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Prestimulus cortical EEG oscillations can predict the excitability of the primary motor cortex

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ABSTRACT

Background: The motor evoked potentials (MEPs) elicited by single-pulse transcranial magnetic stimulation (TMS) vary considerably at rest, but the mechanism underlying this amplitude variation is largely unknown. We hypothesized that prestimulus EEG oscillations modulate the subsequent MEPs in a state-dependent manner.

Objective: We studied the relationship between prestimulus alpha/beta oscillations and MEPs during eyes open (EO)/closed (EC) conditions, and then modulated TMS intensity in the EO condition. Furthermore, we developed an EEG-triggered TMS system ("informed open-loop") to verify our hypothesis.

Methods: TMS was applied to the left motor cortex. We first compared EEG power differences between high- and low-amplitude MEP epochs in the EO and EC conditions when using a high TMS intensity. Next, we evaluated the effects of varying TMS intensities (high vs. low) on the EEG–MEP relationship. Finally, we used EEG-triggered TMS to determine whether prestimulus EEG oscillations predicted MEP amplitudes.

Results: Prestimulus higher-power alpha/low-beta bands produced larger MEPs only in the high-intensity EO condition. A positive relationship between EEG power and MEP amplitude was observed at C3 and left frontal electrodes. This relationship was obscured when using the lower TMS intensity but was observed in the high-intensity condition at the C3 electrode. EEG-triggered TMS demonstrated that higher alpha power predicted higher MEP amplitudes, but beta power at around 20 Hz did not.

Conclusions: A causal relationship between alpha/low-beta oscillations and MEP amplitudes at rest requires high TMS intensity delivered when eyes are open. This association may allow us to develop a new informed open-loop TMS protocol.

Introduction

Motor evoked-potential (MEP) amplitudes reflect the excitability of primary motor cortex (M1) and the spinal cord. MEP and H-reflex amplitudes (a measurement of spinal cord activity) are weakly and positively correlated, with amplitude variability being larger for MEPs [1]. Thus, MEP amplitudes primarily reflect M1 excitability. MEP amplitudes vary considerably, their coefficients of variance are reported to range from 20% to 100% [1,2]. Thus, MEP variability might interfere with the estimation of corticospinal excitability. Indeed, baseline MEP amplitudes have been reported to partially explain response variability in non-invasive brain stimulation (NIBS) [3]. Therefore, a better understanding of the neural substrates that govern MEP-amplitude fluctuation could lead to improved methods for obtaining stable MEP amplitudes and to a more sensitive estimation of NIBS effects.

Electroencephalography (EEG) is widely used to measure cortical activity, and alpha/beta oscillations are generally considered to be linked to several processes, including the inhibition of irrelevant processing, maintenance of movement, and sensorimotor integration during various task conditions [4–6]. In line with this outlook, M1 excitability is enhanced in many motor-task conditions, such as motor execution, observation, and imagery, while at the same time, alpha/beta oscillations are suppressed [7–11]. Additionally, several studies have shown that alpha/beta oscillations are inhibited when MEP amplitudes are large [12–15], although a statistically significant relationship has not always been observed [16,17]. Thus, alpha/beta oscillations are generally

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considered to be negatively correlated with cortical excitability when doing some action, but this relationship is not conclusive for amplitude fluctuations during resting states. Several studies have used transcranial magnetic stimulation (TMS) to study the EEG-MEP relationship, applying an intensity roughly equal to the resting motor threshold (RMT) [12–16]. This is lower than the intensity ordinarily used to obtain 1-mV MEPs (SI_{1mV}). While weak TMS (~RMT) over M1 only activates M1, higher intensity TMS also stimulates surrounding areas, such as the premotor area and primary sensory cortex (S1), which might influence MEP amplitudes. Recently, MEP amplitudes measured after stimulating with an intensity that can result in a half-maximum amplitude have been reported to be positively related to EEG alpha oscillations during resting states [18]. Therefore, the EEG–MEP relationship when using a higher TMS intensity such as SI_{1mV} is worth investigating.

Furthermore, eyes-open (EO) and eyes-closed (EC) states not only determine the visual input to the occipital cortex, but also modulate global connectivity [19]. MEPs are usually recorded during the EO state to ensure participant vigilance. However, if the relationship between EEG signals and MEP amplitudes depends on EO/EC at rest, considering these two conditions is important. To date, while a few studies have reported an effect of EO/EC on M1 excitability [20–22], how EO/EC states influence the EEG–MEPs relationship remains unknown.

Based on these findings, our first aim was to determine the relationship between prestimulus EEG alpha/beta band oscillations and MEP amplitude when delivering TMS at an SI_{1mV} intensity, during both EO and EC conditions. In a second experiment, we compared MEP amplitudes produced by high (SI_{1mV}) and low (RMT) TMS intensity in the EO condition. Finally, TMS modulation such as an informed open-loop or closed-loop stimulation has gained recent attention [23–25]. An informed open-loop refers to state-dependent adjustments in stimulus parameters such as time or intensity, while a closed-loop refers to stimulus-parameter adjustment based on participant feedback [25]. these are thought to have the potential to improve NIBS efficacy. Thus, in a third experiment, we developed an EEG-triggered informed open-loop TMS system to verify the findings of the first and second experiments. We also hoped that the informed open-loop TMS setup would help with the design of a new NIBS protocol for neuromodulation.

Methods

MEPs

A pair of electrodes were attached to the right first dorsal interosseous muscle (Fig. 1). The electromyographic (EMG) signal was amplified by Neuropack 8 (Nihon Kohden, Tokyo, Japan) with a 10–2000 Hz band-pass filter. The signal was sampled at 10 kHz and stored in a Windows PC for offline analysis by MultiScope PSTH (Medical Try System, Tokyo, Japan).A Magstim 200 (Magstim Co. Ltd., Whitland, UK) transcranial magnetic stimulator that delivered a monophasic pulse using a figure-8 coil (70-mm diameter) was used to stimulate the left-hand motor area of each participant. The coil was held so that its center was placed over the scalp with the handle pointed about 45° posterolaterally from the midline, which induced an anteromedial current in the brain. The hotspot was determined as the stimulation point that elicited the largest MEPs using a mild suprathreshold intensity, and was marked on the scalp with a pen to maintain a consistent position throughout the experiment.

EEG recordings

An EEG cap with 19 ring electrodes (EasyCap, EasyCap GmbH, Herrsching am Ammersee, Germany) was attached to the scalp according to the International 10–20 system. Additional electrodes were attached to both earlobes using cup electrodes with collodion, and the right earlobe was used as a reference. Impedance for each electrode was kept below 5 kΩ. A ground electrode was attached to the forehead. All the electrodes were connected to an EEG recorder (NeuroPrax, NeuroConn, Germany) with a sampling rate of 4096 Hz. Because the EEG recorder was a wideband system, EEGs were recorded without an online band-pass filter.

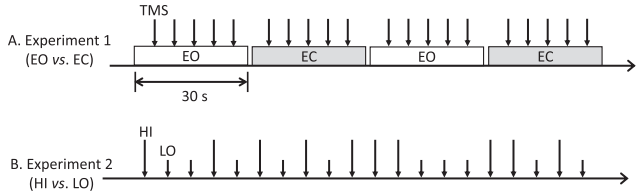

Fig. 1. *Experimental procedure for Experiments 1 and 2.*
(A) In Experiment 1, participants were instructed by a synthesized voice to open or close their eyes for 30 s in a 2-min session while TMS was delivered to their left M1 hotspot. Each session contained 20 pulses, 10 each for EO and EC conditions, and each participant completed at least 10 sessions. (B) In Experiment 2, high-intensity (SI_{1mV}) or low-intensity (RMT) TMS was administered in a pseudo-randomized order.
Abbreviations: *EO*, eyes open; *EC*, eyes closed; *HI*, high TMS intensity; *LO*, low TMS intensity; SI_{1mV}, stimulus intensity to obtain a MEP amplitude of approximately 1 mV; *RMT*, resting motor threshold.

Medical ethics

All participants gave written informed consent before the experiments in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Kyushu University.

Experiment 1. effects of EO and EC on the EEG–MEP relationship

Participants

Eighteen people participated in this experiment (7 females; mean age: 26.5 years; range: 21–50 years). All were right-handed based on self-report. None had a history of neurological or psychiatric disorders.

Procedure

Participants sat in a comfortable chair with a headrest and were instructed to relax their muscles during an approximately 2-min recording session with audiovisual feedback. Participants were instructed to open or close their eyes by a synthesized voice every 30 s within a session. Five seconds after each of these EO/EC instructions, TMS was delivered five times with an inter-stimulus interval ranging from 5 s to 7 s. Twenty TMS pulses were delivered per session, with 10 for each of the EO/EC conditions (Fig. 1A). The intensity was set to induce 0.5–1.5 mV amplitudes (SI_{1mV}) at rest. The condition order (EO/EC) was reversed in each session, and the starting condition (EO or EC) was counter-balanced among the participants. Ten to eleven sessions were recorded for each participant, which included at least 100 MEP and EEG epochs per condition. The audio instructions and the TMS onset time were controlled by Psychopy [26].

EEG and MEP data analysis

EEG data were imported to a personal computer using EEGlab [27]. The data were segmented into 3-s epochs from −3 s to 0 s before TMS onset so as not to include TMS artifacts. Epochs were visually inspected and excluded if EMGs >50 μV were detected in the interval between −250 ms and TMS onset. Fieldtrip [28] was then used for the following analysis. We removed the DC component of the signal by subtracting mean amplitudes from the epochs.

The signal was detrended if we observed a linear trend ≥100 μV. Independent component analysis was applied to identify and remove eye blinks and muscle artifacts. All epochs were then visually inspected and removed if they were contaminated by excessive residual noise. Next, epochs were zero-padded for 1 s after TMS onset and power values were calculated by wavelet analysis after having been remontaged by source derivation using the Hjorth montage [29]. The frequency range was set from 8 to 30 Hz by 1-Hz steps and time in steps of 50 ms between −500 and 0 ms before the TMS stimulus onset. Peak-to-peak MEP amplitudes were measured for each epoch and log-transformed to normalize the amplitude distribution [30]. Prestimulus EMG amplitudes between −100 and −1 ms were calculated using the root mean square. EEG epochs were categorized into two equal-sized groups (high or low MEP amplitude) based on their median MEP values for each participant. Thus, for each participant, the number of high- and low-amplitude epochs was almost the same. After log-transforming the power values and averaging them for each condition, we estimated the difference in EEG power between high- and low-amplitude MEP epochs by subtracting the mean power values of low-amplitude epochs from those of high-amplitude epochs. This was done for each time point, each frequency, and each electrode. Thus, the resulting values at a certain time, frequency, and electrode indicated whether or not EEG power was higher for high-amplitude MEP epochs than for low ones. A correlation analysis between prestimulus EEG power and MEP amplitudes was also performed for each time, frequency, and electrode.

Statistical analysis

We analyzed the power difference between high- and low-amplitude MEP epochs using paired t-tests. Clusters of significant differences ($p < 0.05$) were formed according to their adjacency of time (−500 to 0 ms), frequency (8–30 Hz), and electrode. Then, epochs of each cluster were randomized 5000 times to estimate the probability of less than 0.05 using a cluster-based permutation test [31], in which p-values were estimated by comparing the statistics (summed t-values) of the largest cluster with the histogram of the statistics constructed using the Monte Carlo method. Then, the p-value for the second largest cluster was calculated by comparing the second cluster with the same histogram used for the largest cluster. This technique solves the problem of multiple comparisons. The same analysis was conducted for the EO and EC conditions. MEP and prestimulus EMG amplitudes for the EO and EC conditions were compared using a linear mixed-effect model with a fixed effect of EO/EC conditions and a random effect of participants. Raw amplitudes (rather than mean amplitudes) were analyzed for each participant. A p-value less than 0.05 was considered to be significant for all analyses. Data are presented as the mean ± standard error of the mean if not specified.

Experiment 2. effects of high and low TMS intensities on the EEG–MEP relationship

We recruited 26 participants (11 females; mean age: 24.8 years; range: 20–40 years; 2 left-handed) for Experiment 2, among whom were 7 participants from Experiment 1. The entire recording session was conducted as an EO condition for all participants, and TMS intensity was set to high intensity (HI, SI_{1mV}) or low intensity (LO, RMT). RMT was determined as the intensity that elicited MEPs >50 μV in at least 5 out of 10 trials. In a session lasting about 2 min, 20 TMS pulses consisting of 10 HI and 10 LO pulses were delivered in a pseudo-randomized fashion (Fig. 1B). TMS intensity and time were controlled by Pulse Timer (Medical Try System, Tokyo, Japan). Each participant completed 10 to 11 sessions, and at least 100 HI and 100 LO epochs were obtained from each recording. EEG and MEP data were processed in the same way as in Experiment 1. Data from HI and LO conditions were analyzed separately.

Experiment 3. EEG-triggered TMS system

We recruited 18 participants (3 females; mean age: 26.1 years; range: 21–47 years; 1 left-handed) for this study, 5 of whom had participated in Experiments 1 and/or 2. Fig. 2 shows the experimental settings. In this experiment, C3 and four surrounding electrodes (F3, T3, P3, and Cz) were attached to the scalp, which was referenced to the linked earlobes. C3 was selected because it had exhibited a significant relationship to MEP amplitudes in Experiments 1 and 2, and because C3 was the closest electrode to the TMS coil. MEP electrodes were attached in the same way as in Experiments 1 and 2. EEG and MEP signals were amplified by Neuropack 8 with a band-pass filter of 1–200 Hz for EEG and 10–500 Hz for MEPs. The EEG and MEP data were digitized at 1000 Hz using an A/D converter (USB-6009, National Instruments, Austin, TX, USA), then transferred to a Windows PC for online processing. Signal processing was performed using the data acquisition toolbox in Matlab 2015b (Mathworks, Natick, MA, USA).

EEG data at C3 were re-referenced using recordings from the four surrounding electrodes, as in the Hjorth montage [29]. Thus, only data at C3 were analyzed in the following procedure (Fig. 2). EEG power was calculated by fast Fourier transform using 1-s data bins to achieve a 1-Hz resolution, which was updated every 0.1 s; thus, 0.9 s of the data overlapped. The frequencies of interest for alpha and low-beta bands (10–15 Hz) were selected based on the results of Experiments 1 and 2, and peak frequencies were determined in a 1-min preparatory session by recording and averaging the EEG power spectrum at rest in the EO condition. Peaks were identified in 12 participants and ranged from 10 to 13 Hz. In the same way, the 18–24 Hz frequency band was set as a control, and peaks of 19–24 Hz were identified in 12 participants. For the rest of the participants for whom clear peaks were not observed, we used 10 Hz for the alpha band and 20 Hz for the control frequency band. MEP recordings with EEG-triggered TMS were performed for 2 min per session. In each session, TMS was delivered when the power exceeded the upper or lower threshold. The thresholds were determined before each session and were based on the 10th percentile for the lower limit and the 90th percentile for the upper limit. When a trigger pulse was generated, the next trigger was inactivated for at least 4 s to wait for the next TMS. A minimum of 5 sessions was conducted to obtain more than 40 epochs each for the high-power and low-power conditions.

Data analysis

Epochs were excluded from analysis when excessive artifacts were visually observed in prestimulus EMGs or EEGs (which was less than 5 epochs for each participant). Log-transformed MEP amplitudes were calculated for each epoch. Prestimulus EMG amplitudes were estimated as the root mean square for the last 100 ms before TMS onset, as in Experiments 1 and 2. MEP and prestimulus EMG amplitudes were separated for the high-power and low-power conditions. Each amplitude for the two conditions was analyzed using a linear mixed-effect model with a fixed effect of EEG power condition (two levels: high or low power) and with a random effect of participants considering the participant dependency. Raw amplitudes (rather than mean amplitudes) were analyzed for each participant. Alpha-bands and beta-bands (around 20 Hz, the control frequency) were analyzed separately.

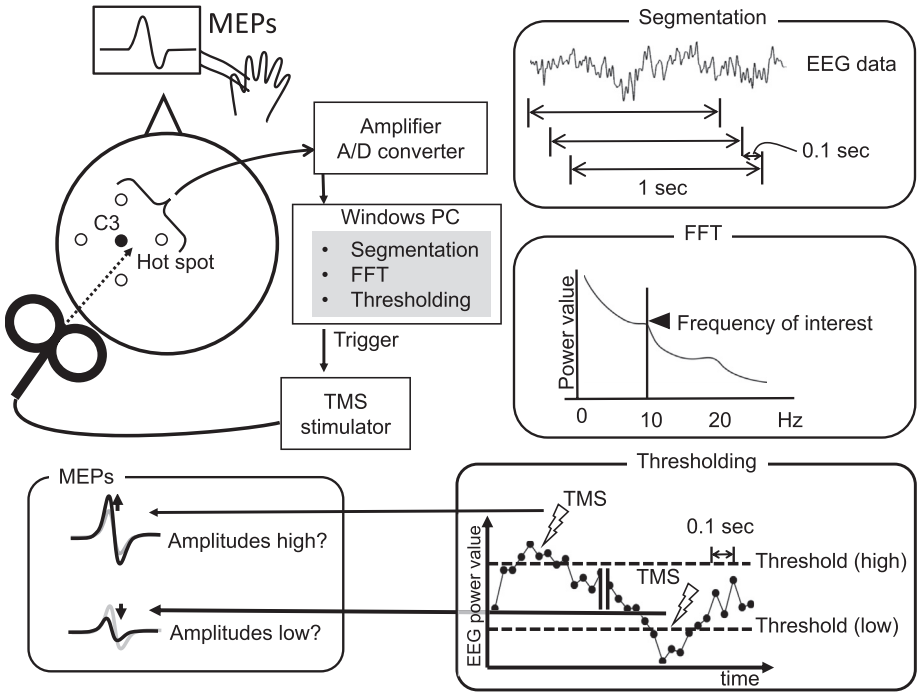

Fig. 2. *A schematic image of the EEG-triggered TMS system.*
(Upper left panel) The EEG-triggered TMS setup. EEGs were recorded at the C3 electrode and at our surrounding electrodes (F3, T3, P3, and Cz). Then, the C3 signal, subtracting the mean of the four surrounding electrode signals, was transferred to a Windows PC through an A/D converter at a sampling rate of 1000 Hz. This signal was segmented into 1-s epochs ("Segmentation"), which were transformed to a new power spectrum with fast Fourier transform ("FFT") every 0.1 s. When the power reached one of the predetermined high-power or low-power thresholds ("Thresholding"), a trigger pulse was delivered to the TMS generators to obtain MEPs ("MEPs").

Results

Experiment 1: differential effects of EO and EC on the EEG–MEP relationship

Power values ranging from 8 to 30 Hz and from −500 to 0 ms before TMS onset were compared between high-amplitude and low-amplitude MEP epochs. The average numbers of epochs were 94.5 ± 5.8 (mean ± SD) for the EO condition and 96.1 ± 5.3 for the EC condition. Data were separated according to the median MEP values in the EO (756.2 ± 373.4 μV) and EC (702.4 ± 311.6 μV) conditions, which did not significantly differ from each other ($p = 0.31$, paired *t*-test). The power was higher for high-amplitude MEP epochs at C3 in the alpha/low-beta bands during the EO condition (Fig. 3A). The power difference in the EC condition was similar to that in the EO condition, but less noticeable (Fig. 3B). The power difference in the EO condition was significant, as revealed by the cluster permutation test (Fig. 3C, $p = 0.0078$). A significant cluster was distributed from C3 to the left frontal region from −200 to 0 ms before TMS onset in the alpha/low-beta bands. We found no significant clusters in the EC condition. Thus, prestimulus alpha/low-beta oscillations were positively related to MEP amplitudes in the EO condition. However, this relationship was not found in the EC condition. Although correlation analysis also showed positive values for the alpha/low-beta band at C3, during EC, the correlation coefficients were generally low and were not statistically significant (Supplementary Figs. S1 and S2). Thus, using the power difference index is more appropriate than using the correlation analysis in this study. Regarding the prestimulus EMGs, we found no significant difference between high MEP epochs and low MEP epochs within the EO condition ($p = 0.298$), although we did find a small but significant difference within the EC condition (2.07 ± 0.08 vs. 1.93 ± 0.09 μV, $p = 0.0313$). Mean MEP amplitudes were 935 ± 82 μV for the EO condition and 883 ± 74 μV for the EC condition, which were significantly different ($p = 0.0158$).

Experiment 2: differential effects of TMS intensities on the EEG–MEP relationship

The TMS intensity was 52.3 ± 9.7% for the HI condition and 43.0 ± 6.3% for the LO condition. The TMS intensity for the HI condition was on average 121% of the RMT. The average numbers of EEG epochs were 94.6 ± 8.6 (mean ± SD) for the HI condition and 95.4 ± 8.3 for the LO condition. Data were separated by the median MEP values for HI (757.1 ± 239.3 μV) and LO (46.7 ± 29.2 μV) conditions. When the power difference was evaluated in the HI condition, as in the EO condition of Experiment 1, a higher EEG power was observed at the C3 electrode for the alpha/low-beta bands (Fig. 4A). Thus, when using an intensity of SI_{1mV}, alpha/low-beta bands had higher power for high MEP amplitudes than for low MEP amplitudes, as in Experiment 1. In contrast, when TMS intensity was lowered to RMT in the LO condition, the power difference was ambiguous (Fig. 4B). Similar to Experiment 1, although the correlation coefficients were also positive at the C3 electrode, they were generally low and were not statistically significant (Supplementary Fig. S3). The cluster permutation test of the power differences indicated no significant clusters for the HI condition. However, when we limited the EEG power estimation to the alpha/low-beta bands (10–15 Hz) based on the results in Experiment 1, a significant cluster was detected at C3 and P3 from −200 to −100 ms before TMS onset in the HI condition (Fig. 4C, $p = 0.0494$). This remained significant after excluding the 7 participants who had also participated in Experiment 1 ($p = 0.0194$), showing that a different sample population could produce results comparable with those from the EO condition in Experiment 1. However, no significant cluster was observed for the LO condition, regardless of

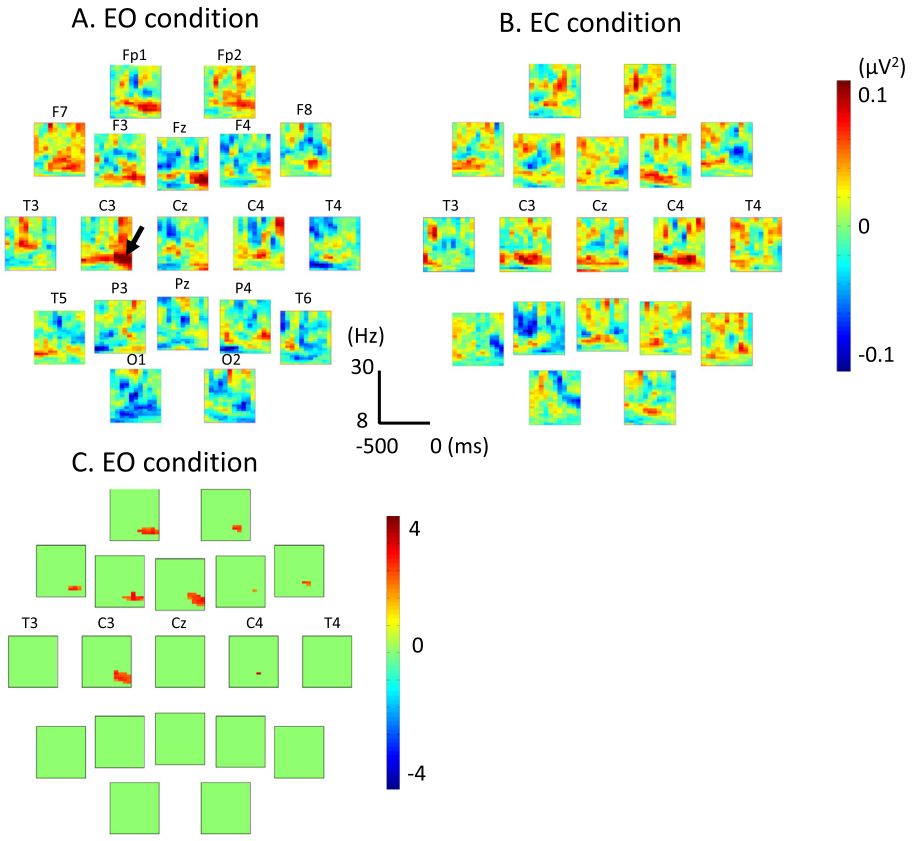

Fig. 3. *EEG power difference between high- and low-amplitude MEP epochs during eyes-open and eyes-closed conditions.*
(A) The grand average of the difference in log-transformed power between high and low MEP-amplitude epochs for the EO condition. Positive values were observed at C3 and left frontal electrodes for the alpha/low-beta bands, showing that the mean power was higher for the epochs of high MEP amplitudes than for those of low amplitudes. (B) The power difference was similar but less marked in the EC condition than in the EO condition. (C) A permutation test showed that the cluster in the left frontocentral region that was identified during the EO condition was statistically significant.
Abbreviations: *EO*, eyes open; *EC*, eyes closed.

whether we limited the frequency range. Therefore, the results suggest that the relationship between EEGs and MEPs depends on TMS intensity. Mean prestimulus EMG amplitudes did not significantly differ for the HI condition ($p = 0.27$). In contrast, a small but significant difference was observed for the LO condition (2.20 ± 0.17 vs. 2.02 ± 0.17 μV, $p = 0.001$).

Experiment 3: MEP modulation by an informed open-loop TMS

Based on the results of Experiments 1 and 2, we developed an informed open-loop system with EEG-triggered TMS, which was used to estimate the effects of EEG oscillations on MEP amplitudes by delivering TMS when the alpha power at C3 was high or low (Fig. 2). When the power value reached the predetermined high- or low-power threshold, TMS was delivered and MEPs were recorded. The delay from EEG acquisition to TMS trigger was 175.7 ± 26.1 ms (mean ± SD). Fig. 5a shows the power spectra for representative data in which high or low power was detected by the system at both the alpha-band and the control frequency band. EEG power values were successfully separated into high- or low-power conditions for all participants (Fig. 5b). The average numbers of MEP epochs were 48.2 ± 3.6 (mean ± SD) for the high-power condition and 45.3 ± 2.8 for the low-power condition in the alpha band, and 45.7 ± 5.2 and 45.9 ± 4.2 for the high- and low-power conditions, respectively at the control frequency band. MEP amplitudes when EEG alpha power was high were significantly higher than those when EEG power was low (Fig. 5c, $p = 0.011$). This was also true after excluding the five participants who had participated in the other experiments ($p = 0.009$), thus replicating the results in different sets of people. In contrast, MEP amplitudes at the control frequency band when the power was high were not significantly different from those when the power was low (Fig. 5B, $p = 0.241$). Thus, the informed open-loop TMS highlighted the importance of prestimulus alpha oscillations in relation to subsequent MEP amplitudes. Prestimulus EMGs did not significantly differ between high- and low-power conditions for either alpha bands ($p = 0.976$) or the control frequency bands ($p = 0.825$).

Discussion

We investigated the relationship between prestimulus EEG power in alpha/low-beta bands and MEP amplitudes while modulating the condition (EO or EC) and TMS intensity (high or low). Analysis revealed that EEG oscillations in the alpha/low-beta power range reflect M1 excitability at rest. Further, an EO state and a TMS intensity of SI_{1mV} were important for estimating the EEG–MEP relationship. The EEG-triggered TMS system confirmed that higher alpha-band power predicted higher MEP amplitudes, and that this relationship was not found at the control frequency. Therefore, the EEG-MEP relationship is likely modulated in a state-dependent manner.

Larger EEG oscillations are necessary for higher MEP amplitudes

We found that higher prestimulus EEG power of alpha/low-beta (10–15 Hz) waves at C3 predicted higher MEP amplitudes. When

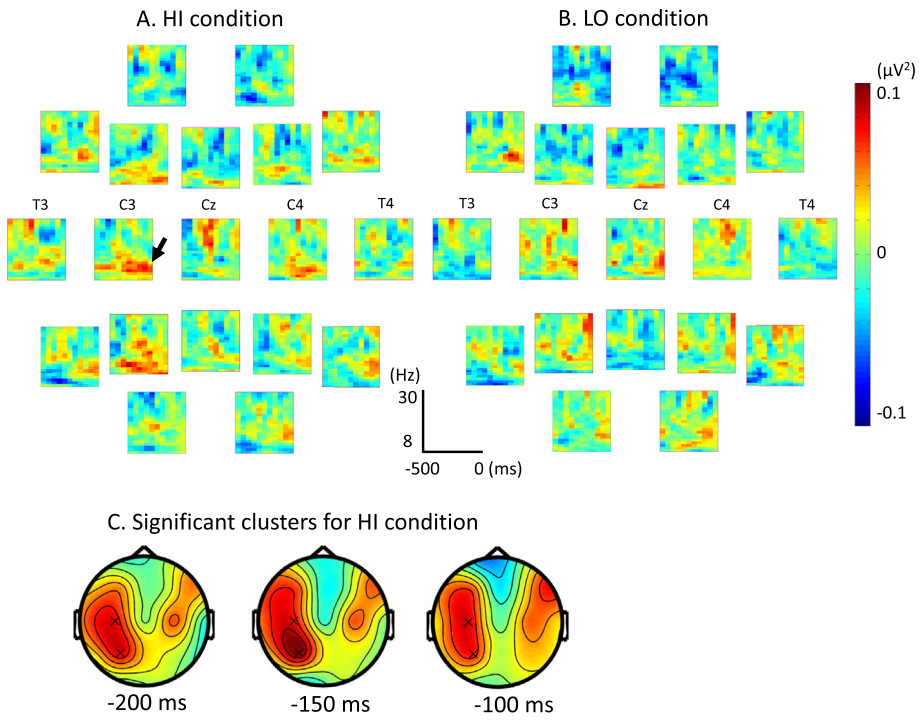

Fig. 4. *EEG power differences between high and low MEP-amplitude epochs when using high or low TMS intensity.*
(A) The grand average power differences between high and low MEP-amplitude epochs for the HI condition using SI_{1mV}. The results for the HI condition were comparable with those of the EO condition in Experiment 1 (Fig. 3A). (B) In contrast, the power difference was not significant for the LO condition using the resting motor threshold. (C) Significant clusters were detected at C3 and P3 for the alpha/low-beta bands in the HI condition but not in the LO condition. Electrodes at which significant clusters were found are marked by an " × ." Abbreviations: *HI*, high intensity; *LO*, low intensity.

eyes are open and limbs are relaxed, alpha oscillations are predominantly visible over the occipital region or the central region at normal EEG settings. These oscillations are generally considered to reflect pulsed inhibition or top-down inhibitory control, depending on their amplitudes and phases [4,6]. Hand movement has been reported to induce decreased alpha power over the lateral region, but not over the midline region, which is linked to leg movement [32]. Using current-source density reduces the smearing effect by volume conduction and is more sensitive to local activity [33]. Thus, the alpha/low-beta oscillations observed in our results are likely to reflect activity of the hand sensorimotor area.

Although alpha/beta oscillations have been negatively correlated with M1 excitability during various motor tasks, such as voluntary movement [32], motor imagery, and motor observation [34,35], this was not true in the current study. We found that higher alpha/low-beta oscillations were linked to larger MEPs. The key difference between studies is that we recorded EEG and MEPs at rest, not during a motor task. The seemingly conflicting results indicate that the relationship between EEG oscillations and M1 excitability could differ depending on the task state. Recently, weak positive correlations between alpha oscillations and MEP amplitudes have been reported at rest [18], which is compatible with our results. In the current study, we primarily used a TMS intensity of SI_{1mV} rather than RMT, which can activate M1 and the surrounding areas. In particular, alpha oscillations have been reported to originate primarily from the S1, and beta oscillations from M1 [36,37]. Thus, it is possible that S1 activity, measured as alpha/low beta oscillations, influences M1 excitability.

M1 and S1 have a close mutual relationship, whereby activity in one area can influence activity in the other. For example, MEPs are inhibited by sensory stimulation, such as short afferent inhibition [38]. Additionally, a couple studies have reported that S1 inhibits M1 excitability [39,40], although this is not conclusive [41,42]. If alpha oscillations reflect S1 activity, and if S1 inhibits M1 activity, then the association between high MEP amplitudes and higher power in the alpha/low-beta band (i.e., lower S1 activity) could result from disinhibition of M1.

Effect of EO/EC state

In Experiment 1, the finding that higher alpha/low-beta band power predicts higher MEP amplitudes was only observed in the EO condition. Previous studies have demonstrated that an EO state either decreased [21] or increased MEP amplitudes [18,20]. However, no previous studies have examined the effect of EO and EC states on the EEG–MEP relationship. Because the difference of mean MEP amplitudes between the EO and EC conditions was rather small, it seems unlikely that they would substantially affect the current results.

The EO/EC state may interact with cortical networks involving the sensorimotor cortex. Visual stimulation inhibits occipital alpha waves and enhances mu rhythms [43,44]. Xu et al. (2014) [45] reported that EO/EC conditions modulate functional brain networks, and may indicate a shift between exteroceptive and interoceptive networks. Thus, shifting between exteroceptive/interoceptive networks via EO/EC condition might influence sensorimotor networks such that the EEG-MEP relationship is modulated. Alternatively, occipital alpha is dominant during the EC state, which may contaminate the central alpha oscillations. However, we used source derivation to improve the localization of oscillations [33,46]. Additionally, no difference was found at the occipital region during the EC condition. This implies that occipital alpha power was comparable between high MEP-amplitude epochs and low MEP-amplitude epochs in the EC condition. Taken together, we suggest that the EO/EC difference resulted from an interaction of cortical

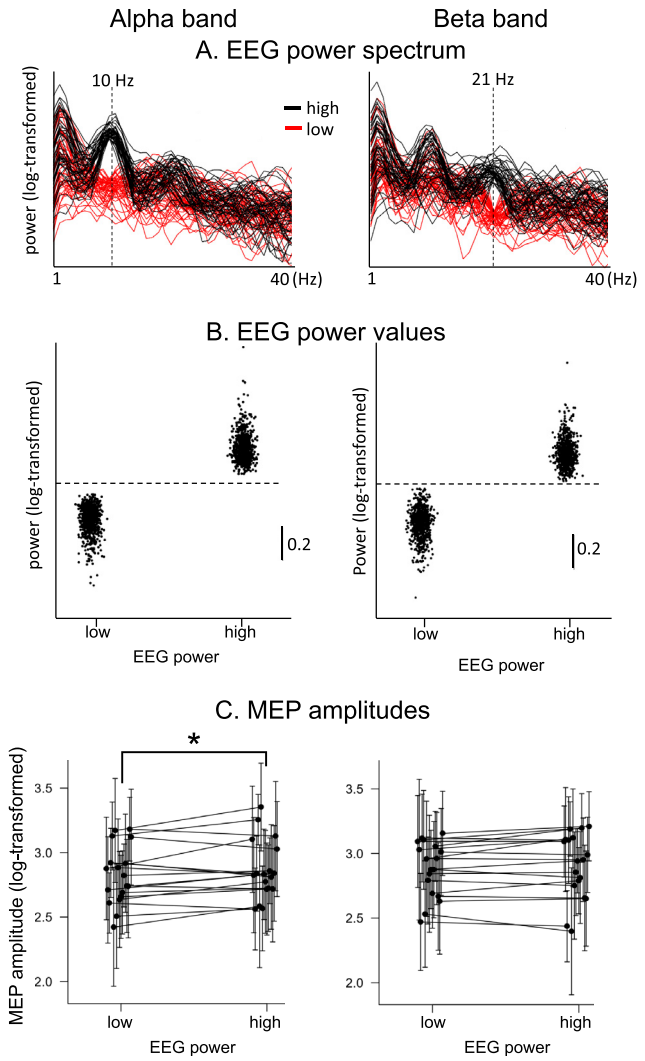

Fig. 5. *EEG power and MEP amplitude estimation by EEG-triggered TMS system.* TMS was delivered when the EEG power reached the predetermined high-power or low-power thresholds using semi-real-time EEG estimation. (A) Power spectra of alpha- and beta-bands in a representative participant. High power epochs (black) and low power epochs (red) were clearly separated at the frequencies predetermined for this participant (10 Hz for the alpha-band, 21 Hz for the beta-band). (B) Power values for high-power and low-power epochs for alpha- and beta-bands in all participants. The power values were log-transformed and normalized by the average of the highest values from low-power epochs and the lowest values from high-power epochs (dotted line) for each participant. There was no overlap between low-power epochs (low) and high-power epochs (high) for any participant. (C) MEP amplitude differences using EEG-power estimation. The resulting MEPs were larger for higher EEG power than for lower EEG power in the alpha-band. There was no significant difference in MEP amplitudes when beta-band power was used. Error bars indicate the standard deviation for each participant. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

activities and that eyes need to be open for central alpha/low-beta oscillations to predict M1 excitability.

TMS intensity influences the EEG–MEP relationship

We found that TMS intensity was also important for observing the EEG–MEP relationship. Significant relationship were observed between them when using an intensity of SI_{1mV} but not the lower-intensity of RMT. Previous studies have reported that lower EEG power of midrange beta- and alpha-bands predicted higher MEP amplitudes at a TMS intensity of RMT [12–15] and that no significant link between EEG oscillations and single pulse MEPs was found for TMS at a relatively weak intensity (110% RMT) [17]. Khademi et al. [15] showed a negative relationship between beta-band EEGs and MEP amplitudes at RMT, but no significant relationship at higher intensities of up to 150% RMT. From these results, the negative relationship is apparent at the lower TMS intensity, but this can be masked at higher intensities. Accordingly, the positive relationship is more evident with higher intensities, as observed in this study. A larger area such as S1 would be affected by a higher-intensity stimulus, as discussed in the previous section. In contrast, weaker TMS would affect only M1 and would not activate S1 inhibitory control on M1. Thus, the relationship between EEG oscillations and MEP amplitudes would be blurred in lower-intensity conditions. Lepage et al. (2008) [8] found a negative relationship between midrange beta-band EEG and MEPs using a high intensity (SI_{1mV}) at rest. However, their methods and ours have a few differences. For example, they used a biphasic pulse, whereas we used a monophasic pulse. A major current is inverted between a biphasic pulse and a monophasic pulse, which causes differential effects on I-waves [47]. Further studies are needed to examine the influence of these factors on the EEG–MEP relationship.

Validity of the informed open-loop estimation of EEG and M1 excitability

We found that EEG-triggered TMS also indicated that larger alpha oscillations predicted higher MEP amplitudes. Closed-loop and informed open-loop NIBS have been recent hot topics in the literature [18,24,25,48,49]. For example, several studies have adopted EEG-triggered M1 stimulation using the beta-band during various tasks [24,49], which monitored the decreased oscillations to trigger TMS. Interestingly, Thies et al. [18] reported a weak positive correlation between individual alpha power over the left central region and MEP amplitude. These results partially support our findings. Our extension of their study suggests the greater importance of the alpha-band over a control frequency band at around 20 Hz. In addition, our methods differed from theirs in several ways. For example, they continuously updated the frequency during recordings, and stressed precise time control of a short delay for delivering TMS, whereas we did not evaluate the individual alpha peaks for the participants and did not update the frequency during the recording sessions. Even though we used a much simpler algorithm for estimating EEG power in this study, we were able to demonstrate that EEG-triggered TMS was useful with a delay of about 175 ms. This is probably because of the slow amplitude modulation, as is observed in the waxing and waning of alpha oscillations. Taken together, these findings indicate that the informed open-loop TMS system can be feasible with a simple implementation using the findings obtained in Experiment 1 and 2. Our results may imply that alpha band EEG oscillations as early as −200 ms reflect M1 excitability. However, we assume that lengthening the time bin before the stimulus will allow us to determine the precise frequency and timing that most influence the relationship between prestimulus EEG oscillations and MEP amplitudes. Thus, we expect that future research will use longer time bins to confirm our findings.

Limitations

It should be noted that we used a small number of channels. Thus, the spatial specificity may be limited, even with the use of source derivation. The EEG oscillations in the EO condition in Experiment 1 were topographically distributed over the left frontocentral regions, while those of the HI condition in Experiment 2

were distributed over the left centroparietal region (Figs. 3 and 4). Thus, although we obtained supportive data, Experiment 2 could not fully confirm the results of Experiment 1. Additionally, while the p-value for the HI condition in Experiment 2 suggested that the difference was marginally significant, the correlation analysis did not show that it was. Thus, the effect size of the current study was modest and further studies are necessary to confirm the current results. Run-to-run variation of the coil position and the different participants between experiments are factors that could have led to the differing topographies of Experiments 1 and 2. The TMS coil was held by an examiner (KO) without a navigation system, which results in coil-position variability up to 10 mm [50]. Thus, the TMS coil position could have been slightly more anterior in Experiment 1 than in Experiment 2, which might have resulted in the involvement of more anterior electrodes in Experiment 1, including C3. However, because C3 was involved in both topographies, we believe that the oscillatory modulation of sensorimotor areas was chiefly represented by C3 oscillations. Further studies are necessary to clarify this issue using a dense channel array with source estimation to locate the origin of the oscillatory activity under the guidance of the TMS navigation system.

The time precision of our analysis was limited because wavelet analysis required several hundreds of milliseconds in Experiments 1 and 2, and a 1-s epoch was employed for EEG analysis in Experiment 3. We assumed that the significant time range would be close to TMS onset (−100 to 0 ms). However, we demonstrated that the informed open-loop stimulation with about a 175-ms delay significantly affected MEPs. Therefore, EEG oscillations as early as −200 ms likely influence M1 excitability. In addition, we only studied two frequency bands, alpha at around 10 Hz and beta at around 20 Hz. Thus, other frequency bands, such as mid-range beta (15–17 Hz) should be explored to confirm the frequency specificity.

There was a slight but significant difference in prestimulus EMGs for the EC condition in Experiment 1 and the LO condition in Experiment 2. Prestimulus EMGs were monitored visually and were excluded when excessive EMGs were detected. By doing so, measured EMG activity was very low, and we do not consider EMG activity to have significantly influenced the MEP amplitudes or EEG-MEP relationship. However, small prestimulus activity could have influenced the results, and further studies should precisely control this to more accurately estimate the EEG-MEP relationship.

Conclusions

We found a relationship between alpha/low-beta EEG oscillations and MEP amplitudes at rest, which depended on an EO state and high TMS intensity. Thus, the EEG-MEP relationship is modulated in a state-dependent manner. The obscured relationship during the EC state may be caused by the switch between exteroceptive and interoceptive networks that link sensorimotor oscillations and M1 excitability. Our informed open-loop TMS system also predicted M1 excitability by alpha-band power. Therefore, our results extend our knowledge of the EEG-MEP relationship and provide a more detailed estimation of brain network states and M1 excitability, which may be applicable in the development of novel NIBS protocols.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.06.013.

References

[1] Kiers L, Cros D, Chiappa KH, Fang J. Variability of motor potentials evoked by transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 1993;89:415–23.
[2] Ellaway PH, Davey NJ, Maskill DW, Rawlinson SR, Lewis HS, Anissimova NP. Variability in the amplitude of skeletal muscle responses to magnetic stimulation of the motor cortex in man. Electroencephalogr Clin Neurophysiol 1998;109:104–13.
[3] Wiethoff S, Hamada M, Rothwell JC. Variability in response to transcranial direct current stimulation of the motor cortex. Brain Stimul 2014;7:468–75. https://doi.org/10.1016/j.brs.2014.02.003.
[4] Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. Front Hum Neurosci 2010;4:186. https://doi.org/10.3389/fnhum.2010.00186.
[5] Khanna P, Carmena JM. Neural oscillations: beta band activity across motor networks. Curr Opin Neurobiol 2015;32:60–7. https://doi.org/10.1016/j.conb.2014.11.010.
[6] Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res Rev 2007;53:63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003.
[7] Munzert J, Lorey B, Zentgraf K. Cognitive motor processes: the role of motor imagery in the study of motor representations. Brain Res Rev 2009;60:306–26. https://doi.org/10.1016/j.brainresrev.2008.12.024.
[8] Lepage J-F, Saint-Amour D, Théoret H. EEG and neuronavigated single-pulse TMS in the study of the observation/execution matching system: are both techniques measuring the same process? J Neurosci Methods 2008;175:17–24. https://doi.org/10.1016/j.jneumeth.2008.07.021.
[9] Mitchell WK, Baker MR, Baker SN. Muscle responses to transcranial stimulation in man depend on background oscillatory activity. J Physiol (Lond) 2007;583:567–79. https://doi.org/10.1113/jphysiol.2007.134031.
[10] Keil J, Timm J, Sanmiguel I, Schulz H, Obleser J, Schönwiesner M. Cortical brain states and corticospinal synchronization influence TMS-evoked motor potentials. J Neurophysiol 2014;111:513–9. https://doi.org/10.1152/jn.00387.2013.
[11] Schulz H, Ubelacker T, Keil J, Müller N, Weisz N. Now I am ready-now i am not: the influence of pre-TMS oscillations and corticomuscular coherence on motor-evoked potentials. Cerebr Cortex 2014;24:1708–19. https://doi.org/10.1093/cercor/bht024.
[12] Zarkowski P, Shin CJ, Dang T, Russo J, Avery D. EEG and the variance of motor evoked potential amplitude. Clin EEG Neurosci 2006;37:247–51.
[13] Sauseng P, Klimesch W, Gerloff C, Hummel FC. Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. Neuropsychologia 2009;47:284–8. https://doi.org/10.1016/j.neuropsychologia.2008.07.021.
[14] Mäki H, Ilmoniemi RJ. EEG oscillations and magnetically evoked motor potentials reflect motor system excitability in overlapping neuronal populations. Clin Neurophysiol 2010;121:492–501. https://doi.org/10.1016/j.clinph.2009.11.078.
[15] Khademi F, Royter V, Gharabaghi A. Distinct beta-band oscillatory circuits underlie corticospinal gain modulation. Cerebr Cortex 2018;28:1502–15. https://doi.org/10.1093/cercor/bhy016.
[16] Berger B, Minarik T, Liuzzi G, Hummel FC, Sauseng P. EEG oscillatory phase-dependent markers of corticospinal excitability in the resting brain. BioMed Res Int 2014;2014:936096. https://doi.org/10.1155/2014/936096.
[17] Iscan Z, Nazarova M, Fedele T, Blagovechtchenski E, Nikulin VV. Pre-stimulus alpha oscillations and inter-subject variability of motor evoked potentials in single- and paired-pulse TMS paradigms. Front Hum Neurosci 2016;10:504. https://doi.org/10.3389/fnhum.2016.00504.
[18] Thies M, Zrenner C, Ziemann U, Bergmann TO. Sensorimotor mu-alpha power is positively related to corticospinal excitability. Brain Stimul 2018;11:1119–22. https://doi.org/10.1016/j.brs.2018.06.006.
[19] Sadaghiani S, Scheeringa R, Lehongre K, Morillon B, Giraud A-L, Kleinschmidt A. Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a simultaneous electroencephalography/functional magnetic resonance imaging study. J Neurosci 2010;30:10243–50. https://doi.org/10.1523/JNEUROSCI.1004-10.2010.
[20] Chen K-H, Huang Y-Z. The change of motor cortical excitability between eyes open and closed conditions. Neuroreport 2017. https://doi.org/10.1097/WNR.0000000000000955.

[21] Leon-Sarmiento FE, Bara-Jimenez W, Wassermann EM. Visual deprivation effects on human motor cortex excitability. Neurosci Lett 2005;389:17–20. https://doi.org/10.1016/j.neulet.2005.06.061.
[22] Rossini PM, Desiato MT, Lavaroni F, Caramia MD. Brain excitability and electroencephalographic activation: non-invasive evaluation in healthy humans via transcranial magnetic stimulation. Brain Res 1991;567:111–9.
[23] Bergmann TO, Mölle M, Schmidt MA, Lindner C, Marshall L, Born J, et al. EEG-guided transcranial magnetic stimulation reveals rapid shifts in motor cortical excitability during the human sleep slow oscillation. J Neurosci 2012;32:243–53. https://doi.org/10.1523/JNEUROSCI.4792-11.2012.
[24] Takemi M, Masakado Y, Liu M, Ushiba J. Event-related desynchronization reflects downregulation of intracortical inhibition in human primary motor cortex. J Neurophysiol 2013;110:1158–66. https://doi.org/10.1152/jn.01092.2012.
[25] Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR. Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. Neuroimage 2016;140:4–19. https://doi.org/10.1016/j.neuroimage.2016.02.012.
[26] Peirce JW. PsychoPy-Psychophysics software in Python. J Neurosci Methods 2007;162:8–13. https://doi.org/10.1016/j.jneumeth.2006.11.017.
[27] Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134:9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009.
[28] Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:156869. https://doi.org/10.1155/2011/156869.
[29] Hjorth B. An on-line transformation of EEG scalp potentials into orthogonal source derivations. Electroencephalogr Clin Neurophysiol 1975;39:526–30.
[30] Nielsen JF. Improvement of amplitude variability of motor evoked potentials in multiple sclerosis patients and in healthy subjects. Electroencephalogr Clin Neurophysiol 1996;101:404–11.
[31] Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. J Neurosci Methods 2007;164:177–90. https://doi.org/10.1016/j.jneumeth.2007.03.024.
[32] Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 1999;110:1842–57.
[33] Nunez PL, Silberstein RB, Cadusch PJ, Wijesinghe RS, Westdorp AF, Srinivasan R. A theoretical and experimental study of high resolution EEG based on surface Laplacians and cortical imaging. Electroencephalogr Clin Neurophysiol 1994;90:40–57.
[34] Jäncke L, Lutz K, Koeneke S. Converging evidence of ERD/ERS and BOLD responses in motor control research. Prog Brain Res 2006;159:261–71. https://doi.org/10.1016/S0079-6123(06)59018-1.
[35] Pfurtscheller G. The cortical activation model (CAM). Prog Brain Res 2006;159:19–27. https://doi.org/10.1016/S0079-6123(06)59002-8.
[36] Salmelin R, Hari R. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. Neuroscience 1994;60:537–50.
[37] Salmelin R, Hämäläinen M, Kajola M, Hari R. Functional segregation of movement-related rhythmic activity in the human brain. Neuroimage 1995;2:237–43.
[38] Turco CV, El-Sayes J, Savoie MJ, Fassett HJ, Locke MB, Nelson AJ. Short- and long-latency afferent inhibition; uses, mechanisms and influencing factors. Brain Stimul 2018;11:59–74. https://doi.org/10.1016/j.brs.2017.09.009.
[39] Jacobs MF, Tsang P, Lee KGH, Asmussen MJ, Zapallow CM, Nelson AJ. 30 Hz theta-burst stimulation over primary somatosensory cortex modulates corticospinal output to the hand. Brain Stimul 2014;7:269–74. https://doi.org/10.1016/j.brs.2013.12.009.
[40] Tsang P, Jacobs MF, Lee KGH, Asmussen MJ, Zapallow CM, Nelson AJ. Continuous theta-burst stimulation over primary somatosensory cortex modulates short-latency afferent inhibition. Clin Neurophysiol 2014;125:2253–9. https://doi.org/10.1016/j.clinph.2014.02.026.
[41] Kojima S, Onishi H, Miyaguchi S, Kotan S, Sugawara K, Kirimoto H, et al. Effects of cathodal transcranial direct current stimulation to primary somatosensory cortex on short-latency afferent inhibition. Neuroreport 2015;26:634–7. https://doi.org/10.1097/WNR.0000000000000402.
[42] Sasaki R, Miyaguchi S, Kotan S, Kojima S, Kirimoto H, Onishi H. Modulation of cortical inhibitory circuits after cathodal transcranial direct current stimulation over the primary motor cortex. Front Hum Neurosci 2016;10:30. https://doi.org/10.3389/fnhum.2016.00030.
[43] Koshino Y, Niedermeyer E. Enhancement of Rolandic mu-rhythm by pattern vision. Electroencephalogr Clin Neurophysiol 1975;38:535–8.
[44] Pfurtscheller G. Event-related synchronization (ERS): an electrophysiological correlate of cortical areas at rest. Electroencephalogr Clin Neurophysiol 1992;83:62–9.
[45] Xu P, Huang R, Wang J, Van Dam NT, Xie T, Dong Z, et al. Different topological organization of human brain functional networks with eyes open versus eyes closed. Neuroimage 2014;90:246–55. https://doi.org/10.1016/j.neuroimage.2013.12.060.
[46] Kayser J, Tenke CE. Issues and considerations for using the scalp surface Laplacian in EEG/ERP research: a tutorial review. Int J Psychophysiol 2015;97:189–209. https://doi.org/10.1016/j.ijpsycho.2015.04.012.
[47] Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I. Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. Exp Brain Res 1997;113:24–32.
[48] Zrenner C, Desideri D, Belardinelli P, Ziemann U. Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. Brain Stimul 2018;11:374–89. https://doi.org/10.1016/j.brs.2017.11.016.
[49] Kraus D, Naros G, Bauer R, Khademi F, Leão MT, Ziemann U, et al. Brain state-dependent transcranial magnetic closed-loop stimulation controlled by sensorimotor desynchronization induces robust increase of corticospinal excitability. Brain Stimul 2016. https://doi.org/10.1016/j.brs.2016.02.007.
[50] Julkunen P, Säisänen L, Danner N, Niskanen E, Hukkanen T, Mervaala E, et al. Comparison of navigated and non-navigated transcranial magnetic stimulation for motor cortex mapping, motor threshold and motor evoked potentials. Neuroimage 2009;44:790–5. https://doi.org/10.1016/j.neuroimage.2008.09.040.