Pinging the brain with transcranial magnetic stimulation reveals cortical reactivity in time and space

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ABSTRACT

Background: Single-pulse transcranial magnetic stimulation (TMS) elicits an evoked electroencephalography (EEG) potential (TMS-evoked potential, TEP), which is interpreted as direct evidence of cortical reactivity to TMS. Thus, combining TMS with EEG can be used to investigate the mechanism underlying brain network engagement in TMS treatment paradigms. However, controversy remains regarding whether TEP is a genuine marker of TMS-induced cortical reactivity or if it is confounded by responses to peripheral somatosensory and auditory inputs. Resolving this controversy is of great significance for the field and will validate TMS as a tool to probe networks of interest in cognitive and clinical neuroscience.

Objective: Here, we delineated the cortical origin of TEP by spatially and temporally localizing successive TEP components, and modulating them with transcranial direct current stimulation (tDCS) to investigate cortical reactivity elicited by single-pulse TMS and its causal relationship with cortical excitability.

Methods: We recruited 18 healthy participants in a double-blind, cross-over, sham-controlled design. We collected motor-evoked potentials (MEPs) and TEPs elicited by supra-threshold single-pulse TMS targeting the left primary motor cortex (M1). To causally test cortical and corticospinal excitability, we applied tDCS to the left M1.

Results: We found that the earliest TEP component (P25) was localized to the left M1. The following TEP components (N45 and P60) were largely localized to the primary somatosensory cortex, which may reflect afferent input by hand-muscle twitches. The later TEP components (N100, P180, and N280) were largely localized to the auditory cortex. As hypothesized, tDCS selectively modulated cortical and corticospinal excitability by modulating the pre-stimulus mu-rhythm oscillatory power.

Conclusion: Together, our findings provide causal evidence that the early TEP components reflect cortical reactivity to TMS.

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Introduction

Combined transcranial magnetic stimulation (TMS) and electroencephalography (EEG) allows for quantification of brain network dynamics by pinging them with TMS [1]. The TMS-evoked potential (TEP), which is considered to reflect TMS-induced cortical reactivity, has been shown to have diagnostic value in a variety of neurological and psychiatric disorders [2]. However, there is ongoing controversy about the origin of the TEP. A recent study claimed that the TEP amplitude may be confounded by the stimulation of peripheral nerves and the loud clicking sound of the TMS coil [3]. Specifically, sham TMS elicited EEG potentials were highly correlated with those produced by real TMS, despite the use of sophisticated procedures to attenuate the somatosensory and auditory confounds. A rebuttal to this publication suggested that...
insufficient TMS intensity and incomplete auditory masking may explain the sensory-dominant evoked potentials in the experiment [4]. Nonetheless, residual auditory input is unavoidable in TMS studies [5] because the TMS clicking sound is conducted through air and bone [6,7]. Thus, it continues to be debated whether the TEP represents genuine cortical reactivity elicited by single-pulse TMS or cortical reactivity contaminated by peripherally- and auditory-evoked potentials.

Here we sought to resolve this controversy and delineate TEPs by localizing the electrophysiological response using high-density EEG, structural magnetic resonance imaging (MRI), and digitized EEG electrode locations. If a TEP is localized in the auditory and somatosensory cortical areas, then it can be determined that auditory input and peripheral nerve stimulation drive TEPs, respectively. We chose the primary motor cortex (M1) as a stimulation target because the corticospinal response (motor-evoked potential, MEP) should also reflect cortical reactivity and have a causal relationship with cortical reactivity. To causally test the validity of our approach, we applied transcranial direct current stimulation (tDCS) to modulate cortical and corticospinal excitability [8,9]. We observed that single-pulse TMS targeting the M1 elicited six TEP components. The earliest TEP was 25 ms (P25) post-TMS onset and was localized to the hand area of the left M1, the TMS target location. The following two TEP components were localized to the primary somatosensory cortex (N45 and P60), which may reflect afferent input by hand-muscle twitches in response to suprathreshold TMS. The later TEP components (N100, which may relocalize to the primary somatosensory cortex (N45 and P60), which may reflect afferent input by hand-muscle twitches in response to suprathreshold TMS. The later TEP components (N100, P180, and N280) were primarily localized to the auditory cortex. Further, tDCS reliably modulated cortical reactivity and corticospinal responses by modulating the pre-stimulus mu-rhythm oscillatory power. Together, our findings demonstrate that the earliest TEP component reflects genuine cortical reactivity, whereas the subsequent TEP components may reflect sensory processing.

Materials and methods

Study design

We performed a crossover, double-blind, sham-controlled study with three tDCS conditions (anodal, cathodal, and sham) at the University of North Carolina at Chapel Hill. All protocols were approved by the university’s Biomedical Institutional Review Board. The study protocol was registered before participants were recruited (ClinicalTrials.gov, NCT03481309). We recruited 19 healthy, right-handed, male participants free of any neurological disorders. All participants provided written informed consent before participation. After a telephone screening to assess their eligibility for the study, structural MR images (T1-weighted) were obtained using a 3T-MRI scanner (Magnetom Prisma, Siemens AG, Berlin, Germany) at the University of North Carolina Biomedical Research Imaging Center. One of the participants dropped out of the study because of perceived scalp discomfort attributable to TMS. All remaining participants completed the three tDCS sessions. The order of the tDCS conditions was randomized, counterbalanced, and distributed equally (three participants/tDCS order). There was at least a 3-day interval between the sessions to minimize any potential long-lasting tDCS effects. Each session consisted of the following procedures (Fig. 1): determining the resting motor threshold (RMT), EEG, and MEP recordings during 100 single-pulse TMS (5 min, 120% relative to RMT); tDCS (11 min, 2 mA); EEG and MEP recordings during 100 single-pulse TMS (5 min), and digitization of the EEG electrode locations using a stereo-camera tracking digitizer (GeoScan Sensor Digitization Device, Philips Neuro Inc., Eugene, OR).

EEG and MEP recordings during TMS

Based on the structural MR images, we performed brain segmentation and determined the hand area of the left M1 as the initial target area using a frameless neuronavigation system (Localite GmbH, Sankt Augustin, Germany). According to the initial target location, a figure-of-eight coil (C—B60, MagVenture Inc., Farum, Denmark) was tangentially placed on the scalp with the handle pointing backwards and laterally at a 45° angle from the mid-sagittal line. Participants sat in a comfortable armchair with their hands positioned on the armrests. Three electromyography (EMG) electrodes (15 × 21 mm, Ambu Neuroline 700, Ambu Inc., Columbia, MD) were placed in a tendon-belly arrangement on the first dorsal interosseous muscle (active and reference EMG electrodes) and the styloid process of the ulna on the right hand (ground EMG electrode). Biphasic single-pulse TMS was applied at the initial location and the location was adjusted to obtain the highest MEP at the same intensity. MEP traces were visualized in a built-in display on the TMS device (MagPro X100, MagVenture Inc., Farum, Denmark). The RMT was defined by the minimum TMS intensity required to evoke MEPS of at least 50 μV in 50% of 5–10 consecutive trials [10]. The target motor hotspot (hand area on the left M1) was determined at this step (Fig. 1b, Fig. S1). We used a Physio 16 input box (EGI Inc., Eugene, OR) connected to the EEG amplifier to record MEPS. This configuration allowed us to record MEP and EEG data on the same amplifier. We used a TMS-compatible EEG system with a 128-channel net (EGI Inc., Eugene, OR) at a sampling rate of 1 kHz. Channel Cz and one channel between Cz and Pz were used as a reference and ground, respectively. Participants wore air-conducting earphone tubes (ER-3C, Etymotic Research Inc., Elk Grove Village, IL) with white-noise masking to attenuate auditory evoked potentials [11]. We also applied a thin foam layer underneath the TMS coil to attenuate peripherally-evoked potentials. We applied 100 single TMS pulses (120% intensity relative to RMT) with a jittered inter-trial interval between 2 and 3 s to minimize any anticipatory effect. All TMS pulse locations were tracked in real-time using the neuronavigation system and saved for verification of stimulation on the left motor hotspot. The EEG and MEP recording procedures were performed before and after tDCS application.

tDCS

We applied two carbon-silicone electrodes (5 × 5 cm) to the scalp with Ten20 conductive paste (Bio-Medical Instruments, Clinton Township, MI) and used the UCSITE 100 stimulator (Pulvinar Neuro LLC, Chapel Hill, NC). The stimulator does not display any information about the stimulation conditions (verum or sham). The two electrodes were placed at the left motor hotspot (determined by RMT, Fig. 1c) and the right supra-orbital area (FP2 EEG location based on the 10–20 international coordinate system). Stimulation montage and modeling of electric field distributions were calculated by the tES LAB 2.0 software (Neurophet Inc., Seoul, South Korea). In anodal tDCS, we delivered 11 min of constant current, including 60 s of ramp-up and -down (10 min of -2 mA constant current). In cathodal tDCS, we delivered 11 min of stimulation, including -2mA of constant current and 60 s of ramp-up and -down (10 min of -2mA constant current). In sham tDCS, we delivered 30 s of +2 mA constant current with 60 s of ramp-up and -down. The choice of such an “active” sham is an established strategy to enhance blinding of the participants to the stimulation condition [12]. After the trials, all participants were asked to fill out a questionnaire indicating whether they received electrical stimulation or not (Yes or No) and side-effect questionnaires (Fig. S2). We found...
no significant differences in the side-effect questionnaires among the tDCS conditions.

Data analysis

MEP and EEG data analysis

Offline data processing was performed with custom-built scripts in MATLAB (R2015b, Mathworks Inc., Natick, MA) and the EEGLAB toolbox [13]. The collected MEP data were visually inspected and epochs that had less than 50 μV MEP were removed (4.4 ± 7.2 of 100 epochs). MEP data were averaged for each tDCS condition (before and after TMS) and the ratio (pre/post) was calculated. The ratio at each session represents tDCS-induced MEP modulation. To analyze the EEG data during single-pulse TMS, we first identified the TMS onset and TMS-induced artifacts (−10 to 20 ms to the TMS onset). This artifact time period was replaced by a value randomly selected from a Gaussian distribution made by the standard deviation and mean of a reference period (−50 to −10 ms to the TMS onset) [14]. Second, the data were band-pass filtered from 1 to 50 Hz. Third, the data were preprocessed by an artifact subspace reconstruction (ASR) algorithm [15] to identify high-variance data epochs and reconstruct missing data. Briefly, the algorithm first finds a minute of data that represents clean EEG as a baseline. Then, principal component analysis is applied to the whole data set with a sliding window to find the subspaces in which there is activity that is more than five standard deviations away from the baseline EEG. Once the function has identified the outlier subspaces, it treats them as missing data and reconstructs their content using a mixing matrix that is calculated on the clean data. Fourth, bad channels identified in the previous step were interpolated and common average referencing was performed. Thereafter, infomax independent component analysis (ICA) [16] was performed to remove eye blinking, eye movement, muscle activity, and heartbeat artifacts. All ICA components were inspected visually and noise components were selected manually for rejection (25.41 ± 10.19). The selection of ICA components were verified by the ICLabel classification [17].

The preprocessed EEG data were epoched from −100 to 500 ms to the respective TMS onset. Each epoch was inspected visually and noisy epochs were removed (3.7 ± 6.1 of 100 epochs). We found no significant differences between the three conditions in the number of rejected epochs (one-way ANOVA, F2,51 = 0.72, p = 0.49). To obtain a grand-averaged TEP for each channel, we averaged the 5255 epochs that remained following epoch rejection across the participants and conditions (before tDCS) as a function of time (−100 to 500 ms). We used the Morlet wavelet transform (7 cycles) with a frequency resolution of 1 Hz and temporal resolution of 1 ms to compute time-frequency maps of the entire epoch (−200 to 500 ms) for each channel. The power in the time-frequency maps was obtained and used for statistical tests across tDCS conditions.

EEG source localization

After obtaining structural MR images for each participant, we performed skull stripping, gray-white matter segmentation, reconstruction of cortical surface models (gray-white boundary surface and pial surface), and labeled cortical regions using FreeSurfer 5.3 [18]. Preprocessed and segmented MR images were imported in the BrainStorm toolbox [19]. Three fiducial points (nasion and left/right preauricular points) and anatomical points (anterior/posterior commissure and inter-hemispheric point) were defined on the MR images. We built a scalp model consisting of 10,000 vertices from the MR images and co-registered it with digitized EEG electrode locations for each session. During this step, we confirmed that all scalp EEG electrodes were properly projected onto the head model (Fig. S3). We used the boundary element method with OpenMEEG [20,21] to compute the lead field matrix (forward modeling). The forward model consisted of 9808 vertices from the MR images and co-registered it with digitized EEG electrode locations for each session. During this step, we confirmed that all scalp EEG electrodes were properly projected onto the head model (Fig. S3). We used the boundary element method with OpenMEEG [20,21] to compute the lead field matrix (forward modeling). The forward model consisted of 9808 vertices from the MR images and co-registered it with digitized EEG electrode locations for each session. During this step, we confirmed that all scalp EEG electrodes were properly projected onto the head model (Fig. S3). We used the boundary element method with OpenMEEG [20,21] to compute the lead field matrix (forward modeling). The forward model consisted of 9808 vertices from the MR images and co-registered it with digitized EEG electrode locations for each session. During this step, we confirmed that all scalp EEG electrodes were properly projected onto the head model (Fig. S3).
computed from the time period from 0 to 500 ms (501 samples) and the baseline period (−200 ms to −1 ms, 200 samples) was used for noise covariance block by block to avoid effects of slow shifts in data. The neural activity index [22] was used for scaling units of noise covariance. For the source model, cortical sources were constrained for only normal components to the cortical surface. The data regularization was performed with the diagonal matrix of the data covariance matrix. The same spatial filters were used for all TEP components. We projected scalp EEG signals to the cortex model consisting of 15,000 vertices. We averaged all projected source activity on the individual cortex model across trials and projected it onto the template cortex model (FSAverage, 15,000 vertices) for group-level analysis [23].

Statistical testing

We used the linear mixed-effects model in R (R Foundation for Statistical Computing, Vienna, Austria) to investigate modulation of cortical and corticospinal excitability with the fixed factors “tDCS condition” (anode, cathode, and sham) and “session” (sessions 1, 2, and 3), with the random factor, “participant”. The dependent variables were the ratio of averaged MEPs and the ratio of averaged TEPs over the EEG channels. To calculate the spatio-temporal statistical significance for TEPs in the sensor and source spaces for each tDCS condition, we used a non-parametric cluster-based permutation test [24] to address the multiple comparison problem of high-density EEG. First, t-tests were conducted for each channel (vertices for source space) and time point across the participants to compare before and after tDCS in each tDCS condition. We used the entire vertices in the averaged cortex model for source space. We then constructed clusters from the spatio-temporal significant t-value map (p < 0.05), separately summed all the positive or negative t-values within the clusters, and clustered the significant t-values based on spatio-temporal adjacency. The minimum size of a cluster was set to two points. A neighboring channel (vertices for source space) was defined as spatially adjacent within 4 cm [24]. For the permutation test, we shuffled all trials and divided them into two datasets. We then conducted t-tests for the two datasets to obtain a t-value map. We repeated this procedure using Monte Carlo simulation with 1000 iterations, and extracted the largest cluster from each permutation test to compare with the original dataset. Lastly, we constructed a histogram of the 1000 values from the cluster-level statistics and calculated a probability density function (PDF) to estimate cluster-level p-values. The input for the PDF was the cluster-level statistics from the original dataset and the output was a p-value for each cluster-level statistic. The cluster-level p-values were corrected and approximated using this cluster-based permutation test. We used the same approach to calculate the spatio-spectral-temporal significance for the computed time-frequency maps for each EEG channel. In this case, we used 3-dimension of EEG data as an input for the cluster-based permutation tests, thus the identified clusters were in the form of spatio-spectral-temporal set. We used the same parameters with the ones for spatio-temporal data.

Results

Cortical reactivity to single-pulse TMS

Single-pulse TMS elicits multiple TEP components in TMS-EEG recordings [11,25]. To determine whether single-pulse TMS targeting the hand area of the left M1 elicits TEPs, we computed grand-averaged TEPs (5255 epochs after rejecting bad epochs) for each EEG channel from the TMS-EEG recordings prior to tDCS application. A butterfly plot of TEPs (Fig. 2a, gray lines) was obtained as a function of time (−100 to 500 ms with respect to TMS onset) for each of the 128 EEG channels. An averaged TEP over the left sensorimotor area (C3 channel and the 6 channels surrounding C3; see inset in Fig. 2a) was computed in the sensor space (Fig. 2a, thick black line). We found that the averaged TEP on the left sensorimotor area exhibited three positive and three negative peaks relative to the baseline period (−100 to 0 ms). We refer to these peaks by their canonical names: P25, N45, P60, N100, P180, and N280.

To investigate the spatial distribution of these TEP components across the scalp, we computed topographical distributions at each TEP time point (Fig. 1b). The topographical distributions were based on a single time-point according to the peak for each participant and it was averaged across the participants. We found that the left sensorimotor area was the primary area of activation up to 60 ms (P25, N45, and P60). After P60, the centroid of activation drifted towards the midline until it centered entirely at 280 ms (N100, P180, and N280).

As the sensor-space representation captures the summed cortical activity on the scalp, we next localized the TEPs to the cortical source space. First, we localized the TEPs to participant-specific cortex models (15,000 vertices, Fig. S2) and then projected the localized TEPs to a template cortex model (15,000 vertices, FSAverage) for group analysis and computed the grand-averaged TEP (5255 epochs). For each component depicted in the sensor space (Fig. 2b), we projected the grand-averaged TEP onto the template cortex model (Fig. 2c). We found that P25, the earliest TEP component, was localized to the hand area of the left M1 (TMS target, Fig. 1b). The N45 TEP component was spread between the M1 and the primary somatosensory cortex (Fig. 2c, second column) and the P60 TEP component was localized to the primary somatosensory cortex (Fig. 2c, third column). We confirmed that the N45 and P60 TEP components were not affected by direct cortico-cortical connections [26] by dividing all trials into two classes (Fig. S4): one class did show clear MEP (MEP trials), the other class did not show clear MEPs (non-MEP trials). In contrast, the N100 and P180 peaks were primarily localized to the auditory cortex and reflected the N100−P180 auditory complex [6, 7]. N280, the last TEP component was also localized to the auditory cortex but exhibited additional activation in the frontal cortex. For the right hemisphere, as expected, we did not find any significant activation for the first three TEP components (P25, N45, and P60) but found bilateral activation on the auditory cortex for the later TEP components (N100, P180, and N280, Fig. 2c). To confirm the source-localized cortical reactivity does not rely on a specific method, in addition, we performed source localization for each TEP component using the minimum-norm estimation [27]. We found activation patterns that are similar to the ones found by the beamforming algorithm (Fig. S5). Overall, our findings demonstrate that single-pulse TMS targeting the hand area of the M1 elicits multiple TEP components. Notably, the earliest TEP component (P25) reflects genuine cortical reactivity to TMS. Based on this finding, we hypothesized that the N45 and P60 reflect the afferent signal from the corticospinal tract attributable to hand-muscle twitches. Conversely, the later TEP components (N100, P180, and N280) may reflect auditory processing of the coil’s clicking sound.

Cortical reactivity and corticospinal response

Having identified cortical reactivity using single-pulse TMS targeting the hand area of the left M1 and finding of an afferent signal from the primary somatosensory cortex, we next investigated how each TEP component was associated with the TMS-induced corticospinal response measured by MEPs. We averaged the TEPs and MEPs before tDCS application for each session and...
obtained 54 TEPs and MEPs (3 sessions, 18 participants). We extracted the six TEP components for each participant and performed correlation analyses using the Pearson correlation between the MEPs and TEPs at each EEG channel. We found positive correlation clusters for the P25 (9 EEG channels) and P60 (6 EEG channels), and a negative cluster for the N45 (5 EEG channels) in the left sensorimotor area (Fig. 3a, top row, r-value topographical maps). The black dots in the topographical maps indicate significant EEG channels (p < 0.05). In contrast, we found no significant cluster for the N100, P180, or N280 (Fig. 3a, bottom row, p > 0.05).

To clarify the relationship between cortical reactivity and the corticospinal response, we selected the significant EEG channels for each TEP component and averaged them to obtain scatter plots with MEP amplitude (Fig. 3b, n = 54 for each TEP component). As expected, we found significant positive correlations for the P25 (r = 0.52, p < 0.001) and P60 (r = 0.51, p < 0.001), and a significant negative correlation for the N45 (r = -0.58, p < 0.001). Note that right green y-axis corresponds to the N45 amplitude (negative amplitude).

Next, we investigated how the localized TEP components in the source space were correlated with MEPs. Because of their location in the sensory cortex, the N45 and P60 may reflect afferent input by hand-muscle twitches.

**Modulation of motor cortex excitability by tDCS**

Having identified cortical reactivity in the sensor and source spaces of single-pulse TMS and verifying that the evoked activity predicted the corticospinal response, we next causally tested whether cortical reactivity drove the corticospinal response using tDCS targeting the left M1. Previous studies have shown that tDCS modulates corticospinal excitability depending upon polarity [8,9].

We hypothesized that if tDCS modulates cortical excitability in a polarity-dependent manner, then it modulates cortical reactivity, corticospinal responses and afferent input elicited by single-pulse TMS to the M1. We applied three different tDCS conditions (anode, cathode, and sham) at 2 mA for 10 min and recorded MEPs and TEPs before and after tDCS. To investigate tDCS-induced modulation of corticospinal excitability, we averaged the MEPs and calculated the ratio (post/pre) for each tDCS condition. Using a linear mixed-effects model, we found a significant effect of tDCS condition (Fig. 4a, anode vs. cathode vs. sham, F2,28 = 255, p < 0.0001, η² = 0.906), but not of session (the three experimental sessions’ temporal order, F2,28 = 0.86, p = 0.43, η² = 0.003) or their interaction (F4,56 = 1.56, p = 0.21, η² = 0.011). As hypothesized, this finding demonstrated that tDCS modulated corticospinal excitability as measured by MEPs. Thereafter, we investigated whether tDCS modulated cortical excitability. We calculated the TEPs’ local interactions.
mean field power in the left sensorimotor area for the entire epoch by averaging the 7 previously described EEG channels and calculating the ratio (post/pre) for each tDCS condition. We found that the TEP period from 25 to 60 ms was significantly altered by tDCS condition (Fig. 4b, shaded period; linear mixed-effect model, $F_{2,28} = 129, p < 0.0001$), but not for session ($F_{2,28} = 1.12, p = 0.34$) or their interaction ($F_{2,28} = 1.31, p = 0.29$). Conversely, we found no significant effects of tDCS condition on the other TEP components (100–280 ms, $p > 0.05$).

Fig. 3. Cortical reactivity and corticospinal response. Correlation between cortical reactivity and corticospinal response. (a) Topographical distributions of correlations between each TEP component (P25, N45, P60, N100, P180, and N280) and MEPs. Black dots in topographical maps indicate significant EEG channels ($p < 0.05$). P25, N45, and P60 were correlated significantly with MEPs in the left sensorimotor area, while no significant relation was found for the N100, P180, and N280. (b) Scatter plot of the averaged significant EEG channels for the P25, N45, and P60. Note that the right, green y-axis corresponds to the N45 amplitude (negative amplitude). Significant correlations were found for the P25 ($r = -0.52, p < 0.001$), N45 ($r = -0.58, p < 0.001$), and P60 ($r = -0.51, p = 0.001$). (c) Selection of a ROI on the template cortex model (P25: 74 vertices, 6.47 cm², N45: 76 vertices, 8.29 cm², P60: 206 vertices, 22.71 cm²). (d) Scatter plot of the ROI for each localized TEP component with MEPs. Significant correlations are obtained for the P25 ($r = -0.62, p = 0.001$), N45 ($r = -0.57, p < 0.001$), and P60 ($r = -0.45, p < 0.001$). The density plot shows the way the TEP components were correlated with MEPs. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

We then performed correlation analyses to investigate whether tDCS modulated TEPs (cortical excitability) and MEPs (corticospinal excitability) similarly across participants (Fig. 4d, scatter plot). We found significant positive correlations in the anodal tDCS condition for the P25 ($r = 0.54, p = 0.022$), N45 ($r = 0.53, p = 0.023$), and P60 ($r = 0.56, p = 0.015$). In the cathodal tDCS condition, we found significant positive correlations for the P25 ($r = 0.51, p = 0.032$) and N45 ($r = 0.56, p = 0.016$), but not for the P60 ($r = -0.14, p = 0.57$). We found no significant correlations in the sham tDCS condition for the P25 ($r = -0.15, p = 0.54$), N45 ($r = -0.36, p = 0.14$), or P60 ($r = -0.19, p = 0.46$). Thus, the amplification or attenuation of cortical excitability measured in the sensor space was consistent with the modulation of corticospinal excitability. Anodal tDCS amplified early TEP components and the degree of amplification predicted an increase in MEP amplitude, while cathodal tDCS attenuated early TEP components, which predicted a decrease in MEP amplitude.
We then performed correlation analyses to investigate whether modulation of localized cortical TEPs and corticospinal MEPs were similar across participants (Fig. 4f). We chose the ROI based on the cortical model (Fig. 3c) for each localized TEP component. In the anodal tDCS condition, we found significant positive correlations for the P25 \((r = 0.65, p = 0.0034)\), N45 \((r = 0.53, p = 0.022)\), and P60 \((r = 0.50, p = 0.034)\). In the cathodal tDCS condition, we found significant positive correlations for the P25 \((r = 0.49, p = 0.04)\) and N45 \((r = 0.49, p = 0.037)\), but not for the P60 \((r = 0.41, p = 0.09)\). We found no significant correlations in the sham tDCS condition for the P25 \((r = 0.29, p = 0.24)\), N45 \((r = -0.12, p = 0.65)\), and P60 \((r = 0.1, p = 0.68)\). These findings support a model in which tDCS selectively modulates the cortically localized TEP components that drive the corticospinal response.

**Modulation of pre-stimulus mu-rhythm by tDCS**

These results indicate that tDCS modulated corticospinal and cortical excitability in a targeted and robust manner. These different TMS-induced responses suggest that tDCS altered the overall state of the targeted network. Thus, we next investigated how tDCS modulated the network’s excitability and the oscillatory structure of this activity. We computed time-frequency representations for the entire epoch \((-200 to 500 ms)\) and performed non-parametric cluster-based permutations to assess changes between the periods before and after tDCS. We found that anodal tDCS significantly increased the pre-stimulus mu-rhythm (Fig. 5a, first row, \(t\)-value time-frequency map, clustered region), and this increased mu-rhythm was located in the left sensorimotor area.
(inset, topographical distribution, black dots indicate significant EEG channels, $p < 0.05$). In contrast, cathodal tDCS significantly decreased the pre-stimulus mu-rhythm (Fig. 5a, second row, $t$-value time-frequency map, clustered region) and the post-stimulus mu-rhythm around 250 ms. The decreased mu-rhythm was located in the left sensorimotor area (topographical distribution, black dots indicate significant EEG channels, $p < 0.05$). No significant differences were observed in the time-frequency map (Fig. 5a, third row, $t$-value time-frequency map) and topographical distribution (no significant EEG channel) under the sham tDCS condition.

Next, we investigated the relation between the pre-stimulus oscillatory modulation and the modulation of corticospinal and cortical excitability. Correlations were calculated between the modulated pre-stimulus mu-rhythm power and MEPs and the P25 TEP component in the sensor and source spaces for each participant (Fig. 5b). We found that the pre-stimulus mu-rhythm ratio (post/pre to tDCS) was correlated with the MEP ratio (post/pre to tDCS) for anodal ($r = 0.56, p = 0.017$) and cathodal tDCS ($r = 0.49, p = 0.037$), but not for sham tDCS (Fig. 5b, first row, $r = -0.08, p = 0.75$). We also found that the pre-stimulus mu-rhythm ratio...
was correlated with the P25 ratio in the sensor space for anodal ($r = 0.50, p = 0.034$) and cathodal tDCS ($r = 0.47, p = 0.047$), but not for sham tDCS ($r = 0.16, p = 0.53$). Similarly, we found that the pre-stimulus mu-rhythm was correlated with the P25 ratio in the ROI-based source for anodal ($r = 0.66, p = 0.0028$) and cathodal tDCS ($r = 0.51, p = 0.032$), but not for sham tDCS ($r = 0.15, p = 0.56$). These results show that tDCS modulates the pre-stimulus mu-rhythm, thereby altering network oscillations reflecting corticospinal and cortical excitability.

**Discussion**

TMS-EEG studies have recently gained attention because they may provide important insights into disease processes in the central nervous system, as well as mechanistic understanding of how clinical TMS paradigms engage brain networks [2,28]. However, there is controversy regarding whether TEPs reflect genuine cortical reactivity to TMS or reactivity from peripherally- and auditory-evoked potentials [3–5]. The current study directly addressed this question through a unique combination of brain stimulation and imaging methods. We used sophisticated procedures to attenuate peripheral and auditory confounds and performed source localization with high-density EEG data, structural MR images, and digitized EEG electrode locations. We observed six TEP components and found that the P25, the earliest TEP component, was localized to the stimulated cortical area, the left M1. The following two TEP components (N45 and P60) were largely localized to the primary somatosensory cortex, which may represent afferent input by hand-muscle twitches. The remaining TEP components (N100, P180, and N280) were primarily localized to the auditory cortex. Importantly, TDCS selectively modulated the P25 and N45 TEP components in a polarity-dependent manner in our double-blind, placebo-controlled study. In addition, we found evidence that cortical reactivity played a causal role in predicting corticospinal excitability. Thus, our findings demonstrate that early TEP reflects genuine cortical reactivity, whereas later TEP components are associated with somatosensory and auditory processing in the brain.

A recent study investigating neural effects at the single-cell level showed that suprathreshold single-pulse TMS elicits a stereotyped burst of action potentials within the first 10–30 ms following TMS onset in the macaque parietal cortex [29]. Another study in human participants found that single-pulse TMS targeting the M1 elicited significantly different responses in the 60 ms following stimulation compared to sham TMS [30] and a pilot study found that early cortical reactivity within 30 ms (N15–P30 complex) was correlated with corticospinal responses [31]. Consistent with these recent findings, we found that the P25 was localized to the left M1 (TMS target location), demonstrating that the P25 represents genuine cortical reactivity to single-pulse TMS targeting the M1. Although we were unable to obtain earlier TEP components, such as the P10 [11] or P15 [32] because of TMS artifacts in our recordings, a response latency within 30 ms is consistent with previous findings. We also observed N45 and P60 components that were largely localized in the primary somatosensory cortex and might have reflected afferent input by hand-muscle twitches produced by suprathreshold TMS. We further demonstrated that these somatosensory-evoked potentials were correlated with MEP amplitude (Fig. 3b) and comparable to the conventional somatosensory evoked potentials with respect to response latency [33]. We also obtained the typical N100–P180 TEP components that reflect the auditory complex [5] during single-pulse TMS (Fig. 2a), even though we applied auditory masking using white noise that removed the auditory perception of TMS pulses. This phenomenon may derive from inevitable bone- and air-conducted sound from the TMS coil [7]. For the right hemisphere activation, previous studies showed that cortical activation by suprathreshold TMS could be spread over the contra-lateral side [34–38]. We also examined the spread of cortical reactivity to the contra-lateral side but the amount of spread was scarcely seen in the source space except for auditory cortex. The overall conclusion is that each TEP component elicited by single-pulse TMS has a distinct network representation in the brain, with the P25 representing genuine cortical reactivity from TMS targeting the M1.

Since the first attempt to modulate motor cortex excitability by weak direct current on the scalp [39], it has been consistently shown that TDCS modulates motor cortex excitability in a polarity-dependent manner [8,9,40–45]. We also found significant modulation of corticospinal responses resulting in a high effect size (0.906). This effect size indeed higher than averaged effect size (0.67) from a recent meta-analysis [46]. We believe our strict inclusion criteria for age (18–35 years) to minimize aging effect [47–52] and for sex to minimize any effect of menstrual cycle [53,54] would minimize variability. We further posit that precise TMS targeting and electrode attachment for tDCS with a neuro-navigation system and MRI, and collecting a large number of MEP trials up to 100 to increase signal-to-noise ratio also contributed the high effect size. In our study, we hypothesized that if TDCS modulated corticospinal excitability, then it modulates cortical reactivity, corticospinal responses, and afferent input by single-pulse TMS to the M1. We found that tDCS successfully modulated the P25 in the stimulated cortical area in a polarity-dependent manner (Fig. 4e). tDCS similarly modulated the N45, but only anodal tDCS modulated the P60. Consistently, the relationship between changes in the MEP and P60 amplitude was not significant in the sensor or source spaces. We assume that this unexpected finding might be due to the reduction of post-stimulus mu-rhythm (around 200–300 ms after onset) by cathodal tDCS (Fig. 5b, second row, time-frequency t-value map). We hypothesized that tDCS would only modulate only the pre-stimulus mu-rhythm. However, cathodal tDCS also reduced the post-stimulus mu-rhythm, which was not observed in the anodal tDCS condition. This inconsistency in cortical reactivity modulation should be investigated in the future. While we adopted the conventional M1-SO montage for tDCS, which uses two stimulation electrodes (5 × 7 rectangular electrodes, one on the motor area and another on the supraorbital area) to modulate motor cortex excitability, a recent study used a 4 × 1 montage that consisted of smaller, ring-shaped electrodes to increase the focality of the induced electric field, known as high-definition tDCS [55]. One study comparing the ability of the two montages to modulate motor cortex excitability found comparable effectiveness [41]. Our study used the M1-SO montage with two smaller electrodes (5 × 5 cm, 25 cm²) to increase efficacy via a greater current intensity [42]. We performed electric field modeling with structural MR images and confirmed that the induced electric field was comparable to previous tDCS studies (Fig. 1c). As an exploratory analysis, we investigated how the induced electric field in the target stimulation area is related to MEP changes (Fig. 57) based on a study [56] that found that the electric field intensity in the primary motor cortex can explain inter-individual variability in MEP. However, we found no relationship between these variables. This finding may suggest that alternative factors, such as phase-dependent excitability, affected motor cortex excitability modulation in our data [57].

The corticospinal responses measured by MEPs elicited by single-pulse TMS targeting the M1 vary between trials [58–61]. Recent studies have shown that this variability is associated with neural oscillation power [62–68], phase [57,69,70], or their interaction [71], although one study failed to replicate these findings [72]. Our study showed that pre-stimulus mu-rhythm oscillatory
power was correlated with the modulation of cortical and corticospinal excitability (Fig. 5b). This finding indicates that tDCS modulates oscillatory power, which in turn causes modulation of cortical and corticospinal excitability. Consistent with this causal role of oscillatory power, a previous study showed that anodal tDCS increased neural oscillatory power and altered functional connectivity in a non-human primate model [73]. Importantly, recent TMS-EEG studies have found that pre-stimulus oscillatory power is positively correlated with MEP amplitude [66,68]. Together, our findings may indicate a causal role of oscillatory power in motor cortex excitability.

As with any scientific investigation, this study has limitations. First, we were unable to study earlier TEP components at 10 [11] or 15 ms [32] because of TMS pulse artifacts. We used a TMS-compatible EEG amplifier, but we observed that the TMS pulse artifact lasted up to 20 ms in raw EEG traces (Fig. S8). This may be have arisen from the low sampling rate due to technical limitation of the amplifier. Although we demonstrated that the P25 was localized to the hand area of the M1, future investigations of the earlier TEP components should be conducted using an EEG amplifier that has a faster recovery period and high sampling rate up to 5 kHz. Second, although we demonstrated that the P25 reflects genuine cortical reactivity from TMS targeting the M1, we did not investigate the TEP dynamics of single-pulse TMS targeting other brain regions, such as the dorsolateral prefrontal cortex, which is the main target for depression [74,75]. Previous studies have shown that TEPs exhibit different target dynamics [76–79], thus comparing stimulation to different cortical regions should be investigated in the future to confirm our findings. Third, a comparison with sham TMS is necessary to fundamentally demonstrate that the TEP is genuine cortical reactivity. Appropriate sham conditions would be subthreshold TMS or tilting the TMS coil by 90° over the scalp to minimize the stimulation to the motor cortex. In line with this limitation of the current experimental design, the first TEP component may contain some leakage of the TMS artifact and it also may affect the following two TEP components (N45 and N60). Although we demonstrated that these TEP components were significantly correlated with the MEP responses, a new experimental design including a sham condition with sophisticated methods to remove any TMS artifact could fully address the current limitation. We are considering these control conditions in a follow-up study.

The event-related potential (ERP), which is an evoked EEG potential in response to an external stimulus, has been well-studied over the past several decades [80]. Each ERP component represents specific brain processing. For example, the P300, a positive peak potential at approximately 300 ms, reflects cognitive processing [81], whereas the N170, a negative peak potential at approximately 170 ms, is a face-recognition ERP component over the ventral area of the visual cortex [82]. However, in the TMS-EEG field, few efforts have been made to determine how each TEP component is associated with specific sensory processing, and the underlying mechanisms remain unclear. Because the number of studies that used TMS as a treatment tool has tremendously increased in recent years, understanding the brain’s response to TMS is imperative for the research and clinical fields. Rational design and subsequent optimization of network-based treatment strategies using non-invasive brain stimulation is jeopardized by the inability to appropriately interpret TEP components.

In summary, we demonstrated that the early P25 TEP component reflects genuine cortical reactivity elicited by single-pulse TMS. We identified each TEP component in the sensor and source spaces and used tDCS to successfully modulate the TEP components in a polarity-dependent manner. We found that tDCS-induced modulation of the pre-stimulus mu-rhythm caused changes in excitability. Further, we found that the cortical TEP components were significantly correlated with corticospinal MEP amplitude. These findings suggest that each TEP component plays a distinct functional role.

Data availability
All data, as well as analysis codes that were used to perform analyses, can be made available from the corresponding author upon reasonable request.

CRediT authorship contribution statement
Sandae Ahn: Formal analysis, Writing - original draft. Flavio Frohlich: Writing - original draft, designed the study. S.A. collected and analyzed the data. S.A. and F.F. wrote the manuscript.

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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.2021.01.018.

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