure 2. *Schematic representation of repeated measures study design.*

approximately 1.5 hours. Data collection was conducted by trained individuals and standardized to take place at the same time each day. The movement task for each testing phase was identical and consisted of a gait initiation protocol in which participants stood with their feet shoulder width apart and were instructed to walk forward as quickly as possible following the sound of an

auditory cue "BEEP". To ensure consistency between trials, the amplitude of auditory cueing did not change from trial to trial and participants were asked to select and maintain a lead stepping foot based on personal preference. They were also asked to complete a minimum of 6 steps before returning to the starting position on top of the force plate, as this was assumed to allow for enough movement follow through such that authentic gait initiation was emulated. This movement was repeated for a total of 10 gait initiation trials per testing phase.

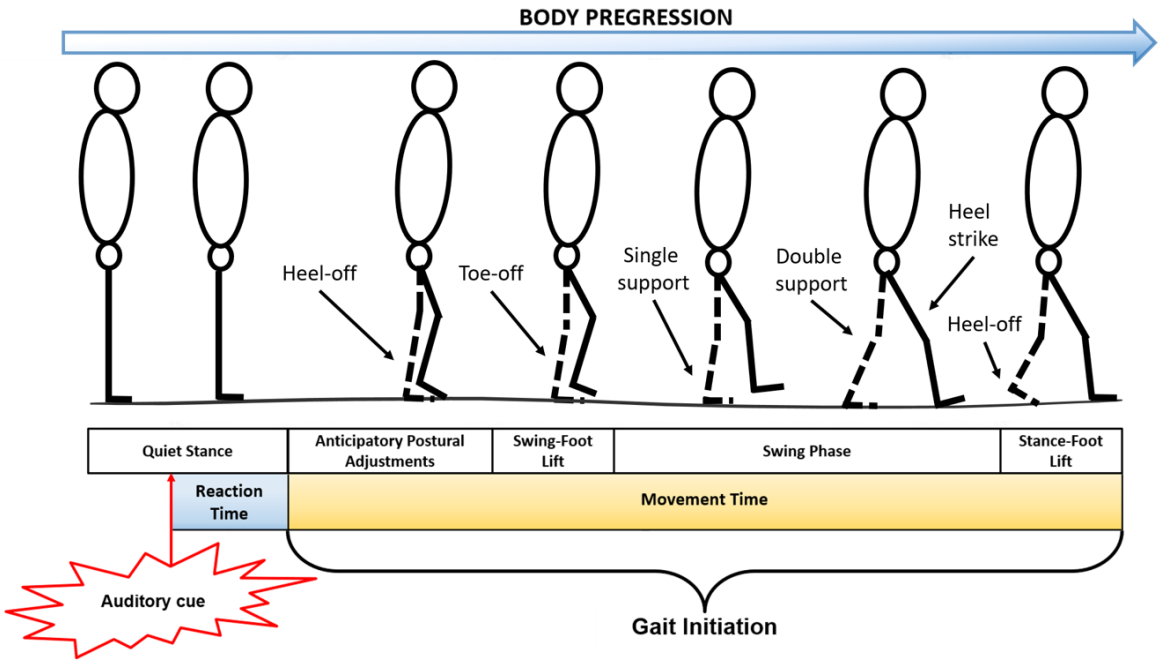

Figure 3. *Schematic representation of gait initiation task and key events.*

Each test phase was separated by 10 minutes of continuous weak electrical stimulation over the SMA. A Chattanooga INOTO™ dual channel iontophoresis system (DJO International) which included two electrodes, was used. The "active" self-adhesive sponge electrode (1.5cc, 7.8 cm2, Ionto+ Inc.) was positioned directly above the centroid of the SMA, 1.8 cm anterior to the measured Cz 'vertex' location at the top of the skull. The sponge on the active electrode was soaked with a saline solution (0.9% NaCl). To ensure optimal contact of the electrode to the

scalp, foam under wrap was used to secure the electrode in place. A self-adhesive carbon-foam buffered return electrode (39 cm2, Ionto+ Inc.) was placed over the center of the forehead directly above the eyebrows. Anodal stimulation was set at 1mA (current density at the active electrode was thus 0.128 mA/cm2). For sham stimulation, testing was comparable to that of the anodal stimulation, except that once the stimulation device ramped up to 1 mA (<15 seconds) it was turned OFF without the participants' awareness.

Ground reaction forces were collected at a rate of 500Hz from a single piezoelectric force plate (Kistler). Muscular activity was recorded at 1000Hz using non-invasive bipolar surface electrodes connected to an external amplifier (Delsys Bagnoli-8; Delsys Inc., Natick, MA). Muscles of interest (right/left TA and MG) were cleaned and EMG electrodes were aligned parallel to muscle fibers in order to reduce electrical impedance.

2.4 – Signal Processing

Signal processing was conducted using MatLab (Mathworks, 2017), with customized scripts for both force and EMG data reduction. Kinetic data were processed using an 8Hz zero-lag lowpass Butterworth filter (Schreven, Beek, & Smeets, 2015). Appropriate cut-off frequencies were adjusted based on residual analysis. All kinetic data were detrended to remove the effect of participant position on the force plate. Variables pertaining to APAs were derived from both EMG (RT, DoB_{TA}, Amp_{TA}, Amp_{MG}, and $CCI_{TA\text{-}MG}$) and postural data (CoP_{ML} and CoP_{AP} displacement and velocity, and MT), where means and standard deviations were calculated for phase of 10 cued gait initiation trials.

EMG onsets and offsets were classified using a threshold-based protocol to explore the differences in APAs under each treatment condition. EMG onset and offset detection occurred

when signal magnitudes rose above or fell below, a threshold set at 5 standard deviations above a baseline resting potential, respectively. Baseline resting potential was calculated as the mean signal amplitude during the first 0.5s of quiet standing prior to the auditory cue. RT was defined from the time of auditory cueing to the time of EMG onset detection. Calculations for RT also incorporated a Teager-Kaiser Energy Operator to increase the accuracy of EMG onset detection (Solnik, Rider, Steinweg, DeVita, & Hortobagyi, 2010). When necessary, bilateral EMG onsets and offsets of the TA were hand selected by an experienced examiner to quantify RTs, TA and MG amplitudes, and duration of anticipatory TA muscle bursts that occurred during gait initiation.

To measure $CoI_{TA\text{-}MG}$, EMG signals were time-normalized to the shortest number of frames present in TA muscle burst of the initiating limb (ie. DoB-TA) (Boudarham et al., 2016). Both EMG signals were then amplitude normalized to the largest values of activation observed in each muscle respectively. An ensemble average was calculated across all 10 gait initiation trials. Finally, the ensemble averages of TA and MG were overlaid atop one another. The area of overlap (integral) between the muscles was divided by the overlap duration (number of time-normalized data points) to calculate mean co-contraction indices under each stimulation condition (Unnithan, Dowling, Frost, & Bar-Or, 1996; Yang & Winter, 1984).

MT was defined from the time of the first observed CoP deviation from quiet stance – the onset of gait initiation (Hiraoka et al., 2014) (the point at which either ML or AP forces deviated from their norm during quiet stance by a factor of two standard deviations) to the point at which the participant stepped off the force plate (as vertical forces approached and reached zero). Lastly, CoP displacement in ML and AP was calculated by dividing the respective moments of

force in each direction by the vertical ground reaction force (Winter, 2009), while CoP velocity in ML and AP was calculated by dividing the resulting CoP displacements by the calculated MT.

2.5 – Statistical Analysis

For all statistical analyses SPSS v.25 computer software (IBM, 2018) was used. Prior to analysis, Shapiro-Wilk's tests of normality were conducted for all variables. For all variables that represented a normal distribution, separate two-way repeated measures ANOVAs were performed to determine the between (anodal tDCS and sham stimulation) and within (pre-post) group effects of intervention on gait initiation metrics. All non-parametric parameters were log-transformed and if normality permitted, the appropriate parametric analysis as described above was performed. Otherwise, all variables that maintained non-normal distributions, underwent separate related-samples Wilcoxon signed rank tests to evaluate asymptotic differences between (anodal tDCS and sham stimulation) and within (pre-post) groups. Post-hoc analyses included independent-samples t-tests with Bonferroni corrections for parametric data to determine which groups were significantly different from one another.

3 – Results

3.1 – Participant Data

The mean age of our sample was 63 years (± 9.2), with a disease duration of 7.8 years (± 4.8), UPDRS III score of 9.3 (± 3.5) and Hoehn and Yahr score of 1.5 (± 0.9). All participants were right-hand dominant and 7 out of 12 participants, initiated walking with the right leg. As for the laterality of the disease, 7 participants were most impaired on the left-hand side and 5 were most impaired on the right-hand side. There was no knee trembling present within our sample, however mild upper arm tremors were common in all but 3 participants and was mostly present

on the most affected side. There were no adverse effects to the anodal tDCS other than a few minor and expected reports of itching and/or tingling sensations.

3.2 – Dynamic Postural Control

The two-way repeated measures ANOVA indicated a significant main effect of time for CoP_{ML} displacement ($F(1,11) = 8.876$, $p = .014$, $n2 = 0.470$), and CoP_{ML} velocity ($F(1,11) = 8.160$, $p = .017$, $n^2 = 0.449$) respectively. Post-hoc analyses indicated a significant reduction in CoP_{ML} displacement (17.64cm ± 4.31cm) from pre-tDCS to post-tDCS intervention (16.50cm ± 4.59cm), 95% CI [0.41554, 1.86853], $t(10) = 3.503$, $p = .006$.

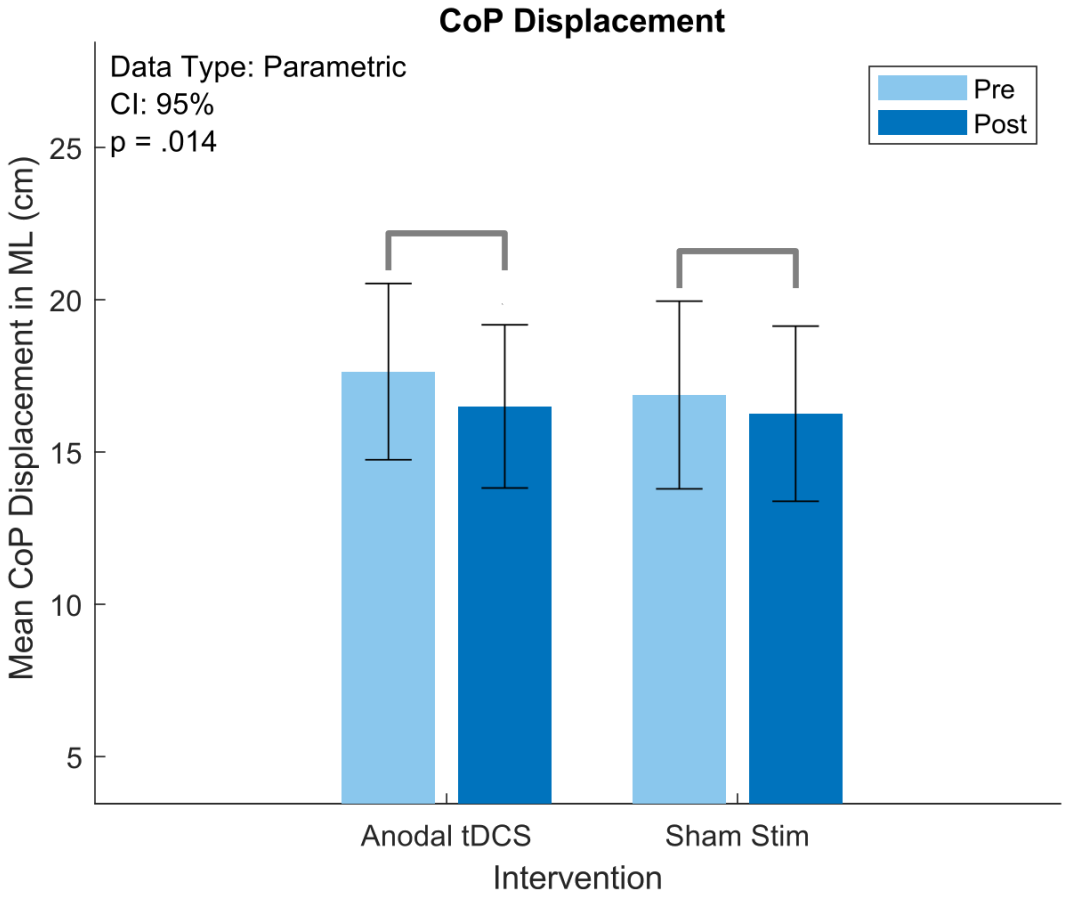

Figure 4. *CoPML displacement (cm) of individuals with PD who received both anodal tDCS and sham stimulation between gait initiation trials. Interventions were separated by one week. (*) Indicates significant differences (p<0.05).*

Similarly, post-hoc analyses indicated a significant reduction in CoP_{ML} velocity (16.96cm/s ± 4.275cm/s) from pre-tDCS to post-tDCS intervention (15.88cm/s ± 4.282cm/s) , 95% CI [0.462, 1.716], t(10) = 3.872, p = .003. CoP_{AP} displacement showed no main effects for intervention and time, nor was there a significant interaction between anodal tDCS and sham stimulation. Similarly, CoP_{AP} velocity showed non-significant main effects for intervention and time, as well as a non-significant interaction between them.

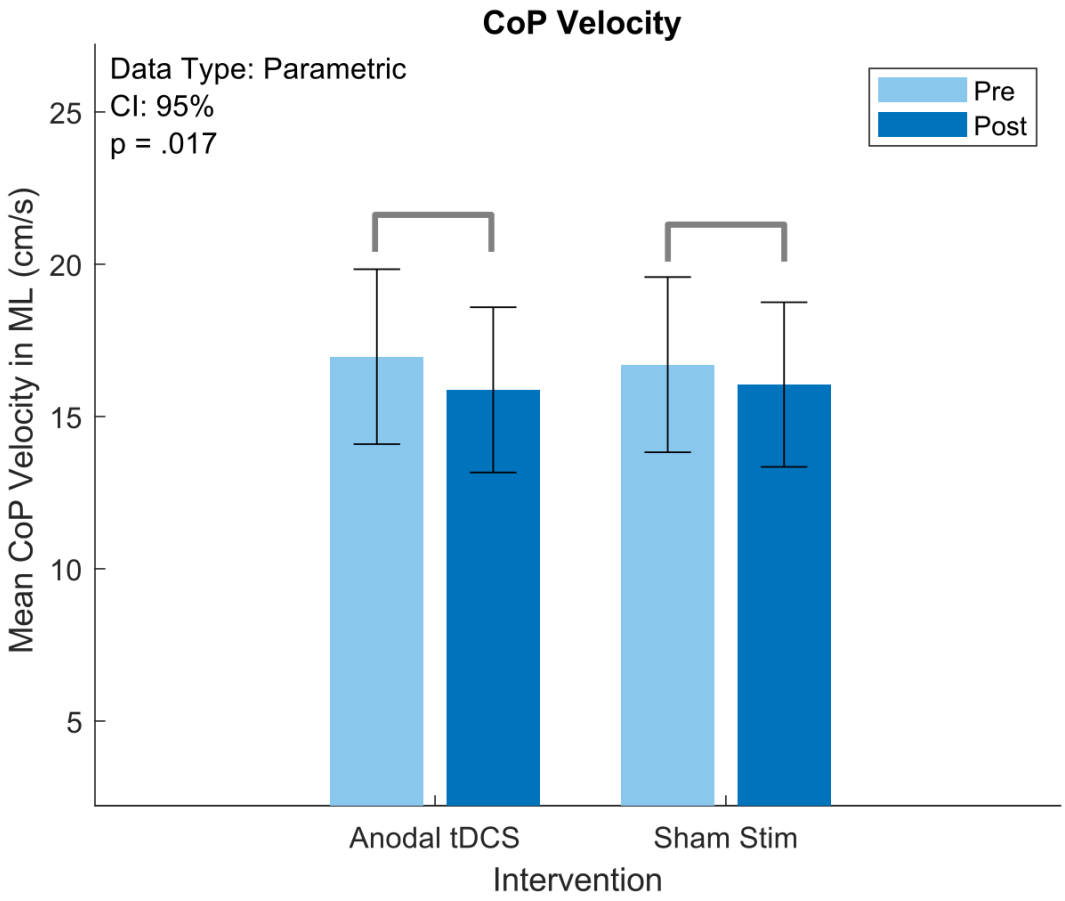

Figure 5. *CoPML velocity (cm/s) of individuals with PD who received both anodal tDCS and sham stimulation between gait initiation trials. Interventions were separated by one week. (*) Indicates significant differences (p<0.05).*

3.3 – Muscle Activity and Movement Efficiency

As seen in Table 1 below, the remaining variables (RT, MT, DoB_{TA}, Amp_{TA}, Amp_{MG}, and $CCI_{TA\text{-}MG}$) showed no statistical difference from pre-post and for both anodal tDCS and sham stimulation conditions.

Table 1. *Overall results of biomechanical analysis for gait initiation in PD, pre-post tDCS and sham stimulation.*

	tDCS				Sham			
	Pre		Post		Pre		Post	
Postural Stability (n=11)	M	SD	M	SD	M	SD	M	SD
CoP_{ML} displacement (cm)	***17.64***	4.31	***16.50***	4.59	16.87	3.99	16.26	4.28
CoP_{AP} displacement (cm)	23.21	1.51	23.12	2.35	23.23	1.93	23.32	1.87
CoP_{ML} velocity (cm/s)	***16.96***	4.27	***15.88***	4.28	16.70	4.04	16.05	4.02
CoP_{AP} velocity (cm/s)	22.34	2.01	22.68	3.13	23.06	2.91	23.28	3.23
MT (s)	1.044	.0502	1.031	.0645	1.015	.0625	1.013	.0762
Muscle Activity (n=12)	M	SD	M	SD	M	SD	M	SD
RT (s)	*.1656*	.0973	*.1310*	.0198	.1360	.0199	.1313	.0198
DoB_{TA} (s)	.3769	.1955	.3877	.1821	.4133	.2693	.4054	.2027
Amp_{TA} (mV)	.0522	.0485	.0522	.0467	.0456	.0315	.0437	.0286
Amp_{MG} (mV)	.0028	.0032	.0020	.0019	.0026	.0023	.0028	.0027
$CCI_{TA\text{-}MG}$	.4394	.2605	.4613	.3407	.4856	.3271	.5021	.3704

(*) Indicates variables of significant difference ($p<0.05$)

Regarding the differences observed in CoPML displacement and velocity, mean differences by participant during anodal tDCS are presented in Table 2.

Table 2. *CoP_{ML} results by participant during gait initiation in PD, pre-post tDCS.*

		tDCS				
		Pre		Post		
CoP_{ML} displacement (cm)	Subject ID	M	SD	M	SD	Mean Differences (cm)
	1	22.57365	0.999612	20.91659	1.329317	**-1.65706**
	2	21.48471	1.546254	18.75526	1.790735	**-2.72945**
	3	16.10612	2.337561	16.32855	2.069692	0.22243
	4	10.99413	2.934145	8.078696	3.124835	**-2.91543**
	5	14.19618	0.598736	12.86814	4.750678	**-1.32804**
	6	23.79287	1.12667	24.08598	2.231007	0.293112
	7	15.65815	1.517388	13.96747	1.139398	**-1.69069**
	8	17.53647	0.533942	16.8221	1.288856	**-0.71436**
	9	12.02486	0.766682	11.98584	1.113546	**-0.03902**
	10	21.43198	2.229589	20.61511	1.315971	**-0.81687**
	11	18.22341	1.51567	17.0364	1.505049	**-1.18701**
CoP_{ML} velocity (cm/s)	Subject ID	M	SD	M	SD	
	1	20.91659	1.589618	21.26347	2.101752	**-1.64039**
	2	18.75526	1.649511	17.10392	1.312953	**-2.8907**
	3	16.32855	2.689033	16.85914	1.969601	0.587468
	4	8.078696	2.549552	8.520235	3.026087	**-2.06446**
	5	12.86814	0.799967	12.60162	4.587553	**-0.52407**
	6	24.08598	1.689555	22.95706	2.242974	**-0.40893**
	7	13.96747	1.647302	12.75562	1.316039	**-1.34332**
	8	16.8221	0.823436	15.03979	0.928287	**-0.7106**
	9	11.98584	1.022927	11.87955	1.054362	**-0.52625**
	10	20.61511	2.055358	19.01762	1.651635	**-1.08162**
	11	17.0364	2.410539	16.63221	1.580949	**-1.37742**

4 – Discussion

In the present study, we hypothesized that the application of tDCS over the SMA would facilitate the execution of gait initiation, as it has been shown to modulate postural components of APAs and movement preparation in healthy young adults (Carlsen et al., 2015) and may show promising effects for those with freezing of gait in PD (Lu et al., 2018). Our findings may only lend partial support to this hypothesis. To our knowledge, the present study is among the first to evaluate the effects of tDCS on cued gait initiation among those with PD on medication, who do not exhibit freezing of gait.

4.1 – Dynamic Postural Control

It has long been established that excessive postural sway can increase the risk of falling in those with PD and as the disease progresses (Mancini et al., 2012; Piirtola & Era, 2006), particularly in the ML direction (Ferrazzoli et al., 2015; Maki, Holliday, & Topper, 1994) during dynamic conditions (Frenklach et al., 2009). In the present study, it was shown that CoP_{ML} displacement and velocity were simultaneously reduced following the delivery of anodal tDCS to the SMA while variables in the AP direction remained unchanged. This finding appears to suggest that ML postural control is the most susceptible motor feature to respond to the upregulation of cortical excitability in the SMA during gait initiation among those with PD.

Our results are different from a recent pilot study (Lu et al., 2018), which examined the effects of anodal tDCS over the supplementary motor area on gait initiation in PD with freezing of gait. In this pilot study an important comparison was made between cued and self-initiated gait. Although their protocol did not lead to significant differences in self-initiated gait following stimulation, they did observe a significant improvement in APA magnitude and duration when participants were provided with an auditory stimulus. From the findings of Lu et al. (2018), it

may be inferred that these individuals had both a neurological and functional capacity for improved gait initiation. Perhaps the two gait initiation strategies implemented (self-initiated and cued) operate on different neural circuitry, which could explain conflicting results (Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000). It is difficult however, to make a direct comparison, since Lu et al. (2018) included those with freezing of gait off medication. While the present study excluded freezers and all participants were tested in their best 'ON' medicated state, since low dopamine levels can impair the modulatory effects of tDCS (Schabrun, Lamont, & Brauer, 2016).

The lack of significant effect of tDCS intervention on the CoP_{AP} displacement and velocity is perhaps a consequence of the task demands. Naturally, gait initiation relies on a substantial contribution from ML postural control mechanisms when transitioning from quiet stance to steady state walking (Yiou et al., 2017). In a prospective study that analyzed postural stability in ambulatory and independent elderly as a predictor of falling, it was found that lateral spontaneous-sway amplitude was the single best predictor of future fall risk (Maki et al., 1994). This finding highlights the importance of gaining ML postural control as a fundamental priority in the achievement of safe and effective forward locomotion. This also agrees with an interactive model presented by Mille et al. (2014) which describes the coupling of posture and locomotion during gait initiation. The findings from these groups (Mille, Johnson Hilliard, Martinez, Simuni, & Rogers, 2007; Mille et al., 2014), showed that a lateral postural assist facilitated step initiation in PD, suggesting that ML postural control prior to forward progression is a prerequisite for safe and effective movement during gait initiation. In agreement with the present results, Mille et al. (2014) did not observe a significant difference in the CoP_{AP} displacement following ML perturbation. Therefore, it is possible that contrary to the regulation of postural control in the ML

direction, CoP_{AP} regulation is not a critical component in the coupling of posture and locomotion.

4.2 – Muscle Activity

All metrics associated with EMG activity in the TA and MG muscles (amplitude, duration, and CoI), were not significantly different from pre to post-testing under both anodal tDCS and sham conditions. This is supporting of our insignificant COP_{AP} metrics as the TA and MG are primarily responsible for motor activity in the AP direction (Crenna & Frigo, 1991). From the literature, it appears that both TA and MG muscles undergo various activation patters and have been reported as both hyperactive (Albani et al., 2003) and hypoactive (Egerton, McCandless, Evans, Janssen, & Richards, 2015) in PD respectively. Altogether, non-significant findings in the variables pertaining to muscle activity in the present study, may be a consequence of the large variability that was observed in their respective EMG signals.

Recently, Cantu, Nantel, Millan, Paquette, and Cote (2019) justified the importance of collecting EMG activity in the proximal muscles of the lower limbs as they appear to be characteristic of compensatory increases in amplitude and variability following the abnormal firing of distal postural muscles. In light of their findings, perhaps the observed differences in CoP_{ML} displacement and velocity following anodal tDCS in the present study, would have been better supported with the addition of EMG activity recorded from the proximal muscles of the lower limbs rather than the distal TA and MG muscles alone. Therefore, an avenue of interest may be to conduct a similar study in which hip adductor and abductor muscle activity is recorded – since these are the primary movers responsible for postural control in the ML direction (Jian et al., 1993; Winter, 1995; Winter, Prince, Stergiou, & Powell, 1993)

4.3 – RT and MT

In contrast to the non-significant differences in both RT and MT found in the present study, Caetano et al. (2018) evaluated stepping reaction time (RT) and gait adaptability in people with PD and found that total movement response time was significantly slower in those with PD compared to controls following a Stroop stepping test. Moreover, RT intra-individual variability was significantly greater among those with PD following a choice stepping task. These findings were associated with disease severity, reduced cognition and previous falls, perhaps highlighting attentional control deficits in PD as an influential factor in regulation of RT and MT. The authors proposed that RT may be a product of one's attentional (Cools, Rogers, Barker, & Robbins, 2010), cognitive, and motor capacity, and that MT may stem form one's motor capacity alone (Bloxham et al., 1987; Hallett & Khoshbin, 1980; Jordan et al., 1992; Kaneoke et al., 1989). A lack of significance in both RT and MT in the present study may reside in their disintegration with the SMA and potential interconnectedness with other brain areas. Perhaps future studies would benefit from the stimulation of brain regions more closely linked to attention, cognition, and motor control for example, the right prefrontal cortex (Posner & Petersen, 1990) and/or primary motor cortex (M1) (Seidler et al., 2010)).

4.4 – Limitations

It is worth noting that our results may not fully generalize to those undergoing deep brain stimulation, since members of this population were excluded from our sample. In addition, it has been reported that people with PD off medication generally exhibit reduced APAs – in size and speed compared to both the elderly and healthy young adults (Halliday et al., 1998). Our study did not include an equivalent age-matched control; therefore, it remains unclear as to how CoP measures in our sample compare to 'normal' values, both at baseline and post-anodal tDCS. In

addition, since there was no interaction effect, and this formed the basis of our study design, a post-hoc power analysis in G*Power was conducted. To observe a significant interaction between intervention conditions and CoP_{ML} displacement and velocity, it was determined that 175 (CoP_{ML} displacement) and 279 (CoP_{ML} velocity) participants would be necessary to achieve a power of at least 0.8. Nonetheless, our findings seem to suggest that tDCS intervention may benefit those who exhibit increased postural sway as a result of PD or medication related postural instabilities. Ultimately, the use of anodal tDCS as an adjunct regulator of ML postural stability, could lead to a reduced risk of falling during gait initiation for those with PD on medication.

5 – Conclusion

The results of this study demonstrate a reduction in CoP_{ML} displacement and velocity during gait initiation following a single 10-minute session of anodal tDCS. From these findings, when combined with an optimally medicated state, tDCS appears to have a significant modulatory effect on ML postural control. It is worth noting however, that the interaction between medication and tDCS remains unclear and was not explored in this study. Contrary to our hypotheses, insignificant findings pertaining to muscular activity (DoB_{TA}, Amp_{TA}, Amp_{MG}, and $CCI_{TA\text{-}MG}$), postural stability (CoP_{AP} displacement and velocity), and movement efficiency (RT and MT) could be a consequence of the underlying physiological mechanisms of tDCS which lack conclusive insight. Given our small sample size however, it should be noted that further research is necessary to confirm these findings for all those with PD on medication. Nonetheless, these results could provide meaningful insight regarding selection of individuals who would benefit from this therapy. For example, those who naturally present with large APAs due to postural instabilities associated with PD, may be targeted as a sub-population of interest to

receive this intervention, as tDCS would help minimize the speed and range of CoP_{ML} during gait initiation among this group. Since anodal tDCS has the potential to regulate balance in the ML direction, it could be used as an adjunct therapy alongside pharmacological treatment in the maintenance of postural stability during gait initiation among those with PD.

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Chapter IV: General Discussion and Conclusion

1 – Discussion

The results of this study demonstrate that 1 mA of anodal tDCS applied to the SMA can be used to modulate cortical activity such that it may facilitate motor control during gait initiation in some, but not in all individuals with PD (see Table 2.) – depending on their baseline postural needs. It was hypothesized that anodal tDCS would elicit significant enhancements to postural stability (CoP_{ML} and CoP_{AP} displacements and velocities) and movement efficiency (RT, MT, Amp_{TA}, Amp_{MG}, and $CCI_{TA\text{-}MG}$) during gait initiation in those with PD on dopaminergic medication. In partial confirmation of these hypotheses, it appears that CoP_{ML} displacement and velocity showed significant reductions during gait initiation following a single 10-minute session of anodal tDCS. Reducing CoP_{ML} displacement and velocity could have a stabilizing effect for those who experience excessive postural sway in the ML direction due to large postural instabilities that are either inherent to PD or emerge as side-effects of dopaminergic medication. The remaining variables that were examined (CoP_{AP} displacement and velocity, as well as all EMG derived variables) showed no significant differences between pre and post testing regardless of the stimulation condition. The lack of significant effect of tDCS intervention on these variables, is perhaps a consequence of the task at hand. Indeed, gait initiation relies mainly on the contribution of the hip abductors to control postural stability in the ML direction and consequently to ensure safe forward step execution. Therefore, regulation of the motor activity in the AP direction might not be as critical a factor in gait initiation for individuals with PD at risk for falling.

1.1 – Limitations

Regarding the neuromotor effects of tDCS on postural stability during gait initiation in the present study, symptom heterogeneity across the sampled participants could present as a limiting factor. However, we controlled for this in our exclusion criteria since participants' Hoehn & Yahr stage were of 2 or less. The small sample size as well as the larger number of males (11) compared to females (1) made it impossible to determine sex difference. Polarity effects are also dependent on the state of the participants' cortical activity upon arrival for testing, which can be affected by a multitude of factors (e.g., alertness, caffeine intake). This can cause some participants to show facilitatory anodal effects, and others inhibitory effects (Krause & Cohen Kadosh, 2014). To overcome this issue, we scheduled sessions at the same time each week to help ensure that a participant's routine did not interfere with polarity effects. Sequence Effect: Under both treatment conditions (tDCS vs. sham stimulation), improved performance may have depended on the order in which stimulation was delivered. While those who received sham treatment first should have experienced no immediate performance gains relative to their baseline measures, a placebo effect may have persisted. This was not the case however, since we were able to report no significant differences under the sham stimulation condition. Finally, it was established in previous research and current brain imaging technologies that behavioral and therapeutic outcomes of tDCS may be linked to the targeted brain region, but we have no objective evidence that the applied current reached the SMA of the brain as intended. It is possible that a 'shunting' effect may have taken place (Thair, Holloway, Newport, & Smith, 2017). It is well established that the most accurate method for targeting specific brain regions should incorporate devices such as EEG, among others which measure brain excitability for visually guided electrode placement. In the absence of this technology, a trained examiner

accurately located the SMA from its relative distance to Cz. This was based on the international 10–20 system for EEG electrode placement (Homan, Herman, & Purdy, 1987). Moreover, it is possible that simply the proximity of neurons which separate different brain regions could have allowed some of the exogenously generated electric current to travel beyond the targeted SMA towards other widespread brain regions (Meinzer et al., 2014). This could alter our understanding of the precise mechanisms by which specific motor functions may be altered as a result of anodal tDCS. Lastly, in the anodal tDCS trials where we observed significant results, a learning effect may have been observed due to the repetition of our gait initiation task within a lab environment. However, this was controlled for, as a washout period of 1 week was incorporated in our study design. Nonetheless our findings may not be generalizable to 'real world' conditions. Therefore, any differential results of this study should be taken with some caution and consideration.

2 – Conclusion: Significance and Implications

The present study showed that anodal tDCS can modulate postural control in the ML direction, and therefore it could reduce the risk of falling in individuals with PD who display excessive CoP_{ML} displacement and velocity. Future research should examine the effects of long term, and repetitive tDCS therapy and its ability to facilitate neurorehabilitation. Another important avenue of research in addition to quantifying proximal EMG data (ie. TA and MG), would be to quantify that of the abductor and stabilizing muscles of the lower limbs and trunk (ie. rectus femoris, biceps femoris, gluteus medius, external oblique, rectus abdominis, and erector spinae), as previously recorded in studies evaluating gait initiation and APAs (Claudino, dos Santos, & Santos, 2013; Jacobs, Nutt, Carlson-Kuhta, Stephens, & Horak, 2009; Khanmohammadi, Talebian, Hadian, Olyaei, & Bagheri, 2016; Lee, Liang, Chen, & Aruin, 2019). Such research may provide an explanation for the observed ML postural differences in the

present study and contribute to a deeper understanding of the neuromotor effects associated with tDCS.

Likewise, the results obtained in this study may provide clinicians and researchers alike, with extended knowledge regarding the effects of tDCS as an interesting alternative to more invasive brain stimulation. Ultimately, the findings presented in this research highlight the importance of assessing the effectiveness of neuromodulation and its capacity to enhance motor control and postural stability in those with neurological impairments.

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Appendices

A) UPDRS III Motor Examination

Unified Parkinson's Disease Rating Scale

PD workbook
THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

I. Mentation, Behavior and Mood

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florrid psychosis. Not able to care for self.

3. Depression
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. Activities of Daily Living
(for both "on" and "off")

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

Fahn S, Elton R, Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information 1987, 153-163, 293-304.

PD WORKBOOK—THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE | UNIFIED PD RATING SCALE | ©WE MOVE 2006 23

Unified Parkinson's Disease Rating Scale

PD workbook
THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting Food and Handling Utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in Bed and Adjusting Bed Clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (Unrelated to Freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when Walking
0 = None.
1 = Rare freezing when walking; may have start hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory Complaints Related to Parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

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Unified Parkinson's Disease Rating Scale

PD workbook
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III. Motor Examination

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face."
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at Rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of Hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

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26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

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Unified Parkinson's Disease Rating Scale

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IV. Complications of Therapy
(In the past week)

A. Dyskinesias

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1–25% of day.
2 = 26–50% of day.
3 = 51–75% of day.
4 = 76–100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. Clinical Fluctuations

36. Are "off" periods predictable?
0 = No
1 = Yes

37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1–25% of day.
2 = 26–50% of day.
3 = 51–75% of day.
4 = 76–100% of day.

C. Other Complications

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis? (Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

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Unified Parkinson's Disease Rating Scale

PD workbook
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V. Modified Hoehn and Yahr Staging

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. Schwab and England Activities of Daily Living Scale

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.

90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.

80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.

60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.

50% = More dependent. Help with half, slower, etc. Difficulty with everything.

40% = Very dependent. Can assist with all chores, but few alone.

30% = With effort, now and then does a few chores alone or begins alone. Much help needed.

20% = Nothing alone. Can be a slight help with some chores. Severe invalid.

10% = Totally dependent, helpless. Complete invalid.

0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

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Unified Parkinson's Disease Data Form

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Name _____ Unit Number _____

Date																
DOPA mg/day	hrs DOPA lasts															
		ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
1. Mentation																
2. Thought Disorder																
3. Depression																
4. Motivation/Initiative																
Subtotal 1–4 (maximum = 16)																
5. Speech																
6. Salivation																
7. Swallowing																
8. Handwriting																
9. Cutting food																
10. Dressing																
11. Hygiene																
12. Turning in bed																
13. Falling																
14. Freezing																
15. Walking																
16. Tremor																
17. Sensory symptoms																
Subtotal 5–17 (maximum = 52)																
18 Speech																
19. Facial expression																
20. Tremor at rest: face,lips,chin																
Hands: right																
left																
Feet: right																
left																
21. Action tremor: right																
left																
22. Rigidity: neck																
Upper extremity: right																
left																
Lower extremity: right																
left																

Unified Parkinson's Disease Data Form

PD workbook
THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

Date																
	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
23. Finger taps: right																
left																
24. Hand grips: right																
left																
25. Hand pronate/supinate: right																
left																
26. Leg agility: right																
left																
27. Arise from chair																
28. Posture																
29. Gait																
30. Postural stability																
31. Body bradykinesia																
Sub-total:18–31 (maximum=108)																
Total points: 1–31 (max=176)																
32. Dyskinesia (duration)																
33. Dyskinesia (disability)																
34. Dyskinesia (pain)																
35. Early morning dystonia																
36. "Offs" (predictable)																
37. "Offs" (unpredictable)																
38. "Offs" (sudden)																
39. "Offs" (duration)																
40. Anorexia, nausea, vomiting																
41. Sleep disturbance																
42. Symptomatic orthostasis																
Blood Pressure: seated																
supine																
standing																
Weight																
Pulse: seated																
standing																
Name of Examiner																
	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST
Hoehn & Yahr Stage																
% ADL Score (PD)																
% ADL (with dyskinesia)																

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B) Hoehn and Yahr (H&Y) Scale

Hoehn and Yahr Scale
1: Only unilateral involvement, usually with minimal or no functional disability
2: Bilateral or midline involvement without impairment of balance
3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
4: Severely disabling disease; still able to walk or stand unassisted
5: Confinement to bed or wheelchair unless aided

C) Consent Forms

Formulaire de consentement pour la recherche en contrôle moteur

Titre de l'Étude: **Étudier comment la modulation de l'excitabilité corticale affecte la performance motrice.**

Chercheur principal: Dr Anthony N. Carlsen
Affiliation: École des sciences de l'activité physique, Université d'Ottawa

Co-chercheurs: Erin K. Cressman, PhD. Professeure associée, École des sciences de l'activité physique, Université d'Ottawa
Julie Nantel, Professeure adjointe, École des sciences de l'activité physique, Université d'Ottawa

Assistants de recherche : Neil Drummond, étudiant au doctorat, École des sciences de l'activité physique, Université d'Ottawa.
Amanda Chiucchi, Student, School of Human Kinetics, University of Ottawa

Invitation à participer: Vous êtes invités à participer à cette étude réalisée par les chercheurs ci-dessus parce que vous êtes un adulte en bonne santé, ou parce que vous avez été diagnostiqué avec la maladie de Parkinson (MP).

But de l'étude: Cette étude s'intéresse à la production des mouvements simples ainsi qu'à la façon dont une faible stimulation électrique du cerveau affecte le mouvement et l'excitabilité du cerveau. La présente étude est conçue pour répondre à plusieurs questions en ce qui concerne la façon dont les humains représentent et contrôlent l'exécution de réponses discrètes et rapides ainsi que leur coordination (en cours). Cette recherche est financée en partie par le conseil de recherches en sciences naturelles et en génie du Canada (CRSNG).

Participation: Durant cette étude, vous serez assis dans une chaise, les bras possiblement placés sur des '*manipulandums'* (leviers simples) ou au-dessus de boutons simples. Il vous sera demandé d'effectuer des mouvements, ou des réponses à boutons ou de faire une extension (ou une flexion) des membres vers une cible dans un mouvement. Vous répondrez en déplaçant votre membre après un stimulus auditif ou visuel. Alternativement, vous pouvez être invité à effectuer un mouvement d'initiation de la marche (pas) à partir d'une position debout.

Les sessions expérimentales sont composées de quatre phases; la pratique, le pré-test, la stimulation, et les post-tests. La durée totale de la séance est d'environ 90 minutes. La pratique et les tests consistent à générer des mouvements de flexion ou d'extension du coude ou du poignet, avec un affichage graphique en temps réel de votre mouvement sur un écran d'ordinateur. Pendant le protocole de recherche, votre activité musculaire sera enregistrée. Pour ce faire, des électrodes d'électromyographie (EMG) seront placées sur certains de vos muscles dont les biceps, triceps, les muscles des avant-bras, et les muscles de la jambe inférieure. De très petites portions de votre peau pourraient être rasées et nettoyées avant de fixer les électrodes à votre peau. Entre les essais pré-

test et post-test un stimulus électrique faible sera appliqué sur une partie de votre cuir chevelu pendant 10 minutes.

Si avisé de tel, le test impliquera l'emplacement d'une bobine de fils de cuivre isolé positionné au-dessus de votre tête qui transmettra une pulsation magnétique. La bobine émet un son cliquant et produit parfois une contraction musculaire rapide et involontaire dans les muscles ciblés. La pulsation magnétique produit un faible courant électrique dans votre cerveau, de la même façon que vous produisez un faible courant dans votre cerveau quand vous contractez volontairement un muscle. Des électrodes seront placées au-dessus des muscles employés par le bras pour effectuer les mouvements afin d'identifier le courant électrique que vos muscles génèrent quand ils se contractent ou quand ils sont stimulés par la bobine magnétique.

Risques: Les risques associés à la participation à cette expérience sont minimes, toutefois, l'utilisation de la stimulation magnétique et de la stimulation électrique peuvent présenter des risques légèrement plus élevés que ceux qui sont impliqués dans la vie quotidienne. Plus précisément, un stimulus électrique faible sera appliqué sur une partie de votre cuir chevelu, ce qui peut provoquer une légère sensation de picotement pendant les 30 à 60 premières secondes suivant la stimulation. Il a été rapporté que la stimulation magnétique du cerveau peut causer des convulsions dans de rares cas, cependant aucun effet à long terme n'a été rapporté dans ces cas. Quelques personnes éprouvent une sensation de "tapotement" sur le haut de la tête lorsque le stimulateur magnétique est déclenché. Parfois, les gens s'aperçoivent qu'un œil "cligne" ou que leur mâchoire referme légèrement quand le stimulateur magnétique est déclenché. Certains effets secondaires potentiels peuvent inclure la fatigue, des maux de tête, des nausées ou des vertiges. Si un de ces symptômes se produit, l'expérience sera terminée sans pénalité pour vous. Puisque vous allez faire des mouvements répétés, vos muscles peuvent devenir fatigués. Ce risque sera diminué par l'entremise de périodes de repos offertes toutes les 10 minutes. L'activité musculaire sera enregistrée en utilisant des capteurs en plastique fixé avec du ruban adhésif à la surface de votre peau. La peau sous chaque capteur sera légèrement nettoyée, ce qui peut causer une irritation mineure de courte durée. Comme l'électrode est collante, vous pouvez ressentir un léger inconfort lorsque l'électrode sera retirée (semblable à un diachylon). Soyez assuré que tous les efforts possibles seront faits pour minimiser ces risques.

Avantages: Votre participation à cette étude mènera à une meilleure compréhension de la façon dont le cerveau humain se prépare pour et contrôle les mouvements rapides chez les individus sains ainsi que les personnes atteintes de la MP. Cette recherche ne peut pas vous bénéficier directement, mais il est possible que les connaissances acquises à partir de cette étude mènent à des bénéfices et la création de nouveaux traitements pour les personnes ayant des troubles du mouvement.

Confidentialité: Toutes les informations et les données recueillies sont codées pour préserver la confidentialité et l'anonymat du sujet. Plus précisément, les données brutes seront entreposées à l'aide d'un système de codage alphanumérique afin que personne ne puisse être en mesure de vous identifier. De plus, votre nom n'apparaîtra pas sur ces fichiers.

Les données seront analysées sur des ordinateurs protégés par un mot de passe auquels seuls les chercheurs directement impliqués dans l'étude auront accès. Une fois analysées les

données seront conservées dans une pièce fermée à clé à l'Université d'Ottawa, dans des classeurs verrouillés. Seuls les chercheurs directement impliqués dans l'étude y auront accès.

Aucun dossier portant votre nom ne quittera l'institution. Vous êtes encouragés à demander d'examiner les résultats des essais expérimentaux à tout moment.

Les données de ce projet seront publiées dans des journaux scientifiques. Les données seront conservées pendant une période minimum de 5 ans suivant la date de publication et seront ensuite détruites par le service des ressources physiques de l'Université d'Ottawa.

S'il vous plaît, soyez conscient que vous n'êtes pas obligé de participer. Pendant toute la durée de l'étude, vous avez le droit de refuser de participer ou de vous retirer de l'étude, sans question ni pénalité, et les données collectées seront détruites. À tout moment vous pouvez poser aux chercheurs toute question qui vous semble pertinente au sujet de la recherche effectuée.

Acceptation: Je, _____ accepte de participer à l'étude de recherche ci-dessus menée par Dr Anthony Carlsen de l'École des sciences de l'activité physique à l'Université d'Ottawa.

Si j'ai des questions, je peux communiquer avec *le chercheur principal*.

Si j'ai des questions concernant l'éthique de cette étude, je peux communiquer au Comité d'éthique de la recherche en sciences de la santé et en sciences, aux soins du Responsable de la déontologie en recherché, Université d'Ottawa, Pavillon Tabaret, 550, rue Cumberland, pièce 154, Ottawa, ON K1N 6N5.
Tél.: (613) 562-5387
Courriel: ethics@uottawa.ca

Il y a deux copies du formulaire de consentement, dont l'une est à vous.

Signature du participant: _____ Date: _____

Signature du Chercheur: _____ Date: _____

Informed Consent Form for Motor Control Research

Title of the study: **Investigating how modulating cortical excitability affects motor performance**

Principal Investigator: Dr. Anthony N. Carlsen
Affiliation: School of Human Kinetics, University of Ottawa

Co-Investigators: Erin K. Cressman, PhD. Associate Professor, School of Human Kinetics, University of Ottawa
Julie Nantel, Assistant Professor Professor, School of Human Kinetics, University of Ottawa

Research Assistants: Neil Drummond, PhD Student, School of Human Kinetics, University of Ottawa
Amanda Chiucchi, Student, School of Human Kinetics, University of Ottawa

Invitation to Participate: You are invited to participate in the abovementioned research study conducted by the above researchers because you are an otherwise healthy adult, *or* because you have been diagnosed with Parkinson's disease (PD).

Purpose of the Study: This research is concerned with the production of simple limb movements and how weak electrical brain stimulation affects the production of those movements and the excitability of the brain. It is designed to answer several questions that relate to how human subjects represent and control the execution of rapid discrete responses and ongoing coordination. This research is funded in part by the Natural Sciences and Engineering research Council of Canada.

Participation: During the experiment, you will be positioned in a chair and your arms may be placed on manipulandums (simple levers) or over simple buttons. You will be asked to make button responses or limb extension and/or flexion movements between a 'home' position and a target in a single, continuous motion. You will respond by moving your limb after an auditory or visual stimulus. Alternatively, you may be asked to perform a stepping motion from a standing position.

Testing will consist of four phases: practice, pretest, stimulation, and post-testing. The total time for this testing session will be approximately 1.5 hours. Practice and testing trials consist of performing the stepping movements, or movements of your elbows or wrists, with real-time graphical display of your movement on a computer screen. During the experiment, we will be recording muscular activity. In order to do this, surface electromyography (EMG) electrodes will be attached to various locations on your body including your biceps and triceps muscles, forearm muscles, and muscles of the lower leg. Very small patches of skin may be shaved and cleaned prior to attaching the surface electrode to your skin. Between the pretest and post-test trials a weak electrical stimulus will be applied over part of your scalp for 10 minutes.

If so informed, testing will also involve the placement of an insulated copper wire coil positioned over top of your head which delivers a magnetic pulse. The coil makes a clicking sound and sometimes produces a twitch in targeted muscles. The magnetic pulse causes a weak electrical current in your brain, in the same way that you produce a weak electric current in your brain when you voluntarily contract a muscle. Electrodes will be placed over the arm muscles used to make the movements to pick up the electric current your muscles generate when they contract or are stimulated by the magnetic coil.

Risks: The risks involved in participating in this experiment are minimal, however the use of investigational magnetic and electrical stimulation may pose risks slightly greater than those involved in everyday life. Specifically, a weak electrical stimulus will be applied over part of your scalp which may cause a slight tingling sensation for the first 30 seconds to 1 minute. Magnetic stimulation of the brain has been reported to have caused a seizure in rare instances. No lasting effects were reported in these rare cases. Some people experience a "tapping" sensation on top of the head when the magnetic stimulator is triggered. Sometimes people notice that one eye "winks", or their jaw closes slightly when the magnetic stimulator is triggered. Some potential side effects may include fatigue, headache, nausea or dizziness. If any of these symptoms should arise the experiment will be terminated without penalty to you. Since you will be making repeated targeted movements your muscles may become slightly tired. This risk will be decreased by providing rest periods every 10 minutes. Muscle activity will be recorded using plastic sensors attached with tape to the surface of your skin. The skin beneath each sensor will be lightly scrubbed, which may cause brief minor irritation. As the electrode is sticky, you may experience some very minor discomfort when the electrode is removed (it is similar to removing a Band-Aid). Be assured that every effort will be made to minimize these risks.

Benefits: Your participation in this study will lead to a greater understanding of how the human brain prepares and controls movements in healthy individuals and people with PD. Although this research may not benefit you directly, it is possible that the knowledge gained from this study will lead to future benefits and treatments for people with movement disorders.

Confidentiality and anonymity: All information and data collected are coded to maintain confidentiality. Specifically, raw data will be stored using an alphanumeric coding system so that no one will be able to identify you as your name will not appear on these files.

The data will be analyzed on password protected computers that only the researchers directly involved in this study will have access to. Once analyzed the data will be kept in in a locked room at the University of Ottawa, in locked filing cabinets and only the researchers directly involved in this study will have access to your data.

No records bearing your name will leave the institution. You are encouraged to request and discuss the results of the experimental trials at any time.

The data collected in this study will be published in scientific journals. The data will kept for a period of 5 years post-publication and will subsequently be destroyed by the physical resources service of the University of Ottawa.

Please be aware that you are under no obligation to participate. For the entire duration of the study, you may refuse to participate or withdraw from the study at any time, without question or penalty and any data collected will be destroyed. In addition, you are free to ask the researcher any question about any part of the research being conducted at any time.

Acceptance: I, _____ agree to participate in the above research study conducted by Dr. Anthony Carlsen of the School of Human Kinetics at the University of Ottawa.

If I have any questions, I may contact the *principal investigator*.

If I have any questions regarding the ethical conduct of this study, I may contact the Protocol Officer for Ethics in Research, University of Ottawa, Tabaret Hall, 550 Cumberland Street, Room 154, Ottawa, ON K1N 6N5
Tel.: (613) 562-5387
Email: ethics@uottawa.ca

There are two copies of the consent form, one of which is yours to keep.

Participant's signature: _____ Date: _____

Researcher's signature: _____ Date: _____