The Effect of Intermittent Theta Burst Stimulation Applied to the Primary Motor Cortex and Dorsolateral Prefrontal Cortex on Running Performance in Endurance-Trained Runners

Thesis by

Isabella Sierra

Department of Kinesiology and Physical Education

McGill University, Montreal

March 2025

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

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Abstract

Increasing cortical excitability has been studied to enhance athletic performance for over a decade, but its effectiveness remains unknown, particularly in endurance running. The current literature contains discrepancies regarding optimal parameters, including stimulation site, testing protocols and outcome measures. Few studies have investigated the effect of stimulating multiple sites to address the various factors that contribute to running performance. Historically, the motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) have been targeted due to their roles in both the physical and cognitive aspects of performance. For testing protocols, studies have examined the effects of increasing excitability using laboratory-based methods, such as time to exhaustion tests on cycle ergometers or treadmills, rather than overground running assessments that better reflect a natural environment for runners. Additionally, total time may not fully capture all aspects of performance that change throughout a run. Targeting multiple brain regions and utilizing an overground running task that evaluates multiple performance metrics throughout the run may provide greater insight into the effect of increasing excitability. Therefore, this thesis aims to investigate the impacts of increasing cortical excitability through intermittent theta burst stimulation (iTBS) targeted to the M1, DLPFC, and both M1 and DLPFC compared to sham on total time, speed, rating of perceived exertion (RPE) and spatiotemporal parameters and variability in endurance-trained runners during an exhaustive 3,000m time-trial run. We hypothesized that iTBS applied to the M1 leg and DLPFC would enhance performance by measures of faster completion times, faster speeds, reduced RPE and decreased spatiotemporal variability. Ten endurance-trained runners (7 males, 3 females, age: 26 ± 7 years, height: 1.75 ± 0.92 m, body mass: 65± 10 kg, years of training: 8±5) were included in the analysis. Runners underwent four separate sessions in randomized order: iTBS of both M1 and DLPFC, iTBS of M1 and sham stimulation of DLPFC, sham stimulation of M1 and iTBS of DLPFC, and sham stimulation of both M1 and DLPFC. After stimulation, runners performed the 3,000m time-trial run on an indoor track. RPE was taken every three laps. Spatiotemporal measures of stride time (ST), step frequency (SF), stride length (SL) and duty factor (DF) were collected through APDM opal sensors. Speed, magnitude of spatiotemporal parameters, and their coefficient of variation (CV) were analyzed in three phases of the run: initial, steady state and final acceleration. Although significance was not reached, the M1+DLPFC condition produced the fastest time, nearly 3 seconds faster than sham and 1 second faster than stimulation of either area alone. Speed was significantly faster in the

M1+DLPFC condition in the initial lap. Additionally, ST was significantly faster, and SF was significantly higher in the M1+DLPFC condition in the initial lap. No significant differences in RPE were found between the four conditions at any point in the run. Contrary to our hypothesis, increasing excitability of the M1 and DLPFC alone or in combination did not affect the magnitude of variability in any spatiotemporal parameters at any phase of the run. Overall, stimulation of the M1 and DLPFC appeared to have a positive effect in the early phase of the run, primarily by increasing speed without increasing feelings of exertion. Future research should investigate optimal timing to deliver stimulation to extend its impact during the run. Considering the number of factors related to possible target brain regions, NIBS modalities and protocols, and running performance, determining the efficacy of utilizing iTBS to increase cortical excitability remains challenging and would require repeated research with uniform protocols.

Résumé

Bien que l'augmentation de l'excitabilité corticale ait été étudiée depuis plus d'une décennie comme moyen d'améliorer les performances athlétiques, son efficacité reste incertaine, en particulier dans le cadre de la course d'endurance. La littérature actuelle présente de nombreuses divergences concernant les paramètres optimaux, notamment le site de stimulation, les protocoles de test et les mesures des résultats. Peu d'études ont exploré l'effet de la stimulation de multiples sites pour aborder les divers facteurs contribuant à la performance en course. Historiquement, le cortex moteur primaire (M1) et le cortex préfrontal dorsolatéral (DLPFC) ont été ciblés en raison de leurs rôles dans les aspects physiques et cognitifs de la performance. En ce qui concerne les protocoles de test, la plupart des études ont examiné les effets de l'augmentation de l'excitabilité en utilisant des méthodes contrôlées en laboratoire, telles que des tests de temps jusqu'à l'épuisement sur des cycloergomètres ou des tapis roulants, plutôt que des évaluations de course à l'extérieur qui seraient plus représentatives d'un environnement naturel pour les coureurs. De plus, le temps total seul peut ne pas saisir pleinement les différents aspects de la performance susceptibles de changer au cours d'une course. Cibler plusieurs régions cérébrales et utiliser une tâche de course à l'extérieur qui évalue plusieurs mesures de performance tout au long de la course pourrait fournir une meilleure compréhension de l'effet de l'augmentation de l'excitabilité corticale. Par conséquent, cette thèse vise à étudier les impacts de l'augmentation de l'excitabilité corticale par stimulation intermittente à rafales thêta (iTBS) ciblant le M1, le DLPFC, et à la fois le M1 et le DLPFC comparés à une stimulation fictive sur le temps total, la vitesse, le taux d'effort perçu (RPE) ainsi que les paramètres spatiotemporels et leur variabilité chez des coureurs entraînés en endurance lors d'une course chronométrée de 3 000 m jusqu'à l'épuisement. Nous avons émis l'hypothèse que l'augmentation de l'excitabilité du M1 et du DLPFC améliorerait la performance, se traduisant par des temps de réalisation plus rapides, des vitesses plus élevées tout au long de la course, une réduction du RPE et une diminution de la variabilité spatiotemporelle. Dix coureurs entraînés en endurance (7 hommes, 3 femmes, âge : 26 ± 7 ans, taille : 1,75 ± 0,92 m, masse corporelle : 65 ± 10 kg, années d'entraînement : 8 ± 5) ont participé à cette étude et disposaient de mesures complètes des données spatiotemporelles pour les quatre sessions. Les coureurs ont effectué quatre sessions distinctes dans un ordre randomisé : iTBS du M1 et du DLPFC, iTBS du M1 et stimulation fictive du DLPFC, stimulation fictive du M1 et iTBS du DLPFC, et stimulation fictive du M1 et du DLPFC. Après la stimulation, les coureurs ont réalisé une course chronométrée

de 3 000 m sur une piste intérieure. Le RPE a été enregistré tous les trois tours. Les mesures spatiotemporelles, y compris le temps de foulée (ST), la fréquence des pas (SF), la longueur de foulée (SL) et le facteur de devoir (DF) ont été recueillies à l'aide de capteurs APDM Opal. L'amplitude des paramètres spatiotemporels et leur coefficient de variation (CV) ont été analysés. La vitesse, les paramètres spatiotemporels et leur variabilité ont été analysés en trois phases de la course : initiale, état stable et accélération finale. Aucune différence significative n'a été observée entre les trois types de conditions de stimulation et la stimulation fictive en termes de temps total ; cependant, la condition M1+DLPFC a produit le temps le plus rapide, près de 3 secondes plus rapide que la stimulation fictive et 1 seconde plus rapide que la stimulation de chaque zone seule. La vitesse était significativement plus élevée dans la condition M1+DLPFC lors du tour initial. De plus, le ST était significativement plus court et le SF significativement plus élevé dans la condition M1+DLPFC lors du tour initial. Aucune différence significative dans le RPE n'a été constatée entre les quatre conditions à aucun moment de la course. Contrairement à notre hypothèse, l'augmentation de l'excitabilité du M1 et du DLPFC, seules ou en combinaison, n'a pas affecté l'amplitude de la variabilité des paramètres spatiotemporels à aucune phase de la course. Globalement, la stimulation du M1 et du DLPFC semble avoir un effet positif dans la phase initiale de la course, principalement en augmentant la vitesse sans accroître la sensation d'effort. Cependant, ces effets ont disparu après la phase initiale. De futures recherches devraient explorer le moment optimal pour administrer la stimulation afin de prolonger son impact pendant la course. Étant donné le nombre de facteurs liés aux régions cérébrales cibles potentielles, aux modalités et protocoles de stimulation non invasive du cerveau, et à la performance en course, déterminer l'efficacité de l'augmentation de l'excitabilité corticale reste un défi et nécessiterait des recherches répétées avec des protocoles uniformes.

Acknowledgments

This project was financially supported by the Sylvan Adams Sports Science Institute (SASSI), Dr. Caroline Paquette and the Canadian Institute for Health Research (CIHR). These sources and organizations allowed me to pursue the research necessary for the completion of this thesis.

I would like to sincerely thank my supervisor, Dr. Caroline Paquette, for allowing me the opportunity to perform research and receive my master's in the Human Brain Control of Locomotion Laboratory. I am very grateful for her guidance and patience in writing this thesis and in my academic journey over the last three years. Your support was invaluable in completing my master's. I also wanted to thank Fabien Basset and Julie Côté for sharing their expertise in the field of running and performance and providing such helpful feedback for my manuscript.

I am grateful for the help and support of all the members of the HBCL lab who I have had the pleasure of working with and who I've learned so much from. Thank you especially to Alexandra, Frédérike, and Henri who provided guidance, support and kindness in my first year when I needed it the most. I also want to express my gratitude to Yiyang, who contributed greatly to writing the code. Thank you so much for your help and patience.

I would like to thank my family and loved ones for supporting me and helping me through the hardest parts of this process. To my mother, who is always there for me whenever I need her and has done so much for me throughout my life. Your belief in me has led me here today, and I am so grateful for that. To my sister Olivia, my best friend, who I've always looked up to. Thank you for all the Thursday night FaceTime dinners that brought me happiness even in the most stressful times. To my brother-in-law Jeremy, who I now get to annoy for the rest of his life, thank you for being the closest thing to a brother I've ever had. To my partner, Matheus, who has provided more support, encouragement and love than I can describe. You have never stopped motivating me and assuring me that I could get through this, even when I wasn't sure I could. You've brought so much happiness, laughter and positivity to this journey and I couldn't have done it without you. Te amo muito.

Contribution of authors

I, Isabella Sierra, was responsible for collecting data, adapting code and analyzing the data as well as writing and editing this thesis. Yiyang Chen was responsible for writing the original code to analyze accelerometer data and contributed to data collection. Gleydciane Alexandre Fernandes, Julien Clouette, Jenna Gibs, Julie Côté, Fabien Basset and Caroline Paquette were responsible for conceptualization of the larger study that I took data from. Gleydciane Alexandre Fernandes, Henri Lajeunesse, Alejandra Martinez Moreno, Julien Clouette, and Alexandra Potvin-Desrochers were involved with data collection. Julie Côté and Fabien Basset provided revisions on the manuscript. Dr. Caroline Paquette supervised the writing and revising of this thesis and the manuscript.

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List of abbreviations

AMT: Active motor threshold

CNS: Central nervous system

CT: Contact time

CV: Coefficient of variation

DF: Duty factor

DLPFC: Dorsolateral prefrontal cortex

EMG: Electromyography

FDI: First dorsal interosseous

FT: Flight time

IMU: Inertial measurement unit

iTBS: intermittent theta burst stimulation

M1: Primary motor cortex

MEP: Motor evoked potential

MRI: Magnetic resonance imaging

MVC: Maximum voluntary contract

NIBS: Non-invasive brain stimulation

RM-ANOVA: Repeated measures analysis of variance

RPE: Rating of perceived exertion

rTMS: Repetitive transcranial magnetic stimulation

SF: Step frequency

SL: Stride length

ST: Stride Time

TA: Tibialis Anterior

TBS: Theta burst stimulation

tDCS: Transcranial direct current stimulation

TMS: Transcranial magnetic stimulation

VO_2max: Maximal oxygen uptake

Chapter 1: Introduction

1.1 Rationale

Non-invasive brain stimulation (NIBS) is a technique that modulates brain excitability through an external stimulus to the scalp (Albizu et al., 2019) and has been explored as a means to enhance endurance performance. The primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) have been identified as regions of interest. Stimulation of the M1 may slow the decrease in neural drive that is a result of exercise-related fatigue (Lorenz et al., 2003; Radel et al., 2017). The DLPFC plays a role in pain perception (Byrne & Flood, 2019), and stimulation of this area has been shown to increase pain thresholds in healthy subjects (Boggio et al., 2008). Limited evidence suggests that upregulation of both the M1 and DLPFC may provide greater benefits than stimulation of either area alone (Banaei et al., 2023).

The efficacy of modulating excitability in the M1 and DLPFC to improve endurance performance remains unknown. Some studies have shown promising results, with improvements in performance after increasing excitability in the M1 or DLPFC regions (Angius, Mauger, et al., 2018; Angius et al., 2019; Vitor-Costa et al., 2015). However, others report no measurable benefits after intervention (Baldari et al., 2018; Byrne & Flood, 2019; da Silva Machado et al., 2021; Judge et al., 2021). Testing protocols across these studies vary, with some studies measuring endurance using time-to-exhaustion or time trial tests on cycle (Filipas et al., 2022; Holgado et al., 2019; Judge et al., 2021; Pollastri et al., 2021; Vitor-Costa et al., 2015), while others measured endurance only by way of tests of sustained isokinetic or isometric contraction to exhaustion (Byrne & Flood, 2019).

For runners, these tests might not accurately represent natural running environments or reflect their performance capability. Research on overground running, which would more accurately represent performance, is limited. Only one study has been found to date that used overground running as a performance test. Following excitatory transcranial direct current stimulation (tDCS) over the M1, Dos Santos et al. (2023) found that the time to complete a 5,000m run on an indoor track was significantly faster compared to sham stimulation. These findings suggest the potential of NIBS interventions when applied in a more natural environment. However, this study failed to collect other objective measures throughout the run. Relying on total time alone may not account for

variations in pacing strategies that are critical in middle-distance running. One common strategy, negative pacing, involves maintaining a steady pace for most of the race before accelerating in the final stages (Abbiss & Laursen, 2008). Analyzing different phases of the run separately can provide a clearer understanding of how and when increasing cortical excitability affects running strategy.

Examining a combination of metrics and different phases in the run could provide an enhanced view of running performance strategies. Stimulating the M1, which has shown improvements in total time (Dos Santos et al., 2023; Park et al., 2019) and speed (Koganemaru et al., 2018), in combination with stimulating the DLPFC, which has shown improvements in rating of perceived exertion (RPE) and spatiotemporal variability (Teymoori et al., 2023; Wrightson et al., 2015), may lead to overall better performance compared to either area alone.

1.2 Objectives

The purpose of this master's thesis was to determine whether stimulation of the M1 and DLPFC in a single session could enhance endurance running performance and give insight into running strategy, measured by total time, speed, RPE, spatiotemporal measures, and spatiotemporal variability more than stimulation of either area alone or sham stimulation. This study aimed to answer the following questions:

1. Does brain stimulation of the M1 only and the M1 + DLPFC produce faster overall time and faster lap speeds throughout the entirety of a 3,000m time-trial run compared to stimulation of the DLPFC only or sham stimulation?
2. Does brain stimulation of the DLPFC only and M1 + DLPFC decrease RPE throughout the 3,000m time-trial run compared to stimulation of M1 only or sham stimulation?
3. Does brain stimulation of the DLPFC only and M1 + DLPFC effect spatiotemporal variability in stride time (ST), step frequency (SF), stride length (SL) and duty factor (DF) throughout the 3,000m time-trial run more than stimulation of M1 only or sham stimulation?

1.3 Hypotheses

The hypotheses of this study are as follows:

1. The M1 only and M1 + DLPFC conditions will produce the faster total times to complete the 3,000m time-trial run and faster lap speeds compared to stimulation of the DLPFC only or sham stimulation.
2. Runners will show decreased RPE in the DLPFC only and M1+DLPFC condition throughout the entirety of the 3,000m time-trial, compared to stimulation of M1 only or sham stimulation.
3. Variability of ST, DF, SF and SL will increase during the steady state phase, however, stimulation of the DPLFC only and M1 + DLPFC conditions will mitigate the increase in variability more so than stimulation of the M1 only or sham stimulation.

Chapter 2: Review of the literature

2.1 Mechanisms of Increasing Cortical Excitability for Improving Endurance Performance

Increasing cortical excitability has been explored as a way to enhance endurance performance. Two of the most commonly explored regions are the M1 and the DLPFC, due to their implications in endurance running. The M1 controls voluntary muscle contraction and the execution of movements (Moscatelli et al., 2021). It has a somatotopic organization so that certain locations in the M1 innervate specific muscles (Wise, 2001). Muscle contraction is driven by motor neurons in the spinal cord, called the motor neuron pool, which send signals from the brain to the muscles (Heckman & Enoka, 2012), with the upper motor neurons located in the M1. During endurance exercise, the motor neuron pool experiences decreased excitability, and results in reduced muscle capacity and leads to neuromuscular fatigue (Gandevia, 2001). Increasing excitability of M1 may help to slow this decrease in neural drive that occurs due to exercise-related fatigue (Lorenz et al., 2003; Radel et al., 2017). Increased neural drive could lead to greater muscle output, potentially enhancing endurance performance (Etemadi et al., 2023).

Another common brain region of interest is the DLPFC, which is involved in pain perception, motivation and cognitive control (Byrne & Flood, 2019; Lorenz et al., 2003). Previous studies suggest that an athlete's ability to tolerate exercise-induced pain is associated with performance levels (Astokorki & Mauger, 2017; Pettersen et al., 2020). These perceived elements play a role in determining exercise cessation, as studies have shown that activity in the prefrontal cortex decreases just prior to exercise termination (Robertson & Marino, 2016). Increasing excitability of the left DLPFC has been linked to a lower degree of pain perception (Lorenz et al., 2003), which may allow athletes to endure discomfort caused by exercise for longer periods of time. Interest in these interventions for sports has been increasing, partly due to evidence that psychological interventions in sports can lead to physical improvements in performance (Brown & Fletcher, 2017). Since physical and cognitive factors can impact athletic ability (Raglin, 2001), increasing excitability in either region could lead to endurance performance enhancement.

2.1.1 Non-invasive brain stimulation

Increasing cortical excitability can be achieved through NIBS, which describes any technique that modulates brain excitability from the outer surface of the head (Albizu et al., 2019). tDCS and transcranial magnetic stimulation (TMS) are the two most common types of NIBS (Kesikburun,

2022). With tDCS, two electrodes are placed on the scalp, and a low-level current flow between them (Pelletier & Cicchetti, 2014). The location of the electrodes is typically determined by the 10-20 EEG system map for tDCS, which uses measurements and landmarks of the scalp (Klem et al., 1999). Electrodes are then placed at these landmarks based on the desired brain region for stimulation. The direction of current flow in tDCS determines the neuromodulatory effects it produces. Anodal stimulation, where the anode is placed over the target region, generally increases cortical excitability, whereas cathodal stimulation, with the cathode over the target region, typically decreases excitability (Nitsche & Paulus, 2000). Electrode size can vary with conventional tDCS using larger electrodes ranging from 25 cm^2 to 35 cm^2 in size, while high definition tDCS uses smaller electrodes that produce a more focused current targeting a specific brain region (Solomons & Shanmugasundaram, 2020). tDCS is often described as the more portable and inexpensive of the two methods (Zaghi et al., 2009), leading to its frequent use in sports-related studies.

TMS induces electrical currents in the brain cortex through a magnetic field, which can generate action potentials (Elder & Taylor, 2014). The magnitude of these action potentials, known as motor-evoked potentials (MEPs), is recorded by electromyography (EMG). The area that produces the highest MEPs is considered the optimal spot for stimulation. A branch of TMS called repetitive transcranial magnetic stimulation (rTMS) delivers multiple pulses in sequence, with the direction of its effects depending on stimulation frequency (Chail et al., 2018). Low-frequency rTMS which is less than 1 Hz generally decreases or inhibits cortical excitability, while high-frequency rTMS which is greater than 5 Hz, increases excitability (Rossini et al., 2015). Theta burst stimulation (TBS) is a subset of rTMS that delivers these repetitive pulses in patterned bursts of 50Hz. Intermittent theta burst stimulation (iTBS) increases brain excitability (Schwippel et al., 2019) and has been shown to produce effects up to 60 minutes after treatment (Wischnewski & Schutter, 2015). Although rTMS can be more costly, this method has more established and uniform protocols (Elder & Taylor, 2014) and can stimulate a specific area more precisely than conventional tDCS (Deng et al., 2013). Many studies utilizing tDCS rely on predetermined measurements of the 10-20 EEG system, but TMS uses neuronavigation systems that can identify the optimal stimulation site on an individual basis (Giboin et al., 2016), which may be more beneficial.

Both tDCS and rTMS have been studied for many years and have various clinical applications, including rehabilitation for stroke or Parkinson's disease, depression, and schizophrenia (Chail et al., 2018). However, rTMS has received approval from regulating agencies such as the FDA for the treatment of major depressive disorder (Lefaucheur et al., 2020), while tDCS continues to be studied for its potential (Fregni et al., 2021; Rossi et al., 2009). More recently, there has been increased interest in exploring NIBS as a tool for modulating brain excitability to enhance sports performance (Angius, Pascual-Leone, & Santarnecchi, 2018).

2.2 Varying Protocols of NIBS for Endurance Performance

Although many studies have investigated using NIBS to increase excitability in the M1 or DLPFC to enhance endurance sports performance, there is no consensus on its efficacy. Some studies have reported increases in performance when using anodal tDCS to increase excitability of the M1 or DLPFC (Angius, Mauger, et al., 2018; Angius et al., 2019; Cogiamanian et al., 2007; Dos Santos et al., 2023; Fortes et al., 2022; Okano et al., 2015; Park et al., 2019; Vitor-Costa et al., 2015; Wang et al., 2022), yet others found no effect (Angius et al., 2015; Baldari et al., 2018; Byrne & Flood, 2019; da Silva Machado et al., 2021; Judge et al., 2021; Liang et al., 2022; Radel et al., 2017). These discrepancies may exist for various reasons, including stimulation protocols, characteristics of participants, location of stimulation, and testing procedures and outcome measures, all of which will be explored in the following sections.

2.2.1 Participants

Levels of athletic ability have greatly varied in literature. Studies have utilized healthy adults (Byrne & Flood, 2019; Radel et al., 2017), active adults (Angius, Mauger, et al., 2018; Judge et al., 2021; Vitor-Costa et al., 2015), non-elite athletes (Baldari et al., 2018) and elite athletes competing at the national level (Liang et al., 2022; Okano et al., 2015). Athletic ability did not correlate with increases in performance, as both positive and negative results were found within the same population.

Several studies utilized only male participants (Baldari et al., 2018; da Silva Machado et al., 2021; Okano et al., 2015; Vitor-Costa et al., 2015). Due to the differences in hormone levels, brain excitability, cortical thickness, and location of brain regions (Mylius et al., 2013) in males and

females, comparisons can be challenging. Even among females, different phases of the menstrual cycle have been associated with greater fatigability following NIBS (Deters et al., 2022).

Additionally, many studies had very small sample sizes, with fewer than 15 participants (Angius, Mauger, et al., 2018; Baldari et al., 2018; da Silva Machado et al., 2021; Deters et al., 2022; Liang et al., 2022; Okano et al., 2015; Vitor-Costa et al., 2015). Especially when trying to recruit athletes, smaller sample sizes can be beneficial to ensure that the sample is of similar performance level. However, these small sample sizes make it more challenging to generalize results to the larger target population.

2.2.2 Stimulation Protocol

Most studies investigating using NIBS for endurance performance have used tDCS instead of rTMS. Although some studies have explored rTMS in sports settings, these studies have primarily focused on anaerobic power (Canino et al., 2023; Giboin et al., 2016), reaction times (Schlaghecken et al., 2003), and resistance training (Hortobágyi et al., 2009), not endurance exercise. Despite the majority of studies using tDCS as the method to increase cortical excitability, variability still exists within tDCS stimulation protocols.

Stimulation intensity for tDCS can range from 0.5 mA to 4.0 mA (Solomons & Shanmugasundaram, 2020) . The majority of studies targeting endurance performance utilized 2.0 mA; however, some used 2.2 mA (Liang et al., 2022), 2.4 mA (da Silva Machado et al., 2021), and 4.0 mA (Deters et al., 2022). Different sizes of electrodes used can further affect how tolerable stimulation is, with larger electrodes distributing the current over a larger surface area, making the stimulation more comfortable (Flodin et al., 2022). Electrode size was not consistent across studies, even within studies that utilized the same current intensity.

Stimulation durations also varied from 10 minutes (Angius, Mauger, et al., 2018; Judge et al., 2021), 13 minutes (Vitor-Costa et al., 2015), 20 minutes (Baldari et al., 2018; Byrne & Flood, 2019; da Silva Machado et al., 2021; Okano et al., 2015), and 30 minutes (Angius et al., 2019). There was no relationship between intensity or stimulation length and increase in performance. Despite the cost and portability benefits of tDCS, these differences in protocol could be considered a weakness of this method. Therefore, it may be beneficial to explore other types of NIBS, such as iTBS, due to its more regulated and individualized protocols. Although iTBS has not been

explored in an endurance context, it may be preferable for future studies to allow for direct comparisons of results.

2.2.3 Location of stimulation

Electrode placement is another variable in NIBS that differs between studies. tDCS requires an anodal electrode to be placed over the desired stimulation site, while a cathodal electrode is placed in a secondary location to inhibit activity (Angius et al., 2017). Many studies have positioned the anodal electrode over the M1 to increase motor output (Angius, Mauger, et al., 2018; Baldari et al., 2018; da Silva Machado et al., 2021; Vitor-Costa et al., 2015). However, the electrodes used in tDCS lack the precision to target specific parts of the M1 (Solomons & Shanmugasundaram, 2020). Therefore, multiple muscles could have been stimulated simultaneously. Even among studies targeting the M1, further differences exist, with some stimulating the bilateral M1 (Angius, Mauger, et al., 2018; Yang et al., 2024) as opposed to the unilateral M1, and others inhibiting additional brain regions such as the DLPFC (Angius et al., 2015), in addition to M1 stimulation. These studies have reported both positive effects and no significant changes.

Similarly, mixed evidence exists for studies targeting the DLPFC. Some research has found benefits such as lower RPE and longer time to exhaustion (Angius et al., 2019; Lattari et al., 2018). However, other studies have observed no changes in performance after stimulation of the DLPFC (Byrne & Flood, 2019; Judge et al., 2021). Additional brain regions, including the temporal lobe (Barwood et al., 2016; Okano et al., 2015) and the orbital prefrontal cortex (Fortes et al., 2022) have also been targeted, but no specific pattern of efficacy has emerged from stimulation of any of the specified locations.

Some studies have directly compared M1 to DLPFC stimulation within the same participants. Results have varied, with some showing no difference between either stimulation site and sham (Radel et al., 2017), while others found an increase in endurance performance after DLPFC stimulation but not M1 (Etemadi et al., 2023). Further studies tested the upregulation of both M1 and DLPFC in the same session. Banaei et al. (2023) found that cycling time to exhaustion and Stroop test scores improved; however, this study was performed in a state of hypoxia, and the tDCS intervention was combined with the consumption of dark chocolate. Despite interest in both brain regions, limited research has investigated combined stimulation of both targets in a single

session. Further research on dual-site stimulation could provide insights into its potential benefits for endurance performance.

Placement of the cathodal electrode varied across all studies, with some opting for a cephalic montage, which places the cathode on a region inside the brain, and others utilizing an extracephalic montage, such as the shoulder (Noetscher et al., 2014). Only one study specifically placed the cathode over one of the two regions typically targeted by the anodal electrode. However, positioning the cathode over the DLPFC (Angius et al., 2016), produced no effect compared to sham.

2.2.4 Testing procedures

Further discrepancies exist in testing protocols and outcome measures. Endurance tests typically involve either single-joint isometric contractions or whole-body dynamic exercises, with cycling being the most common (Angius et al., 2017). However, research on full-body exercises such as swimming, rowing, and treadmill and overground running remains limited.

Isometric contractions are often used to test endurance because they allow for targeted muscle testing under controlled conditions, making them easier to standardize compared to full-body exercises (Angius et al., 2017). Some studies have reported increased time to exhaustion during a sustained contraction of the elbow flexors following stimulation with the anodal electrode placed over the M1 and with an extracephalic (Cogiamanian et al., 2007) or cephalic (Wang et al., 2022) placement of the cathodal electrode. However, others found no significant effects for the same muscle with anodal M1 or DLPFC stimulation and a cephalic return electrode (Radel et al., 2017). Results for stimulation of the knee extensors have been inconsistent, with reports of increased time to exhaustion during contraction after M1 stimulation with an extracephalic cathode placement, but not a cephalic cathode placement that decreased excitability in the DLPFC (Angius et al., 2016). Declines in in overall force production after fatiguing maximum contraction tasks following anodal M1 stimulation with a cephalic montage (Savoury et al., 2023) have also been found. Although single-muscle testing provides greater control and standardization amongst participants, its relevance to real-word scenarios is unclear.

Testing the effects of tDCS by cycle ergometer combines the practicality of whole-body exercise while retaining some degree of control with the athlete seated on a stationary machine where speed

can be regulated. Several studies reported have reported increases in time to exhaustion following cephalic and extracephalic anodal stimulation over the M1 or temporal cortex (Angius, Mauger, et al., 2018; Okano et al., 2015; Vitor-Costa et al., 2015), with some showing improvements of as much as 23% (Angius, Mauger, et al., 2018). However, this success is not consistent across the literature, as multiple studies demonstrated no discernable effects on performance (da Silva Machado et al., 2021; Judge et al., 2021), following cephalic anodal stimulation of the M1 or DLPFC. Although using a cycle ergometer may be the most appropriate method to assess the effects of increasing excitability on performance in cyclists specifically, it should be noted that some tests have used a mix of cyclists and runners in their sample.

Rowing and swimming have also been tested for whole-body endurance, but to a lesser extent. No performance benefits were found for elite female rowers using a rowing ergometer after anodal tDCS delivered to the M1 with a cephalic montage (Liang et al., 2022). Yang et al. (2024) explored the effects of six weeks of anodal M1 tDCS combined with physical training on running and swimming in national-level swimmers. Increases in performance were found only in anaerobic endurance of 400m running, with no significant improvements in aerobic endurance in running (1,000 m), or in anaerobic (200 m) and aerobic (400 m) endurance tests of swimming. Similarly, Valenzuela et al. (2019) found no effect on elite triathletes 800m swimming performances after anodal M1 stimulation. However, some positive findings exist, with increased resistance to muscle fatigue and aerobic capacity observed in amateur female swimmers after stimulation with the anodal electrode placed over the left orbital prefrontal cortex and the cathodal electrode over the right orbital prefrontal cortex (Fortes et al., 2022).

Despite running being highly transferable to competitive environments, few studies have assessed the use of NIBS for enhancing running performance by a running test. Only three studies were found that performed excitatory tDCS over the M1 and assessed performance with a treadmill. All three studies utilized an all-male participant sample with similar maximal oxygen uptake (VO_2max), but other differences existed for testing protocols and outcome measures. A study done by Park et al. (2019) was the only study that reported positive results, with a significant increase in time to exhaustion during a constant load to exhaustion test with runners performing the test at 80% of their VO_2max. They utilized a tDCS protocol of 20 minutes of anodal stimulation at 1.98 mA with the anodal electrode placed at the Cz area of the M1 and the cathodal electrode placed at

C5 and C6 based on the 10-20 EEG system map (Park et al., 2019). These results conflicted with the findings of Baldari et al. (2018), who reported no differences in time to exhaustion during an incremental ramp test. Duration and anodal electrode placement were identical to that of Park et al. (2019), however the current was 2 mA and the return electrode was placed on the occipital protuberance. Martens et al. (2024) similarly found no significant improvements, but the testing protocol utilized was a constant load to exhaustion test ran at 90% of VO_2max and the current delivered was 4 mA. More electrodes were utilized with five anodal electrodes (Cz, C1, C2, C3, C4) and three cathodal electrodes (P3, P4, Fz). These differences make it very challenging to compare these studies directly. Although treadmill running allows for controlled and uninterrupted straight running, it differs from real-world competitions, which rarely occur in such controlled conditions.

Only one study has been found to use overground running as a performance test. Dos Santos et al. (2023) employed a tDCS protocol of 20 minutes of 2mA anodal stimulation over the M1 at the C3 and C4 with the cathodal electrode over the occipital protuberance. The time to complete a 5,000m run on an indoor track was significantly faster in the stimulation conditions compared to the sham condition. Although these results are promising, several factors should be considered. Notably, the study used a between-subjects design rather than a within-subjects design. Since there was no pre-test to determine baseline running performance, it is unknown if the runners in the sham group already had slower times on average than the treatment group. Using two different groups also disregards other differences that may exist in participants including responsiveness to brain stimulation. Therefore, although promising, these results should be interpreted with caution.

2.3 Running Performance Metrics

In addition to variations in testing protocols, multiple measures exist to quantify running performance and experience. Running economy, time to exhaustion or failure, speed, and RPE are among these metrics. Running economy measures the oxygen consumption rate during submaximal running (Heise & Martin, 2001) and is considered a better performance indicator than maximal oxygen uptake (Morgan et al., 1989). However, measuring oxygen consumption, either maximally or sub-maximally, requires runners to wear a mask, which typically restricts testing to laboratory setting. Additionally, the unfamiliar equipment may influence running mechanics and exercise, but it does not account for changes occurring throughout the task. Speed changes during

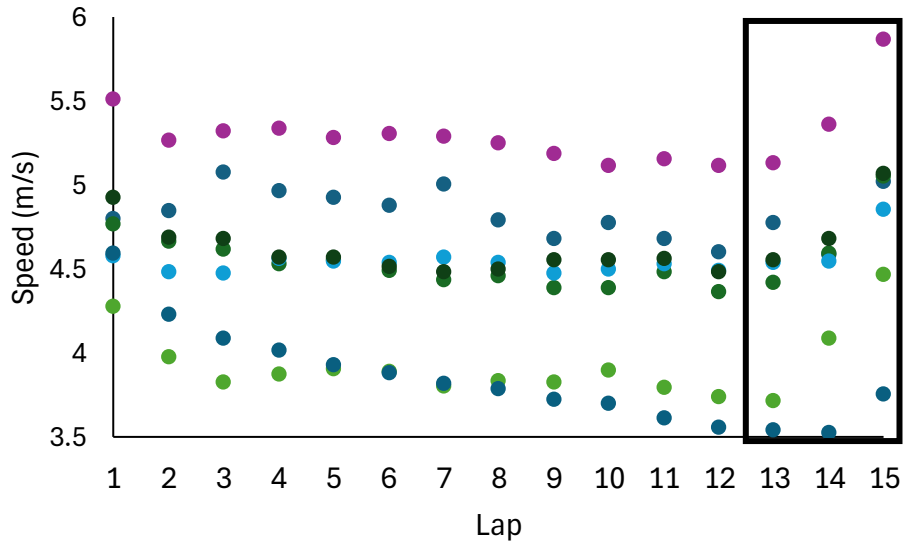

Figure 2.1 Speed in m/s of runners over 15 laps on a 200m track (3,000m) showing a negative pacing strategy. The majority of the run is performed at a steady pace until runners accelerate at the end, shown in the black box. Each color represents a different individual.

a run could be attributed to fatigue, but they could also reflect different pacing strategies, in which runners decide how to distribute the intensity of exercise over a middle or long-distance run (Cuk et al., 2021). A common strategy, negative pacing, involves maintaining a steady pace for most of the race before accelerating in the final stage (Abbiss & Laursen, 2008). A visual representation of this strategy is shown in Figure 2.1performance. Time to exhaustion provides insight into how long someone can sustain a given exercise. RPE is a subjective measure commonly measured by the Borg scale, which starts at six (no exertion) and ends at 20, which is maximal exertion (Borg, 1982). However, RPE can be influenced by individual pain tolerance levels and may be over or underestimated depending on experience level (Pirscoveanu & Oliveira, 2024). Each of these measures reveal unique information about the different aspects of running, all of which can contribute to overall performance.

2.3.1 Spatiotemporal Parameters

Spatiotemporal parameters are measures of time and distance that can be calculated from the gait events of foot strike and toe-off (Iwai et al., 2019). Specifically in running, several spatiotemporal factors have been associated with better performance and higher running economy (Tartaruga et

al., 2012). These measures are frequently studied in gait analysis in clinical (Gouelle & Mégrot, 2017) and sports settings (Lohman et al., 2011). By identifying foot strike and toe-off events from acceleration data (Figure 2.2), several parameters can be identified. This includes step frequency (SF), the number of steps per minute; stride time (ST), the number of seconds to complete one stride, as measured from one foot strike to the next consecutive foot strike on the same side; contact time (CT), the number of seconds between heel strike and toe-off of the same foot; flight time (FT), the number of seconds between one foot leaving the ground and the opposite foot striking the ground; and step length, the distance between one heel strike and the next consecutive heel strike (Felipe García-Pinillos et al., 2020). It should be noted that step length and stride length (SL) are sometimes used interchangeably, but step length traditionally refers to distance of one step, either right or left, while stride length is the distance between one stride, both right and left steps (Rodríguez-Molinero et al., 2019).

Spatiotemporal parameters have been associated with performance, but there are varying results

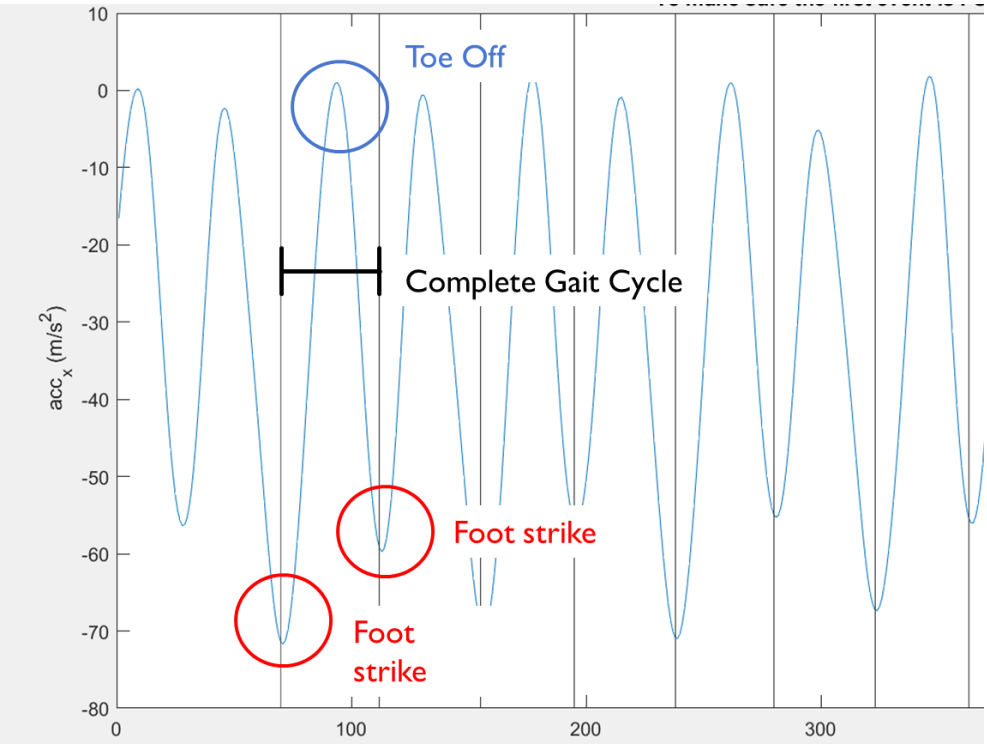

Figure 2.2 Foot strikes and toe-offs were identified by analyzing the derivative of the filtered right-foot acceleration in the forward running direction (x-axis: seconds). Events showing deceleration (negative peaks circled in red) were determined to be ground contact and labeled as foot strike. Positive peaks were labeled as toe-off (circled in dark blue). A complete gait cycle was defined as the time between two consecutive right-foot strikes.

across the literature. For example, both SF and SL are self-optimized by runners to reduce the amount of oxygen uptake (Hunter et al., 2017; van Oeveren et al., 2017). Self-optimization would indicate that the magnitude of the value itself would not necessarily be a good indicator of performance. Yet, some studies will report a higher SF being more beneficial to performance (Gómez-Molina et al., 2017; Slawinski & Billat, 2004) and associated with lower energy cost (Van Hooren et al., 2024), whereas others show evidence of a relationship between lower SF and higher performance (da Rosa et al., 2019). There is an inverse relationship between SF and SL at a given running speed (Van Hooren et al., 2024), indicating that if a higher SF were more beneficial, a lower SL would be helpful and vice versa. Similar discrepancies have been reported for duty factor (DF), which measures the ratio of time spent in CT to total ST (Patoz et al., 2019). Shorter CT may seem optimal for reducing energy costs and fatigue, but it also requires more force and, therefore, may be higher in metabolic cost (Moore, 2016). Other evidence has suggested that runners with a lower DF had a more symmetrical running step (Patoz et al., 2019). On the other hand, higher DF runners showed less vertical oscillation of their center of mass trajectory (Patoz et al., 2022), which is another indicator of a better running economy (Barnes & Kilding, 2015). Despite the differences in literature, observing how these parameters change with increased cortical excitability could still offer valuable information on how runners adapt their gait in response to increased excitability which could potentially allow for individualized training strategies.

Examining spatiotemporal factors is also advantageous because they can be measured with small, portable inertial measurement units (IMU) that can be placed directly on the body. Utilizing IMUs allows for overground testing protocols and is usually less of a hindrance for runners than wearing masks for an oxygen consumption test. Additionally, these parameters are calculated from each gait cycle. Examining middle or long-distance running yields numerous gait cycles that can provide insight into these factors over a longer period of time and allow for comparisons within a factor to assess variability.

2.3.2 Variability in Spatiotemporal Parameters

Variability refers to variations in movements when completing the same task multiple times (Marineau et al., 2024). Research suggests that at least 10 seconds of measurement is required for

an accurate assessment of variability (García-Pinillos et al., 2018). Although it may seem that longer-distance events are best to measure variability, variability has been shown to increase with higher running velocity (F. García-Pinillos et al., 2020). Therefore, middle-distance running may be the best candidate for observing these patterns as it has increased speed compared to longer-distance events but maintains many gait cycles compared to sprinting.

While some variability can be protective against overuse injuries (Hafer et al., 2019), generally, excessive variability has been associated with lower performance levels (Nakayama et al., 2010) and a higher risk of injury (Hamill et al., 2012) in sports, including running. Evidence suggests that higher-level runners typically display more consistent kinematic and spatiotemporal parameters than lower-level runners (Jiang et al., 2023; Nakayama et al., 2010). For instance, Fadillioglu et al. (2022) found that expert runners had lower SF variability and vertical oscillation of center of mass than novice runners.

Beyond skill level, fatigue, the inability for muscle to sustain output due to sustained physical activity (Enoka & Stuart, 1992), is another factor associated with increased variability in spatiotemporal measures. Felipe García-Pinillos et al. (2020) found that the coefficient of variation (CV) increased significantly in CT, FT, SF, and SL between non-fatigued and fatigued states. Fatigue has also been associated with lower performance and a greater risk of injury (Riazati et al., 2020), suggesting that spatiotemporal variability associated with fatigue could be an underlying cause of these detrimental effects.

Although other studies have found no change in variability after a prolonged overground run (Brahms et al., 2022; Meardon et al., 2011), these studies controlled the runner's speed by using instrumented foot pods to maintain a 5,000m race pace and were instructed to run until exhaustion. Meardon et al. (2011) failed to report the average distance running before exhaustion, while Brahms et al. (2022) reported that elite runners stopped before they reached 5,000m on average. In an actual event, where speed would not be externally controlled, greater variability would most likely be present since runners could not stop when they could not maintain the same pace. A time-trial run, in which runners self-regulate their pace, would provide a more realistic reflection of a more competitive environment.

2.3.3 Spatiotemporal Parameters and NIBS

Although research on using spatiotemporal parameters and variability to assess endurance performance after increasing cortical excitability is scarce, several studies have examined gait in other populations following brain stimulation. Much of this research has been conducted in rehabilitation settings, where the goal is to improve unstable and highly variable gait (Wong et al., 2022). In a review of studies that looked at using tDCS to increase cortical excitability for gait in people with Parkinson's disease, the majority of studies increased excitability in the M1 and half of studies that increased excitability in the DLPFC, found reduced variability and improved walking parameters (Pol et al., 2021), including cadence, speed, SL, and double support time.

In healthy populations, there is limited literature on the subject. Studies stimulating the M1 targeted the tibialis anterior (TA) muscle specifically due to its importance before heel strike in the swing phase of gait (Koganemaru et al., 2018). Studies that have increased excitability in the M1 TA region found increased force propulsion (van Asseldonk & Boonstra, 2016), and increased speed and SL (Koganemaru et al., 2018). After excitatory stimulation of the DLPFC in healthy individuals, Wrightson et al. (2015) found decreases in ST variability, and Zhou et al. (2014) found improved gait speed while dual-tasking in healthy individuals. In one study that investigated stimulation of DLPFC and M1 together (Orcioli-Silva et al., 2021), although there were no overall effects on gait parameters, increases in activity of DLPFC measured by functional near-infrared spectroscopy were associated with decreased SL variability. Similarly, Schneider et al. (2021) demonstrated that anodal tDCS of both M1 and DLPFC in healthy older adults resulted in increased gait speed and reduced ST variability during dual-tasking. These findings suggest that increasing cortical excitability can also impact spatiotemporal parameters in healthy individuals and these benefits might be transferable to running gait.

Chapter 3: Manuscript

The Effect of Intermittent Theta Burst Stimulation Applied to the Primary Motor Cortex and Dorsolateral Prefrontal Cortex on Running Performance in Endurance-Trained Runners

Isabella Sierra[a,b] , Yiyang Chen[a], Gleydciane Alexandre Fernandes[a,b], Henri Lajeunesse[a,b], Julien Clouette[a], Alexandra Potvin-Desrochers[a,b,d], Julie Côté[a], Fabien A. Basset[c], Caroline Paquette[a,b]

[a] Department of Kinesiology and Physical Education, McGill University, Canada

[b] Jewish Rehabilitation Hospital - Research Site of CRIR and CISSS Laval

[c] Memorial University of Newfoundland, Canada

[d] Centre de recherche, Centre Intégré de Santé et des Services Sociaux de l'Outaouais, Gatineau, Canada

To be submitted to the Scandinavian Journal of Medicine & Science in Sports

3.1 Abstract

Background: Applying forms of non-invasive brain stimulation (NIBS) to the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) may improve running performance by increasing muscle output and decreasing feelings of pain unpleasantness. Several studies have examined the impact of utilizing NIBS to alter cortical excitability and improve endurance performance, but few have focused on running performance specifically. Additionally, studies have primarily increased excitability in only one region. This study examines the impact of excitatory stimulation, in the form of intermittent theta burst stimulation (iTBS), applied to both the primary motor cortex M1 and DLPFC compared to stimulation of either area alone or sham stimulation on performance metrics during a 3,000m time-trial run in endurance-trained runners. **Methods:** Ten endurance-trained runners (7 males, 3 females) completed one initial and four experimental stimulation sessions in randomized order: M1+DLPFC, M1 only, DLPFC only, or sham stimulation. After stimulation, runners performed the 3,000m time-trial run at maximal effort. Metrics including total run time, lap speeds, rating of perceived exertion (RPE), and spatiotemporal parameters (stride time, step frequency, stride length, and duty factor) and their variability were collected and analyzed in three phases of the run: initial, steady-state, and final acceleration. **Results:** The M1+DLPFC condition resulted in the fastest overall time-trial completion at 11:01 (mm:ss), averaging one second faster than the condition stimulating either area alone and three seconds faster than the sham condition, however this difference was not statistically significant (F= 0.21, p = .889, η^2_p = .023). Notably, lap speed in the initial lap of the M1+DLPFC condition was significantly faster than the DLPFC only condition by 0.17 m/s. Despite the increase in speed, RPE remained unchanged between conditions, throughout the entirety of the run. The increased speed in the M1+DLFPC condition was not maintained in the steady state or final acceleration phase. In fact, the speed in the final acceleration lap in the sham condition was significantly faster than the M1+DLPFC conditions by 0.11 m/s. Spatiotemporal parameters of stride time and step frequency showed significant improvements in the M1+ DLPFC condition in the initial lap compared to the M1 only condition Spatiotemporal variability was not significantly affected by brain stimulation condition. However, the DLPFC only condition showed the most stable steady state phase for stride time, step frequency, and stride length, with a significantly smaller increase throughout the phase compared to sham. **Conclusion**: iTBS applied to both M1 and DLPFC produced the fastest, though not statistically significant, overall running

times and significantly fastest running speed in the initial lap without changing perceived exertion. Our findings suggest that brain stimulation targeting the M1 and DLPFC may enhance performance by influencing total time, speed, and magnitude of spatiotemporal parameters but not variability. Future research should investigate the optimal timing of testing after stimulation to extend the potential benefits of utilizing NIBS to enhance endurance performance.

3.2. Introduction

Utilizing non-invasive brain stimulation (NIBS) to increase cortical excitability has been explored as a potential method to enhance endurance running performance. Although several brain regions are associated with factors relevant to athletic performance, the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) are among the most commonly explored regions. The M1 is responsible for voluntary muscle contraction and the execution of movements (Moscatelli et al., 2021). It has a somatotopic organization, meaning specific areas of the cortex correspond to the control of particular muscles (Wise, 2001). Muscle contraction is driven by motor neurons in the spinal cord, collectively known as the motor neuron pool, which send signals from the brain to the muscles (Heckman & Enoka, 2012). During endurance exercise, the motor neuron pool experiences decreased excitability, and results in reduced muscle capacity, contributing to fatigue (Gandevia, 2001). Increasing excitability of M1 may help to slow this decrease in neural drive that occurs due to exercise-related fatigue (Lorenz et al., 2003; Radel et al., 2017). Increased neural drive could lead to greater muscle output, potentially allowing runners to produce greater force to maintain high levels of exercise for longer durations (Etemadi et al., 2023).

Failure to sustain sufficient muscle output alone is not the sole factor determining exercise termination, as studies have shown that activity in the prefrontal cortex decreases just prior to exercise termination (Robertson & Marino, 2016). The DLPFC specifically is involved in pain perception, motivation and cognitive control, all of which influence endurance exercises (Byrne & Flood, 2019; Lorenz et al., 2003). Previous studies suggest that an athlete's ability to tolerate exercise-induced pain is associated with performance levels (Astokorki & Mauger, 2017; Pettersen et al., 2020). Additionally, increased excitability of the left DLPFC has been linked to reduced rating of perceived exertion (RPE) and a lower degree of pain perception (Angius et al., 2019; Lorenz et al., 2003; Teymoori et al., 2023), which may allow athletes to endure discomfort caused by exercise for longer periods of time.

The limited research that has examined applying NIBS to either the M1 or DLPFC in the context of running performance has produced mixed results. The discrepancy in findings may be partially attributed to differences in stimulation protocols. The majority of studies have used a type of NIBS called transcranial direct stimulation (tDCS). Although tDCS is cost-effective and portable (Zaghi et al., 2009), the lack of uniform protocols makes it challenging to compare studies directly. For instance, in the few studies that have examined running performance after excitatory M1 stimulation, variances existed in stimulation intensity, electrode size and electrode placement.

Only one study found to date has examined tDCS in an overground running setting. Following stimulation, Dos Santos et al. (2023) found in overall time to complete a 5,000m run on an indoor track compared to a sham stimulation group. However, this study used a between-subjects design with no baseline testing for either group. Therefore, the difference in time to complete the time-trial run could be explained by differing performance levels in individuals, as performance levels of each group were not reported. Of the studies that assessed running performance on a treadmill, only one reported an increase in time to exhaustion (Park et al., 2019), with the other two finding no significant difference in exercise tolerance compared to sham (Baldari et al., 2018; Martens et al., 2024). Despite all three studies recruiting male participants with similar values of maximal oxygen uptake (VO_2max), further discrepancies were evident in sample size with a range of 10-45 participants, and treadmill protocols such as using a constant load test compared to a graded test. These methodological differences may influence how well the results translate to actual running performance. Although fixed-speed treadmill protocols offer greater control, they prevent runners from using natural pacing strategies that are typically observed when individuals can adjust their own speed, such as on a self-paced treadmill or during overground running. Even on self-paced treadmills, however, the absence of visual feedback can make it challenging for runners to pace themselves naturally. This limitation of treadmill testing could fail to show potential effects of increased cortical excitability that vary across different phases of a run.

The optimal magnitudes of several spatiotemporal parameters may be more telling of running style, as opposed to performance levels (van Oeveren et al., 2021). For example, although past studies have associated lower step frequency (SF) with better performance (da Rosa et al., 2019), other studies have found seen an association between higher SF and higher performance (Gómez-Molina et al., 2017). Similar discrepancies exist for duty factor (DF), which measures the

proportion of contact time (CT) to total time to complete one gait cycle. A smaller DF is characterized by shorter CT and a longer flight phase. Longer flights phases have been associated with better performance (da Rosa et al., 2019), but at the same time, the shorter CT that accompanies a longer flight phase may also demand more force which could negatively impact performance (Moore, 2016). Even if a specific magnitude is not indicative of performance, observing how these parameters change could still offer valuable information on how runners adapt their gait in response to increased excitability.

Excessive variability in these spatiotemporal parameters, particularly when induced by fatigue can impair performance (Hamill et al., 2012). Although a certain amount of variability in running is inevitable (Cowin et al., 2022), higher-level runners typically exhibit more consistent biomechanics and reduced variability compared to lower-level runners (Jiang et al., 2023). More experienced runners have shown reduced variability in SF (Fadillioglu et al., 2022), CT (Watanabe et al., 2023) and ST (Clermont et al., 2019; Nakayama et al., 2010). Collecting information on both spatiotemporal parameters and spatiotemporal variability throughout a run may provide further meaningful objective insight compared to time alone.

Spatiotemporal parameters and variability have not been used as outcome measures in studies that increase cortical excitability to enhance endurance performance specifically. However, studies on healthy young individuals performing walking tasks have shown increased stride length (SL) and speed (Koganemaru et al., 2018) after M1 stimulation and reduced stride time (ST) variability (Wrightson et al., 2015) during dual-tasking after DLPFC stimulation. This effect of reduced variability could be attributed to the DLPFC's role in cognitive functions such as task prioritization (Byrne & Flood, 2019), which in the context of middle-distance running, could be beneficial for pacing strategies and regulation of effort.

Although there is interest in both M1 and DLPFC separately, limited studies have explored stimulating both regions together to improve multiple aspects of performance at the same time. One study from Schneider et al. (2021) found that stimulating both M1 and DLPFC in healthy older adults led to increased gait speed and reduced ST variability during dual-tasking. Based on previous research, it could be assumed that the increase in speed was driven by M1 stimulation, while the reduction in variability resulted from DLPFC stimulation. However, as the study did not

stimulate each region separately, it is impossible to determine whether these effects were due to the combined influence of both areas or if one region was primarily responsible.

Since M1 stimulation could lead to greater muscle activation, improving endurance performance, and DLPFC stimulation may reduce perceived exertion and variability and improve task prioritization, applying excitatory stimulation, in the form of intermittent theta burst stimulation (iTBS) to both the M1 and DLPFC has the potential to enhance endurance performance more than either area alone. Accordingly, this study examines how applying iTBS to the M1, DLPFC, or both influence total time, speed, RPE, and spatiotemporal parameters of ST, SF, SL and DF and their variability throughout a 3,000m time-trial. We hypothesize the following:

1. The M1 only and M1 + DLPFC conditions will produce faster total times to complete the 3,000m time-trial run and faster lap speeds compared to stimulation of the DLPFC only or sham stimulation.
2. Runners will show decreased RPE in the DLPFC only and M1+DLPFC condition throughout the entirety of the 3,000m time-trial, compared to stimulation of M1 only or sham stimulation.
3. Variability of ST, DF, SF and SL will increase throughout the run, however, stimulation of the DPLFC only and M1 + DLPFC conditions will mitigate the increase in variability more so than stimulation of the M1 only or sham stimulation.

3.3. Methods

3.3.1 Participants

This study was part of a larger investigation on increasing excitability on the M1 and DLPFC and running performance (Sierra, 2023). Thirty-seven runners signed a consent form for the study, however, only 23 completed all sessions. From these 23 runners, exclusions were made due to inconsistent performance due to illness, failure to adhere to provided guidelines, incorrect intensity of iTBS applied due to discomfort, or incomplete kinematic data for all four sessions. The final sample for this study included ten endurance-trained runners (3 females, 7 males, mean age= 26 years, SD = 7, range = 18–41 years; Table 3.1).

Table 3.1

Description of runner characteristics

ID	Sex	Age	Height (cm)	Weight (Kg)	Edinburgh Hanedness Score	Waterloo Footedness Score	Specialization (distance)	Years of trainnig	Training volume per week (km)	Vo2 Max (mL/kg/min)	Best 5km (min)	Best 10km (min)	Mercier Performance Index
RUN_01	M	26	183	72	90	17	Middle	12	50	56.5	-	33.25	574
RUN_11	M	21	183	65	100	15	Middle	7	60	61.6	15:30	32:45	610
RUN_03	M	22	191	64	100	1	Middle	9	65	75.4	14:45	-	703
RUN_06	M	37	172	75	80	18	Long	10	55	57.3	20:00	43:00	195
RUN_20	M	29	172	71	80	0	Long	10	100	64.1	-	34:00	554
RUN_05	M	22	182	70	100	4	Long	3.5	60	64.7	19:34	39.34	226
RUN_17	M	31	167	70	100	6	Long	3	50	73.4	17:00	35:00	447
RUN_25	F	18	172	70	79	8	Long	2	35	47.3	20:00	50:00	513
RUN_16	F	41	167	51	100	5	Long	20	50	52.2	20:00	43:00	513
RUN_15	F	20	162	46	100	15	Long	4	32	56.2	22:00	-	395
Average	-	27	175	65	93	9	-	8	56	60.9	18:36	39:37	473
SD	-	8	9	10	10	7	-	5	19	8.9	2:32	6:12	162

Runners were recruited via outreach to the McGill cross country and track teams, as well as coaches at nearby schools and universities, and posts in running groups on social media. Inclusion criteria required enrolment in an endurance running training program, participation in competitive running events for at least 2 years preceding the study, specialization in running events of 3,000m or longer, and a training volume of > 30 km/week. Exclusion criteria included musculoskeletal injury in the year preceding the study, use of central nervous system-acting medications such as antidepressants, and contraindications for TMS and magnetic resonance imaging (MRI) such as metallic hardware or fragments in the head, cochlear implants, deep brain stimulator, pacemaker, history of seizures, and claustrophobia (Rossi et al., 2021). All runners provided written informed consent according to the McGill Faculty of Medicine Institutional Review Board regulations and the Declaration of Helsinki.

3.3.2 Experimental Protocol

Runners visited the laboratory on five occasions: an initial visit followed by four experimental visits. The initial session was used to acquire structural MRI, collect runner training profiles and general health habits, familiarize runners with the experimental procedures, set individual TMS stimulation target locations to be used in the experimental visits and perform a VO_2max test.

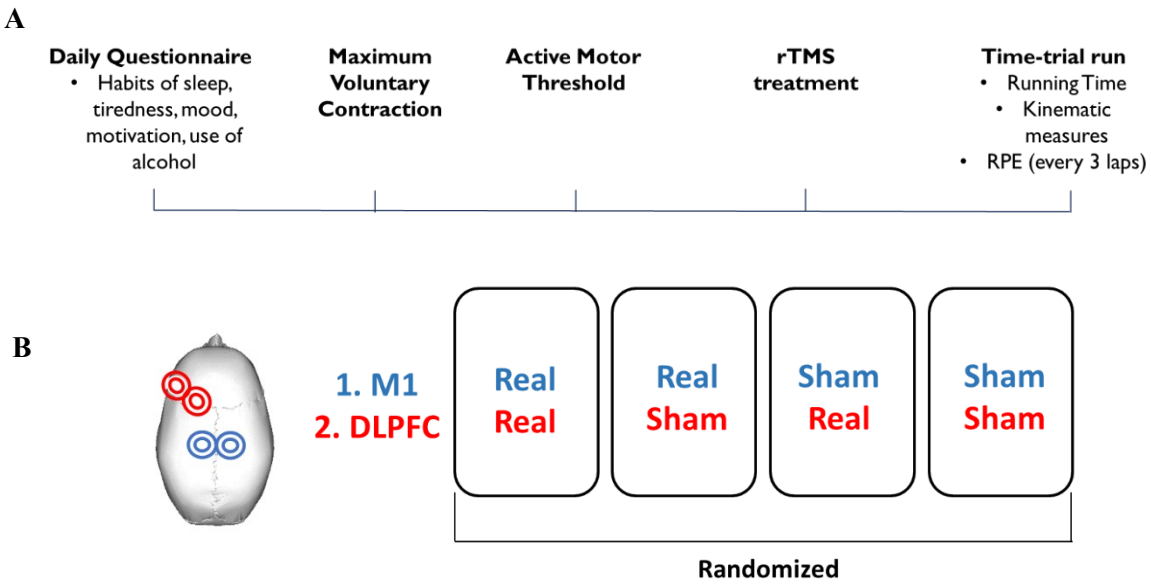

Figure 3.1. A. Timeline of experimental sessions and measures taken. B. The four rTMS treatments. Runners first received real or sham stimulation of the M1 (stimulation location shown in blue), then received real or sham stimulation over the left DLPFC (shown in red). Order of sessions was randomized and were spaced at least 72 hours apart.

During the four experimental visits (Figure 3.1), runners were administered one of four iTBS conditions shortly before performing an all out 3,000m time-trial run.

3.3.3 Initial session

MRI was acquired for each individual to allow for precise coil placement of the DLPFC which has no direct TMS output. The MRI image was acquired on a Siemens 3T (Siemens, Knoxville, TN) at the McConnell Brain Imaging Centre of the Montreal Neurological Institute (MNI; echo time = 2.96ms; repetition time=2,300ms, flip angle=9°, 192 slices, voxel size=1mm^3 isotropic).

Stimulation points for M1 TA were identified using a Magstim 200^2 TMS machine (Magstim Company, UK) by delivering single monophasic pulses during hotspot mapping. For bilateral M1 TA stimulation, the optimal location for TMS was based on the motor responses. The "hotspot" was identified by mapping the scalp area that produced the greatest response to TMS stimulation. Responses were measured by electromyography (EMG) and required to be similar in magnitude in the right and left TA muscles. The EMG set-up was the same for the initial and experimental sessions with two 2.5 cm X 2.5 cm Ag/AgCl surface gel electrodes (Biopac EL504) placed on each of the right and left TA muscle bellies per the SENIAM standard (Stegeman & Hermens, 2007) along with a ground electrode at the patella. EMG signals were recorded with a Biopac MP150 acquisition system (Biopac Systems, Inc., California, United States), sampled at 5 kHz on a 16-bit analog-to-digital board, amplified and bandpass filtered (10-2000 Hz). Pulses were delivered to the motor cortex region corresponding to the bilateral TA, located in the interhemispheric fissure anterior to the central sulcus. A 60mm dome coil (Jaltron LLC, United States) was placed on top of the runner's head in a posterior-anterior (PA) coil current directed anteriorly orientation, and the location that elicited the largest and most consistent (between trials and between right and left TA) motor-evoked potentials (MEPs) was marked in Brainsight (Brainsight neuronavigation system; Rogue Research Inc, Montreal, Canada). The location was the M1 stimulation target of the experimental sessions.

The left DLPFC location was specified by MNI coordinates (Rusjan et al., 2010) and marked in Brainsight (x=-50, y=30, z=36). The stimulation intensity for the non-motor DLPFC target was based on the resting motor threshold of the M1 of the left first dorsal interosseous (FDI). This region was used because it is a motor region that lies at similar depth as the DLPFC (Potvin-Desrochers et al., 2023). Pulses were delivered over the left M1 FDI region with a 50mm figure of

eight coil (Magstim Company, UK) placed tangential to the runner's head in a PA orientation 45 degrees from midline. The location eliciting the largest and most consistent MEPs was marked in Brainsight.

Lastly, VO_2max was measured via an incremental treadmill test to assess the cardiorespiratory fitness of the runner. The procedure began with the runner standing still and breathing normally for two minutes to obtain baseline metabolism. To begin the test, runners warmed up for 5 minutes on the treadmill at a self-selected pace. Following the warm-up, the test started at a speed of 10 km/h for females and 12 km/h for males. The speed was increased by 1 km/h every 2 minutes until volitional exhaustion was reached (Léger & Boucher, 1980). After a five-minute rest, runners then ran at 105% of the final speed reached in the initial test until volitional exhaustion, to verify maximal effort.

3.3.4 Experimental Sessions

The four experimental conditions (Figure 3.1) were given in randomized order, and runners were blinded to the condition they received. Stimulation of the M1 was always delivered before DLPFC stimulation. TMS responses were recorded in the bilateral tibialis anterior (TA) muscles, as they are known to play a crucial role in gait and balance (Maharaj et al., 2019). Sessions were typically scheduled one week apart, with a minimum separation of 72 hours to avoid carry-over effects.
At the start of each experimental session, a questionnaire was administered to document runners' previous 12 hours regarding sleep, tiredness, mood, hunger, motivation, and use of alcohol or drugs. Stimulation intensity was set based on active motor threshold (AMT). Maximum voluntary contraction (MVC), the peak muscle force, was acquired to standardize active muscle contraction when finding motor threshold. Visual feedback of muscle contraction was provided on a monitor placed in front of the runners displaying EMG activity with a target set at +/- 20% MVC, so that runners could maintain this contraction as pulses were delivered to the target. AMT was determined as the lowest possible stimulation intensity that could elicit an MEP. Intensities for the TMS were set to 80% of the AMT.

MVC for the TA was found by having the runner place both feet under a slanted wooden board and instructing them to dorsiflex using their TA muscles as hard as they could for about three seconds. A researcher stood on top of the board to provide resistance. Runners repeated this

dorsiflexion three times, and the EMG output from each foot was separately recorded. The largest force value from the right foot and the largest value from the left foot were compared. The smaller of these two values was taken as the runner's MVC. The MVC measurement was then repeated for the FDI muscle, with runners performing an isometric contraction by abducting their index finger against a wooden stick while keeping their arm placed on top of the chair's armrest. The largest value of the three trials was taken as the runner's MVC for the FDI.

The lowest possible intensity that could produce 10 out of 20 MEPs while runners maintained this contraction was determined to be the AMT and multiplied by 0.8 to obtain the stimulation intensity for bilateral TA and DLPFC stimulation (Huang et al., 2005). iTBS was given at a rate of 50Hz of stimuli at an interval of 5Hz in 2-second periods, repeated every 10 seconds for 192 seconds total (Huang et al., 2005). Real or sham stimulation of the M1 was performed first, and then immediately

Figure 3.2. Placement of coils for sham stimulation is shown. A. shows the dome coil (M1 stimulation) rotated 90 degrees to the side. B. shows the primary figure of eight coil (DLPFC stimulation) flipped and placed over a secondary figure of eight coil which was not connected to the stimulator.

after, real or sham stimulation was delivered to the DLPFC. For sham treatment of the M1, the dome coil was rotated at 90 degrees to the side of the coil, so pulses were not directed into the brain (Figure 3.2A). For sham treatment of the DLPFC, a secondary figure of eight coil was disconnected from the stimulator and placed over the DLPFC hotspot (Figure 3.2B). The original figure of eight coil was flipped then placed on top of the secondary coil (Potvin-Desrochers et al., 2023). These methods provided a similar sensation on the scalp and the same auditory stimulus. Sham stimulation was delivered at a lower intensity of 40% of the stimulation intensity.

After stimulation, runners jogged to a 200m indoor track about two minutes from the stimulation laboratory. To measure movement kinematics and spatiotemporal parameters, seven APDM Opal movement Sensors (APDM Wearable Technologies Inc, Portland, Oregon, United States) were then placed on the runner on the sternum, lumbar, right wrist, right upper leg, right lower leg, and right and left foot. Acceleration data from the sensors was collected through APDM Moveo Explorer software at a frequency of 128 Hz.

Next, runners performed a 10-minute warm-up. The runners self-selected their warm-up routine in their first experimental session. The actions of the warm-up were documented, and in all subsequent experimental sessions, runners were reminded of their initial warm-up and told to repeat it. Runners were instructed to give a maximal effort while running in lane one of the indoor track (banked at an 11-degree angle) for 15 laps. A video camera was placed at the start line to record each instance they crossed the line, and a researcher stood at the start line with a stopwatch to provide runners with their lap times. Every 600m (three laps), runners verbally reported their RPE using the Borg 6–20 scale (Borg, 1982). Runners were informed that the Borg scale is used to identify the intensity of exercise based on how hard they perceived their effort to be, with 6 being no exertion and 20 being the hardest they could possibly exert themselves. Runners were informed when they had two laps remaining and again when they had one lap to go. No other feedback or encouragement was provided. Runners were not given their total time until all four experimental sessions were completed.

3.3.5 Data Processing

Data recorded from the APDM sensors were imported into MATLAB R2024a (MathWorks, Massachusetts, United States) for processing. The forward acceleration of the lumbar sensor was utilized to calculate angular velocity. A threshold of 80% of the median was used to separate

straight running from turning events (Novak et al., 2014) and turning events were eliminated. Analysis was then performed only on the straight-running segment on the side of the track closest to the APDM receivers. Since the majority of the runners were right foot dominant, gait events were determined by the right foot.

Foot strikes and toe-offs were identified by analyzing the derivative of the filtered right-foot acceleration in the forward running direction. Instances where acceleration changed direction were identified. Events showing deceleration (negative peaks) were determined to be ground contact and labeled as foot strike. Positive peaks were labeled as toe-off. A complete gait cycle was defined as the time between two consecutive right-foot strikes (Chew et al., 2018). The final lap was omitted, as the runners crossed the finish line before completing the entire length of the straightaway.

3.3.6 Outcomes

Total time recorded by the stopwatch was verified against start-line video data. Expected time-trial performance time was calculated by converting the initial session's VO_2max to METS to estimate running speed (km/h), which was then converted to meters per second. The total distance of 3,000m was divided by speed, yielding a predicted 3,000m time-trial run time in seconds (Léger & Mercier, 1984). This equation predicted the total time of the runner for the 3,000 m time-trial run based on their measured VO_2max. Percentage of expected time was calculated by subtracting the expected time from the measured time, dividing by the expected time and then multiplied by 100%. Lap speed was calculated by dividing the lap distance (200m) by lap time (seconds). Five measurements of RPE were reported by the runner every three laps of the time-trial run.

Stride time was defined as the duration of a full gait cycle, from one right heel strike to the next. Duty factor was calculated as CT divided by ST, then multiplied by 100%. Stride frequency was calculated as 60 divided by CT, yielding the number of strides per minute, then multiplied by two to account for both steps. SF was normalized by multiplying by the distance from the right anterior superior iliac spine to the medial malleolus (Fadillioglu et al., 2022). Stride length referred to the length between one right foot strike and the next consecutive right foot strike. It was calculated as running speed (m/s) during the straight portion multiplied by CT and normalized using the same method as SF. The coefficient of variability (CV) for ST, DF, SF, and SL was calculated for each

lap as the standard deviation of all gait cycles in a lap, divided by the mean gait cycle, multiplied by 100%.

Three phases of the run were determined by graphing speed data over the course of the run. The steady state phase where speed was relatively stable with no major increases or decreases was found to be in laps 4 to 12. The initial phase (1-3) and the final acceleration phase (laps 13-15) were faster than the steady state phase. When comparing values of speed, spatiotemporal parameter and spatiotemporal variability, lap 1 was used as the initial lap, lap 12 was used as the steady state lap. Lap 15 for speed and lap 14 for spatiotemporal parameters and variability were used as the final acceleration lap. When comparing percent change, the change in the initial phase was from lap 1 to lap 3, the change in the steady state phase was between laps 4 and 12 and change in the final acceleration phase was between laps 13 and 15 for speed and between laps 13 and 14 for spatiotemporal parameters and variability.

3.3.7 Statistical Analysis

All data were analyzed in SPSS 29 (IBM, New York, United States). Normality was assessed with Shapiro-Wilk tests ($p > 0.05$), and Mauchly's test assessed sphericity ($p > 0.05$). When sphericity was violated, Greenhouse-Geisser corrections were applied. Effect sizes are reported using partial eta squared (η^2_p) and Cohen's *d*. Thresholds for interpreting effect sizes are small ($\eta^2_p = .01$, $d = 0.2$), medium ($\eta^2_p = .06$, $d = 0.5$), and large ($\eta^2_p = .14$, $d = 0.8$; Cohen, 1988).

Two one-way repeated-measures analysis of variance (RM-ANOVA) on the condition factor (4 levels) were used to compare total running time and percentage of the runner's actual time to their expected time. Nine two-way RM-ANOVAs (conditions-4 levels: Sham, M1 only, DLPFC only, M1 + DLPFC X lap-3 levels: Initial, steady state, final acceleration) were used to compare the values of the following factors: lap speed, spatiotemporal parameters (ST, SF, SL DF), and CV of spatiotemporal parameters. The normality assumption was violated for percent change in lap speed, ST, SF and SL and CV of ST, SF and SL. These factors were assessed with seven non-parametric Friedman's tests. In the event of significance, Wilcoxon signed rank tests were performed to compare factors across conditions. The normality assumption was not violated for percent change in DF or CV of DF, and two additional two-way RM-ANOVA was done to assess

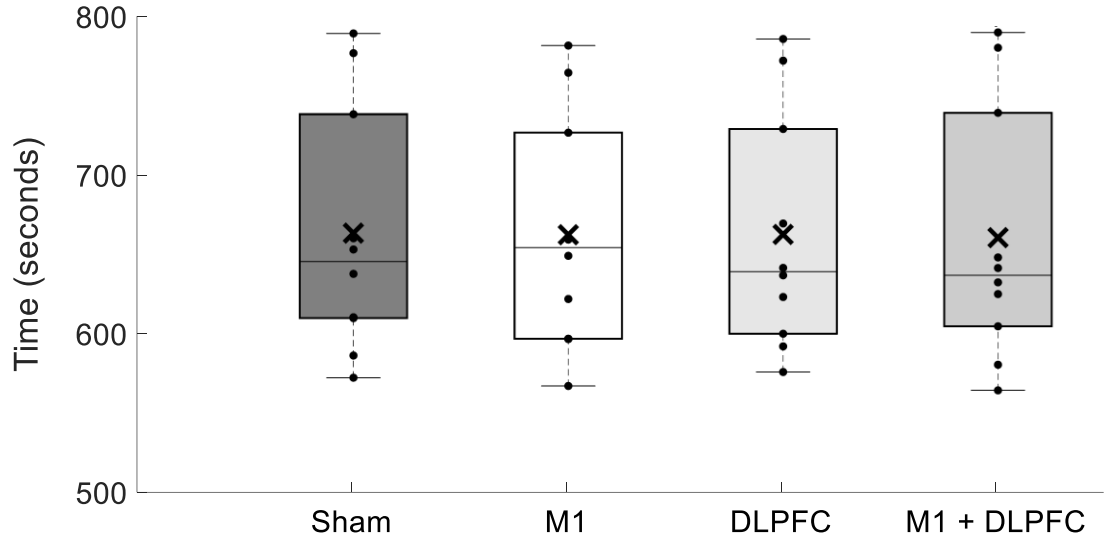

Figure 3.3 Total time (in seconds) to complete the 3,000m time-trial run across the four stimulation conditions: M1, DLPFC, Real, and Sham. Box plots show the group median as the horizontal line inside the box. Individual runner data are shown as black dots. The mean is represented by an X. No significant differences were observed between conditions.

these factors (conditions-4 levels: Sham, M1 only, DLPFC only, M1 + DLPFC X phase-3 levels: Initial, steady state, final acceleration). One two-way RM-ANOVA (conditions-4 levels: Sham, M1 only, DLPFC only, M1 + DLPFC X lap-5 levels: laps 3,6,9,12 and 15) was used to assess RPE. Least significant difference adjustments were utilized when analyzing the significance of pairwise comparisons.

3.4. Results

3.4.1 Athletic Profile

Mean VO_2max was 24.7% higher in males compared to females (Table 3.1). Mercier performance index scores were calculated based on sex and personal best 5km time-trial run times (Mureika & Covington, 2000). For two participants who did not provide a 5km time, their 10 km time was used. The average Mercier score of our sample was 473, comparable to the Mercier score of the 25th nationally ranked 5km time for males (462) and 17th nationally ranked 5km time for females (433) in 2024 in Canada, according to *Athletics Canada* (2025).

3.4.2 Running Performance

The average time to complete the 3,000m time-trial run across all conditions was 10:19 (minutes: seconds; SD= 32 seconds) for males and 12:46 (SD=25 seconds) for females. The average intersession variability was 7 seconds for males and 8 seconds for females. Total running time was similar across the four conditions (F=0.21, p =.889, η^2_p=0.02), as seen in Figure 3.3. However, the sham condition did produce the slowest average time of 11:04. The M1 only and DLPFC only conditions were faster than sham on average by 1 second (M1 only: d=0.08; DLPFC only: d=0.10) and the M1 + DLPFC condition was faster than sham on average by 3 seconds (d=0.30).

On average across all conditions, runners completed the time-trial 5.5% slower than the running time predicted by their VO_2max. No significant difference was found between conditions when comparing the predicted time to the runner's actual time in each condition (F=0.34, p=.798, η^2_p=0.04).

As shown in figure 3.4, runners followed typical pacing strategies observed in a 3,000m time-trial run (Abbiss & Laursen, 2008) where they showed the fastest speed in the initial lap at an average speed of 4.81 m/s. They maintained a steady pace for most of the time-trial run with the slowest lap occurring at lap 12 at an average speed of 4.46 m/s (Lap 1> Lap 12; Sham: t=2.57, p=.015, d=0.38; M1 only: t=2.63, p=.014, d=0.36; DLPFC only: t=2.26, p=.025m, d=0.32; M1+ DLPFC: t=2.61, p=.014, d=0.68). Lap 12 was considered the end of the steady state phase. Then, runners increased to an average speed of 4.80 m/s for the final lap. There was a significant interaction of condition and lap for lap speed (F=3.50, p=.047, η^2_p=0.28), showing that the

M1+DLPFC was significantly faster than the DLPFC only condition (+0.17 m/s, p=.043, d=0.74) in the initial lap and that the sham condition was significantly faster than the M1+DLPFC condition in the final acceleration lap (+0.11 m/s, p=.031, d=0.80). Significant differences were found between the percent change across phases and conditions (χ^2 = 48.99; p<.001), however, no significant differences were found when comparing conditions in each phase. Across all conditions speed consistently decreased in the initial phase (Sham: -3.32%, M1 only: -2.87%, DLPFC only: -3.48%, M1+DLPFC: -5.99%) and steady state phase (Sham:-2.59%, M1 only: -3.39%, DLPFC only: -1.80%, M1+DLPFC: -3.99%), and increased in the final

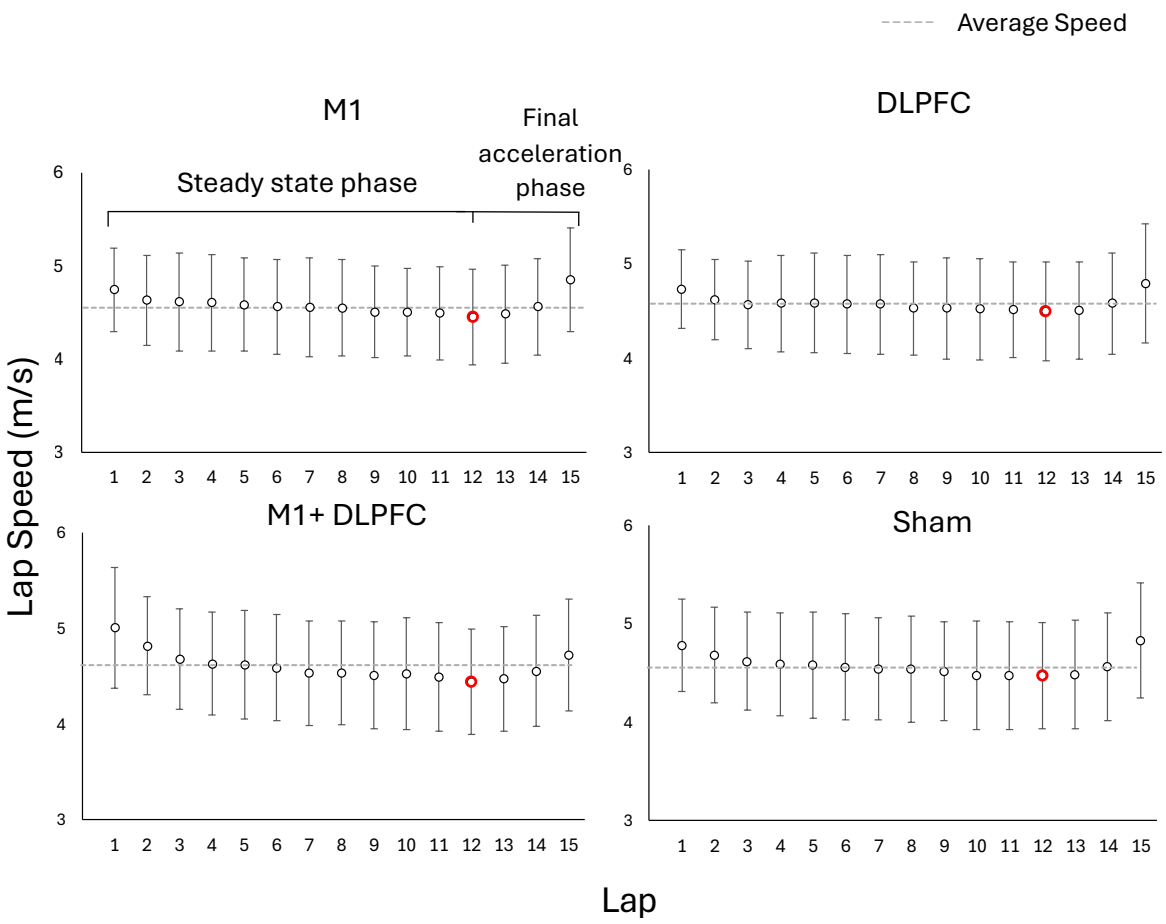

Figure 3.4 Lap speed (m/s) across 15 laps for each stimulation condition: M1 only, DLPFC only, M1 + DLPFC, and sham. Data points represent the mean speed for all runners for each lap and error bars show standard deviation. The dotted line represents the average speed across all laps within a condition. The slowest lap in each condition is circled in red. The steady state phase was determined to be the initial lap to the slowest lap and the final acceleration phase was between the slowest lap and the final lap (shown on the M1 graph).

acceleration phase (Sham: +7.71%, M1 only: +8.36%, DLPFC only: +6.35%, M1+DLPFC: +5.62%).

3.4.3 Perceived Exertion

The average RPE for lap 15 across all conditions was 19.5 indicating that runners finished the time-trial run near maximal exertion (Table 3.2). Average RPE significantly increased from lap 3 to 15 in all conditions (F=122.98, p<.001, η^2_p=0.93). No significant differences were found by condition (F=0.59, p=.628, η^2_p=0.06) or by the interaction of condition and lap (F=0.75, p=.704, η^2_p=0.08).

Table 3.2

Average (SD) rating of perceived exertion by lap and condition and results of RM-ANOVA

Condition	Lap				
	3	6	9	12	15
M1	11.4 (3.3)	14.2 (1.5)	16.2 (1.0)	17.6 (0.8)	19.4 (0.7)
DLPFC	12.3 (1.4)	14.4 (1.2)	16.2 (1.0)	18.1 (1.1)	19.5 (0.7)
M1 + DLPFC	12.1 (1.7)	14.8 (1.4)	16.5 (1.2)	17.9 (1.0)	19.7 (0.5)
Sham	12.4 (2.3)	14.6 (1.8)	15.9 (1.6)	17.5 (1.2)	19.3 (0.5)

RM-ANOVA	Condition	Lap	Condition X Lap
F-value	0.59	122.98	0.75
p-value	0.63	p<0.01*	0.70

*statistically significant

3.4.4 Spatiotemporal Running Parameters

There was a significant interaction of condition and lap for stride time (F= 3.58, p=.032, η^2_p=0.29), showing that the M1+DLPFC condition had a faster stride time compared to the M1 only condition in the initial lap (M1+DLPFC: 0.66 seconds, M1 only: 0.68 seconds, p=.011, d=1.00), as seen in Figure 3.5A. Significant differences were found between the percent change across phases and conditions (χ^2: 34.89, p< .001), with the M1 only condition showing a significantly smaller percent increase in stride time in the initial phase compared to the DLPFC only (Z=2.60, p=.009), M1+DLPFC (Z=2.60, p=.009) and sham (Z=2.19, p=.028) conditions (Sham: + 1.75%, M1 only: +0.11%, DLPFC only: +1.63%, M1+DLPFC: +2.52%), and the DLPFC only showing a significantly smaller percent increase in the steady state compared to the sham condition (DLPFC only: +0.2%, sham: +1.1%, Z=2.50 p=.013).

There was a significant interaction of condition and lap in SF (F= 3.61, p=.030 η^2_p=0.29), showing that the M1+DLPFC condition had a higher SF compared to the M1 only condition in the initial lap (M1+DLPFC:182 steps/minute, M1 only: 176 steps/min, p=.011, d=1.01), as seen in Figure 3.5B. Significant differences were found between the percent change across phases and conditions (χ^2: 34.83; p<0.01), showing a smaller percent decrease in the DLPFC only compared to the sham condition in the steady state phase (DLPFC only: -0.17%; sham: -1.07%; Z=2.50, p=.013).

No significant interaction was found between condition and lap in SL (F= 0.59; p=.739, η^2_p=0.06), as seen in Figure 3.5C. Significant differences were found between the percent change across

phases and conditions (χ^2: 38.35, p< .001), showing a significantly smaller percent decrease in the DLPFC only condition compared to the M1 only condition in the steady state phase (M1 only: -4.35%, DLPFC only: -0.73%, Z=2.09, p=.037), and a significantly larger percent increase in the DLPFC only compared to the M1 only (Z=2.40, p=.017) and the sham condition (Z=2.40, p=.017) in the final acceleration phase (Sham: +2.61%, M1 only: +0.09%, DLPFC only: +10.92%, M1+DLPFC: +6.51%).

No significant interaction was found between condition and lap in DF (F= 0.45, p=.716, η^2_p=0.05), as seen in Figure 3.5D. No significant interactions were found between conditions and phase in DF (F=0.93, p=.482, η^2_p=0.09). Across all conditions DF increased in the initial phase (Sham: +0.91%, M1 only: +1.13%, DLPFC only: +1.47%, M1+DLPFC: +1.38%) and steady state phase (Sham: +0.65%, M1 only: +0.71%, DLPFC only: +1.25%, M1+DLPFC: +0.28%). In the final acceleration phase M1 only, DLPFC only and M1+DLPFC conditions showed minor decreases (M1 only: -0.47%, DLPFC only: -0.16%, M1+DLPFC: -0.09%) and the sham condition showed a minor increase (Sham: +0.06%).

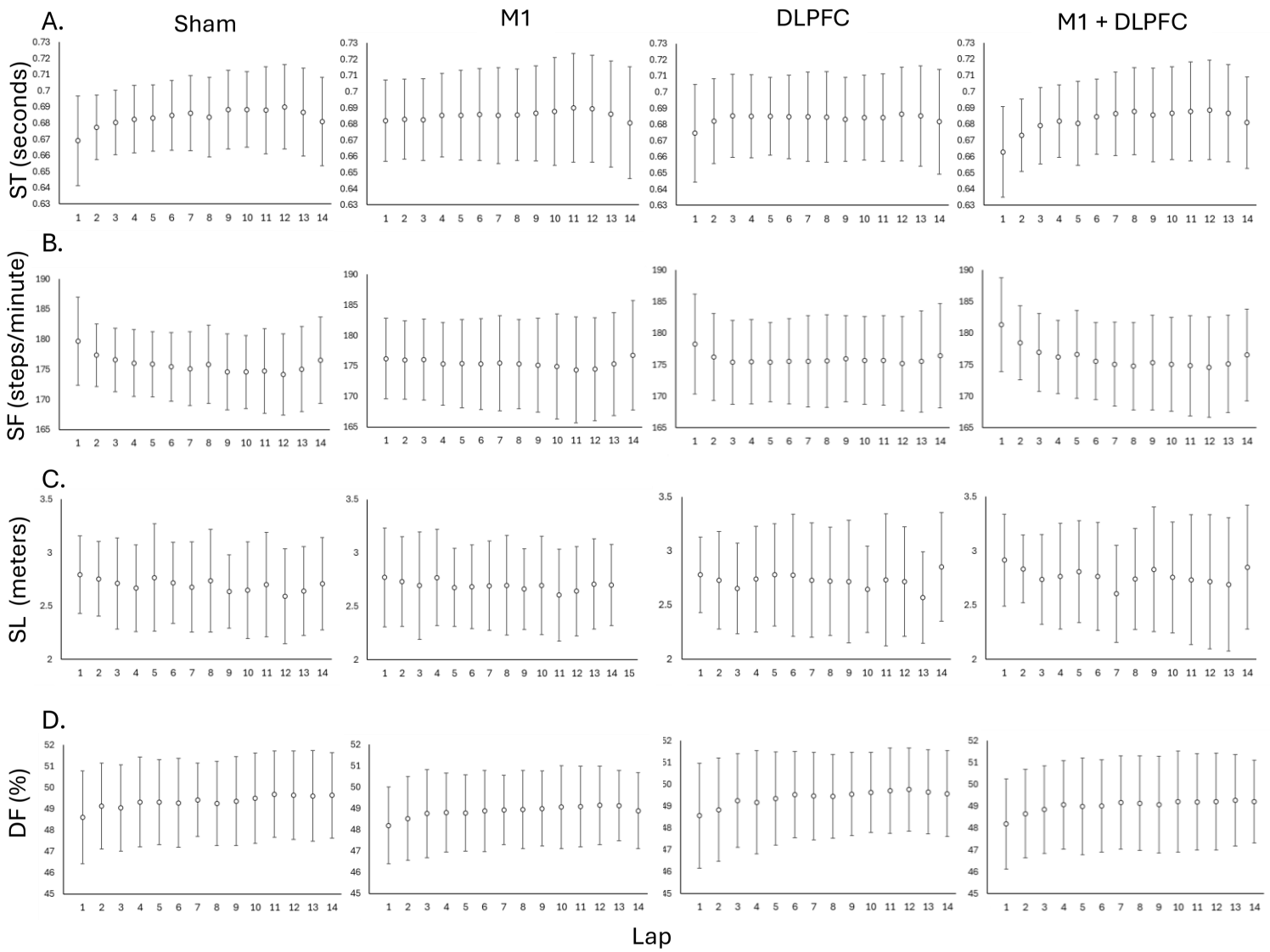

Figure 3.5. Average spatiotemporal running parameters in A. ST, B. SF, C. SL, D. DF across 14 laps for each stimulation condition: M1, DLPFC, M1 + DLPFC, and Sham. Data points represent the mean speed for all runners for each lap and error bars show standard deviation.

3.4.5 Variability of Spatiotemporal Parameters

Unlike speed, variability of ST, SF, SL and DF fluctuated around a stable mean, with small and irregular increases and decreases throughout the run (Figure 3.6). There was no significant interaction between conditions and lap for CV of any of the spatiotemporal parameters. (ST: F=0.43, p=.854, η^2_p= 0.05; SF: F=0.44, p=.846, η^2_p= 0.05; SL: F=0.43, p=.854, η^2_p= 0.05; DF: F=1.18, p=.338, η^2_p= 0.12). There was also no significant interaction between conditions and phase in the change in variability in any of the spatiotemporal parameters. (ST: χ^2=7.25, p=.779; SF: χ^2=7.57, p=.751; SL: χ^2=7.25, p=.779; DF: F=0.97, p=.452, η^2_p= 0.09).

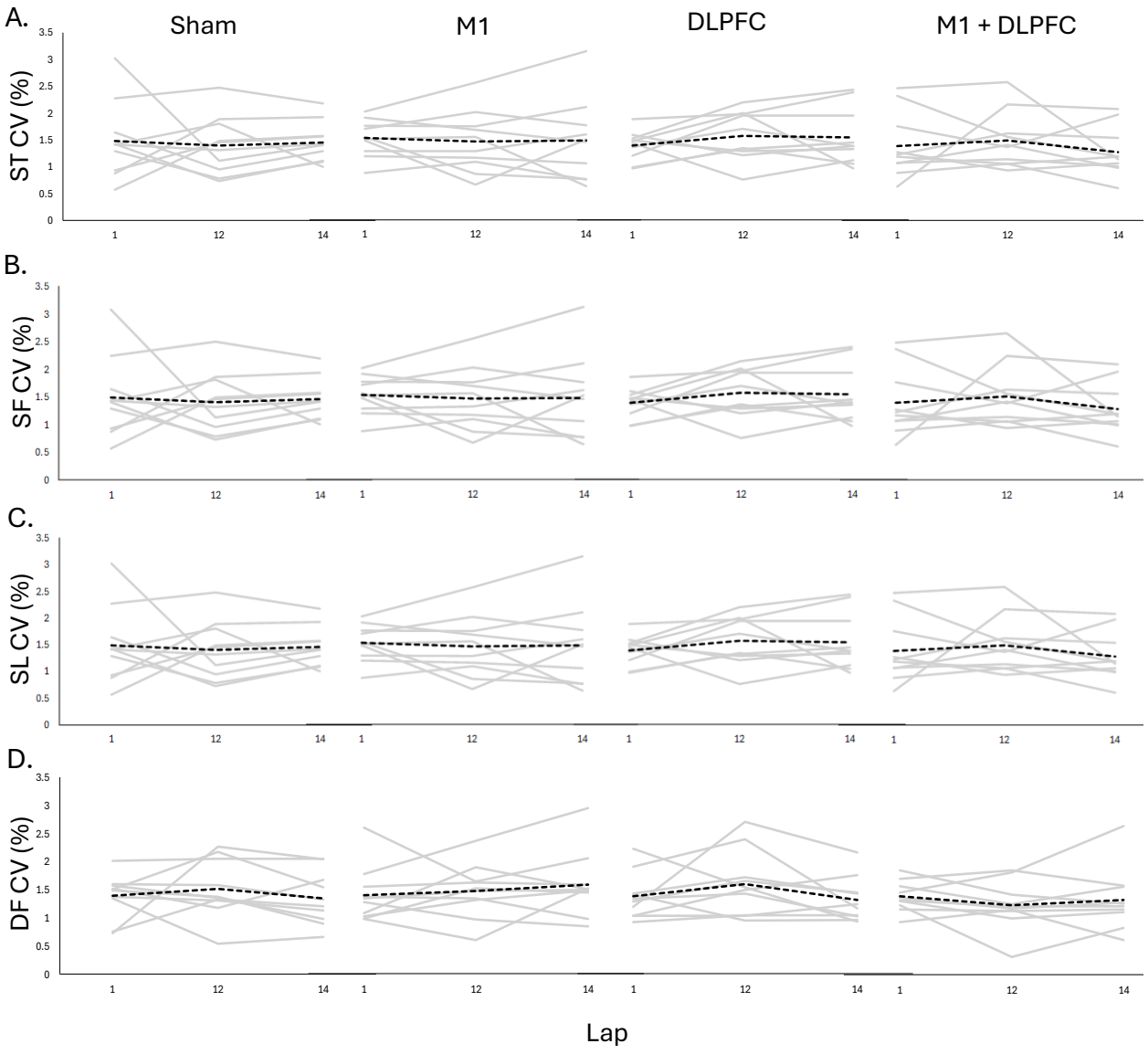

Figure 3.6. Mean and individual trends of CV of A. ST, B. SF, C. SL, D. DF in the steady state phase (lap 1 to lap 12) and final acceleration phase (lap 12 to lap 14) for each condition: M1, DLPFC, M1+DLPFC, and Sham. Gray lines show individual runner data, and the dotted black line represents the group average. No significant differences were found in CV in any variable in any lap between the four conditions.

3.5 Discussion

This study aimed to examine the effects of increasing the excitability of the M1 and DLPFC on running performance measured by changes in overall time, speed, spatiotemporal parameters, and their variability during a 3,000m time-trial run. We hypothesized that stimulation of M1+ DLPFC would enhance running performance by improvements in total time, speed, RPE and spatiotemporal variability. Stimulation of the M1 only was expected to show improvements only in total time and speed, and stimulation of the DLPFC only was expected to show improvements only in RPE and spatiotemporal variability. Our hypotheses were partially supported, with the M1+ DLPFC showing the fastest overall time and the fastest speeds in the initial lap across all conditions. However, the M1 only showed no benefit in time or speed compared to DLPFC only or sham condition. RPE and spatiotemporal variability were not affected by any type of brain stimulation with no differences between conditions as expected.

The M1 + DLPFC condition recorded the fastest time overall, nearly three seconds faster than the sham condition, and about one second faster than stimulation of either area alone. In competitive running, even just three seconds could determine podium placement. However, three seconds is within the typical intersession variability for our sample, indicating that other external or internal factors, outside of brain stimulation could have caused this difference. It is important to note that higher level runners are expected to show more minor improvements, with Barbosa et al. (2022) showing that average improvements of 3,000m world record holders from the season they set the record to the previous season was about seven seconds. Comparatively, the one other study that assessed running performance on a track after increasing excitability found that the stimulation group was 69 seconds faster than the sham group in a 5,000m run (Dos Santos et al., 2023). However, this study used different runners in each group, further highlighting the idea there were preexisting differences between groups. When investigating running performance, smaller effects in the same runner can often be more meaningful than larger effects between different runners.

The M1 + DLPFC condition also showed the fastest initial lap speed in all conditions, which was significantly faster compared to the DLPFC only condition as expected. However, this increased speed was not present in the M1 only condition, contradicting our hypothesis. Notably, RPE taken after the initial phase, and throughout the run, was not significantly different between conditions, similar to previous running studies (Baldari et al., 2018; Dos Santos et al., 2023; Martens et al.,

2024; Park et al., 2019). This may indicate that increased neural drive caused from increasing excitability in the M1 is less meaningful without also increasing excitability in the DLPFC, leading to enhanced task prioritization. Since the central nervous system continuously integrates multiple signals to determine exercise intensity (St Clair Gibson et al., 2006), it is possible that enhancing both motor and cognitive control signals at the same time is necessary to translate into meaningful performance improvements. This demonstrates how multiple metrics of running performance taken at different points may reveal more subtle differences than total time alone. The stability of RPE when examined in conjunction with other metrics like lap speed revealed increased physical performance without an increase in perceived effort. The initial increased speed also gave further insight into how total time was affected. The faster lap speeds in the beginning were enough to produce the fastest overall time in the M1 + DLPFC condition, even with the M1 + DLFPC showing the greatest decrease in speed in the steady state phase and the smallest increase in speed in the final acceleration phase.

Increased speed in the M1+DLPFC condition disappeared in the steady state phase of the run with no significant differences in RPE or lap speed after the initial phase. This may suggest that the increase in cortical excitability of both M1 and DLPFC was not sufficient to last throughout the entirety of the time-trial run and combat the inevitable effects of fatigue experienced during endurance exercise. Additionally, runners did not start the time-trial for at least 12 minutes with the time to arrive at the track and complete their warmup. Although iTBS has been found to have lasting effects for 60 minutes, these effects have shown to peak at 15 minutes before beginning to decline back to baseline (Wischnewski & Schutter, 2015), possibly indicating that the runners only experienced meaningful effects for the first three minutes of the run. Future studies may consider performing a warmup prior to the stimulation and then beginning the run immediately after the intervention to test during the period of peak effectiveness.

Due to the lack of consensus in the literature regarding magnitude of spatiotemporal parameters, no specific hypothesis was made for each parameter. In general, our results found increases in ST and DF and decreases in SF and SL between the initial lap and the steady state lap, suggesting that lower ST and DF and higher SF and SL are seen in the earlier laps when the runner was most likely not experiencing fatigue. Increasing excitability in both the M1+DLPFC appeared to have an effect early in the run, with the lowest values for ST and DF and the highest values of SF and SL seen in

the initial lap of the M1+DLPFC condition. Similar to speed, ST, SF and SL then showed the greatest percent change in the M1+DLPFC in the steady state phase, further supporting the idea that the effects of brain stimulation may only impact non-fatigued running or wear off soon after beginning the run. These changes in spatiotemporal parameters seemingly induced by increased excitability could be beneficial for some runners depending on their personal running style.

The lack of effect that increasing excitability had on spatiotemporal parameter variability in our running study contrasts with findings in walking studies, where gait variability was reduced in healthy adults after stimulation of the DLPFC. This may be attributed to fundamental differences between walking and running mechanics. Running introduces a flight phase, which leads to increased variability, while walking includes a double support phase, which contributes to greater stability (Williams & Martin, 2019). Increased excitability may enhance stability during walking's double support phase, but its impact on the flight phase in running may be more limited. The other consideration that is important to note is that the reduced variability was seen during dual tasking (Wrightson et al., 2015). Although there are cognitive processes involved in running related to optimal pacing strategies (Brick et al., 2016), runners were not performing a more demanding cognitive test such as a Stroop task. Therefore, the usefulness of increasing excitability in the DLPFC may lie in stabilizing walking patterns that are disrupted when the brain must simultaneously complete a straining cognitive task.

Another explanation for the lack of effect on variability is that while increasing the excitability DLPFC has been found to improve motor variability (Schneider et al., 2021; Wrightson et al., 2015), targeting the cerebellum may be a more effective approach to increasing stability of running patterns. The cerebellum is important for balance, coordination, and making small adjustments (Sherrard, 2011). It plays a role in integrating multiple inputs and then adjusting motor outputs. In stroke patients, iTBS applied to the cerebellum has shown promising results. For example, a study from Koch et al. (2019) demonstrated that cerebellar iTBS led to significant improvements in stabilizing gait and balance. Further, the cerebellum's involvement in coordinating various brain regions suggests its importance in managing the multiple factors that contribute to running performance (Rudolph et al., 2023). By increasing excitability in the cerebellum, it may be possible to achieve more stable and efficient running patterns, more so than stimulation of the DLPFC.

Several limitations of this study should be noted. Due to challenges with recruitment and retention, the final sample size was small, consisting of only ten runners. This sample included both males and females and all runners were analyzed together, despite that there are known sex-differences in hormones, cortical excitability and response to iTBS (Kan et al., 2024). As a result, some of the variability between conditions may be influenced by factors that vary by sex. While many studies include only male participants to minimize these differences, female runners were included so the findings could be generalized to the larger population of runners. However, this sample was not able to sufficiently address the current underrepresentation of female runners in the literature, as there were only three females in the sample, which did not allow for a meaningful analysis of sex-differences. A final limitation to note is that the analysis was performed only on the straight running segment that was closest to the APDM receiver. Further differences could have been observed in the turning segments that were not accounted for in this analysis.

To our knowledge, this is the first study that utilized iTBS directed to the M1 and DLPFC to enhance performance in endurance-trained runners. Utilizing an indoor track setting, rather than a treadmill, allowed participants to use typical pacing strategies they would in competition, making the findings more applicable to real-world conditions. Additionally, the use of well-established iTBS protocols, along with both objective and subjective performance measures, allowed for the assessment of the effects of cortical excitability on multiple components of running.

3.6 Conclusion

Our findings suggest that acute iTBS stimulation of both the M1 and DLPFC in endurance-trained runners shows potential for improving overall time and in speed, ST, and SF in the initial laps. Faster lap speeds in the initial phase without an increase in RPE may suggest that brain stimulation of both M1 and DLPFC has the ability to enhance motor output and efficiency, allowing for greater speed without a corresponding increase in perceived effort. Future research should investigate testing in the first 15 minutes after stimulation to maximize effect or exploring stimulation of other brain regions such as the cerebellum that may lead to improvements in variability, balance and coordination. These findings highlight the potential of increasing excitability in both the M1 and DLPFC to enhance multiple aspects of running performance, however further studies with similar protocols would need to be completed before any definitive conclusions can be made on its efficacy.

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Chapter 4: Scholarly Discussion

4.1 Summary of Results

The aim of this investigation was to examine the effects of increasing excitability in the M1 leg region and DLPFC, as well as a combination of both compared to sham stimulation on running performance measured by changes in overall time, speed, RPE spatiotemporal parameters and their variability during a 3,000m time-trial run. We hypothesized that stimulation of both M1 and DLPFC would enhance running performance compared to a sham condition, with the combination of M1 + DLPFC producing more pronounced effects than either area alone. Our findings partially supported these hypotheses. Although not statistically significant, all three stimulation conditions resulted in faster overall race times compared to sham, with the M1+DLPFC showing the greatest improvement in run time. Faster lap speed, faster ST and higher SF were seen in the initial lap in the M1 + DLPFC conditions, but no significant or meaningful differences were observed in stimulation of either area alone or sham. There were no direct effects of brain stimulation on RPE and CV of spatiotemporal parameters throughout the race. Interestingly, in the M1 + DLPFC condition, the faster lap speeds at the beginning of the race were not accompanied by an increase in RPE. This may suggest that enhancing excitability in both regions enables the DLPFC to regulate and integrate the increased motor output from M1, allowing for a more efficient pacing strategy without increasing the perception of exertion.

4.2 Variability

4.2.1 Variability in Walking Versus Running

Although previous research has shown that NIBS can reduce variability in spatiotemporal parameters in healthy individuals during walking, this effect was not observed in our study on running. The only shared outcome between walking and running in our study was the increase in speed (Koganemaru et al., 2018). Despite that walking and running involve engaging in similar brain regions (Bishnoi et al., 2021; Wollseiffen et al., 2016), there are key biomechanical differences between the two that may influence how variability is affected (Nicola & Jewison, 2012).

One major difference is the presence of a flight phase in running, which introduces greater inherent variability compared to walking (Cappellini et al., 2006). In walking, increasing cortical

excitability may work to enhance stability, specifically during the double support phase, when both feet are in contact with the ground and balance control is critical (Williams & Martin, 2019). If increasing excitability leads to more stable variability in the double support phase, the same effect of reduced variability would not be seen in running. The flight phase may require more targeted or intense interventions to meaningfully influence variability. While our findings suggest that using iTBS directed to the M1 and DLPFC has the potential to improve endurance running performance by improving speed and total time, its effects on variability remain uncertain

4.2.2 Prioritization of Variability in Specific Factors

It is important to note that variability in specific spatiotemporal factors may vary depending on how important that factor is for completing the running task. The central nervous system will decide which parameters need to be prioritized and kept stable while allowing for greater variability in less important factors (Fadillioglu et al., 2022). Therefore, it may be more beneficial to calculate the variability of multiple spatiotemporal parameters in the context of each other. One such way to do this is to examine the coordination variability between various parameters, such as multiple muscles and joints that contribute to a movement pattern (Hamill et al., 2012). This type of variability is shown to be increased in athletes with greater experience and skill (Hafer et al., 2019). The measure used in this study, coefficient of variation, looked at each parameter separately. This approach may not have been sensitive enough to fully capture the complexities of variability. Our results showed the same patterns of increasing or decreasing variability in all three phases in ST, SF, and SL, but not in DF. This may indicate there is a higher coordination between ST, SF and SL. One study to support this showed that runners will allow more variability in stance time to allow for the same speed instead of changing SF or SL (Möhler et al., 2021). Understanding how these variables change in relation to one another, rather than in isolation, could provide a better understanding of running mechanics and how increasing excitability impacts the prioritization of specific spatiotemporal factors.

4.2.3 Additional Considerations for Variability

Other equipment may allow for more in-depth analysis of variability. The IMU utilized in this study, APDM opal, was used for its portability and allowed the tracking of spatiotemporal parameters and variability on an indoor track as opposed to a treadmill. However, it cannot accurately estimate velocity or position through integration methods (Holmstrom, 2019), which

could be useful in calculating center of mass. Center of mass is a variable known to be relatively stable and other variables can be calculated and compared to how much they vary compared to how much center of mass changes. Although the portability of the IMU is useful, variability might best be measured with more sensitive equipment. Portable motion capture systems and force plate mats, which could be set up on a track, would allow for more complex calculation while still allowing runners to perform in a natural environment. Utilizing additional measurement tools could aid in determining which factors the CNS prioritizes and how different variables relate to overall performance.

Although increasing excitability in the DLPFC has been found to improve motor variability (Schneider et al., 2021; Wrightson et al., 2015), targeting the cerebellum may be an alternative that could be more effective. The cerebellum is involved in balance, coordination, and making small adjustments (Sherrard, 2011). Promising results have been found in stroke patients receiving iTBS to the cerebellum, with studies demonstrating significant improvements in gait stability and balance (Koch et al., 2019). However, the same differences between walking and running could be true here. Other studies potentially more relevant to sports performance have reported positive results for increasing muscular strength (Kenville et al., 2020), and increasing pain inhibition (Stacheneder et al., 2023) after excitatory cerebellar stimulation. By increasing excitability in the cerebellum, it may be possible to achieve more stable and efficient running patterns, potentially offering greater benefits than DLPFC stimulation.

4.3 Effectiveness of iTBS

4.3.1 On an Individual Level

Similar to other interventions to enhance performance in any sport, the effectiveness of increasing excitability with NIBS can vary at an individual level. Group analyses may not reveal that while some athletes benefit from this intervention, others may not. Part of this is due to responsivity to brain stimulation, as certain individuals may be more responsive than others based on age, genetics and baseline excitability (Li et al., 2015). Some studies have found that only 43% of subjects showed an increase of cortical excitability as expected after iTBS (López-Alonso et al., 2014). In our sample, only five of the ten runners showed the fastest time in the M1+DLPFC condition compared to stimulation of either area alone or sham stimulation, as expected. Although utilizing

NIBS still has potential for enhancing performance, its effectiveness is highly variable, and individual differences should be taken into consideration when designing interventions.

Additionally, improvement in running patterns may look very different between runners. Previous research has suggested that spatiotemporal parameters are best viewed on an individual level (Zandbergen et al., 2023). If optimal parameters were found on an individual level, runners could individualize which location (M1, DLPFC, or both) to target to best improve their performance. Finding one stimulation intervention that effectively reduces variability for all spatiotemporal parameters may also not be necessary.

4.3.2 Expected Improvement Rate

Although a three second improvement in performance may seem ineffective, it is important to note that higher level runners are typically expected to show more minor improvements. Barbosa et al. (2022) showed that average improvements of 3,000m world record holders from the season they set the record to the previous season was about seven seconds or about 1.5%. Comparatively, the percentage improvement between the sham condition and the M1+DLPFC condition in our study was 0.43% on average. Although small, this level of improvement can still be meaningful for higher level runners.

Surprisingly, the one other study that assessed running performance on a track after increasing excitability found that the stimulation group was 69 seconds faster than the sham group in a 5,000m run (Dos Santos et al., 2023). Although these results appear to show greater performance gains, this change does not seem realistic, further highlighting the idea there were preexisting differences in between groups. When investigating running performance, smaller effects in the same runner can often be more meaningful than larger effects between different runners.

4.3.3 Timing of ITBS for Optimal Effectiveness

The timing of iTBS and the running strategy employed by the runner can significantly impact the efficacy of the intervention. In general, utilizing the negative pacing strategy of keeping a relatively even pace throughout a run while still conserving enough energy for an increased intensity at the end of the race, is thought to be the most beneficial for middle-distance races. (Abbiss & Laursen, 2008). Even if this is thought to be the ideal strategy, some runners may use different strategies or in our study, not be as familiar with ideal pacing strategies for a middle-distance race. Although

effects of iTBS can last up to 60 minutes, effects usually begin to decrease after 15 minutes (Wischnewski & Schutter, 2015). Runners who try to conserve more energy at the beginning may not have experienced the same benefit as much as someone who made a greater push at the start of the race. Due to the location of the laboratory and the indoor track, by the time runners relocated to the track and completed their 10-minute warm-up, the peak effectiveness period had already passed. However, it remains unclear whether the observed improvements at the start of the race were due to the initial impact of iTBS or if NIBS might be the most effective in a non-fatigue state. Despite the seeming decline of the effects in later laps, the M1 + DLPFC stimulation still resulted in the fastest overall time across all conditions. This suggests that iTBS may still have a meaningful effect, even if it decreases over time during the run.

4.4 Sex-Differences

4.4.1 Considerations for the Sample

As highlighted in the literature review, studies greatly varied regarding the sex of participants used, with several reporting only on male athletes (Baldari et al., 2018; da Silva Machado et al., 2021; Martens et al., 2024; Okano et al., 2015; Vitor-Costa et al., 2015). This is an important consideration. We aimed to have 10 males and 10 females in our sample to be able to investigate sex-differences. However, despite recruiting 22 females, only 11 females completed all sessions. There were a number of reasons for withdrawal including injury obtained outside the study, discomfort with TMS, pregnancy and scheduling conflicts. From the 11 females that completed all four session, further exclusions were made due to: incorrect stimulation intensity/coil overheated because thresholds were too high, learning effects and incomplete APDM data. The final sample included only three females, which made it difficult to make comparisons between males and females. Due to the low number of females and total athletes, males and females were analyzed together. This can be thought of as a limitation to our study since there are known sex-differences in hormones, cortical excitability and response to iTBS (Kan et al., 2024). Even among females, differences in hormone levels related to different phases in the menstrual cycle have been found to impact brain excitability and fatigue (Deters et al., 2022).

4.4.2 Impact of the Menstrual Cycle and Contraceptives

We asked females in the initial session if they used contraception and experienced a normal menstrual cycle. Of our three females, only two experienced a regular menstrual cycle. The date

of their last period was documented in the initial visit, so we had an approximation of which phase of the menstrual cycle they were in. However, the other female had not had normal menstruation in over 6 months. Since we did not do blood testing to check for hormones, we did not have an estimate of her hormone levels. The best phase in the cycle to test performance is still debated (Meignié et al., 2021), but for comparable results, we would ideally test each of the four conditions at this same point of the cycle. This would pose additional logistical challenges since it would take longer to complete all sessions, which is why we were unable to test the females in our sample in this manner.

Although the use of oral contraceptives is advantageous for tracking these hormone levels, they are not always commonly used in runners, specifically in the three females we had, none of them were currently using contraceptives. More research should be done, focusing on females and how testing at different phases of the cycle impacts endurance performance. Regulating hormone levels can be more challenging, but mores studies should do their best to examine the effects of increasing excitability in female runners as there is limited research in the area.

4.5 Future Directions for Enhancing Endurance Performance with NIBS

4.5.1 Larger Stimulation Regions

The uncertainty of efficacy in this field allows for many directions the following studies could take. A recent systematic review of tDCS, which focused on its effect on lower limb endurance (Zhen et al., 2024), found that increased endurance performance during full-body exercises was linked to larger electrodes. Larger electrodes have been found to stimulate a broader region (Salehinejad et al., 2022), which may be more advantageous for full-body exercises for running. In our study, the TA muscle was chosen as it is known to play a crucial role in running (Koganemaru et al., 2018), and studies have found that the EMG recordings of the TA during a run show fatiguing patterns that could give insight into performance (Honert et al., 2022). However, evidence has shown that muscles show different activation patterns based on the mass of the shoe (Wakeling et al., 2002; Wang et al., 2020) and foot strike patterns (Lin et al., 2021). Mass of shoe and individual foot strike patterns were kept consistent in each individual, but not across our whole sample. This may indicate that participants who used shoes that activated the TA muscle more, could have benefited from the intervention more than runners who wore shoes that may have relied on a different muscle more. Stimulating a broader region that may target additional

muscles in the legs and in the core, which could benefit whole-body exercises, including running, cycling, and swimming.

4.5.2 Long-term Interventions

Another promising direction for future research involves long-term NIBS interventions, which have been suggested in several studies but rarely implemented. Even if NIBS is not practical for use in competition, there could still be potential for this treatment to be worked into a training schedule. If runners can enhance their performance during training, it could lead to better outcomes in future competitions. Like many training strategies, a single intervention wouldn't be expected to produce results immediately. Therefore, consistent long-term treatment could be more beneficial.

One recent study found that three repeated sessions of tDCS over the DLPFC in professional soccer players improved technical performance and psychological state (Shiravand et al., 2024). Repeated interventions over a longer time period may improve performance due to increased neural plasticity and long-term potentiation (Vestring et al., 2024). Neuroplasticity is the brain's ability to adapt to repeated stimulation over time, (Cai et al., 2014), leading to improvements in both motor and cognitive aspects related to running. Future studies could further explore these longer-term interventions by using long-term protocols similar to that of treatment for depression. For example, rTMS interventions for depression may consist of one session per day, from one to six weeks in length (Benster et al., 2023). This type of long-term treatment has not been widely explored despite many other studies suggesting this as a direction for future research.

Chapter 5: Conclusion and Summary

To our knowledge, this was the first study to utilize iTBS for increasing cortical excitability in the M1 and DLPFC in a single session to compare performance on a 3,000m time-trial run on an indoor track. Although insignificant, our results suggest that increasing excitability of the M1 and DLPFC has the potential to reduce total time compared to sham. Faster speeds in the initial lap of the run were significantly faster in the M1+DLPFC condition. This effect faded in the steady state and final acceleration phases of the run. Spatiotemporal variability remained stable throughout the race indicating it was not influenced by brain stimulation. Longer and more intensive protocols and more sensitive measures of variability may have provided greater insight into how NIBS affects performance. Unlike many previous studies, our study was performed on an indoor track to simulate real-life running conditions. This represented the variability of what runners may experience during actual competitive environments.

Our findings indicate that an acute intervention of increasing cortical excitability in the M1 and DLPFC may be promising to improve performance, but they highlight the complexities of applying brain stimulation in endurance running. The growing number of studies with differing results shows that experiments with brain stimulation should be more regulated to allow for comparisons across studies. This could help reveal patterns of effectiveness related to the type of brain stimulation, application site or individualized factors. Using individualized approaches that account for variables such as brain excitability, hormone levels, and running strategies, may yield more success on an individual basis.

Targeting broader stimulation sites may prove more beneficial than focusing on specific muscles in whole-body exercises such as running, as broader sites could target multiple muscles that are working in coordination. Additionally, exploring long-term stimulation protocols could be beneficial, particularly for training rather than competition. Multiple sessions could provide cumulative benefits, similar to other training strategies that aim to improve performance over time. In conclusion, despite promising results, the practical applications and efficacy of NIBS in running remain uncertain. Research would benefit from repeating existing protocols with multiple performance measurements to allow for more accurate comparison. Optimal timing of stimulation should also be explored to ensure the maximum effect on performance. Running performance

relies on many factors but interventions that could improve performance by even three seconds could be significant for well-trained runners.

Chapter 6: References

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