Effects of theta burst stimulation of the posterior parietal cortex on the excitability of the upper and lower limb in healthy young adults. A sham-controlled study.

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April 2022

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

Table of Contents

Abstract ***4***

Résumé ***5***

Acknowledgements ***6***

Preface and Contribution of Authors ***7***

1. Introduction ***8***

1.1 Rationale **8**

1.2 Objectives **9**

1.3 Hypotheses **9**

2. Background ***10***

2.1 Locomotion **10**

2.2 Posterior Parietal Cortex **11**

2.3 Transcranial magnetic stimulation **14**

2.3.1 Single pulse TMS 17

2.3.2 Paired Coil TMS 18

2.3.3 Repetitive transcranial magnetic stimulation 19

2.3.4 Theta burst stimulation 20

2.3.4.1 Repetitive transcranial magnetic stimulation on the posterior parietal cortex 20

3. Manuscript ***22***

3.1 Abstract **23**

3.2 Introduction **24**

3.3 Materials and methods **26**

3.3.1 Participants 26

3.3.2 Experimental design 26

3.3.3 Electromyographic measurements 27

3.3.4 Image Acquisition 28

3.3.5 Transcranial magnetic stimulation 28

3.3.5.1 TMS devices 28

3.3.5.2 Stimulation targets 28

3.3.5.3 Motor thresholds 29

3.3.5.4 Modulation of PPC excitability 30

3.3.6 Outcome measures 31

3.3.7 Data processing 32

3.3.8 Statistical analyses 33

3.4 Results **33**

3.4.1 Motor thresholds 33

3.4.2 Tibialis Anterior Outcomes 35

3.4.2.1 Measuring TA excitability 35

3.4.2.2 Effect of the PPC conditioning at baseline 36

3.4.2.3 Immediate effects of PPC TBS on the excitability of the TA 37

3.4.2.4 After-effects of PPC TBS 38

3.4.3 First Dorsal Interosseous Outcomes 39

3.4.3.1 Effect of the PPC conditioning at baseline 39
3.4.3.2 Immediate effects of PPC TBS on the excitability of the FDI 39
3.4.3.3 After-effects of PPC TBS on the excitability of the FDI 40

3.5 Discussion **41**
3.5.1 Feasibility of TA muscle Stimulation 42
3.5.2 Altering the excitability of the PPC 42
3.5.3 Effects of PPC preconditioning M1 43

3.6 Manuscript References **45**

4. Scholarly Discussion ***48***

5. Conclusion and Summary ***49***

6. References ***50***

7. Appendices ***59***

Abstract

The posterior parietal cortex (PPC) is a cortical region involved in the planning of locomotion and is functionally and anatomically connected to the primary motor cortex (M1). This functional connectivity has previously been assessed with dual-coil TMS (dcTMS), targeting the upper limb. Currently, no studies have investigated the connection between the PPC and the lower limb M1. The objectives of this study were thus to determine the feasibility of measuring lower limb excitability with TMS and to assess the connectivity between the PPC and the M1 of upper and lower limb, with a dcTMS protocol, after modulating the PPC with theta burst stimulation (TBS). Ten healthy young adults (aged 26 ± 4) were recruited. The study consisted of 4 sessions conducted at least 72 hours apart. During the initial session, the hotspot locations for the first dorsal interosseous (FDI) and the tibialis anterior (TA) were determined, as well as their motor thresholds. During the following three experimental sessions, participants received either iTBS, cTBS or sham iTBS over the PPC. To quantify the effects of TBS on the PPC, the PPC+M1 connection was assessed with dcTMS, in both hand and leg M1 representations. The dcTMS measurements were acquired immediately before and 0, 20 and 40 minutes after TBS. Our results demonstrate that increasing the excitability of the PPC resulted in a delayed increase of the excitability of the TA, 40 minutes after PPC modulation by TBS. It is feasible to stimulate the TA M1 region and measure its excitability by its motor thresholds, in order to avoid excluding a large number of participants, when an MEP response of 0.5 mV is not achieved. We conclude that TBS stimulation on the PPC can provoke remote effects on the TA M1 and delayed after-effects on the TA excitability.

Résumé

Le cortex pariétal postérieur (CPP) est une région corticale impliquée dans la planification de la locomotion et est fonctionnellement et anatomiquement connecté au cortex moteur primaire (M1). Cette connectivité fonctionnelle a déjà été évaluée avec la stimulation magnétique trascraniale (SMT) à double bobine (dbSMT), ciblant le membre supérieur. Actuellement, aucune étude n'a investigué la connexion entre le CPP et le M1 du membre inférieur. Les objectifs de cette étude étaient donc de déterminer la faisabilité de mesurer l'excitabilité des membres inférieurs avec la TMS et d'évaluer la connectivité entre le CPP et le M1 du membre supérieur et inférieur, avec un protocole dcTMS, après avoir modulé le CPP avec la stimulation thêta-burst intermittente (STBI). Dix jeunes adultes en santé (âgés de 26 ± 4 ans) ont été recrutés. L'étude consistait en 4 visites menées à au moins 72 heures d'intervalle. Au cours de la visite initiale, la localisation optimal de stimulation sure le M1 pour les muscles premier interosseux dorsal (MPID) et tibial antérieur (TA) ont été déterminés, ainsi que leurs seuils moteurs. Au cours des trois sessions expérimentales suivantes, les participants ont reçu soit de la iSTBI, cSTBI ou iSTBI placebo sur le CPP. Pour quantifier les effets du STBI sur le CPP, la connexion CPP+M1 a été évaluée avec dcTMS, dans les représentations M1 de la main et de la jambe. Les mesures dbSMT ont été acquises immédiatement avant et 0, 20 et 40 minutes après la TBS. Nos résultats démontrent que l'augmentation de l'excitabilité du CPP a entraîné une augmentation retardée de l'excitabilité du TA 40 minutes après la modulation du CPP par la STBI. Il est possible de stimuler la région TA du M1 et de mesurer son excitabilité par ses seuils moteurs, afin d'eviter d'exclure un grand nombre de participants, lorsqu'une contraction musculaire évoquée de 0.5 mV n'est pas atteinte. Nous concluons que la stimulation du TBS sur le CPP peut provoquer des effets éloignés sur la TA M1 et des effects retardés sur l'excitabilité du TA.

Acknowledgements

This thesis was supported by a scholarship from the National Council of Science and Technology of México (CONACYT), which allow me to pursue my master's degree.

I would first like to thank my supervisor Dr. Caroline Paquette for her patience, guidance and advice on all the steps of my research project.

I am also grateful to Alexandra Potvin-Desrochers, who from the first minute shared her lab knowledge with me and has guided me with her experience in all the aspects of my research.

I would like to acknowledge all the members of the HBCL Lab, Julien Clouette, Frédérike Parent-L'Ecuyer, Gleydciane Alexandre Fernandes, Audrey Parent, Freddie Seo, Henri Lajeunesse and Michelle Cheng, without their assistance and support I would not have been able to do my data collection in the uncertain times that we lived a couple of years ago.

In addition, I would like to thank my parents and my brother, for their support in this new journey that I started in 2019.

Finally, I am extremely grateful with Mike for his love, understanding and support in these years of becoming a student again.

Preface and Contribution of Authors

Alejandra Martínez Moreno conducted this project in her master's thesis and was responsible for the study design, the recruitment of subjects, data collection, data analysis, writing of the thesis and manuscript preparation. Alexandra Potvin-Desrochers contributed to the study design, data collection, data analysis, and corrections of the manuscript. Alexander Fulford contributed with the study design and the piloting sessions. Julien Clouette, Henri Lajeunesse, Freddie Seo, Gleydciane Alexandre Fernandes, Frédérike Parent-L'Ecuyer, Audrey Parent and Michelle Cheng contributed to data collection. Caroline Paquette supervised the manuscript and thesis preparation and contributed to design of the research study, data analysis, corrections to the manuscript and received funding for this project.

1. Introduction

1.1 Rationale

The posterior parietal cortex (PPC) is a brain region involved in complex locomotion such as planning of visually guided locomotion (Drew & Marigold, 2015). The PPC is functionally and anatomically connected to the primary motor cortex (M1) (Picard & Strick, 2001; Rizzolatti, Luppino, & Matelli, 1998), and sends inputs that elicits gait modifications by M1 (Drew & Marigold, 2015). Previous studies have assessed the connections of the PPC with the first dorsal interosseous (FDI) M1 with dual-coil transcranial magnetic stimulation (TMS) (Koch et al., 2007; Koch, Fernandez Del Olmo, et al., 2008). Moreover, it has been demonstrated that the parieto-motor connections are involved in reaching and grasping objects (Fogassi et al., 2005; Murata, Gallese, Luppino, Kaseda, & Sakata, 2000; Rozzi, Ferrari, Bonini, Rizzolatti, & Fogassi, 2008; Sakata, Taira, Murata, & Mine, 1995). As of today, we know that there exists a connection between the PPC and the leg representation of the M1, but this connection has not previously been assessed with TMS. While there is a direct cortico-motoneuronal pathway from the M1 to the hand-muscle motoneurons (Isa, Kinoshita, & Nishimura, 2013; Lemon, 2008), whereas the pathway to lower limb has connections with interneurons before reaching motoneurons (Lemon, 2008). The research on the connections between PPC and the M1 of the hand area may not be directly applicable to the lower limb area due to the different motor connections. The paired coil PPC+tibialis anterior (TA) will provide new insight on the functional connectivity between these two regions. Furthermore, paired coil TMS (PPC+M1) can assess changes in the PPC excitability by having a measurable output, such as motor evoked potentials (MEP), that can be compared to the stimulation of M1 alone.

Theta burst stimulation (TBS), a patterned form of repetitive TMS (rTMS), can modulate cortical excitability by increasing or decreasing it (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Targeting the PPC with TBS can modulate the excitability of the cortical motor circuits from the PPC to the lower limb M1 and can

help in a better understanding of the role of PPC in locomotion. Nevertheless, previous studies had measured the tibialis anterior (TA) excitability, but demonstrated the challenge that represents the lower limb M1 stimulation with TMS due to its deeper location in the interhemispheric fissure (Hand, Opie, Sidhu, & Semmler, 2020; Mrachacz-Kersting, Stevenson, & Ziemann, 2021).

Therefore, the purpose of this study was to determine if the excitability of upper and lower limb changes when targeting other non-motor brain regions, such as the PPC, with TBS.

1.2 Objectives

The objectives of this project are:

a) To quantify the effects of modulating the PPC with intermittent TBS (iTBS) or continuous TBS (cTBS) on the connectivity between the PPC+FDI and the PPC+TA.
b) To determine the feasibility of measuring lower limb excitability with TMS.
c) To quantify the PPC excitability with the PPC+M1 connectivity.

1.3 Hypotheses

The corresponding hypotheses are:

a) iTBS of the PPC will increase the excitability of the FDI and TA.
b) cTBS of the PPC will decrease the excitability of the FDI and TA.
c) The TA motor thresholds would be higher and more variable than the FDI, but yet quantifiable with TMS.
d) The PPC excitability can be measured with a dual-coil protocol when comparing the changes between the PPC+M1 to the M1 alone.

2. Background

2.1 Locomotion

Locomotion is a complex task that allows humans explore the environment by moving from one place to another (Jahn et al., 2008). The neural control of locomotion is hierarchically organized and includes the spinal cord and supraspinal structures. First, the coordination of locomotion is generated by first order interneurons named the central pattern generators (CPG), that are groups of interneurons located in the spinal cord that generate gait pattern and rhythm (Beloozerova & Sirota, 2003; Grillner, 2006), which are modulated by afferent feedback from the environment, influencing the selection of motor patterns (Rossignol, Dubuc, & Gossard, 2006). The locomotor pattern of each limb is regulated then by second order interneurons, which subsequently transmit their signals to the motoneurons (McCrea & Rybak, 2008). Finally, the supraspinal locomotion centers receive the information of the locomotor rhythm and pattern through the spinothalamic, reticular and cerebellar tracts (Rossignol et al., 2006; Takakusaki, 2013).

Second, adaptations to the locomotor network are performed by supraspinal locomotion centers. These centers act as a rhythm-generating system that controls CPGs (Rossignol et al., 2006; Takakusaki, 2013), and are also involved in complex locomotion such as planning of locomotion, gait initiation, turning, stopping and avoidance of obstacles while walking (Drew & Marigold, 2015; la Fougere et al., 2010; Nutt et al., 2011).

The motor programs are responsible for the postural control in locomotion by assembling the tasks adjustments of posture and movement. These programs are formed in the frontal lobe and they project to the CPGs, bypassing brain, brainstem and cerebellar regions to initiate locomotion (la Fougere et al., 2010; Rossignol et al., 2006), and play a role in stepping and postural adjustments. (Drew, Prentice, & Schepens, 2004)

2.2 Posterior Parietal Cortex

As shown in Figure 1, the PPC is located posterior to the central sulcus of the brain, between the visual cortex and the somatosensory cortex (Whitlock, 2017). It consists of two lobules: the inferior parietal lobule (IPL) and the superior parietal lobule (SPL), separated by the intraparietal sulcus (IPS) (K Mai Jürgen, 2012; Rizzolatti et al., 1998).The PPC is considered an associative region, that has not only sensory and motor functions, but that also links the inputs from different brain regions, such as visual, somatosensory, auditory, motor, cingulate and prefrontal areas (Whitlock, 2017).

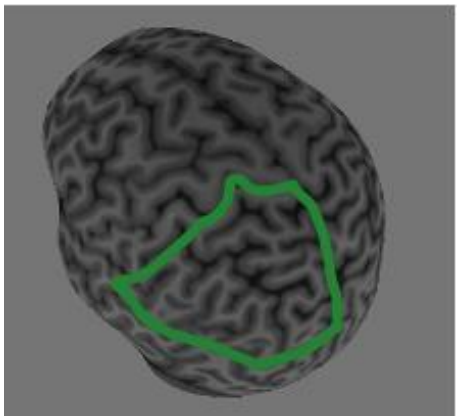

Figure 1. Lateral view of the human brain, with the posterior parietal cortex colored delimited in green.

Little is known about the somatotopy of the PPC. It is well known that several brain areas are somatotopically organized. The seminal work by Wilder Penfield showed that in M1 and in the primary somatosensory cortex, the representations of the upper and lower limb have distinct locations. In humans, the motor hand area is located on the knob-like structure in the precentral gyrus (Yousry et al., 1997), and the motor leg hand area is, on the other hand, located deeper at the midline of the brain in the interhemispheric fissure (Schott, 1993).

Recent studies suggest that the PPC encompasses an extensive representation, at least in the upper limb (Cattaneo, Giampiccolo, Meneghelli, Tramontano, & Sala, 2020). The hand representation within the PPC can be found on the rostral parietal convexity, specifically on the anterior intraparietal area, which is a functional node

specialized for grasping objects (Cui & Andersen, 2007; Murata et al., 2000). A PPC representation of the lower limb has not been demonstrated.

The parieto-frontal connections are the basic elements of the motor cortical system. (Rizzolatti et al., 1998).The PPC has different connections within the brain, as shown in Figure 2. The PPC, similarly to the prefrontal lobe and the cingulate cortex, is connected to the frontal motor areas by the cingulum bundle (Rizzolatti et al., 1998). In non-human primates, M1 is connected to the PPC principally to the parietal convexity (PE) and rostral parts of the medial bank of the IPS (Hadjidimitrakis, Bakola, Wong, & Hagan, 2019). An indirect connection of the PPC with the upper limb M1 through the premotor cortex has been previously demonstrated (Rizzolatti, Cattaneo, Fabbri-Destro, & Rozzi, 2014; Wise, Boussaoud, Johnson, & Caminiti, 1997), where reach related signals circulate from the superior parietal lobule to the dorsal premotor cortex (Burman, Bakola, Richardson, Reser, & Rosa, 2014; Dea, Hamadjida, Elgbeili, Quessy, & Dancause, 2016), but also with direct monosynaptic connections to the upper limb M1 in the macaque monkeys (Bruni et al., 2018; Rozzi et al., 2006). In humans, functional connectivity has previously been shown in multiple studies with a dual-coil TMS protocol targeting the PPC and the ipsilateral M1 of the hand (Koch et al., 2007; Koch, Fernandez Del Olmo, et al., 2008)

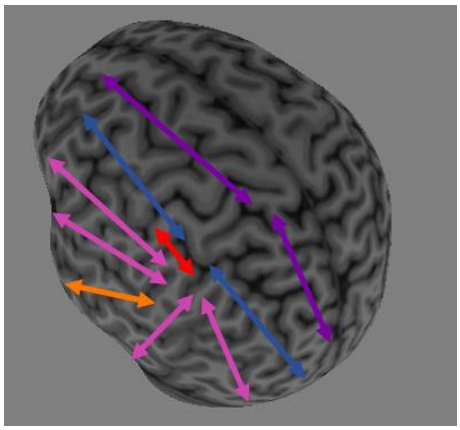

Figure 2. Corticocortical connectivity pattern of the human parietal cortex. Red arrows: connections to the primary somatosensory cortex, purple arrows: connections of the superior parietal lobule to the frontal and occipital lobule, blue arrows: connections of the intraparietal sulcus to the frontal and occipital lobule, pink arrows: connections of the inferior parietal lobule to the occipital, temporal and frontal areas, and orange arrow connections to the secondary somatosensory cortex. Figure adapted from (Caspers & Zilles, 2018).

Using functional magnetic resonance imaging (fMRI), previous studies found that the planning of hand and foot movement evoked similar PPC activation, except in the Broadman area 5, located in the anterior part of PPC (Heed, Beurze, Toni, Roder, & Medendorp, 2011). Moreover, when using fMRI repetition suppression (RS), which is a fMRI pattern that results in diminished neural activation after repeated stimuli (Henson, 2003), it was demonstrated that limb-specific effects exist between the PPC. The lateral and posterior regions of the SPL were specific for hand movements, whereas the medial regions were foot-specific. Another area of the PPC showed region-specific effects for both limbs. This region is located in the anterior part of the SPL, between the limb specific regions and enclosed by the IPS and postcentral sulcus (Heed, Leone, Toni, & Medendorp, 2016).

The PPC has two different type of neurons that are involved in the planning and execution of visually guided locomotion (Drew & Marigold, 2015). The first group shows activity during stepping over an obstacle, whereas the second group activates 200 milliseconds before the step over the obstacle. These results suggest that one population of PPC neurons contributes to the execution of the movement, and the

other population contributes to the planning process that precedes gait modifications (Andujar, Lajoie, & Drew, 2010; Beloozerova & Sirota, 2003). The PPC has increased activity when modifications to the gait pattern are needed in response to unpredictable external perturbations, such as speed changes on split-belt treadmill (Hinton, Thiel, Soucy, Bouyer, & Paquette, 2019), and to changes in planned gait trajectory as repeated turns overground (Mitchell, Potvin-Desrochers, et al., 2019; Mitchell, Starrs, Soucy, Thiel, & Paquette, 2019).

2.3 Transcranial magnetic stimulation

TMS is a non-invasive brain stimulation tool that, based on its stimulation pattern, can be used to map brain functions and/or modulate brain excitability (Hallett, 2007). To perform magnetic stimulation, a magnetic coil that produces a high-pulse current is placed over the scalp. When a pulse is elicited, an amount of charge, determined by the percentage of maximal stimulator output (Fried et al.) (Fried et al., 1991), is sent to the coil circulating through wire loops and producing a magnetic field (Valero-Cabre, Amengual, Stengel, Pascual-Leone, & Coubard, 2017). The latter penetrates skin, scalp and skull painlessly creating an electric current in the cerebral cortex that depolarizes cell membranes and generates action potentials (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of, 2009). When applied to the M1, this pulse activates the corticospinal tract and produces muscle activity, that is referred as a motor evoked potential (MEP) recorded with electromyography (EMG), and that can also be visualized as a twitch in the corresponding muscle (Badawy, Loetscher, Macdonell, & Brodtmann, 2012; Rothwell, 1997). TMS generates a series of descending volleys in the spinal cord, known as direct or indirect waves, D- and I- waves, respectively, when applied to the M1. D- waves originate in the subcortical white matter or in the initial part of the axon from the stimulation of the corticospinal axons (Di Lazzaro et al., 1998). I-waves originate from the stimulation of neural circuits of the M1 and its connections to motoneurons (Di Lazzaro et al., 2012; Niemann, Wiegel, Kurz, Rothwell, & Leukel, 2018). Changes in TMS stimulation intensity and current direction regulates D- and early I- waves. Depending on coil orientation, TMS activates D- waves at high intensities with posterior-anterior stimulation, and at lower

intensities with latero-medial stimulation (Di Lazzaro et al., 2004; Rossini et al., 2015). When the TMS pulse current is directed posterior-anterior (PA), it recruits an early I1 wave in the pyramidal tract, and with higher stimulus intensities it recruits later waves, such as I2, I3. Early and later I-waves are named by the number of neural circuits stimulated, early waves recruit less and later waves recruit more neural circuits (Niemann et al., 2018). When directed anterior-posterior (AP), evokes only later I waves. With high TMS intensity, AP pulses evoke D waves rather than PA pulses (Di Lazzaro et al., 2001).

TMS devices have two different pulse configurations, monophasic (unidirectional) or biphasic (bidirectional) (Arai et al., 2005; Hallett, 2007). Monophasic pulse has a shorter duration and it includes an initial and a return current, being the initial one that produces current in the brain (Rossini et al., 2015), they are usually used for single pulse TMS and for the evaluation of corticospinal tract integrity and excitability (Sommer et al., 2018). In a biphasic pulse, there is an initial current followed by a reversed current, and then an increase in it. Both phases of this pulse produce current in the cerebral cortex (Rossini et al., 2015). This type of pulse is mainly used for repeated TMS protocols, aimed at modulating cortical excitability, because it can reach higher frequencies of stimulation (Sommer et al., 2018) and is more effective in producing MEPs (Kammer, Beck, Thielscher, Laubis-Herrmann, & Topka, 2001).

For the effective stimulation of brain regions, coils can be found in different shapes and sizes, as shown in Figure 3. These characteristics are responsible for the magnetic field penetration in the brain. Coils with larger diameters, are less focal, but allow the stimulation of deeper brain regions. The figure-of-eight coil, the most commonly used, consists of two adjacent circular wings with the current flowing in opposite directions. Depending on its diameter, the figure-of-eight coil can be used for focal stimulation of superficial brain regions, in the centre of the coil the electric field is twice than elsewhere under the coil (Pascual-Leone & Rothwell, 2002). The double cone coil is another type of coil that consists in two large adjacent circular wings. This coil induces a deeper stimulation of brain regions, due to its larger

diameter, and it is used to stimulate lower limbs and cerebellum, but because of its diameter and power can be uncomfortable (Rossi et al., 2009). Lastly, the domed coil consists of two angled and curved windings, and it can be used to stimulate lower limb because it has a deeper penetration.

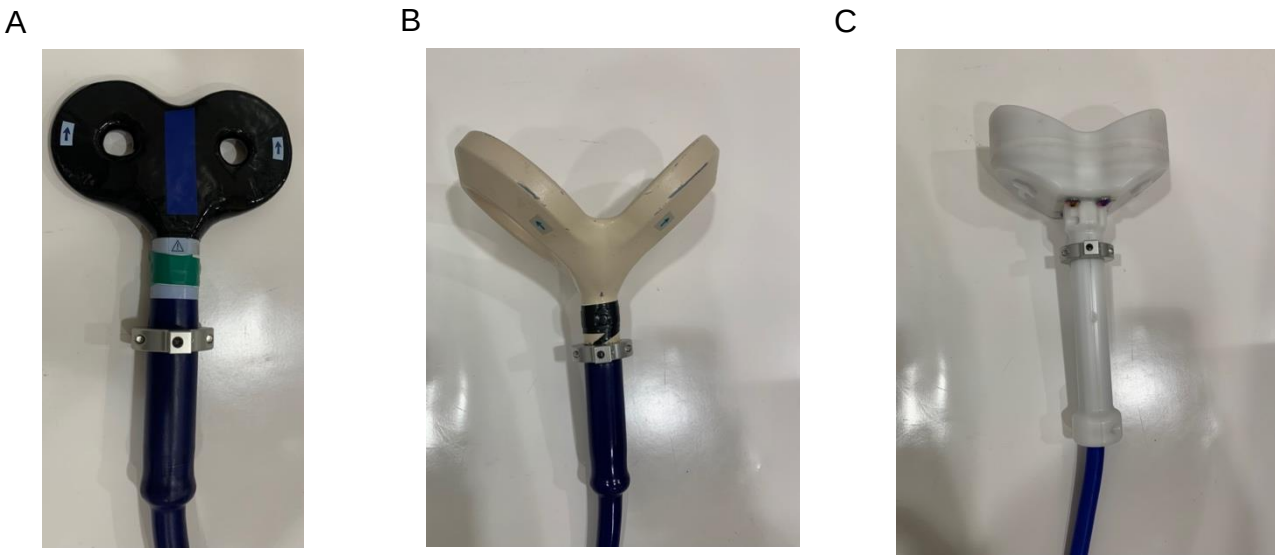

Figure 3. Stimulating coils. Figure *A*, figure-of-eight coil, *B*, double cone coil and *C,* domed coil.

For the correct use of TMS, it is imperative to ensure the correct placement of the coil on the brain area to be stimulated, because subtle changes in the coil position over the brain can alter TMS outcomes. With the use of stereotaxic neuronavigation system, the system tracks in real time the position of the coil in a 3D reconstruction of the participants' rendering brain. Using a set of standardized anatomical landmarks, the rendered brain and the subjects' head are registered in a common space, enabling a correlation between the real brain and the 3D images (Lefaucheur, 2019). This allows the monitoring of the head and coil positions during the TMS session, in order to have an exact stimulation site, for more reliable outcomes (Rossini et al., 2015).

2.3.1 Single pulse TMS

Single pulse TMS is used to assess the corticospinal tract integrity and excitability by recording MEPs. When a stimulus is applied over the M1, it provokes an MEP, and when recorded with EMG, acts as an objective measurement of M1 excitability. The cortical mapping helps in the location of the motor map and the motor hotspot (Lefaucheur, 2019). The MEP amplitude size is usually expressed as the peak-to-peak amplitude of the EMG signal. Variability in the neural excitability in the cortical or spinal levels can induce variability of the MEP amplitude from trial to trial, for this reason, several trials must be performed, to obtain an accurate MEP size (Lefaucheur, 2019).

With increasing stimulus intensity, the MEP amplitude increases, and this relationship between stimulus intensity and MEP amplitude is called the “stimulus-response curve” (Rossini et al., 2015). This curve has a sigmoid form that indicates the relationship between stimulus intensity and the MEP amplitude (Lefaucheur, 2019) and is determined by the number of corticospinal fibers recruited (Rossini et al., 2015).

The measurements of MEPs can be done in the relaxed muscle, or in the contracted muscle when we want to facilitate MEPs without an increase in stimulus intensity (Rossini et al., 2015). For a given stimulation intensity, the MEPs in the contracted muscle are larger in amplitude than the MEPs in the relaxed muscle (Pascual-Leone & Rothwell, 2002), due to the higher level of activity of the motor neuron pool, compared to the muscle at rest (Hallett, 2007).

The intensity of the TMS is regulated individually based on each individual motor threshold (Rossini et al., 2015). The cortical motor threshold is the lowest intensity of the motor cortex stimulation needed to obtain a MEP of minimal amplitude in the target muscle (Rossini et al., 2015). The resting motor threshold (RMT) is measured during a resting state of the muscle, whereas, the active motor threshold (AMT), is

established when the muscle is at contraction of 20% of the maximal muscle strength (Rossini et al., 2015).

2.3.2 Paired Coil TMS

Paired coil TMS investigates and assesses the connections of the M1 with other motor and non-motor brain regions (Koch et al., 2007). Paired-coil stimulation is utilized in a conditioning-test stimulus protocol. A conditioning stimulus (CS) is first applied to activate intracortical circuits to the M1 from another location in the brain , then a test stimulus (TS) is applied over the M1 to detect any changes produced in the excitability by the CS (Koch et al., 2007); the MEP resulted from the paired coil is compared to the TS alone as a baseline (Lefaucheur, 2019). Paired-coil protocols have been established for the M1 with the PPC, the ventral and dorsal premotor cortices, the supplementary motor area, the pre-supplementary motor area, the cerebellum and the contralateral M1 (Hallett et al., 2017). Paired-coil TMS allows the evaluation of intracortical facilitation and inhibition between neural circuits (Lefaucheur, 2019). Previous studies assessed intracortical connections with a paired-coil TMS study, in which MEPs were facilitated in the right M1 of the relaxed FDI muscle with a CS over the right PPC at 90% RMT and with an interstimulus interval (ISI) of 4 and 15 ms (Koch et al., 2007). On the left hemisphere, MEPs were facilitated with an ISI of 4 and 6 ms (Koch et al., 2007). Whereas, when the participant is preparing a contralateral reach of an object, facilitation is detected on the right hemisphere when the CS over the right PPC is at 90% RMT with an ISI of 4 ms, and on the left hemisphere when the CS over ipsilateral PPC is at 90% RMT with an ISI of 6 ms (Koch, Fernandez Del Olmo, et al., 2008).

Other paired-coil TMS studies stimulated the left M1 preceded by 4 ms of a CS of 90% RMT over the left angular gyrus (AG) or supramarginal gyrus (SMG). The results showed increased on the excitability of the M1 when preconditioned by the AG during preparation of reaching and grasping, but only when the action was made with a whole hand grasp towards the contralateral space. On the other hand, when preconditioned the M1 by SMG, there was an increase on the M1 excitability when

the grasping was made with only one finger, but it was independent of the position of the object in the space (Koch et al., 2010).
The stimulation of the anterior part of the IPL resulted in inhibition of the ipsilateral M1 in both hemispheres with a CS at 90% RMT of the FDI and an ISI of 8 ms. With the same CS and ISI parameters, stimulation of the central and posterior IPL resulted in facilitation of the ipsilateral M1 in both hemispheres (Karabanov, Chao, Paine, & Hallett, 2013).

2.3.3 Repetitive transcranial magnetic stimulation

rTMS uses repeated TMS pulses to modify cortical excitability, by increasing or decreasing it, and its effects go beyond the stimulation period for several minutes (Hallett, 2007). The after-effects of rTMS indicates long-term changes in the synaptic plasticity that are similar to long-term depression (LTD) or long-term potentiation (LTP). LTP corresponds to an increase in the neuronal synaptic transmission that occurs after a high-frequency stimulation, whereas LTD consists in a decrease in the neuronal synapse activity (Duffau, 2006; Hoogendam, Ramakers, & Di Lazzaro, 2010).

As a treatment tool, rTMS contributes to brain plasticity mechanisms (Valero-Cabre et al., 2017). Neuroplasticity is the ability of adaptation, reorganization and remodeling of the central nervous system (Kleim & Jones, 2008). rTMS induces effects that declines over time, but when recurrent sessions are applied less than 24 hours apart, long-term effects can be achieved by modulating the cortical activity, upgrading its therapeutic effect (Valero-Cabre, Pascual-Leone, & Rushmore, 2008)

The rTMS protocols encompasses two types of protocols, conventional and patterned. In the conventional protocol the slow or low-frequency rTMS refers to stimulus rate of 1 Hz or less that decreases brain excitability (Hallett, 2007). Several studies demonstrated the reduction of MEP amplitude after the low-frequency stimulus over the M1 (Chouinard, Van Der Werf, Leonard, & Paus, 2003; Heide, Witte, & Ziemann, 2006; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000).

The fast or high-frequency rTMS involves stimulus rate higher than 1 Hz that increases brain excitability (Hallett, 2007), as suggested by the increase in MEP amplitudes after a protocol of rTMS over the M1 (Arai et al., 2007; Gilio et al., 2007; Maeda et al., 2000; Peinemann et al., 2004).

On the other hand, the patterned rTMS protocols refers to repetitive applications of short bursts of rTMS at a high frequency with short pauses without stimulation, the best known is the TBS (Huang et al., 2005; Rossini et al., 2015).

2.3.4 Theta burst stimulation

TBS protocols refers to the delivery of short bursts of 50 Hz rTMS repeated in the theta range (5 Hz) as cTBS or iTBS trains (Rossi et al., 2009). The excitatory iTBS protocol consists of 10 bursts of high-frequency stimulation applied at 5 Hz every 10 seconds for a total 600 pulses (Huang et al., 2005). This method produces an increase in cortical excitability of the M1, as suggested by an increase in the MEP amplitude (Di Lazzaro, Pilato, Dileone, Profice, Oliviero, et al., 2008; Huang et al., 2005; Stefan, Gentner, Zeller, Dang, & Classen, 2008; Zafar, Paulus, & Sommer, 2008). The inhibitory cTBS protocol consists of 3 pulses of stimulation delivered at 50 Hz, repeated every 200 ms for a total of 600 pulses (Huang et al., 2005), that derives in a decrease of motor cortex excitability when applied to the M1, proven by the reduction of MEP amplitude (Di Lazzaro et al., 2005; Huang et al., 2005; Zafar et al., 2008). The effects of TBS on synaptic plasticity are stronger, less variable between individuals and outlast longer than the effects seen with standard rTMS (Huang et al., 2005).

2.3.4.1 Repetitive transcranial magnetic stimulation on the posterior parietal cortex

rTMS protocols have been applied to the PPC in hemispatial neglect syndrome. This syndrome often results from a unilateral stroke lesion (particularly right hemisphere lesion), causing a pathologic hyperexcitability of the contralateral hemisphere. (Katz, Hartman-Maeir, Ring, & Soroker, 1999; Oliveri et al., 1999). When an inhibitory 1 Hz

rTMS (Koch, Oliveri, et al., 2008) or cTBS is applied over the left PPC on patients with right hemispheric stroke, it resulted in improvement of the neglect syndrome symptoms in the daily living activities (Cazzoli et al., 2012; Koch et al., 2012). In other studies, cTBS was applied to the right PPC and a paired coil protocol was used to explore facilitation between PPC and the contralateral M1 bilaterally. With a CS set at 90% and 110% RMT and an ISI of 8 ms, the results showed a decrease in the facilitation between the right PPC and the left M1 of the FDI (Killington, Barr, Loetscher, & Bradnam, 2016).

3. ***Manuscript***

Effects of theta burst stimulation of the posterior parietal cortex on the excitability of the upper and lower limb in healthy young adults. A sham-controlled study.

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To be submitted to Brain Stimulation

3.1 Abstract

Introduction: The posterior parietal cortex (PPC) is a brain region involved in the planning of visually guided locomotion. The PPC is functionally and anatomically connected to the primary motor cortex (M1). Previous studies have modulated the PPC excitability with repetitive transcranial magnetic stimulation (TMS) in the form of theta burst stimulation (TBS) and afterwards, assessed changes in the connectivity of the PPC with the M1 of the upper limb with paired-coil TMS. However, there is a paucity of studies targeting lower limb. Therefore, the purpose of this study is to determine the feasibility of measuring lower limb excitability and to assess if the excitability of the upper and the lower limbs changes when targeting the PPC with repetitive TMS in the form of TBS. **Methods:** Ten healthy adults (26±4 years old) were recruited. The study consisted of 4 sessions conducted at least 72 hours apart. During the initial session, hotspots location and motor threshold for the tibialis anterior (TA) and the first dorsal interosseous (FDI) were determined. In the three experimental sessions participants received either iTBS, cTBS or sham iTBS over the PPC. To quantify the effects of TBS on the PPC, the PPC+M1 excitability was assessed with paired-coil TMS, in both hand and leg representations. The measurements were acquired before TBS, immediately after and at 20 and 40 minutes. **Results**. All participants had a measurable resting motor thresholds in the FDI and the TA. In 5 participants, it was not possible to scale the stimulation to yield TA M1 motor evoked potential responses >0.5 mV. There were no immediate effects of PPC stimulation on the amplitude of TA M1 motor evoked potentials however, 40 minutes after TBS, there was a significant increase in the TA M1 excitability. No immediate or late effects were detected on the FDI excitability. **Conclusions:** The remote effects of the ITBS can be detected on the TA excitability 40 minutes after TBS stimulation. No effects were observed in the FDI excitability.

3.2 Introduction

The posterior parietal cortex (PPC) is involved in complex locomotion such as planning of visually guided locomotion (Andujar et al., 2010; Beloozerova & Sirota, 2003; Drew & Marigold, 2015). The PPC shows increased activity when modifications to the gait pattern are needed in response to unpredictable external perturbations, such as speed changes in the belt speed of a split-belt treadmill (Hinton et al., 2019), or changes in planned gait trajectory such as repeated turns overground (Mitchell, Potvin-Desrochers, et al., 2019; Mitchell, Starrs, et al., 2019). The left PPC plays an active role in monitoring and planning gait movement, whereas the right PPC is entangled in different types of attention (Pizzamiglio, Abdalla, Naeem, & Turner, 2018).

Non-invasive brain stimulation (NIBS) can alter transiently the excitability of cortical regions such as the PPC and would allow us to better understand the role of the PPC in locomotor behavior. Theta burst stimulation (TBS) is a patterned form of repetitive transcranial magnetic stimulation (TMS) that can increase or decrease the cortical excitability painlessly (Huang et al., 2005). The facilitatory after-effects of intermittent TBS (iTBS) can last as long as 30 minutes (Katagiri et al., 2020) , whereas continuous TBS (cTBS) inhibitory effects can be seen for nearly for 60 minutes after the stimulation (Huang et al., 2005). The effect of PPC modulation has been previously assessed in contexts outside locomotion. When cTBS is applied to the left PPC in patients with right hemispheric stroke and hemispatial neglect syndrome, ameliorate their spatial neglect symptoms in activities of daily living (Cazzoli et al., 2012). On the other hand, cTBS of the right PPC in the context of cognitive functions results in faster learning of sequence tasks (Whybird et al., 2021). However, these studies did not quantify the direct effect of the cTBS modulation on brain excitability, instead reporting only behavioral outcomes. Killington et al. (2016) stimulated the PPC with cTBS and quantified magnitude of the induced changes in PPC on brain excitability using a paired-coil paradigm with motor evoked potentials (MEP) from the contralateral first dorsal interosseous (FDI) as a measurable output. Their results showed a decrease on the FDI MEPs amplitude. This study

demonstrated the feasibility of using a paired-coil protocol (PPC+FDI) to quantify the effects of TBS on the PPC.

The contribution of the PPC in the planning of locomotion is thought to be achieved by the PPC sending inputs to the primary motor cortex (M1), via the longitudinal fasciculus, allowing proper execution of gait modifications by M1 (Drew & Marigold, 2015). Quantifying the connectivity between the PPC and the lower limb representation of M1 can be used as a tool to better understand the role of PPC in locomotion. Paired-coil TMS can assess changes in the PPC excitability using M1 as a measurable output, which is not available from PPC stimulation alone (Koch et al., 2007). A conditioning stimulus (CS) is first applied to the PPC that activates intracortical circuits projecting to the M1. A test stimulus (TS) is then applied over the M1 to detect any changes produced in the M1 excitability induced by the CS. By comparing to the CS+TS vs TS alone, the inhibitory or excitatory effect of PPC is quantified (Koch et al., 2007).

Previous studies found a facilitatory effect of the left PPC on the ipsilateral M1 with an interstimulus interval (ISI) between the CS and the TS of 4 and 6 ms (Koch et al., 2007), when stimulating the central or posterior inferior-parietal lobule (IPL) (Karabanov et al., 2013; Koch et al., 2007). On the other hand, stimulating the anterior IPL inhibits the M1 excitability (Karabanov et al., 2013). These studies used the hand representation of the M1 as the motor output. However, no research has been done on the connectivity of the PPC with the M1 representation of the leg. Such studies are needed to understand the role of the PPC+M1 interaction in locomotion. Recent studies have however demonstrated that stimulating the tibialis anterior (TA) is more challenging due to its M1 representation is located deeper in the interhemispheric fissure but nevertheless feasible (Hand et al., 2020; Mrachacz-Kersting et al., 2021)

As of today, it is unclear whether changes that were previously demonstrated by Killington et. (2016) can be replicated when targeting the PPC and an ipsilateral

more direct connection to the lower limb muscle, such as the TA. Thus, the objectives of this study were to a) quantify the effects of modulating the PPC with TBS on the connectivity between the PPC+FDI and the PPC+TA, b) determine the feasibility of measuring lower limb excitability with TMS and c) to quantify the PPC excitability with the PPC+M1 connectivity. iTBS, cTBS and sham iTBS were applied to the PPC. A paired-coil TMS protocol was used to assess if the modulation of PPC excitability led to changes in the excitability of the ipsilateral M1 of the FDI and the TA.

3.3 Materials and methods

3.3.1 Participants

Eleven young healthy adults (4 males, 26 ± 4 years old) with no history of neurological or psychiatric disorders and not taking central nervous system acting medications were recruited in the study. Based on a convenience sample, only McGill university students were recruited. Participants were right handed (92 ± 10 laterality quotient) as measured with the Edinburgh Handedness Inventory (Oldfield, 1971). All participants were right leg dominant, as determined by the Waterloo-Footedness Questionnaire-Revised. The study followed the principles of the Declaration of Helsinki and was approved by the McGill Faculty of Medicine Institutional Review Board for Human Subjects. Participants provided written informed consent.

3.3.2 Experimental design

As shown in Figure 4, this study was a single-blind sham-controlled (participants were blinded to the treatment) randomized study consisting of 3 experimental sessions conducted at least 72 hours apart to avoid carry-over effects (Huang et al., 2017). All the sessions were performed at the same time of the day for each participant in order to reduce inter-session variability. Participants avoided caffeine and vigorous physical activity 24 hours prior to each experimental session. In an initial visit, participants were familiarized with the TMS procedures. During this visit, the hotspot location for the FDI and the TA were determined as well as the resting

motor threshold (RMT) for both the FDI and the TA, and active motor threshold (AMT) for the FDI only. In the three experimental sessions, participants received either iTBS, cTBS of sham iTBS in a randomized design targeting the PPC.

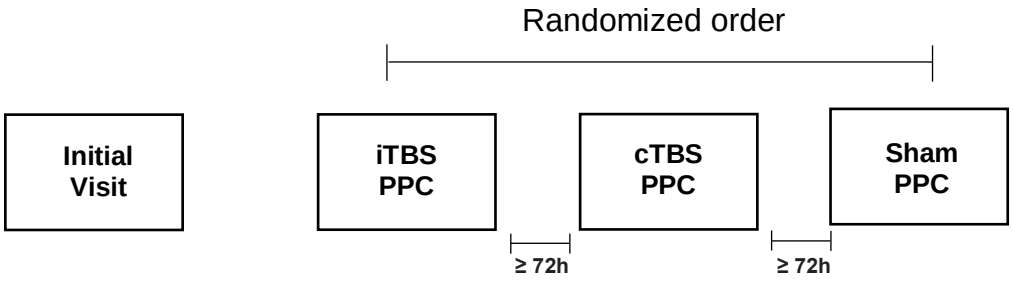

Figure 4. Experimental design. Participants attended 1 initial visit and 3 experimental sessions separated by at least 72 hours.

3.3.3 Electromyographic measurements

Bipolar electromyographic (EMG) recordings from the right FDI and the right TA muscle were obtained via disposable surface Ag-AgCL electrodes of 2.5 cm x 2.5 cm (Biopac Systems, Inc, USA) positioned in a belly-tendon montage over the FDI and in a bipolar array over the TA. Before the placement of the electrodes, and for optimal signal transmission, the skin was shaved when needed, and cleaned with alcohol. The signals were acquired via a Biopac EMG100C EMG amplifiers connected to a Biopac MP150 data acquisition system. The EMG signal was sampled at 5kHz on a 16-bit analog card.

Maximal voluntary contraction (MVC) was determined at each visit, before TMS procedures, by having the participants maximally contract their muscle for 3 seconds by index finger abduction against a fixed wood structure. This procedure was repeated 3 times and the maximal EMG amplitude of the 3 trials was deemed as the MVC for the muscle.

3.3.4 Image Acquisition

Prior to the TMS session, a T-1 weighted magnetic resonance imaging (MRI) (echo time= 2.96 ms; repetition time= 2300 ms, flip angle=9º, 192 slices, voxel size=1mm3 isotropic), was acquired for each participant on a Siemens 3T Prisma MRI Scanner (Siemens, Knoxville, TN) at the McConnell Brain imaging Centre. To precisely guide the position of the coils over the brain the native MRI was registered to each participant's head using Brainsight, a frameless stereotaxic neuronavigation system (Rogue Research Inc, Montreal, Canada).

3.3.5 Transcranial magnetic stimulation

3.3.5.1 TMS devices

In this protocol, two 50 mm figure-of-eight coated coils (Magstim Company, UK)., one 25 mm figure-of-eight coil (Magstim Company, UK) and one 60 mm domed coil (Jaltron Lcc) were connected to one of two Magstim 200^2 (Magstim Company, UK). machines or one Super Rapid^2 machine (Magstim Company, UK).

3.3.5.2 Stimulation targets

The hotspot of the right FDI muscle was acquired by mapping the FDI M1 region while the muscle was relaxed with a 50 mm figure-of-eight coil connected to a Magstim 200^2. The coil was placed tangentially to the scalp at a 45º angle from the midline to induce a posterior-anterior current (Rossini et al., 2015). The intensity of the coil was initially set at 50% MSO. The intensity was increased if there were low or no responses, and it was decreased if the responses were too high. The intensity that elicited the most consistent responses was selected for mapping. To ensure the most accurate hotspot location, a grid was centered over the highest response recorded. Each point of the grid was mapped with two TMS pulses with the same intensity selected for mapping. Based on the responses, the form, size and diameter of the grid were personalized to each participant in a way that it covered all the relevant responses. The hotspot of the right FDI muscle was then defined as the site

of the grid at which TMS elicited the largest MEP amplitude in two consecutive trials in the relaxed muscle.

The same procedure was repeated to acquire the hotspot of the right TA muscle, but with the muscle slightly contracted, with visual feedback to remain within the targeted contraction. The mild voluntary muscle contraction lowers the stimulus intensity because the motoneurons are closer to their discharge threshold (Rossini et al., 2015). A 60-mm domed coil, connected to a Magstim 200^2, was positioned over the scalp parallel to the interhemispheric fissure to induce a medio-lateral current directed towards the left hemisphere, as this is considered the best position to elicit MEPs in the leg area (Smith, Stinear, Alan Barber, & Stinear, 2017; Terao et al., 2000).

The left PPC location was marked in Brainsight using the MNI coordinates *(x,y,z)* -37.8, -68.3, 47.2 (Koch et al., 2011), corresponding to the left caudal IPL (BA39) (Caspers et al., 2008) . For dual-coil stimulation, the PPC was stimulated with a 25 mm figure-of-eight coil connected to a Magstim 200^2, in order to facilitate positioning the two coils over the head. For the TBS protocols, a larger coil was used to stimulate at higher intensities and avoid the heating up of the coils. A 50 mm figure-of-eight coil connected to a Magstim Super Rapid^2 stimulator were used for the TBS protocols. The PPC coil was oriented at a 10º angle from them midline to induce a posterior-anterior current (Koch et al., 2007).

3.3.5.3 Motor thresholds

The RMT was defined as the lowest stimulator intensity that evoked 10 responses of at least 0.05 mV out of 20 stimuli in the muscle at rest (Rossini et al., 2015). RMT of the FDI was acquired with the 50 mm figure-of-eight coil connected to a Magstim 200^2 to determine the MSO required to evoke a 1 mV response in the relaxed FDI muscle, and with a 25 mm figure-of-eight coil connected to a Magstim 200^2 to adjust the MSO of the PPC on the dual-coil trials. RMT of the TA was acquired with a domed coil connected to a Magstim 200^2.

AMT was acquired to set TBS intensity. AMT was defined as the minimal intensity required to induce an MEP in the FDI of at least 200 μV in 10/20 stimuli while the muscle was contracted at 20% of its MVC (Rossini et al., 2015). The AMT was acquired with the Super Rapid^2 (Magstim, Company, UK), the stimulator used to deliver TBS.

During the initial visit, the stimulator intensity for acquiring RMT and AMT was set at 50% MSO, and then increased or decreased by 5% MSO until it consistently evoked a peak-to-peak amplitude of at least 0.05 mV. Afterwards, the intensity was decreased on 1% MSO until there were less than 10 responses out of 20 trials. During subsequent visits, thresholds were validated by setting the stimulator at the previously recorded AMT or RMT values. The intensity of stimulation was increased or decreased by 1% MSO, according to the 10/20 response criteria. In each experimental session, the measurement of AMT was done as the first step, in order to minimize the effect of muscle contraction on TBS effects (Gentner, Wankerl, Reinsberger, Zeller, & Classen, 2008; Huang, Rothwell, Edwards, & Chen, 2008), followed by the measurement of the RMTs and single- and dual-coil trials.

3.3.5.4 Modulation of PPC excitability

The excitability of the left PPC was modulated using TBS, delivered using a 50 mm figure-of-eight coil connected to a Super Rapid^2 machine. Because the PPC is located at a similar cortical depth as the FDI, the FDI thresholds were used to set the stimulation intensity of the FDI, as was done in previous studies (Killington et al., 2016; Koch et al., 2007). The PPC TBS stimulation intensity was set at 80% of the FDI AMT (Huang et al., 2005). cTBS was delivered with 50Hz bursts of stimuli at an interval of 5Hz for a period of 40 seconds. iTBS consisted of 50Hz bursts of stimuli in 2 seconds periods and repeated every 10 seconds (Huang et al., 2005). For sham stimulation, a second 50 mm figure-of-eight coil was positioned over the other coil resting on the skull. The top coil was flipped so that the stimulation side was pointing away from the skull. The top coil delivered the iTBS at an intensity of 80% AMT of

the FDI, preserving sound and sensation of vibration on the head while minimizing the effects of stimulation (Chen et al., 2019).

3.3.6 Outcome measures

Considering that PPC stimulation does not produce a measurable outcome, to quantify the effects of TBS on the PPC, the PPC+M1 excitability was assessed in both hand and leg representation immediately before and after TBS (immediately, 20 minutes and 40 minutes post-TBS), as shown in Figure 5. Measurements consisted of 25 randomized trials over the M1 of the FDI and the TA, and 25 randomized trials of dual site stimulation (PPC+FDI and PPC+TA). The single- and dual-coil trials were randomized targeting blocks of TA trials and always followed by blocks of FDI trials. For dual-coil stimulation, a CS was applied over the left PPC at 90% RMT of the FDI followed by a TS 4 ms later (Koch et al., 2007). The setup for the dual-coil trials on FDI, TA and PPC are shown in Figure 6. The TS was applied over the right FDI muscle representation on M1. The intensity of the TS was adjusted, a priori, by increasing 5% MSO until an average MEP of ~1 mV peak-to-peak in the relaxed FDI muscle was obtained in 10 trials. The same protocol was repeated targeting the right TA muscle. Dual- and single-site TMS were delivered using two high-power Magstim 200^2. One connected to the 50 mm figure-of-eight coil used for stimulating FDI and the domed coil for stimulating TA; and the other Magstim 200^2 connected to the 25 mm figure-of-eight coil, used for stimulating PPC. The effects of the stimulus over the PPC were measured by quantifying the changes in the MEP amplitude of the FDI and the TA, with single and dual-coil, before and after being modulated by TBS. The mean of the FDI and TA single coil trials was compared with the mean of the FDI and TA dual-coil trials when preconditioned by PPC.

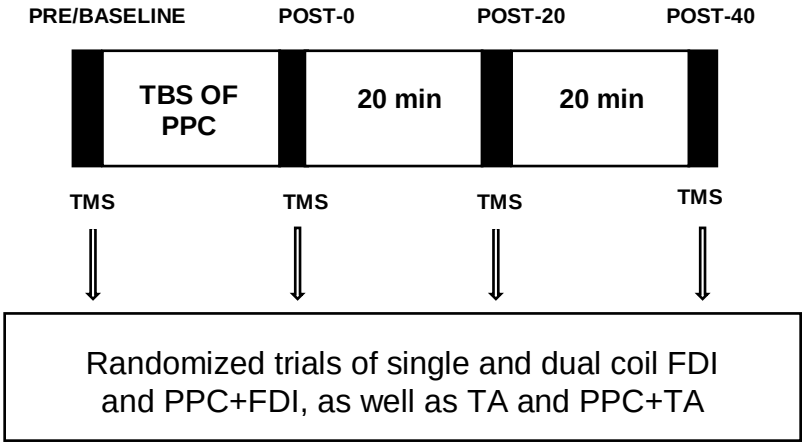

Figure 5. Timeline of each experimental session. Excitability of the M1 was measured prior to the TBS protocol with single pulse and dual-coil TMS of FDI and PPC+FDI, as well as TA and PPC+TA, to establish pre conditions, and at 0-, 20- and 40- minutes after the PPC TBS.

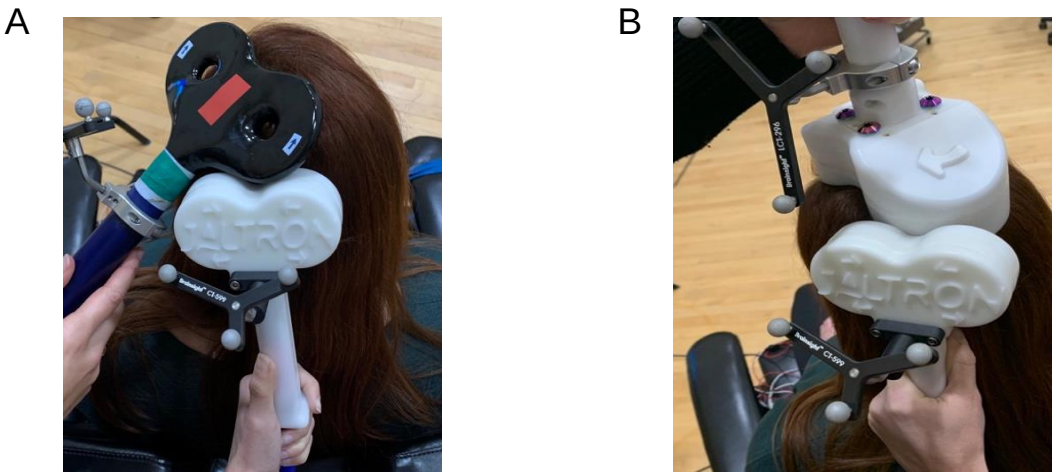

Figure 6. Setup of the coils when performing the dual coil trials on PPC-FDI (A), and PPC-TA (B).

3.3.7 Data processing

Responses <0.05 mV peak-to-peak amplitude were discarded. All the trials with background activity of ≥0.1 mV preceding a TMS pulse were rejected. In total, only 1 trial was removed from the FDI trials and none from the TA trials. To minimize the effect of any outliers, for every condition and for each participant, the trials with the

largest and smallest were discarded. For each condition, any data point that was over or under 3 times the interquartile range (3*IQR) (Ammann et al., 2020; Manikandan, 2011) was also removed, resulting in 7 trials excluded from the TA trials and 26 from the FDI trials. Results are presented as means ± SD.

3.3.8 Statistical analyses

The single- and dual-coil peak-to-peak MEP amplitudes, at baseline (PRE condition only, in Figure 5) were compared using a Wilcoxon signed-rank test. The conditioning effect of the PPC on M1 was expressed as a ratio of (PPC+M1)/M1, and its effect across time was compared using a 1-way repeated measures ANOVA with time (day 1, day 2, day 3) as the factor. The TBS immediate effects on the MEPs amplitude from the FDI and the TA were each compared using a 2-way ANOVA with repeated measures on both condition (M1 and PPC+M1) and time (pre- and post-0). The TBS after-effects on the MEP amplitude from the FDI and the TA, normalized to their respective PRE condition, and were each compared using a 2-way repeated measures ANOVA with condition (M1 and PPC+M1) and time (post 0, post 20 and post 40). All significant differences reported were normally distributed and significance was set at $p<0.05$. The complete statistical analysis was conducted using SPSS version 28 (IBM, NY, USA).

3.4 Results

3.4.1 Motor thresholds

One of the eleven participants was excluded from the study because, despite increasing the MSO to 85%, no responses >0.05 mV could be obtained in neither the relaxed FDI or TA. In five out of the ten remaining subjects, MEP responses >0.5 mV in the TA muscle at rest could not be obtained. Therefore, these 5 participants were excluded from all TA muscle assessments. Figure 7 illustrates both intraindividual and interindividual variability of motor thresholds. Intraindividual variability was very low ~3%MSO (individual standard deviation: RMT FDI 50 mm: 3 ± 2 SD %MSO, RMT FDI 25 mm: 3 ± 2 SD %MSO, RMT TA: 4 ± 3 SD %MSO and

AMT FDI: 2 ± 1 SD %MSO) with much larger interindividual variability ~10%MSO (group standard deviation: RMT FDI 50 mm: 9.0%MSO, RMT FDI 25 mm: 10%MSO, RMT TA: 14%MSO and AMT FDI: 7%MSO).

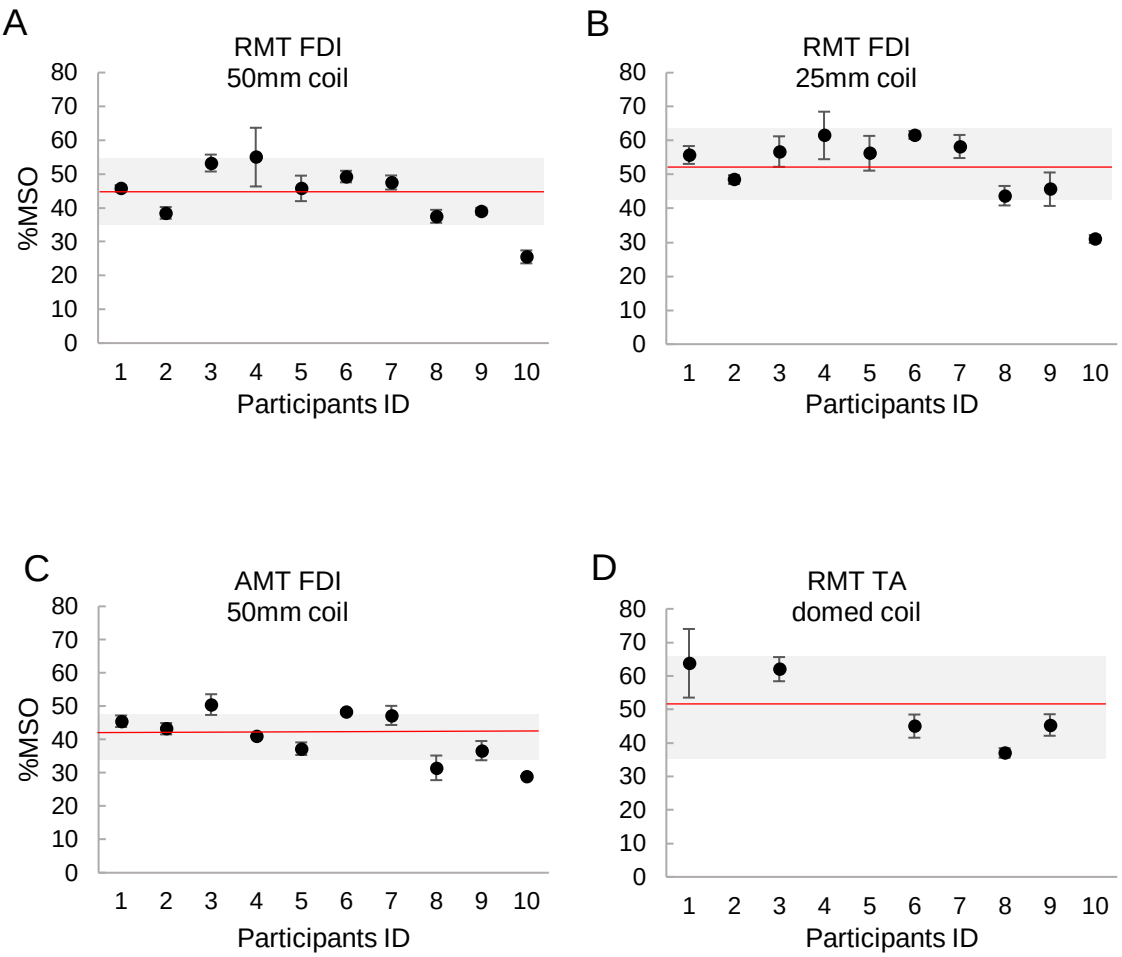

Figure 7. Motor thresholds of the primary motor cortex. *A,* RMT of the FDI with the 50 mm figure-of-eight coil. *B,* RMT of the FDI with the 25 mm figure-of-eight coil. *C*, AMT of the FDI with the 50 mm figure-of-eight coil. *D,* RMT of the TA with the domed coil. The red line shows the mean of the group and the shaded area the range of the standard deviations. RMT of the FDI and TA were acquired with the coils connected to a Magstim 200[2] and AMT of the FDI to a Super Rapid[2]. %MSO: %Maximal Stimulator Output. RMT: resting motor threshold. AMT: active motor threshold. FDI: first dorsal interosseous. TA: tibialis anterior.

Figure 8 shows the correlation between the RMTs of the FDI and TA muscles. No significant correlation was found when considering all participants (r=0.409, n=22,

p=0.059). However, when excluding participants that did not take part in the TA muscle assessments, a significant positive correlation was found (r=0.578, n=17, *p*=0.015).

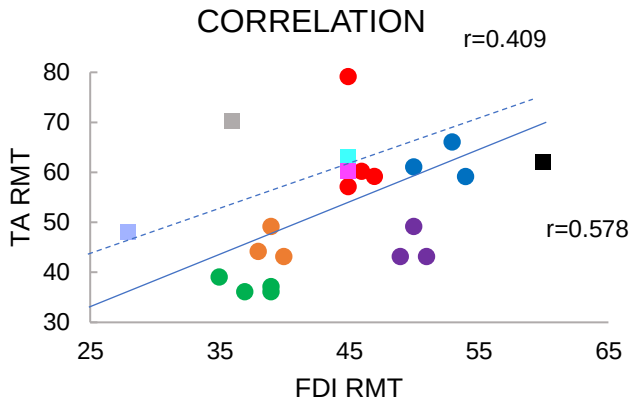

Figure 8. Correlation between the RMT of the FDI and the RMT of the TA. Each color represents a participant and each data point represents a session. Single points in square shape represents the participants that were excluded from the TA measurements, but have the RMT of the TA from the initial session. Rounded shape points represent the participants that were included in the TA measurements. The dotted line is the correlation between the excluded participants. The solid blue line shows the correlation between the included participants. RMT: resting motor threshold. TA: tibialis anterior. FDI: first dorsal interosseous.

3.4.2 Tibialis Anterior Outcomes

3.4.2.1 Measuring TA excitability

Figure 9A shows that in 5 participants, increasing MSO did not increase MEP TA amplitude to reach a reliable ~0.5 mV, despite a measurable RMT in the TA (mean 61± 8%MSO). Further, in 2 participants (Figure 9A lines blue and pink) MEP amplitudes decreased with increasing %MSO. In the remaining 5 participants, MEP amplitudes increased with increasing %MSO (Figure 9B). In these participants, MSO was set to yield a TA MEP muscle responses ~0.5 mV (0.89 ± 0.24 mV).

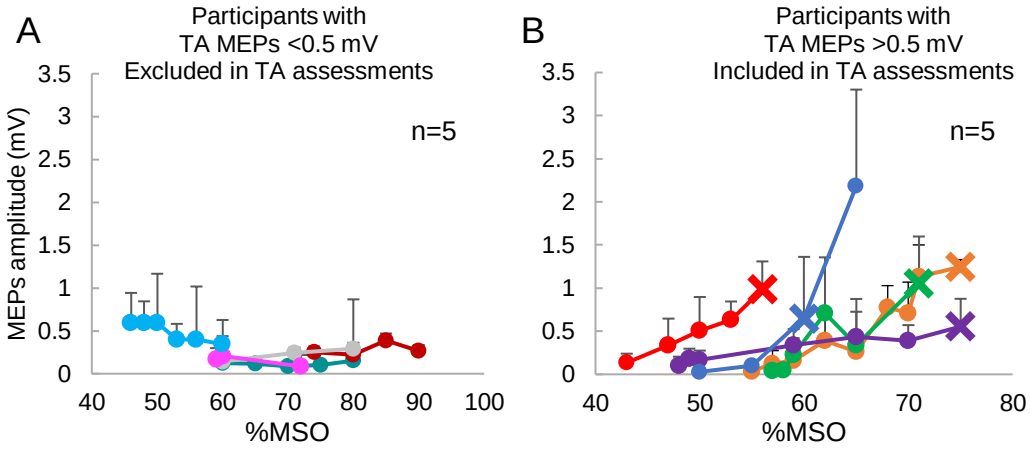

Figure 9. *A,* TA MEPs responses of the participants that did not reach an MEP response >0.5 mV and that were excluded from the TA measurements. *B,* TA MEPs responses of the participants that achieved responses >0.5 mV, included in the TA assessments, the X shows the MSO at which the trials in the experimental sessions were performed. Note that in 4 participants we were able to reach responses >0.5 mV, and in 1 participant the highest response was 0.5 mV at 75%MSO. MEPs: motor evoked potentials. TA: tibialis anterior. mV: millivolts. %MSO: %Maximal Stimulator Output.

3.4.2.2 Effect of the PPC conditioning at baseline

The pre-TBS session data did not show any significant preconditioning effect of the PPC on the TA (p=0.225), as shown in Figure 10A. No significant effect of time was found on the ratio (PPC+TA)/TA alone, when comparing across experimental sessions (F(2,8)=0.075 p=0.929), as shown in Figure 10B.

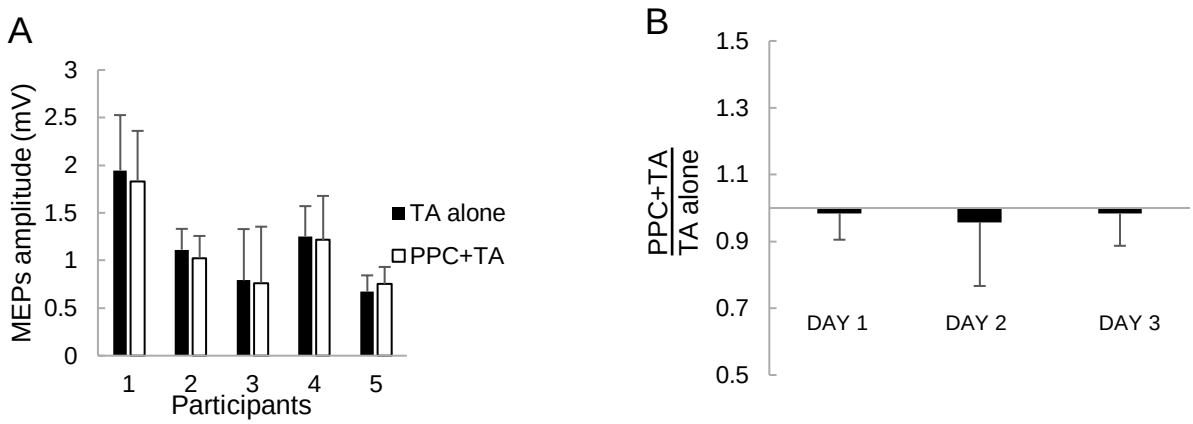

Figure 10. Baseline measurements. *A,* Effect on the excitability of the TA when preconditioned by the PPC. B, Ratio between the (PPC+TA)/TA that demonstrates the effect of PPC over TA across the experimental sessions. MEPs: motor evoked potentials. mV: millivolts TA: tibialis anterior. PPC: posterior parietal cortex.

3.4.2.3 Immediate effects of PPC TBS on the excitability of the TA

As shown in Figure 11, there was no immediate effect between post 0 timepoint and the baseline measurements, in any of the TBS protocols (iTBS, p=0.535; cTBS, p=0.519 and sham, p=0.220), in both TA alone and PPC conditioned trials.

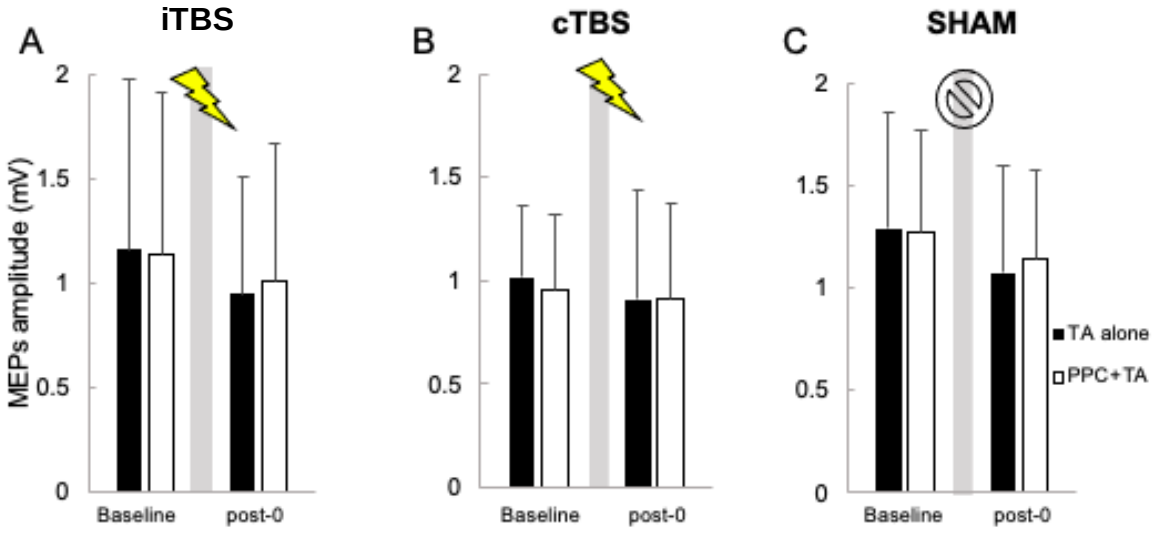

Figure 11. Excitability of the TA alone and the PPC+TA, at baseline and immediately after the PPC TBS. *A,* iTBS protocol. *B,* cTBS protocol. *C,* sham protocol. MEPs: motor evoked potentials. mV: millivolts. TA: tibialis anterior. PPC: posterior parietal cortex. iTBS: intermittent theta burst stimulation. cTBS: continuous theta burst stimulation.

3.4.2.4 After-effects of PPC TBS

As shown in Figure 12A, post-iTBS effects resulted in a significant main effect of time on TA MEP amplitude ($F(2,8)=5.40$ $p=0.033$) such that the amplitude of MEPs increased with time for both TA alone and PPC-conditioned trials. Post hoc tests identified that the excitability was increased 40 minutes following iTBS compared to immediately after, with an increase of 37% between post 0 to post 40 similarly for TA and PPC+TA ($p=0.006$). In the cTBS and sham protocols, ANOVA did not show significant effect on the TA excitability, as shown in Figures 12B and 12C.

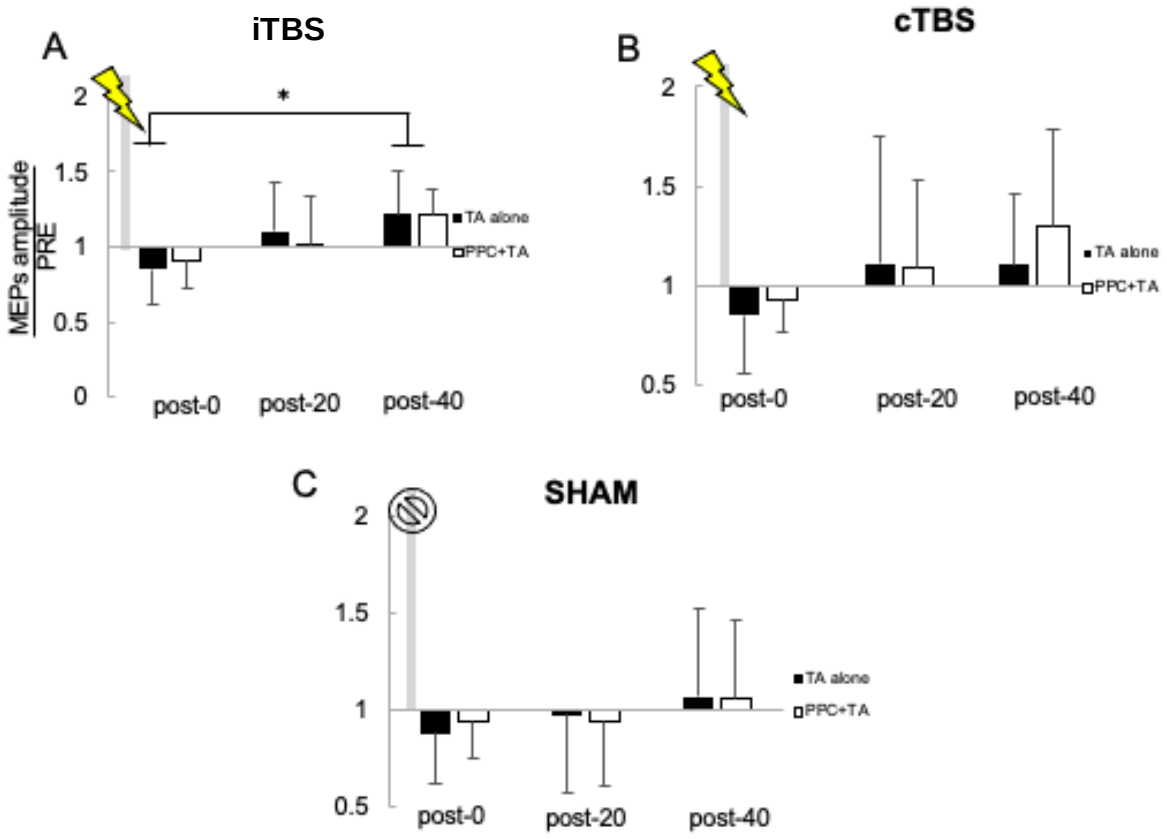

Figure 12. Excitability of the TA alone and the PPC+TA after the PPC was modulated by TBS. Data is normalized to the baseline measurements and shown immediately (post-0), 20 minutes (post-20) and 40 minutes (post-40) following TBS. *A,* iTBS protocol. *B,* cTBS protocol. *C,* sham protocol. MEPs: motor evoked potentials. TA: tibialis anterior. PPC: posterior parietal cortex. iTBS: intermittent theta burst stimulation. cTBS: continuous theta burst stimulation.

3.4.3 First Dorsal Interosseous Outcomes

3.4.3.1 Effect of the PPC conditioning at baseline

The pre-TBS session data did not show any significant preconditioning effect of the PPC on the FDI (p=0.678), as shown in Figure 13A. No significant effect of time was found on the ratio (PPC+FDI)/FDI alone, when comparing baseline across experimental sessions (F(2,14)=1.65 p=0.226), as shown in Figure 13B.

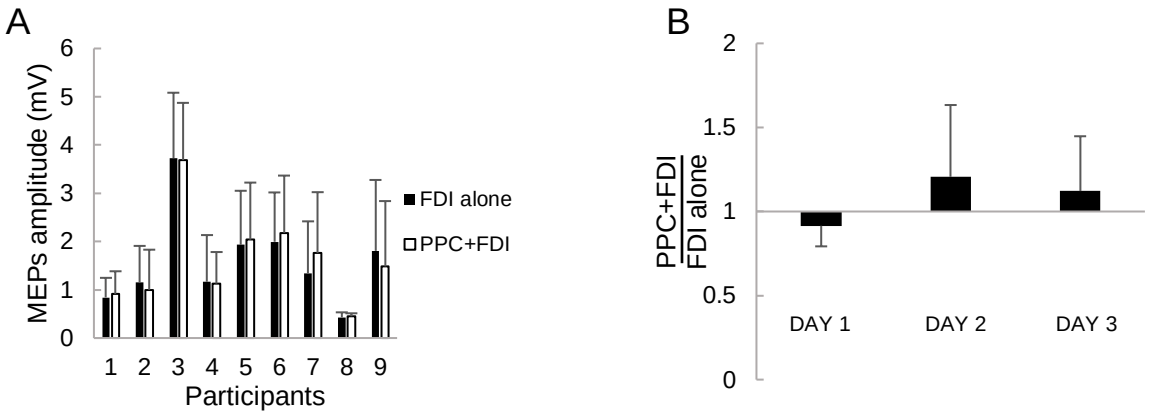

Figure 13. Baseline measurements. *A,* PPC preconditioning on the excitability of the FDI. *B,* PPC+FDI data normalized to FDI alone across the experimental sessions. MEPs: motor evoked potentials. FDI: first dorsal interosseous. PPC: posterior parietal cortex.

3.4.3.2 Immediate effects of PPC TBS on the excitability of the FDI

As shown in Figure 14, there was no change in MEP amplitude immediately (post-0) following the TBS protocols when compared to the baseline measurements, in either FDI alone and PPC-conditioned trials (iTBS p=0.979; cTBS p=0.516, sham p=0.417).

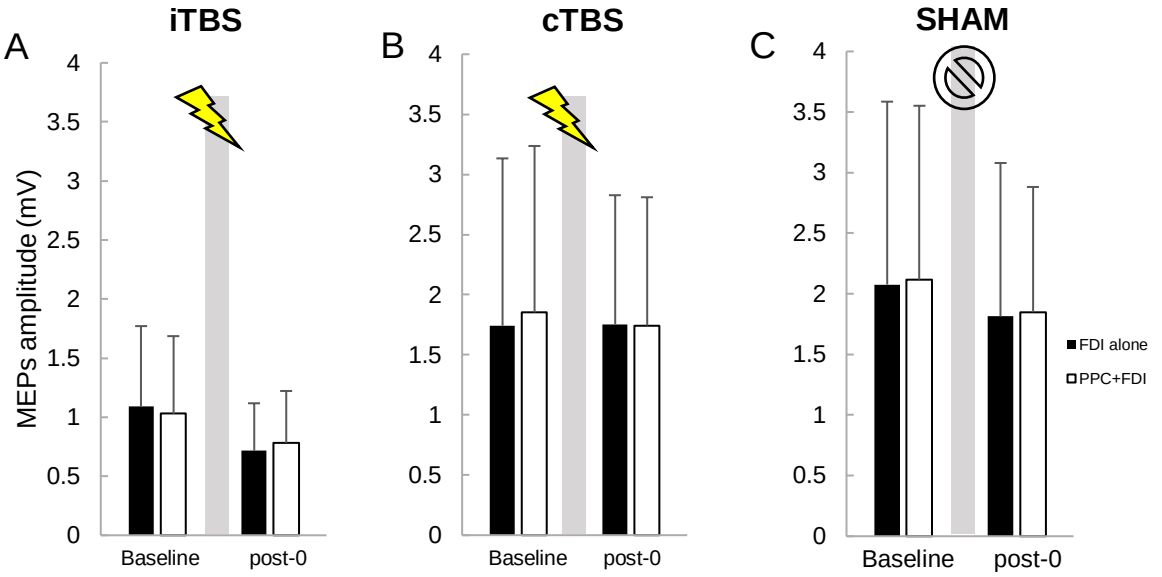

Figure 14. Excitability of the FDI alone and the PPC+FDI, at baseline and immediately after the PPC TBS. *A,* iTBS protocol. *B,* cTBS protocol. *C,* sham protocol. MEPs: motor evoked potentials. mV: millivolts. TA: tibialis anterior. PPC: posterior parietal cortex. iTBS: intermittent theta burst stimulation. cTBS: continuous theta burst stimulation.

3.4.3.3 After-effects of PPC TBS on the excitability of the FDI

As shown in Figure 15, there was no significant change in the FDI excitability, whether or not preconditioned by PPC, within the 40 minutes following each TBS stimulation protocol (iTBS, cTBS, sham). The variability of the FDI was larger than the TA. As shown in Figure 15A, it is a possibility that we have the same trend for FDI than TA, an increase on the excitability following 40 minutes TBS, but it was not significant due to the variability in the MEP amplitudes.

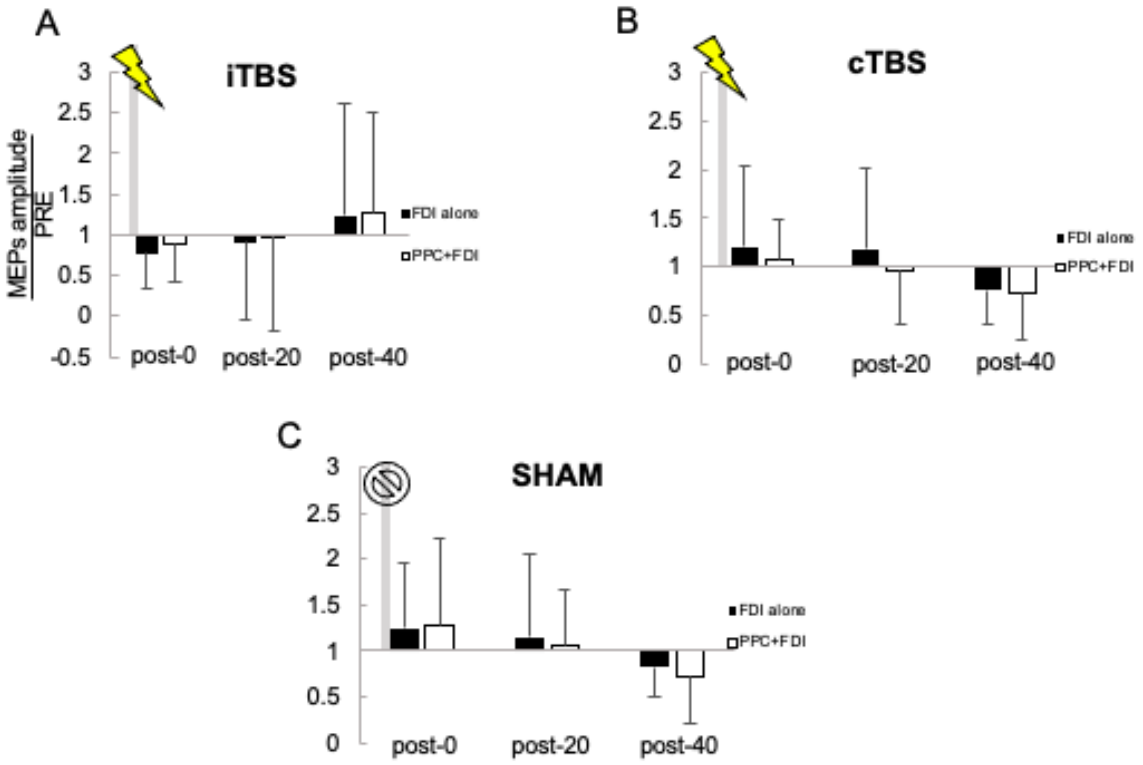

Figure 15. After-effects of TBS on the excitability of the FDI alone and preconditioned by the PPC, at 0, 20 and 40 minutes after. *A,* iTBS protocol. *B,* cTBS protocol. *C,* sham protocol. MEPs: motor evoked potentials. mV: millivolts. FDI: first dorsal interosseous. PPC: posterior parietal cortex. iTBS: intermittent theta burst stimulation. cTBS: continuous theta burst stimulation.

3.5 Discussion

According to our objectives, we demonstrated the feasibility of measuring lower limb excitability, but we were unable to quantify significant changes in PPC excitability using a dual-coil paradigm. Increasing the PPC excitability led to a delayed increase in the TA muscle excitability, suggesting a remote effect on the M1 from the TBS of the PPC, rather than the PPC conditioning the TA.

3.5.1 Feasibility of TA muscle stimulation

In our study, we successfully measured lower limb excitability by obtaining RMTs in the TA muscle of all participants. However, responses in the TA muscle ≥0.5 mV were only acquired in half of the participants. Based on our results, it is feasible to target the TA muscle but measuring its excitability may be more widely representative by its motor thresholds than its MEP amplitude. The lower limb representation of the M1 lies between the interhemispheric fissure, making it more difficult to stimulate (Allison, McCarthy, Luby, Puce, & Spencer, 1996; Terao et al., 2000), thus hindering its appropriate excitability measurement and regulation. In order to avoid excluding a large number of participants from TA studies, we suggest using RMT as an outcome measure

and, when possible, the MEP amplitude to measure the TA excitability, as 50% of our sample was excluded because of the inability to acquire an MEP amplitude of at least 0.5 mV.

We showed that RMT is a reliable measure of TA excitability over multiple sessions (or days). Indeed, the motor thresholds recorded from the FDI and TA muscles showed a low intraindividual variability and were stable across time. The RMT of the FDI showed a positive correlation with the RMT of the TA, which can be considered as a predictive value to determine feasibility of obtaining RMT of the TA when acquiring RMT of the FDI in individual participants. This approach can be used as a tool for including or excluding participants when our goal is to measure TA excitability.

3.5.2 Altering the excitability of the PPC

Interestingly, increasing the excitability of the PPC led to a delayed increase in the TA excitability. After the iTBS over PPC, we did not find an immediate effect, but rather an after-effect at 40 minutes following the modulation. These results are in agreement with another study that found an effect on the M1 after modulating with TBS the dorsolateral prefrontal cortex, another non-motor region (Cao et al., 2018). In our study, the sham protocol did not provoke changes in the excitability of the TA,

which reassures that our significant results actually come from the iTBS stimulation rather than from a placebo effect. Because the PPC preconditioning did not result in any significant effect in TA excitability, we can conclude that the after-effects on the excitability of the TA alone after PPC iTBS, can reflect a possible network of remote effect that comes from the PPC stimulation, but not a direct effect from the PPC on the TA. Previous studies have demonstrated that TBS may induce remote physiological effects on brain sites distant but connected to each other (Stefan et al., 2008).

On the other hand, increasing the excitability of the PPC with iTBS did not show any immediate or delayed effects on the excitability of the FDI. Even though no remote effect was demonstrated from the PPC to the FDI, we have the same tendency of an increase in the excitability of PPC+FDI and FDI at 40 minutes following TBS, but it was not statistically significant likely due to the larger variability that the FDI MEPs have. We consider that by reducing the variability of the FDI MEPs, we can demonstrate the remote effect that PPC has over the FDI.

No immediate or delayed effects were seen on the cTBS protocols on neither the TA or the FDI excitability. Previous literature have concluded that the responsiveness to cTBS can be variable, as low as 42% on upper limb M1 (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013), and as high as 63% on the lower limb M1 (Katagiri et al., 2020). Therefore, the absence of effect on the cTBS protocol might be due to the variability in response to cTBS.

3.5.3 Effects of PPC preconditioning M1

Contrary to what was previously reported in the FDI (Koch et al., 2007; Koch, Fernandez Del Olmo, et al., 2008), we did not observe any conditioning effect of the PPC on the excitability of the FDI nor TA.

Several factors could explain the absence of effect of PPC preconditioning the TA M1. The optimal ISI for excitatory effects of the PPC+M1 leg connectivity may be different from the used in this study. We used an ISI optimized for the FDI (Koch et

al., 2007) as no previous research had assessed the connectivity between the PPC and the TA M1. Because the PPC has indirect connections to the upper limb M1 via the premotor cortex, possibly using a longer ISI may have showed different results. The location of the PPC used in this study was previously targeted in studies showing the connectivity between the PPC and FDI MI. This location referred to the caudal IPL and has shown to provoke a facilitation effect over the ipsilateral FDI M1 (Koch et al., 2011). Previous studies that found an effect on the left FDI M1 when stimulating the right PPC with TBS, used the same location, but marked with the 10-20 EEG system (Killington et al., 2016), which can be a reason why our results differ. Additionally, we suggest to map around the PPC region until the MEP of the M1 reaches an amplitude larger than with the M1 alone, demonstrating the facilitation between PPC and M1. Previous studies mapped the PPC at baseline and excluded participants that did not show any facilitatory effect between PPC and M1 (Killington et al., 2016). Mapping the PPC will add a considerable length to the experiment, and it will require to analyze the data in the moment. New experiments should explore PPC regions that provoke a facilitatory effect on the TA M1 excitability.

In opposition to other studies, we did not find any effect on the FDI excitability when it was preconditioned by the PPC. The ISI used in this study was 4 ms, but ISI of 6 ms has also previously been shown to provoke a facilitation between the left PPC and the left FDI M1 (Koch et al., 2007). We suggest future studies to explore 6 ms as ISI to assess PPC+FDI connectivity. Furthermore, we cannot guarantee that the position of the coils was the most appropriate when performing the dual coil PPC+FDI trials. This because to the challenge that was positioning the two coils due to the proximity of the PPC with the FDI M1. This situation may hinder the stimulation and therefore affected our results. One of the participants in the study had to be excluded because the coils were overlapping when trying to position them on the PPC and FDI M1, even though one of the coils had a 25 mm diameter. Previous studies that have done dual coil TMS on PPC+FDI did not report this challenge. It is thus necessary to clarify and specify any exclusion of participants with respect to proper coil positioning.

The limitations of this study include the small sample size, which may not represent the entire population behavior. We did not have the same number of participants on the FDI (10 participants) and the TA (5 participants) measurements, which limits the possibility to compare the TA with the FDI outcomes. In this study, we only used electrophysiological measures as outcomes, thus we do not know if the observed changes in the excitability could result in differences in the gait performance. It can be important to add a behavioral outcome to such studies, but this approach might be only relevant on clinical populations that already have gait impairments related to neurological disorders. Because this study recruited only healthy physically active young adults and focused on brain circuitry, gait analysis was not considered a relevant outcome.

This study is the first to show delayed after-effects from PPC TBS had on the TA M1 excitability 40 minutes following the stimulation. These effects are likely explained by a network remote effect from the PPC modulation rather than from the PPC preconditioning the TA.

3.6 Manuscript References

Allison, T., McCarthy, G., Luby, M., Puce, A., & Spencer, D. D. (1996). Localization of functional regions of human mesial cortex by somatosensory evoked potential recording and by cortical stimulation. *Electroencephalogr Clin Neurophysiol, 100*(2), 126-140. doi:10.1016/0013-4694(95)00226-x

Andujar, J. E., Lajoie, K., & Drew, T. (2010). A contribution of area 5 of the posterior parietal cortex to the planning of visually guided locomotion: limb-specific and limb-independent effects. *J Neurophysiol, 103*(2), 986-1006. doi:10.1152/jn.00912.2009

Beloozerova, I. N., & Sirota, M. G. (2003). Integration of motor and visual information in the parietal area 5 during locomotion. *J Neurophysiol, 90*(2), 961-971. doi:10.1152/jn.01147.2002

Cao, N., Pi, Y., Liu, K., Meng, H., Wang, Y., Zhang, J., . . . Tan, X. (2018). Inhibitory and facilitatory connections from dorsolateral prefrontal to primary motor cortex in healthy humans at rest-An rTMS study. *Neurosci Lett, 687*, 82-87. doi:10.1016/j.neulet.2018.09.032

Caspers, S., Eickhoff, S. B., Geyer, S., Scheperjans, F., Mohlberg, H., Zilles, K., & Amunts, K. (2008). The human inferior parietal lobule in stereotaxic space. *Brain Struct Funct, 212*(6), 481-495. doi:10.1007/s00429-008-0195-z

Cazzoli, D., Muri, R. M., Schumacher, R., von Arx, S., Chaves, S., Gutbrod, K., . . . Nyffeler, T. (2012). Theta burst stimulation reduces disability during the activities of daily living in spatial neglect. *Brain, 135*(Pt 11), 3426-3439. doi:10.1093/brain/aws182

Chen, Y. J., Huang, Y. Z., Chen, C. Y., Chen, C. L., Chen, H. C., Wu, C. Y., . . . Chang, T. L. (2019). Intermittent theta burst stimulation enhances upper limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *BMC Neurol, 19*(1), 69. doi:10.1186/s12883-019-1302-x

Drew, T., & Marigold, D. S. (2015). Taking the next step: cortical contributions to the control of locomotion. *Curr Opin Neurobiol, 33*, 25-33. doi:10.1016/j.conb.2015.01.011

Gentner, R., Wankerl, K., Reinsberger, C., Zeller, D., & Classen, J. (2008). Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. *Cereb Cortex, 18*(9), 2046-2053. doi:10.1093/cercor/bhm239

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., & Rothwell, J. C. (2013). The role of interneuron networks in driving human motor cortical plasticity. *Cereb Cortex, 23*(7), 1593-1605. doi:10.1093/cercor/bhs147

Hand, B. J., Opie, G. M., Sidhu, S. K., & Semmler, J. G. (2020). TMS coil orientation and muscle activation influence lower limb intracortical excitability. *Brain Res, 1746*, 147027. doi:10.1016/j.brainres.2020.147027

Hinton, D. C., Thiel, A., Soucy, J. P., Bouyer, L., & Paquette, C. (2019). Adjusting gait step-by-step: Brain activation during split-belt treadmill walking. *Neuroimage, 202*, 116095. doi:10.1016/j.neuroimage.2019.116095

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201-206. doi:10.1016/j.neuron.2004.12.033

Huang, Y. Z., Rothwell, J. C., Edwards, M. J., & Chen, R. S. (2008). Effect of physiological activity on an NMDA-dependent form of cortical plasticity in human. *Cereb Cortex, 18*(3), 563-570. doi:10.1093/cercor/bhm087

Karabanov, A. N., Chao, C. C., Paine, R., & Hallett, M. (2013). Mapping different intra-hemispheric parietal-motor networks using twin Coil TMS. *Brain Stimul, 6*(3), 384-389. doi:10.1016/j.brs.2012.08.002

Katagiri, N., Yoshida, S., Koseki, T., Kudo, D., Namba, S., Tanabe, S., . . . Yamaguchi, T. (2020). Interindividual Variability of Lower-Limb Motor Cortical Plasticity Induced by Theta Burst Stimulation. *Front Neurosci, 14*, 563293. doi:10.3389/fnins.2020.563293

Killington, C., Barr, C., Loetscher, T., & Bradnam, L. V. (2016). Variation in left posterior parietal-motor cortex interhemispheric facilitation following right parietal continuous theta-burst stimulation in healthy adults. *Neuroscience, 330*, 229-235. doi:10.1016/j.neuroscience.2016.05.056

Koch, G., Cercignani, M., Bonni, S., Giacobbe, V., Bucchi, G., Versace, V., . . . Bozzali, M. (2011). Asymmetry of parietal interhemispheric connections in humans. *J Neurosci, 31*(24), 8967-8975. doi:10.1523/JNEUROSCI.6567-10.2011

Koch, G., Fernandez Del Olmo, M., Cheeran, B., Ruge, D., Schippling, S., Caltagirone, C., & Rothwell, J. C. (2007). Focal stimulation of the posterior parietal cortex increases the

excitability of the ipsilateral motor cortex. *J Neurosci, 27*(25), 6815-6822. doi:10.1523/JNEUROSCI.0598-07.2007

Koch, G., Fernandez Del Olmo, M., Cheeran, B., Schippling, S., Caltagirone, C., Driver, J., & Rothwell, J. C. (2008). Functional interplay between posterior parietal and ipsilateral motor cortex revealed by twin-coil transcranial magnetic stimulation during reach planning toward contralateral space. *J Neurosci, 28*(23), 5944-5953. doi:10.1523/JNEUROSCI.0957-08.2008

Mitchell, T., Potvin-Desrochers, A., Lafontaine, A. L., Monchi, O., Thiel, A., & Paquette, C. (2019). Cerebral Metabolic Changes Related to Freezing of Gait in Parkinson Disease. *J Nucl Med, 60*(5), 671-676. doi:10.2967/jnumed.118.218248

Mitchell, T., Starrs, F., Soucy, J. P., Thiel, A., & Paquette, C. (2019). Impaired Sensorimotor Processing During Complex Gait Precedes Behavioral Changes in Middle-aged Adults. *J Gerontol A Biol Sci Med Sci, 74*(12), 1861-1869. doi:10.1093/gerona/gly210

Mrachacz-Kersting, N., Stevenson, A. J. T., & Ziemann, U. (2021). Short-interval intracortical inhibition and facilitation targeting upper and lower limb muscles. *Sci Rep, 11*(1), 21993. doi:10.1038/s41598-021-01348-6

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113. doi:10.1016/0028-3932(71)90067-4

Pizzamiglio, S., Abdalla, H., Naeem, U., & Turner, D. L. (2018). Neural predictors of gait stability when walking freely in the real-world. *J Neuroeng Rehabil, 15*(1), 11. doi:10.1186/s12984-018-0357-z

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., . . . Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol, 126*(6), 1071-1107. doi:10.1016/j.clinph.2015.02.001

Smith, M. C., Stinear, J. W., Alan Barber, P., & Stinear, C. M. (2017). Effects of non-target leg activation, TMS coil orientation, and limb dominance on lower limb motor cortex excitability. *Brain Res, 1655*, 10-16. doi:10.1016/j.brainres.2016.11.004

Stefan, K., Gentner, R., Zeller, D., Dang, S., & Classen, J. (2008). Theta-burst stimulation: remote physiological and local behavioral after-effects. *Neuroimage, 40*(1), 265-274. doi:10.1016/j.neuroimage.2007.11.037

Terao, Y., Ugawa, Y., Hanajima, R., Machii, K., Furubayashi, T., Mochizuki, H., . . . Kanazawa, I. (2000). Predominant activation of I1-waves from the leg motor area by transcranial magnetic stimulation. *Brain Res, 859*(1), 137-146. doi:10.1016/s0006-8993(00)01975-2

Whybird, M., Coats, R., Vuister, T., Harrison, S., Booth, S., & Burke, M. (2021). The role of the posterior parietal cortex on cognition: An exploratory study. *Brain Res, 1764*, 147452. doi:10.1016/j.brainres.2021.147452

4. Scholarly Discussion

In this study, we demonstrated that modulating the PPC with iTBS increases the excitability of the TA M1 at 40 minutes. There was no increase on the FDI excitability after TBS was delivered to the PPC. Nevertheless, there was a tendency in the FDI, similar to that of the TA, with an increase on the excitability 40 minutes after PPC TBS. The results in the FDI were not significant, likely due to the high variability observed in the FDI compared to the TA.

Although it is always feasible to acquire FDI MEPs to assess the M1 excitability, this is not the case in the TA M1. It is challenging, and sometimes impossible, to achieve a response of at least 0.5 mV on the relaxed TA muscle. In this study we suggest to evaluate the cortical excitability not only by the amplitude of the MEPs, but also by the motor thresholds, to allow the inclusion of more participants in the population sample.

In opposition to previous literature, we did not find any effect of PPC conditioning on the excitability of the FDI nor the TA. No previous research had explored if the functional connectivity between the TA and PPC can be assessed by TMS, thus the dual-coil parameters used in this study may not been the appropriate ones, such as ISI and CS intensity. Surprisingly, the PPC did not exerted a preconditioning effect on the excitability of the FDI, probable due to the same factors (ISI and CS intensity).

The remote and delayed after effects of the TBS on the TA excitability is a novel finding that can be applied to research focused on rehabilitation for patients with gait impairments due to neurological disorders. An example of the latter is a stroke, a condition that provokes a decrease in the cortical excitability of the injured ischemic brain hemisphere (Clarkson, Huang, Macisaac, Mody, & Carmichael, 2010). Previous study applied 10 days of consecutive high frequency rTMS on the ipsilateral injured hemisphere of stroke patients. They concluded that rTMS elicits an increase in corticomotor excitability of the upper limb and an improvement in the response of the patients to physical therapy (Khedr, Ahmed, Fathy, & Rothwell, 2005). Other

studies applied iTBS to the ipsilesional hemisphere and cTBS to the contralesional hemisphere, resulting in a positive effect in both motor recovery and electrophysiological outcomes (Di Lazzaro, Pilato, Dileone, Profice, Capone, et al., 2008; Talelli, Greenwood, & Rothwell, 2007). We suggest that delivering TBS can help improve gait deficits in patients where the injury affects the lower limb M1. We expect that delivering TBS to the lower limb M1 may improve the execution of movement. Furthermore, applying TBS to the PPC will provoke an increase in the excitability of the parieto-motor connections at 40 minutes following the stimulation, thus improving complex locomotion. By modulating the motor and non-motor cortical regions involved in locomotion, we can provide a new type of non-invasive rehabilitation, that, added to physical therapy, can accelerate the recovery of the patients with any type of gait impairments. However, it is acknowledged that inter- and intra-individual variability exists in response to cTBS and iTBS protocols (Hamada et al., 2013) which could affect the expected response to each protocol, thus, hindering the stimulation effect on the cerebral cortex. Perhaps, not every individual will achieve neuroplasticity following TBS protocols.

We cannot dismiss that a delayed effect can be found also on the FDI excitability, but new studies need to explore if even though it is not statistically significant because of its high variability, it can provoke any behavioral changes that can improve the rehabilitation of the motor upper limb impairments.

5. Conclusion and Summary

This is the first study that demonstrated an increase on the TA excitability after the PPC was modulated with iTBS. Previous studies had assessed this connectivity but only on the FDI, due to its accessible location on the M1.

We also showed that is feasible to acquire RMT of the TA, but not in all cases an MEP amplitude of at least 0.5 mV will be achieve. Thus, we suggest to measure the TA excitability with either RMT, MEP amplitude or, if it's the case, with both.

Surprisingly, contrary to other studies, we did not find an effect on the excitability of the M1 of the FDI and the TA when they were preconditioned by the PPC. Based on other studies, we expected to see a facilitation on the connectivity of PPC-FDI (Koch et al., 2011; Koch et al., 2007), but the absence of effects can be due to the parameters that we used in this study, as ISI and PPC location. These same parameters applied to justify the absence of effect when performing a dual-coil PPC+TA, as this is the first study that approach it, the parameters used need to be adjusted until we find a facilitation between PPC+TA.

We conclude that modulating the PPC can produce an after and remote effect on the TA excitability 40 minutes after the stimulation, but not an immediate effect.

6. ***References***

Allison, T., McCarthy, G., Luby, M., Puce, A., & Spencer, D. D. (1996). Localization of functional regions of human mesial cortex by somatosensory evoked potential recording and by cortical stimulation. *Electroencephalogr Clin Neurophysiol, 100*(2), 126-140. doi:10.1016/0013-4694(95)00226-x

Ammann, C., Guida, P., Caballero-Insaurriaga, J., Pineda-Pardo, J. A., Oliviero, A., & Foffani, G. (2020). A framework to assess the impact of number of trials on the amplitude of motor evoked potentials. *Sci Rep, 10*(1), 21422. doi:10.1038/s41598-020-77383-6

Andujar, J. E., Lajoie, K., & Drew, T. (2010). A contribution of area 5 of the posterior parietal cortex to the planning of visually guided locomotion: limb-specific and limb-independent effects. *J Neurophysiol, 103*(2), 986-1006. doi:10.1152/jn.00912.2009

Arai, N., Okabe, S., Furubayashi, T., Mochizuki, H., Iwata, N. K., Hanajima, R., . . . Ugawa, Y. (2007). Differences in after-effect between monophasic and biphasic high-frequency rTMS of the human motor cortex. *Clin Neurophysiol, 118*(10), 2227-2233. doi:10.1016/j.clinph.2007.07.006

Arai, N., Okabe, S., Furubayashi, T., Terao, Y., Yuasa, K., & Ugawa, Y. (2005). Comparison between short train, monophasic and biphasic repetitive transcranial magnetic stimulation (rTMS) of the human motor cortex. *Clin Neurophysiol, 116*(3), 605-613. doi:10.1016/j.clinph.2004.09.020

Badawy, R. A., Loetscher, T., Macdonell, R. A., & Brodtmann, A. (2012). Cortical excitability and neurology: insights into the pathophysiology. *Funct Neurol, 27*(3), 131-145. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23402674

Beloozerova, I. N., & Sirota, M. G. (2003). Integration of motor and visual information in the parietal area 5 during locomotion. *J Neurophysiol, 90*(2), 961-971. doi:10.1152/jn.01147.2002

Bruni, S., Gerbella, M., Bonini, L., Borra, E., Coude, G., Ferrari, P. F., . . . Rozzi, S. (2018). Cortical and subcortical connections of parietal and premotor nodes of the monkey hand mirror neuron network. *Brain Struct Funct, 223*(4), 1713-1729. doi:10.1007/s00429-017-1582-0

Burman, K. J., Bakola, S., Richardson, K. E., Reser, D. H., & Rosa, M. G. (2014). Patterns of cortical input to the primary motor area in the marmoset monkey. *J Comp Neurol, 522*(4), 811-843. doi:10.1002/cne.23447

Cao, N., Pi, Y., Liu, K., Meng, H., Wang, Y., Zhang, J., . . . Tan, X. (2018). Inhibitory and facilitatory connections from dorsolateral prefrontal to primary motor cortex in healthy humans at rest-An rTMS study. *Neurosci Lett, 687*, 82-87. doi:10.1016/j.neulet.2018.09.032

Caspers, S., Eickhoff, S. B., Geyer, S., Scheperjans, F., Mohlberg, H., Zilles, K., & Amunts, K. (2008). The human inferior parietal lobule in stereotaxic space. *Brain Struct Funct, 212*(6), 481-495. doi:10.1007/s00429-008-0195-z

Caspers, S., & Zilles, K. (2018). Microarchitecture and connectivity of the parietal lobe. *Handb Clin Neurol, 151*, 53-72. doi:10.1016/B978-0-444-63622-5.00003-6

Cattaneo, L., Giampiccolo, D., Meneghelli, P., Tramontano, V., & Sala, F. (2020). Cortico-cortical connectivity between the superior and inferior parietal lobules and the motor cortex assessed by intraoperative dual cortical stimulation. *Brain Stimul, 13*(3), 819-831. doi:10.1016/j.brs.2020.02.023

Cazzoli, D., Muri, R. M., Schumacher, R., von Arx, S., Chaves, S., Gutbrod, K., . . . Nyffeler, T. (2012). Theta burst stimulation reduces disability during the activities of daily living in spatial neglect. *Brain, 135*(Pt 11), 3426-3439. doi:10.1093/brain/aws182

Chen, Y. J., Huang, Y. Z., Chen, C. Y., Chen, C. L., Chen, H. C., Wu, C. Y., . . . Chang, T. L. (2019). Intermittent theta burst stimulation enhances upper limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *BMC Neurol, 19*(1), 69. doi:10.1186/s12883-019-1302-x

Chouinard, P. A., Van Der Werf, Y. D., Leonard, G., & Paus, T. (2003). Modulating neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. *J Neurophysiol, 90*(2), 1071-1083. doi:10.1152/jn.01105.2002

Clarkson, A. N., Huang, B. S., Macisaac, S. E., Mody, I., & Carmichael, S. T. (2010). Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. *Nature, 468*(7321), 305-309. doi:10.1038/nature09511

Cui, H., & Andersen, R. A. (2007). Posterior parietal cortex encodes autonomously selected motor plans. *Neuron, 56*(3), 552-559. doi:10.1016/j.neuron.2007.09.031

Dea, M., Hamadjida, A., Elgbeili, G., Quessy, S., & Dancause, N. (2016). Different Patterns of Cortical Inputs to Subregions of the Primary Motor Cortex Hand Representation in Cebus apella. *Cereb Cortex, 26*(4), 1747-1761. doi:10.1093/cercor/bhv324

Di Lazzaro, V., Oliviero, A., Mazzone, P., Insola, A., Pilato, F., Saturno, E., . . . Rothwell, J. C. (2001). Comparison of descending volleys evoked by monophasic and biphasic magnetic stimulation of the motor cortex in conscious humans. *Exp Brain Res, 141*(1), 121-127. doi:10.1007/s002210100863

Di Lazzaro, V., Oliviero, A., Pilato, F., Saturno, E., Dileone, M., Mazzone, P., . . . Rothwell, J. C. (2004). The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clin Neurophysiol, 115*(2), 255-266. doi:10.1016/j.clinph.2003.10.009

Di Lazzaro, V., Oliviero, A., Profice, P., Saturno, E., Pilato, F., Insola, A., . . . Rothwell, J. C. (1998). Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. *Electroencephalogr Clin Neurophysiol, 109*(5), 397-401. doi:10.1016/s0924-980x(98)00038-1

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Capone, F., Ranieri, F., . . . Tonali, P. A. (2008). Modulating cortical excitability in acute stroke: a repetitive TMS study. *Clin Neurophysiol, 119*(3), 715-723. doi:10.1016/j.clinph.2007.11.049

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., . . . Rothwell, J. C. (2008). The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. *J Physiol, 586*(16), 3871-3879. doi:10.1113/jphysiol.2008.152736

Di Lazzaro, V., Pilato, F., Saturno, E., Oliviero, A., Dileone, M., Mazzone, P., . . . Rothwell, J. C. (2005). Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *J Physiol, 565*(Pt 3), 945-950. doi:10.1113/jphysiol.2005.087288

Di Lazzaro, V., Profice, P., Ranieri, F., Capone, F., Dileone, M., Oliviero, A., & Pilato, F. (2012). I-wave origin and modulation. *Brain Stimul, 5*(4), 512-525. doi:10.1016/j.brs.2011.07.008

Drew, T., & Marigold, D. S. (2015). Taking the next step: cortical contributions to the control of locomotion. *Curr Opin Neurobiol, 33*, 25-33. doi:10.1016/j.conb.2015.01.011

Drew, T., Prentice, S., & Schepens, B. (2004). Cortical and brainstem control of locomotion. *Prog Brain Res, 143*, 251-261. doi:10.1016/S0079-6123(03)43025-2

Duffau, H. (2006). Brain plasticity: from pathophysiological mechanisms to therapeutic applications. *J Clin Neurosci, 13*(9), 885-897. doi:10.1016/j.jocn.2005.11.045

Fogassi, L., Ferrari, P. F., Gesierich, B., Rozzi, S., Chersi, F., & Rizzolatti, G. (2005). Parietal lobe: from action organization to intention understanding. *Science, 308*(5722), 662-667. doi:10.1126/science.1106138

Fried, I., Katz, A., McCarthy, G., Sass, K. J., Williamson, P., Spencer, S. S., & Spencer, D. D. (1991). Functional organization of human supplementary motor cortex studied by electrical stimulation. *J Neurosci, 11*(11), 3656-3666. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1941101

Gentner, R., Wankerl, K., Reinsberger, C., Zeller, D., & Classen, J. (2008). Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. *Cereb Cortex, 18*(9), 2046-2053. doi:10.1093/cercor/bhm239

Gilio, F., Conte, A., Vanacore, N., Frasca, V., Inghilleri, M., & Berardelli, A. (2007). Excitatory and inhibitory after-effects after repetitive magnetic transcranial stimulation (rTMS) in normal subjects. *Exp Brain Res, 176*(4), 588-593. doi:10.1007/s00221-006-0638-9

Grillner, S. (2006). Biological pattern generation: the cellular and computational logic of networks in motion. *Neuron, 52*(5), 751-766. doi:10.1016/j.neuron.2006.11.008

Hadjidimitrakis, K., Bakola, S., Wong, Y. T., & Hagan, M. A. (2019). Mixed Spatial and Movement Representations in the Primate Posterior Parietal Cortex. *Front Neural Circuits, 13*, 15. doi:10.3389/fncir.2019.00015

Hallett, M. (2007). Transcranial magnetic stimulation: a primer. *Neuron, 55*(2), 187-199. doi:10.1016/j.neuron.2007.06.026

Hallett, M., Di Iorio, R., Rossini, P. M., Park, J. E., Chen, R., Celnik, P., . . . Ugawa, Y. (2017). Contribution of transcranial magnetic stimulation to assessment of brain connectivity and networks. *Clin Neurophysiol, 128*(11), 2125-2139. doi:10.1016/j.clinph.2017.08.007

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., & Rothwell, J. C. (2013). The role of interneuron networks in driving human motor cortical plasticity. *Cereb Cortex, 23*(7), 1593-1605. doi:10.1093/cercor/bhs147

Hand, B. J., Opie, G. M., Sidhu, S. K., & Semmler, J. G. (2020). TMS coil orientation and muscle activation influence lower limb intracortical excitability. *Brain Res, 1746*, 147027. doi:10.1016/j.brainres.2020.147027

Heed, T., Beurze, S. M., Toni, I., Roder, B., & Medendorp, W. P. (2011). Functional rather than effector-specific organization of human posterior parietal cortex. *J Neurosci, 31*(8), 3066-3076. doi:10.1523/JNEUROSCI.4370-10.2011

Heed, T., Leone, F. T., Toni, I., & Medendorp, W. P. (2016). Functional versus effector-specific organization of the human posterior parietal cortex: revisited. *J Neurophysiol, 116*(4), 1885-1899. doi:10.1152/jn.00312.2014

Heide, G., Witte, O. W., & Ziemann, U. (2006). Physiology of modulation of motor cortex excitability by low-frequency suprathreshold repetitive transcranial magnetic stimulation. *Exp Brain Res, 171*(1), 26-34. doi:10.1007/s00221-005-0262-0

Henson, R. N. (2003). Neuroimaging studies of priming. *Prog Neurobiol, 70*(1), 53-81. doi:10.1016/s0301-0082(03)00086-8

Hinton, D. C., Thiel, A., Soucy, J. P., Bouyer, L., & Paquette, C. (2019). Adjusting gait step-by-step: Brain activation during split-belt treadmill walking. *Neuroimage, 202*, 116095. doi:10.1016/j.neuroimage.2019.116095

Hoogendam, J. M., Ramakers, G. M., & Di Lazzaro, V. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul, 3*(2), 95-118. doi:10.1016/j.brs.2009.10.005

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201-206. doi:10.1016/j.neuron.2004.12.033

Huang, Y. Z., Lu, M. K., Antal, A., Classen, J., Nitsche, M., Ziemann, U., . . . Rothwell, J. (2017). Plasticity induced by non-invasive transcranial brain stimulation: A position paper. *Clin Neurophysiol, 128*(11), 2318-2329. doi:10.1016/j.clinph.2017.09.007

Huang, Y. Z., Rothwell, J. C., Edwards, M. J., & Chen, R. S. (2008). Effect of physiological activity on an NMDA-dependent form of cortical plasticity in human. *Cereb Cortex, 18*(3), 563-570. doi:10.1093/cercor/bhm087

Isa, T., Kinoshita, M., & Nishimura, Y. (2013). Role of Direct vs. Indirect Pathways from the Motor Cortex to Spinal Motoneurons in the Control of Hand Dexterity. *Front Neurol, 4*, 191. doi:10.3389/fneur.2013.00191

Jahn, K., Deutschlander, A., Stephan, T., Kalla, R., Hufner, K., Wagner, J., . . . Brandt, T. (2008). Supraspinal locomotor control in quadrupeds and humans. *Prog Brain Res, 171*, 353-362. doi:10.1016/S0079-6123(08)00652-3

K Mai Jürgen, P. G. (2012). The Human Nervous System

Kammer, T., Beck, S., Thielscher, A., Laubis-Herrmann, U., & Topka, H. (2001). Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. *Clin Neurophysiol, 112*(2), 250-258. doi:10.1016/s1388-2457(00)00513-7

Karabanov, A. N., Chao, C. C., Paine, R., & Hallett, M. (2013). Mapping different intra-hemispheric parietal-motor networks using twin Coil TMS. *Brain Stimul, 6*(3), 384-389. doi:10.1016/j.brs.2012.08.002

Katagiri, N., Yoshida, S., Koseki, T., Kudo, D., Namba, S., Tanabe, S., . . . Yamaguchi, T. (2020). Interindividual Variability of Lower-Limb Motor Cortical Plasticity Induced by Theta Burst Stimulation. *Front Neurosci, 14*, 563293. doi:10.3389/fnins.2020.563293

Katz, N., Hartman-Maeir, A., Ring, H., & Soroker, N. (1999). Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. *Arch Phys Med Rehabil, 80*(4), 379-384. doi:10.1016/s0003-9993(99)90273-3

Khedr, E. M., Ahmed, M. A., Fathy, N., & Rothwell, J. C. (2005). Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology, 65*(3), 466-468. doi:10.1212/01.wnl.0000173067.84247.36

Killington, C., Barr, C., Loetscher, T., & Bradnam, L. V. (2016). Variation in left posterior parietal-motor cortex interhemispheric facilitation following right parietal continuous theta-burst stimulation in healthy adults. *Neuroscience, 330*, 229-235. doi:10.1016/j.neuroscience.2016.05.056

Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res, 51*(1), S225-239. doi:10.1044/1092-4388(2008/018)

Koch, G., Bonni, S., Giacobbe, V., Bucchi, G., Basile, B., Lupo, F., . . . Caltagirone, C. (2012). theta-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect. *Neurology, 78*(1), 24-30. doi:10.1212/WNL.0b013e31823ed08f

Koch, G., Cercignani, M., Bonni, S., Giacobbe, V., Bucchi, G., Versace, V., . . . Bozzali, M. (2011). Asymmetry of parietal interhemispheric connections in humans. *J Neurosci, 31*(24), 8967-8975. doi:10.1523/JNEUROSCI.6567-10.2011

Koch, G., Cercignani, M., Pecchioli, C., Versace, V., Oliveri, M., Caltagirone, C., . . . Bozzali, M. (2010). In vivo definition of parieto-motor connections involved in planning of grasping movements. *Neuroimage, 51*(1), 300-312. doi:10.1016/j.neuroimage.2010.02.022

Koch, G., Fernandez Del Olmo, M., Cheeran, B., Ruge, D., Schippling, S., Caltagirone, C., & Rothwell, J. C. (2007). Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. *J Neurosci, 27*(25), 6815-6822. doi:10.1523/JNEUROSCI.0598-07.2007

Koch, G., Fernandez Del Olmo, M., Cheeran, B., Schippling, S., Caltagirone, C., Driver, J., & Rothwell, J. C. (2008). Functional interplay between posterior parietal and ipsilateral motor cortex revealed by twin-coil transcranial magnetic stimulation during reach planning toward

contralateral space. *J Neurosci, 28*(23), 5944-5953. doi:10.1523/JNEUROSCI.0957-08.2008

Koch, G., Oliveri, M., Cheeran, B., Ruge, D., Lo Gerfo, E., Salerno, S., . . . Caltagirone, C. (2008). Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. *Brain, 131*(Pt 12), 3147-3155. doi:10.1093/brain/awn273

la Fougere, C., Zwergal, A., Rominger, A., Forster, S., Fesl, G., Dieterich, M., . . . Jahn, K. (2010). Real versus imagined locomotion: a [18F]-FDG PET-fMRI comparison. *Neuroimage, 50*(4), 1589-1598. doi:10.1016/j.neuroimage.2009.12.060

Lefaucheur, J. P. (2019). Transcranial magnetic stimulation. *Handb Clin Neurol, 160*, 559-580. doi:10.1016/B978-0-444-64032-1.00037-0

Lemon, R. N. (2008). Descending pathways in motor control. *Annu Rev Neurosci, 31*, 195-218. doi:10.1146/annurev.neuro.31.060407.125547

Maeda, F., Keenan, J. P., Tormos, J. M., Topka, H., & Pascual-Leone, A. (2000). Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. *Exp Brain Res, 133*(4), 425-430. doi:10.1007/s002210000432

Manikandan, S. (2011). Measures of dispersion. *J Pharmacol Pharmacother, 2*(4), 315-316. doi:10.4103/0976-500X.85931

McCrea, D. A., & Rybak, I. A. (2008). Organization of mammalian locomotor rhythm and pattern generation. *Brain Res Rev, 57*(1), 134-146. doi:10.1016/j.brainresrev.2007.08.006

Mitchell, T., Potvin-Desrochers, A., Lafontaine, A. L., Monchi, O., Thiel, A., & Paquette, C. (2019). Cerebral Metabolic Changes Related to Freezing of Gait in Parkinson Disease. *J Nucl Med, 60*(5), 671-676. doi:10.2967/jnumed.118.218248

Mitchell, T., Starrs, F., Soucy, J. P., Thiel, A., & Paquette, C. (2019). Impaired Sensorimotor Processing During Complex Gait Precedes Behavioral Changes in Middle-aged Adults. *J Gerontol A Biol Sci Med Sci, 74*(12), 1861-1869. doi:10.1093/gerona/gly210

Mrachacz-Kersting, N., Stevenson, A. J. T., & Ziemann, U. (2021). Short-interval intracortical inhibition and facilitation targeting upper and lower limb muscles. *Sci Rep, 11*(1), 21993. doi:10.1038/s41598-021-01348-6

Murata, A., Gallese, V., Luppino, G., Kaseda, M., & Sakata, H. (2000). Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. *J Neurophysiol, 83*(5), 2580-2601. doi:10.1152/jn.2000.83.5.2580

Niemann, N., Wiegel, P., Kurz, A., Rothwell, J. C., & Leukel, C. (2018). Assessing TMS-induced D and I waves with spinal H-reflexes. *J Neurophysiol, 119*(3), 933-943. doi:10.1152/jn.00671.2017

Nutt, J. G., Bloem, B. R., Giladi, N., Hallett, M., Horak, F. B., & Nieuwboer, A. (2011). Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol, 10*(8), 734-744. doi:10.1016/S1474-4422(11)70143-0

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113. doi:10.1016/0028-3932(71)90067-4

Oliveri, M., Rossini, P. M., Traversa, R., Cicinelli, P., Filippi, M. M., Pasqualetti, P., . . . Caltagirone, C. (1999). Left frontal transcranial magnetic stimulation reduces contralesional extinction in

patients with unilateral right brain damage. *Brain, 122 (Pt 9)*, 1731-1739. doi:10.1093/brain/122.9.1731

Pascual-Leone, A., & Rothwell, J. (2002). *Handbook of Transcranial Magnetic Stimulation*. New York.

Peinemann, A., Reimer, B., Loer, C., Quartarone, A., Munchau, A., Conrad, B., & Siebner, H. R. (2004). Long-lasting increase in corticospinal excitability after 1800 pulses of subthreshold 5 Hz repetitive TMS to the primary motor cortex. *Clin Neurophysiol, 115*(7), 1519-1526. doi:10.1016/j.clinph.2004.02.005

Picard, N., & Strick, P. L. (2001). Imaging the premotor areas. *Curr Opin Neurobiol, 11*(6), 663-672. doi:10.1016/s0959-4388(01)00266-5

Pizzamiglio, S., Abdalla, H., Naeem, U., & Turner, D. L. (2018). Neural predictors of gait stability when walking freely in the real-world. *J Neuroeng Rehabil, 15*(1), 11. doi:10.1186/s12984-018-0357-z

Rizzolatti, G., Cattaneo, L., Fabbri-Destro, M., & Rozzi, S. (2014). Cortical mechanisms underlying the organization of goal-directed actions and mirror neuron-based action understanding. *Physiol Rev, 94*(2), 655-706. doi:10.1152/physrev.00009.2013

Rizzolatti, G., Luppino, G., & Matelli, M. (1998). The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol, 106*(4), 283-296. doi:10.1016/s0013-4694(98)00022-4

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of, T. M. S. C. G. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol, 120*(12), 2008-2039. doi:10.1016/j.clinph.2009.08.016

Rossignol, S., Dubuc, R., & Gossard, J. P. (2006). Dynamic sensorimotor interactions in locomotion. *Physiol Rev, 86*(1), 89-154. doi:10.1152/physrev.00028.2005

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., . . . Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol, 126*(6), 1071-1107. doi:10.1016/j.clinph.2015.02.001

Rothwell, J. C. (1997). Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *J Neurosci Methods, 74*(2), 113-122. doi:10.1016/s0165-0270(97)02242-5

Rozzi, S., Calzavara, R., Belmalih, A., Borra, E., Gregoriou, G. G., Matelli, M., & Luppino, G. (2006). Cortical connections of the inferior parietal cortical convexity of the macaque monkey. *Cereb Cortex, 16*(10), 1389-1417. doi:10.1093/cercor/bhj076

Rozzi, S., Ferrari, P. F., Bonini, L., Rizzolatti, G., & Fogassi, L. (2008). Functional organization of inferior parietal lobule convexity in the macaque monkey: electrophysiological characterization of motor, sensory and mirror responses and their correlation with cytoarchitectonic areas. *Eur J Neurosci, 28*(8), 1569-1588. doi:10.1111/j.1460-9568.2008.06395.x

Sakata, H., Taira, M., Murata, A., & Mine, S. (1995). Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cereb Cortex, 5*(5), 429-438. doi:10.1093/cercor/5.5.429

Schott, G. D. (1993). Penfield's homunculus: a note on cerebral cartography. *J Neurol Neurosurg Psychiatry, 56*(4), 329-333. doi:10.1136/jnnp.56.4.329

Smith, M. C., Stinear, J. W., Alan Barber, P., & Stinear, C. M. (2017). Effects of non-target leg activation, TMS coil orientation, and limb dominance on lower limb motor cortex excitability. *Brain Res, 1655*, 10-16. doi:10.1016/j.brainres.2016.11.004

Sommer, M., Ciocca, M., Chieffo, R., Hammond, P., Neef, A., Paulus, W., . . . Hannah, R. (2018). TMS of primary motor cortex with a biphasic pulse activates two independent sets of excitable neurones. *Brain Stimul, 11*(3), 558-565. doi:10.1016/j.brs.2018.01.001

Stefan, K., Gentner, R., Zeller, D., Dang, S., & Classen, J. (2008). Theta-burst stimulation: remote physiological and local behavioral after-effects. *Neuroimage, 40*(1), 265-274. doi:10.1016/j.neuroimage.2007.11.037

Takakusaki, K. (2013). Neurophysiology of gait: from the spinal cord to the frontal lobe. *Mov Disord, 28*(11), 1483-1491. doi:10.1002/mds.25669

Talelli, P., Greenwood, R. J., & Rothwell, J. C. (2007). Exploring Theta Burst Stimulation as an intervention to improve motor recovery in chronic stroke. *Clin Neurophysiol, 118*(2), 333-342. doi:10.1016/j.clinph.2006.10.014

Terao, Y., Ugawa, Y., Hanajima, R., Machii, K., Furubayashi, T., Mochizuki, H., . . . Kanazawa, I. (2000). Predominant activation of I1-waves from the leg motor area by transcranial magnetic stimulation. *Brain Res, 859*(1), 137-146. doi:10.1016/s0006-8993(00)01975-2

Valero-Cabre, A., Amengual, J. L., Stengel, C., Pascual-Leone, A., & Coubard, O. A. (2017). Transcranial magnetic stimulation in basic and clinical neuroscience: A comprehensive review of fundamental principles and novel insights. *Neurosci Biobehav Rev, 83*, 381-404. doi:10.1016/j.neubiorev.2017.10.006

Valero-Cabre, A., Pascual-Leone, A., & Rushmore, R. J. (2008). Cumulative sessions of repetitive transcranial magnetic stimulation (rTMS) build up facilitation to subsequent TMS-mediated behavioural disruptions. *Eur J Neurosci, 27*(3), 765-774. doi:10.1111/j.1460-9568.2008.06045.x

Whitlock, J. R. (2017). Posterior parietal cortex. *Curr Biol, 27*(14), R691-R695. doi:10.1016/j.cub.2017.06.007

Whybird, M., Coats, R., Vuister, T., Harrison, S., Booth, S., & Burke, M. (2021). The role of the posterior parietal cortex on cognition: An exploratory study. *Brain Res, 1764*, 147452. doi:10.1016/j.brainres.2021.147452

Wise, S. P., Boussaoud, D., Johnson, P. B., & Caminiti, R. (1997). Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. *Annu Rev Neurosci, 20*, 25-42. doi:10.1146/annurev.neuro.20.1.25

Yousry, T. A., Schmid, U. D., Alkadhi, H., Schmidt, D., Peraud, A., Buettner, A., & Winkler, P. (1997). Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain, 120 (Pt 1)*, 141-157. doi:10.1093/brain/120.1.141

Zafar, N., Paulus, W., & Sommer, M. (2008). Comparative assessment of best conventional with best theta burst repetitive transcranial magnetic stimulation protocols on human motor cortex excitability. *Clin Neurophysiol, 119*(6), 1393-1399. doi:10.1016/j.clinph.2008.02.006

7. ***Appendices***

Appendix A

McGill

Department of
Kinesiology and Physical Education

Département de
kinésiologie et d'éducation physique

INFORMED CONSENT DOCUMENT

Project Title: Theta burst stimulation of the posterior parietal cortex in healthy young adults: does it affect upper limb and lower limb differently? A sham-controlled study.

Principal Investigator:

Caroline Paquette, Ph.D., Associate Professor
Kinesiology and Physical Education, Faculty of Education, McGill University

Sponsoring: NSERC

Introduction:

We are asking you to participate in a research project to understand how different parts of the brain are connected within each other. Before agreeing to participate in this project, please take time to read and carefully consider the following information.
This consent form explains the reason for this study, the procedures, disadvantages, advantages, as well as the persons to contact, if necessary.
This consent form may contain words that you do not understand. We invite you to ask any question that you deem useful to the researcher or other members of the staff assigned to the research project. Ask them to explain any word or information that is not clear to you.

Reason for the Study:

With this study, we are investigating how a specific brain area is connected with the hand and leg motor regions of the brain. We want to know if using a type of brain stimulation that is not invasive over this brain area, we will produce changes in the excitability of the brain

motor region. We want to understand the brain circuits that interconnect the brain, and if there exist a difference in the brain interconnections between leg and hand area.

Procedures:

Your participation in this study will involve 4 visits of about 2 to 2.5 hours at McGill University at the Currie Gymnasium (475 Pine Ave West, Montreal QC, H2W 1S4).
Please note that the following health and safety protocols have been put in place to minimize risk of transmission of COVID-19 during your study participation. These measures have been devised based on current federal and provincial public health directives as well as recommendations from the World Health Organization (WHO).

- 2-metre distancing will be respected whenever possible;
- Every person in the laboratory will wear a face covering (cloth or procedure mask) to protect all parties from each other's respiratory droplets (you will be provided with a face mask if you do not have one);
- Hand washing will occur before, during and after study participation;
- When 2-metre distancing is not possible (e.g. when we are connecting you to instruments or administering stimulation), the researcher will wear a high quality procedure mask and visor;
- High-touch surfaces and objects are disinfected daily, and disinfected between users.

All research team members are required to have training on preventing the spread of infection and all McGill students and employees must respond each day to a required self-assessment health questionnaire. All participants will be screened before accessing the research site and will be asked if they have symptoms of COVID-19 or have been in close contact with anyone who has or has had COVID-19. Participation will be cancelled or postponed when responding yes to

any of the screening questions. Wearing a mask that covers the mouth and nose is mandatory inside all McGill buildings, in accordance with Quebec public health regulations.

By agreeing to participate in this study, you acknowledge that you have been informed of the health and safety procedures in place and agree to follow them. Please be reminded that participation is voluntary and you may decline or postpone participation at any time.
The goal of the first visit will evaluate your health and physical activity by filling various questionnaires and forms (such as this consent form) with an investigator and to determine if you are eligible for brain stimulation.
If you are a new participant in our laboratory, your first visit will also include magnetic resonance imaging (MRI). During sessions, you will be receiving brain stimulation.
General health evaluation, physical activity assessment and brain stimulation will take place in our laboratory at the Currie Gymnasium. The MRI will take place at the Montreal Neurological Institute, within 5 minutes walking distance from our laboratory.

Non-invasive brain stimulation: You will be asked to sit comfortably on a chair and three electrodes will be fixed over your skin over your hand and leg muscles in order to record muscle contractions. A stimulating coil will be positioned over different parts of your head and will be used to stimulate your brain. The intensity of stimulation will be increased until a muscle twitch is recorded by the electrodes and a small movement is observed on the hand. Depending on the stimulation site, you may experience a minimal discomfort caused by slight muscle contraction of the hand or leg muscles. This stimulation procedure will be repeated several times to find the desired intensity and correct location for stimulation. Once the intensity and position have been determined, we will stimulate the brain with bursts of pulses applied continuously or intermittently, for respectively 40 seconds and 3 minutes. Afterwards, two coils will be positioned over two brain regions in order to stimulate them and record the activity of your leg or hand muscles. The electrodes and coil will then be removed.

MRI Imaging: If this is the first time you participate in a study with us, you will be asked to perform a short session of MRI before the first

visit. You will be asked to lie on a bed that will be moved into a cylindrical opening where images of your head will be taken during a period of 15 minutes. The cylindrical opening is very narrow and persons with claustrophobia should refrain from participating in the study as they may feel strong discomfort from being in a confined space. The MRI machine will be quite noisy during the scan. To reduce the noise, you will wear headphones. You will be able to communicate with the technician during the procedure.

THE FOLLOWING ARE CONTRAINDICATIONS FOR THE MRI AND/OR BRAIN STIMULATION PROCEDURES:

- History of convulsions or seizures,
- Pacemaker,
- Neurostimulator,
- Aneurysm Clip,
- Heart/Vascular Clip,
- Prosthetic Valve,
- Cochlear implants,
- Brain electrodes
- Metal Prosthesis,
- Pregnancy,
- Claustrophobia,
- Splinters, clips, fragments or other metal in the brain or skull,
- Metal fragments in the body,
- Transdermal patches (must be removed prior to scanning). There is a concern that the magnetic field from the MRI will affect the drug release from your transdermal patch. You should bring an additional patch to re-apply post scanning. If interruption of the transdermal drug application is not possible for 25 minutes, you cannot take part in this study.

  A coronary artery or other stent may also prevent you from partaking in MRI scanning, depending on the type of stent.

Potential Risks of Participating in this Study:

The type of brain stimulation we are using has been extensively used in patients with depression and have shown to be quite safe. Since this method was invented, several thousands of stimulation protocols have been used and are in use throughout the world. Consensus guidelines for its safe application have been published and our protocol strictly adheres to these guidelines. There has

been one case of seizure following the type of protocol you will be receiving. In order to eliminate this minimal possibility, we will stimulate at lower intensity.
If your participation requires an MRI, you will be exposed to a strong magnetic field. No long-term negative side effects have been observed from this type of study. If you have metallic implants, you cannot participate in the study because these implants may become dislocated or may heat up during the measurement due to the strong magnetic field. Metal earrings, body piercings, and necklaces must be removed prior to the study. The MRI produces loud noises that can cause earing damage if appropriate sound protection is not used. Earplugs and/or headphones will be provided to protect your ears. When you are inside the MRI scanner, the MRI scanner surrounds are very narrow. If you feel anxious in confined spaces you may not want to participate. Tattoos with metallic inks can also potentially cause burns. Any heating or burning sensations during a scan in progress should be reported to the operators immediately and we will discontinue the scan.
At all times a person will be present to provide any assistance. You may however feel tired following the evaluation. You can request to stop the experiment if you are too tired or uncomfortable to participate further in the experiment.

Potential benefits of Participating in this Study:

You will not benefit directly from participating in the study. However, with this study we will determine the connectivity between two different brain regions.

Subject Rights and Withdrawal from the Study:

At any time during the study, you have the right to ask questions. Your participation in this study is voluntary. You may refuse to participate or if you agree to participate, you may leave the study at any time.

Discontinuation of the Study by the Investigator:

At any time during the testing, the investigator has the right to terminate the study for any reason. If this was to occur, the reason(s) will be explained to you.

Compensation:

There are no costs to you for participating in this study other than your time.

Confidentiality:

A number of precautions will be taken to guarantee the confidentiality of the information you will provide. Results from this study will be analyzed in group form. Furthermore, in all databases and documentation, participants will be

identified by unique identification number only (random values containing no identifier). All personal and identifying information will be kept confidential and under lock and key. Data recorded on computers will be transferred and kept on a server with limited access. The research data will appear only in the form of a scientific presentation or publication, without your name, or any potentially identifying information being disclosed. Imaging data will be stored in a secure room at the Brain Imaging Centre. The Research Ethics Board may consult the study data to ensure the sound management of this study.
Data sharing makes data collected available to other investigators so that more research can potentially done with the data. Most of the data we acquire may be shared with other researchers. It will not be possible to link shared data to you because personal or identifying information (e.g., name, address, contact information, date of birth) about you will be removed. Only your age and sex will be linked to the data. Data will be shared via a secure online platform with local servers that respects Canadian laws and regulations.

Results of the Research:

Any relevant information regarding the results of the research will be communicated to you, upon your request. Brain images and other test results obtained in this study are not routinely scanned for abnormalities. Should there be any incidental findings, and should you wish to receive this information, it will be communicated to you and your physician.

For More Information:

The following are the names, addresses and telephone numbers of persons you may contact for questions about the research or any injuries or adverse reactions:

Caroline Paquette
(514) 398-4184 ext. 00890

Alejandra Martínez Moreno
(514) 398-4184 ext. 09833

Department of Kinesiology and Physical Education
475 Pine Avenue West
Montreal, Quebec, H2W 1S4

Contact Information for Subjects:

If you have any questions regarding your rights as a research volunteer and wish to discuss with someone other than the individual conducting the study, you may contact the following impartial third parties, who are not associated with the study. You may contact:

The Ethics Officer of McGill University, Ms. Ilde Lepore, at **(514) 398-8302**.

You will be informed of any major new findings during the course of your participation in this study, which may affect your willingness to continue in the study.

SIGNATURE/CONSENT: I have read (or have had read to me) this consent form. This consent form should only be signed if I did have a chance to ask and receive satisfactory answers to all my questions. I voluntarily consent to participate in this study. I have received a copy of this signed consent form.

I have asked that this consent form be provided in English.

I do not waive my legal rights by signing this form.

Research Participant:

_____ Date: _____
(Signature)

_____ Tel: _____
(Print Name)

Investigator:

_____ Date: _____
(Signature)

_____ Tel: _____
(Print Name)

Person Explaining Consent Form:

_____ Date: _____
(Signature)

_____ Tel: _____

(Print Name)

Incidental Findings:

Test results obtained in this study are not routinely scanned for abnormalities. Should there be any incidental findings do you wish to receive this information?

☐ Yes, I would like to receive this information. *If applicable, it will be communicated to you and your physician.*

☐ No, I do not wish to receive this information.

_____

Research Participant Initials

Appendix B

Subject last name:_____ First name:_____

Date of birth:_____
dd / mm / yy

Sex: F ☐ / M ☐

Previous surgery?	NO	YES	If yes indicate the type
Head			
Heart			
Eyes			
Abdomen			
Extremities			
Spine			

Others:_____

Do you have a:	NO	YES	
Cardiac Pacemaker / Defibrillator			
Cochlear implant or implanted hearing aid			
Implanted insulin pump			***If yes, must be removed for scan***
Coloured contact lenses			***If yes, must be removed for scan***
Transdermal delivery system (e.g. patch)			***If yes, must be removed for scan***
Body piercing			***If yes, must be removed for scan***
IUD			
Foreign metallic objects (e.g. bullets or metal splinters)			
Permanent make-up / tattoos			
Ocular implants or devices			▶
Cardiac valve prosthesis			▶
Neurostimulator			▶
Artificial limb or joint			▶
Implanted orthopedic device			▶
Penile implant			▶
Aneurysm Clip			▶
Filter, catheter or stent in a blood vessel			▶
Shunt (programmable)			▶

Specify type

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

	NO	YES
Are you pregnant?		
Have you ever been injured by a metallic piece? (e.g. in your eyes)		
Have you ever undergone Magnetic Resonance Imaging?		
Do you suffer from claustrophobia?		

If yes when: _____

_____ _____
Subject signature Date (dd-mm-yy)

_____ _____
Physician / Researcher signature Date (dd-mm-yy)

Appendix C

Edinburgh Handedness Inventory

(OLDFIELD RC, *NEUROPSYCHOLOGIA* 9:97-113, 1971)

SUBJECT ID CODE: _____

Please indicate your preferences in the use of hands in the following activities in the column for each activity listed.

+2: if you always use the right hand and never the left hand, unless forced to;
+1: if you use your right hand more often;
0: if you use either hand interchangeably;
-1: if you use your left hand more often;
-2: if you always use the left hand and never the right hand, unless forced to.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

	Which hand do you use for:	**LEFT always -2**	**LEFT usually -1**	**Equally often 0**	**RIGHT usually +1**	**RIGHT always +2**
1	WRITING					
2	DRAWING					
3	THROWING					
4	SCISSORS					
5	TOOTHBRUSH					
6	KNIFE (WITHOUT FORK)					
7	SPOON					
8	BROOM (UPPER HAND)					
9	STRIKING A MATCH (MATCH)					
10	OPENING A BOX (LID)					

Appendix D

Waterloo Footedness Questionnaire-Revised

SUBJECT ID CODE: _____

Instructions: Answer each of the following questions as best you can. If you *always* use one foot to perform the described activity, circle **Ra** or **La** (for **right always** or **left always**). If you **usually** use one foot circle **Ru** or **Lu**, as appropriate. If you use **both** feet **equally often,** circle **Eq.**

Please do not simply circle one answer for all questions, but imagine yourself performing each activity in turn, and then mark the appropriate answer. If necessary, stop and pantomime the activity.

	Left always	*Left usually*	*Equally often*	*Right usually*	*Right always*
1. Which foot would you use to kick a stationary ball at a target straight in front of you?					
2. If you had to stand on one foot, which foot would it be?					
3. Which foot would you use to smooth sand at the beach?					
4. If you had to step up onto a chair, which foot would you place on the chair first?					
5. Which foot would you use to stomp on a fast-moving bug?					
6. If you were to balance on one foot on a rail track, which foot would you use?					
7. If you wanted to pick up a marble with your toes, which foot would you use?					
8. If you had to hop on one-foot, which foot would you use?					
9. Which foot would you use to help push a shovel into the ground?					
10. During relaxed standing, people initially put most of their weight on one foot, leaving the other leg slightly bent. Which foot do you put most of your weight on first?					
11. Is there any reason (i.e., injury) why you have changed your foot preference for any of the above activities?	YES		NO		
12. Have you ever been given special training or encouragement to use a particular foot for certain activities?	YES		NO		
13. If you have answered YES for either question 11 or 12, please explain:					

Elias, L.J. Bryden, M.P. & Bulman-Fleming M.B. (1998). Footedness is a better predictor than is handedness of emotional lateralization. *Neuropsychologia,* 36(1), 37-4

Appendix E

Healthy Subject Questionnaire

Date of Birth: ____ - ____ - ____ Sex: M_____ F_____ Phone: (___) _____-_____

Emergency Contact: _____ Address: _____

Email: _____

HEALTH HABITS AND PERSONAL SAFETY

ALL QUESTIONS CONTAINED IN THIS QUESTIONNAIRE ARE OPTIONAL AND WILL BE KEPT STRICTLY CONFIDENTIAL.						
Caffeine	☐ None	☐ Coffee	☐ Tea	☐ Cola		
	# of cups/cans per day?					
Alcohol	Do you drink alcohol?				☐ Yes	☐ No
	How many drinks per week?					
Drugs	Do you currently use recreational or street drugs?				☐ Yes	☐ No
	How often?					

Screening Questions:

Cochlear implants y__ n__ Pacemaker y__ n___

Deep brain stimulator y__ n__ Metallic hardware in the brain y__ n__

History of seizures, convulsions or epilepsy y__ n__ Stroke y__ n__

Fainting y__ n__ Current pregnancy y__ n__

Head injury y __ n __ Previous concussion y__ n__

Muscular problems (TA/FDI) y _____ n_____ _____

Paralysis/numbness (TA/FDI) y _____ n_____ _____

Brain tumors y _____ n _____ _____

Meningitis, encephalitis, brain abscess y _____ n _____ _____

Past surgeries: y _____ n _____ _____

Medical diagnosis: _____

_____

Medications Currently Taking: _____