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Investigation into the influence of stimulation area and coil orientation on the results of navigated transcranial magnetic stimulation (nTMS) mapping of lower limb intracortical excitability

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) is widely used to assess corticomotor excitability. Coil orientation and stimulation location are crucial for eliciting motor-evoked potentials (MEPs) and determining resting motor thresholds (RMT). Since the cortical foot area is challenging to examine, identifying the optimal coil angle and location is essential.
Method: Eleven healthy volunteers underwent navigated TMS mapping using a predefined protocol. Stimulation was applied at six locations around the tibialis anterior (TA) motor hotspot, with coil direction varied in 45° increments. Mapping was performed using the Nexstim NBS 5.0 system, and statistical analysis was conducted in RStudio 2024.
Results: TA cortical representation mapping was successful in all participants. The mean hotspot was located in the precentral gyrus, 6–13 mm lateral to the midline. The highest MEP amplitude was observed at a stimulation angle of 90°, perpendicular to the falx cerebri.
Comparison with Existing Methods: Unlike previous studies with limited coil orientations or without MRI-guided neuronavigation, our approach systematically evaluated multiple directions and locations. The findings align with prior research regarding optimal stimulation sites and angles.
Conclusion: We refined the anatomical stimulation area and preferred angle for lower-extremity TMS. These findings may improve clinical applications, especially when considering individual and pathological differences.

1. Introduction

Since its initial introduction by Barker et al. in 1985, transcranial magnetic stimulation (TMS) has emerged as a pivotal non-invasive technique for assessing corticomotor excitability in both healthy and diseased human brains (Barker et al., 1985; George et al., 1999; Noohi and Amirsalari, 2016). As a result, the method is nowadays widely used for both diagnostic and therapeutic as well as scientific purposes (Hallett, 2000; Lefaucheur et al., 2020; Noohi and Amirsalari, 2016).

Apart from factors like coil positioning, stimulation intensity, drug intake, pulse duration, skull thickness, and others, stimulation coil orientation is known to be an influential factor on motor-evoked potential (MEP) response and, thereby, motor thresholds (MT) (Bashir et al., 2013; Gomez-Tames et al., 2018; Groppa et al., 2012; Herbsman et al., 2009; Kammer et al., 2001; Lazzaro et al., 2004; Oliviero et al., 2011; Rossini et al., 2015). In motor mapping studies of the hand and arm regions, the impact of coil orientation has been well-documented in multiple publications (Werhahn et al., 1994, Sakai et al., 1997, Bashir et al., 2013; Janssen et al., 2015; Kesar et al., 2018; Souza et al., 2018). For instance, a posterior-to-anterior current direction, perpendicular to the gyrus, is recommended for TMS motor mapping of the hand knob area when using monophasic pulses (Gomez-Tames et al., 2018; Siebner et al., 2022). Conversely, with biphasic pulses, lower thresholds are achieved when the initial phase induces an anterior-to-posterior current direction (Kammer et al., 2001).

However, existing optimization methods have primarily been

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validated for the motor hand area, which is anatomically more accessible and lies closer to the cortical surface. Thus, these methods may not directly translate to the lower limb representation due to distinct anatomical constraints. The hand area lies on the lateral convexity of the precentral gyrus, whereas the cortical representation of the lower limb is anatomically more complex, residing near the falx cerebri with a characteristic gyral-sulcal pattern and folding along the midline. This positioning within the interhemispheric fissure presents challenges in eliciting MEPs (Allison et al., 1996; Kesar et al., 2018; Smith et al., 2017; Terao and Ugawa, 2002). Consequently, there is no consensus on the optimal stimulation area or direction for targeting the cortical lower limb area (Hand et al., 2020; Smith et al., 2017; Terao and Ugawa, 2002; Volz et al., 2015).

This study seeks to address the current lack of consensus regarding optimal TMS coil orientation for lower limb motor mapping. By systematically evaluating stimulation angle effects over the cortical foot area, the work aims to refine TMS application in this region and contribute to the development of more precise and reliable stimulation protocols tailored to the anatomical challenges of lower limb representation.

2. Patients and methods

2.1. Patients

11 healthy subjects (7 men, 4 women) between 25 and 36 years old were included in this prospective study after giving informed, written consent. Our local ethics committee approved the study (Ulm University, Nr. 340/16). Three technical pilot mappings were performed before subject recruitment to establish feasibility and to refine the planned protocol.

2.2. Stimulation protocol

The nTMS mapping was performed using Nexstim NBS 5.0 (Nexstim Oy, Helsinki, Finland) with a figure eight coil and electromyography (EMG) surface electrodes (NeuroTab, spes medica, Genova, Italy). The maximum E-field strength of this device is specified as 172 V/m, and the maximum magnetic field strength is 1,42 T by Nexstim. It delivers a biphasic pulse with a pulse length of 230 microseconds (μs). EMG responses were automatically rated as positive above 50μV amplitude by the stimulation software. However, all EMG responses were re-evaluated retrospectively and rated as positive below the 50μV limit if a reliable EMG response could be recognized. The study was carried out by means

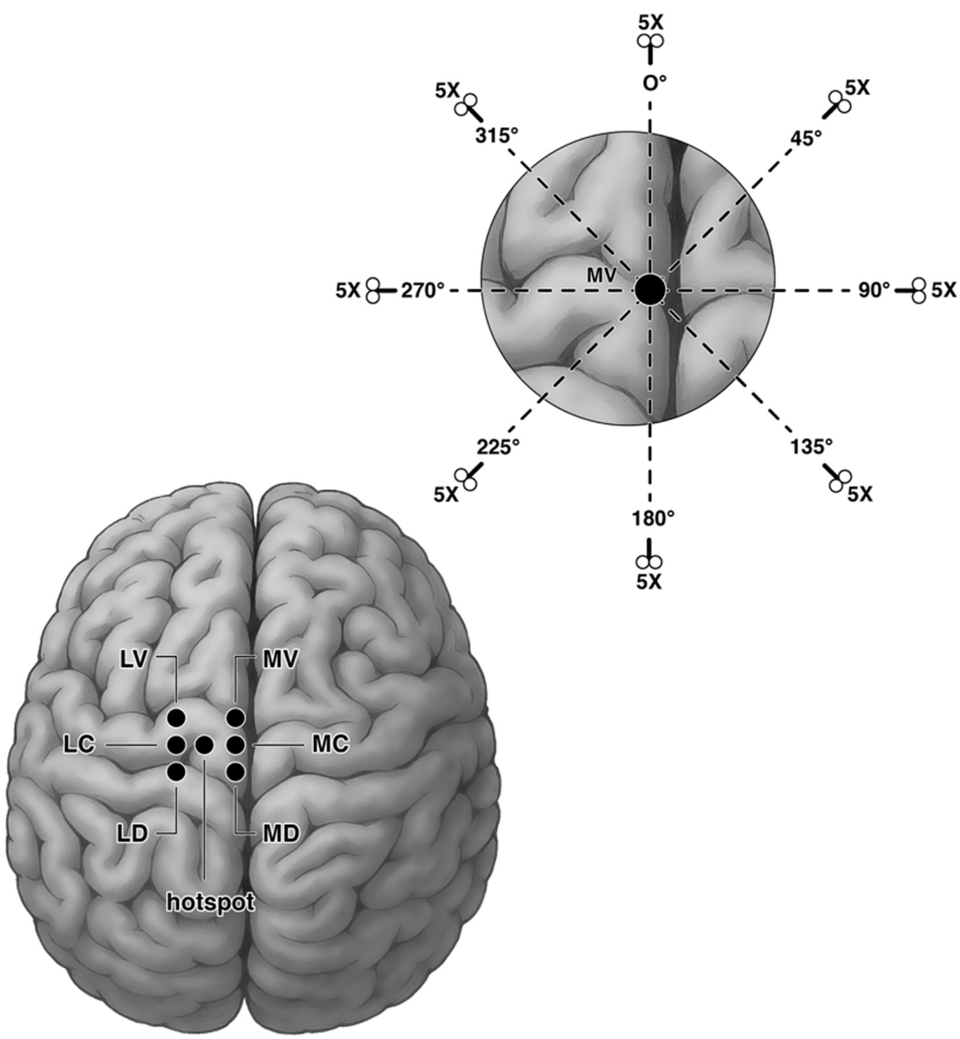

Fig. 1. Illustration of the anatomy and stimulation protocol in correlation to the MRI imaging from A. The stimulation points are numbered in the order in which they were stimulated and labeled according to the stimulated cortex hemisphere. Five stimulations were performed on each stimulation point and in each of the marked stimulation directions. LV = Lateral Ventral, MV = Medial Ventral, LC = Lateral Central, MC = Medial Central, LD = Lateral Dorsal, MD = Medial Dorsal. All labels refer to their relative position to the hotspot, depending on the stimulated hemisphere.

of a single examination per subject. Dominant and non-dominant hemispheres were mapped.

After confirming a stable electromyographic (EMG) baseline and completing the navigation registration, the resting motor threshold (RMT) was determined following a standardized protocol in accordance with the predefined RMT algorithm provided by the manufacturer (Awiszus, 2003; Coburger et al., 2011). The tibialis anterior (TA) muscle was selected as a representative target muscle for the cortical representation of the foot area. Subsequently, motor mapping of the leg area was conducted at 100 % of the individual RMT to identify the motor hotspot. To ensure precise and consistent stimulation, the device's integrated optical navigation system was utilized, which facilitated accurate coil positioning. Special attention was given to maintaining the coil orientation perpendicular to the head surface throughout the stimulation procedure.

Subsequently, six stimulation points were systematically defined around the identified motor hotspot to encompass a substantial portion of the leg area. Using a system-integrated target grid, these points were arranged in a standardized rectangular configuration, aligned parallel to the midline (see Fig. 1). To ensure the highest possible consistency across the numerous stimulations per participant, stimulation was guided by a stimulation grid integrated into the device, with a grid spacing of 3.7 mm (1/8 in.). For each of the six defined stimulation points, eight distinct stimulation directions were applied in a dorso-frontal vector orientation at 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315°. Each stimulation direction was repeated five times, maintaining a consistent coil tilt throughout the procedure. The stimulation sequence followed a structured clockwise pattern: starting at the first stimulation point (defined as the left frontal point), the initial stimulations were performed at 0°, followed by a sequential shift to the remaining five stimulation targets while adjusting the orientation to 45° in the next round (see Fig. 1).

In total, per individual 240 stimulations were performed. The stimulation intensity for this final mapping phase was set to 100 % of the device's maximum output strength to ensure robust motor responses.

2.3. Data processing and statistical analysis

Statistical analysis was conducted using RStudio 2024.09.1. Given the substantial interindividual variability in the amplitude of the evoked potentials, all amplitudes were standardized within each subject. The highest recorded amplitude for each individual was set to 100, and all other values were expressed as a percentage relative to this maximum (ranging from 0 to 100 per subject). Continuous data are presented as mean +/- standard deviation. The assumption of normality was assessed using the Kolmogorov-Smirnov test, as well as visual inspection via histograms and Q-Q plots. To evaluate potential differences in amplitude levels across the six stimulation areas and the eight stimulation directions, a one-way ANOVA was performed. Post-hoc comparisons were conducted using the Tukey-HSD test. A p-value of < 0.05 was considered statistically significant. A spline curve was fitted to the mean-values of the stimulation directions using GraphPad Prism 10.

3. Results

3.1. Variation with stimulation points

The ANOVA revealed a statistically significant effect for the stimulation points ($p < .001$; $F = 7.302$). Post-hoc analysis demonstrated that the stimulation site immediately lateral to the hotspot (95 % CI 0.295 – 0.334) elicited a significantly higher amplitude compared to all other stimulation sites (95 % CI 0.216 – 0.294) ($p < .05$), as illustrated in Fig. 2. However, no significant differences were observed in latencies ($p > .05$). Given that stimulation points directed toward the midline did not cross it and the horizontal grid spacing was 13 mm, the leg motor area including the hotspot can be localized in the precentral gyrus, on a perpendicular line approximately 6–13 mm lateral to the midline.

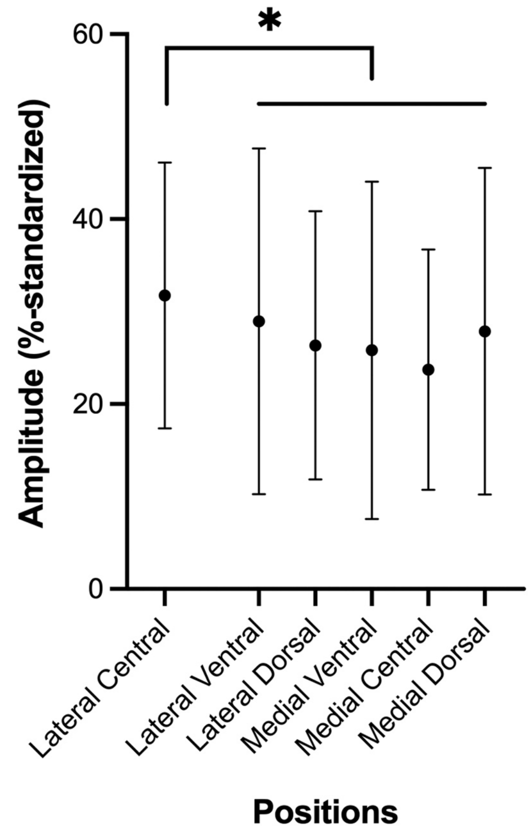

Fig. 2. Illustration of the statistically significant difference in standardized mean stimulation amplitudes between the stimulation point lateral to the hotspot (Lateral Central) and the other five stimulation points. * = $p < .05$.

3.2. Variation with current direction

The ANOVA revealed a statistically significant effect ($p < .027$; $F = 2.319$). Post-hoc analysis indicated that stimulation angles of 90° (95 % CI 0.276–0.322) and 135° (95 % CI 0.264–0.310) relative to the falx elicited significantly higher amplitudes compared to angles between 255° and 315° (95 % CI 0.230–0.276, 0.232–0.275 and 0.227 – 0.273), as illustrated in Fig. 3($p < .05$). Although 135° also showed statistically significant differences compared to angles between 255° and 315°, these findings did not consistently meet the criteria with respect to the confidence interval. Descriptive analysis further showed that the highest average amplitude of the evoked potential occurred at a stimulation angle of 90°, corresponding to a perpendicular orientation to the falx cerebri. Given the apparent curved pattern of median values in the graph, a spline curve was fitted to the mean amplitude values, resulting in a sinusoidal distribution of stimulation amplitudes with a peak at 90° (see Fig. 4). In an individual analysis for each participant, a statistically significant amplitude difference dependent on stimulation angle was observed in four out of the eleven participants (Table 1). No statistically significant differences in latencies were observed ($p > .05$).

Overall, the results indicate both a spatial and directional gradient of stimulation effects. Spatially, the optimal stimulation site was located laterally to the hotspot in the precentral gyrus. Additionally, stimulation efficacy exhibited a directional dependence, following a sinusoidal pattern with a descriptive peak at 90°.

4. Discussion

In a cohort of 11 healthy volunteers, transcranial magnetic

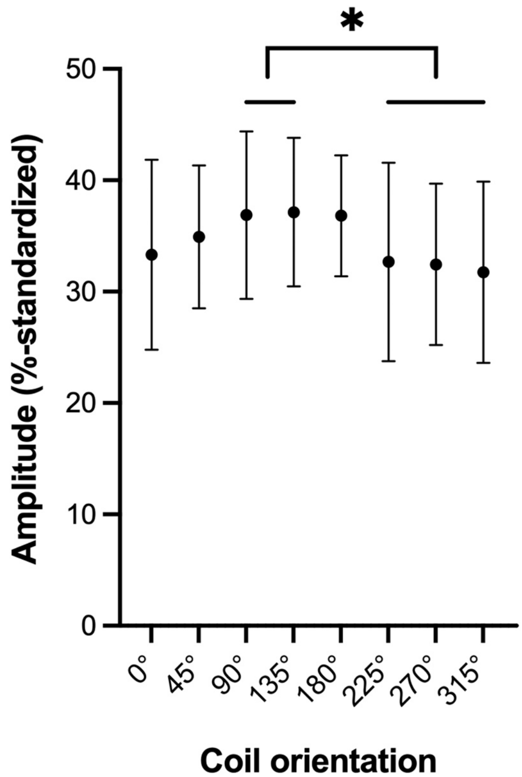

Fig. 3. Illustration of the statistically significant difference in stimulation amplitudes between the perpendicular stimulation angle to the midline (90°) or the slightly dorsolateral angle (135°) and the stimulation angles ranging from 225° to 315°. * = p < .05.

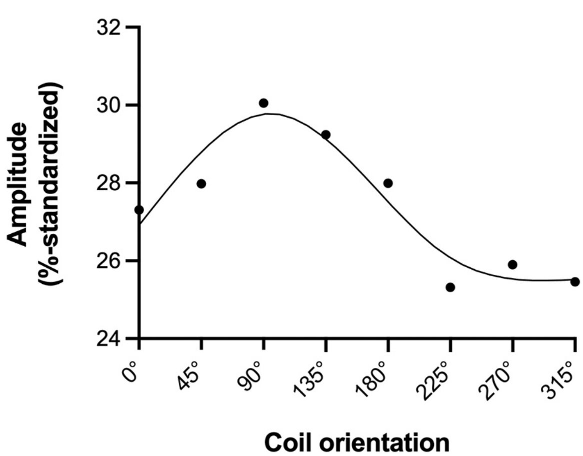

Fig. 4. Illustration of the spline curve fitted to the standardized mean amplitude values as a function of stimulation angles.

stimulation was applied to six stimulation points surrounding the identified motor hotspot. The results demonstrated that stimulation at the site immediately lateral to the hotspot elicited significantly higher motor evoked potentials (MEPs) compared to the other stimulation points. The hotspot itself was consistently located in the precentral gyrus and the stimulation points facing the midline did not cross it. In this study, the optimal stimulation site for the leg area was located between the hotspot and the immediately lateral stimulation point. Considering the anatomical location of the initially identified hotspot and the grid spacing of 3.7 mm (Fig. 1), this region corresponds to an anatomical area approximately 6–13 mm lateral to the midline. A descriptive analysis of MEP amplitudes as a function of stimulation direction

Table 1
Provides subject-specific parameters, including the minimum and maximum amplitude responses, resting motor threshold values determined at the identified hotspot as well as the individual optimal coil orientations.

ID	Min. Amplitude [μV]	Max. Amplitude [μV]	Hotspot Resting Motor Threshold (RMT) [%]	Optimal Coil Orientation
1	289	2480	73	90°
2	174	2062	70	90°
3	103	1368	69	90°
4	206	1695	53	225°
5	50	1503	71	135°
6	50	666	59	90°
7	140	1169	52	135°
8	122	989	57	0°
9	51	851	80	90°
10	50	1322	61	90°
11	52	772	66	315°

revealed a sinusoidal response pattern. The highest MEP amplitudes were observed at stimulation angles perpendicular (90°) and dorsolateral (135°) to the midline, whereas the lowest amplitudes occurred at angles inverse-orthogonal to the midline (225–315°). Statistical analysis confirmed a significant difference in MEP amplitudes between stimulation directions of 90°–135° and those between 225°–315°, whereas no significant differences were found between 90°–135° and the neighboring angles. However, in an individual analysis for each participant, a statistically significant amplitude difference dependent on stimulation angle was observed in only four out of the eleven participants. The remaining participants showed no statistically significant differences in the ANOVA testing and therefore no consistent preference for a specific global stimulation orientation.

When reviewing the literature on coil orientation for TMS mapping of the leg area, only a limited number of studies have been conducted, and their findings remain inconsistent. In line with our results, Terao et al. reported that a current directed anteriorly or toward the hemisphere contralateral to the recorded muscle was more effective in eliciting larger motor responses than a posteriorly directed current or one oriented toward the ipsilateral hemisphere (Terao et al., 2000). This was observed using both a figure-of-eight coil and a double-cone coil. Similarly, Richter et al. demonstrated that optimal stimulation responses were achieved when the coil was positioned perpendicular to the postcentral gyrus using a biphasic pulse (Richter et al., 2013). In their nomenclature, 0° corresponded to a lateral-to-medial current direction toward the midline, with the optimal coil orientation identified at 30°, which corresponds to 45° in our nomenclature. Notably, Richter et al. utilized MRI guidance to determine the optimal anatomical location and systematically varied the coil orientation in 10°-20° increments, testing a total of 15 different orientations. In contrast, other studies, such as that by Hand et al., employed a more limited approach, investigating only two different coil orientations using single- and paired-pulse TMS (Hand et al., 2020). Their comparison of posterior-anterior and mediolateral orientations for TA mapping revealed that resting motor thresholds (RMTs) and test TMS intensity were significantly lower for mediolateral stimulation in a single-pulse setup (all p < .05).

Smith et al. also reported that a medial-to-lateral current flow over the medial wall of the precentral gyrus, directed away from the interhemispheric fissure, resulted in lower resting motor thresholds (RMT) and shorter motor evoked potential (MEP) latencies (Smith et al., 2017). This finding, based on single-pulse TMS in a cohort of 22 participants, contrasts with our results. However, their study tested only two coil orientations—posterior-anterior and medial-lateral—potentially limiting the scope of comparison. Another possible explanation for this discrepancy is the absence of MRI guidance in their methodology.

In our own research, we have observed that various factors, such as MEP amplitude and RMT, can change considerably with the distance from the motor hotspot, sometimes to a significant extent. Given these variations, we consider the use of a neuronavigated system to be beneficial in optimizing stimulation accuracy.

Although the anatomical location differs, it is valuable to consider similar studies examining the hand region. Souza et al., along with other researchers, found that the optimal stimulation direction for the hand area was either perpendicular to the midline or slightly deviated from it, such as at an angle of 45° (Balslev et al., 2007; Bashir et al., 2013; Janssen et al., 2015; Souza et al., 2018).

A review of the literature highlights several studies that have investigated the optimal stimulation site for lower limb representation. In a navigated TMS (nTMS) study mapping the tibialis anterior (TA) in a cohort of 59 healthy subjects, Niskanen et al. reported that optimal stimulation is achieved near the longitudinal fissure (Niskanen et al., 2010). Additionally, they found that variations in localization did not correlate with age or head circumference. Sivaramakrishnan et al. examined the spatial localization of the TA representation in both healthy individuals (n = 32) and post-stroke patients (n = 42). In the healthy cohort, the optimal coordinates were identified as 1.6 cm lateral and 0.8 cm posterior to the vertex, whereas in lesioned hemispheres, the coordinates shifted to 1.25 cm lateral and 0.5 cm posterior (Sivaramakrishnan et al., 2016). Similarly, in a TMS study involving 16 healthy participants, Davies et al. used a 9 × 7 cm grid (63 stimulation sites) to map lower limb representation (Davies, 2020). She reported that the mean distance of the motor hotspot from the midline was approximately 10 mm for the plantar flexors and quadriceps and 15 mm for the hamstrings. However, she also emphasized the challenges of reliably mapping leg representation due to substantial interindividual variability.

It is essential to recognize that these localizations pertain specifically to TMS stimulation and are best interpreted as projection effects. Neurophysiological and neurosurgical studies utilizing direct cortical stimulation have demonstrated that the functional representation of the leg area is primarily located near the medial wall of the hemisphere (Sato et al., 2022). Due to the perpendicular placement of the stimulation coil on the curved skull, the electromagnetic impulse travels through the precentral gyrus before reaching the leg area in the medial wall. Consequently, the digital cortical marking of the positive response reflects the site of the first gyral “contact” rather than the actual functional representation. This consideration has also been noted by Richter et al. in their hotspot determination (Richter et al., 2013).

From the authors’ perspective, the finding is consistent with neuroanatomical considerations: Due to the convexity of the skull, the stimulation direction is slightly angled. Therefore, to effectively stimulate neurons in the leg area along the interhemispheric fissure, the stimulation site must be located approximately 1 cm lateral to the interhemispheric fissure in order to reach these neurons at depth.

Regarding the averaged response potentials, the differences between stimulation points and angles were relatively small in purely quantitative terms, despite reaching statistical significance. Given that TMS intensity decreases with depth and the leg area relevant for TMS is located significantly deeper compared to the hand area, it is plausible that the stimulation may not be sufficiently strong to consistently produce large potential differences depending on the stimulation direction (Deng et al., 2013). Due to the anatomical course of the motor cortex along the medial wall and within the depth of the interhemispheric fissure, the leg area — unlike the hand area — is oriented more longitudinally rather than approximately perpendicular to the stimulation direction. Consequently, it is challenging to selectively target individual leg muscles located deep within the interhemispheric fissure using TMS (Kesar et al., 2018; Smith et al., 2017). Additionally, the considerable inter-individual variability of the anatomical motor representation further complicates the ability to obtain statistically robust results across multiple subjects (Sivaramakrishnan et al., 2016; Thielscher et al., 2011; Weiss et al., 2013).

Recent research, such as the work by Gordon et al. has significantly advanced our understanding of the motor cortex beyond the classical somatotopic organization proposed by Penfield’s homunculus (Gordon et al., 2023). Their findings suggest that the motor cortex is not simply a continuous representation of body parts but rather interspersed with inter-effector regions, which play a crucial role in integrating motor control and cognitive action planning. These regions, which alternate with effector-specific areas (foot, hand, and mouth), exhibit distinct connectivity patterns and are functionally linked to the cingulo-opercular network, a key structure involved in action planning, physiological control, and error processing. Considering these insights, it is plausible that the stimulation outcomes in TMS mapping of the lower limb motor representation are not solely determined by direct effector activation but may also be influenced by these inter-effector regions. Given that these regions facilitate coordination between different motor areas, their activation could modulate response potentials, thereby contributing to variations in motor threshold and evoked potential amplitudes. This could, in part, explain the observed discrepancies between studies focusing on lower limb representation, particularly regarding optimal coil orientation and stimulation site. Furthermore, the findings by Gordon et al. highlight the importance of viewing motor cortex stimulation within a broader network framework. Instead of being confined to isolated effector sites, TMS effects may propagate through interconnected cortical networks, affecting both local and global motor control mechanisms. This aligns with our observation that stimulation at sites immediately lateral to the hotspot elicits stronger responses, possibly due to the involvement of adjacent integrative regions. Consequently, future studies may benefit from incorporating these novel insights into TMS protocols, potentially optimizing stimulation parameters for more precise and functionally relevant motor mapping.

In summary, we were able to further narrow down both the anatomical stimulation area and the preferred stimulation angle for the lower extremity. However, it remains essential to account for individual variability in practical applications (Gomez-Tames et al., 2018).

4.1. Limitations

It should be noted that there are certain limitations to the work that has been carried out. First, the sample size (11) was relatively small. A larger number of subjects would have increased the statistical significance of the findings. Additionally, while our mapping study included hotspot determination, this aspect was not incorporated into the rotation study. Finally, the lack of randomization in the stimulation angles may have contributed to cumulative stimulation effects.

5. Conclusion

We conducted a study to optimize TMS mapping of motor function in the foot area, aiming to identify the optimal stimulation site and coil orientation. Our findings indicate that the most effective configuration is a coil alignment perpendicular to the falx cerebri, positioned approximately 6–13 mm lateral to the midline. We anticipate that these results will enhance TMS mapping in this region, ultimately enabling faster and more precise assessments in clinical practice.

CRediT authorship contribution statement

Gregor Durner: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Conceptualization. **Thomas Kammer:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Jan Coburger:** Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Sabrina Lorenz:** Validation, Methodology, Conceptualization. **Andrej Pala:** Writing – review & editing, Formal analysis. **Christian Rainer Wirtz:** Validation, Supervision. **Ralf Becker:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Formal analysis, Data curation.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used the applications DeepL and ChatGPT in order to improve the readability of the text. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Declaration of Competing Interest

We hereby declare, that none of the authors of "Investigation into the influence of stimulation area and coil orientation on the results of navigated transcranial magnetic stimulation (nTMS) mapping of lower limb intracortical excitability" have potential conflicts of interest. This includes employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications, registrations, grants or any other funding from public, commercial, or not-for-profit sectors.

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Data Availability

Data will be made available on request.

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