NEUROMODULATION USING TRANSCRANIAL DIRECT CURRENT STIMULATION TO IMPROVE DUAL-TASK PERFORMANCE IN PEOPLE WITH PARKINSON'S DISEASE

by
Ram kinker Mishra

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Chair of Committee: T. Adam Thrasher, Ph.D.

Committee Member: Pranav J Parikh, Ph.D.

Committee Member: Charles S. Layne, Ph.D.

Committee Member: Bijan Najafi, Ph.D.

University of Houston
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Ram kinker Mishra

APPROVED:

_____

T. Adam Thrasher, Ph.D.
Committee Chair

_____

Pranav J Parikh, Ph.D.
University of Houston

_____

Charles S. Layne, Ph.D.
University of Houston

_____

Bijan Najafi, Ph.D.
Michael E. DeBakey Department of Surgery
Baylor College of Medicine

_____

Antonio D. Tillis, Ph.D.
Dean, College of Liberal Arts and Social Sciences
Department of Hispanic Studies

DEDICATION

I dedicate this dissertation to two important pillars of my life, my wife and mother. My wife, Sameeksha, stood by my side in every situation and provided me much needed strength to keep moving forward. This phase of our life has been particularly challenging and tested our patience to its limit. My mother has always been an inspiration for my life. Whenever I felt low, her voice reverberated in my mind and rejuvenated my spirit and it will always be there with me. Lastly, my father made many sacrifices. He taught me to stay grounded and humble. I am deeply grateful and blessed to have these special people in my life.

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ABSTRACT

Despite advances in pharmacological treatments and surgical processes, the problem of postural instability and cognitive impairments persists in people with Parkinson's disease (PD). These symptoms deteriorate further under dual-task conditions. Dual-tasking is common in every-day life; therefore, it has become a crucial aspect of PD rehabilitation. Recently, transcranial direct current stimulation (tDCS) applied to the dorsolateral prefrontal cortex (DLPFC) has shown the potential to improve dual-tasking in patients with PD. However, there is inconsistency in the results reported in the literature. One of the primary reasons for heterogeneous findings is the gap in understanding about the timing of tDCS priming relative to task performance. To address this gap, in this dissertation, the online and sustained effects of left DLPFC stimulation with anodal tDCS was investigated to determine time-dependent tDCS priming.

We recruited twenty participants with PD in a double-blinded, sham-controlled, and cross-over study. Each subject completed two visits separated by a minimum of a one-week wash-out period. The left DLPFC was stimulated using anodal tDCS with 2mA current intensity for 30 minutes. Each subject performed dual-task during gait and timed up and go (TUG) with phonemic verbal fluency task given as the secondary cognitive task. Moreover, the motor-cognitive performance was evaluated using instrumented trail making tests (iTMT). The effect of tDCS on dual-task performances was assessed during, immediately after, post 15, and 30 minutes of stimulation. The gait performance was assessed using gait speed, stride time variability, and stride length. The functional-mobility was evaluated in terms of time taken to complete the sub-component of TUG (sit-to-stand transition, turning180^{o}, stand-to-sit, and straight walk). Cognitive task performance was measured using the number of words generated. The iTMT test performance was quantified by using average ankle velocity and time taken to complete iTMT tasks.

We found a significant increase ($p=0.023$) in gait speed under dual-task conditions due to anodal tDCS compared to sham. However, there was no significant effect of tDCS on TUG performance. Moreover, anodal tDCS led to a greater improvement ($p=0.017$) in motor performance during iTMT,

as demonstrated through an increase in ankle velocity compared to sham. Anodal tDCS also led to more significant improvement in cognitive task performance when performed concurrently with walking ($p<0.01$) or TUG ($p<0.01$). In conclusion, the left DLPFC stimulation using anodal tDCS can improve dual-task performance in patients with PD. The effects of tDCS on dual-tasking can be task-specific as gait speed and cognitive performance improved post-stimulation, but there were no tDCS related changes in TUG performance. Furthermore, anodal tDCS improved iTMT related motor performance peaked during stimulation but not post-stimulation.

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CHAPTER I

1 INTRODUCTION

1.1 Background

Parkinson disease (PD) is a progressive neurodegenerative disease affecting nearly one percent of the elderly population in the US [1]. PD is considered a movement disorder, and patients with PD are at higher risk of falling especially while performing dual-tasks [2]. Dual-tasking is one of the most frequently performed activities in everyday life, e.g., walking while having a conversation [3]. According to the evidence-based rehabilitation guidelines, people with PD are recommended to avoid dual-task situations and divide complex tasks into easier subcomponents [4]. Despite advances in pharmacological treatments and surgical processes, the problem of impaired dual-tasking persists in people with PD [5]. Transcranial direct current stimulation (tDCS) is emerging as a viable rehabilitation technique for patients with PD. It is a non-invasive brain stimulation technique which can modulate neural activity in the brain region by passing low-amplitude currents between two or more surface electrodes placed upon the scalp. The effects of tDCS depend on the polarity, timing of stimulation, and location of stimulation. Studies have shown stimulating dorsolateral prefrontal cortex (DLPFC) can improve locomotion, functional-mobility, and cognitive performance in patients with PD [6] [7]. However, there is a gap in understanding about the effect of DLPFC stimulation on dual-task performance in patients with PD, during stimulation and its retention period.

Dual-task paradigms are generally used to assess the relation between motor and cognitive abilities [3]. These paradigms involve the concurrent performance of a motor task and a secondary cognitive task. The dual-task cost is estimated to measure the interference between motor and cognitive performance. The dual-task cost is the percentage change in the outcome measure (e.g., gait speed) from single to dual-task condition (dual-task cost = [dual-task – single-task]/single-task $*$ 100) [1]. A decrease in dual-task cost value indicates improved dual-task performance, i.e., lesser dual-task interference. A decrease in dual-task cost value indicates improved dual-task performance, i.e., lesser

dual-task interference. Individuals with PD often find it challenging to accomplish dual-tasks due to the presence of PD associated motor and cognitive impairments.

Gait impairment is a debilitating motor symptom of PD that frequently causes falls [8,9], loss of independence, and limits functional-mobility [10]. Over 85% of the people with PD develop gait problems within three years of diagnosis [11]. Gait impairment includes reduced walking speed, short strides, absent arm swing, increased gait variability, and longer double limb support time [12,13].

It is well established that in PD, the primary cause of impaired motor control during walking is defective basal ganglia functioning [14]. The basal ganglia play an essential role in the execution of the repetitive sequence of movements that become automatic once learned, i.e., requiring minimal attentional resources [15]. Due to basal ganglia dysfunction, patients with PD begin to lose movement automaticity [16]. Consequently, individuals with PD need to direct more attention toward movements that healthy people usually execute automatically [16].

Attention is a limited cognitive resource. During the concurrent performance of two tasks, this limited resource is divided among the tasks and executed successfully in the presence of adequate attentional resource. However, when the available resource capacity is inadequate, the performance of one or both tasks declines. In other words, the concurrent performance of the motor and cognitive tasks can put more pressure on the attentional resource and have a marked effect on gait in patients with PD.

Moreover, cognitive deficits are common in patients with PD and may be present for several years before motor impairments become apparent [17]. The executive dysfunction is the most common cognitive deficit reported in patients with PD [17]. Executive functioning is closely associated with attentional control and important for cognitive control of the motor behavior, i.e., initiation, planning, regulation, and monitoring of goal-directed, adaptive behavior [17]. Furthermore, depression, anxiety, and fatigue are all present to varying extents in PD that can increase difficulty in maintaining the attention and contribute to executive dysfunction [18].

The primary mechanisms responsible for the above mentioned cognitive deficits are under-activation of the prefrontal cortex [19,20] or dysfunction of the fronto-striatal dopaminergic network

[21]. Imagining based studies have shown fronto-striatal circuits are part of the executive functions and connect frontal lobe regions with the basal ganglia (striatum) that mediate motor, cognitive, and behavioral functions within the brain [22].

Cognition and gait are closely associated with each other [12,23,24]; therefore, PD related cognitive deficits can exacerbate gait impairments. To elicit impaired dual-tasking, cognitive task should be challenging enough to affect the primary motor task performance. Verbal fluency has been one of the most frequently used instruments in clinics and research to examine cognitive functioning [25]. Studies have reported verbal fluency exhibits high inter-rater agreement, test-retest reliability [25,26], and no effect of aging [27]. Verbal fluency tasks require generating words spontaneously under pre-specified search conditions [28]. In patients with PD, phonemic verbal fluency has been widely used to assess executive dysfunction [29]. It is a variant of verbal fluency that is not affected by PD related depression [30]. Completing phoneme verbal fluency task requires generating words from an initial letter (generally F, A, S, C, P, and L) in given time [25,27]. The number of words generated is used to quantify the phoneme verbal fluency task performance.

Furthermore, impaired dual-task performance in people with PD is often reported in a variety of movements, including postural control tasks [31,32], and walking [33]. Several dual-task paradigms have evolved to examine the distinct characteristics of dual-tasking and identify early signs of impaired dual-tasking. Dual-task gait assessment is the most common and sensitive method to identify impaired dual-tasking. Accomplishing a dual-task gait needs a steady state gait performance while performing a concurrent cognitive task. Moreover, instrumented timed up and go test (TUG) has shown to be sensitive in detecting functional-mobility deficits in early-to-mid-stage PDs [34]. Recently, a novel technique, instrumented trail making task (iTMT), was used to identify motor-cognitive performance among older adults, individuals with amnestic mild cognitive impairment, and Alzheimer's disease without a need to walk [35]. These paradigms are sensitive to identify an impaired ability to perform dual-task and provide different perspectives about dual-task performance.

Despite advances in medication and surgical treatments, the problem of impaired dual-tasking persists in patients with PD [36]. The effective strategy to address this problem is to bring different techniques restoring the ability to perform dual-task. Non-invasive brain stimulation technique tDCS has attracted a lot of attention due to its ability to facilitate neuroplasticity, convenience for operation, and cost-effectiveness. The tDCS can produce inhibitory or excitatory effect depending on the polarity of stimulation, such as that cathodal tDCS induces a decrease in cortical excitability, and anodal tDCS induces an increase in cortical excitability. These effects of tDCS after a single session can last for several minutes (>30 minutes) [37]. Based on this knowledge, earlier studies have used tDCS for rehabilitation in various conditions such as major depression [38], chronic pain [39], stroke [40,41], Alzheimer's [42], Parkinson's [43], and schizophrenia [44] with no major side effects.

Therapeutic effect of tDCS can be due to the elevated concentration of neurotransmitters in the stimulated brain region [45–49]. However, due to discrepancies on the effect of tDCS, more studies focusing on different approaches towards applying tDCS are required. The timing of administration of tDCS in relation to task execution has been identified as important for behavioral outcomes with tDCS [50]. Most of the studies are focused on the after effect of tDCS. Hone-Blanchet et al. (2016) suggested task performance can improve more while getting the tDCS than after tDCS. They observed a significant elevation in the concentration of neurotransmitters in left DLPFC and left striatum during tDCS (i.e., online tDCS), applied on DLPFC brain region, but not after stimulation [51]. Their results can partially explain some discrepancies on the effects of tDCS and suggest online tDCS to have more influence on behavior and cognitive performance compared to after tDCS [51].

Furthermore, the location of stimulation plays a crucial role in defining the effect of tDCS on the execution of a given task. The left DLPFC has been implicated in the allocation of cognitive resources between the two tasks performed concurrently [52]. A growing body of evidence supports the idea of stimulating left-DLPFC applying tDCS to improve dual-tasking. Zhou et al. (2014) showed stimulation of left-DLPFC brain region using tDCS reduced dual-task cost in young adults during over-ground walking and standing condition [53]. In another study, Wrightson et al. (2015) reported reduced

stride time variability, dual-task cost associated with stride time variability, and improved cognitive task performance in healthy young adults due to left DLPFC stimulation using tDCS during treadmill walking [54]. Furthermore, Schabrun et al. (2015) recommended stimulating DLPFC as applying tDCS on primary motor cortex (M1) in patients with PD showed no change in gait performance, but served in improving the cognitive performance, during dual-task gait assessment. Previous studies using tDCS targeted over DLPFC have shown to improve functional-mobility [6] and cognitive functioning separately in people with PD [7]. Based on the findings mentioned above, we propose to examine the effect of DLPFC stimulation on dual-task performance in patients with PD, during stimulation and its retention period.

1.2 Statement of the Problem

In the last decade, tDCS has emerged as a promising brain stimulation intervention for rehabilitation in PD. The non-invasive nature, convenience of operation, cost-effectiveness, and the ability to facilitate neuroplasticity are the desirable characteristics of tDCS that have motivated researchers to determine the potential of tDCS for rehabilitation [55]. There is a growing demand to translate the positive findings of tDCS studies upon motor and non-motor PD symptoms into mainstream clinical practice [56]. However, no consensus has been reached on the optimal way to use tDCS. Recent studies have shown that DLPFC stimulation with anodal tDCS can improve locomotion, functional-mobility, and cognitive performance in patients with PD [6] [7]. However, there is a gap in understanding about the change in concurrent performances of cognitive and motor tasks due to anodal tDCS delivered to left DLPFC during task performance and its sustained effect compared to sham tDCS.

Question 1: Can patients with PD perform dual-task gait better due to concurrent anodal tDCS and retain the performance longer in comparison to sham tDCS?

Question 2: Can patients with PD perform dual-task TUG better due to concurrent anodal tDCS and retain the performance longer in comparison to sham tDCS?

Question 3: Can concurrent anodal tDCS improves motor-cognitive performances improve more than sham tDCS in patients with PD, assessed using iTMT tests and retain the performance longer?

1.3 Aims and Hypotheses

The following aims and hypotheses are intended to address the gaps of knowledge discussed in the statement of the problem:

Aim 1: To investigate the online and sustained effects of anodal tDCS on dual-task performance during gait in patients with PD.

This aim will examine the changes in dual-task gait performance due to concurrent and after effects of stimulation delivered on left DLPFC using anodal tDCS in patients with PD compared to sham tDCS. Participants will perform over-ground walking as the primary motor task along with a phoneme verbal fluency task as the secondary cognitive task, besides, performing both tasks exclusively. The effect of dual-task on gait and phoneme verbal fluency task will be defined as dual-task cost. The dual-task cost will be estimated as the relative change in outcome measures from single to dual-task conditions

$$Dual\ task\ cost = \left({Single\ task_{Gait\ speed} - Dual\ task_{Gait\ speed}} \Big/ {Single\ task_{Gait\ speed}} \right) * 100)$$

The gait speed, double-limb support phase, and stride time variability will be used to assess the gait performance [57]. Patients with PD often walk at a slower speed, especially under complex conditions such as dual-tasking, to manage the forces and moments in gait, and the cognitive load. An increase in the gait speed shows improved stability during walking [58]. Furthermore, stride time variability is another important gait parameter that is independent of the stride length and gait speed. Increase in gait variability can be found at all stages of the PD. The amount of variability tends to increase with disease severity and is related to increased instability [57]. Phoneme verbal fluency can present an adequate cognitive challenge to the patients with PD during dual-tasking. Generally, the number of words generated are used to quantify the attention or level of concentration in the participants.

Expected Results: Decrease in stride time variability and double limb support will indicate an improved gait performance. Also, an increase in the number of words produced will show improved cognitive performance. Thus, we expect the dual-task cost will reduce, due to changes in gait and cognitive parameters, more due to anodal tDCS compared to sham tDCS.

H1.1: The dual-task cost associated with gait will reduce more due to online effect of anodal tDCS compared to sham tDCS among patients with PD.

H1.2: The dual-task cost associated with cognition will reduce more due to online effect of anodal tDCS compared to sham tDCS among patients with PD.

H1.3: The improvement in dual-tasking will retain longer due to anodal tDCS compared to sham tDCS among patients with PD.

Aim 2: To examine the online and sustained effects of anodal tDCS on dual-task performance during functional-mobility task in patients with PD.

The purpose of this aim is to compare the effect of anodal tDCS with sham tDCS on dual-task TUG assessed during, immediately after, 15 minutes, and 30 minutes after tDCS. The tDCS will be delivered over the left DLPFC brain region. Although functional-mobility tests may include components of gait and balance, functional-mobility tasks provide a way to quantify the different aspects of motor control in patients beyond just gait or balance alone. The TUG test includes many different functional-mobility skills such as sit-to-stand transition, turning, stand-to-sit transition, and straight walk [34].

In dual-task TUG, participants will perform TUG as the primary motor task along with the phoneme verbal fluency task as the secondary cognitive task. The performance of the TUG test will be measured using the time taken to complete each component of TUG task (i.e., sit-to-stand, walking seven meters, turning, and stand-to-sit transition), identified with the help of the body-worn sensors. Furthermore, the phoneme verbal fluency task will be given as the secondary cognitive task. The number of words produced will be used to evaluate cognitive performance under single and dual-task conditions.

Expected Results: Improved functional-mobility will result in the reduced time taken to complete the subcomponent tasks of TUG. Also, an increase in the number of words generated will demonstrate an improved cognitive performance by the participants. Therefore, we expect the dual-task cost will reduce, due to changes in durations of TUG sub-component tasks and cognitive parameters, more in anodal tDCS condition compared to sham tDCS.

H2.1: The dual-task cost associated with functional-mobility will reduce more due to online effect of anodal tDCS compared to sham tDCS among patients with PD.

H2.2: The dual-task cost associated with cognition will reduce more due to online effect of anodal tDCS compared to sham tDCS among patients with PD.

H2.3: The improvement in dual-tasking will retain longer due to anodal tDCS compared to sham tDCS among patients with PD.

Aim 3: To study the online and sustained effects of anodal tDCS on motor-cognitive performance, assessed by iTMT test, in individuals with PD.

Impaired executive functioning is the most common cognitive deficit that is found in patients with PD [17]. Executive functioning plays a crucial role in planning and executing the movement that is commonly evaluated using trail making tasks (TMT) [59]. Recently, an instrumented version of TMT, also referred as iTMT, was designed and used to quantify motor-cognitive performance among older adults, individuals with amnestic mild cognitive impairment, and Alzheimer's disease without the need to walk [35].

The iTMT test combined TMT tasks with an essential component of the reaching task that involves leaning the body to maneuver the center of mass and produce ankle movements. The reaching task is an activity that is associated with falls and can provoke postural instability in patients with PD [60]. During iTMT, subjects make ankle movement without lifting the feet while wearing a sensor on the lower shin. The sensor detects the ankle motion and navigates the cursor on the screen. Participants control the curser to complete a series of trail-making tasks visible on the screen positioned in front of

them. The performance metrics for iTMT task involve time taken to complete iTMT task, and average of maximum ankle velocities.

Expected Results: We expect anodal tDCS will increase the average of maximum ankle velocities that demonstrate an improvement in motor performance. Moreover, anodal tDCS will decrease the average time taken to complete the iTMT tasks that will indicate an improved cognitive performance.

H3.1: The average of maximum ankle velocities will increase more due to online effect of anodal tDCS compared to sham tDCS among individuals with PD.

H3.2: The average duration to complete the iTMT tasks will reduce more due to online effect of anodal tDCS compared to sham tDCS in patients with PD.

H3.3: The improvement in dual-tasking will retain longer due to anodal tDCS compared to sham tDCS among patients with PD.

1.4 Significance of the Study

Improving dual-tasking is an important rehabilitation outcome for individuals with PD. An impaired ability to perform concurrent tasks can severely limit functional independence and elevate the risk of falling in patients with PD. Previous studies have shown DLPFC stimulation using anodal tDCS can improve cognition, gait, and functional-mobility separately in patients with PD. However, there is a lack of studies focusing on improving the concurrent performance of cognitive and motor tasks using tDCS in people with PD. The findings of this study will help in filling the current gap in understanding about the effect of DLPFC stimulation using tDCS to improve dual-tasking in people with PD.

Furthermore, the results of this study will explore the time-dependent priming effect of anodal tDCS on dual-tasking among patients with PD. There is a lack of studies investigating changes in task performances in individuals of PD. Examining the time-dependent effect of tDCS will optimize the use of tDCS and help develop the treatment as a rehabilitation tool for patients with PD.

CHAPTER II

2 Manuscript I: Transcranial Direct Current Stimulation of Dorsolateral Prefrontal Cortex Improves Dual-Task Gait Performance in Patients with Parkinson's Disease: A Double Blind, Sham-Controlled Study

Ram kinker Mishra [a*] and Adam T. Thrasher [a]

[a] Center for Neuromotor and Biomechanics Research, University of Houston, Texas, USA

*Corresponding author: Ram kinker Mishra,

3855 Holman Street, 104 Garrison Gym, Houston, TX, 77204, USA.

Tel.: 470-435-0949; E-mail address: rmishra2@uh.edu

2.1 Key Points

1. Left DLPFC brain region is appropriate for stimulation to enhance dual-task performance.
2. Priming of the tDCS effect occurred 15 minutes after stimulation ceased.
3. Anodal tDCS can facilitate cognitive performance under single- and dual-task condition.

2.2 Abstract

Background: Despite advances in pharmacological treatments and surgical processes, the problem of postural instability and cognitive impairments persists in people with Parkinson's disease (PD). These symptoms deteriorate further under dual-task conditions. Recently, transcranial direct current stimulation (tDCS) applied to the dorsolateral prefrontal cortex (DLPFC) have shown potential to improve dual-task walking in patients with PD. However, there is no consensus on the ways to apply tDCS in individuals with PD.

Objective: To study the time-dependent priming effects of left DLPFC stimulation with anodal tDCS on dual-task walking in patients with PD.

Methods: Twenty patients with PD participated in this sham-controlled, cross-over study. Participants completed two sessions with at least one-week gap to avoid any carry-over effect. Subjects walked 30 m with or without concurrent cognitive task and performed cognitive task while sitting. In each session, these tasks were repeated before, during, immediately after, 15, and 30 minutes after stimulation ceased.

Stimulation involved transferring 2mA current through left DLPFC for 30 minutes. The cognitive task given was verbal fluency task assessed through number of words generated. Gait speed, stride length variability, and double-limb support (%) were used to determine gait performance. Dual-task cost (DTC) was calculated as percent change in performance between dual and single-task conditions to assess dual-tasking.

Result: In dual-task condition, participants walked faster fifteen minutes ($p=0.017$) and thirty minutes after ($p<0.01$) stimulation ceased due to anodal tDCS compared to sham. Similarly, participants generated a greater number of words at T3 ($p=0.05$), and T4 ($p<0.01$) due to anodal tDCS compared to sham. Furthermore, DTC associated with gait speed was significantly lower ($p=0.022$) at T4 due to anodal tDCS compared to sham tDCS. However, no significant effect of tDCS was observed on gait and cognitive performance under single-task condition.

Conclusion: The priming effects of tDCS can be time-dependent, and we observed improvement in both cognitive and gait performance under dual-task condition fifteen minutes after stimulation ceased.

Keywords - Neuromodulation; Brain stimulation; Transcranial direct current stimulation; Parkinson's Disease; Dual-tasking

List of Abbreviations – tDCS: Transcranial direct current stimulation; DLPFC: Dorsolateral prefrontal cortex; PD: Parkinson's Disease; DTC: Dual-task Cost

2.3 Introduction

Despite advances in pharmacological and surgical treatments, the problem of impaired dual-tasking persists in patients with Parkinson's disease (PD) [5,18]. Dual-tasking is an integral part of everyday life; therefore, it has become a critical rehabilitation outcome in patients with PD. Transcranial direct current stimulation (tDCS) is a non-invasive brain-stimulation technique that provides a viable method for rehabilitation in PD [61]. It is known to modulate neural activities in the brain region by transferring low-amplitude current (1-2 mA) between two or more surface electrodes placed upon the scalp. Studies have shown that dorsolateral prefrontal cortex (DLPFC) stimulation using anodal tDCS can improve locomotion, functional-mobility, and cognitive performance in individuals with PD [6,62–66]. The

behavioral effects of tDCS primarily depend on the polarity (i.e., anodal tDCS excites, whereas cathodal tDCS inhibits the neuronal activity), site of stimulation, and the relative timing of the stimulus and task. Previous studies have suggested tDCS can have superior behavior effects on the motor or cognitive task performed while receiving the tDCS (online) compared to post-stimulation (offline) [61,67,68]. According to our knowledge, no study has assessed the time-dependent priming effect of left DLPFC stimulation using anodal tDCS on dual-task walking among people with PD.

In individuals with PD, gait disturbances are exacerbated while performing a concurrent cognitive task [69]. These gait impairments manifest as slower walking with increased double limb support, reduced arm swing, and impaired postural control [57,70–72]. Additionally, there are PD related gait disturbances that are difficult to assess in routine clinical observation but become apparent when gait is evaluated quantitatively with gait analysis system such as stride-to-stride variability [57].

Gait impairments and cognitive deficits are inevitable consequences of PD [33,73,74]. Within three years of diagnosis, over 85% of the people with PD develop gait problems [11]. Furthermore, mild cognitive impairment (MCI) may be present for several years before motor impairments become apparent [17]. Cognitive deficits in PD typically consist of impaired executive functioning and reduced attention [75]. Executive functioning is essential for the cognitive control of motor behavior [76]. Moreover, other factors such as depression, anxiety, and fatigue can further deteriorate executive functioning and make it difficult for individuals with PD to maintain their attention.

Generally, the complex interplay between cognitive functioning and gait performance is assessed through dual-task walking [33]. Patients with PD find it particularly challenging to perform a cognitive dual-task while walking [18]. During dual-task walking, gait, and the secondary cognitive task compete for the limited attentional resource, ending up interfering with each other [3]. In the case of PD, this dual-task interference can reach an unacceptable level making them vulnerable to fall. Therefore, people with PD are recommended to avoid dual-task situations [4].

It is well established that the DLPFC brain region plays a crucial role in dual-tasking. Previous studies reported that anodal tDCS targeted on left DLPFC could reduce dual-task cost in young adults

during walking and upright standing [53,54]. Moreover, Schabrun et al. (2015) recommended stimulating DLPFC against the primary motor cortex (M1) in patients with PD as the only improvement reported was in cognitive performance; there was no change in dual-task gait performance after M1 stimulation using anodal tDCS [43]. Therefore, left DLPFC is an ideal candidate for stimulation to improve dual-tasking.

The therapeutic effect of tDCS is attributed to different mechanisms such as the change in concentration of neurotransmitters, or reduction in resting potential, which is reported to trigger at different timing relative to stimulation [45,77]. Most of the studies assessed task performance before and immediately after stimulation [61]. In this study, a sham-controlled experiment was conducted to determine dual-task gait performance before, during, and three times post left DLPFC stimulation using anodal or sham tDCS in patients with PD. We hypothesized that anodal tDCS would improve both gait and cognitive performance in single- and dual-task conditions compared to sham tDCS.

2.4 Materials and Methods

2.4.1 Participants

We recruited 20 patients with idiopathic PD (female 6, mean age of 63.9 ± 8.7 years, age range 49–77 years; HY stage 2.4 ± 0.2 in "on" medication). The inclusion criterion for the study participants with PD were presence of mild-moderate disease severity (stage I-III on the Hoehn and Yahr scale), and ability to walk and stand independently with-out a walking aid for minimum 10 minutes. Participants were excluded if they had a history of seizures, substance abuse, severe dementia, musculoskeletal dysfunction, severe visual impairment, major head trauma, any brain implant, or pacemaker, and level of functional independence below a score of 60. A self-reported medical history questionnaire was used to determine the inclusion and exclusion criteria. The severity of PD was determined using the modified Hoehn and Yahr scale that classify PD in five stages depending on the symptoms. The experiments were performed according to the Declaration of Helsinki. The local ethics committee of the University of Houston at Texas approved the study.

2.4.2 Transcranial Direct Current Stimulation

During anodal tDCS, a constant electric current of 2 mA was delivered by 1 x 1 tDCS low-intensity stimulator (Soterix medical Inc., New York, NY) for 30 minutes using a pair of saline-soaked 35 cm^2 (7 x 5 cm^2) electrodes (current density of 0.057 mA/cm^2). The anode electrode was placed over the left-DLPFC brain region (i.e., the F3 region of the 10/20 electroencephalographic electrode placement system). The cathode electrode was placed over the right supraorbital region. In sham tDCS, the electrode montage and duration remained the same; however, the current automatically faded out to zero after 15 seconds of stimulation and ramped up in the last 15 seconds of stimulation [68].

2.4.3 Experimental Protocol

This study was designed as a randomized, double-blind, crossover, and sham-controlled experiment. Each participant finished two sessions on separate days receiving either sham or anodal tDCS with a minimum of one-week washout period in between (see figure 2.1 below). The order of tDCS conditions was randomized and counterbalanced. Each session was approximately 2.5 hours long. All the measurements were done during "on" state of medication.

In the first visit, before experiment, the cognitive assessment was done using the Montreal Cognitive Assessment (MoCA), level of depression and anxiety were assessed using Hospital Anxiety and Depression Scale (HADS), and their functional independence was determined using Schwab and England Activity of Daily Living Scale (SE-ADL). In both sessions, gait and cognitive performances were assessed before, during, and three times after (immediately after, post 15, and 30 minutes) stimulation. The GAITRite walkway system was kept in the middle of the pathway to measure the spatiotemporal gait parameters. The GAITRite[a] system (CIR Systems, Inc., Clifton, New Jersey) is a pressure-sensitive carpet that encapsulate an active grid of 48 x 288 sensors for a total of 13,824 sensors. The mat walkway measures, interprets, and records gait data using the accompanying GAITRite[a] software.

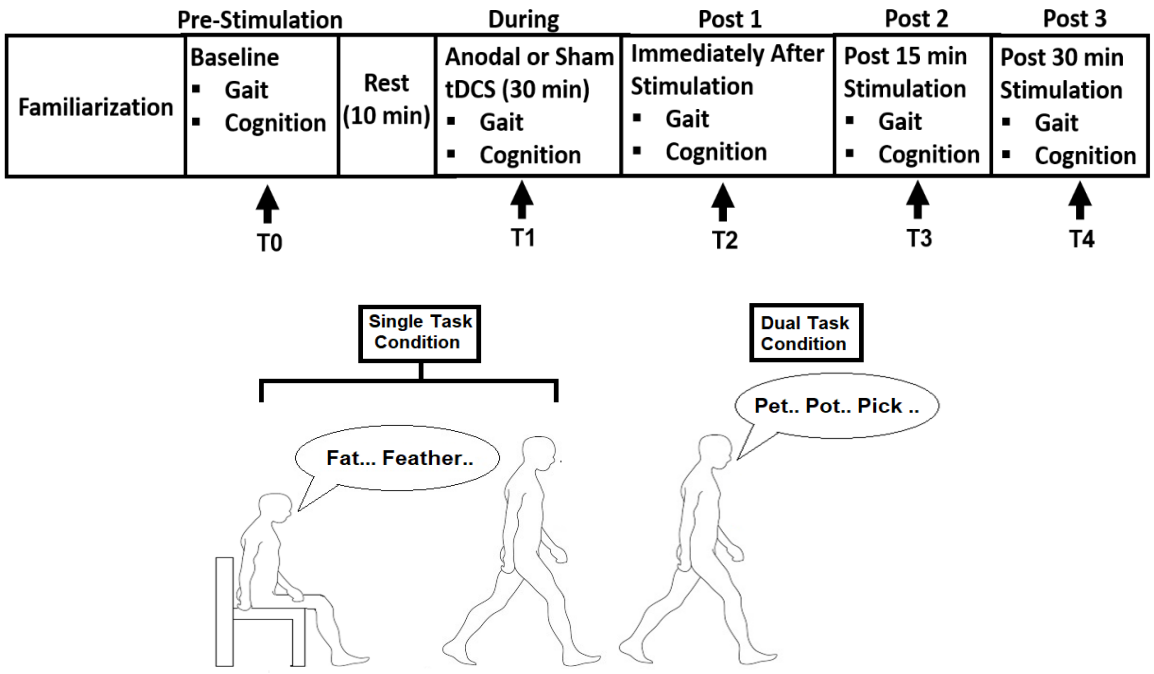

Figure 2.1 In this study, subjects completed two experimental sessions separated by a minimum of one-week wash-out period. During each visit, dual-task walking was assessed before and during either anodal or sham tDCS targeting the left DLPFC. To determine the sustained effects of anodal and sham tDCS, each participant performed dual-task walking immediately after, 15, and 30 minutes after stimulation ceases. The order of tDCS condition were randomized, as well as the testing order of gait in single and dual-task condition within each assessment period. Performing dual-task during gait involved three components 1) over-ground walking of 30 meters only, 2) over-ground walking of 30 meters while performing a concurrent phoneme verbal fluency, and 3) Phoneme verbal fluency task exclusively while sitting

During each assessment, the subject performed gait and cognitive tasks in single and dual-task conditions. In single-task condition, participants performed over-ground walking for 30 meters and performed cognitive task exclusively while sitting, as shown in figure 2 below. In dual-task condition, subjects performed over-ground walking for 30 meters along with the concurrent cognitive task. The cognitive task comprised of phoneme verbal fluency task that required the spontaneous generation of words starting from a given alphabet. Participants were instructed to walk at a self-selected comfortable speed under single and dual-task conditions. No explicit instructions regarding prioritization to tasks were given during the dual-task condition. After each assessment, level of concentration and fatigue were determined using a visual analog scale (i.e. one represented ‘no concentration or no fatigue’ and 10 expressed ‘highest levels of concentration or fatigue’).

2.4.4 Data Analysis

Gait performance was evaluated in terms of gait speed, double-limb support (%), and stride length variability (expressed in terms of coefficient of variation). The cognitive performance was determined in terms of the number of correct responses. The effect of dual-task condition was assessed by calculating dual-task cost (DTC) using the formula shown below.

$$DTC(\%) = \frac{(ST_{OutcomeMeasure} - DT_{OutcomeMeasure})*100}{ST_{OutcomeMeasure}}$$

where DT outcome measure represented outcome parameters (e.g., gait speed) measured during dual-task condition similarly ST outcome measure represents outcome parameters measured in single-task condition. Decrease in DTC was interpreted as improved dual-tasking. The main effects of tDCS (anodal and sham) and time (pre, during, immediately after, post 15, and post 30 minutes) on gait, cognition, and dual-task performance were examined using a two-way repeated measure analysis of variance (ANOVA).

Furthermore, Wilcoxon signed-rank test was conducted to identify any significant difference in level of fatigue and concentration between tDCS condition. Post hoc comparisons were performed using paired t-test after appropriate Bonferroni correction to account for multiple comparisons. Huyn-Feldt correction was applied in case of violation of sphericity assumption. The alpha level for statistical significance was set as $\alpha = 0.05$. All values in the text and figures represent group mean and standard error unless specified. All the analyses were performed using SPSS 13.0 statistical software (Chicago, Illinois, USA).

2.5 Results

All participants tolerated the stimulation well, and there was no complaint of pain or discomfort during the stimulation. Subject characteristics are summarized in Table 2-1. No subject reported any abnormal level of depression and anxiety as determined through HADS. The effect of tDCS on gait parameters and DTC are shown in figure 2.2 and summarized in table 2-2. There was no significant difference in the baseline gait and cognitive performances.

Table 2-1 Participants' (n = 20) characteristics at baseline (Mean ± SD)

Age	63.9 ± 8.7	**Modified H & Y score**	1.9 ± 0.9
Gender (Male/ Female)	14/6	**Depression Score**	4.1 ± 2.2
Weight (kg)	82.6 ± 14.9	**Anxiety Score**	4.9 ± 2.6
Height (cm)	172.3 ± 10.5	**Functional Independence Level (1-100%)**	84.0 ± 15.0
PD Duration	4.8 ± 3.8		
Years of Education	16.2 ± 2.7		
MoCA Score	26.1 ± 2.2		

In the dual-task condition, we found a significant effect ($F_{(1,19)}$=6.14, η^2=0.24, p=0.023) of tDCS condition and time of assessment ($F_{(4,19)}$=4.85, η^2=0.20, p<0.01) on the gait speed. Post-hoc pairwise comparison on tDCS showed that due to anodal tDCS participants walked at higher gait speed at T3 ($F_{(1,17)}$=6.83, η^2=0.26, p=0.017) and T4 ($F_{(1,17)}$=12.03, η^2=0.39, p<0.01) compared to sham tDCS. Additionally, within the anodal tDCS session participants walked faster (p=0.036) at T3 compared to T0 and similar trend at T4 compared to T0 (but not significant, p=0.058).

Table 2-2 Dual-task costs associated with gait and cognition (mean and standard error)

		Before	During	Immediately After	Post 15 min.	Post 30 min.
DTC (%) on Gait Speed	Sham	14.1 ± 1.6	14.3 ± 1.6	13.9 ± 1.5	12.7 ± 1.9	15.2 ± 1.3
	Anodal	12.5 ± 1.8	11.5 ± 1.3	11.3 ± 1.7	10.6 ± 1.7	8.7 ± 1.8[a]
DTC (%) on Cognition	Sham	11.3 ± 8.2	37.4 ± 3.4	34.5 ± 5.4	29.5 ± 5.4	36.5 ± 2.7
	Anodal	18.9 ± 6.1	33.9 ± 5	31.4 ± 3.5	30.9 ± 4.1	24.8 ± 3.8

[a] Significant at p < 0.05 vs. sham.

Moreover, results showed significant effect of time of assessment ($F_{(4,76)}$=4.57, η^2=0.19, p<0.01) on cognitive task performed while walking. We found within the anodal tDCS session participants generated a greater number of words at T2 (p=0.019), T3 (p=0.014), and T4 (p=0.018) compared to baseline (T0). Additionally, there was a significant interaction ($F_{(4,76)}$=4.38, η^2=0.19, p<0.01) between

tDCS condition and time of assessment on cognitive performance. Pairwise post-hoc analysis showed due to anodal tDCS the number of words generated at T3 ($p=0.05$) and T4 ($p<0.01$) were greater than sham tDCS. Moreover, anodal induced greater reduction in DTC associated with gait speed ($F_{(1,17)}=6.21$, $p=0.022$) compared to sham tDCS. Post hoc analysis showed that the DTC was significantly lower ($F_{(1,19)}=8.25$, $p=0.01$) at T4 due to anodal tDCS compared to sham tDCS. There was no change in other gait parameters tDCS or time of assessment.

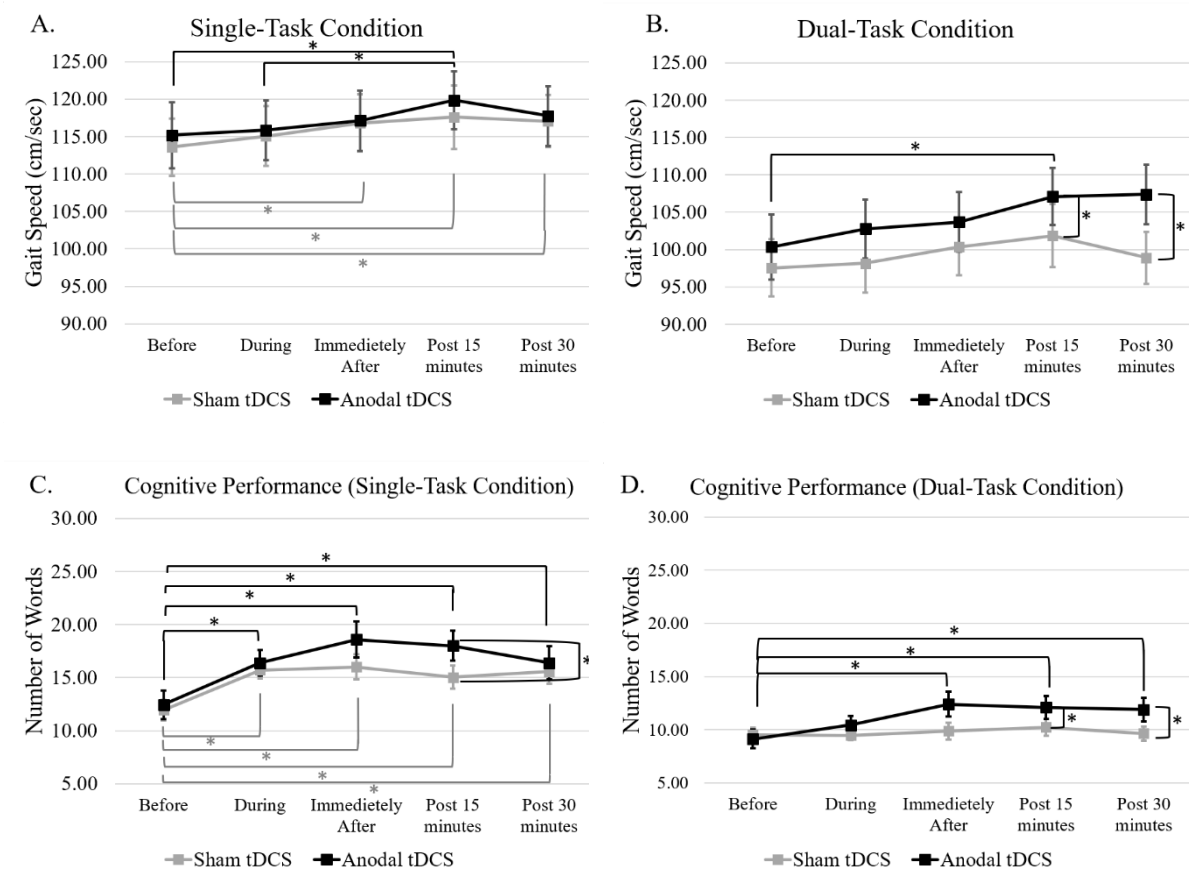

Figure 2.2 The effects of noninvasive tDCS on gait speed in patients with PD. Gait speed was assessed before, during, immediately after, post 15, and 30 minutes of stimulation. Anodal tDCS led to no significant change in gait speed in the single-task condition. In the dual task condition, subjects appeared to walk faster post 15 and 30 minutes of anodal tDCS compared to sham tDCS. Data has been represented as mean and standard error. (*) sign represent significant difference between anodal and sham tDCS whereas (+) represent significant difference between two assessment time.

In single-task condition, repeated measure ANOVA showed no effect of tDCS on the gait performance; however, there was a significant effect ($F_{(4,76)}=5.55$, $\eta^2=0.23$, $p<0.01$) of assessment time

on gait speed. Post-hoc analysis showed significant changes in single-task gait speed within both the sessions. In the session with sham tDCS, participants walked significantly faster at T2 ($p=0.024$), T3 ($p<0.01$), T4 ($p<0.01$) compared to baseline T0 and during the session with anodal tDCS gait speed was higher ($p<0.01$) at T3 compared to T0 and T1. Furthermore, the results of repeated measure ANOVA showed a significant effect ($F_{(1,19)}=4.36$, $\eta^2=0.19$, $p=0.05$) of tDCS condition and time of assessment ($F_{(4,76)}=19.161$, $\eta^2=0.50$, $p<0.01$) on the cognitive task performance under single-task condition. After pairwise post-hoc analyses, we found participants generated a greater number of words at T3 ($F_{(1,19)}=6.23$, $p=0.022$) due to anodal tDCS in comparison to sham tDCS. Moreover, the post-hoc analysis showed a significant increase ($p<0.01$) in the number of words generated at T1, T2, T3, and T4 compared to baseline within both the sessions. Furthermore, the progression in level of fatigue and decline of concentration were similar during both sessions as we found no significant difference in the level of fatigue and concentration between the sessions.

2.6 Discussion

In the previous literature, it was suggested that timing is essential in determining the behavioral effects of tDCS [61,67,77]. To our knowledge, this is the first study to investigate the time-dependent priming effects of tDCS on dual-task walking in patients with PD. There are two primary findings of current study. First, improved dual-task gait performance demonstrated by anodal tDCS led significant increase in dual-task gait speed at T3 and T4 with greater reduction in DTC at T4 compared to sham. Second, better cognitive performance while walking as participants generated a greater number of words generated at T3, and T4 compared to sham. These results partially support our hypotheses showing improvement in gait performance in terms of gait speed during dual-task condition due to anodal tDCS but not during single-task condition. There were no conclusive tDCS related changes in the stride length variability and double-limb support (%) under single or dual-task conditions. However, since adequate walking speed is required for the daily functional activities, therefore improved gait speed is often regarded as the most significant positive outcome of gait rehabilitation.

Benninger et al. (2010) suggested that tDCS can potentially improve gait performance in patients with PD. They conducted eight sessions of tDCS interventions over 2.5 weeks and reported significant improvement in the timed test of gait 24 hours after anodal tDCS during the "off" state of medication. However, unlike our findings, they reported no significant improvement in gait performance during "on" state of medication. The explanation for this discrepancy could be that the gait task was not challenging enough in "on" state. On the other hand, the timed test of walking performed in the "off" state was challenging enough, which was matched by dual-task walk performed in the present study under "on" state of medication.

Patients with PD often find dual-tasking challenging as PD related gait impairments, and cognitive deficits can exacerbate under dual-task conditions. Consistent with previous studies, our data demonstrate worse gait performance in individuals with PD when dual tasking than walking alone. Schabrun et al. (2016) investigated the effect of nine sessions of gait training combined with tDCS, applied on M1 brain region, on dual-task performance in individuals with PD [43]. However, unlike our results, they reported no benefit of tDCS above and beyond the gait training. The reason for discrepancies in the results can be the site of stimulation. Schabrun et al. (2016) recommended to stimulate the DLPFC instead of M1 brain region as the DLPFC brain region plays a crucial role in dual-task performance. Consistent with Swank et al. (2016), our results showed left DLPFC stimulation with anodal tDCS lessened DTC associated with gait [78]. Swank et al. (2016) and other studies endorsed pairing tDCS with a motor task can enhance the overall performance effect due to increased neuron excitability [67,78–81].

Recently, various studies suggested anodal tDCS combined with concurrent training (e.g., tango dancing) may augment beneficial effects on walking and balance compared with tDCS alone [80–82]. Criminger et al. (2018) investigated the effect of DLPFC stimulation using bi-hemispheric tDCS paired with a concurrent activity on walking-associated DTC in people with PD.[81]. Unlike our results, active tDCS did not lessen the DTC in participants with PD. The reason for not finding a significant effect of active tDCS on DTC associated with walking can be the possibilities of fatiguing the participants after

20 minutes of physical activity that might have affected their physical capacity to perform dual-task walking. In our study, we found significant effect of time on fatigue and concentration level or similar trend (though non-significant) during both (sham and anodal tDCS) sessions. Therefore, it is possible that physical activities and cognitive tasks involved in the experiment may have fatigued the participants and declined their concentration level.

There are several limitations of the present study. First, single tDCS might not be enough to show improvement in gait performance under single-task condition. Furthermore, large electrode size might have caused interference in the adjacent brain region functioning. Future studies should consider recruiting participants with PD with more severe gait impairments than reported in current study.

2.7 Conclusion

We conclude that anodal tDCS applied to left DLPFC can improve gait performance in patients with PD under dual-task conditions. Furthermore, the priming of tDCS effects can be time-dependent, and we observed improvement in both cognitive and gait performance under dual-task condition fifteen minutes after stimulation ceased.

CHAPTER III

3 Manuscript II: Investigating the Effect of Transcranial Direct Current Stimulation of Dorsolateral Prefrontal Cortex on Mobility in Patients with Parkinson's Disease: A Double Blind, Sham-Controlled Study

Ram kinker Mishra [a*], and Adam T. Thrasher [a]

[a] Center for Neuromotor and Biomechanics Research, University of Houston, Texas, USA

*Corresponding author: Ram kinker Mishra,

3855 Holman Street, 104 Garrison Gym, Houston, TX, 77204, USA.

Tel.: 470-435-0949; E-mail address: rmishra2@uh.edu

3.1 Abstract

Background: Postural instability is among the major consequences of Parkinson's disease (PD) that leads to reduced mobility. Recent studies have demonstrated Dorsolateral Prefrontal Cortex (DLPFC) stimulation using anodal transcranial direct current stimulation (tDCS) can be an effective intervention to improve balance and mobility. However, there is no clear consensus regarding the time-dependent priming of the tDCS relative to the balance and mobility assessment tasks in individuals with PD.

Objective: To study the time-dependent priming effects of left DLPFC stimulation with anodal tDCS on TUG performance under single and dual-task conditions in patients with PD.

Methods: Twenty patients with PD were recruited in this sham-controlled and cross-over study. Participants completed two sessions with a minimum one-week gap to avoid any carry-over effect. Stimulation was applied on the left DLPFC for 30 mins at 2 mA. Subjects repeated an instrumented Timed Up and Go (TUG) task under single and dual task conditions before, during, and post stimulation (immediately after, post 15, and 30 minutes).

Result: In the dual-task condition, we found a significant effect ($F_{(1,19)}$=11.77, η^2=0.38, $p<0.01$) of tDCS condition, time of assessment ($F_{(4,76)}$=5.99, η^2=0.24, $p<0.01$), and their interaction ($F_{(4,76)}$=5.02, η^2=0.21, $p<0.01$) on the cognitive performance. Moreover, there was significant effect of tDCS condition ($F_{(1,19)}$=5.51, η^2=0.23, p=0.03) and time of assessment ($F_{(4,76)}$=8.13, η^2=0.30, $p<0.01$) on the

DTC associated with cognition. In the single-task condition, the results of repeated measure ANOVA showed a significant effect ($F_{(1,19)}$=4.36, η^2=0.19, p=0.05) of tDCS condition and time of assessment ($F_{(4,76)}$=19.161, η^2=0.50, p<0.01) on the cognitive task performance. No differences were observed for TUG conditions between tDCS sessions.

Conclusion: We can conclude that left DLPFC stimulation using anodal tDCS can potentially improve cognitive functioning under dual-task condition in patients with PD. However, the TUG task may not be an appropriate task to assess the effect of tDCS on mobility under complex situation in patients with early stage PD.

Keywords - Transcranial direct current stimulation; Dorso-Lateral Prefrontal Cortex; Parkinson's Disease; Dual Task

List of Abbreviations – tDCS: Transcranial direct current stimulation; DLPFC: Dorso-Lateral Prefrontal Cortex; PD: Parkinson's Disease; DT: Dual Task

3.2 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder in elderly adults characterized by progressive motor and non-motor symptoms [83]. Motor symptoms such as gait impairments may contribute to progressive loss of mobility directly, and indirectly due to bradykinesia and rigidity [84]. Moreover, non-motor symptoms such as cognitive impairments, depression, and fatigue can have severe repercussions in PD functional mobility [84]. Functional mobility is the physiological ability of people to move independently and safely in a variety of environments in order to accomplish functional tasks [85]. Functional mobility is increasingly used as a rehabilitation outcome for patients with PD, as it can predict future falls [86]. Even with optimal medical management, people with PD experience deterioration in bodily functions leading to progressive loss of mobility [87]. There is a need for complementary treatment that can facilitate in improving mobility in patients with PD.

There are different components of mobility, such as standing, bending, walking, and climbing, which is crucial for activities of daily living (ADL) [88]. Under challenging conditions such as motor-cognitive dual task performance, motor performance can get worse in patients with PD due to

interference from the concurrent cognitive task leading to severely compromised mobility [89]. Therefore, to improve mobility in people with PD, it is crucial to investigate motor and cognitive task performance simultaneously.

The instrumented Timed Up & Go test (TUG) can identify any impairment to mobility in the early stage of PD in which balance seems to be intact [90]. Unlike the conventional TUG, during instrumented TUG performance, wearable sensors are used to record kinematic data, and walking distance is extended from 3 m (traditional TUG) to 7 m. The kinematic data recorded during TUG provide specific information about the postural transitions performed sequentially, i.e., sit-to-stand, walking 7 m, turning, and stand-to-sit, each of which is eventually affected by PD [91]. Additionally, an elongated pathway provides a reliable steady-state gait. Previous studies have shown that the simultaneous performance of a cognitive task with TUG can improve the test's detection of falls in people with PD [89].

The objective of the present study is to assess the time-dependent effect of transcranial direct current stimulation (tDCS) on mobility, determined through dual task TUG, in patients with PD. The tDCS is a non-invasive brain stimulation technique emerging as a potential adjunct treatment approach for patients with PD. It is known to modulate neural activities in the brain region by transferring low-amplitude current between two or more surface electrodes placed upon the scalp. The behavioral effects of tDCS depend on the polarity (i.e., anodal tDCS excites, whereas cathodal tDCS inhibits the neuronal activity), site of stimulation, and the relative timing of the stimulation and task. Studies have shown that dorsolateral prefrontal cortex (DLPFC) stimulation using anodal tDCS can improve locomotion, functional-mobility, and cognitive performance in patients with PD [4–9]. However, according to our knowledge, no study has assessed the time-dependent effect of left DLPFC stimulation using anodal tDCS on mobility under dual-task condition among people with PD. In this study, a sham-controlled experiment was conducted to assess dual task TUG performance before, during, and three times post left DLPFC stimulation using anodal tDCS in patients with PD. We hypothesized anodal tDCS would

improve both TUG and cognitive task performance in single and dual task conditions compared to sham tDCS.

3.3 Materials and Methods

3.3.1 Participants

Twenty patients with idiopathic PD (age 63.9 ± 8.7 years, HY stage 2.4 ± 0.2 while "on" medication, 6 women) received both sham and anodal tDCS at left DLPFC brain region. Participants were included if they were diagnosed with PD according to the modified Hoehn and Yahr criteria (stage I-III), able to walk and stand independently with-out a walking aid for minimum 10 minutes. The exclusion criteria involved a history of seizures, substance abuse, severe dementia, musculoskeletal dysfunction, presence of severe visual impairment, major head trauma, any brain implant, or pacemaker. A self-reported medical history questionnaire was used to determine the inclusion and exclusion criteria. The experiments were performed according to the Declaration of Helsinki. The local ethics committee of the University of Houston at Texas approved the study.

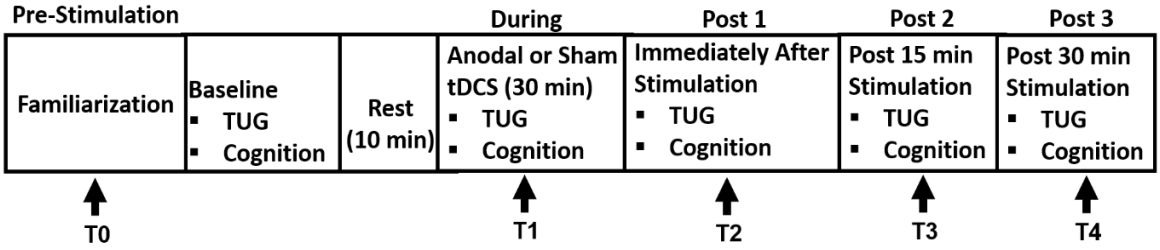

Figure 3.1 The experimental protocol. Subjects completed two experimental sessions separated by a minimum of one-week wash-out period. During each visit, dual-task walking was assessed before and during either anodal or sham tDCS targeting the left DLPFC. To determine the sustained effects of anodal and sham tDCS, each participant performed dual-task walking immediately after, 15, and 30 minutes after stimulation ceases. The order of tDCS condition were randomized, as well as the testing order of gait in single and dual-task condition within each assessment period. Performing dual-task during gait involves three components 1) over-ground walking of 30 meters only, 2) over-ground walking of 30 meters while performing a concurrent phoneme verbal fluency, and 3) Phoneme verbal fluency task exclusively while sitting

3.3.2 Transcranial Direct Current Stimulation

During anodal tDCS, a constant electric current of 2 mA was delivered for 30 minutes using a pair of saline-soaked 35 cm^2 (7 x 5 cm^2) electrodes (current density of 0.057 mA/cm^2). The anode electrode was placed over the left-DLPFC brain region (i.e., the F3 region of the 10/20

electroencephalographic electrode placement system). The cathode electrode was placed over the right supraorbital region. In sham tDCS, the electrode montage and duration remained the same; however, the current automatically faded out to zero after 30 seconds of stimulation and ramped up in the last 30 seconds of stimulation.

3.3.3 Experiment Protocol

Each participant completed two sessions of tDCS with a minimum of one-week washout period (shown in figure 4.1) to avoid any carry-over effect. The order of tDCS conditions (anodal and sham) was randomized in counterbalanced manner and each session was approximately 2.5 hours long. In the first visit, the cognitive assessment was done using the Montreal Cognitive Assessment (MoCA), level of depression and anxiety were assessed using Hospital Anxiety and Depression Scale (HADS), and their functional independence was determined using Schwab and England Activity of Daily Living Scale (SE-ADL).

Table 3-1 Participants' (n = 20) characteristics at baseline (Mean ± SD)

Age	63.9 ± 8.7	**Modified H & Y score**	2.4 ± 0.2
Gender (Male/ Female)	14/6	**Depression Score**	4.1 ± 2.2
Weight (kg)	82.6 ± 14.9	**Anxiety Score**	4.9 ± 2.6
Height (cm)	172.3 ± 10.5	**Functional Independence Level (1-100%)**	84.0 ± 15.0
PD Duration	4.8 ± 3.8		
Years of Education	16.2 ± 2.7		
MoCA Score	26.1 ± 2.2		

3.3.4 Procedures

Subjects completed TUG test under single and dual-task condition and performed them before, during, and three times after (immediately after, post 15, and 30 minutes) stimulation (shown in figure 1). In dual task condition, subjects performed TUG along with the concurrent cognitive task. The cognitive task comprised of phoneme verbal fluency task that required the spontaneous generation of

words starting from a given alphabet. To complete TUG, subject required to stand up at a normal safe pace, walk 7 m, turn 180^{o}, walk back, and sit down (shown in figure 2). It has been observed that in PD each of these components of TUG are impaired, therefore time taken to complete each component was estimated as mentioned in previous study [34]. Furthermore, we used a longer walkway to get sufficient gait cycles for analysis [90]. No explicit instructions regarding prioritization to tasks were given during the dual-task condition. Moreover, in single task condition, subjects performed TUG alone and phoneme verbal fluency task exclusively while sitting. Each component of TUG will be identified using kinematic data recorded by Xsens MVN system. After each assessment, level of concentration and fatigue were determined using a visual analog scale (i.e. 1 represented 'no concentration or no fatigue' and 10 expressed 'highest levels of concentration or fatigue'). Each participant was tested during medication "ON" times for all conditions.

3.3.5 Equipment

The kinematic data will be collected by using a full-body motion tracking system (Xsens MVN Biomech Awinda wireless system, Xsens Technologies B.V., Enschede, The Netherlands). This system constructs a full body biomechanical model based on seventeen inertial motion trackers comprised of three orthogonally mounted gyroscopes, accelerometers, and magnetometers housed in a plastic casing. The locations for these trackers are the head, the sternum, the posterior pelvis, and bilaterally on the shoulders, upper arms, forearms, hands, upper legs, lower legs, and feet. The data will be collected at the sampling frequency or frame rate of 60 Hz for each tracker using MVN Analyzer software. The biomechanical model can estimate the joint angles, linear and angular speed and acceleration of individual segments, and linear and angular speed and acceleration of the individual trackers.

3.3.6 Data Analysis

The functional-mobility was assessed using the time taken to complete each component of TUG task (Sit-to-Stand transition, straight walking, turning, and stand-to-sit change). The cognitive performance was determined in terms of the number of correct responses. The effect of dual task condition was assessed by calculating dual task effect (DTC) using the formula shown below:

$$DTC(\%) = \frac{\left(DT_{Outcome\_measure} - ST_{Outcome\_measure}\right)*100}{ST_{Outcome\_measure}}$$

where DT outcome measure represents outcome parameters (e.g. time taken to turn around 180^{o}) measured during dual task condition similarly ST outcome measure represents outcome parameters measured in single task condition. The main effects of tDCS condition (anodal and sham), time (pre, during, immediately after, post 15, and post 30 minutes), and their interaction on dual-task performance were examined using a two-way repeated measure analysis of variance (ANOVA). The non-gaussian data was transformed using logarithmic and square root transformations. If the data remained nonparametric after transformation, the effect of stimulation and time of assessment was analyzed using a two-way Freidman's ANOVA. Moreover, the level of fatigue and concentration measured at different times were analyzed using repeated-measures ANOVA. The significance level will be set at $p = 0.05$. Tukey's posthoc test was conducted on significant findings to identify differences between variable means within each tDCS condition and time point combination. The assumptions for the repeated-measures ANOVA were tested. The normality assumption of each variable was checked via histograms, skewness, and kurtosis statistics of the residuals of outcome variables. Furthermore, the relation between depression, ability to perform daily activities and walking speed was measured using the Pearson correlation coefficients (r). R-Studio statistical software package was used to perform all statistical analyses.

3.4 Results

All participants completed the study with no adverse effects. The Subject characteristics are summarized in Table 1. There were no cases of an abnormal level of depression and anxiety as determined through HADS. There was no significant difference in the baseline TUG and cognitive performances.

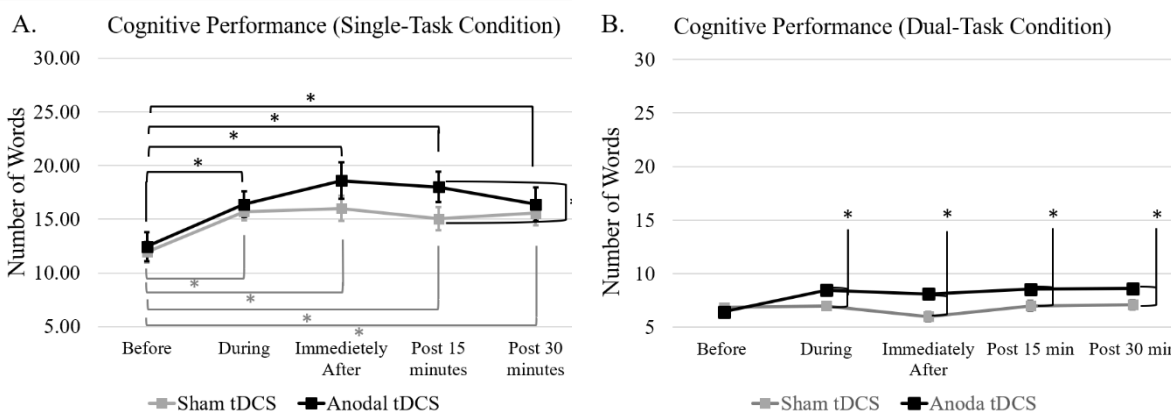

Figure 3.2 The effects of noninvasive tDCS on gait speed in patients with PD. Gait speed was assessed before, during, immediately after, post 15, and 30 minutes of stimulation. Anodal tDCS led to no significant change in gait speed in the single-task condition. In the dual task condition, subjects appeared to walk faster post 15 and 30 minutes of anodal tDCS compared to sham tDCS. Data has been represented as mean and standard error. (*) sign represent significant difference between anodal and sham tDCS whereas (+) represent significant difference between two assessment time.

In the dual-task condition, we found a significant effect ($F_{(1,19)}$=11.77, η^2=0.38, p<0.01) of tDCS condition, time of assessment ($F_{(4,76)}$=5.99, η^2=0.24, p<0.01), and their interaction ($F_{(4,76)}$=5.02, η^2=0.21, p<0.01) on the cognitive performance. Post-hoc pairwise comparison on tDCS showed that due to anodal tDCS participants significantly greater number of words at T1 ($F_{(1,19)}$=7.33, p=0.014), T2 ($F_{(1,19)}$=13.76, p=0.01), T3 ($F_{(1,19)}$=9.61, p<0.01) and T4 ($F_{(1,17)}$=6.63, p=0.019) compared to sham tDCS. Within the anodal tDCS session, compared to baseline (T0), participants generated significantly higher number of words ($F_{(4,76)}$=11.72, p<0.01) at all the time points (T1 to T4). However, within the session with sham tDCS, there was no significant change in the number of words generated. Moreover, there was significant effect of tDCS condition ($F_{(1,19)}$=5.51, η^2=0.23, p=0.03) and time of assessment ($F_{(4,76)}$=8.13, η^2=0.30, p<0.01) on the DTC associated with cognition. Post-hoc analysis showed anodal tDCS lessened the DTC only during stimulation ($F_{(1,19)}$=7.56, η^2=0.29, p=0.013) compared to sham tDCS. Furthermore, there was no significant effect of time of assessment and tDCS on TUG related parameters under dual-task condition.

Table 3-2 TUG Performance (mean and standard error)							
			Before	**During**	**Immediately After**	**Post 15 min.**	**Post 30 min.**
Total Time (sec)	Sham	ST	18.94 ± 0.96	18.86 ± 0.89	18.53 ± 0.66	18.06 ± 0.77	17.84 ± 0.73
		DT	21.79 ± 1.05	21.63 ± 0.92	22.09 ± 0.88	21.53 ± 0.93	20.99 ± 0.86
	Anodal	ST	18.25 ± 0.71	18.42 ± 0.65	18.61 ± 0.84	17.82 ± 0.65	17.80 ± 0.63
		DT	21.50 ± 0.96	21.17 ± 0.89	21.46 ± 0.95	21.32 ± 0.90	20.91 ± 0.86
Mid-Turn (sec)	Sham	ST	2.86 ± 0.09	2.79 ± 0.10	2.90 ± 0.08	2.82 ± 0.09	2.92 ± 0.08
		DT	3.04 ± 0.10	3.00 ± 0.10	3.11 ± 0.07	2.95 ± 0.11	2.92 ± 0.10
	Anodal	ST	2.87 ± 0.09	2.81 ± 0.12	2.90 ± 0.10	2.80 ± 0.11	2.82 ± 0.11
		DT	2.89 ± 0.13	3.00 ± 0.09	3.06 ± 0.09	3.11 ± 0.07	2.97 ± 0.10
Last Turn (sec)	Sham	ST	2.38 ± 0.13	2.24 ± 0.13	2.36 ± 0.13	2.29 ± 0.12	2.40 ± 0.13
		DT	2.38 ± 0.13	2.24 ± 0.13	2.36 ± 0.13	2.29 ± 0.12	2.40 ± 0.13
	Anodal	ST	2.26 ± 0.13	2.21 ± 0.13	2.42 ± 0.14	2.35 ± 0.11	2.21 ± 0.09
		DT	2.26 ± 0.13	2.21 ± 0.13	2.42 ± 0.14	2.35 ± 0.11	2.22 ± 0.09
Sit-to-Stand duration (sec)	Sham	ST	1.62 ± 0.12	1.83 ± 0.20	1.87 ± 0.18	1.57 ± 0.10	1.34 ± 0.08
		DT	1.80 ± 0.14	1.91 ± 0.12	1.66 ± 0.12	1.83 ± 0.15	1.66 ± 0.14
	Anodal	ST	1.50 ± 0.06	1.60 ± 0.08	1.46 ± 0.08	1.43 ± 0.07	1.45 ± 0.07
		DT	1.82 ± 0.11	1.78 ± 0.13	1.73 ± 0.12	1.74 ± 0.13	1.68 ± 0.12
Stand-to-Sit duration (sec)	Sham	ST	2.30 ± 0.11	2.02 ± 0.14	2.10 ± 0.07	1.92 ± 0.08	1.97 ± 0.10
		DT	2.01 ± 0.10	2.00 ± 0.12	2.17 ± 0.15	2.14 ± 0.12	2.01 ± 0.09
	Anodal	ST	2.08 ± 0.13	1.95 ± 0.13	1.85 ± 0.13	2.04 ± 0.12	1.89 ± 0.08
		DT	1.97 ± 0.13	1.94 ± 0.12	1.89 ± 0.11	1.87 ± 0.15	1.91 ± 0.09

In the single-task condition, the results of repeated measure ANOVA showed a significant effect ($F_{(1,19)}$=4.36, η^2=0.19, p=0.05) of tDCS condition and time of assessment ($F_{(4,76)}$=19.161, η^2=0.50, p<0.01) on the cognitive task performance. After pairwise post-hoc analyses, we found participants

generated a greater number of words at T3 ($F_{(1,19)}$=6.23, p=0.022) due to anodal tDCS in comparison to sham tDCS. Moreover, the post-hoc analysis showed a significant increase ($p<0.01$) in the number of words generated at T1, T2, T3, and T4 compared to baseline within both the sessions. We found no effect of tDCS condition, time of assessment, or their interaction on TUG related parameters under single-task conditions. Furthermore, the progression in level of fatigue and decline of concentration were similar during both sessions as we found no significant difference in the level of fatigue and concentration between the sessions.

3.5 Discussion

Previous studies have shown positive results related to DLPFC stimulation using tDCS may improve the motor and cognitive abilities in patients with PD [6,92]. However, there are inconsistencies in the results reported in the literature [56]. One of the primary reasons for heterogeneous findings is the lack of understanding about the timing of tDCS priming relative to task performance [37,81,93]. In the current study, we investigated the time-dependent priming effect of left DLPFC stimulation using anodal tDCS on functional mobility in individuals with PD. The main findings of this study are that anodal tDCS enhanced cognitive performance and reduced DTC associated with cognition during stimulation (shown in figure 4.1). However, tDCS induced no change in the TUG performance under either single or dual-task conditions.

The improvement in verbal-fluency task performance under dual-task condition was visible during (T1) and post-stimulation (T2-T4). In the single-task condition, the cognitive performance improved only 15 minutes (T3) after stimulation ceased. Perhaps, the findings in the current study related to cognitive functioning can be explained by the results of Pereira et al. (2013) that used the fMRI verbal fluency paradigm to investigate the effect of DLPFC stimulation in patients with PD [94]. They performed free-model independent component analyses (ICA) to show increased functional connectivity in phoneme verbal fluency task-related networks due to left DLPFC tDCS in patients with PD [94]. Although not directly comparable, Boggio et al. (2006) demonstrated anodal tDCS targeted

on the DLPFC brain region improved accuracy and decreased error frequency during 3-back letter working memory test in patients with PD [62].

Moreover, no change in TUG performance in the present study, can be explained by the "Posture second" task prioritization strategy, as proposed by Bloem et al. (2006). According to the "Posture second" strategy, individuals with PD often prioritize cognitive task performance at the cost of the motor task under dual-task conditions [95]. However, this may not always be valid and may depend on the motor and cognitive tasks selected for dual-task performance. Recently, Yogev-Seligmann et al. (2012) proposed a Model of Task Prioritization, which suggests under the dual-task condition, the allocation of attentional resources depends on factors that minimize the danger but not necessarily chooses "Posture first" in all situations [96]. The factors include the physical capacity to respond to a postural threat (termed as postural reserve), ability to recognize potential hazards in the environment (hazard estimation), intrinsic individual factors (i.e., skilled tasks, mood, personality), and task complexity. In the present study, the TUG test may not have presented an adequate postural threat to the participants. As a result, they focused more on cognitive performance, which is further enhanced by anodal tDCS.

Furthermore, Manenti et al. (2014) findings partially supported our results as they reported no change in TUG performance after anodal tDCS was applied on left DLPFC; however, anodal tDCS targeted on right DLPFC reduced TUG duration [65]. In another study, unlike our results, Lattari et al. (2016) reported substantial improvement in balance and functional mobility in PD patients due to anodal tDCS delivered to left DLPFC [6]. The reasons for these discrepancies can be choosing the modified version of TUG in the present study that involved walking seven meters instead of three meters. Another reason can be that in the current study, the duration of PD of recruited participants was significantly lower than in previous studies. Therefore, TUG may not be an appropriate motor test for the patients in the early stage of PD to test the effect of tDCS. This explanation is further corroborated by Schabrun et al. (2016), which showed no effect of M1 stimulation using anodal tDCS on TUG performance; however, anodal tDCS increased the correct cognitive response rate in participants with

PD during dual-task TUG [43]. Closest to our study is the work by Criminger et al. (2018) that examined the influence of a single session of bi-hemispheric tDCS paired with a concurrent activity on walking-associated DTC in people with PD [81]. However, unlike our study, they gave a non-walking aerobic exercise activity (pedaling a stationary bicycle) and a novel activity (playing a video game of golf on Wii™) as the concurrent task to assess changes in subsequent dual-task walking [81]. In line with our findings, they reported no tDCS led improvement in dual-task walking in participants with PD but reduced DTC associated with cognition [81]. The main limitation of present study is its inability to make any conclusive point regarding tDCS associated mechanisms with its current experiment design. Future studies can focus on including imaging modalities that can provide further information regarding tDCS led changes in brain functioning.

3.6 Conclusion

We can conclude that left DLPFC stimulation using anodal tDCS can potentially improve cognitive functioning under dual-task condition in patients with PD. However, the TUG task may not be an appropriate task to assess the effect of tDCS on mobility under complex situation in patients with early stage PD.

CHAPTER IV

4 Manuscript III: Investigating the effect of combining transcranial direct current stimulation with motor-cognitive task in patients with Parkinson's Disease: A double blind, sham-controlled study

Ram kinker Mishra [a*], He Zhou [b], Bijan Najafi [b], and Adam T. Thrasher [a]

[a] Center for Neuromotor and Biomechanics Research, University of Houston, Texas, USA

[b] Interdisciplinary Consortium on Advanced Motion Performance (iCAMP), Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX 77030, USA

*Corresponding author: Ram kinker Mishra,

3855 Holman Street, 104 Garrison Gym, Houston, TX, 77204, USA.

Tel.: 470-435-0949; E-mail address: rmishra2@uh.edu

4.1 Key Points

1. Anodal tDCS applied on left DLPFC can enhance motor control while standing.
2. Priming of the tDCS effect may occur during stimulation rather than post-stimulation in patients with PD.

4.2 Abstract

Background: Transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) has shown the potential to improve motor and cognitive task performance in patients with PD. In literature, most of the studies have focused on using tDCS to enhance postural control during walking. However, the effects of tDCS can be task-specific; therefore, there is a need for studies examining tDCS influence on postural control while standing, especially under complex situations, in patients with PD.

Objective: Investigate the effects of left DLPFC stimulation with anodal tDCS on motor-cognitive task performance during standing in patients with PD.

Methods: Sixteen patients with PD participated in this double-blind, sham-controlled, cross-over study. Participants completed two sessions at least one week apart to avoid any carry-over effect. The

concurrent motor-cognitive performance was assessed using instrumented trail making test (iTMT). The motor task involved ankle reaching task, which requires dynamic postural control and cognitive task comprised of a digital trail-making task presented on the screen placed in front of the subjects. Within each session, iTMT tests were repeated before, during, immediately after, 15, and 30 minutes after stimulation ceased. The stimulation involved transferring 2mA current through left DLPFC for 30 minutes. The cognitive task performance was assessed in terms of time duration of completing the iTMT tests and motor task performance was measured in terms of ankle velocity.

Result: Our results showed anodal tDCS induced significant increase ($F(1,15) = 6.17$, $p=0.025$) in ankle velocity compared to sham tDCS during stimulation and similar trend post-stimulation (but not significant). Furthermore, anodal tDCS led greater increase ($F(1,15) = 7.20$, $p=0.017$) in ankle velocity during stimulation compared to sham tDCS.

Discussion and Conclusion: Most of the studies assessed effect of tDCS on task performance post stimulation. However, our results show combining tDCS with task performance can be superior to stimulating prior task performance; as it would facilitate motor performance by enhancing the activity of task-related networks and strengthening of relevant synaptic connections.

Keywords - Neuromodulation; Brain stimulation; Transcranial direct current stimulation; Parkinson's Disease; Dual-tasking

List of Abbreviations – tDCS: Transcranial direct current stimulation; DLPFC: Dorsolateral prefrontal cortex; PD: Parkinson's Disease; DTC: Dual-task Cost

4.3 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive postural instability and cognitive impairments [12]. Postural instability is common in PD that often contributes to falls and reduced mobility [97]. Furthermore, cognitive impairments can be present several years before motor symptoms become apparent [17] and interfere with motor functioning [98]. Due to impaired postural control and cognitive deficits, many patients with PD find it challenging to perform motor-cognitive dual-tasks such as walking while having a conversation [33]. Dual-tasking is an

integral part of everyday life. Therefore, rehabilitation of dual-tasking is crucial for improving the quality of life in patients with PD [33]. The current pharmacological and surgical treatments have a limited effect on dual-tasking [99]. Currently, the best approach to manage PD is through the multidisciplinary modalities [10]. Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, has shown the potential to be used as an adjunct to existing PD treatments [100]. However, despite several studies showing positive results of tDCS on the PD related motor and cognitive symptoms [61], there is no consensus on the ways of using tDCS to improve dual-tasking in patients with PD.

Studies have shown tDCS can modulate cortical excitability by delivering the weak current (1-2mA) which provides a valuable approach to improve PD symptoms [67]. It is believed that the change in the excitability are related to transient changes in the synaptic efficacy of different neurotransmitter systems [77]. The effects of tDCS depend on factors such as polarity (i.e., anodal tDCS excites, whereas cathodal tDCS inhibits the neuronal activity), site of stimulation, and the relative timing of the stimulus and task [67,101].

A growing body of evidence supports the idea of stimulating left-DLPFC by applying tDCS to improve dual-tasking [53,54,78]. It is well established that the DLPFC brain region plays a crucial role in dual-tasking [102]. Furthermore, studies have shown that DLPFC stimulation using anodal tDCS can improve locomotion, functional-mobility, and cognitive performance in patients with PD [6,62–66]. However, most of the studies investigated the effects of tDCS on task performance after the stimulation (off-line), rather than during tDCS (on-line). Delivering tDCS while patients are performing the task (on-line design) can be superior to off-line design [56,67] as it would facilitate motor performance by enhancing the functional connectivity in task-specific networks and improve the learning rate for a motor task [67,94,103,104].

Furthermore, most of the studies that assessed the effects of tDCS on dual-tasking in patients with PD evaluated postural control while walking in combination with a cognitive task. In this study, we used instrumented trail making task (iTMT) that examines postural control while standing in

combination with a cognitive task [35]. The iTMT is a wearable sensor-based platform that combines the ankle-reaching task as the primary motor task with the digital version of different trail-making tasks performed as the secondary cognitive task [105,106]. Assessing postural control using iTMT would further expand the array of motor-cognitive tasks that incur dual-task interference in individuals with PD. Moreover, no study has evaluated online effect of tDCS on motor-cognitive task performance focused on postural control while standing in individuals with PD.

To address this gap, in this study, the left DLPFC was stimulated using anodal tDCS in patients with PD while performing iTMT. The performance was assessed before, during, and three times (immediately after, post 15, and 30 minutes) after stimulation ceased in patients with PD. We hypothesized that anodal tDCS would lead to improved iTMT performance, and the improvement would retain in performance post-stimulation compared to sham tDCS. A decrease in time taken to complete iTMT would demonstrate enhanced cognitive functioning, and increased ankle velocity would show improvement in motor performance.

4.4 Materials and Methods

4.4.1 Participants

Sixteen patients with idiopathic PD (5 women, mean age 65.5 ± 8.5 years; HY stage 1.6 ± 0.5 in "on" medication) were recruited. The inclusion criterion for the study participants with PD were presence of mild-moderate disease severity (stage I-III on the Hoehn and Yahr scale), and ability to stand for 10 minutes with-out any assistance. Participants were excluded if they had a history of seizures, severe dementia, musculoskeletal dysfunction, severe visual impairment, major head trauma, and any brain implant, or pacemaker. A self-reported medical history questionnaire was used to determine the inclusion and exclusion criteria. The severity of PD was determined using the modified Hoehn and Yahr scale that classify PD in five stages depending on the symptoms. The experiments were performed according to the Declaration of Helsinki. The local ethics committee of the University of Houston at Texas approved the study.

Table 4-1 Participants' (n = 16) characteristics at baseline (Mean ± SE)

Age	65.5 ± 8.5	**Modified H & Y score**	1.6 ± 0.1
Gender (Male/ Female)	10/6	**Depression Score**	4.4 ± 0.7
Weight (kg)	84.5 ± 15.8	**Anxiety Score**	5.13 ± 2.7
Height (cm)	173.4 ± 10.3	**Functional Independence**	85.3 ± 11.8
PD Duration	3.7 ± 2.5	**Level (1-100%)**	
Years of Education	16.1 ± 2.9		
MoCA Score	26.7 ± 2.5		

4.4.2 Transcranial Direct Current Stimulation

During anodal tDCS, a constant electric current of 2 mA was delivered by 1 x 1 tDCS low-intensity stimulator (Soterix medical Inc., New York, NY) for 30 minutes using a pair of saline-soaked 35 cm^2 (7 x 5 cm^2) electrodes (current density of 0.057 mA/cm^2). The anode electrode was placed over the left-DLPFC brain region (i.e., the F3 region of the 10/20 electroencephalographic electrode placement system). The cathode electrode was placed over the right supraorbital region. In sham tDCS, the electrode montage and duration remained the same; however, the current automatically faded out to zero after 15 seconds of stimulation and ramped up in the last 15 seconds of stimulation [68].

4.4.3 Experiment Protocol

This study was designed as a randomized, double-blind, crossover, and sham-controlled experiment. Each participant finished two sessions on separate days receiving either sham or anodal tDCS with a minimum of one-week washout period in between (see figure 3.1 below). The order of tDCS conditions was randomized and counterbalanced. Each session was approximately 2.5 hours long. All the measurements were done while medication was effective. In the first visit, before the experiment, the cognitive assessment was done using the Montreal Cognitive Assessment (MoCA); levels of depression and anxiety were assessed using Hospital Anxiety and Depression Scale (HADS),

and their functional independence was determined using Schwab and England Activity of Daily Living Scale (SE-ADL).

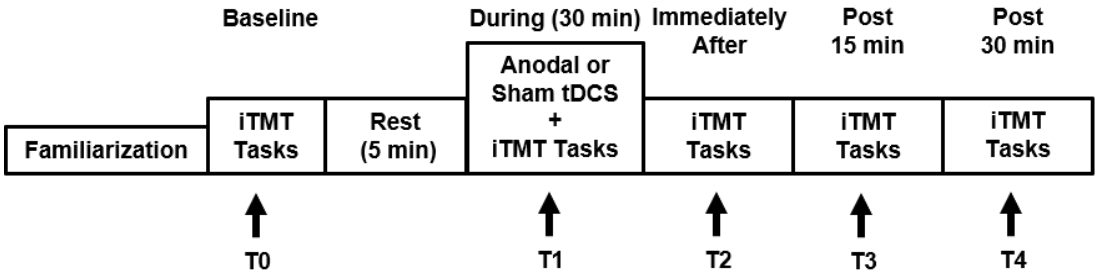

Figure 4.1 In this study, subjects completed two visits separated by a minimum of one-week wash-out period. During each visit, iTMT tasks were assessed before, during, and post stimulation (immedietely after, post 15, and 30 minutes). The testing order of iTMT tests were randomized within each assessment period in addition to tDCS conditions which were randomized in counterbalanced manner.

In both sessions, iTMT tasks were performed to assess motor-cognitive performances before, during, and three times after (immediately after, post 15, and 30 minutes) stimulation. The details of iTMT platform design are given in a previous study [105]. During each assessment, the subject stood in front of a screen with a wearable sensor (LegSys^{TM}, BioSensics, MA, USA) attached to the lower shin and secured with an elastic Velcro (Fig. 3.2). The sensor detected the ankle rotation produced by swaying the hips in the anterior-posterior direction. Participants performed ankle rotations to navigate the cursor on the screen and completed the trail-making tasks presented on the screen. The trail-making tasks consisted of six circles – one circle for start position and the other five for the target position. The target circle had a number (“1”, “2”, or “3”) or letter (“A” or” B”) depending on the task. There were three different types of trail-making tasks repeated three times each: 1) fixed-order trail making ($iTMT_{fixed}$), 2) random-order trail making ($iTMT_{random}$), and 3) number-letter order trail making ($iTMT_{number\text{-}letter}$) described below:

Fixed-Order Trail-Making Task ($iTMT_{fixed}$ task): In this task, the numbers were arranged in ascending order from number 1 to 5 in the left to right direction, as shown in figure 4.2. Subjects navigated the cursor from the start position to the target-circle with the number “1” and brought it back

to the start position. The participant continued to move the cursor from the start location to the target circle carrying the next number in the order.

Random-Order Trail Making Task ($iTMT_{random}$): During this task, the numbers (within the range of 1 to 5) were arranged in the random order. Subjects searched for the correct order and moved the cursor back and forth from the start position to the target circle in the identified order. The $iTMT_{random}$ presented a higher cognitive challenge to the participants than $iTMT_{fixed}$ due to greater involvement of the working memory.

Number-Letter-Order Trail-Making Task ($iTMT_{number\text{-}letter}$): The $iTMT_{number\text{-}letter}$ presented the highest level of cognitive challenge. In this task, apart from randomizing the order of numbers, letters were mixed with the numbers. Participants needed to switch between numbers and letters while searching in the correct order. The exact order for this task was "1"," A," 2"," B," and "3" (fig. 4.2).

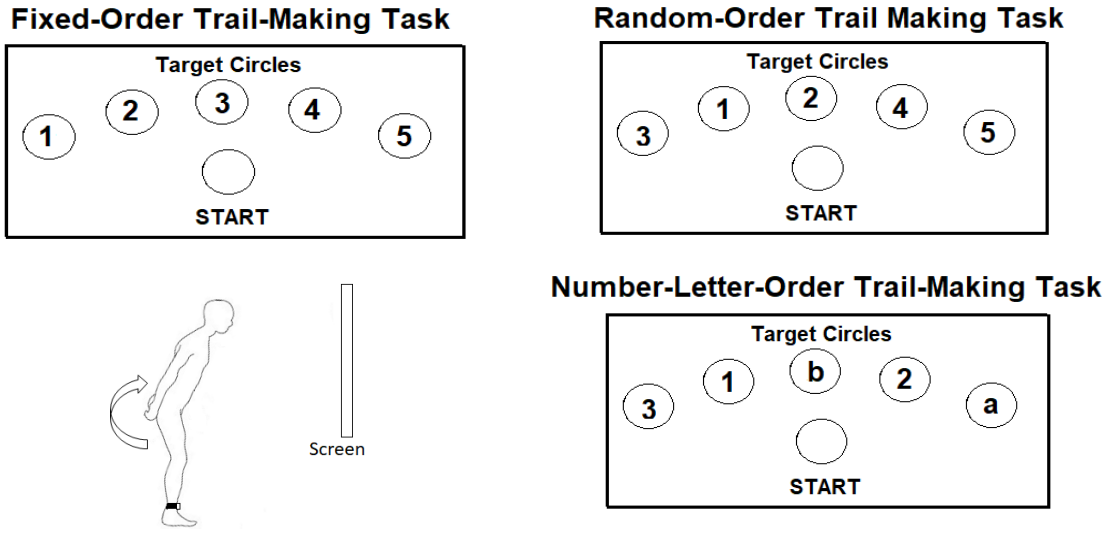

Figure 4.2 Reaching task involves performing hip movement in anterior posterior direction to generate ankle movement. Cognitive performance is evaluated using a virtual trail making task which involves visual search of correct order of displayed numbers or combination of numbers and alphabets and connecting them. The three sets of trail-making tasks: 1) fixed-order trail making ($iTMT_{fixed}$); 2) random-order trail making ($iTMT_{random}$); and 3) number-letter order trail making ($iTMT_{number\text{-}letter}$).

After each assessment, level of concentration and fatigue were determined using a visual analog scale (i.e. one represented 'no concentration or no fatigue' and 10 expressed 'highest levels of concentration or fatigue'). Further details about estimating angular velocity and time duration to complete iTMT are given in previous studies [105,106].

4.4.4 Data Analysis

The main effects of tDCS (anodal and sham) and time (pre, during, immediately after, post 15, and post 30 minutes) on time taken to complete the tasks and ankle velocity were examined using a two-way repeated measure analysis of variance (ANOVA). Huyn-Feldt correction was applied in case of violation of sphericity assumption. Moreover, Wilcoxon signed-rank test was conducted to test significant difference between sessions on level of fatigue and concentration. Post hoc comparisons were performed using paired t-test after appropriate Bonferroni corrections when required. A p-value below 0.05 was regarded as significant. All values in the text and figures represent group mean and standard error unless mentioned. All the analyses were performed using SPSS 13.0 statistical software (Chicago, Illinois, USA).

4.5 Results

All participants tolerated the stimulation well, and there was no complaint of pain or discomfort during the stimulation. Subject characteristics are summarized in Table 3-1. No subject reported an abnormal level of depression and anxiety (i.e., Scores on HADS were below 10). The effect of tDCS on time duration to complete iTMT and angular velocity are shown in figure 3.3. There were no significant differences in the baseline iTMT derived parameters.

Fixed Order Trail-Making Task

We found that participants improved their cognitive performance during the $iTMT_{Fixed}$ task over time irrespective of tDCS condition which is demonstrated as the decrease in time taken to finish the $iTMT_{Fixed}$ task (Figure 3.3.a). Results from the repeated measure ANOVA showed a significant effect ($F_{(4,60)} = 14.39$, $p<0.01$) of assessment time but no effect of tDCS condition. Through post hoc analysis, it was determined that within both sessions, participants finished the $iTMT_{Fixed}$ task in a smaller time duration at T1 to T4 compared to baseline (T0). Similarly, there was no effect of tDCS but a significant effect ($F_{(4,60)} = 6.09$, $p<0.01$) of assessment time on motor performance that is measured through ankle velocity (figure 3.3.b). However, there were no significant pairwise post-hoc comparisons on ankle velocity within the sessions.

Random Order Trail-Making Task

The time duration for completing the $iTMT_{Random}$ task showed a trend towards reduction over time within both the sessions suggesting improved cognitive performance due to learning (Figure 3.3.c).

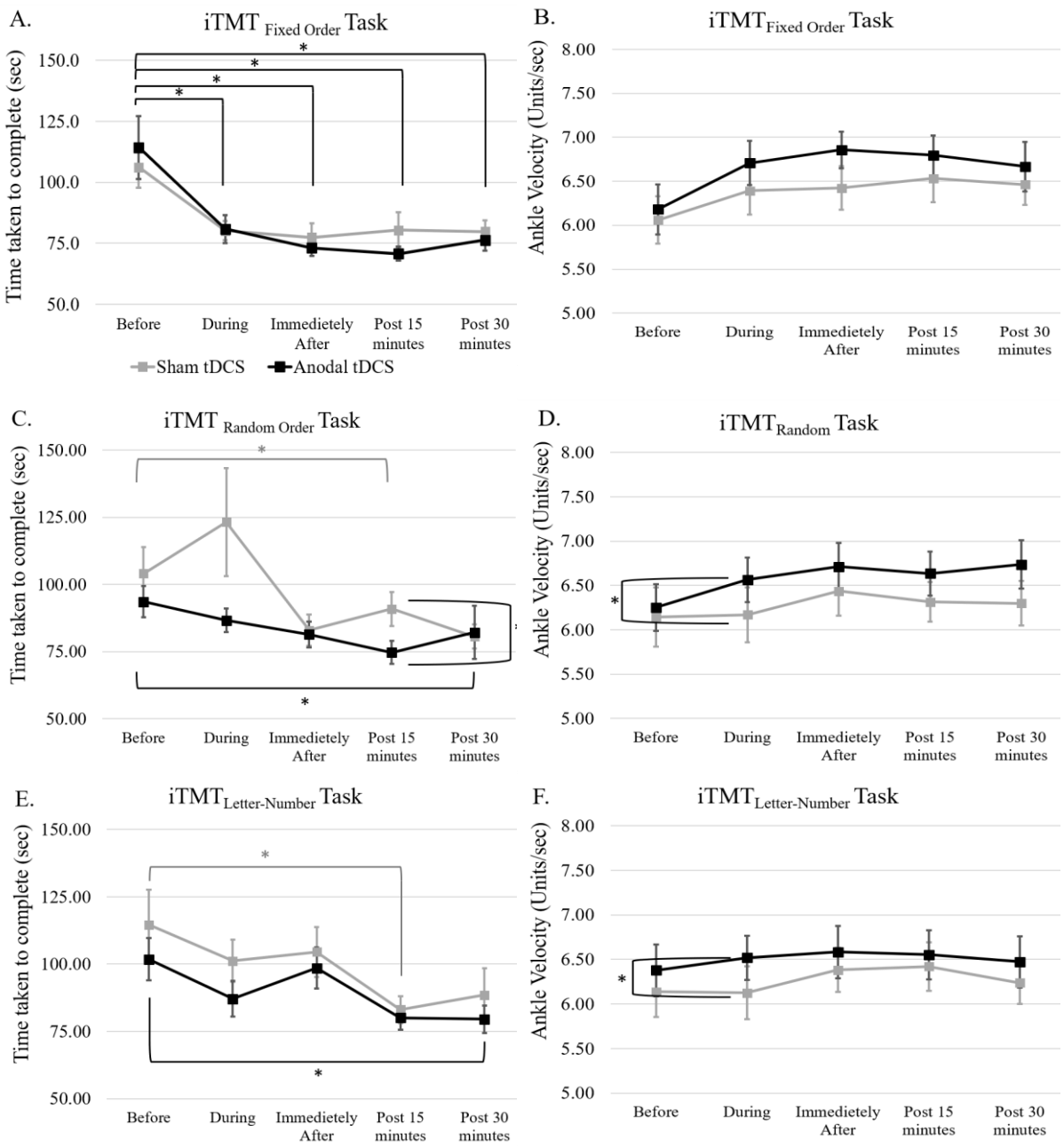

Figure 4.3 The cognitive performance of participants with PD was assessed in terms of the time taken to finish iTMT tasks. A decrease in time duration for completing iTMT tasks represented the improvement in cognitive functioning. Furthermore, the motor-cognitive performance was evaluated in terms of ankle velocity measured while performing iTMT tasks. In crease in ankle velocity represented improved motor-cognitive performance.

Results from repeated measure ANOVA showed significant effect of assessment time ($F_{(4,60)}$ = 5.70, $p<0.01$) and tDCS condition ($F_{(1,15)}$ = 8.01, p=0.013). The post-hoc analysis demonstrated time duration was significantly lower at T2 vs. T0 within the session comprising sham tDCS and at T3 vs. T0 within the session consisting of anodal tDCS. Furthermore, compared to sham tDCS, the anodal tDCS reduced time duration to finish $iTMT_{Random}$ task significantly ($F_{(1,15)}$ = 9.88, $p<0.01$) at fifteen minutes after stimulation ceased. Moreover, we found a significant effect of tDCS condition ($F_{(1,15)}$ = 7.65, p=0.014) and assessment time ($F_{(4,60)}$ = 2.96, p=0.027) on motor performance determined through ankle velocity measured during $iTMT_{Random}$ task performance (Figure 3.3.d). Post hoc analysis showed anodal tDCS induced significant increase ($F_{(1,15)}$ = 6.17, p=0.025) in ankle velocity compared to sham tDCS at T1 and similar trend later at T2 toT4 (but not significant).

Number-Letter-Order Trail-Making Task

There was no significant effect of tDCS on time taken to complete $iTMT_{Number\text{-}Letter}$ task. Moreover, there was a significant effect ($F_{(4,60)}$ = 7.94, $p<0.01$) of the time of assessment on completion time for the $iTMT_{Number\text{-}Letter}$ task (Figure 3.3.e). The post hoc analyses showed that anodal tDCS reduced ($F_{(4,60)}$ = 5.57, $p<0.01$) the time taken to finish the $iTMT_{Fixed}$ task at T3 (p=0.039) and T4 (p=0.032) compared to baseline (T0) but there was no significant change due to sham tDCS. Furthermore, there was a significant effect of tDCS on ankle velocity recorded during $iTMT_{Number\text{-}Letter}$ task (Figure 3.3.f). Post-hoc analyses showed that anodal tDCS led greater increase ($F_{(1,15)}$ = 7.20, p=0.017) in ankle velocity at T1 compared to sham tDCS. Moreover, results from the Wilcoxon signed-rank test showed no difference between level of fatigue and concentration between sessions with anodal and sham tDCS.

4.6 Discussion

Studies have suggested combining tDCS concurrent with task performance can induce better behavioral effects than stimulating before task performance [50,61,67,77,80,103,107,108]. However, no study has investigated the online effects of tDCS on the motor-cognitive performance in patients with PD. We investigated the online and post-stimulation effects of tDCS on the motor-cognitive

performance in patients with PD. In this study, a sensor-based digital platform known as iTMT provided the objective measures of motor-cognitive performance. We found anodal tDCS led a significant increase in the ankle velocity compared to sham tDCS, which demonstrates an improved motor performance (shown in figure 4.d and 4.f). However, participants were not able to retain the anodal tDCS related improvement post-stimulation. Furthermore, a lack of significant difference between baseline outcome measures shows no carry-over effect from the first session to the second session. Perhaps, the beneficial effect of online tDCS may be explained by findings of Hone-Blanchet et al. (2016) which conducted a magnetic resonance spectroscopy (MRS) based study [51]. They reported during DLPFC stimulation there was a significant increase in prefrontal striatal glutamate [51]. Glutamate is an excitatory neurotransmitter that facilitates the strengthening of connections between the existing neurons. However, after stimulation, the anodal tDCS did not induce any significant differences in glutamate levels in the left DLPFC compared to sham tDCS [51]. Therefore, single session of tDCS

may not be strong enough to cause substantial behavior changes related to iTMT post stimulation.

Our result seems to extend the results of Kaski et al. (2014), where combining tDCS with physical training improved gait and balance in patients with Parkinson's disease. These results can be explained by the facilitatory effect of anodal tDCS on motor-skill learning [93]. Consistent with our results, Sriraman et al. (2014) showed that anodal tDCS, when combined with motor practice, can improve motor performance on ankle-visuomotor skill learning task in healthy adults. Earlier, Ziemann et al. (2013) demonstrated anodal tDCS combined with motor practice could improve the skill acquisition of object manipulation tasks in older adults.

Furthermore, we found no improvement in cognitive functioning as there was no significant difference between time duration of iTMT task. However, unlike our results Boggio et al. (2006) demonstrated online application of anodal tDCS on left DLPFC among patients with PD improved cognitive functioning in terms of accuracy measured during working memory task [109]. The reason for this discrepancy can be prioritization of tasks. In the current study, even though no instruction

regarding prioritization of task was given, the participants seems to prioritize ankle reaching task. Consequently, subject made mistakes in selecting the correct target circle but increased the ankle velocity.

The main limitation of the current study was the use of a single session of tDCS, as it may not be enough to enhance motor performance adequately. As a result, even though there was a trend towards higher ankle velocity post anodal tDCS compared to sham tDCS, participants were no able to retain the improved motor performance post-stimulation. Furthermore, in the current study cannot determine the exact underlying mechanisms (e.g., change in concentration of neurotransmitters or membrane potentials) responsible that future studies can consider addressing.

4.7 Conclusion

We conclude that the effect of anodal tDCS on iTMT related motor task performance primed during stimulation compared to sham. However, single session of anodal tDCS may not be adequate to produce substantial behavioral changes in iTMT.

CHAPTER V

5 SUMMARY

This dissertation aimed to determine the time-dependent priming effects of anodal tDCS on dual-task performance under three different situations. The purpose of including three different dual-tasks was to evaluate postural control involved in steady-state walking, performing mobility-related activities, and balancing in the upright standing position. Furthermore, it is well established that the DLPFC plays a critical role in cognition [53,110], decision making [111,112], working memory [112,113], locomotion, and performing complex motor tasks [114]. Therefore, we stimulated the left DLPFC brain region to improve dual-tasking in patients with PD.

Overall, our results showed that the effects of tDCS could be timing-dependent and task-specific. We found that the improvement in dual-task walking occurred due to anodal tDCS post fifteen minutes of stimulation and not during or immediately after stimulation. Perhaps, this can explain the reasons for inconsistencies in the previous studies, which investigated the effects of tDCS on dual-task walking. There may be a possibility that most of the studies assessed task performance immediately after stimulation and overlooked the behavior changes associated with tDCS.

Moreover, we found improvement in iTMT related motor performance (i.e., increased ankle velocity) due to anodal tDCS during stimulation but not post-stimulation. It may be possible that the effect of single-session tDCS was not strong enough; therefore, even though there was a trend for improved motor performance post-stimulation, but it was not significant. Furthermore, we found no tDCS related changes in TUG performance, which may be due to the ceiling effect, and the participants were able to perform TUG without many issues. Furthermore, in line with previous studies, we found tDCS improved cognitive performance that can be attributed to stimulated DLPFC activity. However, with the current data, we cannot determine the mechanism responsible for the tDCS related behavioral changes.

In conclusion, anodal tDCS delivered to left DLPFC can improve dual-tasking while walking and balancing to maintain upright standing position. However, future studies should consider including

multiple time-points of assessment and multiple tDCS sessions to observe tDCS related effects on dual-tasking. Furthermore, the TUG may not be sensitive enough to identify tDCS related behavioral changes in early stage of PD.

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