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Visual Attention Affects the Amplitude of the Transcranial Magnetic Stimulation-Associated Motor Evoked Potential: A Preliminary Study With Clinical Utility

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Abstract

Background—The transcranial magnetic stimulation (TMS)-elicited motor evoked potential (MEP) is a valuable measure for clinical evaluations of various neurological disorders and is used to determine resting motor threshold for repetitive TMS dosing. While MEP amplitude is primarily associated with motor system function, there is evidence that nonmotor factors may also influence amplitude. This experiment tested the hypotheses that manipulation of 2 factors (visual attention, cognitive regulation) in human participants would significantly affect MEP amplitude.

Methods—Blocks of MEPs were recorded from the dominant right hand as participants ($N = 20$) were instructed to shift their visual attention (toward and away from the hand) and cognitively regulate the MEPs (rest, attenuate MEP amplitude, potentiate MEP amplitude) using their thoughts (6 blocks, 20 pulses/block, randomized, 110% resting motor threshold).

Results—MEP amplitude was significantly affected by the direction of visual attention; looking away from the hand led to higher amplitudes ($P = 0.003$). The relationship with cognitive regulation was nonsignificant.

Conclusions—The significant effect of visual attention on MEP suggests that this should be a standardized parameter in clinical and research studies. These data underscore the importance of rigorous reporting of methods and use of standardized practices for MEP acquisition and TMS dosing to ensure consistent clinical measurement and treatment.

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The authors declare no conflicts of interest.

Keywords

transcranial magnetic stimulation; motor evoked potentials; resting motor threshold; visual attention; cognitive regulation; procedure standardization

Transcranial magnetic stimulation (TMS) administered over the motor cortex generates a motor evoked potential (MEP) in peripheral target muscles, which is typically recorded in the hand using surface electromyography (EMG) electrodes. MEPs are a tolerable, noninvasive measure of cortical excitability and have clinical utility in various neurological disorders including stroke,¹ multiple sclerosis,² and Bell's Palsy.³ MEPs are also used in determining an individual's resting motor threshold (RMT), which is used as the primary dosing parameter for repetitive TMS (rTMS).⁴ While RMT will vary between individuals, RMT typically has very high test-retest reliability within an individual,^{5,6} which is important for rTMS treatment regimens involving multiple visits over several weeks in which RMT is typically measured only on the first visit.

A growing body of research suggests that it is possible to change an individual's corticomotor excitability through manipulation of attention and cognitive state. Ruge et al⁷ have demonstrated decreases in MEP amplitude when attention is directed internally to the hand receiving TMS relative to when attention is directed toward a visual search task. In addition, Fadiga et al⁸ have shown that the observation of another's arm movements and grasping of objects increases MEP amplitude. Cognitive manipulations, such as motor imagery, have also been shown to increase MEP amplitude.⁹ Motivationally relevant positive and negative emotional pictures have also been shown to increase MEP amplitude, further underscoring the state-dependent nature of corticomotor excitability.¹⁰ Additional studies have shown that MEP amplitude can be reduced as subjects attempt to cognitively regulate TMS-evoked perturbations to movement,¹¹ imagine suppression of TMS-induced twitching,¹² and inhibit motor responses as part of a go/no-go task.¹³ Together these data suggest that MEPs may be vulnerable to influence in a patient receiving TMS by both visual attention to external phenomena and internal cognitive states, which may have significant clinical implications. Furthermore, it is also possible that visual and cognitive influences on MEP amplitude may co-occur during TMS administration; however the interactive effects of these manipulations are unclear. Taken together, these findings warrant an examination of state-effects on MEPs that may decrease the clinical reliability of this measure. State-effects on MEPs may also affect RMT and point to the need for further evaluation of RMT as a reliable method for determining individual rTMS dosage, as recently highlighted by Siebner and Ziemann.¹⁴

The purpose of this clinically relevant research study was to investigate the effects of visual attention to the target hand responding to appropriately placed cortical TMS as well as the effects of a participant's cognitive regulation on resultant MEP amplitude and latency. Healthy participants were instructed to attempt to influence the amplitude of an MEP through thoughts directed toward active potentiation or attenuation of the response, while either directing gaze toward or away from the target hand. We hypothesized that visual attention to the target hand would decrease MEP amplitude and that cognitive potentiation

and attenuation of the TMS response would lead to relatively greater and lesser MEP amplitude, respectively. We further hypothesized that MEP latency would be relatively unaffected by the experimental manipulations. An additional exploratory aim of the study was to examine relationships between individual variability in MEP amplitude and self-reported confidence in the effectiveness of cognitive regulation during the experiment.

METHODS

Subjects

Healthy, right-handed participants were recruited from the Charleston, South Carolina area. Participants provided written informed consent to participate in procedures approved by the Medical University of South Carolina Institutional Review Board. Exclusion criteria included a current chronic health condition, history of psychiatric or neurologic disease, presence of metal in the body, and a lifetime history of head injury with loss of consciousness. Data were acquired from 20 participants [11 female, 9 male; mean age (SD) 25.8 (5.6) yr].

Experimental Setup and RMT calculation

Using standardized procedures, the participants were seated comfortably in a chair surrounded by an adjustable metal frame used to position the TMS coil (Magstim D70 Alpha) connected to a Magstim BiStim² Stimulator (The Magstim Company Limited, Carmarthenshire, UK). The frame was adjusted to a position so that the participant could comfortably position his or her chin in a chinrest while the TMS coil was placed over the primary motor cortex of the left hemisphere. Surface EMG was recorded from the right abductor pollicis brevis (APB) muscle using Disposable Silver/Silver Chloride electrodes (VIASYS Healthcare, Neurocare Group, WI, US) in a belly-tendon montage with a ground on the back of the hand. Subjects placed their right hand in a relaxed position on a cushion. The EMG signal was band-pass filtered by a CED 1902 Signal conditioner and 1401 interface (Cambridge Electronic Design, Cambridge, UK) with frequencies of 25 and 1,000 Hz. CED Spike 2 software was used in the EMG recording system. All processing was performed on a computer, which then recorded and displayed each MEP on the screen. The optimal position of the magnetic coil for eliciting an MEP in the APB was determined by holding the coil tangential to the scalp, and moving it in a systematic grid search over the primary motor cortex.

RMT was defined as the minimum intensity needed to induce an MEP > 50 μ V peak-to-peak.¹⁵ In the EMG-parameter estimation by sequential testing (PEST) mode, this output was integrated with the PEST algorithm, and then the results of this calculation were used by the computer to control the subsequent settings on the Magstim TMS stimulator, allowing the PEST program to automatically change the TMS generator output setting according to the algorithm, until the final RMT was calculated.¹⁶ Once the optimal position for TMS stimulation in the left primary motor cortex was determined, it was marked on a plastic skull cap which was tied, secured under the chin, and used to monitor coil movement during the experimental procedure. RMT was then measured for each individual 3 times and the average was used for the following experimental procedure.

Experimental Procedure

Participants received 6 blocks of TMS pulses at 110% of RMT, with 20 single pulses per block (3–5 sec interpulse interval). The intensity level of 110% RMT was chosen to reliably elicit an MEP response while maintaining responses of a small enough magnitude to still be subject to influence by cognitive manipulations (eg, as in a study by Kiers et al¹⁷). The interpulse interval was jittered within each block to minimize the effect of conditioning. The blocks varied on the basis of visual attention (viewing the hand versus looking away from the hand) and cognitive regulation (resting, attempting to attenuate the TMS-evoked twitch, attempting to potentiate the TMS-evoked twitch). These 6 experimental blocks (RV, RNV, AV, ANV, PV, and PNV, with R = rest, A = attenuate, P = potentiate, V = view, NV = no view) were administered in a pseudo-random, counterbalanced order, with the 2 Rest conditions (RV, RNV) administered first and the 4 Cognitive conditions (AV, ANV, PV, PNV) administered next. After 10 pulses within each condition, there was a pause of approximately 3 seconds during which the participants were encouraged to rest their eyes, in order to minimize the effects of visual fatigue on the results. The experimental procedure is outlined graphically in Figure 1.

Participants were given standardized instructions for each block (See Supplemental Digital Content 1 for the script used for giving instructions). Participants were instructed either to keep their eyes fixed on the hand receiving the TMS pulses or to keep their eyes fixed on a standard object on the wall. Immediately prior to the experimental blocks under the attenuate/potentiate conditions, participants were told: “Use your thoughts to make the TMS-induced twitches smaller/larger.” Specific suggestions were also given to participants, using the standard script, for various strategies by which to attenuate and potentiate the MEPs, such as motor imagery (“Imagine you are moving your thumb using the muscle the TMS is causing to twitch”), distraction (“Distract yourself mentally from the twitching”), and focused relaxation (“Focus on relaxing your thumb”). This approach allowed participants to implement individually selected cognitive strategies to achieve their regulatory goals, similar to approaches used in fMRI neurofeedback studies (eg, as in a study by Hartwell et al¹⁸). Participants faced a monitor that displayed brief plain-text reminders of the instructions for each block (eg, “Look at hand, use thoughts to make twitches smaller.”) Pauses of 20 seconds or more between each condition (during which instructions were given and pulse sequence programs were initiated) minimized any effects of hysteresis between conditions.¹⁹

After all 6 experimental blocks concluded, each participant filled out a brief questionnaire regarding strategies employed (i.e. “What strategy did you use to make the TMS twitch smaller/larger?”) and their self-reported confidence in their ability to cognitively regulate the MEPs (i.e. “How effective were you at using your thoughts to make the TMS twitches smaller/larger when you were looking at/away from your hand”, reported on a 1–10 scale).

Data Processing and Analysis

To control for the effects of muscle tension, which occasionally occurred prior to the TMS pulse and which would influence MEP amplitude, traces were visually examined and removed from analysis if EMG activity was evident prior to stimulation onset. MEP

amplitude and latency were computed using a custom-made program in LINQPad. MEP amplitude (in millivolts) was defined as the distance from a negative peak to a positive peak in the waveform. MEP latency was defined as the time (in milliseconds) following the TMS trigger at which amplitude exceeded 5 standard deviations from the mean amplitude of the noise sampled from –210 to –10 msec before the trigger. The program output was validated by randomly selecting 5 data files and comparing the latency measurements with those obtained by manual cursor placement at the apparent onset and offset of the MEP in Spike 2 by 2 independent researchers. Latency data obtained through the program differed from manual measurement by less than 5%. Three subjects' data required complete manual analysis due to small gaps in recording that made the data files incompatible with the analysis program.

The effect of the resting visual condition on MEP amplitude and latency was determined by comparing the two rest conditions using a Wilcoxon signed-rank test for each measure. To determine the interaction of the visual attention and cognitive regulation strategies, a repeated-measures generalized linear model was fitted for the outcome of MEP peak-to-peak amplitude in the 4 cognitive conditions. The outcome was log-transformed because the data were not normally distributed. Visual and cognitive conditions, as well as their interaction, were used as covariates in the model. This model was then repeated for the latency measures. Spearman rank correlations were used to assess the linear relationship between mean MEP amplitude and self-reported confidence ratings. *P* values were considered significant at an alpha level of 5%, except when multiple comparisons were made and a Bonferroni adjustment was needed. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

The mean RMT for the study participants was 41.65% (SD 8.51%) of maximal machine output. The peak-to-peak amplitudes (millivolts [mV]) for the 6 conditions are shown in Table 1. (See the figure in Supplemental Digital Content 2 for distributions of MEP amplitudes for each subject for the Rest conditions.) Although interpulse intervals similar to those we employed have been shown to have a cumulative effect on MEP amplitude over time,²⁰ we did not find significant relationships between pulse order and MEP amplitude in any of the conditions (See the figure in Supplemental Digital Content 3 for plots.). Latency values (seconds) for the 6 conditions are detailed in Table 1.

Rest Conditions (Figure 2)

The Wilcoxon signed-rank test revealed that MEP amplitude (peak-to-peak) was significantly greater during the rest no view (RNV) condition compared to the rest view (RV) condition ($P = 0.003$) (Figure 2). No significant difference in latency was observed between the two conditions.

Cognitive Conditions (Attenuate/Potentiate x View/No View) (Figure 3)

MEP Amplitude—A repeated measures ANOVA revealed a main effect of cognitive strategy ($F(1,1431) = 5.50$, $P = 0.0192$). The main effect of visual attention ($F(1,1431) =$

0.01, $P = 0.93$) and the interaction between the visual and cognitive manipulations were not significant ($F(1,1431) = 0.24$, $P = 0.62$).

Latency—A repeated measures ANOVA revealed a main effect of cognitive strategy ($F(1,1499) = 9.79$, $P = 0.0018$) but no main effect of visual attention ($F(1,1499) = 1.33$, $P = 0.25$) nor of the interaction between cognitive and visual manipulations ($F(1,1499) = 0.54$, $P = 0.46$).

Self-reported confidence ratings, reported on a scale from 1 to 10 for each of the cognitive conditions, were as follows [mean (SD)]: PNV, 4.85 (2.37); ANV, 4.85 (2.56); PV, 5.60 (2.16); 4.85 (2.37). Significant negative Spearman correlations were found between self-reported confidence and mean MEP amplitude in the AV and ANV conditions (AV: $\rho = -0.51$, $P = 0.02$; ANV: $\rho = -0.58$, $P = 0.01$), ie, lower confidence was associated with higher mean MEP when attempting to attenuate, both when directing visual attention toward or away from the hand (Figure 4). Correlations between self-reported confidence and mean MEP amplitude were non-significant in the PV and PNV conditions ($P > 0.1$, data not shown).

DISCUSSION

As the clinical utility of TMS grows, the importance of standardizing procedures in clinical practice and research is increasingly underscored. In this investigation we sought to determine whether visual attention to the hand or cognitive regulation had a reliable effect on MEP amplitude, and whether these factors interact. In line with our hypothesis, our results indicate that direction of visual attention toward or away from the target hand has a significant effect on MEP. Cognitive regulation strategies for potentiating or attenuating, however, failed to reliably produce the intended effects of increasing or decreasing MEP amplitude, contrary to our hypothesis. In addition, we found that the individual's confidence in the ability to attenuate MEPs may influence individual effectiveness in MEP amplitude modulation.

Perhaps the most important and clinically relevant finding of this study was the effect of visual attention on MEP amplitude but not MEP latency. We determined that, at baseline, there was a significant increase in MEP when looking away from the hand receiving stimulation as compared to looking at the hand. We observed a 17.8% increase in MEP amplitude when visual attention was directed away from the hand affected by the cortical stimulation. This effect, while mild, is nevertheless clinically significant—similar in magnitude to the 22% increase in MEP amplitude previously reported following administration of reboxetine, a norepinephrine reuptake inhibitor.²¹

The increase in cortical excitability when looking away from the target hand could be explained by an external versus internal focus of attention when the subjects fixed their gaze on an external target. Although subjects were not explicitly instructed or trained in external attentional focusing strategies, the target of eye fixation is generally tightly correlated with the target of attention.^{22,23} Our result is consistent with the findings of Ruge et al⁷ that MEP amplitude was increased when attention was directed externally to a visual attention task.

Previous fMRI research has also shown that visual attention modulates activity in motor cortex during movement²⁴ and that externally focused attention leads to greater activation in motor cortex than internally focused attention.²⁵ In the study by Zentgraf et al.,²⁵ activity was also more widespread in the external focus condition, perhaps indicating that an exteroceptive focus is associated with less specific activation, as postulated by Ruge et al.⁷ Less focused, increased cortical activation while subjects directed visual attention away from the target hand may explain the increased MEP amplitude we observed in this condition in our study.

We also found that participants were unable to reliably decrease their MEP amplitude when instructed to attenuate it, and they were unable to reliably increase the MEPs when instructed to potentiate. This was true regardless of whether they were looking at or away from the target hand. Although a statistically significant main effect of cognitive condition on MEP amplitude was found, the largest magnitude of difference between potentiate and attenuate conditions was approximately 3%, which is unlikely to represent any clinical significance. This finding was unexpected based on previous literature that has demonstrated some efficacy of individuals to modulate MEP amplitude using various cognitive strategies.^{11,12} These discrepant results may be due to the variability of options suggested to participants in our study with regard to cognitive strategies to employ during cognitive regulation. Subjects were instructed to use their thoughts to potentiate/attenuate the TMS-induced responses and were given suggestions of various cognitive strategies to use in order to reach this goal, including mental imagery, distraction, and focused relaxation. Variability in cognitive strategies employed across subjects and within experimental sessions likely contributed to our null findings. Our objective, however, was not to assess the effects of one specific strategy on MEP, but to assess whether subjects could employ various, self-selected strategies to accomplish a specified directive to manipulate their responses to TMS. We speculate that this aspect of our experimental design, similar to the design of real-time fMRI neurofeedback studies,¹⁸ may be more representative of real-world scenarios. However, it should also be noted that the subjects were not trained in cognitive regulation strategies before the experiment; we therefore cannot conclude from our data that cognitive regulation has no effect on MEP amplitude and recommend future research investigating this question.

We observed a significant main effect of cognitive condition on MEP latency. MEP latency is of interest as it has been shown to have prognostic and diagnostic value in various pathologies. For example, MEP latency has been shown to be significantly longer among patients with amyotrophic lateral sclerosis,²⁶ and abnormalities in MEP latency have been observed in other neurological disorders, including multiple sclerosis²⁷ and stroke.²⁸ The greatest difference we observed between the attenuate and potentiate conditions was 0.2 msec or 1.3% (mean PNV minus mean ANV). We postulate that this slight difference in latency can be explained by the change in MEP amplitude, as changes in amplitude often co-occur with changes in latency.²⁹ As with the main effect of cognitive condition on amplitude, we interpret this main effect with caution as it is likely too small to be clinically significant, unlike our principal finding of a 17.8% difference in amplitude due to visual attention at rest. Average PNV latency was approximately 0.15 standard deviations greater than average ANV latency. In contrast, Kale et al.,²⁷ for example, considered MEP latencies

in multiple sclerosis patients to be abnormal if they were more than 2.5 standard deviations from the normative mean.

Although we found that subjects overall were unsuccessful in achieving their goal of influencing MEP, individual differences in MEP amplitude while attenuating MEPs (regardless of direction of visual attention), were negatively correlated with self-reported confidence in ability to attenuate them (a similar relationship was nonsignificant for the "potentiate" conditions). Although these findings are exploratory, these and other individual differences in capacity to attenuate/potentiate TMS-induced responses (eg, trait mindfulness) warrant further investigation. Perhaps suggestive of a similar effect of self-confidence on cortical excitability, an anxiety-related personality trait has previously been shown to influence motor cortex excitability in a paired-pulse TMS study³⁰ (note, however, that a replication of this study failed to find a similar effect³¹).

From a clinical practice perspective, our findings support the concept that variability could be minimized if clinicians standardized their procedures for direction of visual attention during the administration of TMS. From a research perspective, it also suggests that visual attention should be controlled in a uniform manner as standard procedure in clinical trials. To date, no research manuscripts of which we are aware indicate standardizing direction of visual attention during RMT acquisition or other protocols. In an effort to create robust, replicable studies, our data indicate that controlling for the direction of gaze either toward or away from the hand is an important element to include in manuscripts and protocol designs. The outcomes of this study demonstrate, namely, that MEP amplitude was 17.8% higher when looking away from the hand. This could lead to errors and variability in clinical measurements and subsequent treatment decisions. Although increases in MEP amplitude are not always concurrent with decreases in RMT, the results of this preliminary study also point to the need for further investigation on the effects of visual attention on rTMS dosing procedures.

Primary limitations of this study include the exclusive use of only healthy adult participants; different results might be obtained in clinical populations in which MEPs are measured for diagnostic purposes. In addition, MEP amplitude can be influenced, likely at the spinal level, by subtle postural adjustments.³² Although the chin rest and head frame used during the study minimized postural changes between conditions, the effect of subtle postural adjustments on MEP amplitude (eg, in shoulder abduction) cannot be completely ruled out and represents an additional caveat in the interpretation of the findings. Furthermore, although all participants endorsed right-handedness, this was not assessed in a quantitative manner and therefore it is not clear if degree of handedness or dexterity contributed to variability in the data. Nonetheless, we believe that standardization of the experimental procedures and the repeated-measures design have minimized any effects of this limitation on the results. Applicability to clinical administration of repetitive TMS, in which patients complete multiple TMS sessions, is limited also by the single-session design. Future studies could investigate whether the effects of visual attention on amplitude are durable over multiple sessions.

CONCLUSIONS

From this study, we conclude that direction of visual attention may affect MEP amplitude at rest. We failed to find sufficient evidence to conclude that using thoughts to increase or decrease motor responses to TMS had a clinically significant effect on MEP amplitude, or that visual attention significantly interacted with this manipulation. Our results suggest, however, that confidence in the ability to attenuate the response to TMS is associated with lower MEP amplitude when engaged in this strategy. Considered together, these preliminary results point to the need for more rigorous testing of TMS administration standards in research and treatment as well as suggest possible avenues for future investigation of individual differences in TMS response and the modulation thereof.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Experimental Procedure

After resting motor threshold (RMT) was computed, subjects each completed 6 experimental blocks in a 2×3 factorial design. Subjects received 20 pulses of TMS in each experimental block at 110% of RMT. The 6 conditions varied on the basis of direction of visual attention and cognitive regulation manipulation. Labels RV, RNV, AV, ANV, PV, and PNV indicate the following: R=Rest, A=Attenuate, P=Potentiate, V=View (view hand), NV=No View (do not view hand). Experimental blocks were administered in a pseudo-random, counterbalanced order, with the two Rest conditions always administered first.

Figure 2. Motor Evoked Potential (MEP) Amplitude (a) and Latency (b) Measures During the Rest View (RV) and Rest No View (RNV) Conditions

Wilcoxon signed-rank tests were performed for each measure to determine if there was a difference between viewing conditions at rest (* $P < 0.005$). The mean peak-to-peak MEP amplitudes was significantly larger during the rest no view condition than during the rest view condition. No difference in mean latency was seen between the 2 conditions. Displayed as mean $\pm$ standard error.

Figure 3. Motor Evoked Potential (MEP) Amplitude (a) and Latency (b.) Measures During the Various Cognitive and Visual Manipulations

PV=potentiate view, PNV=potentiate no view, AV=attenuate view, ANV=attenuate no view

A repeated measures analysis of variance (ANOVA) revealed a main effect of cognitive regulation for both measures but no main effect of visual attention interactions of visual attention x cognitive manipulation. Displayed as mean $\pm$ standard error.

Figure 4. Correlations Between Self-Reported Confidence Ratings and Motor Evoked Potential (MEP) Amplitude

Mean MEP amplitude is negatively correlated with self-reported confidence rating during both (a) Attenuate View (AV) and (b) Attenuate No View (ANV) conditions.

Table 1

Motor Evoked Potential Dependent Measures

	Mean Amplitude (SD) (mv)	Mean Latency (SD) (ms)
<i>Rest Conditions</i>		
RV	0.523 (0.682)	0.0235 (0.00149)
RNV	0.616 (0.659)	0.0236 (0.00192)
<i>Cognitive Conditions</i>		
PV	0.573 (0.903)	0.0236 (0.00129)
PNV	0.557 (0.651)	0.0238 (0.00175)
AV	0.593 (0.692)	0.0236 (0.00184)
ANV	0.600 (0.704)	0.0235 (0.00180)

A indicates attenuate, mv millivolts, NV no view, P potentiate, R rest, ms milliseconds, V = view