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## An analytical approach to identify indirect multisensory cortical activations elicited by TMS?

Dear Editor,

Electroencephalography (EEG) is widely used for detecting transcranial-magnetic stimulation (TMS) evoked responses in the human brain. TMS-evoked potentials (TEPs) may contain both direct activations due to the TMS-induced cortical electric field and indirect cortical activations due to the subsequent multisensory responses to TMS [1]. Distinguishing between direct and indirect sources of cortical activation has largely been attempted using careful experimental designs [2–5]. Here, we complement those advances by providing a novel statistical approach. Our results converge with the pattern of indirect activation identified by recent experimental work [3], which provides encouraging support for the potential utility of this novel approach.

Several different experimental strategies have been used to deal with the indirect response of stimulation. One approach is to suppress the sources of multisensory stimulation and consequently minimize indirect cortical activations. This is powerfully illustrated in a recent study, in which the sound of the coil was very efficiently masked by playing noise-masking via earplugs as well as using ear defenders, and the vibrations of the coil were attenuated by using a foam layer beneath the coil [3]. Whether this suppression approach is completely effective is debated (e.g. [4,6]). An alternative experimental approach is to use sham stimulation to mimic, and consequently isolate multisensory sources of indirect cortical activation [3–5]. Yet, this requires techniques to accurately reproduce the multisensory response elicited by TMS [3,4], which is challenging to achieve. Both of these approaches deal with indirect responses to stimulation using experimental manipulations within-subjects. We offer a complementary approach using between-subjects analysis to identify the indirect cortical activations due to stimulation.

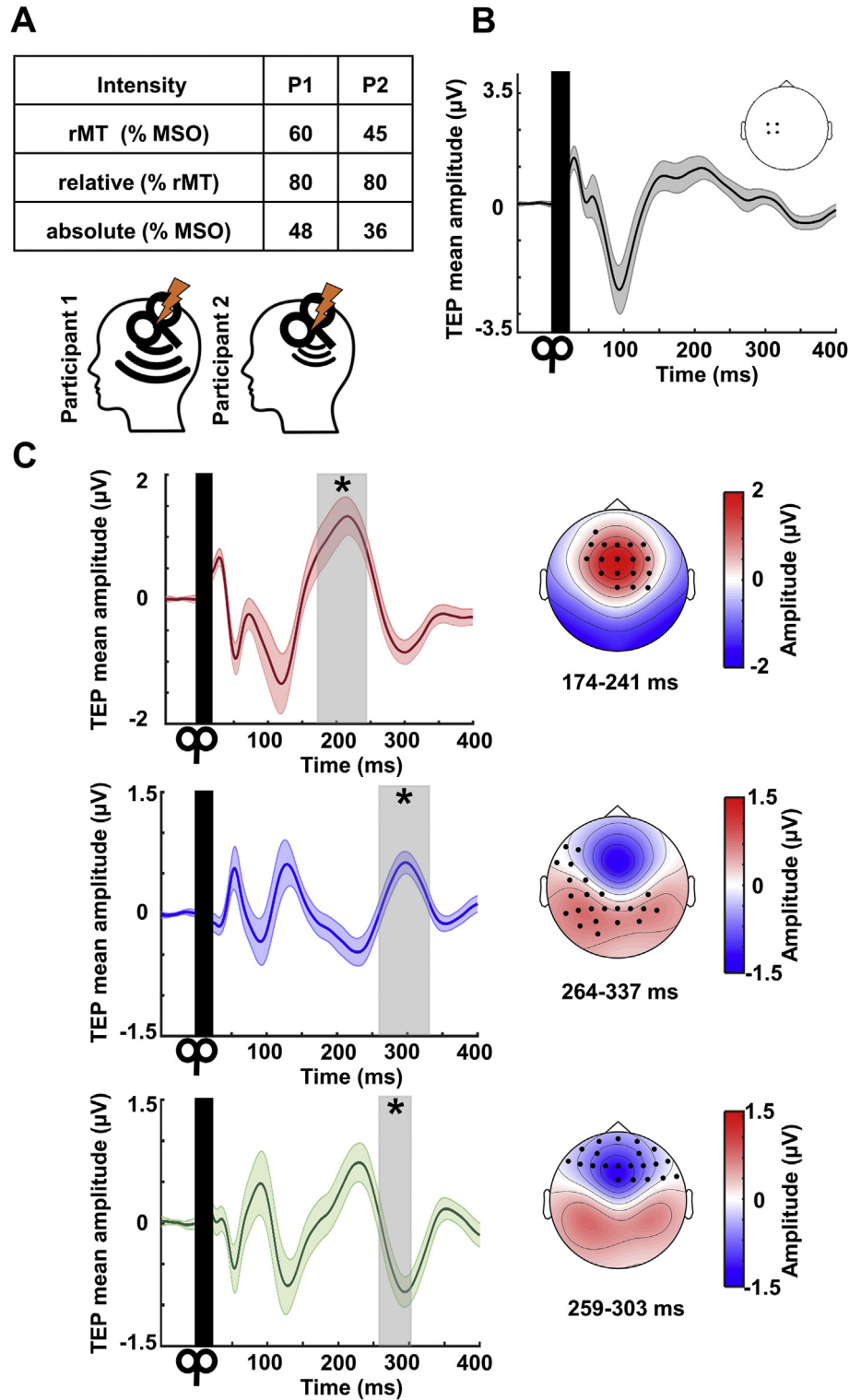
Commonly in TMS–EEG studies, participants receive a stimulation intensity tailored to their individual susceptibility to stimulation. When stimulating the primary motor cortex (M1) this is called the resting-motor threshold (rMT, [7]; relative intensity). This corresponds to a percentage of stimulator output (absolute intensity). For example, for one participant 80% of rMT may require 48% of the maximum stimulator output (MSO); while for another participant 80% of rMT will be achieved with only 36% of MSO (Fig. 1A). The administered relative intensity (e.g. 80% of rMT) represents a normalization implying that the magnitude of direct motor cortical activation should be comparable across subjects. By contrast, the indirect activation of a TMS pulse may be closely related to the amount of sensory input, which itself is higher with higher absolute intensity (e.g. 36% vs 48% of MSO; i.e., louder sound, stronger coil vibration, and stronger stimulation of

somatosensory fibres). As a consequence, in a between-subjects design, those receiving a higher absolute intensity of stimulation may experience more multisensory stimulation, and in turn display a higher amplitude of indirect cortical activation. We tested how well absolute intensity could explain the between-subject variability of EEG responses, and whether this corresponded to the spatiotemporal pattern of indirect cortical activations identified in earlier work [3].

We analysed a pre-existing TMS–EEG dataset (58 participants, 41 females,  $23 \pm 4$  years old (mean  $\pm$  std); right-handed (defined by Edinburgh Handedness Inventory); neurologically and psychiatrically normal participants, meeting the safety criteria for the use of TMS). Participants received 126 neuro-navigated biphasic single TMS-pulses to left primary motor cortex (M1), while EEG (a 62-channel system) was concurrently recorded. Stimulation intensity was set at 80% of participants' rMT ([7];  $54 \pm 8\%$  MSO (mean  $\pm$  std), range from 31 to 77% MSO). Individually adjusted white noise (the volume was gradually increased until participants could not hear the coil click anymore or their threshold of discomfort was reached) was played during the stimulation via padded earplugs.

In our analysis, we concentrated on the most commonly assessed dimension of TMS–EEG signal (i.e., TEPs [3]; Fig. 1B). Initially, the signal was cleaned from the typical noise and TMS-induced artifacts, via the MATLAB-based toolbox EEGLAB and the TMS–EEG signal analyser plugin (TESA [8]). For evaluating the spatio-temporal effects of absolute stimulation intensity, we computed TEPs (as the average time-course over trials) for each channel and each subject separately (in the average reference). Then, at each resulting time point (331; i.e. 20 – 350 ms after the TMS pulse) and at each channel (62 channels) we used linear regression to test whether the independent variable, subject-specific absolute intensity, can predict the subject-specific TEP amplitude (FieldTrip [9]). To test for possible significance, we ran independent-samples regression coefficient t-tests (two-tailed,  $\alpha$  level  $p < 0.025$ ). To control the multiple comparison problem (the familywise error rate [10]), clusters were built by assembling neighbouring significant spatio-temporal samples and tested against corresponding permutation statistics (5000 iterations, cluster  $\alpha$  level  $p < 0.025$  [10]).

We found that absolute stimulation intensity showed a significant regression against TEP amplitude in three different clusters. All three of the clusters occurred at later latencies. One of these was a negative cluster showing a negative TEP deflection (Fig. 1C, bottom row). The first was a positive cluster visible at 174–241 ms after the TMS pulse and mainly involved central



**Fig. 1. Experimental design and results** (A) Despite receiving the same relative intensity (80% rMT), every participant (P1 vs. P2) received a different, absolute intensity (48% vs. 36%; for example), which determines the magnitude of multisensory stimulation (coil vibration, coil click and excitation of nerves in the skin; see table). (B) The grand average TEP (i.e. mean over C1, C3, CP1 and CP3), showing a typical response when targeting M1. (C) On the left are shown the TEPs and the different time windows when their amplitude is related significantly with absolute intensity. The three clusters likely represent non-specific multisensory contributions from multiple sources. TEPs are averaged for those channels included within the significant cluster (black dots on scalp distribution). On the right are shown the respective topographical plots for each of the three clusters. Black box: time-window excluded from the analysis due to TMS-artifacts (i.e., 0-20ms). Grey box: significant time window in the cluster-based analysis. TEPs shadowing: standard error of the mean. Black asterisk (\*):  $p < 0.05$ . Black dots: significant channels in the cluster-based analysis. rMT: resting motor threshold. MSO: maximum stimulator output. TEP: TMS-evoked potential.

electrodes (corrected  $p = 0.025$ ; Fig. 1C, top row). The second positive cluster occurred later at 264–337 ms and was located above the left sensorimotor cortex (corrected  $p = 0.034$ , Fig. 1C, middle row). Finally, the negative cluster was found at 259–303 ms and involved central electrodes as well as electrodes located above left-frontal regions (corrected  $p = 0.038$ , Fig. 1C, bottom row). Based on their spatio-temporal patterns, the three clusters may be due to indirect cortical activations elicited by the sensory stimulation caused by TMS (e.g. a combination of auditory and somatosensory processes [3]).

These results show that the amplitude of late ( $>170$  ms) TEPs were related to the absolute stimulation intensity. This may identify indirect cortical activations, and suggests that in a between-subject design absolute intensity is linked to the multisensory stimulation elicited by delivering TMS. Despite the methodological differences, our results converge both temporally and spatially with the pattern of indirect activation identified by recent experimental work [3]. Hence, our analytical method makes the identification of indirect activations possible – unconstrained by experimental design – allowing new questions to be posed using innovative designs, which were previously impossible. Yet, further work is needed to fully validate this between-subject analytical approach. Nonetheless, it may prove to be a simple yet effective tool to identify and potentially remove multisensory contributions from TMS–EEG data; without the need to include additional experimental conditions within a study.

### Declaration of competing interest

We declare that the research was conducted free from any commercial or financial relationships that could have lead, or be seen to have lead to a conflict of interest.

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