INVESTIGATING MOTOR PREPARATORY AND INITIATION PROCESSES IN PARKINSON'S DISEASE USING TRANSCRANIAL DIRECT CURRENT STIMULATION AND STARTLE

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Abstract

Parkinson's Disease is a slowly progressing neurodegenerative process that is a result of a basal ganglia (BG) dysfunction caused by the death of dopaminergic neurons in the substantia nigra which could lead to difficulties in planning, initiating, and executing movement. One technique for studying movement preparation and initiation is the use of a Startling Acoustic Stimulus (SAS), which has been associated with changes in the movement processing in PD. Transcranial direct current stimulation (tDCS) has been used to modulate cortical excitability and neuroplasticity in humans, providing a potential method to improve motor performance in PD. As such, the purpose of the experiment was to investigate the potential benefits of tDCS applied over the primary motor area (MI) and supplementary motor area (SMA) associated with SAS paradigm to improve preparation and initiation of the movement in individuals with PD. Eleven individuals with PD completed two simple reaction time (RT) tasks, a button-press task (BU) and an elbow extension task (EX) and underwent to a bradykinesia assessment, before and after application of tDCS. Three tDCS testing sessions (Anodal-MI; Anodal-SMA; Sham) were carried-out separated by 48 hours to ensure a complete washout of any residual effects. Results from this experiment reinforce previous findings indicating that following a SAS, participants were able to elicit the prepared motor response in significantly shorter latencies, and movement time and time to peak displacement were improved as well. Additionally, the results also suggest that the premotor RT can be facilitated by tDCS applied over SMA in non-SAS condition. This is indicative that any potential increase in cortical excitability induced by tDCS was able to promote changes in the neural tissue which might have influenced the activation of structures and pathways involved in preparation and initiation – in particular a basal ganglia-thalamo-cortical pathway. We suggest that stimulation of the SMA with anodal-tDCS using simple RT task as strategy can be applied to improve preparatory and initiation processes in individuals with PD.

Keywords: Parkinson's disease, supplementary motor area, tDCS, movement preparation.

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Glossary of Terms

BB: body bradykinesia

BG: Basal ganglia

BU: button-press task

CN: caudate nucleus

CST: corticospinal tract

DBS: deep brain stimulation

DLPFC: dorsolateral prefrontal cortex

ECR: Extensor carpi radialis

EMG: Electromyography

EX: elbow extension task

FT: finger tapping

GPe: globus pallidus external

GPi: globus pallidus internal

HM: hand movement

IS: imperative stimulus

LA: leg agility

MI: Primary motor cortex

MT: movement time

PD: Parkinson's Disease

PkDx: peak displacement

PkVx: peak velocity

PPT: Purdue Pegboard test

PS: pronation and supination

Put: putamen

REB: research ethics board

RT: Reaction time

SAS: Startling acoustic stimulus

SCM: sternocleidomastoid muscle

SMA: Supplementary motor area

SNc: substantia nigra pars compacta

SNr: pars reticulate

STN: subthalamic nucleus

tDCS: Transcranial direct current stimulation

TpkDx: time to peak displacement

TpkVx: time to peak velocity

TT: toe tapping

UPDRS: Unified Parkinson's Disease Rating Scale

VL: lateral thalamus nucleus

VPL ventral posterolateral thalamic nucleus

VT: ventral thalamus nucleus

W: Walking

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Statement of Contribution of Collaborators

I, Aline Tiemi Kami, hereby declare that I am the sole author of this Master's thesis. The conception and design of these experiments was completed by myself, in collaboration with my thesis supervisor Dr. Anthony Carlsen, and with input from my thesis committee consisting of Dr. Julie Natel and Dr. Diane Ste-Marie. The recruitment of the participants was conducted with the help of Dr. Julie Nantel, and data collection was done in collaboration with Christin Sadler and Jonathan Lommen. Finally, data analysis and statistical analyses were completed by myself under the guidance of Dr. Anthony N. Carlsen, who also provided editorial correction.

CHAPTER I: LITERATURE REVIEW

1. Introduction

Parkinson's disease (PD) is a result of a basal ganglia (BG) dysfunction caused by the death of dopaminergic neurons in the substantia nigra (Dorsey et al. 2007). The death of these neurons leads to dopamine depletion in the striatum causing inhibition of the motor thalamic nuclei and decreased excitation of the cerebral cortex providing difficulties in planning, initiating and executing movement (Berardelli et al. 2001; Burciu and Vaillancourt 2018; Schulz, Gerloff, and Hummel 2013). Moreover, the decrease in brain excitability in people with PD has been the focus on a variety of studies that have employed different techniques to modulate brain excitability, and the use of Transcranial Direct Current Stimulation (tDCS) has shown interesting results regarding motor performance in PD.

Overall, tDCS is a non-invasive brain stimulation technique that has been used to modulate cortical excitability and neuroplasticity in humans (Nitsche and Paulus 2011). Specifically, when tDCS was applied over motor and prefrontal cortex in individuals with PD, improvements in walking speed and bradykinesia symptoms were observed (Benninger et al. 2010). Additionally, when anodal-tDCS was applied over the primary motor cortex (MI), individuals with PD had motor improvements and reduction in RT (Fregni et al. 2006). Carlsen, Eagles, and MacKinnon (2015) showed that in healthy individuals tDCS promoted changes in the excitability when applied over SMA leading to decreased RT, thus suggesting an improvement in the preparatory activation of the motor system. Moreover, studies have shown that the hypoactivation of premotor regions, such as SMA, in individuals with PD are related with difficulties in the preparation and initiation/execution of voluntary movements (Berardelli et al. 2001; Haslinger et al. 2001; Sabatini et al. 2000; Lee, Chang, and

Roh 1999; Roland et al. 1980).

One well-established technique for studying the processes involved in movement preparation and initiation is the startling acoustic stimulus (SAS). In a simple RT task, when the auditory “go” signal is replaced by a loud sound that also elicits a startle reflex (process known as SAS), the voluntary reactions can be speed up. This phenomenon is termed “StartReact” effect, and it is believed to happen due to an involuntary triggering release of the prepared movement (Valls-Solé et al., 1999; Carlsen et al., 2004). Additionally, research using startle paradigm showed that StartReact effect is intact in individuals with PD and associated with improvements in RT and bradykinesia symptom. It was suggested study that the prepared motor program can be released involuntarily by activating the reticulo-thalamo-cortical circuits or by indirect activation through BG (Fernandez-Del-Olmo et al. 2013; Carlsen, Almeida, and Franks 2013).

Therefore, further research is needed to address the potentials benefits that tDCS applied over MI and SMA might provide in terms of preparation and initiation process of the movement in PD. Addressing this issue could help to better understand the involvement of subcortical structures, such as BG and thalamus, and their connection with cortical areas, for instance MI and SMA. Thus, the present literature review will outline the relevant background regarding of movement control, preparation and initiation processes of the movement. Additionally, it will be addressed the mechanisms involved in SAS paradigm as well as what is behind the motor alteration in PD. Lastly, it will be outline the considerations regarding the use of tDCS in PD.

2. Voluntary Movement Control

Motor control is an area of science that defines how the nervous system interacts with other parts of the body and the environment to produce coordinated

movements (Fentress 2001; Latash 2012), and the generation of the movement could involve a series of interacting processes that convert the sensation of the environment into an appropriate motor response (Laczko and Latash 2016). Therefore, it could involve a series of processes that allow the brain to perceive the environment, identify a specific object of interest, determine the action in response to the object, and delivered the appropriate motor command to implement the desired action (Wong, Haith, and Krakauer 2015). Additionally, this information processing could be understood into three stages. *Stimulus Identification*, which involves the detection and identification of a stimulus. *Response Selection*, when the individual decides which response should be best performed based on the stimulus perceived. *Response Programming*, it is a process when the individual prepares and initiates the action (Donders 1969).

Furthermore, the motor cortex controls motor behaviors by generating movement-specific signals in the superior brain areas and transmitting them through spinal cord circuits and motoneurons to the muscles. Among the neural structures involved in the motor function are the upper motor neurons that originate in several brainstem centers and cortical areas in the frontal lobe. However, for the purpose of this study I will be focusing mainly on the primary motor cortex (MI) and the supplementary motor area (SMA). Additionally, the motor areas in the cortex are defined by the fact that all of them send axons to the spinal cord and are interconnected with each other (Rothwell 2012). For instance, the MI and premotor areas in the frontal lobe are responsible for mediating voluntary movements, receiving input from different brain areas such as thalamus, BG and cerebellum, as well as from the somatic sensory regions (Purves et al. 2001b; J.C. Rothwell 2012; Vitrac and Benoit-Marand 2017; Feher 2012; Papale and Hooks 2018).

MI contains a vast array of pyramidal neuron types, organized by cortical layer and projection target, as well as many types of local inhibitory interneurons; it is located in the precentral gyrus and has a somatotopic organization with a disproportionate map of the parts of the body called motor homunculus. This brain area is directly engaged in action generation; thus, it is necessary for the initiation and control of voluntary movement (Feher 2012; Dushanova and Donoghue 2010).

The SMA is located medially in the prefrontal cortex, in front of the MI region, and constitutes the Brodmann's area 6. Moreover, the SMA is divided in two subareas known as the pre-SMA and SMA-proper, which are involved in planning processes and motor execution, respectively (Cona and Semenza 2017; Tanji 1994). Additionally, this premotor area is densely connected with MI (Dum and Strick 2002), BG (Cona and Semenza 2017) and somatosensory areas (Roland et al. 1980).

Other structures that play an important role in motor responses are thalamus and BG, which will be discussed in section 5.1.

Additionally, there are several descending spinal pathways that originate in the brain and in the brainstem. The corticospinal tract (CST) is the largest and most important of these motor pathways and arises from the motor cortex. MI is known to provide the largest contribution to the CST, it comprises about 40% of the neuronal fibers. There is also contribution from the SMA and other premotor areas but in a small proportion (Rothwell 2012). This tract is essential for directing voluntary movements and complex spatiotemporal sequences of movements. It provides finecand precise movement in the voluntary control of distal muscle groups (Sengul and Watson 2015; Rea 2015; Feher 2012).

Other distinct pathways are termed extrapyramidal tracts and originate in brainstem areas such as the medulla and pons and comprise the vestibulospinal,

olivospinal, reticulospinal, rubrospinal, and tectospinal tracts (Rea 2015). In general, they terminate primarily in the medial parts of the gray matter where influence the interneurons that coordinate axial and proximal limb muscles (Schepens, B and Drew, T 2006; Purves et al. 2001a).

Interestingly, it is known that a significant processing capability resides within the reticular formation which can modify and shape motor commands (Baker 2011). One known example refer to the StartReact response (see section 4 for more details) which reflects an involuntary release of a pre-planned movement when an unexpected startle cue is presented (Valls-Solé et al. 1999; Carlsen et al. 2004).

3. Simple Reaction Time – Movement preparation and initiation

In a simple RT paradigm is require from the individual to perform a specific movement as fast as possible following the appearance of an imperative stimulus (IS)/ "go" signal. Moreover, prior to the presentation of the "go" stimulus it is informed which motor response to be performed. The knowledge of the required motor action in advance allows participants to prepare and to respond significantly more quickly. This is done by reducing or eliminating the motor programming that must occur after the IS. Additionally, it has long been thought to directly reflect how long it takes to prepare and initiate a movement (Schmidt et al. 2018; Carlsen, Maslovat, and Franks 2012).

The process of executing a movement in a simple RT task can be separated in two different periods: a) *foreperiod* which is defined as the time between the warning signal and the "go" signal, and it is thought to include preparatory processes; b) *RT interval* – defined as the time after the "go" signal until the initiation of the response, and it is related with movement initiation processes (Kennefick, Maslovat, and Carlsen 2014). Additionally, RT interval can be didactically divided in *premotor RT* which is the period from the presentation of the IS to the appearance of increased muscle firing

identified by the EMG onset, whereas the *motor RT* is the period from the muscle firing to the actual movement response (Botwinick and Thompson 1966).

Because changes in premotor RT is thought to be involved in central processing (Weis 1965), the use of RT paradigm gained particular interest in the study of movement control. Consequently, it has been proposed a neural explanation of how a motor program is prepared and initiated. Therefore, the process of preparation of a given motor action involves the activation of a group of cortical neurons, termed “cell assembly”, that presents increased strength on the synaptic connections to a level below the “ignition point”. Thus, just a certain small input would “activate” the assembly leading to motor output. In particular, activating the corticospinal connections and eventually resulting in movement (Wickens, Hyland, and Anson 1994).

4. Startling Acoustic Stimulus (SAS) – StartReact Effect

Associated with the RT paradigm, SAS has also been used as a tool to investigate the processes underlying how movements are prepared and initiated. It provides a non-invasive way to study the contribution of subcortical structures in these processes. Studies have shown when an auditory “go” signal in a RT task is replaced by a loud sound that elicits a startle reflex, the voluntary reactions can be speeded up. This phenomenon has been termed the “StartReact” effect (Valls-Solé et al. 1999; Carlsen et al. 2004). It is thought that the StartReact effect reflects an involuntary release of a pre-planned motor program when an unexpected startle cue is presented (Carlsen, Maslovat, and Franks 2012; Valls-Solé, Kumru, and Kofler 2008). Interestingly, Carlsen, Maslovat, and Franks (2012) argued that the SAS acts to facilitate RT by quickly and directly increasing the activation of the initiation mechanism via a subcortically mediated ascending pathway, such that the cortically stored response is triggered without the usual cortical processing. For instance,

thalamus could play some role by providing the necessary input to a cortical area to result in response initiation.

Therefore, it is possible that the ascending activation generated by the startle response in the reticular formation directly increases activation of the motor relay nuclei in the thalamus which could trigger an early and involuntary response. Moreover, the motor systems are influenced by ascending reticular activation via reticulo-thlamo-cortical circuits or indirect activation via BG. Increased activation of thalamus would then provide the required input to the cortical cell assembly to trigger the prepared movement (Carlsen, Maslovat, and Franks 2012).

Some indicators can be used to verify if a startle response has occurred. For instance, EMG activity in the orbicularis oculi (OOc) and in the sternocleidomastoid (SCM) have been used for this purpose. However, the use of SCM activity is largely employed and it is considered to be a more reliable indicator, since OOc activation from the blink reflex has been shown to occur following presentation of a loud acoustic stimulus regardless of the presence of a startle response (Brown et al. 1991).

5. Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder in later life, thought to arise from a combination of genetic and environmental factors, and manifests with a broad range of symptoms (Dorsey et al. 2007; Kalia and Lang 2015). It is known that PD results from a BG dysfunction caused by the death of dopaminergic neurons in the substantia nigra leading to functional dopamine depletion in the striatum (Berardelli et al. 2001; Schulz et al., 2013). This low level of dopamine induces functional imbalance between the direct and indirect BG circuits, increasing inhibition of the motor thalamic nuclei and subsequently decreasing the excitation of the cerebral cortex, which could lead to motor dysfunction, for instance difficulties in

planning, initiating and executing movement, and with performing sequential and simultaneous tasks (Burciu and Vaillancourt 2018).

Overall, the motor dysfunction is mainly manifested in four cardinal features such as tremor at rest, bradykinesia, rigidity, and postural instability (Jankovic 2008). However, this study focused specifically on bradykinesia, which refers to slowness of movement and can be associated with poverty of spontaneous movements as well as a decrease in movement amplitude (Berardelli et al. 2001).

Specifically, there are some factors that can potentially contribute to bradykinesia in PD, they can be classified in primary and secondary factors. Although the pathophysiology of bradykinesia is not well understood, the primary factor is attributed to reduced dopaminergic function leading to failure of BG outputs that connects to cortical structures related to preparation and execution of movement commends (Berardelli et al., 2001; Cutsuridis and Perantonis, 2006). It has been shown that the depletion of dopamine on the output of the BG provides hypoactivation of the motor areas which result in increased cellular RT (time from the beginning of the stimulus to the change in the neural activity), delay in premotor reaction time, asymmetric increase in the time-to-peak and deceleration time, increase in movement duration and movement variability (Cutsuridis and Perantonis 2006). Moreover, there is evidence from the investigation of movement preparation showing impairment in RT and movement time in PD (Evarts, Teräväinen, and Calne 1981). There are also secondary factors are muscle weakness, rigidity, tremor, movement variability and bradyphrenia (see Berardelli et al. (2001) for more detailed explanation).

Additionally, freezing has been included among classic features in PD. Freezing episodes, or motor blocks, are a well-known characteristic feature although they do not occur in the same way in individuals with PD. Freezing is described as a sudden,

short, and transient inability to move. Freezing can be frequently observed in the lower limb and is referred to as “freezing of gait” (FOG). For instance, the individuals will present difficulties when starting to walk (start hesitation) or a sudden inability to move the feet when turning or walking in a narrow space, and when approaching a destination (Jankovic 2008). Also, freezing can be observed in the upper limb and is called “freezing of the upper limb” (FOUL). FOUL has been observed during manual coordination tasks such as finger tapping (Ziv et al. 1999) and in a simultaneous contraction of opposite muscle groups in sliding movements (Almeida, Wishart, and Lee 2002). Also it has been reported that FOUL and its associated motor changes are well correlated with FOG, suggesting some shared underlaying motor impairment (Nieuwboer et al. 2009; Vercruysse et al. 2014).

5.1 Parkinson’s Disease Treatment

There are different resources used to minimize PD symptoms. For instance, individuals with PD can benefit from drug therapy, which is usually indicated when the symptoms start to interfere in the patient’s functional, occupational, or social activities. The initial medical therapy can be addressed with levodopa preparations, dopamine agonists, and monoamine oxidase-B inhibitors (Armstrong and Okun 2020). Levodopa is the most common medication for treating PD; specifically, its administration has been related with enhanced connectivity between BG and cortical motor areas leading to improvement in bradykinesia (Gao et al. 2016).

Although drug therapy has been shown to be beneficial for treatment of PD, over time individuals commonly require higher doses that could lead to complications. In long-term use, and as PD progresses, individuals can lose the long-duration response to dopaminergic medication, and the short-duration response decreases due to disease-related pathophysiologic changes in the brain, that also lose the ability to

store extra dopamine for later use (Armstrong and Okun 2020).

In general, long-term individuals with PD can experience a “wearing off” phenomenon or dyskinesias. The wearing off effect occurs between doses and it is defined by worsening of the PD symptoms and functional disability. Dyskinesia presents as involuntary movements that often occur at peak medication concentrations (Homayoun 2018); (Gao et al. 2016; Armstrong and Okun 2020).

Deep brain stimulation (DBS) has been incorporated in the treatment of PD as an adjunctive therapy. This treatment involves a surgical placement of electrodes and leads that are attached to a subdermal battery usually placed in the chest, similar to a pacemaker battery. DBS provides a chronic electrical stimulation of the brain, more specifically in subcortical structure such as subthalamic nucleus or the globus pallidus internal (Herrington, Cheng, and Eskandar 2016). Treatment with DBS has proved to provide motor benefits in advanced PD, while reducing dyskinesias and motor fluctuations (Obeso et al. 2001; Rizzone et al. 2014), as well as improvement in quality of life (Dafsari et al. 2018). Although DBS has been shown to provide important benefits in PD, there is a high monetary cost involved and a significant incidence of adverse effects has been associated such as high rate of mortality and morbidity post-surgery. Additionally, the spread of the stimulation to adjacent areas may alter mood state, intensify depression, as well as provide cognitive decline (Rizek, Kumar, and Jog 2016; Umemura et al. 2016).

Lastly, treatments associated with anti-parkinsonian medication and DBS, include rehabilitation therapies such as: exercise programs, physiotherapy, occupational therapy and speech therapy. These therapies can assist in maintaining or improving different motor aspects of PD. Specifically, exercise appears to act by promoting an activity-dependent neuroplasticity when incorporated with parameters

such as intensity, repetition, specificity, difficulty, and complexity of practice (Petzinger et al. 2013). Additionally, rehabilitation therapies have proved to be effective in addressing symptoms such as balance, FOG, gait, cognition, and quality of life (Armstrong and Okun 2020; Ferrazzoli et al. 2018; Petzinger et al. 2013).

5.2 Basal Ganglia Circuitry

Specifically, basal ganglia refers to a set of nuclear structures located deep within the cerebral hemispheres. This group of nuclei is important for the motor function and includes the striatum consisted by caudate nucleus (CN) and putamen (Put), and the globus pallidus with the external (GPe) and internal (GPi) segments. Moreover, this group of nuclei also includes the substantia nigra pars compacta (SNc) and pars reticulata (SNr), as well as subthalamic nucleus (STN). There are observed output connections with the thalamus, more specifically with the ventral (VT) and lateral (LT) segments (Purves et al. 2001a; Groenewegen 2003; Parent and Hazrati 1995; Galvan and Wichmann 2008). Moreover, the BG is involved in input, output, and intrinsic connections. Input function refers to the incoming information from the cortex and thalamus to the striatum. Intrinsic function consists of the connections between the input and output function and include the participation of GPe, STN and SNc. Finally, GPi and SNr play a role in the output function sending BG information to the thalamus (Parent and Hazrati 1995; Lanciego, Luquin, and Obeso 2012).

Moreover, these connections between the input and output structures consist of the direct and indirect pathways (Galvan and Wichmann 2008). Additionally, the appropriate functioning of the BG system requires dopamine to be released from the SNc. For instance, the direct pathway carries dopamine D1-receptors which provides facilitation and has projection towards GPi/SNr, while the indirect pathway carries D2-receptors with inhibitory function, first projecting to the GPe and STN, then to the GPi

(Lanciego, Luquin, and Obeso 2012; Groenewegen 2003). In addition, the direct pathway plays a role inhibiting the GPi activity, which provides an excitation of the thalamo-cortical connection, which results in facilitation of movement. On the other hand, the indirect pathway inhibits the GPe neurons, followed by disinhibition of the STN, which then excites GPi, resulting in increased inhibition of thalamo-cortical neurons (Lanciego, Luquin, and Obeso 2012). Dopamine depletion reduces the facilitation in the direct pathway and increases the activation of indirect circuit neurons. These changes lead to increased activity of the STN which over-activates inhibitory output neurons in the GPi/SNr, thus reducing the cortical excitability and depleting the movement initiation and execution (Parent and Hazrati 1995; Lanciego, Luquin, and Obeso 2012).

5.3 SAS and Parkinson's Disease

Some studies have shown that SAS can be used to probe motor preparatory states in PD individuals. Fernandez-Del-Olmo et al. (2013) investigated the effects of startle and non-startle stimuli comparing healthy participants and individuals with PD in a simple wrist flexion RT task. These authors found that the StartReact effect for the upper limb movement was unimpaired in PD patients, since there was no significant difference in RT between the healthy and PD group. Moreover, in the PD group it was found that the startle and non-startle stimuli had different RT responses. When startle stimulus was presented, PD patients were able to reduce their RT, thus improving their preparatory and initiation process of the movement. Others have indicated the same, Carlsen, Almeida, and Franks (2013) investigated the underlying mechanisms of bradykinesia in PD integrating SAS in an elbow extension RT task. They found that in individuals with PD (whether ON or OFF anti- parkinsonian medication) a SAS was able to involuntarily release the pre-prepared motor response,

leading to a reduction in their RT and decreasing the bradykinetic symptoms of the movement. They concluded that PD patients were able to fully program the response in advance, suggesting that SAS may act as a synthetic response initiation mechanism that activates an ascending reticulo-thalamo-cortico circuit that leads to facilitate the M1.

6. Transcranial Direct Current Stimulation (tDCS)

As a result of the dysfunction in the BG circuitry, bradykinesia symptoms in individuals with PD may stem from a chronic inhibition or hypoactivation of the motor cortex. Studies have employed various techniques to increase brain excitability in individuals with PD, and the use of tDCS has shown positive results regarding motor performance. tDCS is a non-invasive brain stimulation technique that has been used to modulate cortical excitability and neuroplasticity in humans (Nitsche and Paulus 2011). Anodal stimulation leads to tonic hyperpolarization (excitation) of the stimulated brain area, whereas cathodal stimulation results in hypopolarization (inhibition) (Nitsche and Paulus 2000). By applying a low-amplitude direct current through the skull via scalp electrodes, it is thought that tDCS modifies neuronal transmembrane potentials, thereby influencing the levels of excitability and modulating the firing rates of individual neurons. Moreover, it regulates behavioral dysfunctions, such as those seen in PD patients, by modifying the activity of the excited cortex (Li et al. 2015).

In addition, cortical stimulation may induce changes throughout a distributed cortico-subcortical network that connects with and positively affects BG function (Nonnekes et al. 2014). In a study conducted by Benninger et al. (2010), anodal tDCS (2mA for 20 minutes) was applied over the motor and prefrontal cortex in individuals with PD, and they assessed participants using a timed 10m walk test, sequential timed testing of hand and arms in order to assess bradykinesia, as well as the Unified

Parkinson's Disease Rating Scale (UPDRS) over eight sessions. The authors found that following anodal-tDCS, walking speed improved for up to a month in the ON-medication state, there was a significant decrease in sequential timed test for bradykinesia symptoms in OFF-state, but there was no effect for the total score of UPDRS III.

Another study compared the use of anodal and cathodal-tDCS over MI and dorsolateral prefrontal cortex (DLPFC) in PD individuals (Fregni et al. 2006). Following stimulation participants underwent to a functional motor performance testing, including the UPDRS, a simple RT task, and a Purdue Pegboard test (PPT). The results indicated that following anodal-tDCS over MI there were motor improvements in the UPDRS III score and in a simple RT task as compared to anodal DLPFC stimulation and sham-stimulation. It was explained that when tDCS (anodal) is applied over M1, it might induce an increase in the activity of the ventral posterolateral thalamic nucleus (VPL), which could be responsible for the release of neurotransmitters (Fregni et al. 2006).

Recently, the use of tDCS applied over SMA in healthy controls has been investigated. It was shown that anodal-tDCS leads to improvements in motor performance and behavior. Anodal and cathodal-tDCS was applied over the SMA in healthy control subjects before completing a simple wrist extension RT task, and the results showed that cathodal-tDCS over the SMA led to slower RT while anodal- tDCS led to faster RT. These results suggest that changing SMA excitability led to increased or decreased preparatory activation of the motor system in healthy controls (Carlsen, Eagles, and MacKinnon 2015).

Many studies have implicated hypoactivation of premotor regions such as the SMA in PD individuals (Berardelli et al. 2001; Haslinger et al. 2001; Rascol et al. 1994;

Sabatini et al. 2000), which play a role in the preparation and initiation/execution of voluntary movements (Lee, Chang, and Roh 1999; Roland et al. 1980). This impaired activation of the SMA in PD individuals could account for the difficulties shown in the initiation of voluntary movements (Playford et al. 1992). In order to combat this hypoactivation, non-invasive brain stimulation could be used over the affected area to provide the additional stimulus needed to increase cortical excitability and ameliorate deficits in RT.

7. Research Objectives and Hypothesis

In light of the findings presented above and the lack of studies exploring the use of tDCS applied over the SMA in PD, it is worthwhile to investigate potential benefits of tDCS on this brain area to facilitate preparation and initiation of the movement program in this population. The findings from a pilot study involving individuals with PD in our laboratory did not show changes in premotor RT after anodal- tDCS during an elbow extension RT task when a “typical” intensity auditory stimulus (80dB) was provided; however, improvements in kinematic measures, such as movement time, time to peak velocity, and time to peak displacement were observed (Kami et al. 2018). It was suggested that the null effect of tDCS in the premotor RT could have been because participants did not prepare in advance to perform the task, or maybe participants had difficulties to perform the task, thus compromising the RT performance. Therefore, in this present experiment we included a second (simpler) RT button-press task, to verify if complexity of the RT task might interact with the tDCS effects in preparation and initiation processes of the movement.

Furthermore, although the benefits of tDCS applied over MI in improving motor impairment of people with PD have been shown, there is limited evidence in regard to how application of tDCS over MI interacts with presentation of a SAS regarding the

preparation and initiation processes of the movement. It is possible that tDCS applied over SMA affects primarily subcortical structures such as BG, thus the stimulation of the brain area would lead to improvement in the level of preparation and initiation of the pre-planned movement.

Additionally, the inclusion of the SAS paradigm in this experiment combined with tDCS derived from the results found in the previous pilot study already mentioned (Kami et al. 2018). As showed earlier, tDCS over SMA of individual with PD did not improve RT performance in a typical simple RT task. We thought that maybe adding a SAS (which is known to involuntarily engage the subcortical circuitry associated with movement initiation) would optimize the effect of tDCS on those circuits. Specifically, because those subcortical initiation circuits would be forced to be used for initiation by the SAS, the tDCS might have some impact on those “active” circuits.

Therefore, the aim of this study was to investigate whether tDCS applied over MI and SMA facilitates the motor preparatory and initiation process in individuals with PD when the task involves the presentation of a SAS. Moreover, we were also interested to verify if bradykinesia and kinematic measures would be affected by tDCS. It was hypothesized that anodal-tDCS applied over MI and SMA would lead to changes in premotor RT in PD. Because of the different neural connections of these two motor areas with subcortical structures, more specifically with the BG circuit, we expected to see different responses in premotor RT depending on the site of the application of tDCS. Specifically, it was expected that tDCS over SMA would provide faster RT performance stemming from improvements in movement preparation and initiation, since it is well reported that SMA plays a role in these processes involving the movement whereas MI appears to be more related to movement execution.

It was also hypothesized that in SAS condition individuals with PD would be

able to release the pre-programmed movement in shorter latencies compared with control condition (non-SAS condition). Since it is shown that StartReact effect in PD is intact, it was expected that although SAS is involved in engagement of subcortical circuitry related to preparation and initiation of the pre-planned movement, RT performance and movement time in SAS condition would not be largely impacted by anodal-tDCS. Lastly, we hypothesized base on the literature that tDCS would provide improvements in bradykinesia and kinematics measures.

CHAPTER II: RESEARCH PAPER

Transcranial Direct Current Stimulation applied over Supplementary Motor Area facilitates motor preparatory and initiation processes in Parkinson's Disease

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Abstract

Parkinson's Disease is a slowly progressive process that results from a basal ganglia (BG) dysfunction caused by the death of dopaminergic neurons in the substantia nigra leading to decrease in excitation of the cortex, which can provide difficulties in planning, initiating, and executing movement. One technique for studying movement preparation and initiation is the Startling Acoustic Stimulus (SAS), which has been associated with changes in movement processing in PD. Additionally, Transcranial direct current stimulation (tDCS) has been used to modulate cortical excitability and neuroplasticity in humans, providing a potential method to improve motor performance in PD. The purpose of this experiment was to investigate the potential benefits of tDCS applied over the primary motor area (MI) and supplementary motor area (SMA) associated with SAS paradigm to improve preparation and initiation of the movement in PD. Eleven individuals with PD completed two simple reaction time (RT) tasks, a button-press task (BU) and an elbow extension task (EX), and underwent to bradykinesia assessment. Three tDCS sessions (Anodal-MI; Anodal-SMA; Sham) were considered. In the BU and EX, a main effect for stimulus condition was observed (Control vs. SAS) indicating that RT was faster in SAS condition in all tDCS session. Additionally, in the EX, it was also showed a main effect for time (pre- vs. post-tDCS) along with an interaction between time and tDCS session. Post-hoc tests revealed that the premotor RT was significantly reduced following anodal-tDCS over SMA only in control condition. In kinematic outcomes, it was observed only a main effect of stimulus condition in movement time and in time to peak displacement with no interaction effect suggesting that participants had faster execution of the movement in SAS condition, but regardless tDCS session. There were no differences in the clinical measure of bradykinesia assessed by the seven items from UPDRS, since no differences were observed between the three tDCS sessions. Together, the results reinforce previous findings indicating that following a SAS, individuals with PD are able to elicit the prepared motor response in significantly shorter latencies, and movement time and time to peak displacement were improved regardless type of tDCS session. Additionally, it is also observed that premotor RT was facilitated by tDCS applied over the SMA in control condition. This is indicative that any potential increase in cortical excitability induced by tDCS was able to promote changes in the neural tissue which might have influenced the activation of structures and pathways involved in preparation and initiation – in particular, a basal ganglia- thalamo-cortical pathway. It is suggested that the stimulation of the SMA with anodal-tDCS associated with simple RT task as strategy can improve upper limb preparatory and initiation processes of voluntary movement in patients with PD.

Keywords: Parkinson's disease, supplementary motor area, tDCS, movement preparation.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder in later life, a slowly progressive process that is the result of a basal ganglia (BG) dysfunction caused by the death of dopaminergic neurons in the substantia nigra. It is thought to arise from a combination of genetic and environmental factors, and manifests with a broad range of symptoms (Dorsey et al. 2007; Kalia and Lang 2015). The death of these neurons leads to dopamine depletion in the striatum causing inhibition of the motor thalamic nuclei and decreased excitation of the cerebral cortex, providing difficulties in planning, initiating and executing movement (Berardelli et al. 2001; Schulz, Gerloff, and Hummel 2013; Burciu and Vaillancourt 2018). Additionally, the motor impairment is mainly manifested in four cardinal symptomatic features: tremor at rest, rigidity, postural instability, and bradykinesia (Jankovic 2008). One of the most debilitating characteristics of PD is bradykinesia, which is defined as slowness of movement and can be associated with poverty of spontaneous movements as well as to decrease in movement amplitude (Berardelli et al. 2001).

Moreover, as a result of dopamine depletion in the substantia nigra, an inhibition or hypoactivation of central motor areas, such as the primary motor cortex (MI) and the supplementary motor area (SMA) is expected (Berardelli et al. 2001; Haslinger et al. 2001; Sabatini et al. 2000). Thus, in order to help with hypoactivation in cortical areas, non-invasive brain stimulation methods have been employed. Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique that has been used to modulate cortical excitability and neuroplasticity in humans (Nitsche and Paulus 2011). Specifically, studies have shown that when tDCS was applied over MI in PD patients, motor improvements were observed, including a reduction in simple reaction time (RT), as well as clinical improvement as measured

using the UPDRS motor section (Fregni et al. 2006). In addition, following tDCS, improvements in gait have been observed (Costa-Ribeiro et al. 2016), as well as improvements in bradykinesia, as assessed by a sequential timed test of hand and arm (Benninger et al. 2010), and decreases in incidence of upper limb freezing (Broeder et al. 2018). Additionally, when tDCS was applied over SMA in healthy individuals, changes in excitability led to decreased RT, suggesting an increased preparatory activation of the motor system (Carlsen, Eagles, and MacKinnon 2015).

Studies have suggested that hypoactivation of premotor areas, such as SMA, in individuals with PD may be the root cause of difficulties in the preparation and initiation of voluntary movements (Berardelli et al. 2001; Haslinger et al. 2001; Sabatini et al. 2000; Lee, Chang, and Roh 1999; Roland et al. 1980). RT tasks have long been used to infer motor preparation and programming in humans (Donders 1969); however, recent studies have looked at the use of a startling acoustic stimulus (SAS) to involuntarily trigger movement initiation (Carlsen et al. 2004). When an auditory “go” signal is replaced by a loud sound (>120dB) and also elicits a startle reflex, the voluntary reactions can be speeded up. This phenomenon is termed the “StartReact” effect, and it is thought to release a pre-programmed motor response without the usual cortical trigger (Valls-Solé et al. 1999; Carlsen et al. 2004). Studies have shown that the StartReact effect is unaffected in individuals with PD (Valldeoriola et al. 1998), and can reduce RT and decrease bradykinesia, suggesting that a motor program can be released involuntarily by activating subcortical reticulo-thalamic circuits or by indirect activation through BG (Fernandez-Del-Olmo et al. 2013; Carlsen, Almeida, and Franks 2013).

Therefore, the aim of this study was to investigate whether tDCS applied over MI and SMA facilitates the motor preparatory and initiation process in individuals with

PD when the task involves the presentation of a SAS. Moreover, we were also interested to verify if bradykinesia and kinematics measures would be affected by tDCS. It was hypothesized that anodal-tDCS applied over MI and SMA would lead to changes in premotor RT in PD. Because of the different neural connections of these two motor areas with subcortical structures, more specifically with the BG circuit, we expected to see different responses in premotor RT depending on the site of the application of tDCS. Specifically, it was expected that tDCS over SMA would provide faster RT performance leading to improvements in movement preparation and initiation, since it is well reported that SMA play some role in the preparation processes of the movement whereas MI is related with movement execution. It was also hypothesized that in SAS condition individuals with PD would be able to release the pre-programmed movement in shorter latencies compared with control condition (non-SAS condition). Specifically, since it is shown that StartReact effect in PD is intact, it was expected that although SAS is involved in engagement of subcortical circuitry related to preparation and initiation of the pre-planned movement, RT performance and movement time in SAS condition would not be largely impacted by anodal-tDCS. Lastly, we hypothesized base on the literature that tDCS would provide improvements in bradykinesia and kinematics measures.

2. Methods

2.1 Subjects

A power calculation using GPower 3.1.9.2 was used to determine the sample size. Based on a previous study (Carlsen et al., 2015), an effect size (partial eta squared) of .236 for RT differences following anodal-tDCS was used. The power calculation was performed with an F-test involving repeated measures, within-factors effects which gave us an effect size of f = 0.555. The sample size calculation

using an alpha = .05, power = .8, and correlation among repeated measures = .5 indicated that a sample size of 8 would be adequate.

Eleven participants (7 males and 4 females; mean age: 63.45 years, SD: 7.23 years) with idiopathic PD that volunteered to participate in the study were included and tested while “ON” their normal anti-Parkinson's medication. Initially, participants underwent to an assessment with UPDRS III to verify the severity of the disease and FOG questionnaire to identify the presence of freezing. The initial assessment was performed by an experienced professional.

In the motor section of the UPDRS each item has a score range from 0 to 4, where zero is defined as normal and a score of four indicates that the individual can barely perform the task. For the purpose of this study participants were included only if they presented mild impairment characterized by scores from 0 to 2 in the items of the UPDRS motor section which could give a possible total score of 48 points (Williams et al. 2007; Perlmutter 2009). This score range was considered in order to control for cognitive impairment, since it is well reported in the literature the association of moderate and severe motor symptoms with cognitive impairment in PD (Poletti et al. 2012; Aarsland et al. 2004).

Participants were excluded from the study if they were being treated with deep brain stimulation (DBS), had presence of FOG on day of the sessions (since there is a well reported association of FOG with FOUL), had dyskinesias, significant tremor in the upper limb tested (to prevent EMG signal disturbance), had a significant visual or hearing impairment, or any upper body abnormalities that could affect their performance during the RT tasks. Participants’ demographic data is shown in Table 1.

This is a double-blind, randomized crossover, sham-controlled experiment. The sequence of the brain area to be stimulated (MI and SMA) was randomly assigned as

well as the type of stimulation (anodal and sham). The randomization was performed using the *random.com* website and the sequence condition for each participant was allocated in a sealed opaque envelope. Six possible orders existed, considering the three stimulation conditions (anodal-M1, anodal-SMA and sham), then the function random integer set generator was used from the website. Fifteen sets were requested with one unique random integer in each, taken from the [1, 6] range. An external researcher collaborated with the randomization set up. All participants were naïve to the type of stimulation received and asked to provide a written informed consent after receiving a comprehensive description of all protocols. Additionally, one researcher was responsible for the application of tDCS and another for the assessment of the participants who was also naïve to the brain area stimulated in the sessions. All protocols related to the present study were approved by the research ethics board (REB) of the University of Ottawa before the commencement of the project.

Table 1. Participant characteristics.

Subject	Age	Genre	Diagnostic (years)	Upper Limb dominant	Upper Limb less affected	Total UPDRS III
1	48	F	2	R	L	8
2	60	M	7	R	R	4
3	60	M	3	R	R	8
4	64	F	8	R	L	8
5	57	F	14	R	L	9
6	73	M	2	R	L	0
7	71	M	11	R	R	13
8	69	M	14	R	R	13
9	61	F	7	R	L	7
10	67	M	4	R	R	8
11	68	M	16	R	R	10

Note: F: female, M: male, R: right, L: left.

2.2 Procedures

a) Bradykinesia – Functional Assessment:

Bradykinesia was assessed pre- and post-tDCS in each tDCS-session using seven items selected from the original motor section of the MDS-UPDRS. The items were selected in order to assess any potential impact of tDCS in the upper limb. The related upper limb motor tasks included: finger tapping (FT), hand movement (HM), pronation and supination (PS). In addition, in order to verify for additional effects of tDCS on bradykinesia, toe tapping (TT), leg agility (LA), body bradykinesia (BB) and walking (W) items were assessed as well. A maximum total score of 48 points could be possible, this would include the sum of the seven items for right (R) and left (L) upper limbs as followed:

TOTAL SCORE = FTR + FTL + HMR+ HML+ PSR + PSL + TTR + TTL + LAR + LAL + BB + W.

The researcher responsible for applying the partial-UPDRS was trained by an experienced professional, and the scores of the first five participants were compared between the researcher and the experienced professional to ensure similar ratings.

b) Premotor RT - Simple RT tasks Apparatus

Participants were seated upright in a comfortable chair, approximately 1 meter from a 24 inches LCD computer screen. Using the less affected upper limb, participants were asked to perform two simple RT tasks.

The first task, the button-press task (BU), consisted of pressing a telegraph key (Ameco AM-K4B) fixed at 30cm in front of the participant with the hand resting on top of the key (Figure 1A). For the second task, extension of the elbow (EX), participants grasped a handle of a custom-made aluminum manipulandum that moved in the horizontal plane with an axis of rotation about the elbow. The home position was set

at 90º flexion of the elbow with the shoulder flexed and abducted 30º (Figure 1B). Participants were instructed to perform a targeted 20º extension movement of the elbow from the home position to a target shown on the screen (Figure 1C). This external cue was provided only for the EX to ensure a pattern of the movement and completion of the 20º extension movement of the elbow.

For both tasks the participants were asked to react as fast and accurately as possible in response to an auditory go-signal. A warning “Get Ready” signal was presented, and a computer program generated the imperative “go” stimulus. On control (non-SAS) trials the stimulus was a 1 kHz tone (100 ms duration) with an intensity of 80 dB. On SAS trials the stimulus was broadband (20 Hz – 20,000 Hz) white noise pulse (25 ms) with an intensity of 120 dB. The warning signal was delivered by a computer speaker and the imperative stimulus was generated with digital to analog hardware (National Instruments PCIe-6321), and amplified and presented by a loudspeaker (MG Electronics M58-H, frequency response 300 Hz - 11 kHz, rise time <1 ms) located 30 cm behind the participant, as measured on an individual basis from the opening of their auditory canal. Stimulus intensity was confirmed using a precision sound level meter (Cirrus research CR:162C).

Following the movement, participants received feedback regarding their RT for each trial and for both tasks. This information was displayed for 3500ms until the beginning of the next trial. A customized LabVIEW (National Instruments Inc.) program controlled the timeline for each trial, as well as the display of RT information to the participant.

To start each session, participants underwent the seven motor tasks from the UPDRS motor section described above. Next, they were asked to perform one block of 10 practice trials followed by one block of 20 trials for the BU task. Participants then

performed 10 practice trials followed by one block of 20 trials for the EX task. In each task, the block of 20 trials consisted of 15 control (non-startle) trials, and five SAS trials pseudo-randomly dispersed amongst the control trials, where no two consecutive trials nor the first three trials were SAS trials. This randomization of SAS trials is necessary to control for startle response habituation and to provide the unexpected condition for the participant (Carlsen, Maslovat, and Franks 2012).

A two minutes rest period was provided between the tasks. After the completion of the two simple RT tasks, anodal tDCS was applied over MI or SMA, or sham. Finally, after the stimulation participants were reassessed with the seven motor tasks/UPDRS and performed the two RT tasks again for post-testing comparisons.

2.3 tDCS Protocol

Two electrodes were placed on the scalp of the participants, which provided stimulation to the desired brain area. In each participant the midpoint between the nasion and inion, and the left and right preauricular notches were identified (position Cz in the international 10-20 system). In order to stimulate MI, the “active/anodal” electrode, a flexible carbon electrode inside of a sponge electrode (35cm^2), was positioned over motor cortex by measuring four centimeters laterally (contralateral to the tested limb) and one centimeter anteriorly and marking this location. For SMA stimulation, the active electrode was positioned directly above the spot defined with 1.8 cm anterior to the measured Cz location. The location of the SMA has also been previously confirmed with the use of transcranial magnetic stimulation (Müri, Rösler, and Hess 1994). For the sham condition the “active” electrode was placed 2cm backwards from the Cz location. Another flexible carbon electrode inside of a sponge electrode (35cm^2) was placed over the centre of the forehead directly above the eyebrows as a “negative/cathode” electrode (Figure 2).

The Soterix Medical 1x1 tDCS Model 1300A Low-Intensity Stimulator was used to deliver the low-level electrical current set at an intensity of 1.5mA applied for 10 minutes for anodal-MI (A-MI) and anodal-SMA (A-SMA). For sham stimulation, the auto-sham function was selected at the device. It was similar to the anodal condition, except that once the stimulation device ramped up to 1.5mA (about 30 seconds) the current was turned OFF, without the participant's awareness. Therefore, some participants might have felt an initial sensation of the stimulation, but they did not receive active tDCS for the rest of the stimulation period. The stimulation sessions (A-M1, A-SMA, and sham) were conducted with at least 48 hours apart to ensure a complete washout of any residual tDCS effects. Moreover, the post-testing was performed right after the brain stimulation (Molero-Chamizo et al. 2018).

2.4 Data Acquisition

A wireless surface electromyographic (EMG) system (Delsys Trigno) was used to capture the muscle activity. Data was collected from lateral head of the triceps brachii, biceps brachii and fingers/wrist flexors muscles in the less affected side for the premotor RT recordings. For the startle response, EMG was collected from the sternocleidomastoid muscle (SCM) contralateral to the upper limb tested. The surface electrodes were placed in the middle of the muscle bellies and aligned parallel to the muscle fibers and was attached with double-sided adhesive strips. Before the application of the electrodes, the skin surface above the recording sites was cleaned with conductive gel and alcohol swabs in order to decrease electrical impedance. Raw band passed (20-400 Hz) EMG data was digitally sampled at 4000 Hz using a customized LabVIEW program and stored for offline analysis. Data collection was initiated by the computer for each trial 1s prior to presentation of the imperative "go" stimulus and continued for 3s.

2.5 Data Reduction and Analysis

Premotor RT for BU and EX were the primary dependent variables, they were defined as the time between the auditory go-signal and the EMG burst onset of the finger/wrist flexors in BU, and of the triceps muscle in EX. EMG burst onset for all muscles was defined as the point where EMG activity reached two standard deviations above baseline level and remained elevated for at least 20ms. EMG offset was measured and defined as the point where EMG activity dropped below 20% of its maximal amplitude reached in that EMG burst. EMG traces were displayed on a computer monitor along with EMG onset and offset markers computed using a custom LabView algorithm and then manually adjusted to correct for any possible errors due to the strictness of the algorithm. In addition, peak EMG amplitude was defined as the greatest EMG amplitude that occurred within 100 ms of EMG burst onset.

Furthermore, SAS trials with no discernible SCM activation were discarded, as this is considered to be a robust and reliable indicator that a startle reflex was elicited (Carlsen, AN et al. 2007). SCM activation was defined as a SCM burst (see above for EMG burst onset detection criteria) occurring within 50-120 ms of presentation of a SAS. Once these trials were discarded, the startle trials where SCM activation (SCM+) was presented were analyzed, and participants who showed SCM activation on less than 50% of startle trials were excluded from data analysis. In addition, trials where participants anticipated the go-signal or did not pay sufficient attention to the task, indicated by RTs faster than 50 ms or slower than 350 ms, respectively, were discarded as well. A total of 133 trials were discarded out of 2640 trials, 43 trials were due to anticipation, 10 trials slower RT, 40 trials movement error (interrupted movement extension, multiple button presses, no movement), 40 trials with no SCM activity on startle trials.

Kinematic variables were only analyzed from EX task as the button press involved limited ability to assess kinematic variables due to its nature. For the EX task, kinematic variables included peak velocity (pkVx), time to peak velocity (TpkVx), peak displacement (pkDx), time to peak displacement (TpkDx), and movement time (MT). Peak velocity was defined as the maximum angular velocity achieved prior to reaching peak displacement. Time to peak velocity was the time between the movement onset and the peak velocity. Peak displacement was set as the maximum angular displacement attained between movement onset and movement final position. Time to peak displacement was the time between movement onset and peak displacement. The final position was defined as the first point at which angular velocity decreased below 8 deg/s and remained for at least 150 ms. Finally, movement time was defined as the time between movement onset and final position. Movement onset was identified as the first point of change of more than 0.2 degrees of angular displacement from the home position following the “go” signal.

For statistical analysis, the normality of the data was verified by the Shapiro-Wilk test. For premotor RT and kinematic variables, significant differences were established using Repeated Measures ANOVA considering 3 tDCS session (A-MI/A-SMA/Sham) x 2 acoustic stimulus condition (Control/SAS) x 2 time (pre stimulation/post stimulation). For bradykinesia score significant differences were analyzed using Repeated Measures ANOVA considering 3 tDCS session x 2 time conditions, considering the total score of the seven items tested, also a sub-score including the 3 upper limb items (FT, HM, PS) was analyzed to determine if improvements were limited to the upper limbs. All statistical analyses were performed using SPSS and the significance value was set at $p < .05$. Post-hoc Tukey’s HSD tests were conducted to analyze significant interaction effects.

3. Results

3.1 Premotor RT

Premotor RT was analyzed in each of the two simple RT tasks to determine if differences existed between tDCS sessions (A-MI vs. A-SMA vs. sham), stimulus conditions (Control vs. SAS), as well as between time (pre tDCS vs. post tDCS).

3.1.1 Button-Press Task (BU)

No main effect or interactions reached the level of significance for stimulation session or time. However, a large main effect was observed between stimulus conditions, $F (1, 10) = 72.937$, $p < .00001$, $\eta^2_p = .879$, where premotor RT was shorter when a startle cue was presented (see Figure 3).

3.1.2 Elbow Extension Task (EX)

Similar to the BU task, a large main effect was observed for stimulus condition, $F (1, 10) = 108.103$, $p < .00001$, $\eta 2p = .915$. Additionally, a main effect was seen for time, $F (1, 10) = 6.487$, $p = .029$, $\eta 2p = .393$ along with an interaction between time and tDCS session, $F (2, 20) = 5.305$, $p = .014$, $\eta 2p = .347$. The Post- hoc analyses revealed a significant difference only between pre- and post-tDCS in the SMA session for control condition, suggesting that the premotor RT was significantly reduced following tDCS over SMA (pre-tDCS RT mean: 252ms; post-tDCS RT mean: 208ms). Considering this result, additional comparisons were performed. There were significant differences in control condition between MI post-tDCS (RT mean: 236ms) and SMA post-tDCS (RT mean: 208ms), and between Sham post-tDCS (RT mean: 241ms) and SMA post-tDCS. No interaction existed for stimulus condition and tDCS session, $F (2, 20) = .485$, $p = .623$, $\eta 2p = .046$ (see Figure 4).

3.2 Kinematic Measures

Kinematic variables were analyzed using 3 (tDCS session) x 2 (stimulus condition) x 2 (time) RM ANOVAS to determine whether differences existed, and the data are presented in Figure 5. No main effects or interactions were observed for tDCS session or time in movement time, time to peak displacement and time to peak velocity. However, a main effect for acoustic stimulus condition was observed in movement time, $F (1, 10) = 14.740$, $p= .003$, $\eta^2_p = .596$, and for time to peak displacement, $F (1, 10) = 12.055$, $p= .006$, $\eta^2_p = .547$.

3.3 Bradykinesia Score – Functional Assessment

The bradykinesia score of the seven motor tasks (total) and of the three upper limb tasks from the UPDRS were analyzed using a 3 (tDCS session) x 2 (time) RM ANOVA to determine whether differences in the bradykinesia symptoms existed pre- and post-anodal tDCS. No main effect for tDCS session, $F (2, 20) = .015$, $p= .986$, $\eta^2_p = .001$, and no interaction involving tDCS session were observed, $F (2, 20) = 261$, $p= .773$, $\eta^2_p = .025$. However, a main effect was seen for time, $F (1, 10) = 5.985$, $p= .034$, $\eta^2_p = .374$. In order to verify any specific effect of tDCS in the upper limb, the score of the FT, HM, and PS were analyzed. No main effect for tDCS session, $F (2, 20) = .718$, $p= .500$, $\eta^2_p = .067$, and no interaction involving tDCS session were observed, $F (2, 20) = .766$, $p= .478$, $\eta^2_p = .071$, but a main effect for time was seen, $F (1, 10) = 6.675$, $p= .027$, $\eta^2_p = .400$ (see Figure 6).

4. Discussion

The primary aim of the present study was to carefully examine whether initiation and execution of a voluntary movement in individuals with PD could be modulated by anodal tDCS, and whether any interaction existed between the effect of tDCS and

presentation of a SAS. It was observed that RT was significantly shorter following tDCS applied over SMA, but not over MI, and only for the elbow extension task in control condition. In addition, in both RT tasks, participants were able to elicit the pre-planned movement at shorter latencies in the SAS condition in all tDCS sessions, but no interaction between tDCS and SAS existed. The results of the present study suggest that activation levels related to preparatory and/or initiation processes underlying the movement during the elbow extension task can be improved following anodal-tDCS over the SMA. Finally, there were no differences in the clinical measure of bradykinesia assessed by the seven items from the UPDRS, since no differences were observed between the three tDCS sessions.

4.1 Effect of SAS

Similarly, to other studies, in the present experiment participants were able to release the pre-planned movement in a shorter period when a SAS was provided in both RT tasks for all tDCS sessions. This finding reinforces previous results showing that the neural pathway used in the StartReact response is intact in PD. However, the current data extend these findings to show that this pathway is not influenced by tDCS. Fernandez-Del-Olmo et al. (2013) investigated the effects of startle (SAS) and control (non-startle) conditions comparing a healthy group to a PD patient group in a simple wrist flexion RT task, and found that the StartReact effect for the upper limb movement was unimpaired in individuals with PD. This was assumed since there were no significant differences in SAS-elicited RT between the healthy and PD groups. Moreover, when comparing within the PD group, the authors found that RT in the startle and non-startle conditions were statistically different, showing that when SAS was presented the PD group was able to reduce their RT. Additionally, Carlsen, Almeida, and Franks (2013) investigated the underlying mechanisms of bradykinesia

in individuals with PD in an elbow extension RT task using the SAS paradigm as well. They found that PD patients (whether ON or OFF anti-parkinsonian medication) were able to involuntarily release the motor response prepared in advance leading to a reduction in the premotor RT and decreasing the bradykinetic symptoms in SAS condition. Together, these results suggest that the preparatory processes were intact, and the initiation processes were improved by the SAS leading to earlier release of the motor program.

Interestingly, one of the hypothesized mechanisms involved in the RT facilitation by a SAS suggests that SAS acts by quickly and directly increasing the activation of the initiation process via a subcortically ascending pathway, such that the cortically stored response could be triggered without the usual cortical processing (Carlsen, Maslovat, and Franks 2012). That is, the pathway for a startle response involves the activation of subcortical brain structures such as the nucleus reticularis pontis caudalis located in the reticular formation. This nucleus is responsible of conduction of startle reflex related activation to various levels of the spinal cord via the reticulospinal tract, characterizing its descending connections. Also, the startle response is associated with ascending activation which involves projections from the pontine reticular formation to thalamus. This increased activation of the thalamus would provide the required input to trigger the motor program of the prepared movement (Carlsen, Maslovat, and Franks 2012).

Although a RT difference was observed between the control and SAS conditions, when comparing specifically SAS RT pre- and post- tDCS in all sessions, no statistical differences were observed in both tasks. This would suggest that tDCS did not have an additional effect on the time taken for the startle to trigger the motor response and had also no effect on the neural structures involved in response initiation

that mediate the early release of movement by a SAS. Because it has been shown that individuals with PD are able to fully prepare the movement, and because the SAS involuntarily triggers the movement, it was expected that tDCS would not largely impact SAS RT following tDCS. As expected, there were no differences in SAS RT following tDCS applied over MI or SMA, however a trend was observed showing that SAS RT post-tDCS was slightly faster compare to SAS RT pre-tDCS (see Figures 3 and 4). This in in contrast to control trials where tDCS applied over SMA did lead to faster RT in the elbow extension task. A similar finding was reported by Carlsen, Eagles, and MacKinnon (2015), showing that tDCS applied over SMA impacted control trial RT in healthy individuals, but StartReact responses were not further sped up.

4.2 Effect of tDCS

In contrast to the SAS results, when the premotor RT in the control (non- startle) condition was compared pre- and post-tDCS sessions, a significant difference was only observed in the elbow extension task, and only following the SMA stimulation session. This suggests that tDCS applied over MI does not provide significant changes in the level of activation in structures underlying the preparatory and/or initiation processes. This can be concluded since RT following MI stimulation was not different than that following sham. This result contrasts with some previous studies that have investigated the effects of tDCS over MI in PD. For instance, Fregni et al. (2006) observed that individuals with PD had faster RT after single session of tDCS (1mA, 20 min) over MI, it was suggested that motor improvements observed results from the beneficial increase of cortical excitability to compensate for the underactive pallido-thalamo-cortical drive. However, some differences existed between this study and the current experiment including study design (comparisons between subjects vs. within

subject design), state of medication (12 hours without medication vs. on-medication) and stimulation parameters. Moreover, Benninger et al. (2010) showed that applying tDCS (2 mA, 20min) over the motor and premotor areas (which includes stimulation of the MI and SMA as well), in eight sessions led to improvement in walking speed and bradykinesia. These authors explained that the widespread activation of anodal tDCS could have helped in the mechanism of dopamine release leading to the motor benefits. Therefore, because of the placement of the electrodes it is unclear if the improvements observed were due to the stimulation of MI, SMA, or another brain area.

To the best of our knowledge, the present study is the first to verify the effects of tDCS over SMA in PD in terms of RT differences indicating effects on activation underlying the preparation and initiation of the movement. Few studies have investigated the effects of tDCS over SMA in PD. For instance, one study that applied tDCS (1 mA, 10 min) over SMA showed that a single stimulation session had little effect on the performance of self-initiated gait, although motor improvements in the cueing condition (acoustic stimulus) were observed (Lu et al. 2018). Interestingly, results from a study that had applied tDCS over SMA in healthy individuals showed improvements in the premotor RT which the authors attributed to significant changes in the level of preparation and initiation related activation in the upper limb movement (Carlsen, Eagles, and MacKinnon 2015); similar to what was observed in the present study. It is thus possible that in the present study, participants were able to reduce their premotor RT because the stimulation of the SMA led to increased excitability in the neural tissue. This is because the application of anodal-tDCS has previously been shown to lead to excitability changes in the neural tissue underneath the active electrode thought to involve a short-term tonic depolarization as a result of polarizing effects on the resting membrane potential (Nitsche and Paulus 2000). This in turn

might have influenced activation in adjacent connected structures, leading to a net-positive increase in the preparatory and initiation-related activation in basal ganglia-thalamo-cortical pathways and resulting in some normalization of the dysfunction in PD. The SMA is a primary output target of the basal ganglia-thalamo-cortical pathway (Schell and Strick 1984), and because it is related with difficulties in the preparatory and initiation process of voluntary movement in PD (Nachev, Kennard, and Husain 2008; Playford et al. 1992), the improvements observed in the present study could explain the possible changes in the neural connections of SMA with subcortical structures, thus facilitating the movement.

Although the application of tDCS over the SMA provided changes in the premotor RT in the elbow extension task in control condition, which was in contrast of what was found in the pilot study that inspired this experiment (where no differences for RT were seen in the elbow extension task), no differences were observed for the button-press task. There are some possible explanations why premotor RT did not improve with tDCS in the button-press task. First, it is possible that the participants did not prepare appropriately in advance during the button-press task to perform the motor program as required in the RT paradigm. Another possible explanation refers to the nature of the button-press task. Because this task is much simpler compared to the elbow extension task, it is possible that participants did not need to highly prepare this simple task to initiate the motor program with adequate RT. Lastly, in the elbow extension task participants received a visual feedback during the task showing a target to be reached in order to complete the 20º movement, which could have worked as an external cue for the participants. Considering evidence from previous studies, it appears that the improvement in motor performance in PD (e.g. reduced RT) can be facilitated by the presentation of external cues; specifically, it was suggested that the

external cue could act to draw the patient's attention towards some aspect of the movement such as movement length or movement speed (Praamstra 1998; Cunnington, Iansek, and Bradshaw 1999). Additionally, it is reported that neurons in the SMA respond before a movement in the presence of an specific external cue (for example, a visual cue) (Nachev, Kennard, and Husain 2008). Therefore, the improvement of the premotor RT observed only in the elbow extension task after the SMA stimulation might be attributed to the visual cue (target to complete the 20º movement) which could have assisted patients to appropriately prepare the movement in advance.

4.3 Effects on Kinematic Measures (Elbow extension task)

Previous studies involving SAS have indicated that the movement kinematics are largely unaffected in healthy individuals, although some increases in initial force and peak displacement of the movement are sometimes observed (Carlsen, Maslovat, and Franks 2012). In the present study it appears that SAS promoted a faster movement execution resulting in a decrease in movement time (time between movement onset and final position) and time to peak displacement (time between movement onset and peak displacement). Therefore, it is suggested that because the RT task required moving as quickly as possible, the slowness of the movement in individuals with PD could have been susceptible to changes (Carlsen, Eagles, and MacKinnon 2015). Additionally, because no differences were seen between the stimulation sessions, tDCS did not have an additional effect on kinematic variables.

4.4 Effects on Bradykinesia

In the present study significant improvements were observed in the total score of the seven items and in the sub-score of the upper limb items tested from UPDRS pre- and post- the stimulation sessions. However, MI and SMA stimulation were not

different than sham. This suggest that although tDCS applied over SMA did lead to RT improvements, tDCS did not provide functional changes in bradykinesia measured by the seven items from the UPDRS. In contrast, when tDCS was applied over MI in off-medication state improvements were seen in the total score of the motor section of UPDRS (Fregni et al. 2006). Moreover, a significant improvement in upper-limb sequential movements timed test for bradykinesia was observed when tDCS was applied over the prefrontal cortices in the off-medication state. Specifically, only when the items from 23 to 25 (23: finger tapping, 24: opening/closing and 25: pronation/supination of the hands) of the UPDRS were analyzed in off-medication, significant differences were observed (Benninger et al. 2010). Together these evidences suggest that the null effect between the tDCS sessions in the present study could be explained by the fact that participants were on-medication, thus the motor symptoms were already influenced by the anti-Parkinson drugs. Therefore, it is possible that the seven items tested were not sensitive enough to indicate any changes in the bradykinesia symptomology. The pre-to-post session differences observed here could be explained by a learning or placebo effect since no differences were seen between the sessions.

5. Conclusion

In summary, the present study demonstrated that in the SAS condition, participants were able to elicit the prepared motor response in significantly shorter latencies, and the movement time and time to peak displacement were improved, regardless the type of tDCS sessions. The results also showed that premotor RT in the elbow extension task in control condition was improved when tDCS was applied over the SMA. This indicates that any potential increase in cortical excitability induced by tDCS was able to promote changes in the neural tissue which might have

influenced the activation of structures and pathways involved in preparation and initiation – in particular a basal ganglia-thalamo-cortical pathway.

Therefore, we suggest that the use of tDCS in individuals with PD appears to be a promising tool. tDCS by its low cost compared to DBS could be easily used in the clinic as an additional instrument to improve motor symptoms. Specifically, we thoughtfully suggest that the stimulation of the SMA with anodal-tDCS associated with a simple RT task as a strategy can improve upper limb preparatory and initiation processes of voluntary movement in patients with PD.

6. Figures

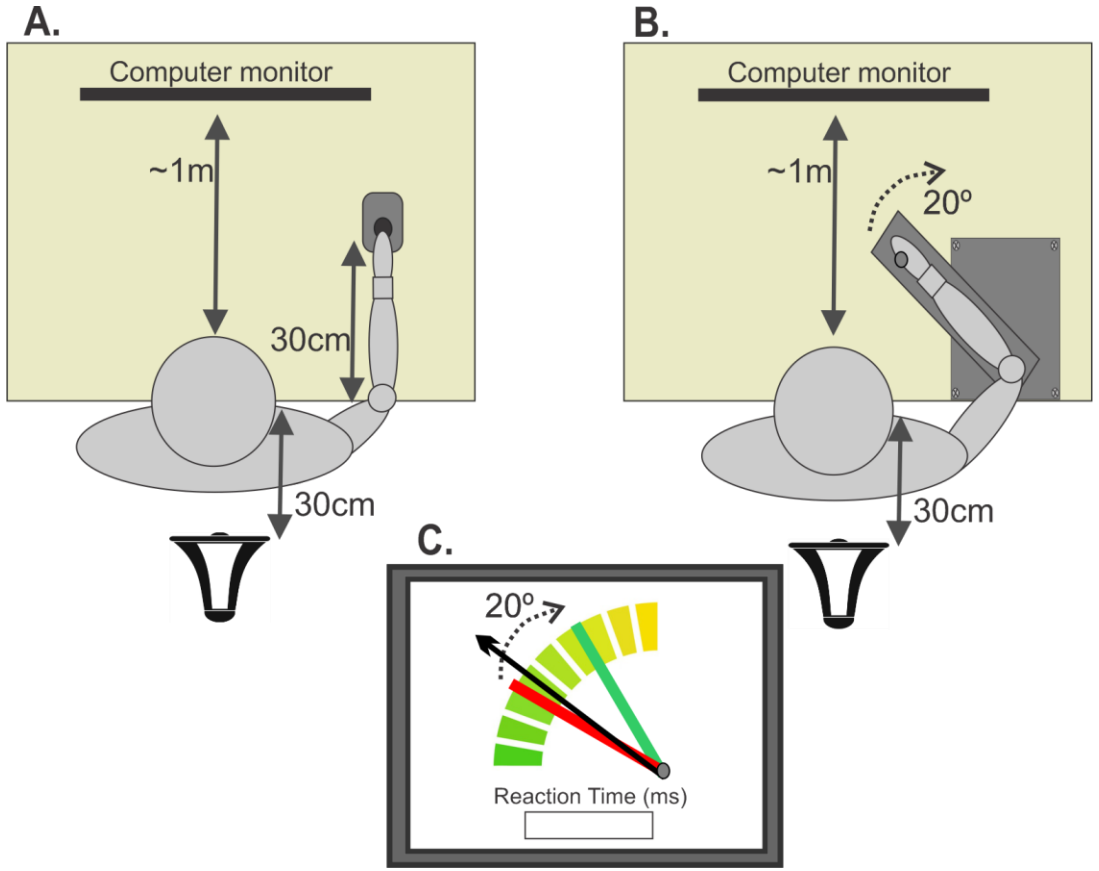

Figure 1. Experimental apparatus and tasks setup. 1A and **1B** show an overview of the participant position and a representation of the experimental task. 1A Button-press task (BU) setup. 1B Elbow extension task (EX) setup. **1C** Screen seen by the participant only for the EX. The 20º extension movement of the elbow was represented by the solid black cursor moving from the red line to the green line. For BU, the screen showed only reaction time feedback after each trial. A loudspeaker placed behind the participant delivered the "go" and startle stimuli. See section 2.2 for further details.

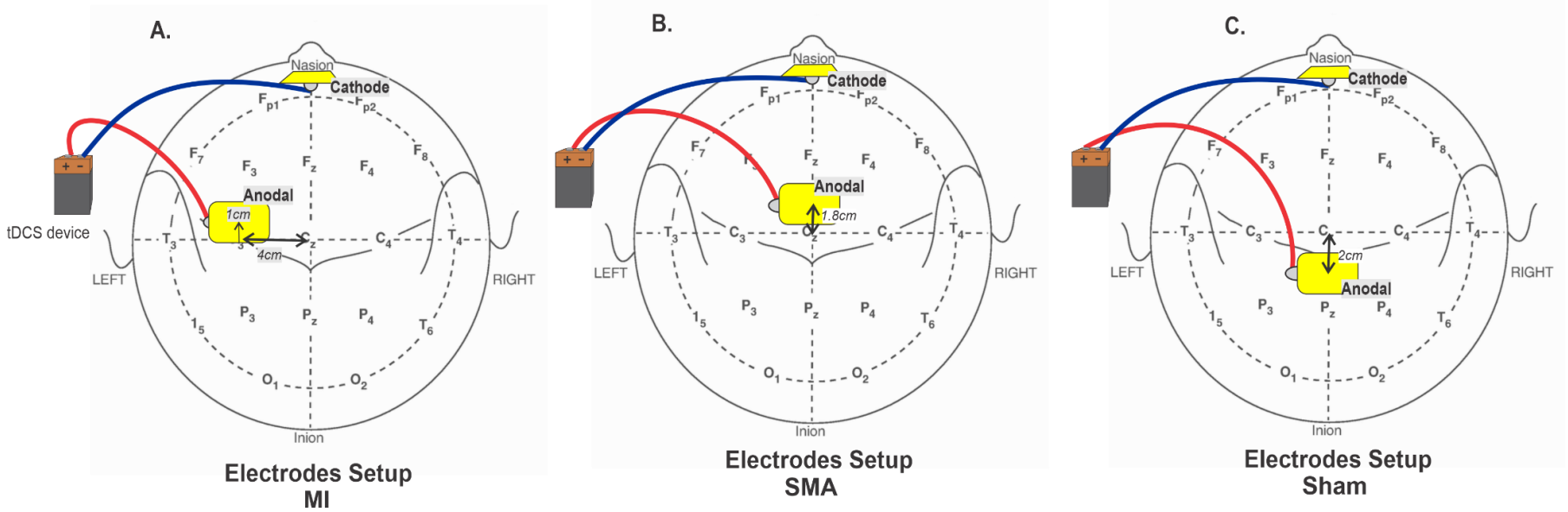

Figure 2. Electrodes Placement for each tDCS session. Figure **2A** illustrates the electrode setup used to stimulate the primary motor area (MI), **2B** represents the electrode setup to stimulate the supplementary motor area (SMA), and **2C** illustrates the electrode setup for the Sham session.

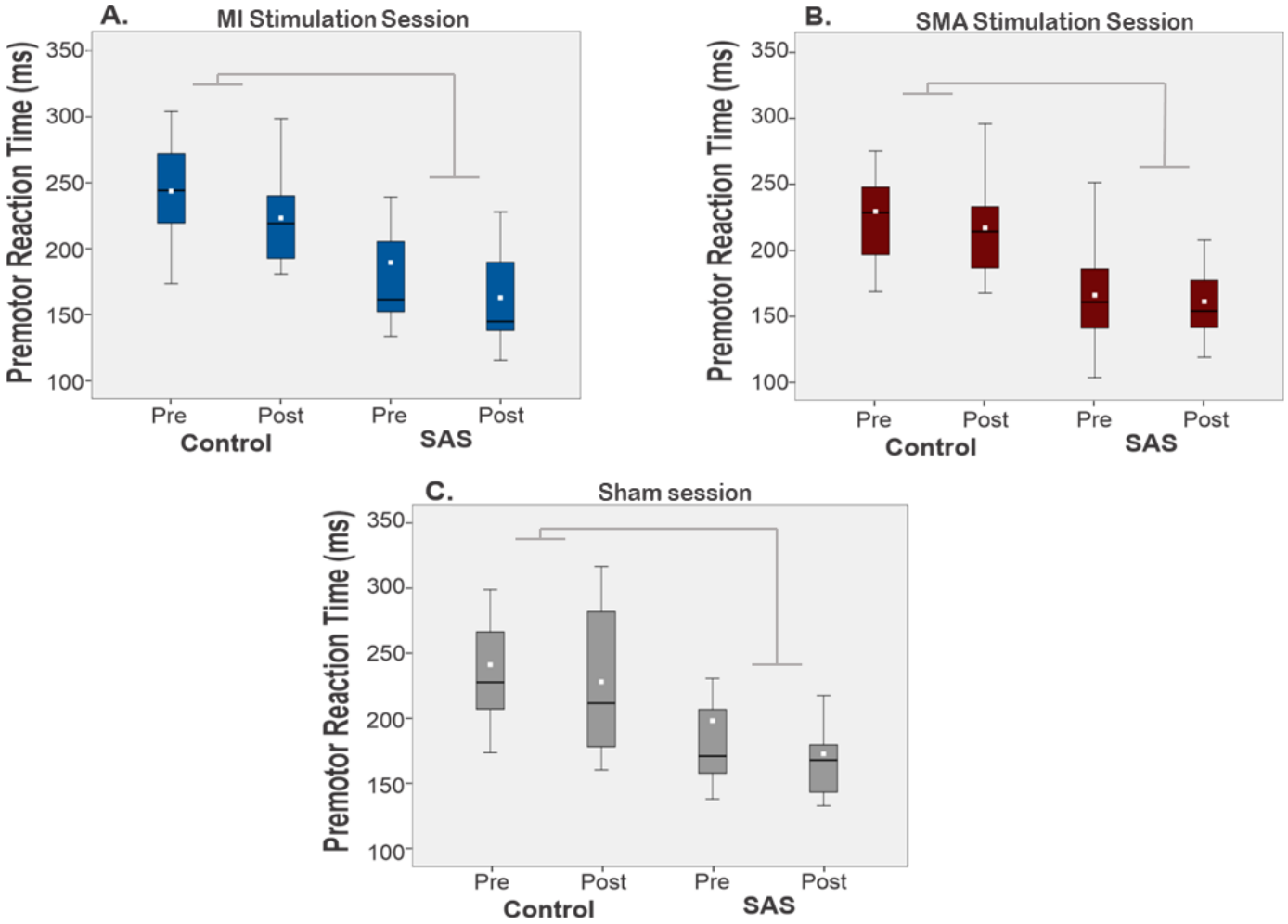

Figure 3. Boxplot charts for Premotor reaction time (RT) in the Button-press task (BU) in pre- and post-tDCS in control and SAS conditions. 3A shows premotor RT in the MI stimulation session, **3B** shows premotor RT in the SMA stimulation session, and **3C** shows premotor RT in Sham session. The box boundaries show the first and third quartiles. The median values are indicated by thick lines. Whiskers indicate the extent of data points within 1.5 times the inter-quartile range from the upper and lower quartiles. Mean is indicated by white filled square. No main effect or interaction were observed for stimulation session or time condition. Main effect was detected for stimulus condition indicated by brackets on top, it was observed faster RT in SAS condition in all stimulation sessions.

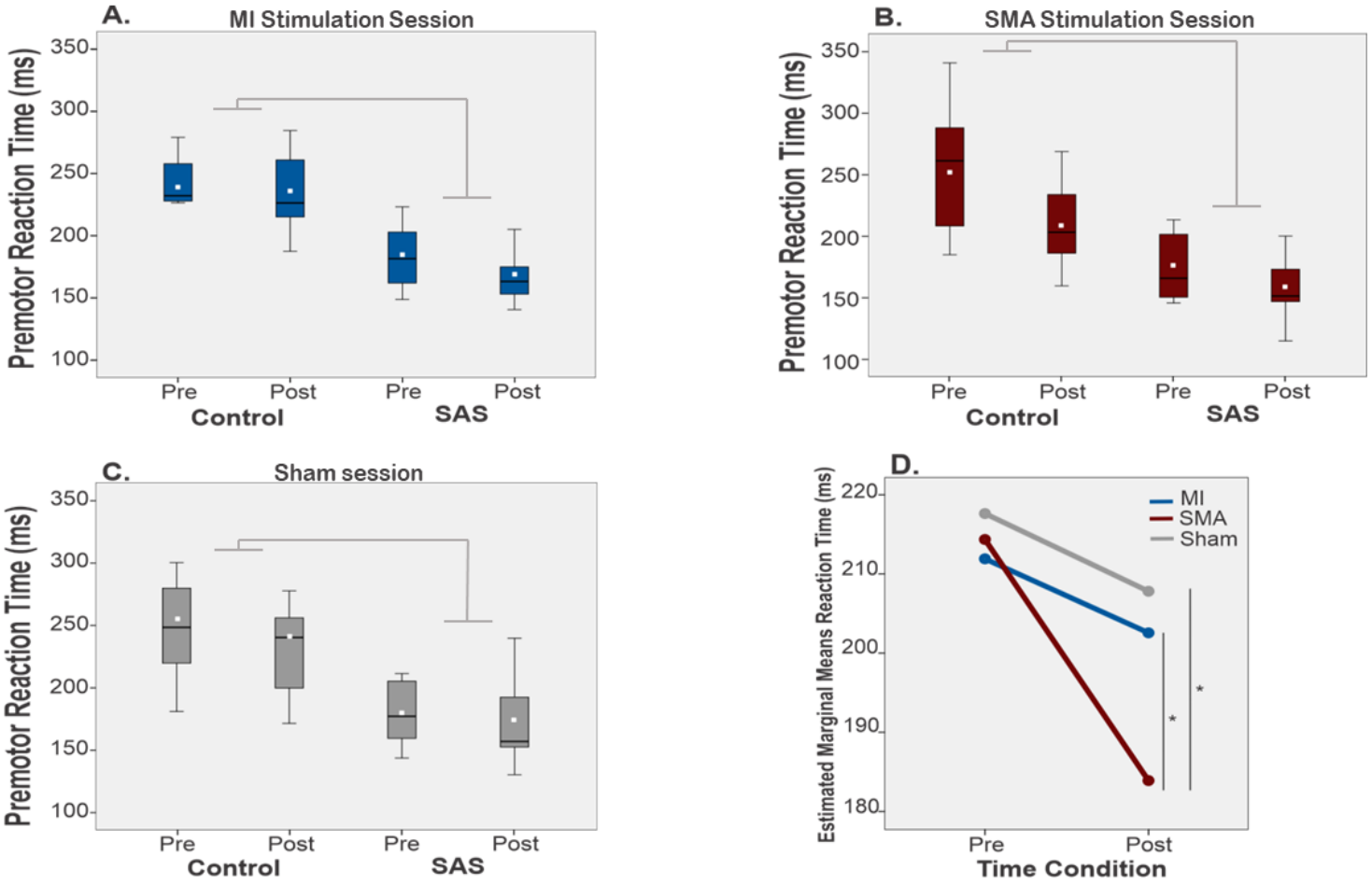

Figure 4. Boxplot charts for premotor reaction time (RT) observed in the Elbow extension task (EX) in pre- and post-tDCS in control and SAS conditions. 4A shows Premotor RT in the MI stimulation session. **4B** shows Premotor RT in the SMA stimulation session. **4C** shows Premotor RT in Sham session. The box boundaries show the first and third quartiles. The median values are indicated by thick lines. Whiskers indicate the extent of data points within 1.5 times the inter-quartile range from the upper and lower quartiles Mean is indicated by white filled square. Main effect was detected for stimulus condition indicated by brackets on top, it was observed faster SAS RT in all stimulation sessions. **4D** shows the interaction effect between the tDCS session pre- and post-testing. Asterisks show significant critical differences between SMA and MI, and SMA and Sham sessions.

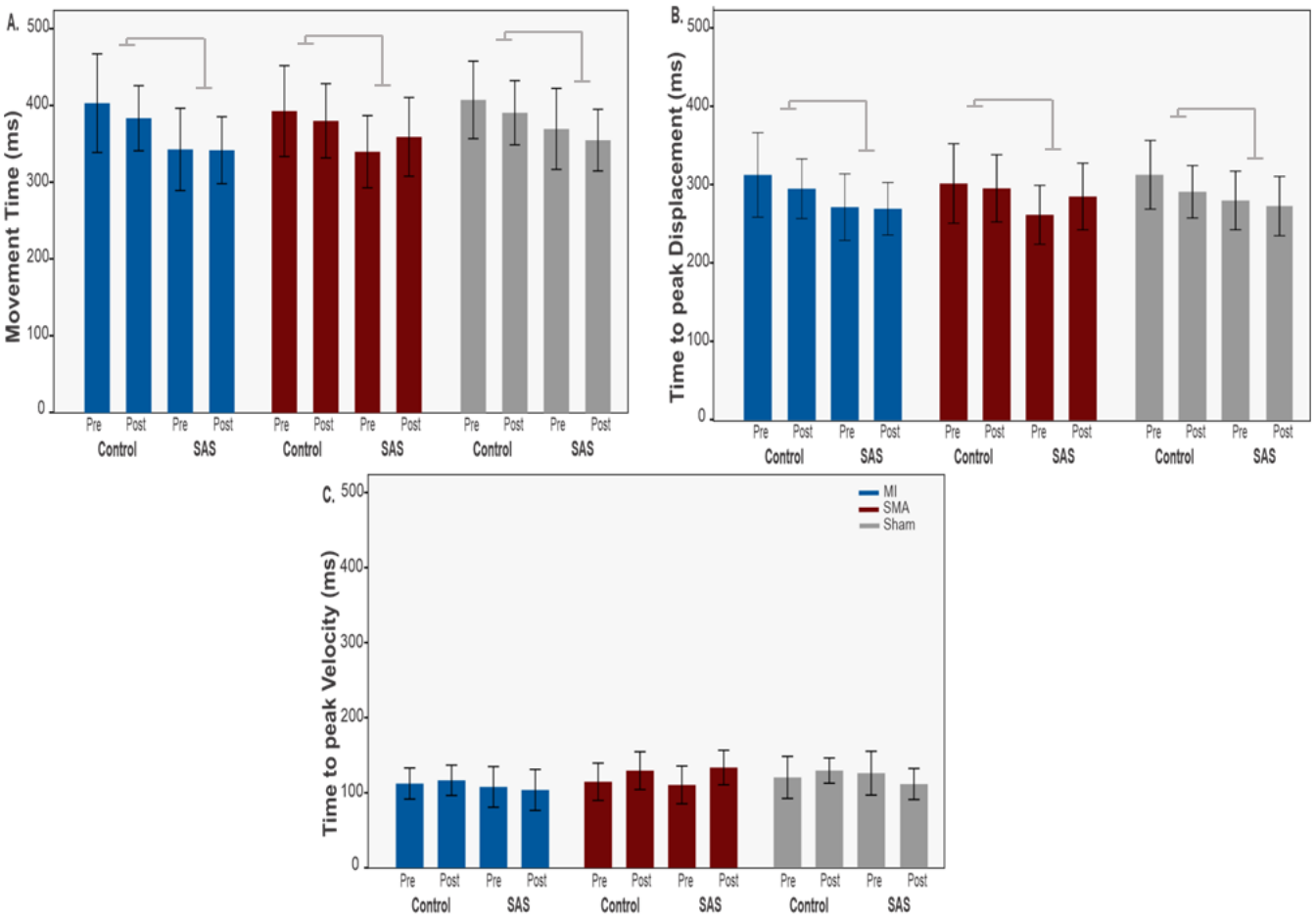

Figure 5. Mean (SE) values observed in kinematic variables. 5A shows Movement Time (MT) indicating the time between movement onset and final position. **5B** shows Time to peak displacement (TpkDx) indicating the time between movement onset and peak displacement. **5C** shows Time to peak velocity (TpkVx) indicating time between the movement onset and the peak velocity. tDCS sessions are represented by colors: blue for MI, red for SMA and gray for Sham session. No main effect or interaction were observed for tDCS session or time condition for MT, TpkDx and TpkVx. A main effect, indicated by brackets on top, was observed for stimulus condition for MT and TpkDx in all tDCS sessions.

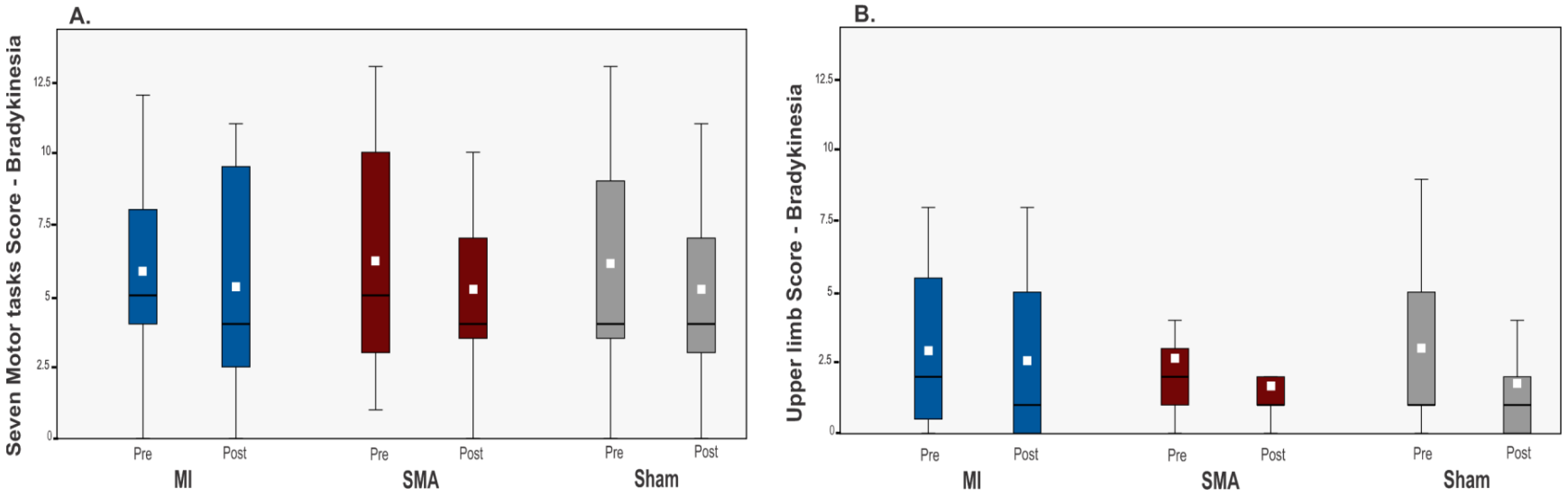

Figure 6. Boxplot charts show bradykinesia score on the motor tasks from UPRDS pre- and post-tDCS sessions. 6A shows the score on the seven motor tasks. **6B** shows the score only for the upper limb tasks. The box boundaries show the first and third quartiles. The median values are indicated by thick lines. Whiskers indicate the extent of data points within 1.5 times the inter-quartile range from the upper and lower quartiles. Mean is indicated by white filled square. In both analyses no main effect for tDCS session was observed, and no interaction involving tDCS session was observed. However, a main effect was seen for time condition, indicating that participants improved bradykinesia score post-stimulation in all tDCS sessions.

CHAPTER III: GENERAL DISCUSSION

The purpose of the present study was to examine the impact of application of tDCS on movement preparation and initiation in individuals with PD. By stimulating two different brain areas we aimed to verify whether initiation and execution of a voluntary movement could be modulated, and whether any interaction existed between the effect of tDCS and the presentation of a SAS.

1. Main findings and Limitations

The main finding of this study shows that premotor RT was significantly shorter following anodal-tDCS applied over SMA, but not over MI, and only for the elbow extension task in control condition. As explained above, it is suggested that the stimulation of the SMA could have led to an increase in the excitability of the neural tissue, which in turn might have influenced activation in adjacent connected structures (e.g., subcortical areas as BG and thalamus), thus providing improvements in the premotor RT. In the present study, the standard international 10-20 system was used to identify the brain areas, and it is well reported that the application of anodal-tDCS leads to excitability changes in the neural tissue underneath the active electrode providing a short term tonic depolarization as a result of a shift in the resting membrane potential (Nitsche and Paulus 2000; 2011). However, the actual brain area stimulated was not verified, thus the present results should be considered with caution. Therefore, one of the limitations in the present experiment is related to the absence of a specific method to the assess the cortical excitability of the brain areas after the stimulation, which could have provided additional information regarding brain activation levels in the stimulated brain areas and help to draw more concrete conclusions regarding the effects of tDCS. For further studies, a suitable method that could be used for evaluating

the cortical excitability changes is Transcranial Magnetic Stimulation (TMS), which allows an indirect measurement of cortical excitability in a painless and non-invasive manner. The effects of TMS lead a muscular twitch in the targeted muscle termed motor-evoked potential (MEP), and its amplitude represents the level of excitability of the motor system (Rothwell, Hallett, and Berardelli 2010).

Considering the results from the SAS condition, in both RT tasks participants were able to elicit the pre-planned movement at shorter latencies, but no interaction between tDCS sessions and SAS existed. It was expected that SAS would not be influenced by tDCS, since studies with individuals with PD have shown that the StartReact effect remained unaffected (Fernandez-Del-Olmo et al. 2013; Carlsen, Almeida, and Franks 2013). In addition, it was also previously demonstrated in healthy individuals that the application of tDCS does not provide additional effect on the time take to trigger the early release of the pre-planned movement in SAS trials (Carlsen, Eagles, and MacKinnon 2015). Therefore, in order to evaluate the impact of including SAS and its association with tDCS in PD, it is suggested that future studies consider the implementation of an extra group into the experiment: a group of healthy participants. This will provide additional information regarding the nature of the earlier release of the pre- planned movement and possible interaction with tDCS in PD when compared to healthy individuals.

In terms of the functional assessment based on the bradykinesia score of the seven motor items from UPDRS, a main effect in time (pre-to-post tDCS) was observed, but no difference between the sessions was seen. Although, we have already discussed the possible reasons for this, it is worthwhile to mention some additional limitations that could have played some role as well. The first one refers to the method used to assess the bradykinesia symptoms. Although the UPDRS is a gold

standard to assess the severity of PD, it is possible that because of a small sample size as well as because participants presented with a large range in the scores (see Figure 6), the seven items selected may not have been sensitive enough to detect significant changes in bradykinesia. As explained by (Koop, Shivitz, and Brontë-Stewart 2008) UPDRS III have limited resolution for detecting small changes and, therefore a large number of subjects should be need to adequately the power of the statistical analyses. These authors also point out that UPDRS has a subjective aspect over the assessment.

Specifically, studies have focused on investigating whether quantitative measures of motor control that includes bradykinesia aspects could be useful and be a good indicator of overall motor dysfunctions associated with Parkinson's disease. For instance, when kinematics measures such as velocity, duration of finger strike, and the interval between strikes was analyzed from a repetitive alternating finger-tapping task of quantitative digitography, it was observed a strong correlation with the bradykinesia sub-score of UPDRS III (Taylor Tavares et al. 2005). Additionally, results from another study showed that movement time in a sequential movements task is correlated with bradykinesia as well (Benecke et al. 1987). Therefore, future studies should consider the use of a more sensitive method to assess bradykinesia. For example, Benninger et al. (2010) showed that bradykinesia assessed with a sequential timed test of hands and arms improved after tDCS whereas the total score of UPDRS III was not different than sham. Moreover, Cosentino et al. (2017) observed that only the UPDRS score for the more-affect side improved after tDCS. It was argued that UPDRS could have been less sensitive in detecting subtle differences in the less-affected side of the body. The implementation of a sensitive methods to assess features of bradykinesia would contribute to better understanding the mechanisms

behind and the benefits of tDCS in bradykinesia. This specific quantitative instrumental assessment of bradykinesia may be worthwhile for applied research and monitoring patients in all stages of the disease, because in contrast to rating scales it can be more sensitive, reliable, and provide better objective measurements.

2. Conclusion

Despite the limitations discussed, the findings of this study provide the first evidence that anodal tDCS applied over the SMA might yield a motor benefit related to the activation levels in preparatory and/or initiation processes underlying the movement during the elbow extension task in individuals with PD. Therefore, we suggest that the use of tDCS in individuals with PD appears to be a promising tool to be used in the clinic as an additional instrument to improve motor symptoms. The stimulation of the SMA with anodal-tDCS associated with simple RT task as a strategy could be implemented to improve upper limb preparatory and initiation processes of voluntary movement in patients with PD.

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Appendix A: Ethics Approval Notice

File Number: H03-17-04 **Date (mm/dd/yyyy):** 06/24/2019

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Anthony	Carlsen	Health Sciences / Human Kinetics	Principal Investigator
Erin	Cressman	Health Sciences / Human Kinetics	Co-investigator
Julie	Nantel	Health Sciences / Human Kinetics	Co-investigator
Aline	Kami	Health Sciences / Human Kinetics	Research Assistant
Faven	Teku	Health Sciences / Human Kinetics	Research Assistant
Christin	Sadler	Health Sciences / Human Kinetics	Research Assistant
Victoria	Smith	Health Sciences / Human Kinetics	Research Assistant

File Number: H03-17-04

Type of Project: Professor

Title: Investigating differential brain contributions to movement production and how modulating cortical excitability affects motor performance

Renewal Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
04/12/2019	04/11/2020	Renewal

Special Conditions / Comments:
N/A

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File Number: H03-17-04 **Date (mm/dd/yyyy):** 06/24/2019

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

This is to confirm that the University of Ottawa Research Ethics Board identified above, which operates in accordance with the Tri-Council Policy Statement (2010) and other applicable laws and regulations in Ontario, has examined and approved the ethics application for the above named research project. Ethics approval is valid for the period indicated above and subject to the conditions listed in the section entitled "Special Conditions / Comments".

During the course of the project, the protocol may not be modified without prior written approval from the REB except when necessary to remove participants from immediate endangerment or when the modification(s) pertain to only administrative or logistical components of the project (e.g., change of telephone number). Investigators must also promptly alert the REB of any changes which increase the risk to participant(s), any changes which considerably affect the conduct of the project, all unanticipated and harmful events that occur, and new information that may negatively affect the conduct of the project and safety of the participant(s). Modifications to the project, including consent and recruitment documentation, should be submitted to the Ethics Office for approval using the "Modification to research project" form available at: http://research.uottawa.ca/ethics/submissions-and-reviews.

Please submit an annual report to the Ethics Office four weeks before the above-referenced expiry date to request a renewal of this ethics approval. To close the file, a final report must be submitted. These documents can be found at: http://research.uottawa.ca/ethics/submissions-and-reviews.

If you have any questions, please do not hesitate to contact the Ethics Office at extension 5387 or by e-mail at: ethics@uOttawa.ca.

Signature:

Marc Alain Bonenfant
Research Ethics Coordinator
For Catherine Paquet, Director of the Office of Research Ethics and Integrity

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