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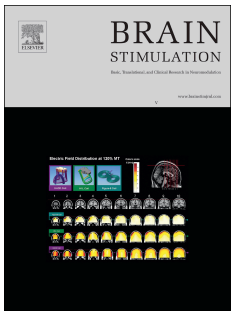

No evidence for interaction between TMS-EEG responses and sensory inputs

Pedro C. Gordon, Yufei Song, Blair Jovellar, Paolo Belardinelli, Ulf Ziemann

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No evidence for interaction between TMS-EEG responses and sensory inputs

Pedro C. Gordon[a,b], Yufei Song[a,b], Blair Jovellar[a,b], Paolo Belardinelli[a,b,c], Ulf Ziemann[a,b]

[a] Department of Neurology & Stroke, University of Tübingen, Germany

[b] Hertie Institute for Clinical Brain Research, University of Tübingen, Germany

[c] CIMeC, Center for Mind/Brain Sciences, University of Trento, Italy

There is considerable ongoing discussion on the relevance of peripherally evoked potentials (PEPs) in TMS-EEG measurements. These PEPs are elicited by the auditory and somatosensory inputs caused by TMS, potentially becoming overlapped with TMS evoked potentials (TEPs). There is consensus that this overlapping presents an inherent challenge for TMS-EEG investigations [1-3]. Nevertheless, there is to this date no agreement on how to best address this issue [4, 5]. Proposed solutions commonly involve the use of a control condition in the form of sham TMS that aims at eliciting sensory input akin to real TMS. In principle, once one has identified the EEG responses to such sensory input, these can be removed from the real TMS response signal [6, 7]. However, previous attempts suffered from methodological flaws [2, 5], as the proposed sham conditions have failed to fully mimic the sensory inputs from real TMS, leaving the issue unresolved.

To overcome these challenges, we have designed a method which aimed at equivalence of EEG responses to sensory inputs from the real and the sham TMS [1]. In brief, our method consisted of causing somatosensory input in both the sham and real TMS conditions by means of high-intensity electrical stimulation (ES) of the scalp, to the extent to saturate the PEP amplitude. Therefore, additional somatosensory input from the real TMS condition becomes negligible in this saturated somatosensory evoked potential. Subtracting the EEG response to sham TMS from the EEG response to real TMS should then remove the somatosensory evoked potentials. The resulting EEG deflections < 80 ms after the TMS pulse are minimally affected by PEPs. Later responses were predominantly localized at the site of the stimulated motor cortex, but obscured by PEPs without the subtraction [1].

Our proposed method, however, was criticized for its use of high-intensity somatosensory inputs. It was suggested that high-intensity peripheral stimulation might interact with the brain response to

TMS. This has been, for example, inferred from recent work that showed modulation of corticospinal excitability by auditory and somatosensory stimuli [8]. Although modulation of TEPs by sensory inputs has not been directly demonstrated to this date, it would imply that EEG responses observed by our method would not correspond to "true" TEPs, but instead to TEPs that are modulated by concomitant sensory input. Moreover, this possible interaction between PEPs and TEPs would also imply that these responses are non-linearly intertwined, which would challenge attempts by us and others to remove PEPs from TMS-EEG responses by simple subtraction.

Given the importance of this unresolved issue for the TMS-EEG field, we sought to experimentally test TEP modulation by somatosensory input. We compared EEG responses from three different single-pulse TMS conditions in 12 healthy right-handed volunteers: 6 female (50%), mean age 25 years, age range 20-32 years. All 3 conditions consisted of REAL TMS targeting the left primary motor cortex at an intensity 90% of the resting motor threshold, and 140 pulses per condition were applied. Moreover, in all conditions 140 trials of SHAM TMS were randomly interleaved with the REAL TMS trials, using a sham coil to produce click sound and ES of the scalp. ES was delivered by 2 pairs of 1 cm diameter electrodes placed between the EEG electrodes, one pair of opposite polarity placed at the FCC4h and CCP4h EEG electrode positions, and the other at TPP7h and TPP9h. These positions were chosen to generate somatosensory input from a broad scalp region around the TMS target. Masking noise was used throughout all measurements (Fig. 1A).

The 3 TMS conditions differed as follows: In Condition 1, ES (pulse width, 200 µs) was applied to the scalp with an intensity of 400% sensory perception threshold, both during the REAL TMS and SHAM trials (as described in our previous report [1]). In Condition 2, ES was also applied in both REAL TMS and SHAM trials, but the intensity was 800% of sensory perception threshold. Condition 3 consisted simply of REAL TMS without concomitant ES. However, somatosensory inputs from the TMS pulse *per se* also cause PEPs in TMS-EEG experiments [2, 9], suggesting that the SHAM condition should contain an equivalent somatosensory input. For this reason, SHAM in Condition 3 consisted of individually titrated ES intensity, so that the PEP amplitude in this SHAM condition matched the PEP amplitude in

the REAL TMS condition (Fig. 1A). In summary, REAL TMS is the same in all conditions, while the intensity of concomitant somatosensory input is considerably different. Crucially, for interpretation of our experimental data, the existence of any significant modulatory effect of somatosensory input on the EEG response evoked by TMS should then translate into differences between conditions, detectable in the EEG responses to REAL TMS after subtraction of the EEG responses to SHAM TMS. In contrast, absence of a significant modulatory effect should result in identical EEG responses after subtraction.

The TMS-EEG signals were processed using established methods, which included visual inspection and exclusion of individual trials containing excessive artifacts, followed by the clipping and interpolation of the signal within the time window around the TMS artifact (-2 ms to 14 ms), and lastly independent component analysis aimed at removing further artifacts, namely eye blinks, eye movement and cranial muscle activity [10]. The resulting TMS-EEG responses from the 3 conditions were statistically compared using a cluster-based ANOVA aimed at identifying time-windows of significantly difference, followed by post hoc cluster-based dependent samples t-tests. The TMS-EEG responses were also compared with respect to their spatial similarity by means of pairwise correlation analysis [2].

Fig. 1B-C shows that the EEG responses to REAL TMS after subtraction of SHAM TMS were similar across the 3 conditions. Moreover, Fig. 1E demonstrates that these responses are significantly correlated in their time course and spatial distribution, especially within the first 100 ms after stimulation. Together, this is compelling evidence in favor of the notion that somatosensory input does not significantly interact with the EEG response caused by TMS. Therefore, the EEG response to REAL TMS after subtraction of the response to SHAM TMS can be considered a “true” TEP.

Only one significant difference was detected in the amplitude of late potentials from Condition 3 compared to Condition 1 (Fig. 1C-D). However, these late potentials are not typical of TEPs, and given their latency and midline distribution, most likely represent PEPs. It is possible that the individually titrated SHAM in Condition 3 did not appropriately match the PEPs from the REAL TMS condition and/or that the 400% ES was insufficient to saturate the PEPs.

In summary, this implies that the optimized sham method that we have proposed [1], which depends on application of high-intensity somatosensory stimulation to saturate the somatosensory evoked potential, is valid for removing PEPs and obtaining the true EEG responses to direct cortical activation by TMS. On a more general note, it follows that methods of PEP removal from the TEP signals that assume independence of the two signals, such as independent component analysis [7], SSP-SIR [6], or a simple arithmetical subtraction, are valid, provided that the PEPs in the SHAM condition match those caused by REAL TMS.

It is important to note that the present data does not constitute incontrovertible evidence against modifiability of motor cortex excitability by sensory input. It is simply possible that TMS-EEG just is not sensitive to this modulatory effect.

Declaration of competing interest

The authors declare no conflict of interest with respect to this work.

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Figure caption

Figure 1.

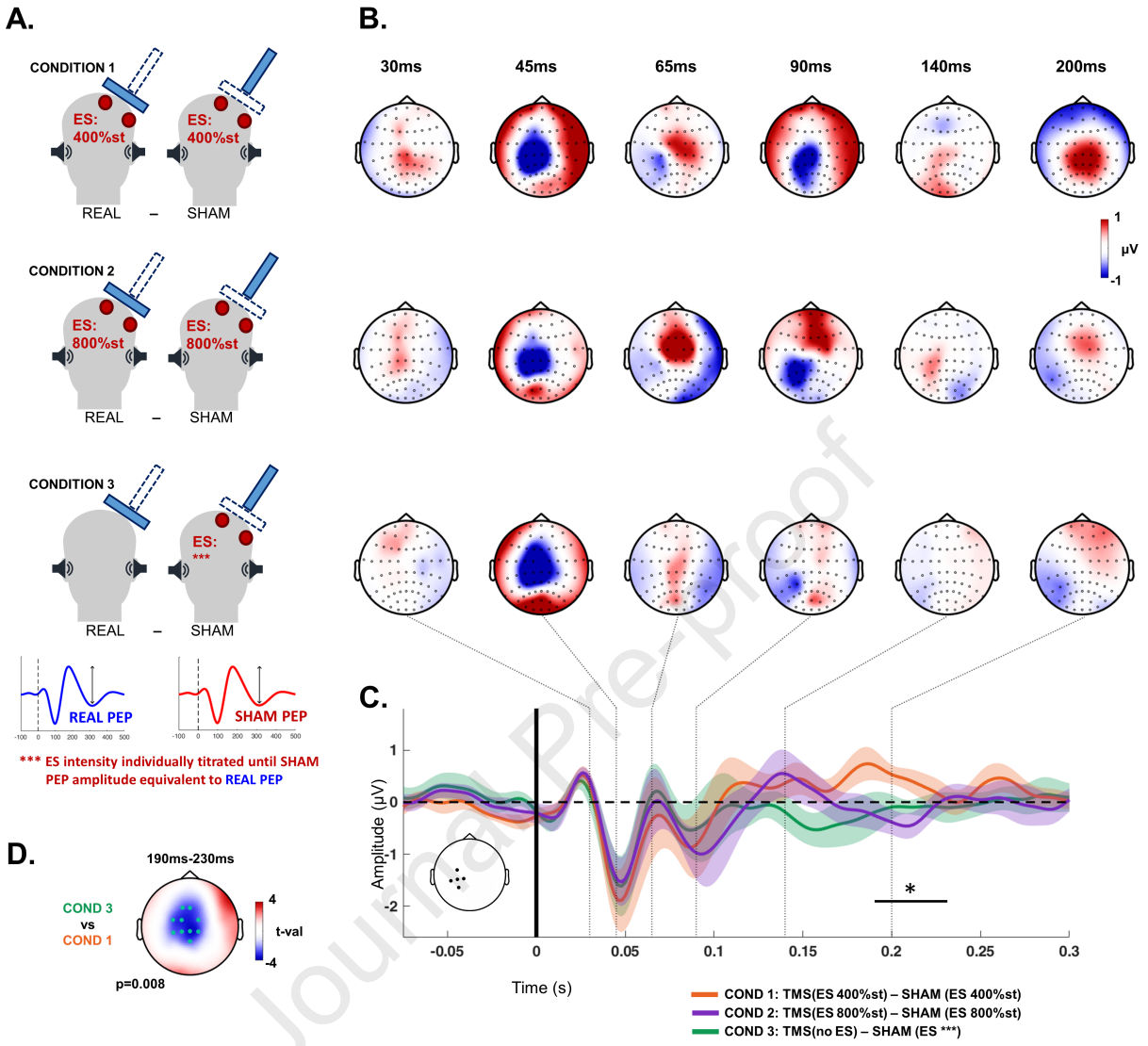
A. Representation of the 3 stimulation conditions. The blue rectangle represents the TMS coil (real coil parallel to the scalp, sham coil perpendicular to the scalp). Black sound icons represent the masking noise. Red dots represent the electrodes for the electric stimulation (ES), with the intensity of the ES specified in the figure. Note that the ES for Condition 3 was individually titrated. This was done by delivering 40 pulses using REAL TMS to left primary motor cortex at 90% of resting motor threshold, and calculating the amplitude of the response signal from electrode FCz (against an average reference) by taking the difference between the positive peak at around 200 ms and the negative peak at around 300 ms. The procedure was then repeated, but using scalp ES instead of the REAL TMS, until the amplitude of the evoked response matched that from the REAL TMS (average of 30 trials per intensity step).

B. Topographical plots representing the scalp distribution of the EEG response amplitudes (REAL TMS minus SHAM TMS) divided by the 3 stimulation conditions, as indicated to the left (A.).

C. Time course of the EEG response from the 3 conditions, averaged across all subjects (n=12) and electrodes around the stimulated region (depicted in the scalp electrodes model). The shaded areas represent ±1 S.E.M. Horizontal black bar (*) indicate the time window where the cluster-based ANOVA identified significant differences between conditions.

D. Topographical plot of the *post-hoc* cluster-based *t*-statistics showing the single statistically significant cluster (between Conditions 1 and 3). Cyan dots represent the electrodes that compose the significant cluster. The p-value is indicated.

E. Spearman correlation statistics of the signals (REAL TMS minus SHAM TMS) between the 3 stimulation conditions, averaged across all subjects (coefficients are z-transformed). Topographical plots display the spatial distribution of the correlation coefficients (ρ) in selected time windows after the stimulus (as in B.). Time course plots display the temporal progression of the correlation coefficients (ρ) averaged across all channels. Red dotted lines represent the significance threshold (p=0.05) for 10 degrees of freedom (df=n–2; n=sample size).


A.
CONDITION 1
ES: 400%st
ES: 400%st
REAL – SHAM
CONDITION 2
ES: 800%st
ES: 800%st
REAL – SHAM
CONDITION 3
ES: ***
REAL – SHAM
REAL PEP
SHAM PEP
*** ES intensity individually titrated until SHAM PEP amplitude equivalent to REAL PEP
B.
30ms
45ms
65ms
90ms
140ms
200ms
1
μV
-1
C.
Amplitude (μV)
Time (s)
*
COND 1: TMS(ES 400%st) – SHAM (ES 400%st)
COND 2: TMS(ES 800%st) – SHAM (ES 800%st)
COND 3: TMS(no ES) – SHAM (ES ***)
D.
190ms-230ms
COND 3
vs
COND 1
t-val
4
-4
p=0.008
E.
corr(COND 1, COND 2)
corr(COND 1, COND 3)
corr(COND 2, COND 3)
Correlation coefficient (ρ)
Time (s)
ρ

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: