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Differentiation of motor cortical representation of hand muscles by navigated mapping of optimal TMS current directions in healthy subjects

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Abstract

The precision of navigated transcranial magnetic stimulation (TMS) to map the human primary motor cortex may be effected the direction of TMS-induced current in the brain as determined by the orientation of the stimulation coil. In this study, we investigated the effect of current directionality on motor output mapping using navigated brain stimulation (NBS). Our goal was to determine the optimal coil orientation (and, thus, induced brain current) to activate hand musculature representations relative to each subject's unique neuroanatomical landmarks. We studied motor output maps for the first dorsal interosseous (FDI), abductor pollicis brevis (APB), and abductor digiti minimi (ADM) muscles in 10 normal volunteers. Monopolar current pulses were delivered through a figure-of-eight shaped TMS coil and motor evoked potentials (MEPs) were recorded using electromyography (EMG). At each targeted brain region, we systematically rotated the TMS coil to determine the direction of induced current in the brain for induction of the largest MEPs. These optimal current directions were expressed as an angle relative to each subject's central sulcus. Consistency of the optimal current direction was assessed by repeating the entire mapping procedure on two different occasions across subjects. We demonstrate that systematic optimization of current direction as guided by MRI based neuronavigation improves the resolution of cortical output motor mapping with TMS.

Keywords

Transcranial Magnetic Stimulation; Navigated Brain Stimulation; Cortical Excitability; Current Direction; Physiology; Electromyography (EMG)

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1 – INTRODUCTION

Transcranial magnetic stimulation (TMS) is a neurophysiologic technique that allows for the non-invasive activation of neuronal circuits in the central nervous system via the application of time-varying magnetic field pulses (Barker et al. 1985; Kobayashi and Pascual-Leone 2003; Wagner et al. 2007). TMS can be used to study intracortical and cortico-cortical connectivity. When TMS is applied to the motor cortex, the resultant stimulus-induced activations of the efferent cortico-spinal projection can be recorded and quantified electromyographically (EMG) as compound motor evoked potentials (MEPs) (Danner et al. 2008). Systematic targeting of adjacent brain areas by the controlled, stepwise movement of the TMS coil over the scalp enables the mapping of motor cortical outputs. The use of MRI guided neuronavigation improves the spatial resolution and reproducibility of such cortical output maps (Gugino et al. 2001) and the resulting cortical motor maps can have a comparable resolution to those obtained via direct cortical stimulation (Kwon et al. 2008).

Previous studies have shown that motor cortical output maps for closely represented muscles, such as hand muscles, can be differentiated using varied orientations of a TMS coil that generates monophasic pulses (Brasil-Neto et al. 1992a,b; Pascual-Leone et al. 1994a; Wassermann et al. 1992). It has been suggested that this technique exploits differences in the orientation of neurons in the precentral gyrus and activates only those neurons maximally oriented to each unique coil position (Pascual-Leone et al. 1994a). However, although the importance of and optimal parameters for coil orientation have been discussed in the past (Brasil-Neto et al. 1992a; Mills et al. 1992), this work was undertaken without the aid of neuronavigation, guided solely by cranial landmarks.

The purpose of the present study was to reassess the directional tuning of motor cortical outputs for specific hand muscles using state-of-the-art MRI based neuronavigation. Unlike unguided TMS, which has been shown to generate interpulse variation of up to several millimeters (Gugino et al., 2001), MRI guided navigation ensures accurate and consistent stimulation. In addition, we were able to utilize each subject's own brain MRI to determine the optimum coil orientation in relation to his/her individual central sulcus. Ultimately, we set out to examine whether systematic exploration of the optimal current direction for each targeted brain region utilizing MRI guided navigation might further improve the spatial resolution of cortical output mapping.

2 - METHODS

2.1 - Subjects

Ten right-handed healthy subjects (7 males and 3 females; mean age: 25.4 years, age range: 19–31 years) were studied. The study was approved by the local Internal Review Board (IRB) and written informed consent was obtained from all participants. The subjects did not have any prior psychiatric, neurologic or medical history, or any contraindications to TMS (Rossi et al., 2009).

2.2 - Experimental Setup

EMG was recorded from first dorsal interosseous (FDI), abductor pollicis brevis (APB), and abductor digiti minimi (ADM) muscles using surface electrode pairs (ME 6000, Mega Electronics Ltd, Kuopio, Finland) and pre-gelled disposable Ag/AgCl electrodes placed on the skin, about 2–4 cm apart in a belly-tendon montage. The EMG signals were filtered (8–500 Hz), amplified, displayed and stored for off-line analysis. The TMS system delivered trigger pulses that synchronized the TMS and EMG systems. Magnetic resonance imaging (MRI) was performed on a 3 tesla GE system and utilized in the navigation software (eXimia 3.1, Nexstim Ltd, Helsinki Finland). The stimulation setup consisted of the

navigation system combined with a magnetic stimulator (Nexstim Ltd, Helsinki, Finland) and focal figure-of-eight TMS coil (outer wing radius of 70 mm). Stimulator output was monophasic in order to control the direction of current induced in the brain (Brasil-Neto et al. 1992a).

2.3 - Experimental Procedure

In each TMS session, the motor cortical output (presumed to represent primary motor cortex representation and hereafter referred to as M1) was mapped carefully around the precentral gyrus (Hannula et al. 2005) to identify optimal representation area of the FDI, APB, and ADM muscles in both hemispheres (Fig. 1A). Each muscle's 'hot spot' location (defined as the location over which TMS evoked MEPs of highest peak-to-peak amplitude in the target muscle - Säisänen et al. 2008) was unique to each subject and marked according to his/her individual MRI. The initial mapping procedure was completed with the coil oriented at '0°' and the center of the coil applied tangentially to the scalp. For this study, 0° was defined as the handle of the coil oriented perpendicular to each subject's unique central sulcus at the point of stimulation (see Figure 1 for a general coordinate scheme). After determining hot spot locations, we determined the motor threshold (MT) of each muscle. According to the recommendations of the International Federation for Clinical Neurophysiology, MT was defined as the lowest stimulator output intensity that produced at least five MEP, out of 10 consecutive stimuli with a minimum of 50 μ V peak-to-peak amplitude.

The TMS mapping procedure was done using single TMS pulses delivered at an intensity of 110% of MT. Utilizing MRI based online neuronavigation monitoring, we examined the optimal direction of current for activation of each target muscle. To do this, we systematically rotated the TMS coil over each hot spot in increments of 45° in a counterclockwise direction, so that the current was oriented at 45°, 90°, 135°, 180°, 225°, 270° and 315° (in relation to the central sulcus). After locating the optimal 45° increment orientation, we rotated the coil in increments of 5° around this position to better refine the final 'optimal' angle. Ten MEPs were recorded at each orientation for each subject (Figure 1). It is important to note that, although the coil was rotated, the center of the coil and tilt were both kept constant (as determined using online neuro-navigation monitoring).

In four subjects, we repeated the entire procedure one week after the first session to assess the reproducibility of the hotspot and optimal direction of induced current for induction of MEPs in each muscle.

2.4 - Data Analysis

For each subject and coil orientation, we calculated the mean ($\pm$ standard deviation) MEP amplitude, latency, and optimal angles for APB, FDI, and ADM. To identify the optimal coil orientation, we measured the angles from the center of the coil held over the optimal scalp position of each muscle on both hemispheres to the orientation of the central sulcus at that level, as visualized by each subject's brain MRI scan.

All statistical analyses were performed using MatLab (Version 7.4.0). A Wilcoxon signed-rank test was used to compare MEP, latency, and optimal angles for the three muscles between hemispheres. To compare optimal angles among the 3 muscles studied we used a Kruskal-Wallis one-way ANOVA. All statistical tests were two-tailed, with statistical significance defined at $p < 0.05$.

3 - RESULTS

Applying the coil at different angles in relation to each subject's unique central sulcus (at the point of stimulation) allowed us to generate cortical output maps of the FDI, APB, and ADM muscles that reflected both current direction and topographic information (Figure 2).

Figure 3 shows the relationship between coil orientation and MEP peak-to-peak amplitude (μV). In the left hemisphere, the FDI and APB muscles were optimally activated when the coil was oriented at an angle of approximately 45° to the central sulcus, while the ADM muscle was optimally activated when the coil was oriented at an angle near 0° . In the right hemisphere, however, all 3 muscles were optimally activated when the coil was oriented at an angle near 45° . Rotating the coil past the 45° angle elicited MEPs with decreasing peak-to-peak amplitudes in all 3 muscles.

The optimal angles and the respective MEP amplitude and latency data across all 10 subjects for each muscle are provided in Table I. The mean angles for the coil positioned on the left hemisphere to elicit maximum MEPs in the right FDI, APB, and ADM were $35.50^\circ \pm 6.75^\circ$, $15.60^\circ \pm 11.68^\circ$, and $32.40^\circ \pm 15.00^\circ$, respectively. Similarly, the mean angles for the coil positioned on the right hemisphere to elicit maximum MEPs in the left FDI, APB, and ADM were $30.10^\circ \pm 4.58^\circ$, $9.00^\circ \pm 4.40^\circ$, and $32.20^\circ \pm 7.35^\circ$, respectively.

The mean angles, MEP, and latency data for maximum muscle activation did not significantly differ between hemispheres for any of the three muscles (Table I: Wilcoxon signed-rank test). Mean angles for muscle activation, however, did show significant differences between the three muscles in the left hemisphere ($\chi^2 = 10.21$, $df = 2$, $p = 0.006$; Kruskal-Wallis one-way ANOVA) and the right hemisphere ($\chi^2 = 19.77$, $df = 2$, $p < 0.001$; Kruskal-Wallis one-way ANOVA). A *post-hoc* multiple comparisons test demonstrated that the mean ranks of the ADM and APB in both the left and right hemispheres were significantly different (Fig. 3 and 4).

In all 4 subjects tested twice at least one week apart, the distance between hotspots was minimal (FDI, APB, and ADM were an average of 1.45 ± 0.68 mm, 2.01 ± 1.10 mm, and 3.47 ± 0.61 mm apart for the left hemisphere, and 2.26 ± 0.98 mm, 2.07 ± 1.31 mm, and 2.25 ± 1.56 mm for the right hemisphere, respectively). Optimal current direction for activation of each muscle remained fairly constant at each hot spot (Fig. 5). The average angle of FDI, APB, and ADM were $33^\circ \pm 3.50^\circ$, $17^\circ \pm 5.80^\circ$, and $30^\circ \pm 11.00^\circ$, for the left hemisphere and $29.50^\circ \pm 3^\circ$, $11.58^\circ \pm 3.50^\circ$, and $30^\circ \pm 5^\circ$ for the right hemisphere, respectively. The interindividual variability in these angles across testing sessions was minimal for the FDI and APB ($2.0^\circ \pm 1.41^\circ$ & $5.5^\circ \pm 6.45^\circ$ for the left hemisphere and $0.25^\circ \pm 3.5^\circ$ & $0.5^\circ \pm 1.91^\circ$ for the right hemisphere, respectively) and slightly higher for the ADM ($2.75^\circ \pm 17.91^\circ$ for the left hemisphere and $3.25^\circ \pm 3.77^\circ$ for the right hemisphere).

4 - DISCUSSION

The effects of human motor cortex stimulation are sensitive to even the most subtle changes in the direction of TMS-induced currents (Brasil-Neto et al. 1992a,b; Hess et al. 1987; Chiappa et al. 1991). More specifically, as different muscle representations display unique pyramidal and interneuronal orientations, axial rotation of the TMS induced current may differentially activate unique muscles in a consistent and exploitable manner (Sakai et al. 1997; Pascual-Leone et al. 1994b). In the present study, we utilized MRI guided neuronavigation to examine the ability of this directional specificity to reliably differentiate the cortical motor representation of three intrinsic hand muscles optimally activated from similar scalp locations. The results of this study suggest that MRI based neuronavigated techniques, which allow for varied parameters to map directly to an individual's unique

neuroanatomical characteristics, enable significant improvement in the specificity of non-invasive cortical output maps. An oft-utilized, non-navigated mapping approach favors a 45° lateral diagonal coil orientation roughly perpendicular to the central sulcus. With unique cerebral architecture, this orientation is only approximate and most likely does not represent a perfectly perpendicular angle. Our results suggest a flush perpendicular angle, although able to evoke strong MEPs, is not the ideal orientation for each examined muscle. In fact, beyond this study, Blaslev and colleagues (2007) have suggested the ideal coil orientation to elicit MEPs lies within a 45° window around perpendicularity. Accordingly, the approximate nature of the blind 45° angle may explain why it has proven successful to date. Moving forward, this approximation is certainly recommended when navigation is not an option; however, if a navigation system is available, orientation around perpendicularity should be explored prior to mapping.

Several researchers have noted varied MEP latencies with differential coil orientations in hand muscles (Sakai et al. 1997; Werhahn et al. 1994; Zoghi et al 2003) and facial muscles (Ortu et al. 2008; Dubach et al. 2004). These differences are thought to reflect either rapid, direct activation of optimally oriented pyramidal tract neurons (generating a D-Wave) or slower, indirect activation of optimally oriented interneurons (generating varied I-waves: Di Lazzaro et al. 2011). Interestingly, we did not obtain similar results. This lack of latency variation may have been due to our pulse parameters (110% rMT) as stronger intensity pulses have been shown to recruit D-wave activity more readily than lower intensities at varied orientations (Werhahn et al. 1994; Di Lazzaro et al. 2004; Guggisberg et al. 2001), however the true cause remains unknown. In addition, we determined several coil orientations (typically around 225°) elicited no measurable MEP response. Returning to the matter of neuronal orientation, it is possible (however, unlikely) that no relevant pyramidal or interneuronal elements were oriented in this particular direction leading to no muscle activation following stimulation. However, we were unable to find any data supporting this finding or this supposition in relevant literature. Another explanation for this finding may be the relatively small MEP threshold values. As pulses from the optimal coil orientation typically elicited MEPs around 200 uV, it is possible muscle activation generated at 225° was negligible. To determine if this was the case, future replication utilizing 110% rMT at extreme angles and varying pulse strengths is necessary.

When right and left hemispheres were compared, a non-significant hemisphere effect was found. There is no clear consensus on whether interhemispheric differences exist in motor cortical output maps. In some studies, asymmetry has been reported between hemispheres (Koski et al. 2005; Macdonell et al. 1991; Triggs et al. 1994), whereas in others no differences were found between the hemispheres (Cicinelli et al. 1997; Civardi et al. 2000; Rossini and Rossi, 1998). The increased precision of our procedure, utilizing both the benefit of the neuronavigation system and relating TMS parameters to each individual's brain anatomy, reveals that, at least in right handers, interhemispheric motor output map differences are minimal.

During TMS, when the stimulation coil is held tangentially to the scalp, the currents induced in the brain flow parallel to the plane of the stimulation coil, approximately parallel to the brain's cortical surface, thus preferentially activating neural elements parallel to the cortical surface (Day et al. 1989; Roth et al. 1991; Saypol et al., 1991). In the proximity of the central sulcus, most of these horizontally oriented elements appear to be interneurons aligned perpendicularly to the central sulcus (Hendry and Jones, 1981; Strick and Preston, 1982). One difficulty in evaluating neuronal excitability is that the depth from the scalp at which the neuronal elements that initiate the motor responses to TMS are located is not exactly known. It has been suggested that sufficient electric field strength is required in a certain three-dimensional volume of neuronal tissue to initiate a muscle response, reflecting

the assumption that the motor responses provoked by TMS result from both direct and transsynaptic neuronal activation (Danner et al. 2008). Additionally, at a given coil orientation, the spread of the induced current in the tissue leads to activation of neighboring neuronal populations, thus limiting spatial resolution. However, different current directions will intersect the precentral gyrus perpendicularly at different levels, thereby preferentially activating only those neuronal nets aligned with the current (Pascual-Leone et al. 1994b). Accordingly, it has been suggested that differences in optimal current directions for activation of different muscles represent differences in the orientation of precentral cortical interneuronal axons in neuronal nets connecting to pyramidal tract neurons targeting different alpha-motoneuronal pools (Pascual-Leone et al. 1994a). Using NBS to map optimal current direction relative to the central sulcus represents an improved framework which, by taking into account inter-individual differences in neuroanatomy, might be used to further investigate the mechanisms by which TMS elicits motor responses and critically enhance the precision of noninvasive cortical mapping.

In conclusion, we found that MRI based neuronavigated TMS, which includes the systematic examination of optimal current directions relative to an individual's unique central sulcus orientation, allows for more precise noninvasive topographic mapping of motor cortical outputs than methods utilizing cranial landmarks.

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Figure 1. Stimulation Schematic

The stimulation area on a 3D-rendering of a single subject's left and right hemisphere. The dots on the scalp are visualized as a small ball and the head of the ball shows the orientation of a single pulse. The dotted blue line shows the central sulcus. The brain visualized as "peeled" into 25mm depth, i.e., the visualized stimulation surface resides at this depth from the scalp (A). The coil position and tilt were maintained, while the coil was rotated in increments of 45° in a counterclockwise direction, so that it was oriented at 45°, 90°, 135°, 180°, 225°, 270° and 315°. After locating this optimal orientation, the coil was rotated once again, in increments of 5° bidirectionally, while using the Nexstim system, to fine-tune the optimal orientation of each muscle (first dorsal interosseous (FDI), abductor pollicis brevis (APB), and abductor digiti minimi (ADM)). Ten MEPs were recorded at each orientation for each subject

Figure 2. Cortical Output Maps

Cortical output maps of the FDI, APB, and ADM muscle in two representative subjects. Current direction and topographic information are indicated on the figure. The angle of measurement from the central sulcus of both hemispheres is shown. The dotted blue line shows the central sulcus.

Figure 3. Orientation Measurements

Coil orientation and MEP peak-to-peak amplitude (μV) the FDI, APB, and ADM muscle for the left and right hemispheres. The data represent means ($\pm$ standard deviation) from ten subjects.

Figure 4. Optimal Orientation (1 visit)

Optimal current direction for inducing MEPs in three muscles (FDI, APB, and ADM) from the hotspot of a single muscle (FDI) in 10 subjects. Note the consistent progression in optimal current direction for activation of the muscle across subjects.

Figure 5. Optimal Orientation (2 visits)

Optimal current direction for inducing MEPs in three muscles (FDI, APB, and ADM) in 4 subjects. The straight line represents the first visit and the arrow line represents the second visit of the subjects.

Table I

FDI

Subject	Angle [deg]		MEP Amplitude [mV] ± SD		Latency [ms] ± SD	
	Left Hemisphere	Right Hemisphere	Left Hemisphere	Right Hemisphere	Left Hemisphere	Right Hemisphere
1	23°	30°	138±112	188±81	21.03±1.01	22.01±1.32
2	34°	30°	282±142	208±108	22.02±.84	21.09±1.11
3	27°	36°	214±98	219±91	22.21±1.06	22.08±.96
4	44°	30°	122±102	178±67	21.8±2.02	20.4±1.21
5	42°	34°	180±88	321±114	20.9±1.42	21.3±0.92
6	37°	26°	144±92	148±61	21.4±0.84	21.9±1.54
7	38°	22°	241±87	199±71	22.02±0.62	20.8±2.32
8	38°	28°	219±111	164±48	21.01±1.03	22.03±1.56
9	41°	37°	232±82	293±94	20.43±1.34	22.01±1.1
10	31°	28°	380±142	219±110	21.08±2.06	21.08±0.94
Mean ± SD	35.5°±6.8°	30.1°±4.6°	215.2±77.1	213.7±54.6	21.4±0.6	21.5±0.6
p value	0.080 $\hat{r}$	0.922 $\hat{r}$	1 $\hat{r}$			

APB

Subject	Angle [deg]		MEP Amplitude [mV] ± SD		Latency [ms] ± SD	
	Left Hemisphere	Right Hemisphere	Left Hemisphere	Right Hemisphere	Left Hemisphere	Right Hemisphere
1	26°	6°	208±103	182±71	21.11±1.01	20.04±1.74
2	14°	7°	222±92	198±66	22.01±0.84	21.08±1.02
3	42°	7°	182±114	280±106	21.02±1.42	22.01±0.94
4	13°	11°	201±92	108±44	22.03±0.76	21.07±.84
5	8°	10°	308±148	203±61	20.04±2.01	20.03±1.04
6	18°	13°	198±71	198±48	21.07±2.2	22.02±1.09
7	4°	7°	204±83	183±58	22.03±1.24	21.09±0.84
8	1°	5°	282±140	242±69	21.02±1.85	22.01±0.94

9	14°	5°	398±201	104±38	20.9±1.1	20.03±1.24
10	16°	19°	148±94	219±72	20.4±2.01	20.09±2.10
Mean ± SD	15.6°±11.7°	9.0°±4.4°	235.1±73.7	191.7±53.9	21.2±0.7	20.9±0.9
<i>p value</i>	0.168 [†]		0.250 [†]			1 [†]
ADM						
Subject	Angle [deg]		MEP Amplitude [mV] ± SD		Latency [ms] ± SD	
	Left Hemisphere	Right Hemisphere	Left Hemisphere	Right Hemisphere	Left Hemisphere	Right Hemisphere
1	47°	38°	198±42	192±41	21.01±1.34	21.03±1.12
2	40°	34°	204±101	188±102	22.02±0.98	22.01±0.24
3	19°	37°	212±82	207±111	19.9±2.14	20.09±1.10
4	23°	42°	133±51	213±119	21.43±1.18	20.4±0.86
5	46°	22°	281±61	178±81	21.21±0.98	21.1±0.74
6	3°	28°	108±34	281±148	22.02±1.3	22.2±0.98
7	20°	19°	188±41	146±51	22.32±0.94	21.9±1.02
8	41°	32°	193±62	118±46	21.09±1.03	20.04±1.84
9	41°	32°	101±29	190±54	22.01±0.84	20.03±1.54
10	44°	38°	223±111	214±84	21.08±0.74	21.4±0.62
Mean ± SD	32.4°±15.0°	32.2°±7.3°	184.1±55.5	192.7±43.3	21.4±0.7	21.0±0.9
<i>p value</i>		0.826 [†]		0.846 [†]		1 [†]

SD: Standard deviation;

[†]Wilcoxon signed-rank test