Mapping and Quantifying the Excitability of a Bilateral Cortical Representation of the Tibialis Anterior Muscles: A TMS Study

Thesis by
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Table of contents

Abstract

The primary motor cortex (M1) follows a somatotopic organization with the upper limb muscles found on the top, lateral aspect of the brain and the lower limb muscles found more medially, deep within the interhemispheric fissure and close to their contralateral representation. This arrangement hinders the application of transcranial magnetic stimulation (TMS) to the lower limb muscles M1 representation like the tibialis anterior (TA) muscle, a dorsiflexor with major contribution to gait and balance. The proximity of the left and right TA representations on M1 implies it may be possible to stimulate both legs at the same time, using a single stimulation target. Thus, the first aim of this thesis was to use a systematic mapping method to locate a midline hotspot for the left and right TA M1 representations that would elicit similar response amplitude bilaterally. The second aim of this thesis was to evaluate the feasibility of using that hotspot as a target for TMS. Thirty participants were recruited and completed the mapping session. During that session, a left, right, and bilateral hotspots were identified in a randomized order. TMS pulses were first delivered in a pseudorandom fashion over the M1 area of the TA to elicit responses in the TA and generate a colored map of the response intensities on M1. Then, a fine grid personalized to each participant was placed over the area where the largest responses were recorded. The left and right TA hotspots were identified as the stimulation location eliciting 3 consecutive motor evoked potentials (MEPs) with the highest average amplitude in their respective TA muscles. The bilateral hotspot was identified with the same criteria, but with the highest average amplitude measured in both TA muscles. Resting motor thresholds (RMTs) and stimulus-response (SR) curves were also acquired for all 3 hotspots to compare the cortical excitability of the bilateral and the unilateral hotspots. The left, right and bilateral hotspots were found in 29/30 participants, with the average bilateral hotspot located at mid-distance from the unilateral hotspot. As expected, higher RMTs were obtained for the bilateral hotspot compared to the unilateral hotspots. The SR curves derived from bilateral hotspot stimulation were similar to those derived from unilateral hotspot stimulation, with their inflection points found at a lower %RMT for responses in both left and right TAs. This suggests that the amplitude of the MEPs elicited by bilateral hotspot stimulation is more sensitive to a small change in stimulation intensity. The bilateral hotspot may therefore be a suboptimal stimulation target, but nevertheless elicits MEPs with similar and, in some cases, even greater amplitude then those elicited by unilateral hotspot stimulation at intensities normalized to RMT. Overall, this demonstrates the potential of the mapping protocol used to identify a targetable

bilateral hotspot for the TA muscles. Considering the bilateral component of locomotion, a bilateral hotspot would be useful to improve the study of gait and balance using TMS and other non-invasive brain stimulation techniques.

Résumé

Le cortex moteur primaire est organisé de façon somatotopique avec les muscles des membres supérieurs représentés latéralement sur le dessus du cortex, alors que les muscles des membres inférieurs sont représentés sur l'aspect médial du cortex, dans la fissure longitudinale, près de leurs représentations controlatérales. Cette disposition entrave l'application de la stimulation magnétique transcrânienne (SMT) aux représentations motrices des membres inférieurs, tels que le tibial antérieur (TA), un muscle important la dorsiflexion de la cheville qui contribue grandement à la marche et à l'équilibre. La proximité entre la représentation motrice du TA droit et du TA gauche représente une opportunité d'amélioration pour les protocoles de SMT car cela implique qu'il pourrait être possible de stimuler les deux jambes en même temps, en utilisant un seul *hotspot* (c.-à-d. cible) de stimulation. Ainsi, l'objectif de cette étude était d'utiliser une méthode de cartographie systématique pour trouver un *hotspot* permettant de stimuler simultanément la représentation motrice droite et gauche du TA et d'évaluer la faisabilité d'utiliser ce *hotspot* comme cible de SMT. Trente participants ont été recrutés et ont participé à la session de cartographie qui a permis d'identifier dans un ordre aléatoire le *hotspot* bilatéral, celui du TA droit et celui du TA gauche. Les impulsions de SMT ont été initialement délivrées de manière pseudo-aléatoire sur la zone du cortex moteur représentant le TA afin de générer une carte colorée des intensités de réponse sur le cortex. Ensuite, une grille personnalisée pour chaque participant a été placée sur la zone où les plus grandes réponses ont été enregistrées. Les *hotspots* du TA gauche et droit ont été identifiés comme l'emplacement suscitant trois réponses consécutives avec l'amplitude moyenne la plus élevée dans leur muscle respectif. Le *hotspot* bilatéral a été identifié de la même façon, en enregistrant les réponses dans le TA droit et gauche. Les seuils moteurs ainsi que les courbes de recrutements pour les trois *hotspots* ont également été obtenus afin de comparer l'excitabilité corticale des *hotspots* unilatéraux avec celle du *hotspot* bilatéral. Les trois *hotspots* ont été identifiés chez 29 des 30 participants et, comme prévu, le *hotspot* bilatéral a été identifié à mi-distance entre les *hotspots* unilatéraux. Le seuil moteur du *hotspot* bilatéral était également plus élevé que ceux des *hotspots* unilatéraux, alors que les courbes de recrutements du *hotspot* bilatéral étaient similaires à celles obtenus pour les *hotspots* unilatéraux. Toutefois, leurs points d'inflexion étaient plus petits que ceux des *hotspots* unilatéraux suggérant un plus grand changement dans l'amplitude des réponses musculaires pour une même intensité de stimulation. Ainsi, malgré le fait que le *hotspot* bilatéral soit un point de stimulation sous-optimal, les réponses engendrées par la

stimulation de cette cible ont une amplitude similaire à et, dans certain cas, plus grande que celles engendrées par la stimulation des *hotspots* unilatéraux. Conséquemment, ces résultats démontrent le potentiel du protocole de cartographie proposé pour identifier un *hotspot* bilatéral pour le TA qui semble utilisable comme cible de SMT. Considérant que plusieurs tâches requièrent la coordination des muscles jambiers bilatéraux, tel que la marche, un *hotspot* bilatéral permettrait d'avancer les interventions de SMT visant à améliorer le contrôle locomoteur.

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Contribution of Authors

I, Frédérike Parent-L'Ecuyer, was responsible for the conception and design of the research as part of my master's thesis. I was also responsible for collecting, processing, analyzing and interpreting data, as well as for writing the thesis and the manuscript. Dr. Alexandra Potvin-Desrochers contributed to the conception of the study and was implicated in data collection and analysis, edited the manuscript, and reviewed this thesis. Henri Lajeunesse and Isabella Sierra provided support during data collection and revised the manuscript. Dr. Caroline Paquette contributed to designing the study as well as analyzing and interpreting the data, and supervised the writing of this thesis and the manuscript.

List of Figures

List of Abbreviations

AMT: Active motor threshold

ANOVA: Analysis of variance

CoG: Center of gravity

D-waves: Direct waves

ED: Euclidean distance

EMG: Electromyography

I-waves: Indirect waves

LTD: Long-term depression

LTP: Long-term potentiation

M1: Primary motor cortex

MEP: Motor evoked potential

MNI: Montreal neurological institute

MRI: Magnetic resonance imaging

MSO: Maximal stimulator output

NIBS: Non-invasive brain stimulation

RMT: Resting motor threshold

rTMS: Repetitive transcranial magnetic stimulation

SR: Stimulus-response

TA: Tibialis anterior

TMS: Transcranial magnetic stimulation

Chapter 1: Introduction

1.1 Rationale

Transcranial magnetic stimulation (TMS) is a form of non-invasive brain stimulation that can map brain functions and assess cortical excitability (Rossini et al., 2015). When applied over the primary motor cortex (M1), TMS can elicit motor evoked potentials (MEPs; Barker et al., 1985) induced by the activation of the corticospinal tract (Valero-Cabré et al., 2017). The size of an MEP, specifically its peak-to-peak amplitude, can be used to quantify motor cortical excitability (Rossini et al., 2015).

The upper limb muscles are represented superficially on the surface of M1. Many TMS studies have, therefore, been conducted in the upper limb muscles to assess the organization and the excitability of M1, and a clear mapping methodology has been established (Davies, 2020; Hand et al., 2020; Rossini et al., 2015). However, the literature is limited when it comes to using TMS for the lower limb muscles, and the upper limbs mechanisms are often extrapolated even if they are not necessarily the same, which is problematic in the context of gait research (Davies, 2020; Hand et al., 2020). Such gap in the literature may be explained by the fact that the lower limb muscles are more challenging to target compared to the upper limb muscles. Specifically, the M1 representation of the tibialis anterior (TA) muscle lies deep within the interhemispheric fissure of the brain and in close proximity to its contralateral representations (Huang et al., 2018; Katagiri et al., 2020). The TA is an important dorsiflexor important for gait and postural control (Capaday et al., 1999; Maharaj et al., 2019; Schubert et al., 1997; Winter, 2009). Weaknesses in the TA is, however, quite common and can have detrimental effects on locomotion and balance (Baker, 2018; Winter, 2009). The proximity between the left and right TA M1 representations could be advantageous as it implies it may be possible to find one optimal target location (i.e., hotspot) that would result in similar stimulation on both left and right sides simultaneously. The use of such bilateral hotspot is significant considering the bilateral nature of several lower limbs tasks such as walking and maintaining balance. However, to the best of our knowledge, the possibility of targeting a bilateral TA hotspot with TMS has never been explored in healthy individuals. Therefore, the feasibility of using a bilateral hotspot for the TA muscles needs to be determined and quantified.

1.2 Objectives

The purpose of my master's thesis was to systematically map the lower limb M1 to further determine the feasibility of using a single hotspot, located at the brain midline, to stimulate both left and right TA muscles simultaneously with TMS. More precisely, the aim of this study was to answer the following research questions:

1. Is it possible to find a bilateral hotspot that would act as a cortical target for the stimulation of the right and left TA muscles simultaneously? If so, where would that bilateral hotspot be located?
2. Is it feasible to use such bilateral TA hotspot as a target in TMS studies? Is the motor cortical excitability of the bilateral TA hotspot comparable to that of the unilateral TA hotspots typically targeted with TMS?
    a. Are the resting motor thresholds of the bilateral TA hotspot and of the unilateral TA hotspots similar?
    b. Are the left and right TA MEPs resulting from the bilateral hotspot stimulation similar to those resulting from the unilateral hotspots stimulation?

1.3 Hypotheses

The following hypotheses corresponding to the aims of this project were tested:

1. A bilateral hotspot is expected to be found and located between the left and right unilateral hotspots, at the midline of the brain, on the lower limbs M1 area.
2. Even though differences in motor cortical excitability between the bilateral TA hotspot and the unilateral TA hotspots are expected, those are likely to be minimal thereby confirming the feasibility of using the bilateral TA hotspot as a TMS target;
    a. the resting motor threshold of the bilateral TA hotspot is expected to be higher than that of the unilateral TA hotspots because it is not an optimal stimulation location (Hand et al., 2020).
    b. the MEPs in the left TA observed following stimulation of the bilateral hotspot are expected to be similar to those observed following stimulation of the left unilateral TA hotspot. The same response pattern is expected for the right TA MEPs following stimulation of the bilateral and of the right unilateral TA hotspots. The MEPs for both legs, however, are expected to be smaller following bilateral hotspot stimulation compared to unilateral hotspots stimulation for the same stimulation

intensity as the unilateral hotspots correspond to the optimal stimulation locations (Rossini et al., 2015).

Chapter 2: Review of the Literature

2.1 Principles of Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) was first introduced in 1985 by Barker and colleagues as a non-invasive brain stimulation technique (NIBS; Barker et al., 1985; Valero-Cabré et al., 2017). TMS is based on Faraday's law stating that a change in magnetic field induces an electric current (Nollet et al., 2003). A transducing coil is connected to a high-voltage and high-intensity capacitors system that initiates the electric current, allowing the induction of a magnetic field with low impedance (Groppa et al., 2012; Nollet et al., 2003). This magnetic field can easily and painlessly cross the skull and meninges to induce a perpendicular electrical field within the neural tissue (Barker et al., 1985; Nollet et al., 2003; Valero-Cambré et al., 2017). When TMS is applied over the primary motor cortex (M1), the induced electric field depolarizes the axons of the descending fast pyramidal tract neurons, giving rise to direct waves (D-waves; Di Lazzaro & Rothwell, 2014; Terao et al., 2002). TMS can also depolarize the grey matter circuits recruiting a transsynaptic pathway to the pyramidal tract, thereby giving rise to indirect waves (I-waves; Di Lazzaro & Rothwell, 2014; Terao et al., 2002). The D-waves and the I-waves elicited by TMS generate muscle twitches, referred to as motor-evoked potentials (MEPs), that can be recorded with surface electromyography (EMG; Barker et al., 1985; Rossini et al., 2015). MEPs are often represented as the peak-to-peak amplitude of the EMG signal and are a reflection of motor cortical excitability (Barker et al., 1985). In fact, different stimulation intensities will elicit MEPs with different peak-to-peak amplitude (Barker et al., 1985; Rossini et al., 1985). The resting and active motor thresholds (RMT and AMT, respectively) are defined as the minimal stimulation intensity required to depolarize the corticospinal circuits in a resting and an active target muscle, respectively, and reflect the excitability thresholds (i.e., cortical excitability; Rossini et al., 2015). Motor cortical excitability can be affected by an array of factors including medications, diseases, motor learning, physical activity, and more (Lefaucheur, 2019; Ortelli et al., 2022; Rossi et al., 2009; Rossini et al., 2015).

The relationship between stimulation intensity and peak-to-peak MEP amplitude can be represented visually by a stimulus-response (SR) curve as illustrated in Figure 2.1. At suprathreshold intensities, the more the stimulation intensity of the TMS pulses is increased, the greater the amplitude of the MEPs (Lefaucheur, 2019; Rossini et al., 2015). When SR curves are fitted, often using the Boltzmann equation, from MEPs recorded in a resting muscle, their initial

segment is close to zero as no MEPs should be elicited by subthreshold intensities (Devanne et al., 1997; Souron et al., 2016). As the stimulation intensity of the pulses reaches the resting motor threshold, there is an increase in the SR curves slope. The point at which 50% of the greatest MEP amplitude is reached is referred to as the inflection point (Devanne et al., 1997; Lefaucheur, 2019). At suprathreshold stimulation intensities, the amplitude of the MEPs increases in size, which is depicted by a steep increase in the slope of the SR curve, until all motoneurons are recruited. At that point, the SR curves show a plateau as the MEPs reach their maximal amplitude. Because the SR curves illustrate the extent of motoneurons recruitment as stimulation intensity of the pulses is increased, they follow a sigmoidal curve pattern (Devanne et al., 1997). SR curves are thus advantageous to measure changes in cortical excitability between different conditions because they are extremely sensitive to the variation of motoneurons recruitment (Lefaucheur, 2019; Rossini et al., 2015). Specifically, SR curves could be obtained in clinical populations to assess the effect of a disease on the cortical excitability, but also in a control population to assess the difference in cortical excitability pre- and post-intervention by comparing the shape and the parameters of the curves (Groppa et al., 2012; Rossini et al., 2015).

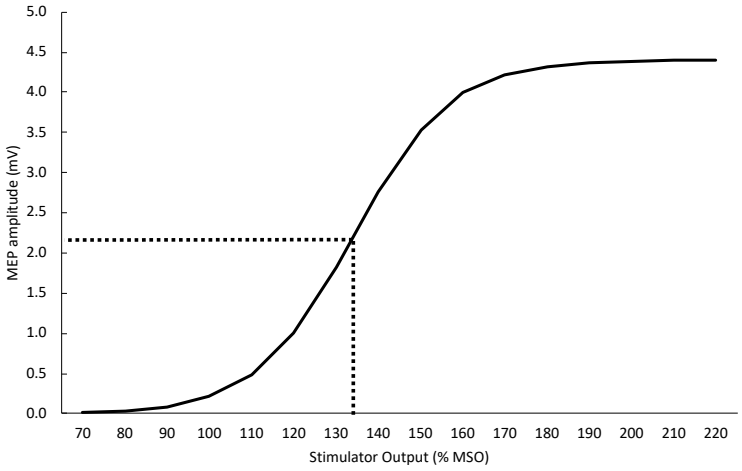

Fig. 2.1 Example of a stimulus-response curve with the solid line depicting the sigmoid function depicting as the solid line, and the dashed line depicting the inflection point (i.e., stimulation intensity at which 50% of the greatest MEP amplitude is reached). MEP: motor evoked potential, mV: millivolt, MSO: maximal stimulator output

2.2 TMS Methodology

2.2.1 Types of Coils

The size and shape of coils influence the intensity, the focality, and the penetration depth of the current induced, which is why there are different types of coils for different brain targets (Deng et al., 2013, Valero-Cabré et al., 2017). Specifically, larger coils, such as the round coil depicted in Figure 2.2a, result in deeper, but less focal stimulation, allowing for the stimulation of large areas (Deng et al., 2013; Di Lazzaro et al., 2004; Nollet et al., 2003; Rossini et al., 2015). To improve focality, other types of coil design are used. The figure-of-eight coil shown in Figure 2.2b is made of two small, overlapping circular wings in which current flows in opposite direction, resulting in a stronger current flow below the centre of the coil improving its focality (Groppa et al., 2012, Rossini et al., 2015). Due to this improved focality, the figure-of-eight coil is therefore less efficient at reaching deeper cortical layers at lower stimulation intensities (i.e., less powerful; Deng et al., 2013; Rossi et al., 2021). The double-cone coil shown in Figure 2.2c is also known as the angled-butterfly coil. Its design is based on the figure-of-eight with two overlapping wings; however, the double-cone have much bigger wings placed at an angle from one another instead of being adjacent on a flat plane (Deng et al., 2013; Rossi et al., 2021). This design is advantageous for stimulation of the lower limbs or the medial prefrontal cortex, for example, because the angled wings allow for greater penetration depth, making it easier to target cortical regions that are embedded within the interhemispheric fissure of the brain (Deng et al., 2013; Rossi et al., 2021; Valero-Cabré et al., 2017). On the other hand, the double-cone coil can be uncomfortable due to its large diameter thus strong stimulation intensity, and it can only induce current in anterior-posterior or posterior-anterior orientations because the angled-wings impede positioning in other directions (i.e., medio-lateral and/or latero-medial; Deng et al., 2013). The double-domed coil (Jaltron Lcc) shown in Figure 2.2d is another coil that can be used to apply TMS. Its design is interesting as it allows to overcome the limitations of the double-cone coil; it has a similar shape with the overlapping wings resulting in deep penetration, but the wings' diameter is smaller making the process more comfortable, and they are less angled allowing TMS to be applied in different orientations.

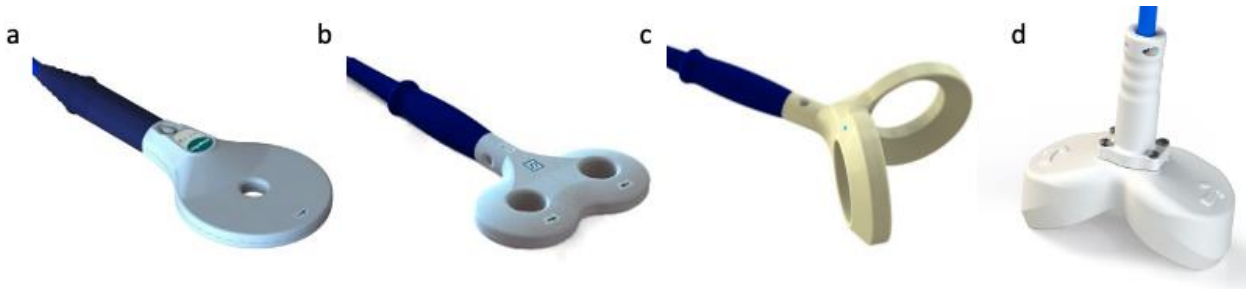

Fig. 2.2 Different stimulation coils used for TMS. (a) round coil, (b) figure-of-eight coil, (c) double-cone coil, and (d) double-domed coil. Images retrieved from Magstim Company (Magstim Company, UK) and from Jaltron Lcc (Jaltron Lcc, USA)

2.2.2 Neuronavigation

Neuronavigation systems can be used concurrently with TMS because they allow to target the precise location for stimulation and coil placement, and to mark these locations to improve reproducibility between sessions (Caulfield et al., 2022; Rossini et al., 2015). These systems are thereby useful to improve accuracy and reproducibility of TMS application by using an infrared camera to track retroreflective markers positioned on the coil and the participant's head (Caulfield et al., 2022; Hannula & Ilmoniemi, 2017). Anatomical landmarks such as the nasion and ear tragi are identified with a pointer to align the subject's head to the 3D reconstructed brain image on the neuronavigation software which allows the tracking of the subject and the coil in real time (Hannula & Ilmoniemi, 2017; Lefaucheur, 2019; Rossini et al., 2015). This can be done with magnetic resonance imaging (MRI) by uploading personalized scans to the software, or with MRI template scans such as the Montreal Neurological Institute (MNI) ICBM-152 template (Caulfield et al., 2022; Lefaucheur, 2019). Neuronavigation is therefore an important tool to facilitate brain mapping because it accounts for anatomical differences between participants. In fact, a study conducted by Caulfield and colleagues (2022) demonstrated that cap-based positioning led to stimulation up to 10.7 mm off-target compared to positioning with neuronavigation with MRI as well as with the MNI-152 template, which was on average only 0.3 mm off-target. These results support the idea that neuronavigation greatly influences accuracy and precision of coil placement compared to other positioning techniques like cap-based targeting.

2.2.3 Hotspot Mapping

TMS is a great tool to map the brain, specifically for mapping cortical muscle representations on M1 as the amplitude of the recorded MEPs can indicate the excitability of the region or point stimulated. Motor cortical maps generated by TMS are similar to and as reliable as

those generated with other techniques such as functional magnetic resonance imaging (Lotze et al., 2003; Weiss et al., 2013). TMS hotspot mapping can be done using a pseudorandom walk technique in which pulses are coarsely applied on the M1 area associated with the target muscle at a relatively high intensity (above motor threshold). For example, when looking for an intrinsic hand muscle M1 representation, the hand-knob region will be mapped. The specific location on the brain where the highest and most consistent peak-to-peak MEP amplitude is recorded would be marked as the M1 location, referred to as the hotspot, representing the targeted muscle (Rossini et al., 2015). This process can also be done using the weighted average of the responses recorded to provide a center of gravity (CoG) that would be used as the hotspot (Rossini et al., 2015). The CoG, however, is not an ideal way to select a hotspot because it may be located between two areas yielding MEPs with great amplitude, at a cortical location that does not result in a response when stimulated (van de Ruit et al., 2015). Because CoG needs to be calculated, it is more challenging and less convenient to acquire the data in real time during the mapping process. It is therefore a technique that is optimal for pre-surgical mapping, but that may not necessarily be suitable for hotspot identification in specific research or clinical settings (van de Ruit et al., 2015). It has therefore been suggested that, instead of using CoG as a mapping technique to identify the hotspot, its use may be restricted to analysis purposes (Julkunen, 2014).

On the other hand, gridding is another mapping technique that can be used with TMS and that yields more reliable maps for research (Cavaleri et al., 2017; van de Ruit et al., 2015). The gridding technique is defined as the gold standard for brain mapping in the context of research (Cavaleri et al., 2017; Jonker et al., 2019; Rossini et al., 2015; van de Ruit et al., 2015; Wassermann et al., 1992) and it consists of pulses applied on the points of a grid projected on the brain. The grid can either be drawn on a cap worn by the participant, which is not necessarily secured on the brain and can therefore impede on the precision of the technique, or it can be drawn on a modelized brain through a neuronavigation system. Using a frameless stereoscopy navigation system is optimal when mapping because it ensures the coil is located where it should be and oriented properly, and the position can be recorded to improve both precision and reproducibility (Rossini et al., 2015; van de Ruit et al., 2015). When a grid is used on its own to find the hotspot, the grid needs to include many points to cover an important part of M1 in order to account for neuroanatomical variations between participants. This is problematic because a large number of pulses are delivered, which can be tiring and uncomfortable for the participants and the

administrator (Cavaleri et al., 2017). Initially, a pseudorandom walk can be done quickly, restricting the number of pulses delivered to select the appropriate stimulation intensity (i.e., intensity rendering MEPs with the highest peak-to-peak amplitude of ± 1.0 mV; Groppa et al., 2012; Rossini et al., 2015) and to determine the general M1 area corresponding to the targeted muscle (i.e., small region of MEPs with high peak-to-peak amplitude, surrounded by a boundary of pulses eliciting no MEPs; Cavaleri et al., 2017; Jonker et al., 2019; van de Ruit al., 2015). Afterwards, a grid can be placed on the small area where the highest MEPs were recorded and 3 to 5 pulses can be delivered on each point of the grid (Cavaleri et al., 2017; van de Ruit et al., 2015; Weiss et al., 2013). The hotspot can then be selected and defined as the grid point consistently eliciting the highest MEPs.

The stimulation intensity can greatly influence the length of the mapping session. In fact, the number of pulses delivered is substantially higher when the stimulation intensity needs to be changed throughout the process. This is often the case because current methodological guidelines suggest mapping should be done at an intensity above motor threshold to obtain MEPs (Groppa et al., 2012; Rossini et al., 2015); however, motor threshold is determined when a hotspot is recorded. Thus, the stimulation intensity required for mapping needs to be estimated and adjusted to appropriately select the hotspot. In fact, if the stimulation intensity is set too low, not enough MEPs will be elicited to produce a map of graded responses; on the other hand, if the stimulation intensity is set too high, MEPs will be elicited on an important area of the cortex, making it hard to identify the distinct M1 region associated with the targeted muscle. Therefore, to optimize mapping sessions by limiting the number of pulses delivered and shortening the length of the sessions, mapping can be done using both pseudorandom walk and gridding techniques concurrently.

Despite the acknowledgement of the limitations related to the mapping process, many research groups are still using either the pseudorandom walk or the grid for mapping instead of combining the two techniques (Cacchio et al., 2011; Charalambous et al., 2019; Davies, 2020; Eibl et al., 2022; Wassermann et al., 1992; Weiss et al., 2013; Wilson et al., 1993; Zhang et al., 2020). The methodology section of TMS publications is also often not detailed thoroughly, especially the subsection relating to mapping (Cacchio et al., 2011; Eibl et al., 2022; Forster et al., 2014; Weiss et al., 2012), making it hard to reproduce the studies and to set methodological recommendations. This lack of proper mapping methodological guidelines increases the discomfort of participants because stimulation parameters, including type of coil used, stimulation intensity and number of

pulses delivered, are not optimized. Furthermore, these methodological guidelines limitation make it challenging for researchers to develop reproducible experimental protocols that yield results with high validity. In fact, reliability of TMS studies' outcomes is often compromised by methodological inconsistencies and poor experimental designs (Beaulieu et al., 2017). TMS mapping studies also tend to have a small sample size (Forster et al., 2012; 2014; Julkunen, 2014; Temesi et al., 2014; van de Ruit et al., 2015; Wassermann et al., 1992; Weiss et al., 2012; Wolf et al., 2004; Zdunczyk et al., 2013), which is problematic as it limits the quality of proposed results (Beaulieu et al., 2017). In many studies, the small sample size is used to justify the high inter- and intra-individual variability observed in the outcome measures (Forster et al., 2012; Fried et al., 2017; Weiss et al., 2012; Zdunczyk et al., 2013). Altogether, these provide evidence supporting the need for a more systematic hotspot mapping methodology.

2.3 Lower Limbs Organization of the Primary Motor Cortex

2.3.1 Basic Anatomical and Physiological Principles

M1 is the brain region corresponding to Brodmann's area 4 and is found directly anterior to the central sulcus (Brodmann, 2006). It has an important role in movement execution and motor programming as it is responsible to forward motor command from the cortex to the skeletal muscles through the corticospinal tract (Takakusaki, 2013, 2017). Penfield's experiments allowed to assess and determine the somatotopic organization of M1 (Penfield & Rasmussen, 1950; Schellekens et al., 2018). In other words, each body part is said to be organized systematically along the precentral gyrus and muscles are grouped by body parts following an organization similar to that of the primary somatosensory cortex where the upper extremities are found more laterally, while the lower extremities are on the medial aspect of the cortex as illustrated in Figure 2.3.

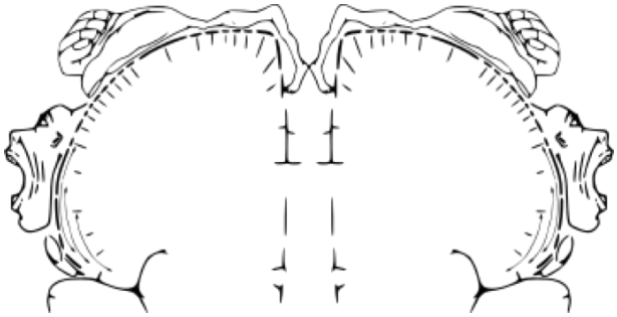

Fig. 2.3 Representation of the motor homunculus, depicting the somatotopic organization of the M1. Adapted from images retrieved from Wikimedia Commons

This idea of a strict somatotopic map has been challenged. Somatotopy infers a systematic organization of the muscles in a 2D plane; however, to produce movements allowing the completion of day-to-day tasks such as walking, the activation of a variety of muscles in a simultaneous fashion is required (Donoghue et al., 1992; Schieber, 2001). The muscles and joints involved in the completion of such complex, functional movements are not always sitting next to one another even if they are often interacting in a 3D plane (Schieber, 2001). Therefore, M1 needs to be organized in a way that facilitate the interaction of different muscles. In fact, electrical stimulation studies showed that M1 probably has a more functional structure where muscles are overlapping over some areas of M1 and are represented on more than one specific region (Branco et al., 2003; Farrell et al., 2007). These studies infer that M1 is organized in a less definite fashion, while preserving the general configuration of M1 thereby encompassing for the potential muscle interactions that would not be possible in the linear structure inferred by a somatotopic organization (Branco et al., 2003; Donoghue et al., 1992; Farrell et al., 2007; Schieber, 2001). Accordingly, the lower limb muscles remain represented deep within the interhemispheric fissure, in close proximity to one another, with significant overlapping between their M1 representations (Davies, 2020; Donoghue et al., 1992, Kesar et al., 2018; Schieber, 2001). On the other hand, the upper limb muscles are found more laterally on M1, on a more superficial part of the cortex (Davies, 2020; Donoghue et al., 1992; Schieber, 2001)

2.3.2 Lower Limb Muscles as TMS Targets

The majority of TMS studies looking at M1 excitability available in the literature were conducted in the upper limbs due to their accessibility, superficially on M1 (Beaulieu et al., 2017; Davies, 2020; Groppa et al., 2012; Kesar et al., 2018). For instance, in a systematic review assessing reliability of M1 excitability measurements in 34 TMS studies, 27 included measurements taken from upper limb muscles, while only 10 included measurements taken from lower limb muscles (Beaulieu et al., 2017). It is more often in clinical populations with lower limbs impairments that TMS is applied to the lower limbs M1 representation to assess the outcomes of a disease (Cacchio et al., 2011, Choo et al., 2021, Iyer & Madhavan, 2019; Peters et al., 2017; Sivaramakrishnan et al., 2016; Smith et al., 2017), the effectiveness of potential treatments (Chieffo et al., 2014; Huang et al., 2018; Kakuda et al., 2013; Kim et al., 2015; Lee et al., 2014; Lin et al., 2019; Lin et al., 2015; Rastgoo et al., 2016), or the feasibility of surgical mapping (Eibl et al., 2022; Forster et al., 2012; Lotze et al., 2003; Weiss et al., 2013; Zhang et al., 2020). In the

healthy population, TMS studies targeting the lower limb muscles usually aim at assessing the effects of repetitive TMS (rTMS; Katagiri et al., 2020; Rambour et al., 2016) or the reliability of cortical excitability measurements (Forster et al., 2014; Peri et al., 2017; Su et al., 2022) to provide a basis for rTMS interventions. The high inter-individual variability observed in TMS studies is further accentuated in those targeting the lower limbs M1 representation as most stimulation parameters used have been optimized for the upper limb (Beaulieu et al., 2017; Chung et al., 2018; Hamada et al., 2013; Huang et al., 2005; Katagiri et al., 2020; Suppa et al., 2016), but not yet for the lower limbs.

Despite the challenging anatomical location of the lower limbs M1 and the limited literature available on the topic, applying TMS to the leg muscles is feasible. However, to overcome these challenges associated with the use of TMS over M1 of the lower limbs, methodological guidelines need to be improved. In addition to defining the mapping method used, other methodological parameters need to be refined. For instance, the type of coil used should be considered. As described in section 2.2.1, coils such as the double-cone coil and the double-domed coil allow the induction of a stronger magnetic field which can improve accessibility to the lower limbs M1 representation (Deng et al., 2013; Rossi et al., 2021; Valero-Cabré et al., 2017). With tools like these, it becomes more feasible to target the lower limbs M1 representation with TMS which is paramount for the study of gait, balance and other activities of daily living requiring the lower limbs.

2.3.3 Specificity and Hotspot Mapping of the Tibialis Anterior

Like the other lower limb muscles, the tibialis anterior (TA) muscles representation on M1 is located within the interhemispheric fissure of the brain, with, however, a more prominent M1 representation (Groppa et al., 2012; Peterson et al., 2003). This larger representation on M1 could be explained by the important role of the TA muscles in a variety of stabilizing mechanisms for gait and postural control (Peterson et al., 2003). Specifically, as one of the primary muscles involved in dorsiflexion, the TAs are responsible for clearing the foot during the swing phase of the gait cycle (Maharaj et al., 2019). Additionally, they are involved in weight bearing, which stabilizes the body throughout the stance phase of the gait cycle as well as during the performance of a static balance task (Capaday et al., 1999; Maharaj et al., 2019; Schubert et al., 1997; Winter, 2009). Due to the TAs prominent M1 representation, the TA muscles are expected to be a good target for TMS (Groppa et al., 2012). It has been a muscle of interest in different TMS studies, not

only because it seems easier to target compared to other smaller muscles, but also because of its various implications in gait and balance (Cacchio et al., 2011; Charalambous et al., 2019; Kakuda et al., 2013; Rambour et al., 2016). In fact, TAs impairments are common, and they may have detrimental consequences on locomotion and balance, which is why it has solicitated great interest in TMS research, even though most research remains restricted to the upper limb muscles.

Mapping of the lower limb muscles representations on M1 is complex as shown by the success rate limited to 42 to 90% in a variety of studies (Eibl et al., 2022; Forster et al., 2014; Krieg et al., 2012; Peters et al., 2017; Weiss et al., 2013; Zhang et al., 2020). This poor success rate can be explained by the deep location of the lower limb muscles on M1, but also by the limited number of methodological guidelines available (Groppa et al., 2012; Kesar et al., 2018). The availabilities of tools needed to map the lower limbs M1 is also challenging; figures-of-eight coils are easily accessible and are therefore often used to apply TMS to the lower limbs M1 representations (Eibl et al., 2022; Forster et al., 2014; Krieg et al., 2012; Peters et al., 2017; Weiss et al., 2013; Zhang et al., 2020). This is problematic because this type of coil is not designed to stimulate deeper cortical areas, as explained in section 2.2.1 (Koponen & Peterchev, 2013; Vilchez Membrilla et al., 2022). The poor success rate of hotspot mapping in the lower limbs accentuate the gap between the available TMS literature of the upper and the lower limbs. Kesar and colleagues (2018) also highlighted the challenge of targeting individual lower limbs M1 representations because of their proximity as a barrier to proper mapping. To overcome this challenge, some studies have tried to target multiple M1 areas, including the contralateral representation of the TA and the rectus femoris, while recording MEPs in only one leg (Kakuda et al., 2013; Lin et al., 2019). This is problematic because it does not provide data on the effectiveness of the stimulation, thereby impeding on the generalizability of these studies.

Chapter 3: Manuscript

Mapping and Quantifying the Excitability of a Bilateral Cortical Representation of the Tibialis Anterior Muscles: A TMS Study

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3.1 Abstract

BACKGROUND The methodology used to apply transcranial magnetic stimulation (TMS) to the primary motor cortex (M1) representation of the tibialis anterior (TA) is not well established due to its deep location within the interhemispheric fissure of the brain. The TA M1 representation is also located in proximity to its contralateral side implying that it may be possible to target both left and right TA simultaneously. OBJECTIVES The purpose of this study was to map the TA M1representation to identify a midline hotspot and to determine the feasibility of stimulating that hotspot to elicit responses in both TAs that would be similar to responses obtained when stimulating the unilateral hotspots. METHODS The right and left M1 representations of the TA of thirty participants were mapped pseudorandomly with TMS, then grids were positioned on the area with the largest responses to find the bilateral hotspot (i.e., grid point eliciting the greatest response in both TAs). The unilateral hotspots were also found with the same process, analyzing responses unilaterally. Resting motor thresholds (RMT) and stimulus-response curves were acquired for each hotspot. RESULTS Hotspots for the left, right and bilateral TAs were found in all but one participant. The average bilateral hotspot was located between the average unilateral hotspots, near the brain midline, and had a higher mean RMT compared to the unilateral hotspots. At the same %RMT, bilateral stimulation resulted in slightly increased MEP amplitude compared to unilateral stimulation suggesting the bilateral hotspot might be more sensitive to a change in stimulation intensity. CONCLUSION A bilateral TA hotspot was found in nearly all participants. When stimulated, the bilateral hotspot responded similarly to the unilateral hotspots. Thus, these results suggest that using a bilateral hotspot as a target for TMS is feasible and could potentially render similar responses as unilateral hotspot stimulation. Considering the bilateral nature of locomotion, our findings have important implications for gait and balance rehabilitation protocols.

3.2 Introduction

The primary motor cortex (M1) is organized following a somatotopic arrangement referred to as the homunculus (Penfield & Rasmussen, 1950). According to this somatotopic organization, the upper limb muscles are represented superficially on the lateral aspect of the cortex, with the lower limb muscles located more medially, lying deep within the interhemispheric fissure of the brain (Cheyne et al., 1990; Penfield & Rasmussen, 1950; Sanes & Donoghue, 2000). Because of their position within the interhemispheric fissure, the lower limb muscles are in proximity with their contralateral representations (Cheyne et al., 1990; Davies, 2020; Donoghue et al., 1992, Kesar

et al., 2018, Schieber, 2000), which can be useful for assessing or modulating the neural pathways involved in bilateral tasks such as gait and balance. For instance, transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that has been used for various purposes including mapping of the M1 and quantifying its cortical excitability (Rossini et al., 2015). When a TMS pulse is delivered to M1 at a suprathreshold intensity, it depolarizes neurons and in turn activates the corticospinal tract (Barker et al., 1985; Valero-Cabré et al., 2017). Motor cortical excitability can then be quantified by recording the motor evoked potentials (MEPs) of specific muscles with electromyography (EMG; Barker et al., 1985; Rossini et al., 2015). For example, the resting motor threshold (RMT) is defined as the lowest stimulation intensity needed to depolarize the corticospinal tract and is a measurement that reflects motor cortical excitability (Rossini et al., 2015). Another way to measure cortical excitability is with stimulus-response (SR) curves which illustrate how a change in stimulation intensity can affect MEP amplitude (Rossini et al., 2015). These measurements are usually taken by applying TMS pulses over the hotspot. The hotspot corresponds to the M1 location consistently eliciting the highest peak-to-peak MEP amplitude (Rossini et al., 2015).

There is currently no systematic methodological procedure to map the lower limb M1 representations with TMS. Studies using TMS to target the lower limb cortical representations are limited, and typically aim at targeting unilateral M1 representations (Beaulieu et al., 2017; Eibl et al., 2022; Forster et al., 2012, 2014; Groppa et al., 2012; Kesat et al., 2018; Lotze et al., 2003; Weiss et al., 2013; Zhang et al., 2020). Two groups of researchers reported using a bilateral TMS target to modulate cortical excitability of the lower limbs M1 representation in a cohort of patients with stroke (Kakuda et al., 2013; Lin et al., 2018). In these studies, the mapping procedure was only partially defined as mapping the midline brain region and only recording MEPs in one leg (Kakuda et al., 2013; Lin et al., 2018). It is thus not possible to assess if the bilateral stimulation was successful. Therefore, the aim of the present study was to systematically map the lower limb M1 to determine the feasibility of using a single bilateral TMS target to stimulate both left and right tibialis anterior (TA) muscles simultaneously. The TA muscles were targeted specifically because of their paramount implication in gait and balance as one of the major dorsiflexors responsible for toe clearance (Capaday et al., 1999; Maharaj et al., 2019; Schubert et al., 1997; Winter, 2009). For instance, weaknesses in the TA muscles can lead to gait perturbations and impairments such as foot drop and steppage gait (Baker, 2018; Winter, 2009).

It was hypothesized that a bilateral hotspot would be located between the left and right unilateral hotspots, over the lower limbs M1 area close to the brain midline. Additionally, because we did not expect the bilateral hotspot to be the optimal stimulation location of each TA muscle, its RMT was expected to be higher than the unilateral hotspots RMTs. In turn, the MEPs elicited from bilateral hotspot stimulation were expected to be smaller compared to those elicited from unilateral hotspot stimulation.

3.3 Methods

3.3.1 Participants

Thirty healthy adults (mean age 25 ± 4 years, 16 women, 1 left-handed/right-footed, 1 right-handed/left-footed) were recruited from a pool of university students. The exclusion criteria were any TMS contraindications (Rossi et al., 2009) including the presence of metallic hardware or fragments in the head (e.g., cochlear implants, deep brain stimulator), pacemaker, and/or personal history of epilepsy or seizures. No participants were excluded based on their health habits. Those were assessed using a questionnaire, including caffeine and alcohol intake, drug consumption, medication prescription, exercise participation, sleep quality, medical history, and long Covid-19 symptoms (Ortelli et al., 2022) to control for variables that can influence cortical excitability (Rossi et al., 2009). The Edinburgh Handedness Inventory questionnaire (Oldfield, 1971), and the Waterloo-Footedness questionnaire (Elias et al., 1998) assessed hand and leg dominance, respectively. All participants provided written informed consent according to the McGill Faculty of Medicine Institutional Review Board regulations and the Declaration of Helsinki.

3.3.2 Data Acquisition

3.3.2.1 Experimental Setup

All TMS pulses were delivered using a 60 mm double-domed coil (Jaltron Lcc) connected to a Magstim 200^2 (Magstim Company UK). The double-domed coil stimulates deeper brain regions such as the leg representation (Koponen & Peterchev, 2013; Vilchez Membrilla et al., 2022) and is generally more comfortable compared to the coils typically used for such stimulation (i.e., figure-of-eight and double-cone coils). The precise location and orientation of the coil over the stimulated area were tracked using Brainsight frameless stereotaxic neuronavigation system (Rogue Research Inc., Montreal, Canada). The coil was positioned in a medio-lateral orientation

when targeting the unilateral hotspots, and in a posterior-anterior orientation when targeting the bilateral hotspot (Hand et al., 2020). The coil was registered with a 3D rendering of the Montreal Neurological Institute (MNI) ICBM-152 template. EMG activity was recorded using disposable surface gel electrodes (Biopac Systems, Inc., California, USA) placed in a bipolar array over the belly of the bilateral TA muscles as shown in Figure 3.1 (Stegeman & Hermens, 2007). Prior to affixing the electrodes, the skin was prepared by shaving the area and cleaning with isopropyl alcohol to facilitate acquisition and reduce impedance. EMG signal was recorded with a Biopac MP150 acquisition system (Biopac Systems, Inc., California, USA), sampled at 5 kHz on a 16-bit analog-to-digital board, amplified and bandpass filtered (10-2000 Hz).

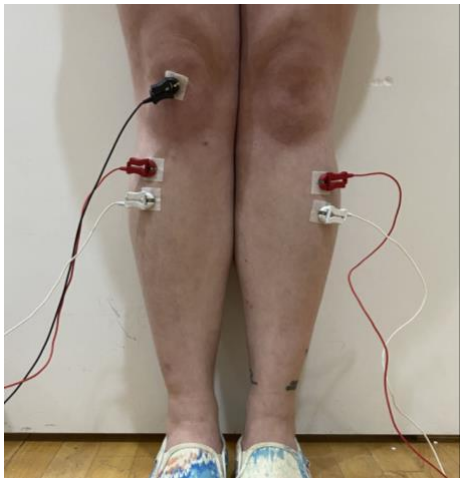

Fig. 3.1 Electrodes placement on the right and left tibialis anterior muscles and left. The red and white electrodes are the recording electrodes, and the black electrode is the ground

3.3.2.2 Hotspot Determination

The mapping process described below was followed to find the left, the right and the bilateral TA hotspots and the order in which the hotspots were mapped was randomized. Single-pulse TMS was initially applied in a pseudorandom fashion (Groppa et al., 2012; Rossini et al., 2015) over one of the M1 TA areas at 35% of the maximal stimulator output (MSO) to obtain an area of responses of ± 1 mV surrounded by pulses of no muscular activation as shown in Figure 3.2a. If most MEPs obtained tended to exceed 1 mV, the TMS intensity was decreased by 2-5% MSO according to the amplitude of the responses. Conversely, if the MEPs were lower than 1 mV, the TMS intensity was increased by 2-5% MSO until the highest responses recorded reached ± 1

mV. The pseudorandom mapping step was deemed complete when a clear set of boundaries without responses (i.e., MEPs of 0 mV) was obtained delineating the full TA M1 representation. Then, to ensure consistent responses and to differentiate between multiple potential hotspots, a fine grid, personalized to each participant (average of 19±6 stimulation points, average of 270±122 mm^2, 5 mm spacing), was positioned over the area where the biggest responses were recorded in the respective TA muscle during the pseudorandom mapping, as illustrated on Figure 3.2b. The TA hotspot was identified as the grid point eliciting 3 consecutive MEPs in its respective TA muscle with the greatest average peak-to-peak amplitude. If more than 1 grid point elicited similarly high MEPs, the stimulation intensity was decreased until 2 MEPs were recorded out of 3 given pulses in only 1 grid point. The grid point at which it was possible to obtained MEPs at the lowest stimulation intensity was selected as the hotspot (adapted from Kleim et al., 2006). The bilateral TA hotspot was selected as the grid point eliciting the 3 consecutive MEPs with the greatest average peak-to-peak amplitude in both left and right TA muscles simultaneously. To facilitate the search of the hotspots, the entire mapping process was conducted with the TAs contracted at 5% of the maximal voluntary contraction (Lefaucheur, 2019; van de Ruit & Grey, 2016). The left, right, and bilateral hotspot locations were marked in MNI coordinates on Brainsight.

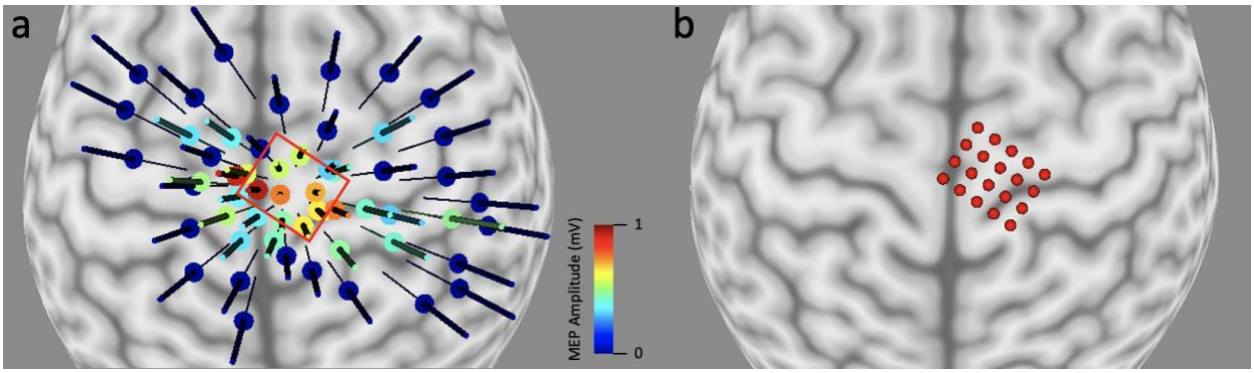

Fig. 3.2 Example of the visual representation on Brainsight of the colored-coded map of MEPs acquired during the hotspot determination process of the left TA. Dark blue trajectories are associated with stimulation points resulting in no responses (0 mV) on the EMG, while red trajectories are associated with responses of higher MEP amplitude (1 mV). (a) Gross pseudorandom map with the red rectangle highlighting the area where the grid will be place according to the distribution of the highest MEPs. (b) Fine personalized grid placed according to the distribution of the highest MEPs during the pseudorandom mapping. MEP: motor evoked potential, mV: millivolt

3.3.2.3 Corticospinal Excitability Measurements

The RMT was determined for each of the left, right, and bilateral TA hotspots as an outcome measure. RMTs were defined as the minimum TMS intensity required to elicit an MEP ≥ 0.05 mV in the resting TA in at least 10 out of 20 trials (Rossini et al., 2015). For the bilateral hotspot, an MEP ≥ 0.05 mV was required in both the left and right TA muscles to be considered a valid response.

The SR curves were obtained for all 3 hotspots by administering 5 pulses of TMS at various intensities. The lowest stimulation intensity administered corresponded to the % MSO at which no responses were recorded in the targeted TA or in both TAs for the bilateral hotspot to ensure the SR curve followed the expected sigmoidal shape. Thus, the lowest stimulation intensity varied from 40% to 70% RMT between participants. The highest stimulation intensity was set at the maximal stimulator capacity (100% MSO), or at the highest intensity tolerated by the participants, corresponding to a RMT of 110% to 260% RMT, depending on individual RMTs. Each intensity was randomized and separated by 10% RMT.

3.3.3 Data Analyses

All statistical analyses were conducted using SPSS v25 (IBM, NY, USA). A Shapiro-Wilk test was conducted on all data to confirm normal distribution. When the data failed to be normally distributed, non-parametric tests were conducted. The level of significance was set at $p \leq 0.05$.

3.3.3.1 Hotspot Location

The success rate of the mapping process was calculated as a percentage by dividing the number of participants in which the 3 hotspots were found by the number of participants who completed the study (i.e., 30 participants). The location of the bilateral hotspot was compared to those of the left and right hotspots by calculating the Euclidean distances (ED) using the following equation (Deza & Deza, 2009):

$$ED\ (mm) = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}$$

where ED represents the Euclidean distance between the bilateral and the left or right TA hotspot, (x_1, y_1, z_1) represents the coordinates of the bilateral TA hotspot, and (x_2, y_2, z_2) represents the coordinates of the unilateral TA hotspots. A Wilcoxon signed rank test was performed to compare the ED between the bilateral and the left TA hotspots to the ED between the bilateral and the right TA hotspots.

The relationship between hotspot location and hand and leg dominance was explored with visual inspection of the individual and group hotspot locations as a descriptive approach to identify if a different pattern of hotspots location emerged in participants that were left hand or leg dominant.

3.3.3.2 Motor Threshold

For each hotspot, the feasibility of finding RMTs was indicated as a percentage by a success rate, which was determined by divided by the number of RMTs acquired by the number of participants in which hotspots were found (i.e., 29 participants). To determine if there was a difference in cortical excitability between the different hotspots, a one-way analysis of variance (ANOVA) was performed to compare the RMTs of the 3 hotspots. A post hoc analysis was carried out using Tukey's honest significant difference to assess the specific differences detected by the ANOVA.

3.3.3.3 Motor Evoked Potentials

SR curves were generated for each participant and hotspot with a Boltzmann equation. Then, the individual SR curves were averaged for the group and refitted using the same equation. The following Boltzmann equation (Devanne et al., 1996) was used to fit the mean peak-to-peak MEP amplitudes for each stimulation intensity using the Microsoft Excel Add-In Solver function (Frontline Systems, NV, USA):

$$MEP\ amplitude\ (mV) = \frac{MEP_{max}}{1 + e^{(\frac{S_{50} - S}{k})}}$$

where S represents the % RMT, S_{50} represents the inflection point where half the maximum MEP amplitude was reached, and k represents the slope constant. The goodness of the fit was deemed high if the coefficient of determination (R^2) was ≥ 0.8 (Devanne et al., 1997; Koski et al., 2007). The mean R^2 was 0.91±0.13 for the left TA MEPs from the bilateral SR curve, 0.91±0.08 for the right TA MEPs from the bilateral SR curve, 0.88±0.10 for the left TA MEPs from the left SR curve, and 0.86±0.08 for the right TA MEPs from the right SR curve. Inflection points were extracted as the S_{50} from the equation above for each participant and were then compared between each leg and each hotspots using independent sample t-tests.

A frequency distribution analysis was conducted to descriptively assess the range of responses recorded in each leg for all the stimulation targets. The MEP amplitudes were correlated with the RMTs using Spearman's rank correlation to determine the relationship between those two

measurements. The amplitude of the highest MEPs obtained from bilateral hotspot stimulation and from unilateral hotspot stimulation were compared for each leg using Mann-Whitney U tests. The feasibility of obtaining MEPs $\geq$ 0.5 mV, which is the threshold from which it is possible to measure a change in cortical excitability (Rossini et al., 2015), was determined with a success rate calculated as a percentage by dividing the number of participants in which MEPs $\geq$ 0.5 mV were obtained by the total number of participants in which hotspots were found (i.e., 29 participants).

3.4 Results

3.4.1 Mapping Methodology and Hotspots Location

All 3 hotspots (left, right and bilateral hotspots) were found in 29 participants, resulting in a mapping success rate of 97%. In 1 participant, it was not possible to find any of the 3 hotspots as it was impossible to distinguish the MEPs from the muscle activity which was consistently activated in a spiked pattern. Figure 3.3 shows the location of the bilateral hotspots (i.e., red dots) located near the brain midline (i.e., MNI y coordinates axis), centrally between the left TA (i.e., green dots) and the right TA hotspots (i.e., blue dots), for all the participants. The average MNI coordinates were x=10±8 y=-22±11 z=103±4 for the left TA hotspot, x=-2±7 y=-19±13 z=100±5 for the bilateral TA hotspot, and x=-15±8 y=-28±11 z=100±4 for the right TA hotspot. The distance between the bilateral and the unilateral hotspots was similar for the left and right sides (mean ED: bilateral hotspot to left TA hotspot 18±9 mm vs bilateral hotspot to right TA hotspot 20±7 mm, p=0.275). As seen on Figure 3.3b by the encircled hotspot dots, the bilateral hotspots of left-handed and the left-footed participants were shifted toward the left, further away from the midline than the unilateral right TA hotspot.

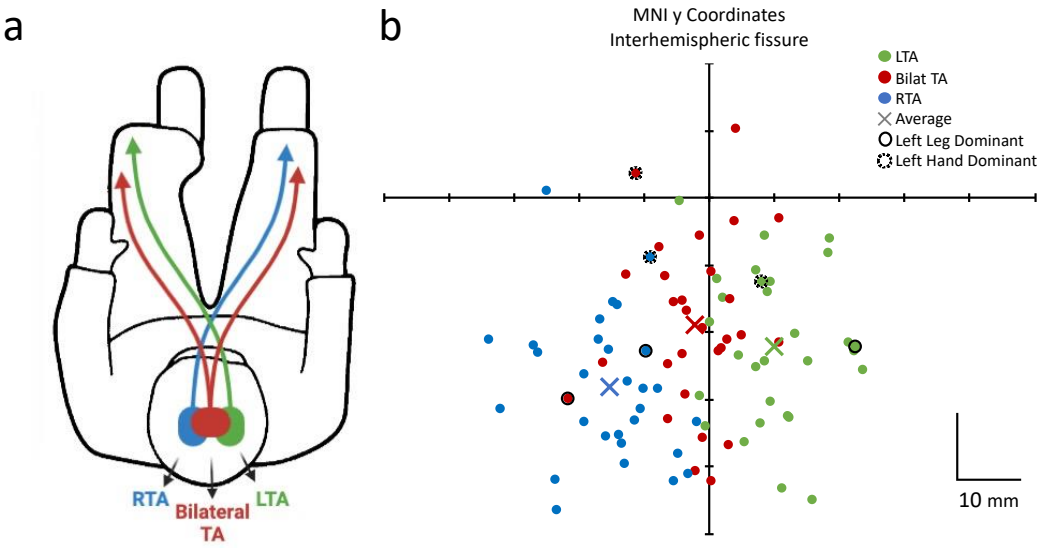

Fig. 3.3 Schematic representation of (a) the hotspots with the arrows highlighting the respective location of the MEPs in the legs, and (b) the individual hotspot location in x and y MNI coordinates for the left TA (green), bilateral TA (red), and right TA (blue), with the group average coordinates represented by a cross, the left-leg dominant participant represented by circled dots, and the left-hand dominant participant represented by the dotted black circled dots. RTA: right tibialis anterior, TA: tibialis anterior, LTA: left tibialis anterior, MNI: Montreal Neurological Institute, mm: millimeters

3.4.2 Motor Thresholds

Out of the 29 participants in which the hotspots were found, RMT was determined in 29 of them (success rate: 100%) for both unilateral hotspots and in 27 (success rate: 93%) for the bilateral hotspot. The bilateral RMT was not found in 2 participants as the stimulation intensity had to be set above 90% MSO, which was too uncomfortable to sustain repeatedly for the participants. Figure 3.4 shows that the RMTs of the unilateral hotspots were similar (mean left TA hotspot RMT 52±9% MSO, mean right TA hotspot RMT 54±10% MSO, $p=0.721$), but significantly lower than the bilateral hotspot RMT by, respectively, 17% MSO and 15% MSO (mean bilateral TA hotspot RMT 69±13% MSO, $p<0.001$).

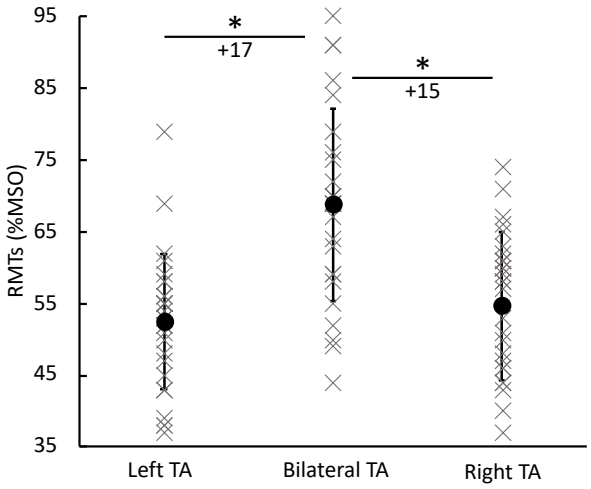

Fig. 3.4 RMTs acquired from the left TA, the bilateral TA, and the right TA hotspots. The black dots represent group mean ± SD and the crosses represent the individual RMT data of each participant. The numbers represent the difference between the unilateral and bilateral RMTs. * denotes a p<.001. RMTs: resting motor thresholds, MSO: maximal stimulator output, TA: tibialis anterior

3.4.3 Motor Evoked Potentials

The SR curves were obtained in 28 of the 29 participants (success rate: 97%, not feasible in 1 participant due to discomfort) for the unilateral hotspots and in 26 of the 29 participants (success rate: 90%, not feasible in 2 participants in which RMTs were > 95% MSO) for the bilateral hotspot. Figure 3.5a and b shows that the SR curves derived from the left and right unilateral hotspots stimulation span a bigger range of stimulation intensities compared to the SR curves derived from the bilateral hotspot stimulation. Additionally, for the same stimulation intensity in %RMT, stimulating the unilateral hotspots resulted in smaller MEPs than stimulating the bilateral hotspot for a range of stimulation of 60-200% RMT. This is also reflected in Figure 3.5c, d, e, and f where the inflection points derived from bilateral hotspot stimulation were reached at a significantly lower %RMT than those derived from unilateral hotspot stimulation for the responses in both the left TA (mean bilateral hotspot inflection point: 118±18% RMT vs mean unilateral hotspot inflection point: 143±15% RMT, t=5.427, p<.001) and the right TA (mean bilateral hotspot

inflection point: 117±18% RMT vs mean unilateral hotspot inflection point: 139±23% RMT, t=3.928, p<.001). The mean inflection points for the SR curves were similar between the unilateral hotspots (t=0.759, p=.451) as well as between legs for the bilateral hotspot (t=0.221, p=.826).

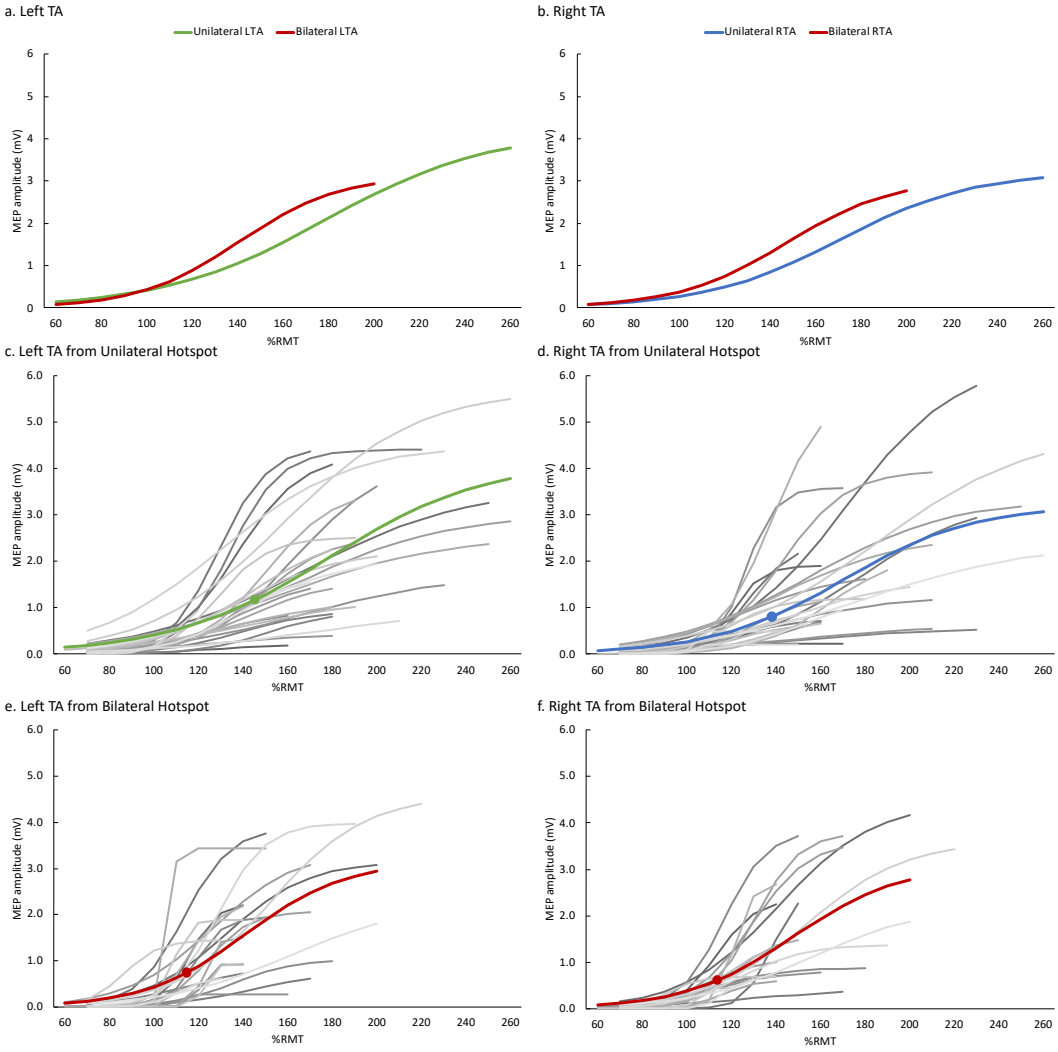

Fig. 3.5 Fitted SR curves recorded in each leg from each hotspot. (a) shows the group fitted SR curves with the MEPs recorded in the left TA for the unilateral hotspot in green and the bilateral hotspot in red, and (b) shows the group SR curves with MEPs recorded in the right TA for the unilateral hotspot in blue and the bilateral hotspot in red. Panels (c) (d) (e) and (f) depict the fitted individual SR curves for each group SR curve shown in panels (a) and (b). Dots represent the inflection points of each curve. TA: tibialis anterior, MEP: motor evoked potential, mV: millivolt, RMT: resting motor threshold

The largest MEP amplitude recorded in the left and right TAs greatly varied across participants as depicted in Figure 3.6a. For both legs, the mean amplitude of the largest MEPs

obtained in each leg from the bilateral hotspot stimulation (mean left TA MEP amplitude 1.8±1.3 mV, mean right TA MEP amplitude 1.7±1.3 mV) was to the MEPs obtained from the unilateral hotspot stimulation (mean left TA MEP amplitude 2.4±1.5 mV, mean right TA MEP amplitude 2.1±1.7 mV, p=.102). Responses ≥ 0.5 mV in both left and right TA muscles were obtained in 73-87% of the participants for all stimulation targets. Figure 3.6b shows a moderate, negative relationship between the highest MEP amplitude for each participant and their RMT, suggesting that participants with the largest MEPs were the ones with the lowest RMT. Specifically, the bilateral hotspot RMT was moderately correlated with the MEP amplitude obtained in both the left (r_s=-.585, p=.002) and the right (r_s=-0.580, p=.002) TAs. The left and right TA hotspots RMTs were also moderately correlated with the MEPs obtained in the left (r_s=-.498, p=.007) and right (r_s=-.448, p=.017) TAs, respectively.

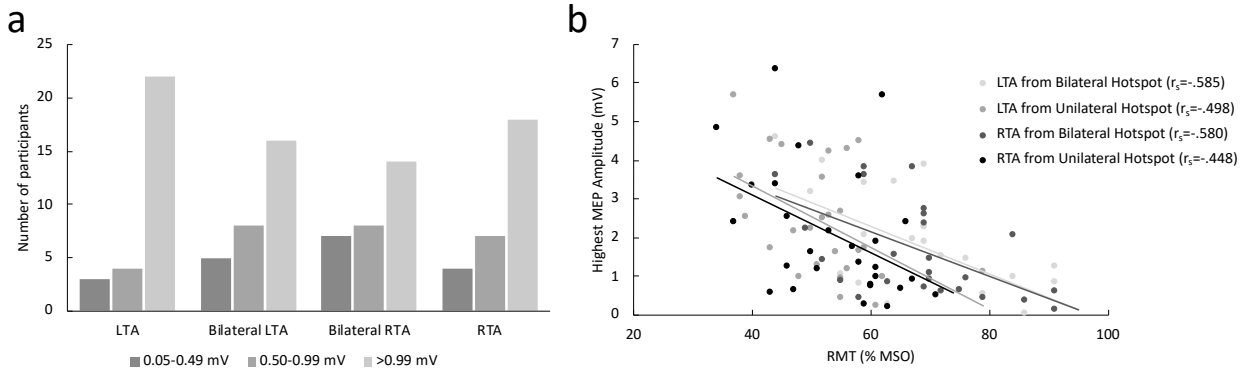

Fig. 3.6 Distribution of (a) the highest MEP amplitude reached in each leg for each hotspot and (b) the correlation between the largest mean MEP amplitude and the RMT of each participant. LTA: left tibialis anterior, RTA: right tibialis anterior, mV: millivolt, MEP: motor evoked potential, RMT: resting motor threshold, MSO: maximal stimulator output, r_s: Spearman's rho

3.5 Discussion

To the best of our knowledge, this is the first study to use a single TMS target to stimulate both the left and right TA representations on M1 simultaneously in a group of healthy participants. A bilateral hotspot was found in all participants with unilateral TA MEP responses. This bilateral hotspot is typically located midway between the left and right unilateral hotspots. Overall, the bilateral hotspot RMT was significantly higher compared to the unilateral hotspots RMTs, but when comparing MEP responses at the same %RMT, stimulation of the bilateral hotspot led to

greater MEP responses than stimulation of the unilateral hotspot. These results provide evidence that a bilateral hotspot could potentially be used as a stimulation target for TMS.

In this study, the systematic mapping protocol followed allowed us to successfully find the hotspot for the left, right and bilateral TA in 97% of the participants. This success rate was superior to previous studies targeting the TA with TMS in which the hotspot mapping success rate was obtained between 42% and 90% for unilateral hotspots (Eibl et al., 2022; Forster et al., 2014; Krieg et al., 2012; Peters et al., 2017; Weiss et al., 2013; Zhang et al., 2020). It is unclear why such a range of success rates were obtained and why it is lower compared to our success rate. In the current study, hotspots were not found in one participant. As touched upon in section 3.4.1, the 5% contraction required for mapping resulted in a voluntary muscle activity following a consistent spiked pattern, making it impossible to distinguish the MEPs elicited by TMS from the voluntary contraction. The type of stimulation coil used to target the TA M1 representation is likely one important factor that contributes to our very good success in obtaining MEPs in the TA. In all these previous studies, a figure-of-eight coil was used to map the M1 (Eibl et al., 2022; Forster et al., 2014; Krieg et al., 2012; Peters et al., 2017; Weiss et al., 2013; Zhang et al., 2020); however, based on the depth-focality trade-off principle, figure-of-eight coils are focal, thereby impeding on their stimulation depth (Koponen & Peterchev, 2013; Vilchez Membrilla et al., 2022). Importantly, it was also possible to determine a RMT in 93% and 100% of the participants with bilateral and unilateral TA hotspots, respectively, which is substantial considering that in the lower limbs, the RMT tends to be higher compared to the upper limbs, and is therefore harder to determine (Forster et al., 2014; Lefaucheur, 2019; Weiss et al., 2013). Cacchio and colleagues (2009) suggested that in healthy individuals, the RMT was the most reliable measure of cortical excitability in the TA muscles. Based on these data, simply acquiring RMT, which was successful in this study, could be enough to measure a change in excitability, further showing the potential of using the bilateral TA hotspot as a TMS target.

In the current study and in agreement with our hypothesis, the bilateral hotspot was found midway between the two unilateral hotspots. Hand and colleagues (2020) showed that a medio-lateral current orientation, the orientation used in our study for the unilateral hotspots, seems to be more optimal for TA stimulation. However, they still suggested that a posterior-anterior orientation could be used to assess cortical excitability of the TA representation on M1 with TMS (Hand et al., 2020), which is the current orientation used in our study for the bilateral TA hotspot. In fact,

the posterior-anterior current orientation might have allowed the depolarization of neurons on both sides of the interhemispheric fissure, corresponding to the lower limb representations on M1. Interestingly, the bilateral hotspots of the left-handed and the left-footed participants were slightly shifted toward their non-dominant hemisphere instead of being close to the midline. Handedness has previously been shown to influence cortical organization and asymmetry between brain hemispheres (Corballis, 2014; Nicolini et al., 2019). For instance, right-handed individuals were reported to have larger motor cortical representations than left-handed individuals (Nicolini et al., 2019), which might partially explain the difference in location of the hotspots in the current study. Even though this finding is interesting, it should be interpreted with caution considering only two participants were identified as left-handed/right-footed or right-handed/left-footed. Future studies should look at the potential link between leg and hand dominance and location of muscular representations on M1 as TMS offer a unique opportunity to clarify the organization of the motor homunculus.

As hypothesized, significantly higher RMTs were obtained from the bilateral hotspot compared to the unilateral hotspots. The hotspot is said to be the optimal stimulation location for a specific target, based on the idea that it is the point eliciting MEPs at the lowest stimulation intensity possible (Hand et al., 2020; Kleim et al., 2006; Rossini et al., 2015), and is therefore expected to be highly excitable. Because the unilateral TA hotspots elicited MEPs at a lower stimulation intensity (i.e., lower RMTs), our results support the idea that the bilateral TA hotspot is a suboptimal target compared to the unilateral TA hotspots. Even if the bilateral hotspot is said to be a suboptimal TMS target due to its higher RMT, it may still be possible to use it as a target. In fact, in the upper limbs, when measuring a change in cortical excitability, the stimulator intensity is usually set at the intensity eliciting MEPs between 0.5 to 1 mV on average, which usually corresponds to 110-120% RMT (Potvin-Desrochers et al., 2023; Rossini et al., 2015). Based on that upper limit value, the highest RMT allowing to stimulate at 120% RMT is 83% MSO, which corresponds to the highest RMT acquired in twenty-three of our participants. For the lower limbs, obtaining MEPs of at least 0.5 mV in a resting state is often limited by the higher RMTs, and is therefore more challenging (Hand et al., 2020; Potvin-Desrochers et al., 2023). This is why, in this study, it was deemed important to assess the feasibility of eliciting responses of at least 0.5 mV for the comparison between the bilateral and the unilateral TA hotspots. Our results show that responses equal or greater than 0.5 mV were obtained in more participants when TMS was applied

to the unilateral hotspots than when it was applied to the bilateral hotspot. However, stimulation of the bilateral hotspot still resulted in MEPs of at least 0.5 mV in most of the participants; MEPs equal or greater than 0.5 mV were obtained in the left and right TAs in 80% and 73% of the participants, respectively. The average amplitude of the highest MEPs obtained was also similar in both legs, regardless of the stimulation target further highlighting the comparability of the bilateral and the unilateral TA hotspots. Furthermore, the relationship between MEP amplitude and RMT was the same for the bilateral and the unilateral TA hotspots, supporting the idea that participants with lower RMTs have a better chance of reaching the 0.5 to 1 mV response needed to properly measure a change in cortical excitability (Devanne et al., 1997; Lefaucheur, 2019; Rossini et al., 2015). Altogether, the quantification of RMTs and the MEPs amplitude achieved in this study suggests that the excitability of the bilateral TA hotspot behaves similarly to that of the unilateral TA hotspots, and therefore represents a potentially great TMS target, especially considering that walking is a simultaneous task requiring the coordination of both legs.

Interestingly, we found that the SR curves of both the left and right TA had their inflection point at a lower %RMT for the bilateral TA hotspot than for the unilateral TA hotspots. Khaslavskaia and colleagues (2012) suggested that a change in the TA cortical excitability can be reflected by a change in inflection point. Specifically, they proposed that a greater motor cortical excitability was associated with an inflection point found at a lower value of stimulator output (Khaslavskaia et al., 2002). This would suggest that the bilateral TA hotspot has higher cortical excitability than the unilateral TA hotspots, contrary to the findings related to the RMTs; however, in this study, the SR curves plotted the MEP amplitude relative to the % RMT instead of the stimulator output. Therefore, because the RMT was deemed significantly higher for the bilateral hotspot than for the unilateral ones, the absolute stimulator output used during the acquisition of the SR curves was greater for the bilateral hotspot than for the unilateral hotspots, which potentially explains the smaller inflection points observed in the bilateral hotspot SR curves. Because the intensities of the SR curves were based on % RMT, it was possible to test a greater range of intensities with the unilateral hotspots as targets because their RMTs were lower than the bilateral hotspot RMT. Any comparison between the SR curves derived from bilateral TA hotspot stimulation and those derived from unilateral TA hotspots stimulation are, therefore, not possible beyond a stimulator output of 200% RMT. In fact, unilateral TA hotspots stimulation resulted in SR curves spanning a greater range of intensities suggesting the MEPs obtained from these TMS

targets could reach greater amplitude; however, the bilateral TA hotspot might have elicited similar maximal MEP amplitude if it would have been possible to target it at an equivalent stimulation intensity. The SR curves obtained in this study show minimal differences between bilateral and unilateral TA hotspots, again highlighting the potential of the bilateral TA hotspot. It is interesting to note that, whether the unilateral or the bilateral hotspot was stimulated, the right and left TA responded similarly. Indeed, when the unilateral hotspots were targeted, the SR curve and the highest MEP amplitude obtained in the left TA were similar to the SR curve and the highest MEP amplitude obtained in the right TA. The same trend was observed between the two legs when the stimulation was delivered over the bilateral hotspot, suggesting that TMS has the same effect in both the left and right TAs when it is applied to the unilateral hotspots, or the bilateral hotspot.

In this study, cortical excitability was quantified through RMT and MEP amplitude, but MEP latencies, which usually indicate the descending volleys recruited by TMS (Rossini et al., 2015), were not analyzed. Specifically, latencies are greatly influenced by a variety of stimulation parameters, including stimulation intensity (Day et al., 1987). Latencies were unfortunately not analysed as part of this study; however, response latencies of bilateral and unilateral TA hotspots should be explored in future studies as it could potentially explain the differences observed in inflection points between the bilateral and unilateral TA hotspots. Additionally, Hand and colleagues (2020) showed that a medio-lateral current orientation seems to be more optimal for TA stimulation as it appears to be the current inducing the lowest activation threshold; however, they still suggested that a posterior-anterior orientation could be used to assess cortical excitability of the TA representation on M1 with TMS and recommended further assessment of the optimal current direction (Hand et al., 2020). Due to the extensive length of the sessions of the current study and the coil overheating, it was not possible to assess different current orientations, which is a limitation of this study. Future studies should explore how different coil orientations affect the responses elicited by stimulation of the bilateral hotspot.

3.6 Conclusion

Overall, we demonstrated that it is possible to identify a bilateral hotspot for the TA muscles using a systematic mapping methodology. Even if the bilateral hotspot is a suboptimal target compared to the unilateral hotspots according to the difference in RMT, the minimal differences observed in the other cortical excitability measurements obtained in this study confirmed that it would still be feasible to stimulate both TA muscles simultaneously using a

bilateral hotspot. Considering that many tasks require the use of both legs simultaneously, such as walking and maintaining balance, our assessment of the bilateral hotspot as a TMS target was of paramount importance. In fact, this study provided the groundwork necessary for future studies aiming at modulating bilaterally the cortical excitability of the lower limbs M1 representation to improve bilateral tasks such as gait in both healthy and clinical populations.

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Chapter 4: Scholarly Discussion

4.1 Summary of Results

The results of the present study support the use of a bilateral TA hotspot for TMS. In addition to a highly successful mapping rate, the cortical excitability measurements obtained suggest a small, probably negligible difference in the outcome between stimulation of the bilateral and the unilateral TA hotspots. Specifically, the bilateral TA hotspot had a higher RMT, but the resulting MEPs measured were equal or greater than those elicited by unilateral TA hotspot stimulation when stimulation intensity was expressed as %RMT of each hotspot. The ability to target the bilateral hotspot supports the idea that the motor homunculus is functionally organized. Furthermore, it opens up new possibilities for studies using NIBS techniques to assess the underlying cortical control mechanisms involved in gait and to modulate cortical excitability.

4.2 Challenging the Somatotopic Organization of the Primary Motor Cortex

The somatotopic organization of the M1 has been challenged with the improvement and the emergence of novel brain mapping techniques. Specifically, studies using electrical stimulation to assess the organization of M1 showed that there is a functional overlapping between the muscular M1 representations (Branco et al., 2003; Donoghue et al., 1992; Farrell et al., 2007; Schiebert, 2001). In addition, previous studies using a variety of techniques including brain imaging, TMS, electrical stimulation, and EMG have revealed that certain conditions including limb immobilization and chronic pain have been involved with plasticity changes and reorganization of M1, supporting the idea that the M1 organization is not definite (Flor, 2003; Langer et al., 2012; Niskanen et al., 2010). Available hotspot mapping protocols state that the optimal stimulation target corresponds to the M1 point with the lowest RMT (Groppa et al., 2012; Lefaucheur, 2019; Rossini et al., 2015). Based on this definition, in our study, the unilateral TA hotspots would correspond to the optimal stimulation targets, while the bilateral TA hotspot would be an additional, suboptimal stimulation target. However, the SR curves data acquired in our study show that the bilateral TA hotspot elicited MEPs with greater amplitude than the unilateral TA hotspot for the same %RMT. Thus, the results of the current study demonstrate that two different stimulation sites (i.e., the bilateral and the unilateral TA hotspots) can elicit strong responses in the TA muscles, supporting the idea that M1 follows a somatotopic organization where the lower limb muscles are represented in close proximity to one another. Altogether, these findings suggest

that TMS has the potential to recruit neurons from the left and right M1 simultaneously, again, aligning with the idea that the motor homunculus may follow a functional, integrative organization.

4.3 Implications for Non-Invasive Brain Stimulation

NIBS can modulate cortical excitability and can thus be used for a variety of purposes, including the treatment of movement disorders, (Groppa et al., 2012; Latorre et al., 2019; Rossini et al., 2015). In the context of rehabilitation, NIBS has been studied extensively as it was shown to have the potential to induce long-term potentiation (LTP) and long-term depression (LTD) like effects in the M1 (Bashir et al., 2010; Rossini et al., 2015; Sanes & Donoghue, 2000). M1 plays an important role in gait initiation and in fine control of locomotion by sending a direct input from the brain to the muscles like the TAs via the descending fast pyramidal tracts (Takakusaki, 2013). Changes in plasticity occurring in response to motor learning induce LTP and LTA effects that similar to those induced by NIBS (Pearson, 2000; Sanes & Donoghue, 2000). Therefore, applying NIBS over M1 prior to gait rehabilitation could bolster the effects of training by reinforcing cortical circuits related to motor retention (Cacchio et al., 2009; Khaslavskaia et al., 2002; Potvin-Desrochers & Paquette, 2021; Rossini et al., 2015).

The findings of the current study support the use of a bilateral TA hotspot for studies aiming at improving gait and/or balance. The pattern of activation of these tasks may elicit different areas on M1 rather than the individual M1 representation traditionally targeted (Donoghe et al., 1992; Schieber, 2001). Therefore, stimulating the M1 of both the left and right lower limbs simultaneously via a single bilateral hotspot may be more ecological considering the bilateral nature of these tasks. Additionally, the use of a bilateral TA hotspot would facilitate NIBS intervention; instead of mapping for two individual hotspots, then stimulating those two hotspots independently, only the bilateral hotspot would be mapped and stimulated. Therefore, the time required for the NIBS intervention would be reduced, and the number of pulses applied in a session would be reducing. Together, this would increase comfort for the participants, and simplify the stimulation protocols. The use of a bilateral hotspot may also facilitate the implementation of NIBS interventions in clinical settings with the potential to bolster training effects and/or reduce the intervention duration for optimal independence in mobility. Improving stimulation protocols could also contribute to fields outside of rehabilitation science such as sport science where priming the brain prior to training may improve performance (Davis, 2013).

4.4 Non-Invasive Brain Stimulation Parameters Optimization

With our findings, we demonstrate that it is feasible to find a bilateral hotspot eliciting similar responses than unilateral hotspots; however, stimulation parameters must be optimized and adapted to the bilateral hotspot. As shown in the upper limbs, the orientation in which the coil is placed plays an important role on the descending volleys elicited by TMS (Di Lazarro & Rothwell, 2014; Hamada et al., 2013; Hand et al., 2020). For instance, in the upper limbs, when the coil is placed perpendicular to the central gyrus (angled at 45 degrees), it induces a posterior-anterior electrical current which is optimal as it predominantly produces D-waves (Di Lazarro & Rothwell, 2014; Gomez-Tames et al., 2018; Hamada et al., 2013; Hand et al., 2020). For the lower limbs, coil orientation is usually determined in relation to the midsagittal plane (i.e., interhemispheric fissure) instead of the central gyrus due to the organization of the lower limbs M1 (Hand et al., 2020). However, the most favorable coil orientation remains unclear (Hand et al., 2020). A medio-lateral current orientation was associated in the TA with decreased RMT and increased MEP amplitude suggesting it may be the optimal orientation for the lower limbs, but the study also provided evidence for the use of a posterior-anterior current orientation (Hand et al., 2020). In the current study, the unilateral TA hotspots were stimulated using a medio-lateral coil orientation to directly stimulate the TA representation on M1 (Hand et al., 2020). The TA representations on M1 are facing one another; therefore, to avoid the induction of a latero-medial current in one side of M1, the bilateral TA hotspot was stimulated using an anterior-posterior coil orientation, which was also shown to elicit MEPs in the TAs (Hand et al., 2020). In the current study, the unilateral TA hotspots had a lower RMT than the bilateral TA hotspot, in accordance with the literature showing an association between posterior-anterior coil orientation and lower TA RMTs (Hand et al., 2020). On the other hand, there was no difference between the amplitude of the MEPs elicited by the bilateral TA hotspot and those elicited by the unilateral TA hotspots. Our findings align with the literature showing that posterior-anterior and medio-lateral coil orientations may be used to stimulate the lower limbs M1 representation. Future studies should thus attempt to determine the optimal coil orientation unilateral and bilateral lower limb hotspots.

Another parameter that needs to be optimized prior to the implementation of NIBS interventions is stimulation intensity. The stimulation intensity is determined with values recorded in the hand muscles because it is typically used to stimulate cortical regions that are found at a similar cortical depth (Chung et al., 2018; Huang et al., 2005; Potvin-Desrochers et al., 2023).

Therefore, it is not optimized for stimulation of the lower limbs M1 representation, nor for the stimulation of a bilateral TA hotspot. Despite the great potential of the bilateral TA hotspot, the RMT measurements obtained in this study indicated lower cortical excitability. This suggests that a higher stimulation intensity may be needed to stimulation a bilateral hotspot than a unilateral hotspot would require to have similar modulation effects on both the left and the right M1. Future work could test different stimulation intensities of NIBS applied to the legs M1 representation and assess their respective effect on cortical excitability to find the optimal stimulation intensity. Additionally, such investigation could also be conducted using the bilateral TA hotspot as a target to assess whether the optimal stimulation intensity is different.

Finally, the type of coil that is used to apply stimulation to the bilateral TA hotspot is also a parameter that can be optimized. In our study, we applied the stimulation with a double-domed coil that was customized to the need of the type of research conducted in our laboratory. However, to our knowledge, there is no study assessing how this type of coil compares to other coils that are more traditionally used for stimulation of the lower limbs such as the double-coned coil. The design of the double-domed coil is similar to the design of the double-coned coil, but its wings are less angled, allowing the coil to be rotated on the head (Deng et al., 2013; Rossi et al., 2021). Therefore, the stimulation strength and the focality of the double-domed coil is expected to be similar to those of the double-coned coil; however, the double-domed coil allows for the induction of current in different orientations. As mentioned in the beginning of this section, orientation can have an influence on the MEP responses elicited by TMS in term of latency and amplitude (Di Lazarro & Rothwell, 2014; Hamada et al., 2013; Hand et al., 2020). This greater freedom in coil orientation yielded by the double-domed coil could potentially explain our greatly successful mapping rate. However, differences in stimulation depth, stimulation strength, and coil focality between the various types of coils available need to be explored more extensively.

4.5 Additional Implications of the Bilateral Hotspot

The findings of the current study are not restricted to the lower limb representations on M1; they could potentially refine stimulation protocols targeting other regions such as the low back and the pelvic floor muscles M1 representations. Similar to the lower limbs, the lower back and the pelvic floor muscles are located medially, deep within the interhemispheric of the brain (Desmons et al., 2023; Yani et al., 2018). They are thereby harder to target with TMS, requiring

the use of specialized coils and/or of a higher stimulation intensity to elicit responses with TMS (Desmons et al., 2023; Yani et al., 2018). Our results proposed that the double-domed coil may be strong enough to target cortical areas that are more deeply embedded within the interhemispheric fissure and could therefore potentially be used for stimulation of low back and pelvic floor muscles. The meta-analysis conducted by Desmons and colleagues (2023) reported an important contribution of the ipsilateral projections in addition to the expected contralateral ones in the control of the low back muscles. These results were also identified in pelvic floor musculature (Yani et al., 2018). The stimulation techniques used in the current study could potentially be extrapolated to these other groups of muscles that are involved in bilateral tasks and are challenging to target using currently established TMS protocols.

Chapter 5: Conclusion and Summary

To our knowledge, this was the first study to assess the feasibility of using a bilateral TA hotspot as a TMS target in healthy populations. The results of the present study demonstrate that it was possible to identify a bilateral TA hotspot in all participants in which unilateral TA hotspots were found. The feasibility of using such bilateral TMS target for the TA was also validated; despite the higher bilateral TA hotspot RMTs, other cortical excitability measurements obtained suggest that the differences in MEPs elicited by bilateral TA hotspot stimulation are neglectable compared to those elicited by unilateral TA hotspot stimulation. Considering the bilateral nature of walking and other tasks that we encounter daily, stimulating both legs simultaneously via a bilateral hotspot is only logical. In fact, it would allow to conduct gait study in a more ecological setting, which could potentially give us better insights on higher levels control of locomotion.

In order to use the bilateral TA hotspot at its full potential, future studies should initially focus on determining the optimal stimulation parameters, including mapping methodology, coil type and current orientation. Additionally, the results obtained in this study could potentially be extrapolated to the cortical representation of other muscle groups with bilateral involvement to assess their own organization with TMS. Finally, the effect of modulating the bilateral hotspot prior to gait or balance training to bolster plasticity changes and motor learning should be explored. According to the promising results obtained in this study, it is likely that the bilateral hotspot could be a favorable target for repetitive TMS and other NIBS techniques; however, the specific underlying mechanisms of action of such modulation and their respective effects on gait and balance are yet to be determined.

Overall, the present study provides the groundwork necessary to support the application of TMS to a bilateral TA hotspot. More studies are needed to provide greater insights on the mechanisms underlying the results obtained, but also to optimize the stimulation protocols targeting the lower limbs M1 representation as well as other muscle groups with bilateral connections. Hopefully, this study will be used as a foundation for future TMS studies aiming at assessing cortical organization to a greater extent, or at improving gait and balance in both healthy and clinical populations.

Chapter 6: References

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