Navigated transcranial magnetic stimulation of the primary somatosensory cortex evokes motor potentials in healthy humans’ flexor carpi radialis muscle - A pilot study

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HIGHLIGHTS
• No interhemispheric differences, but larger peak-to-peak amplitudes and variability of MEPs occurred after M1 as compared to S1 stimulation.
• On the other hand, latency and waveforms of MEPs did not differ between S1 vs. M1 stimulation.
• Our results indicate that TMS over S1 using a 90 mm outer diameter figure-of-eight coil is not selective enough and can excite M1 interneurons thus producing MEPs on the contralateral FCR.
• Future studies should carefully consider these results when targeting S1 with TMS even if using a neuronavigation system.

ABBREVIATIONS
CSE corticospinal excitability
ECR extensor carpi radialis muscle
EMG electromyography
FCR flexor carpi radialis muscle
FDI first dorsal interosseous muscle
M1 primary motor cortex
MEP motor evoked potential
MRI magnetic resonance imaging
rANOVA repeated measures analysis of variance
rMT resting motor threshold
rMTS repetitive transcranial magnetic stimulation
S1 primary somatosensory cortex
S2 secondary somatosensory cortex
TMS transcranial magnetic stimulation

BACKGROUND: Background: Although previous studies targeted S1 by TMS to investigate its effect on the corticospinal pathway, there is no evidence if such stimuli produced by TMS would distinctly be restricted to it and not reach M1 interneurons adjacent to S1.

AIM: The aim of the present pilot study was to determine the effects of stimulation location, i.e., S1 vs. M1, on MEP waveform-related parameters, including amplitude, latency, and variability in the contralateral FCR muscle.

METHOD: Healthy volunteers (n = 8, 2 females, age: 29.9 ± 5.49y) received single-pulse TMS over each hemisphere at each intensity of 90, 100, 110, and 120% of rMT in a randomized order. MEPs from the contralateral FCR were recorded.

RESULTS: We found no interhemispheric differences, but larger peak-to-peak amplitudes and variability of MEPs after M1 as compared to S1 stimulation. However, latency and waveforms of MEPs did not differ between S1 vs. M1 stimulation supporting the idea that TMS over S1 is not selective enough and can excite M1 interneurons thus producing MEPs on the contralateral FCR.

CONCLUSION: Future studies should carefully consider these results when targeting S1 with TMS even if using a neuronavigation system.

KEYWORDS: Brain Stimulation | FCR | Motor Cortex | Neuronavigation | Somatosensory Cortex

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a neurophysiological technique that makes it possible to non-invasively probe the functional integrity of the corticospinal tract.
and the function of the motor cortex, $M1$.

When TMS is delivered to the scalp over $M1$, it may induce short-latency motor evoked potentials (MEPs) in contralateral limb muscles through activating the pyramidal cells indirectly via excitatory interneurons.

These MEPs can be recorded by electromyography (EMG). Although the induced field reaches the target region of stimulation, it may involve adjacent brain regions. A commonly used double-cone magnetic coil may produce a magnetic field in the brain tissue of up to 140mm radial from the center of the target region with smaller peripheral peaks of approximately 50% the amplitude of the central peak on either side of the winding coil, making it difficult to target a particular brain region with high selectivity.

The primary somatosensory cortex (S1), Brodmann areas 3,1 and 2, is known to receive abundant projections from spinal and brain stem neurons that receive input from myelinated afferents. These inputs from peripheral tactile, joint and muscle receptors provide sensory information about limb position, movement sense, muscle tension and force to the central nervous system and this information is used in turn to control voluntary movements.

Somatosensory and motor interactions have a fundamental role in motor control and motor performance, as afferent inputs are key determinants of motor output. Therefore, the ascending somatosensory system plays a key role in movement control and in the acquisition of new motor skills. In animal models, besides these ascending pathways to the somatosensory cortex however, descending efferent fibers from the sensory cortex have been confirmed, which show similar organization in the brains of domestic dogs and cats, raccoons, and in a few species of monkeys and apes.

Brodmann area 3a, contains some of the largest corticospinal neurons outside the motor cortex, area 4 and projections from both areas appear to overlap within the spinal cord, and it appears to project slightly more dorsally within the spinal grey matter than does Brodmann area 4.

Furthermore, areas 3b, 1, 2, and also the secondary somatosensory area (S2) have projection, albeit sparse, from small diameter pyramids, and they terminate chiefly in the dorsal horn. They may be the potential tracts to convey descending signals to the muscles. Although electrophysiological studies describing descending pathways from S1 in animal models suggest that such S1 cells can be excited by induced current, it remains unknown whether such descending pathways exist in human.

In human, there is clear evidence that stimulation of the somatosensory area may result in recordable and reproducible muscle twitches. A somatosensory evoked potential is the electrical activity of the brain generated by the activation of sensory pathways at peripheral, spinal, subcortical and cortical levels of the nervous system, elicited by electrical, tactile, mechanical, or thermal stimuli. Using optimal intensity peripheral sensory stimuli may induce skeletal muscle response. Sensory signals from S1 may reach pyramidal tract cells in layer V through monosynaptic connections or via oligosynaptic connections, with interneurons relaying the signals in layers II and III, resulting in a descending volley to the muscle resulting in an MEP. Reasonably, latency of these MEPs are longer compared with $M1$ TMS-evoked MEPs.

Previous studies have reported a high degree of variability in TMS-evoked MEPs. This variability can affect the interpretation of the results of studies investigating changes in corticospinal excitability (CSE) after TMS. It can pose limitations and can also make it difficult to determine whether reported changes in MEP amplitude are true changes in CSE or whether they are merely a reflection of the inherent variability in TMS-evoked MEPs even if coil placement and stimulation intensity are constant.
TMS over S1 has been extensively used to determine its effect on kinesthetic perception\(^\text{17}\) or in motor learning.\(^\text{18}\) These studies, however, used coils with different size that may pose variable range of influence on the adjacent area of the cortex. Moreover, previous studies have targeted the extensor carpi radialis (ECR)\(^\text{18}\) or the first dorsal interosseous (FDI) muscles\(^\text{19}\) but never the flexor carpi radialis (FCR) muscle. Because we are interested in the contribution of S1 to motor learning, and one of our future targets is the skill acquisition of wrist movement, we focused on the FCR related corticospinal excitability in this study.

Taken together, the aim of the present pilot study was to determine the effects of stimulation location, i.e., S1 vs. M1, on MEP waveform-related parameters, including amplitude, latency, and variability in the contralateral FCR muscle. We hypothesized that stimulating S1 vs. M1 would produce smaller MEP size, greater MEP variability but no difference in MEP latency. These expectations are based on the poor focality of the magnetic pulse: even if TMS is guided by neuronavigation the pulse is wide enough to excite M1 interneurons when S1 is targeted. In addition, sensorimotor performance is known to have a hemispheric asymmetry that underlies dynamic coordination\(^\text{20}\) and may also predict hand selection.\(^\text{21}\) It is therefore possible that MEPs arising from sensorimotor connections may differ between the two hemispheres. Thus, we also hypothesized inter-hemispheric differences in MEPs when stimulating dominant left and non-dominant right S1 or M1.

METHODS

Participants and ethical approval

Healthy volunteers (n = 8, 2 females, age: 29.9 ± 5.49 y), free of neurological disorders, sensorimotor impairments or contraindications to TMS, participated in the study. All participants were right-handed, determined by the Edinburgh Handedness Inventory.\(^\text{22}\) Each subject gave a written informed consent in accordance with the Tohoku University Human Ethics Committee (2018-1-792) and the Declaration of Helsinki.

Experimental procedure

In Japan, the Japanese Society of Clinical Neurophysiology (JSCN) has restricted repetitive TMS (rTMS) administration to medical doctors due to safety concerns. Although we used single pulse TMS to construct recruitment curves by stimulating S1 and M1 in each hemisphere in this study, a trained medical doctor (TM) was always present during the experiments. To increase topical selectivity, we guided TMS by neuronavigation (BrainSight\textsuperscript{TM}, Rogue Research Inc., Montreal, QC), which ensures reliable coil positioning relative to the cortical target locus and allows us to correct any shift in coil position or angulation during the measurements.

First, we performed a 3D MR imaging with a 3T scanner (Philips Intera Achieva 3.0-T Quasar Dual; Philips Healthcare Best the Netherlands) using an 8-channel sensitivity-encoding (SENSE) head coil, operated by an expert MRI technician. Imaging parameters were as follows: repetition time (TR) = 8.8 ms; echo time (TE) = 5.4 ms; flip angle = 8°; field of view (FOV) = 256 mm, 1.07 × 1.07 × 1 mm3 voxels, 60 slices. Each participant’s individual anatomic images were imported into the neuronavigation software...
to allow for stereotaxic registration of the participant’s brain with TMS coil for online control of coil positioning. Subjects were then co-registered with their structural scans using readily identifiable points on the head (nasion, tip of the nose, intertragal notches of the ears).

The TMS measures reported here adhere to a TMS methodological checklist established by international experts. During TMS, participants were seated in a comfortable chair with the forearms placed on armrests. Participants were instructed to remain relaxed throughout the application of TMS. Surface electromyography (EMG) recordings were monitored to ensure relaxation of each FCR muscle. EMG from each FCR was continuously monitored using disposable bipolar surface electrodes (Covidien Kendall, Ag/AgCl, Ref: 31.1245.21, UK). The electrodes were aligned along muscle fibers with a 1cm interelectrode distance and were connected to the MEP element of BrainSight™ software. To minimize noise in the EMG signal, the skin over the muscle belly was shaved, scrubbed with sandpaper, and cleaned with alcohol. A ground electrode was placed on the upper forearm. MEPs were evoked by delivering monophasic pulses with a 90 mm outer diameter figure-of-eight coil connected to a Magstim 200 stimulators (Magstim, Whitland, UK). The TMS coil was oriented tangentially to the scalp with the handle pointing back and away from midline at 45° during stimulation of both M1s and S1s. The optimal location to stimulate the left and right FCR, the so-called hotspots, were determined and marked using the neuronavigation system to minimize variability across trials.

Resting motor thresholds (rMT) in each M1 (mean MNI coordinates: left M1: 44.7, 13.8, 85.7; right M1: -37.9, 14.0, 85.0) was determined as the minimum intensity at the nearest 1% of maximum stimulator output that evoked MEPs in the FCR of at least 50 µV in five out of 10 consecutive stimuli (rMT, % of maximum stimulator output, left M1: 60.1 ± 7.8; right M1: 62.6 ± 8.5). S1 areas (mean MNI coordinates: left S1: 55.9, 24.4, 78.3; right S1: -54.7, 25.9, 74.8) of each hemisphere was targeted by moving the TMS coil one gyrus backward and approximately 1 cm laterally from the FCR M1 hotspots. Figure 1 shows a representative participant demonstrating BrainSight™ localization of targets. Recruitment curves were done over the left dominant and non-dominant right S1 and M1 by delivering 5 single pulses at each intensity of 80, 90, 100, 110, and 120% rMT in a randomized order.
Data and statistical analyses

The average time from the TMS pulse until the onset of the MEP (MEP latency) was measured. Latency was defined as the first time-point after the TMS pulse for which the amplitude exceeded 5% of the baseline-to-first peak amplitude (in absolute value). Furthermore, we quantified peak-to-peak amplitude of each MEP and calculated inter-trial variability of MEPs. Data that differed from the mean by more than two standard deviations (SD) were excluded for each participant separately. In total, 10% of all MEPs were excluded. MEPs from test pulses were normalized by maximal compound action potential.

Statistical analyses were performed with SPSS (version 20, SPSS Inc, Chicago, IL, USA). Values are expressed as mean ± SD. All data were checked for normal distribution using the Shapiro–Wilk test. Each analysis was done on each waveform-related parameter (latency, peak-to-peak amplitudes, and variability) of MEPs (dependent variables). A target (S1, M1) x hemisphere (left dominant, right non-dominant) intensity (80, 90, 100, 110, 120%) repeated measures analysis of variance (rANOVAs) and planned post-hoc tests with Bonferroni correction for multiple comparisons were used to detect if dependent variables differed when stimulating S1s vs. M1s. Compound symmetry was evaluated with the Mauchly’s test and Greenhouse-Geisser correction was used when indicated. Significance was set at p < 0.05.

RESULTS

Peak-to-peak amplitudes did not show significant target x hemisphere (F\textsubscript{1,7} = 2.8, p = 0.137, \eta\textsubscript{p}^2 = 0.29), intensity x hemisphere (F\textsubscript{4,4} = 2.8, p = 0.170, \eta\textsubscript{p}^2 = 0.74), or target x intensity x hemisphere (F\textsubscript{4,4} = 0.8, p = 0.598, \eta\textsubscript{p}^2 = 0.43) interactions, suggesting anatomical symmetry in S1-M1 connections in the left and right hemispheres in each intensity after both M1- and S1 stimulation. These data allowed us to pool data across...
hemispheres into one analysis. Moreover, two subjects did not produce MEPs when stimulating the left dominant or right non-dominant S1, therefore we averaged the other 6 subjects’ data to perform the statistical analyses with equal numbers.\textsuperscript{25}

Table 1 summarizes the descriptive statistics and rANOVA results in each dependent variables. Clear and consistent waveforms were not detectable at 80 and 90% rMT intensities, therefore we performed the statistical analysis for latency data at 100-120% intensities. rANOVA with repeated measures on target and intensity revealed no target x intensity interaction, target- or intensity effect based on significance level, medium/large effect size (Table 1) (Figure 2A) suggest possible differences in latency with increased sample size.

Table 1: Descriptive statistics and the rANOVA results.

<table>
<thead>
<tr>
<th>Target</th>
<th>Intensity</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>80 90 100 110 120</td>
<td>80 90 100 110 120</td>
</tr>
<tr>
<td>SD</td>
<td>5.4 5.4 4.8 4.7</td>
<td>3.6 4.1 4.7</td>
</tr>
<tr>
<td>Peak-to-peak amplitudes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.79 2.82 9.08 19.42 28.21</td>
<td>1.73 2.36 4.86 13.97 19.31</td>
</tr>
<tr>
<td>SD</td>
<td>1.99 2.59 6.67 11.18 17.70</td>
<td>1.44 2.17 5.25 12.30 15.01</td>
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<tr>
<td>Variability</td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>0.89 1.25 4.26 7.62 9.04</td>
<td>0.41 0.60 1.29 7.84 7.04</td>
</tr>
<tr>
<td>SD</td>
<td>2.33 1.34 2.99 5.44 5.63</td>
<td>0.67 0.94 1.42 12.17 7.40</td>
</tr>
</tbody>
</table>

* \( p < .05 \)
** \( p < .01 \)
*** \( p < .001 \)

Figure 2. Latency (Panel A), normalized peak-to-peak amplitudes (Panel B), and variability of S1 vs. M1 stimulation-evoked MEPs (Panel C) after M1 (filled boxes) vs. S1 (empty boxes) stimulation in each intensity. Two subjects did not produce MEPs when stimulating the left dominant or right non-dominant S1, therefore we averaged the other 6 subjects’ data to perform the statistical analyses with equal numbers. Peak-to-peak amplitudes were normalized by maximal compound action potential. The boxplots show the median, the upper, and lower quartiles and the min and max values of the dependent variables. Vertical error bars denote +1SD. \( \dagger \) significant target x intensity interaction.
We found target x intensity interaction ($F_{4.60} = 6.2, \eta_p^2 = 0.29$), and significant effect of target ($F_{1.15} = 18.4, \eta_p^2 = 0.55$) and intensity ($F_{4.60} = 114.7, \eta_p^2 = 0.88$), with the post-hoc analysis showing significantly larger peak-to-peak amplitudes after M1 stimulation, and also with increased intensity, regardless of target (Figure 2B).

Concerning the variability of M1 vs. S1 stimulation-induced MEPs, there were a significant target x intensity interaction ($F_{4.60} = 3.8, \eta_p^2 = 0.20$), a target ($F_{1.15} = 8.1, \eta_p^2 = 0.35$), and an intensity effect ($F_{4.60} = 41.7, \eta_p^2 = 0.74$). Specifically, variability of MEPs was greater after M1 vs. S1 stimulation so that variability increased with stimulation intensity (Figure 2C).

DISCUSSION

The aim of the present pilot study was to determine the effects of stimulation location, i.e., S1 vs. M1, on MEP waveform-related parameters, including amplitude, latency, and variability in the contralateral FCR muscle. We hypothesized that stimulating S1 vs. M1 would produce smaller MEP size, greater MEP variability but no difference in MEP latency. These expectations are based on the poor focality of the magnetic pulse: even if TMS is guided by neuronavigation the pulse is wide enough to excite M1 interneurons when S1 is targeted. Based on previous studies on hemispheric asymmetry, we also hypothesized inter-hemispheric differences in MEPs when stimulating dominant left and non-dominant right S1 or M1. We found no inter-hemispheric differences, but larger peak-to-peak amplitudes and variability of MEPs after M1 as compared to S1 stimulation. However, latency and waveforms of MEPs did not differ between S1 vs. M1 stimulation supporting the idea that TMS over S1 is not selective enough and can excite M1 interneurons thus producing MEPs on the contralateral FCR.

TMS over S1 has been often used to determine its effects on kinesthetic perception\textsuperscript{17} or motor learning.\textsuperscript{18} In these studies, S1 anatomical location was determined by moving the TMS coil one gyrus backward and approximately 1 cm laterally from the M1 hotspots of the targeted muscle, and they proved prior to the rTMS stimulation that single pulse TMS over S1 would not result in MEPs. These studies, however, used different size coils and always targeted the ECR\textsuperscript{18} or FDI\textsuperscript{18}, but never the FCR. Although the coil and intensity used for stimulation, and also the targeted muscle of the previous studies were different from ours, the distance between S1 and M1 for each muscle group is too small to be selective. The difference in the target muscles, therefore, cannot be considered as a potential explanation for the lack of MEPs after S1 stimulation in previous studies. Nevertheless, while these previous studies demonstrated evidence for selective stimulation of S1 and M1 when targeting the FDI or ECR, our results support the idea that stimulation of S1 can result in MEPs in the contralateral FCR through exciting M1 interneurons. It is not surprising because the field induced by TMS is not distinctly confined to the target region,\textsuperscript{26} as the field covers an influential magnetic field in the brain tissue up to 140mm radial area from the center of the double-cone coil with smaller peripheral peaks of approximately 50% the amplitude of the central peak on either side of the winding,\textsuperscript{3} therefore stimulation of S1, 1 cm laterally and one gyrus back from M1 hotspot can reach the interneurons of the motor cortex, nevertheless, at a smaller intensity. This is in line with our results showing that peak-to-peak amplitudes and variability of S1 as compared to M1 stimulation-induced MEPs were significantly smaller. In the present study, only 6 out of 8
subject produced MEPs in response to single pulse TMS, it is therefore possible that the lack of MEPs in previous studies after delivering single pulse TMS over S1 could be due to the large inter-subject and/or inter-trial variability. Moreover, we demonstrated S1 stimulation-induced MEPs only at 100-120% rMT intensities, using a smaller intensity therefore might not result in consistent and observable MEPs thus the used intensity can also affect the results.

Brown et al.\textsuperscript{19} found that MEPs could only be recorded after S1 stimulation with 25mm coils in 4 out of 16 participants (25%) and 7 out of 16 (44%) with 40/50 mm coils with active contraction. In our study, we used an even larger, 90 mm outer diameter figure-of-eight coil, and recorded MEPs after S1 stimulation in 6 out of 8 participants (75%). It is, therefore, likely that the larger the diameter of the coil, the greater the chance for recording MEPs after S1 stimulation. Therefore, we suggest the wing of the coil we used extended over M1 during S1 stimulation, producing MEPs in the FCR.

Hypothetically it could be possible that a TMS stimulus over S1 may induce skeletal muscle response via cortico-motor connections, resulting in a descending volley to the muscle thus inducing an MEP, however, latency of these MEPs would be longer as compared to M1 stimulation-evoked MEPs.\textsuperscript{13} Our results, in contrast, revealed no differences in latency of S1 vs. M1 stimulation-induced MEPs and their similar waveform (Figure 3) also strengthens the idea that MEPs in response to TMS over S1 were due to the excitement of M1 interneurons by the TMS-induced magnetic field. Because sensorimotor performance is known to have a hemispheric asymmetry that underlies dynamic coordination,\textsuperscript{20} we aimed to determine whether inter-hemispheric differences in MEPs occur when stimulating dominant left and non-dominant right S1 or M1. Under the present experimental setup, we found no inter-hemispheric differences, suggesting that TMS over S1 using a figure-of-eight coil is not selective enough and can produce MEPs on the contralateral FCRs, irrespective of hemisphere.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Averaged MEP waveforms in each target, hemisphere and intensity from a representative subject. Each trace the average of five individual trials. The first vertical line represents the TMS onset, while the second and third vertical lines show the measurement window for MEPs.
Limitations of this study are its exploratory nature and the small sample size. These preliminary data however may be useful for researchers who aim to target/stimulate S1 (e.g. using rTMS). If the magnetic field produced by TMS over S1 can reach M1 interneurons, it is possible that the observed changes in motor outcome (improved motor control or learning) is due to the direct stimulation of M1 interneurons and not cortico-cortical connections. Finally, it may be useful for future studies to determine if muscle contraction affect S1 stimulation-induced MEPs the same way as do contractions affect M1 stimulation-induced MEPs.

CONCLUSION

In conclusion, navigated TMS over S1 produced MEPs in healthy adults’ wrist flexors, irrespective of hemisphere most probably due to the excitation of M1 interneurons by the spreading magnetic pulse. Although M1 as compared to S1 stimulation resulted in larger and more variable peak-to-peak amplitudes, latency and waveforms of MEPs did not differ between the two loci supporting the idea that TMS over S1 using a figure-of-eight coil is not selective enough and can produce MEPs on the contralateral FCRs. Future studies should carefully consider these results when targeting S1 with TMS even if using a neuronavigation system.

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