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Intra-Rater Reliability and Validity of Neuro-Mobinavigation: A Mobile App and Laser-Guided System of Motor HotSpot Localization

Abstract

Background: Optimal transcranial magnetic stimulation (TMS) efficacy depends on precise coil placement and orientation, as even minor deviations can significantly change the excitation evoked when stimulating the primary motor cortex (M1). To compare the intra-rater reliability of a novel method for consistent TMS coil orientation over a predetermined hotspot in M1, and to benchmark its accuracy against non-navigated method.

New Method: A three-step method was employed. First, a laser-guided-system stabilized head position. Second, a mobile-app monitored coil tilt and orientation. Finally, coil position was marked on participant's head cap for visual reference for both methods. Twenty-nine healthy-participants underwent six TMS blocks of 20 pulses each. Six experimental blocks, alternating between non-navigated-TMS and Neuro-Mobinavigated-TMS, to investigate the parameters of motor evoked potential (MEP). The experimental blocks were quasi-randomized with a five-minute interval.

Results and comparison with existing method(s): The novel method demonstrated excellent intra-rater reliability (ICC = 0.95, 95% CI: 0.90-0.97) compared to moderate intra-rater reliability of the non-navigated TMS (ICC = 0.73, 95% CI: 0.57-0.85) for MEP peak amplitude. Repeated measures ANOVA for novel-method showed consistent peak amplitude across three blocks ($p = 0.078$), non-navigated TMS exhibited significant variations ($p < 0.0001$). Wilcoxon signed rank test revealed significantly higher mean peak amplitudes for the novel method (1.02 ± 0.74) compared to non-navigated TMS (0.78 ± 0.61) ($p < 0.001$), small effect size ($r = 0.35$).

Conclusions: Neuro-Mobinavigation is superior to non-navigated method and provides a reliable and cost-effective alternative for MEP studies where gold standard neuronavigation is not available.

1. Introduction

Transcranial magnetic stimulation (TMS) employs magnetic fields to generate electrical currents in the brain, providing a means to investigate and alter cortical functions (Hallett, 2007). TMS pulses, when applied with sufficient intensity to the motor cortex, cause neuron depolarization. This can result in either trans-synaptic activation of pyramidal cells through interneurons or direct activation of pyramidal cells when the stimulation's intensity and direction are optimized (Di Lazzaro, 2004; Di Lazzaro et al., 2004). The action potentials generated in the pyramidal cells then travel down the corticospinal tract in volleys and form synapses with spinal motoneurons (Day et al., 1987; Rothwell et al., 1987). Activation of these motoneurons induces muscle responses, referred to as motor evoked potentials (MEPs), which can be measured through electromyography (EMG).

Accurate TMS coil positioning is crucial for effective stimulation. Securing a precise and reliable TMS coil placement is a complex task, as the induced electrical activity rapidly diminishes with distance from the coil's center (Conforto et al., 2004). Proper coil-to-head contact and three-dimensional orientation relative to the patient's head are essential for optimizing stimulation efficiency. Several independent factors can influence stimulation efficacy. Even small gaps between the coil and the scalp can significantly reduce cortical stimulation intensity (Julkunen et al., 2009; Sparing et al., 2008), potentially compromising clinical outcomes (Collins et al., 2024; Koski et al., 2007). Coil orientation is at least as critical as its position. Angle of the coil plays an important role, and a 45-degree angle between the handle of the butterfly coil and midsagittal plane generally considered optimal for generating an excitation perpendicular to the motor cortex (Opitz et al., 2013; Sakai et al., 1997). Similarly, a tangential coil orientation relative to the scalp is ideal; misalignment or non-

tangential positioning away from desired target can diminish efficacy (Brasil-Neto et al., 1992).

The assumption that the coil should be placed directly above the target brain area is often inaccurate due to the brain's irregular topography (Brett et al., 2002; Patel et al., 2014). Moreover, errors in coil orientation can further contribute to targeting inaccuracies (Sparing et al., 2010).

To aid in coil localization, researchers and clinicians have traditionally employed elastic (swimming) caps marked with reference points to approximate the target area (Sparing et al., 2008). These caps utilize 10–20 system which relies on cranial landmarks (e.g., nasion, inion, and preauricular points), which help guide coil placement by providing relative positions for orientation (Meyer et al., 1991). Although this method is cost-effective and does not require specialized training, it remains imprecise. The absence of objective feedback regarding the coil's exact position and contact with the intended target introduces significant potential for error (Conforto et al., 2004), which can negatively impact clinical outcomes (Collins et al., 2024), since observing both of the coil position and orientation relative to the points marked on the swimming cap only by visual observation is generally inadequate to hold the coil in a fixed position throughout the study session.

This lack of precision leads to considerable variability in coil placement between operators, within a single session, and across multiple treatment sessions (Julkunen et al., 2009). As a result, the therapeutic efficacy of TMS may be compromised. Furthermore, conventional procedures do not offer continuous feedback on coil positioning during treatment. Even small movements of the patient's head - whether due to turning, coughing, sneezing, or shifting in the chair - can alter the coil's alignment with the target area, potentially diminishing the clinical effectiveness. Therefore, it is crucial to provide real-time feedback on coil positioning not only during measurement of neurophysiological parameters, but also throughout treatment session.

A more advanced method for reliably positioning the TMS coil is neuronavigation (Ettinger et al., 1998), is considered the gold standard for targeting the primary motor cortex (M1) and is the preferred technique for maintaining consistent coil positioning over the hotspot which result in stable and excellent reliable TMS measures (Therrien-Blanchet et al., 2022) (Cincotta et al., 2010). In this setup, a head tracker equipped with calibrated reflective fiducial markers is affixed to the participant's head. These markers are monitored by an infrared camera, enabling real-time co-registration of the participant's head with their anatomical magnetic resonance imaging (MRI) scans through landmarks on the ears and nose (Ruohonen & Karhu, 2010). Moreover, a tracker with reflective markers is attached to the TMS coil, allowing the operator to continuously observe and adjust the coil's positioning relative to the participant's head in real time (Caulfield et al., 2022).

Despite its precision (Julkunen et al., 2009), neuronavigation is typically reserved for research in universities and centers, compared to limited availability in clinics due to several limitations. It is not widely available because of its high cost which might exceed $50,000 (Roumengous et al., 2021; Vaghefi et al., 2015), the time required to set up and operate, and the need for specialized training to proficiently use the software. Moreover, its routine clinical application is impractical, as patients must wear a head tracker throughout the session, which can cause discomfort and limit relaxation (McMackin et al., 2024).

Finally, the number of studies reporting a specific navigation method, and its subtypes increased threefold, rising from 9 studies between 2002 and 2012 to 41 studies between 2013 and 2021. In contrast, studies on non-navigated methods decreased by approximately 60%, from 33 studies between 2002 and 2012 to 14 studies between 2013 and 2021 (Sondergaard et al., 2021).

In summary, the limitations of current coil positioning methods underscore the need for a novel approach. Ongoing research efforts are focused on developing alternatives that are both

accessible (Ambrosini et al., 2018) and cost-effective (Rodseth et al., 2017; Roumengous et al., 2021; Washabaugh & Krishnan, 2016). An ideal solution would balance the advantages and disadvantages of both neuronavigation and traditional (non-navigated) procedures. Such a method should be easy to implement and use in clinical settings, affordable for widespread adoption, and capable of providing continuous, accurate, and precise feedback on coil placement throughout the TMS session. Additionally, real-time monitoring would allow for necessary adjustments, ensuring that the optimal stimulation intensity is consistently delivered to the targeted brain region (Sparing et al., 2008).

The primary objective of this study was to evaluate the feasibility and applicability of a novel three-step system as a valid, practical, and accessible alternative to neuronavigation-guided TMS. This system comprises: (1) a laser-guided mechanism for stabilizing head position, (2) a mobile application to monitor coil tilt and orientation, and (3) marking the coil position on the participant's head cap for visual reference. The effectiveness of this system was compared with the non-navigated TMS method. The secondary objective was to assess the intra-rater reliability and consistency of MEP parameters within the primary motor cortex (M1) across consecutive repeated measures using both Neuro-Mobinavigated TMS and non-navigated TMS methods. We hypothesized that the novel three-step approach named as (Pharos system) would allow for consistent and precise maintenance of the TMS coil's orientation, and tilt over a pre-determined hotspot in M1. This precision would be evidenced by non-significant differences in MEP parameters across repeated TMS stimuli, even in the presence of potential coil shifts or participant head movements, achieving substantial to excellent intra-rater reliability. Furthermore, we predicted that the enhanced precision of the Neuro-Mobinavigated TMS system would result in significantly higher mean MEP peak amplitudes compared to the non-navigated TMS method when targeting the M1, due to relative positional coil stability throughout the session provided by the novel system.

2. Methods

2.1. Participants

The study was approved by the Koç University Biomedical Research Ethics Board (Protocol code: 2024.242.IRB2.107), adhered to the Declaration of Helsinki. A total of 29 healthy participants, all aged 18 or older and confirmed to be in good health through a medical examination of their general, neurological, and cognitive functions, were recruited for the study. The exclusion criteria were as follows: (1) clinical signs of cardiovascular or cerebrovascular disease; (2) current or past neurological disorders affecting cognitive function, such as epilepsy, stroke, brain lesions, or multiple sclerosis; (3) history of neurosurgical procedures or head injuries leading to neurological deficits; (4) current or previous diagnoses of major depression, bipolar disorder, psychotic disorders, or other significant psychiatric conditions; (5) current use of psychotropic medications, including serotonin-specific reuptake inhibitors (SSRIs); (6) use of any medications known to contraindicate TMS; and (7) presence of intracranial abscesses, tumors, surgeries, or metallic/electronic implants (such as metallic head implants or electronic devices like cardiac pacemakers) (Rossi et al., 2021); ~~and (9) chronic use of medications, particularly sedatives or sleep aids, with contraceptive use permitted.~~ Hand dominance was evaluated using the Turkish version of the Edinburgh Handedness Inventory (EDI) (Tuna, 2020). Baseline characteristics of the subjects are summarized in **Table 1**.

Table 1 Baseline characteristics of participants.

		Study participants
Sample size		29
Age (years)**		23.00 [21.00, 26.00]
Gender	Male n (%)	17 (58.6%)
	Female n (%)	12 (41.4%)
Level of activity	≥150min/week n (%)	15 (51.7%)
	<150min/week n (%)	14 (48.3%)
Smoking	Non-smoker n (%)	19 (65.5%)
	Smoker n (%)	10 (34.5%)
Handedness (right: left)		28:1
EHI LQ (%)		100 [-100, 150]
Body mass (kg)**		72 [60, 80]
Height (cm)*		170 (11)
BMI (kg/cm2) **		24 [22.3, 26]
RMT (%)*		48.03 (8.62)
~~**MEP (RMT 120%)***~~		~~57.64 (10.34)~~

Data expressed as * mean [standard deviation (SD] for normally distributed variables, or **median [min - max] for non-normally distributed variables

P -value (<0.05). BMI: Body Mass Index; EHI LQ: Laterality Quotient assessed by Edinburg Handedness Inventory RMT: Resting Motor Threshold~~; MEP: Motor Evoked Potential~~

2.2. Sample size calculation

Following estimation approach (Borg et al., 2022), the current proposed study aimed to estimate the true Intraclass Correlation Coefficient (ICC) anticipates a value of $\rho = 0.9$. We desire a 95% confidence interval (CI) with a total width of 0.15 (from 0.80 to 0.95). To achieve this with an 80% assurance probability (meaning an 80% chance of obtaining the desired width) and considering 3 repeated measurements per subject ($k = 3$), the sample size needed for this study was 29.

2.3. Recruitment procedures

Participant recruitment for this study occurred between July to August 2024 at the Cognition & Motion Analysis Laboratory, Koç University Research Center for Translational Medicine (KUTTAM). Upon arrival, each participant completed a questionnaire to screen every participant for any risk factors or contraindications to TMS (Rossi et al., 2011), participants with any risk factors were excluded.

2.4. Experimental set-up

Magnetic stimuli (DuoMAG XT, DEYMED Diagnostic s.r.o., Hronov, Czech Republic) were delivered using biphasic pulses from a butterfly-shaped, figure-of-eight coil with two 70mm windings (DuoMag 70BF liquid-cooled coil). Participants sat comfortably in a chair with a headrest, arms bent at about 90º, and hands resting on a pillow placed in their lap. Each participant also wore a cotton cap. The coil was positioned tangentially to the scalp, with the handle angled backward and rotated 45º away from the midsagittal line to direct a posterior-to-anterior current flow across the precentral gyrus.

During stimulation, surface electromyography (EMG) was continuously recorded using disposable, pre-gelled, 20mm Ag/AgCl disc electrodes and a ground plate electrode (Natus® Medical Incorporated, Wisconsin, USA). The active electrode was placed over the belly of the first dorsal interosseous (FDI) muscle in the dominant hand, the reference electrode on the second metacarpophalangeal joint, and the ground electrode on the dorsal side of the ulnar bone of the same hand. EMG signals were filtered (8–500Hz), amplified, displayed, and stored for later analysis. Participants were monitored for drowsiness and instructed to keep their eyes open throughout the procedure. Muscle relaxation was ensured by visually checking the EMG activity continuously (Rossini et al., 2015), MEPs were excluded if there was significant muscle activity (greater than 20 microvolts) in the FDI muscle during the 50 milliseconds before the TMS pulse was delivered.

2.5. Novel Neuro-Mobinavigation Method

Our study employes a novel three-step approach for maintenance of head position, TMS coil position and orientation to ensure precise positioning of the TMS coil over a pre-determined hotspot (**Figure 1**), the setup time for the Neuro-Mobinavigation method is less than 1 minute.

Step 1: Maintaining Head Position with a Laser Guide

We attached a laser diode to each participant's forehead. The participant was instructed to target the laser beam to a specific point of choice among several options found on a board faced to the participant (see Figure 1). That chosen target represented the most comfortable head and neck position for the subject. Participants were then instructed to maintain this position throughout the TMS session, guided by the laser light pointing at the target. This primary step aimed to minimize head movement during the assessment.

Step 2: Monitoring Coil Orientation with a Mobile App

We utilized a pre-developed mobile application with a 3D movement sensor (incorporating X, Y, and Z-axis inclinometers) installed on an iPhone 7 Plus. The mobile phone was positioned horizontally and attached parallel to the TMS coil surface, separated by a protective foam case measuring 15 centimeters in length, 10 centimeters in width, and 5 centimeters in height. The application measured the static tilt angle of the phone (relative to gravity), indicating how much the phone deviated from a flat surface (the coil surface) in degrees (**Figure 2**). Upon locating the hotspot, the investigator recorded and saved the current tilt angle and orientation of the coil as a reference point for the entire session on the mobile application. This reference served as a guide to relocate the coil's position and orientation if it became displaced. This secondary step aimed to fix the coil orientation and tilting angle in the space over the head during the assessment.

Step 3: Marking Coil Position

Once the coil position was confirmed and stabilized, we drew a line around the coil's circumference on the participant's cotton cap to mark its precise location on their head. This last step aimed to provide a visual confirmation of the coil's correct position over the head during the assessment.

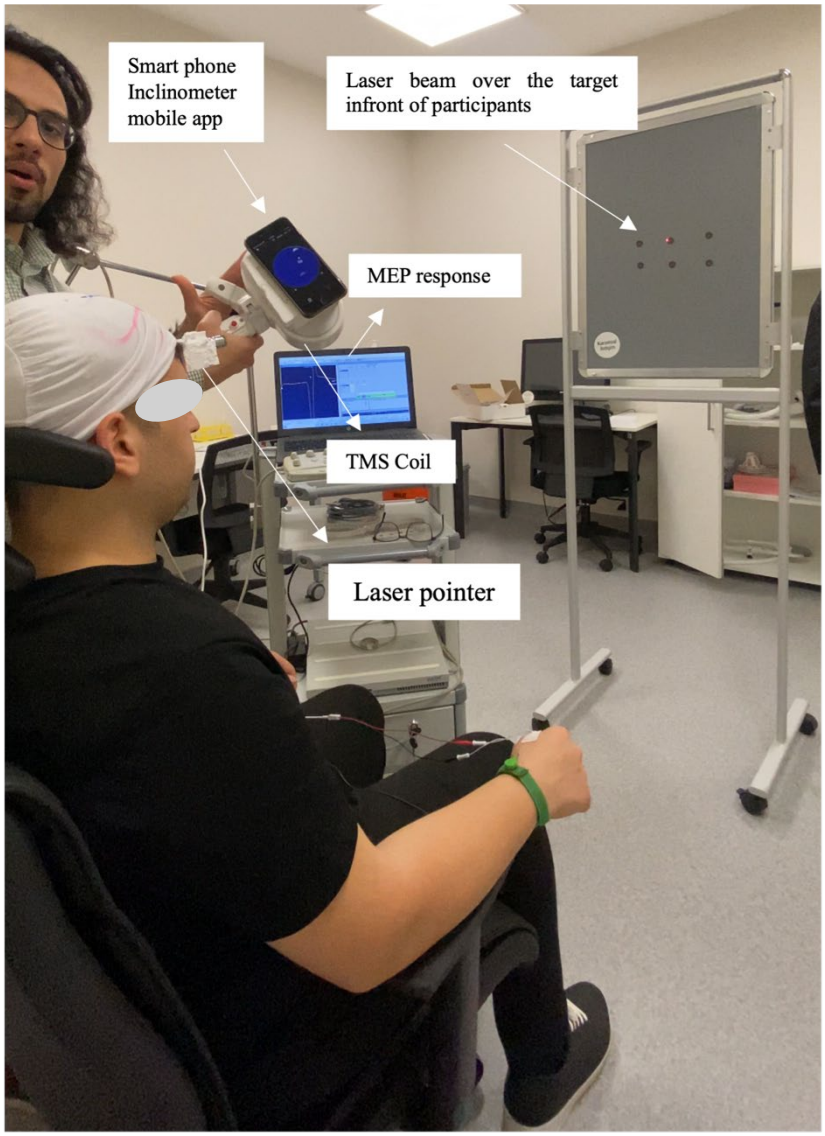


Figure 1 Novel Neuro-Mobinavigation method, three steps approach.

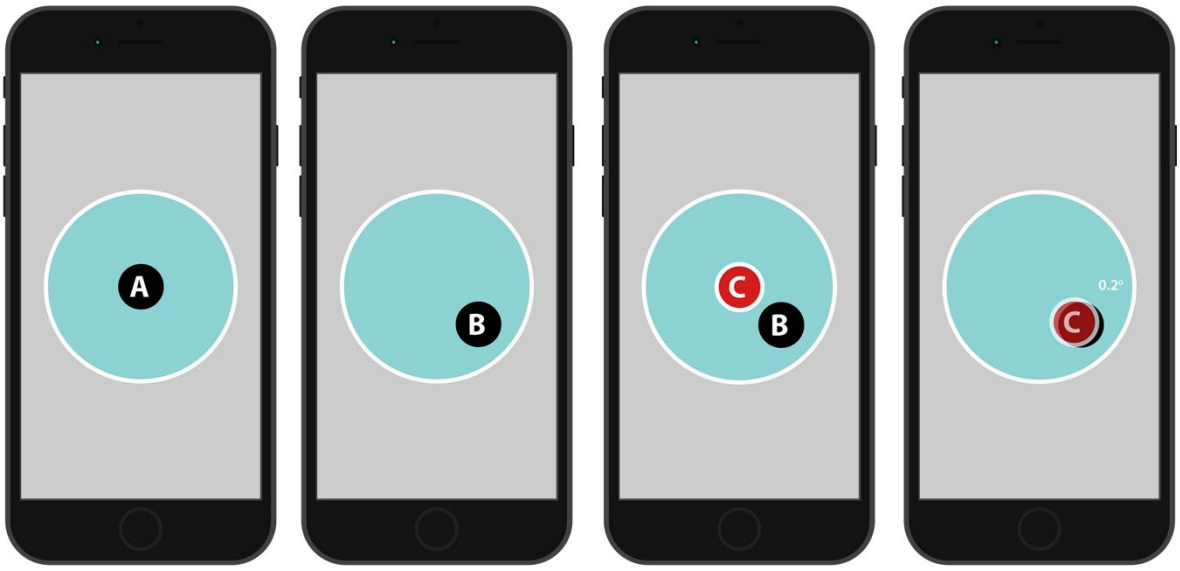


Figure 2 This figure illustrates the user interface of the mobile application. A shows the initial coil orientation before attempting to locate the hotspot. B represents the coil orientation and tilting angle once the hotspot is identified, which remains fixed throughout the TMS session. C depicts the coil orientation during manual manipulation to reach the hotspot represented by point B. Finally, C is positioned close to B (hotspot), with 0.2° representing the angular error relative to the hotspot. 0.2° is the value of error/deviation away from the initial hotspot orientation.

2.6. Single-pulse TMS

The ideal scalp location (HotSpot) for stimulating the first dorsal interosseous (FDI) muscle in the dominant hand was determined by finding the site where TMS consistently elicited motor evoked potentials (MEPs) with the largest and most consistent peak-to-peak amplitude in the dominant hemisphere (Rossini et al., 2015). Initially, the target area was set approximately 5 cm lateral and 1 cm ventral to the vertex for hotspotting.

The resting motor threshold (RMT) was then assessed while ensuring the target muscle was fully relaxed, with no voluntary EMG activity detected at high gain (Rossini et al., 2015). The RMT for each participant was established by adjusting the stimulator output in 1% increments or decrements until the lowest intensity was found that consistently produced MEPs with a peak-to-peak amplitude of at least 50 μV (0.05 mV) in five out of ten consecutive trials (Balloff et al., 2022; Rossini et al., 2015).

2.7. Experimental design and procedure

After identifying the hotspot and determining the resting motor threshold (RMT), each participant underwent six TMS blocks consisting of 20 pulses each to achieve reliable MEP measurements (Biabani et al., 2018; Chang et al., 2016), delivered at 120% of RMT. These six experimental blocks alternated between non-navigated TMS (n=3) and Neuro-Mobinavigated TMS (n=3) (**Figure 3**). The experimental blocks were quasi-randomized with a five-minute interval between each block. In the absence of EMG activity of FDI, TMS pulses were applied at every 5–6 s at 120% of RMT to determine the take-off latency (ms), peak amplitude (mv), negative amplitude area (mv*ms), peak to peak amplitude (mv), and total area (mv*ms) of MEPs.

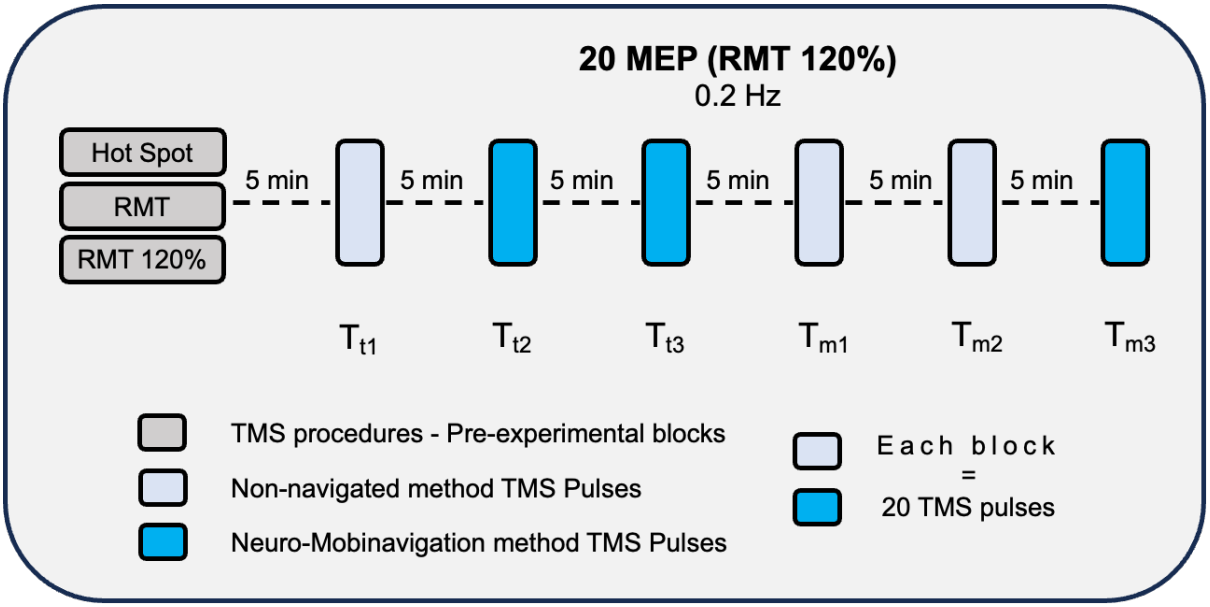


Figure 3 Experimental design and procedure and TMS pulses sequence of each repetition, blocks were quasi-randomised. Tt: non-navigated Method, Tm; Novel Neuro-Mobinavigation method.

2.8. Data and statistical analysis

R-Studio® (Version 4.3.3, RStudio, PBC, Boston, MA, USA), SPSS® statistical software (Version 29.0.1.0, SPSS Inc, Chicago, IL, USA), and JASP® (Version 0.19.0.0, JASP Team, Amsterdam, Netherlands) were used for data analysis and visualization. Descriptive statistics were generated for participant characteristics, such as age, height, body mass, and activity level. The Shapiro-Wilk test was used to evaluate the normality of the data distribution. For data following a normal distribution, means and standard deviations were reported, while medians and interquartile ranges were used for data that did not follow a normal distribution. All measurements from 20 consecutive TMS pulses for each of the six blocks were included in the analysis, regardless of whether an appropriate response was triggered or not (Chang et al., 2016). For each participant, the average parameter was calculated for subsets of consecutive stimuli $\boldsymbol{MEP_n} = \frac{MEP_1 + \cdots + MEP_n}{n\ (n=20)}$, where n: 2...20. In this experiment MEP_n can be assumed as most accurate estimate of the true underlying MEP value (Cuypers et al., 2014).

All MEP analyses were conducted by the same researcher -one year experience- to avoid inter-rater variability.

To assess intra-rater reliability, we calculated the intraclass correlation coefficient (ICC) using a two-way mixed-effects model with absolute agreement. Following established guidelines, ICC values were interpreted as follows: excellent (> 0.9), good (0.75-0.9), moderate (0.5-0.75), and poor (< 0.5) (Koo & Li, 2016). In addition, a Bland-Altman plot was employed to compare the mean differences and 95% limits of agreement (LOA) between the MEP means across the three measurement blocks (Bland-Altman plot only compare maximum two points at the same plot) (Bland & Altman, 2007). Narrow LOA in a Bland-Altman plot indicate high agreement between the two compared measures. In this context, a narrow LOA suggests that the differences between the MEP means of the blocks were minimal and consistent, indicating high reliability and consistency in the rater's measures across time. Conversely, a wide LOA would

suggest substantial differences between the blocks, potentially indicating low reliability and inconsistency. The upper and lower boundaries of the 95% LOA were calculated as the mean values from the two measures ± 1.96 standard deviations. A smaller mean difference and narrower 95% LOA were indicative of better agreement between the measurements.

To compare the two methods, a Wilcoxon signed rank test was employed. For each participant, the average MEP parameters was calculated for subsets of consecutive stimuli of all three blocks (60 pulses), $\boldsymbol{MEP_n} = \frac{MEP_1 + \cdots + MEP_n}{n\ (n=60)}$, where n: 2...60. Additionally, the stability of all MEP parameters was evaluated by analyzing the mean parameters of the first, second, and third blocks of MEPs recorded using both non-navigated and Neuro-Mobinavigated TMS. Repeated-measures analysis of variance (ANOVA) was used for this comparison, considering the data was non-normally distributed data the Friedman test was applied as non-parametric test, in addition to effect size (r) was calculated.

A significance level of $p < 0.05$ was chosen for all statistical tests.

2.9. Methodological quality

The present intra-rater reliability study adhered to the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) for the reporting, interpretation, and synthesis of all study steps, including hypothesis formulation, methods explanation, and results discussion (Kottner et al., 2011). The GRRAS guidelines encompass 15 items to ensure comprehensive and transparent reporting of reliability studies. Additionally, the methodological quality of this study was assessed using a standardized checklist specifically designed for studies employing TMS over the primary motor cortex (M1) (Chipchase et al., 2012). This checklist includes 30 items to evaluate the rigor and consistency of TMS implementation in research.

3. Results

3.1 Intra-rater reliability

For the pooled assessment of intra-rater reliability, the novel Neuro-Mobinavigation method demonstrated excellent intra-rater reliability for MEP peak amplitude (ICC = 0.95, 95% CI: 0.90-0.97) compared to moderate intra-rater reliability of the non-navigated method (ICC = 0.73, 95% CI: 0.57-0.85) for MEP peak amplitude, **Table 2**.

We performed Bland–Altman analysis to measure the degree of difference between the mean peak amplitudes of each block. Bland–Altman plots showed that the mean difference values of the Neuro-Mobinavigation blocks fall in a horizontal line near to the zero value, whereas non-navigated method's blocks were scattered (**Figure 4**). Accordingly, there was a higher level of agreement (LOA) for blocks measured by the Neuro-Mobinavigation method compared to the non-navigated method (**Table S1).**

Table 2 Intra-rater reliability of each method

Proposed measurement methods	**Novel Neuro-Mobinavigation method**					**Non-navigated method**				
MEP parameters	Take-off Latency (ms)	Peak Amp (mv)	Negative Peak Area (mv*ms)	Peak to Peak Amp (mv)	Total Area (mv*ms)	Take-off Latency (ms)	Peak Amp (mv)	Negative Peak Area (mv*ms)	Peak to Peak Amp (mv)	Total Area (mv*ms)
Median (IQR)	22.33 (1.63)	0.87 (0.74)	2.35 (2.46)	1.27 (1.14)	3.92 (4.02)	21.6 (2.71)	0.64 (0.70)	1.82 (2.16)	1.02 (1.05)	3.44 (3.36)
95% CI (lower - upper bound)	0.97 - 0.99	0.90 - 0.97	0.88 - 0.97	0.91 - 0.98	0.90 - 0.97	0.61 - 0.87	0.57 - 0.85	0.52 - 0.83	0.59 - 0.86	0.53 - 0.83
ICC	0.95[a]**	0.95[a]**	0.94[a]**	0.95[a]**	0.95[a]**	0.76[b]**	0.73[c]**	0.697[c]**	0.749[c]**	0.70[c]**

Two-way mixed effects model, and ICC using an absolute agreement definition.
CI, confidence interval; ICC, intraclass correlation coefficient; IQR, Interquartile Range
[a] Excellent correlation (> 0.9); [b] Good correlation (0.75 - 0.9); [c] Moderate correlation (0.5 - 0.75); [d] poor correlation (< 0.5)
**p<0.001; p< 0.05 indicates significant correlation

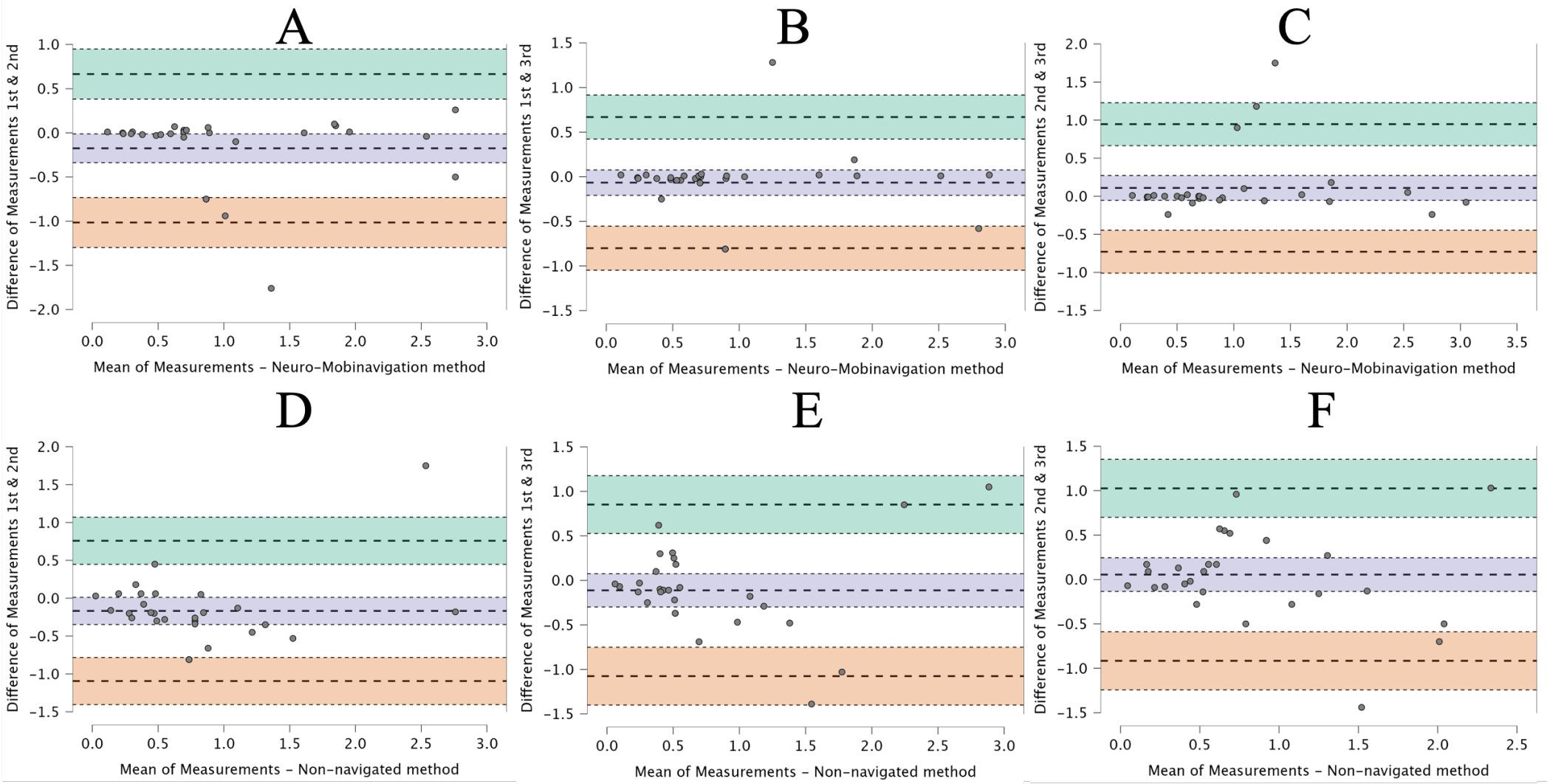


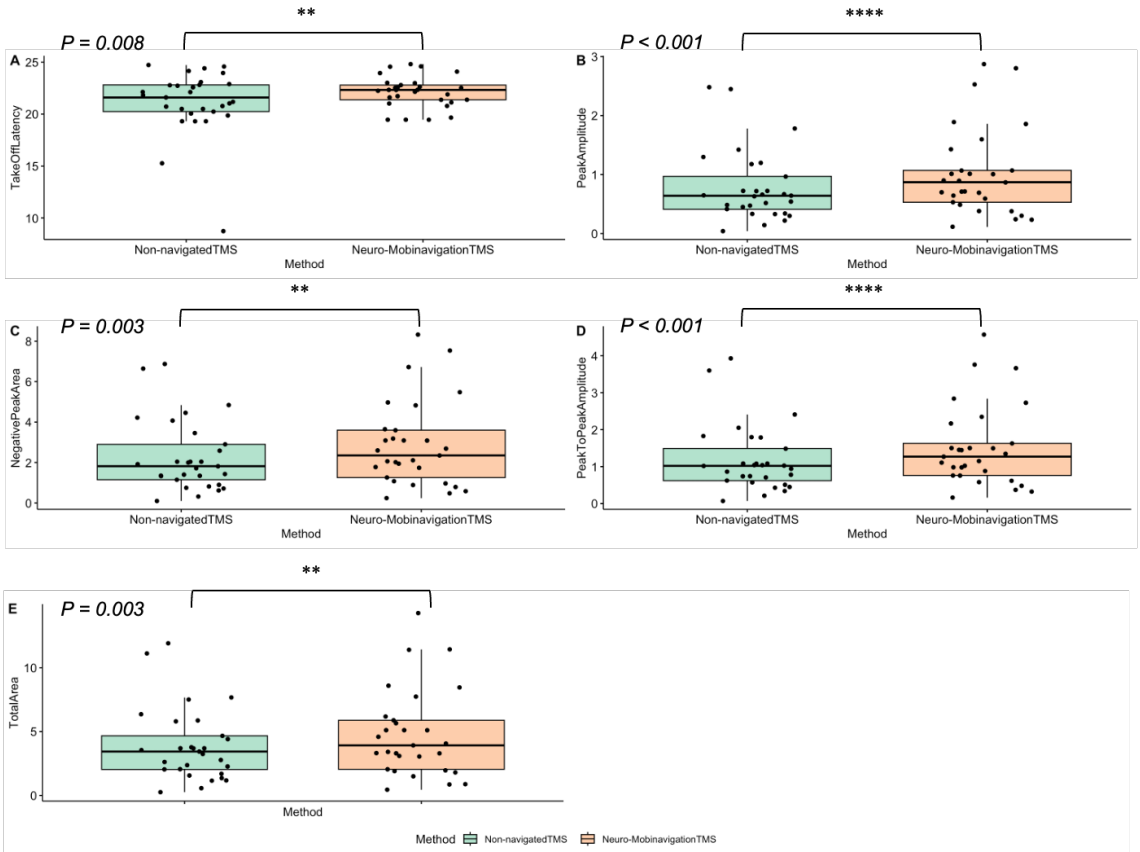
Figure 4 Bland–Altman plots illustrating the differences in MEP amplitudes between blocks measured by the same rater for the Neuro-Mobinavigation method (A-C) and the non-navigated method (D-F). Plots A, B, and C show comparisons between the 1st and 2nd blocks, 1st and 3rd blocks, and 2nd and 3rd blocks, respectively, for the Neuro-Mobinavigation method, while plots D, E, and F depict the same comparisons for the non-navigated method. The x-axis represents the average MEP peak amplitudes (mV) for the two compared blocks, and the y-axis represents the difference in MEP peak amplitudes (mV) between the blocks. In each plot, the bold dashed line indicates the mean difference (bias), and the dashed lines represent the limits of agreement (mean ± 1.96 × SD of the differences). Data points located near zero, highlighted in the purple "Middle" zone, indicate a higher level of agreement. The Neuro-Mobinavigation method shows a greater clustering of points in this zone, demonstrating superior consistency and narrower variability compared to the non-navigated method across blocks.

3.2 Validity of the Neuro-Mobinavigation method

Next, we hypothesized that usage of Neuro-Mobinaigation results in higher amplitudes compared to the non-navigated method. Wilcoxon signed rank tests revealed significant differences between Neuro-Mobinavigation and the non-navigated method for all MEP parameters measured. Specifically, there was a significant difference ($p < 0.001$) the novel method showed higher peak amplitude (1.02 ± 0.74) compared to non-navigated method (0. 78 ± 0.61) (**Table 3**, **Figure 5**).

Table 3 Comparison of single-pulse TMS between the two methods

MEP parameters	Neuro-Mobinavigation	Non-navigated method	*P* value	Effect size *r* value
Take-off Latency (ms)	22.11 ± 1.49	21.14 ± 3.13	0.008	0.40
Peak Amp (mv)	1.02 ± 0.74	0.78 ± 0.61	< 0.001	0.35
Negative Peak Area (mv*ms)	2.86 ± 2.10	2.27 ± 1.76	0.003	0.30
Peak to Peak Amp (mv)	1.51 ± 1.09	1.18 ± 0.91	< 0.001	0.33
Total Area (mv*ms)	4.77 ± 3.42	3.87 ± 2.86	0.003	0.28



Continuous variables are denoted as mean ± standard deviation

3.3 Neuro-Mobinavigation has superior consistency compared to the non-navigated method

Analysis of the difference within three blocks for each method was done with the Friedman test. We found non-significant differences in MEP amplitude-related parameters (Peak Amp, Negative Peak Area, Peak to Peak Amp, and Total Area) across the three blocks of TMS stimulation using the Neuro-Mobinavigation method (**Table 4 A.**, **Figure 6**), while significant differences were found for the non-navigated method (**Table 4 B.**, **Figure 6**). These findings suggest that the Neuro-Mobinavigation method yields more consistent MEP-related parameters across blocks, compared to the non-navigated method. Descriptive statistics, including mean and standard deviation, for each parameter within each specific block are provided in **Table S2 and S3**.

Figure 5 Scatter plot of MEP responses (mean ± SD) measured by either non-navigated TMS and Novel Neuro-Mobinavigation TMS. A. Take off latency, B. Peak amplitude, C. Negative peak area, D. Peak to peak amplitude, and E. Total Area

Table 4. Repeated measures ANOVA of successive series of three blocks of MEP responses measured by A: Novel Neuro-Mobinavigation method, B: non-navigated method

Proposed measurement methods	**A: Neuro-Mobinavigation method (n=29)**														
MEP parameters	Take-off Latency (ms)			Peak Amp (mv)			Negative Peak Area (mv*ms)			Peak to Peak Amp (mv)			Total Area (mv*ms)		
***P* value**	0.168 ^{ns}			0.587 ^{ns}			0.362 ^{ns}			0.756 ^{ns}			0.081 ^{ns}		
F-statistic value	1.919			2.677			2.887			2.588			2.935		
Effect size	0.002			0.009			0.011			0.008			0.009		
Time-factor	T1-T2	T1-T3	T2-T3	T1-T2	T1-T3	T2-T3	T1-T2	T1-T3	T2-T3	T1-T2	T1-T3	T2-T3	T1-T2	T1-T3	T2-T3
Post-hoc test	1.0	0.242	0.552	0.109	1.0	0.543	0.089	0.654	0.696	0.098	0.963	0.651	0.086	0.375	1.0
Proposed measurement methods	**B: Non-navigated method (n=29)**														
MEP parameters	Take-off Latency (ms)			Peak Amp (mv)			Negative Peak Area (mv*ms)			Peak to Peak Amp (mv)			Total Area (mv*ms)		
***P* value**	0.661 ^{ns}			<0.001*			<0.001*			<0.001*			<0.001*		
F-statistic value	2.432			41.755			35.433			41.247			35.07		
Effect size	0.013			0.11			0.116			0.103			0.114		
Time-factor	T1-T2	T1-T3	T2-T3	T1-T2	T1-T3	T2-T3	T1-T2	T1-T3	T2-T3	T1-T2	T1-T3	T2-T3	T1-T2	T1-T3	T2-T3
Post-hoc test	0.284	0.208	1.0	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

T1; First block, T2; Second block, T3; Third block

**p< 0.05 indicates significant difference

ns; non-significant, p>0.05

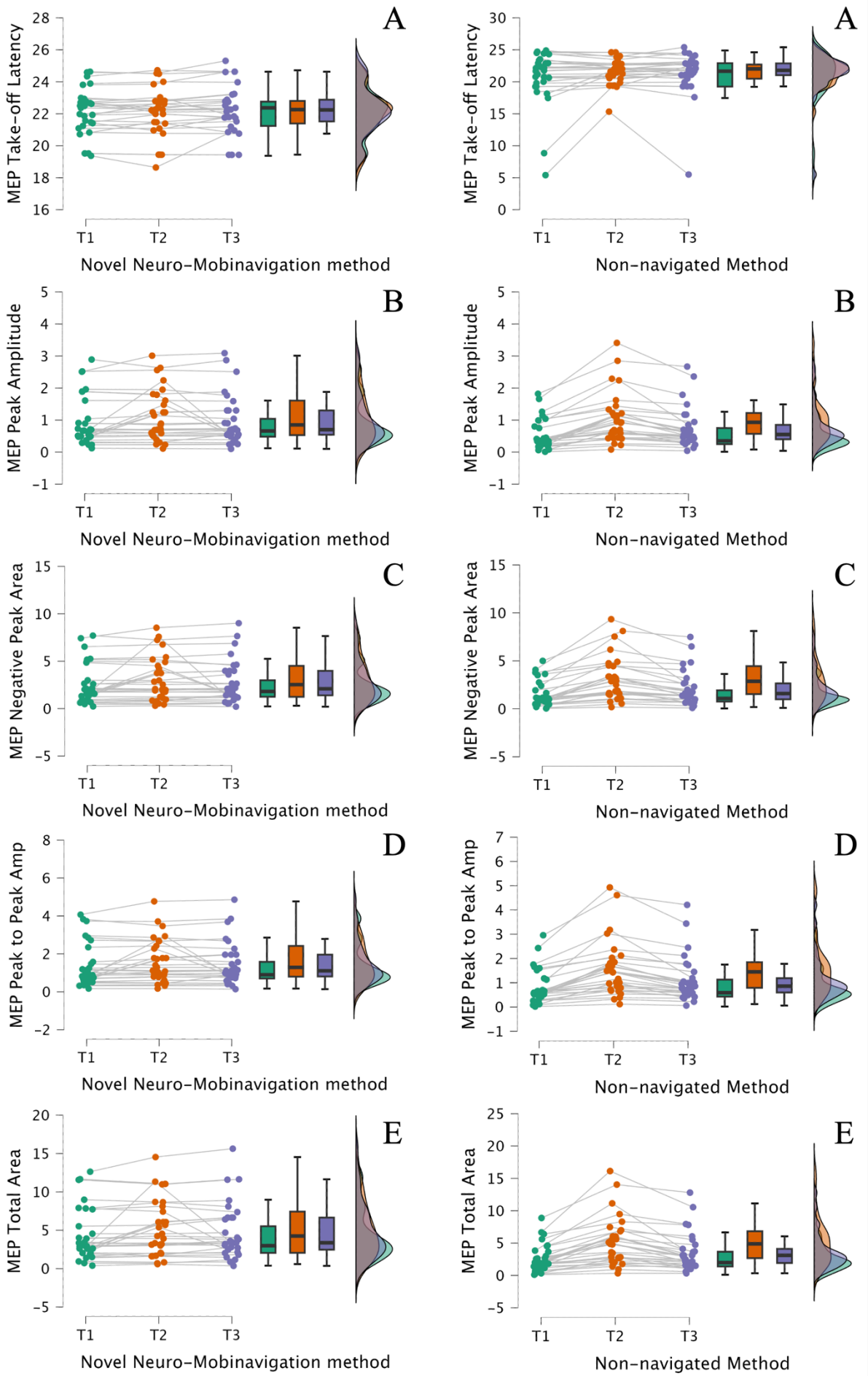


Figure 6 Repeated measures ANOVA of MEP responses (mean ± SD) measured by Neuro-Mobinavigation method (Left column), non-navigated method (Right column). T1; First block, T2; Second block, T3; Third block. A. Take off latency, B. Peak amplitude, C. Negative peak area, D. Peak to peak amplitude, and E. Total Area

4. Discussion

In the present study, consistency and validity of a novel neuronavigation-guided TMS system was tested. The study aimed to 1) evaluate the feasibility of this novel three-step system as a practical and accessible alternative to traditional non-navigated TMS; 2) assess the intra-rater reliability and consistency of MEP parameters across consecutive measurements by comparing Neuro-Mobinavigated TMS with non-navigated TMS; and 3) investigate validity of Neuro-Mobinavigated method to assess MEP parameters.

4.1. Feasibility of a novel three-step system

Current neuro-navigation systems, used in research centers, clinics, and universities, are considered the gold standard for precisely locating the coil over the target area and maintaining its orientation and tilt throughout a session (Sondergaard et al., 2021). However, these systems have notable limitations. The present study introduces a tool with several advantages, including real-time navigation, no need for extensive training, simplicity, time efficiency, cost-effectiveness, and a straightforward setup that does not require complex equipment.

The three-step approach utilized in the novel Neuro-Mobinavigated system addresses the shortcomings of non-navigated methods by offering real-time feedback on coil positioning, orientation, thereby ensuring accurate and consistent targeting of the motor hotspot. Additionally, since TMS experiments can last from several minutes to hours, it is crucial to either securely fix the coil in place or realign it between experimental blocks (Sparing et al., 2010). The novel method's coil registration feature effectively corrects minor errors in coil positioning and orientation, enhancing the overall accuracy of the experiments.

Finally, this novel method underscores the critical importance of maintaining a balance between both coil positioning and orientation to ensure accurate and precise TMS application.

Coil orientation should not be underestimated in relation to coil positioning, as both play equally significant roles. Recent studies have demonstrated that errors in either coil positioning or orientation are the primary sources of inaccuracy in TMS navigation, which can compromise the strength of the induced electric field (E-field) generated by the rapidly changing magnetic field in the brain when the coil is misaligned on the scalp (de Goede et al., 2018; Janssen et al., 2015; Nieminen et al., 2022), and focal excitability of M1 (Reijonen et al., 2020).

4.2. Intra-rater reliability and consistency of MEP using the novel system

The findings of the current study highlight the superiority of the novel Neuro-Mobinavigated TMS system compared to the traditional non-navigated method in terms of intra-rater reliability and consistency of MEP parameters. The novel system demonstrated excellent intra-rater reliability across all MEP parameters, whereas the non-navigated method exhibited only good to moderate reliability. Additionally, the Bland–Altman plots revealed a narrower level of agreement between consecutive TMS pulse blocks for the novel method which guarantee higher consistency, in contrast to the more scattered values observed with the non-navigated method, implicate lower consistency. These results align with previous research, which indicated that navigation-based TMS systems offer greater stability and reduced variation in MEP amplitudes compared to non-navigated TMS systems (Julkunen et al., 2009).

Furthermore, by precisely maintaining coil position and orientation, the novel system reduces variability in stimulation, resulting in more consistent and reliable measurements. When stimulating the M1 and recording MEP responses, the novel approach demonstrated consistent amplitudes across three blocks, with no significant differences observed between blocks. In contrast, the non-navigated method exhibited greater inconsistency, with significant differences in MEP responses between blocks.

4.3. MEP parameters differences between both methods

The increased precision of the Neuro-Mobinavigated TMS system likely contributed to the observed higher MEP amplitudes compared to the non-navigated method (Julkunen et al., 2009). The significant difference in MEP amplitudes between the two methods aligns with previous research, which reported that non-navigated approaches yielded significantly lower MEP amplitudes at M1 compared to neuronavigation-guided techniques (Julkunen et al., 2009; Sparing et al., 2008). Additionally, neuronavigated approaches have demonstrated a stronger behavioral impact, suggesting enhanced effectiveness beyond the motor level (Sack et al., 2009). However, it is worth noting that one study has found no significant difference in MEP amplitude between navigated and non-navigated methods (Jung et al., 2010).

The variability in results observed across TMS blocks using the non-navigated method may be due to stimulation of different areas beyond the M1, which are involved in motor function (Teitti et al., 2008). Additionally, higher MEP amplitudes observed with the Neuro-Mobinavigated TMS system may be attributed to more comprehensive recruitment of cortical neurons and an optimized balance of activation and inhibition for peripheral muscle activation (Julkunen et al., 2009).

Furthermore, there were significant difference in MEP latencies between the two methods in our study, with shorter MEP latencies for the non-navigated TMS. This contrasts with previous research, which found that MEP latencies were shorter with neuronavigated TMS. Although significant differences in MEP latencies were observed between the two procedures in that study, the differences were relatively small, with mean values of 22.5 ± 1.1 ms for neuronavigated TMS and 22.9 ± 1.2 ms for non-navigated TMS (Julkunen et al., 2009). The discrepancy observed in previous studies might be due to the exclusion of MEP responses with amplitudes below 50 μV, whereas our study included all trials. Additionally, other research

supports the finding of shorter latencies associated with larger MEP amplitudes (Vallence et al., 2023), even in the absence of neuronavigation for coil tracking.

The observed shorter latencies with the non-navigated method, despite lower MEP amplitudes, may reflect the inclusion of all trials, slight deviations in coil positioning, or physiological variability in corticospinal conduction. These factors highlight the complexity of interpreting latency-amplitude relationships in TMS studies and underscore the need for further research to elucidate the underlying mechanisms.

In our study, the experimental setup involved starting from the same localization point for the hotspot using both methods, with a consistent resting motor threshold (RMT) applied to all MEP blocks recorded with either neuronavigated or non-navigated TMS. This approach contrasts with the methodology used by (Julkunen et al., 2009), where two distinct starting points were used, separated by 2-7 days. In their study, the hotspot and RMT were determined separately for neuronavigated and non-navigated TMS, resulting in no significant difference ($P = 0.44$) for RMT between the two methods, with mean values of $38 \pm 6\%$ for neuronavigated TMS and $39 \pm 5\%$ for non-navigated TMS. Julkunen's approach may have introduced additional variability due to temporal effects and potential differences in RMT between the two methods, in two different days. In contrast, our study applied a consistent resting motor threshold across all blocks, starting from the same localization point for the hotspot in both neuronavigated and non-navigated TMS within a single experimental session. This difference in experimental design minimized potential confounding factors, leading to a more reliable and directly comparable assessment of both methods.

While high ICC values are often reported for neuronavigation systems, our Neuro-Mobinavigation method achieves comparable precision in maintaining coil position and orientation, as evidenced by excellent intra-rater reliability (ICC = 0.95) and narrow limits of agreement in Bland-Altman plots. These results suggest that our method can provide consistent

and accurate coil placement, similar to neuronavigation, without the need for expensive equipment or specialized training. However, we acknowledge that ICC values alone do not fully capture absolute precision, and future studies should include concurrent validity comparisons with gold-standard neuronavigation systems to further validate our method.

The Neuro-Mobinavigation method offers several practical advantages compared to gold-standard neuronavigation systems. While both approaches allow real-time monitoring and adjustment of coil orientation, the Neuro-Mobinavigation method is significantly more cost-effective, requires no specialized training, and is practical for routine clinical and research applications. In contrast, neuronavigation systems, while highly precise, are prohibitively expensive (often exceeding $50,000), time-consuming to set up, and require specialized training. Their routine clinical use is further limited by the need for patients to wear uncomfortable head trackers, which can impede relaxation. Although the Neuro-Mobinavigation method does not currently provide precise coil positioning, future updates aim to incorporate real-time positioning capabilities, enhancing its accuracy.

4.4. Limitations

We would like to acknowledge a few minor methodological limitations in our study. To mitigate the potential for investigator bias, future studies should consider employing an independent observer for participant recruitment and data acquisition to increase objectivity. Additionally, the current version of the mobile application is limited to recording and saving only a single point at a time. Future iterations should consider implementing the capability to save multiple points, allowing for a more comprehensive comparison of potential hotspot locations before determining the final hotspot. Regarding safety, the emitted pulses of TMS did not interfere with the mobile device, nor did they cause harm. This was ensured by positioning the mobile phone above a non-pulsing surface of the coil and separating it from the

coil surface with 5 cm thick protective foam. Despite the lightweight laser attached to the forehead, some participants reported a heavy sensation on their forehead that intensified toward the end of the session. Future studies may benefit from utilizing a smaller and lighter laser to minimize this potential source of discomfort. Despite efforts to mitigate the limitations of the non-navigated method, the proposed method has a limitation regarding the accuracy of coil positioning relative to its placement on the participant's head. Unlike the gold-standard neuronavigation method, which maintains precise coil positioning with minimal errors, the proposed approach may introduce some variability in coil placement.

4.5. Future Directions

Future studies should explore the concurrent validity of the novel three-step approach in comparison to gold standard neuronavigation systems, which would support its adoption in clinical practice. Furthermore, a test-retest reliability study is necessary to assess the approach's ability to consistently replicate results over different time points (e.g., days, weeks). Additionally, an inter-rater reliability study should be conducted to ensure the consistency of outcomes across different investigators with varying levels of experience in using TMS systems. Moreover, examining the cost-effectiveness and time efficiency of this approach in comparison to both gold standard neuronavigation systems and traditional non-navigated methods would provide valuable insights into its practicality.

Future studies should explore the applications of the Neuro-Mobinavigation system in neurological illnesses, particularly those affecting motor control, such as multiple sclerosis, and stroke (Palm et al., 2014; Youssef et al., 2023). Given its cost-effectiveness, ease of use,

and potential for improved clinical outcomes, the system could play a significant role in therapeutic TMS protocols aimed at restoring motor function. Additionally, larger-scale studies in clinical populations will be necessary to validate the system's efficacy in these contexts. Future developments could also focus on enhancing the system's real-time coil positioning capabilities to support more precise treatments in these therapeutic areas.

5. Conclusion

The Neuro-Mobinavigation TMS is superior to non-navigated TMS and provides a reliable, more stable, and cost-effective alternative for MEP studies where the gold standard neuronavigation is not available. Furthermore, higher MEP amplitudes highlight the importance of accurate coil positioning for TMS research and clinical applications, particularly in settings where precise coil placement is crucial.

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CRediT author statement

Hussein Youssef: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing - Original Draft, Visualization. **A. Emre Öge**: Methodology, Validation, Writing - Review & Editing, Supervision. **Koen Cuypers**: Writing - Review & Editing. **Atay Vural**: Writing - Review & Editing, Supervision, Project administration.

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