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TMS-associated auditory evoked potentials can be effectively masked: Evidence from intracranial EEG

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Dear Editor,

Transcranial magnetic stimulation (TMS) is a noninvasive method of inducing focal electric currents in brain areas via electromagnetic induction. Studying the neurophysiological effects of TMS in humans using electroencephalography (TMS-EEG) is confounded by TMS-induced artifacts, including equipment-related (e.g., amplifier artifacts) and physiologic (e.g., auditory and somatosensory artifacts) [1]. The TMS-EEG approach is also limited by the coarse spatial resolution of EEG, which prevents accurate localization of the cortical sources underlying EEG responses to TMS.

One of the most pervasive artifacts observed in TMS-EEG is the auditory evoked potential (AEP) in response to acoustic clicks that accompany TMS pulses [2]. This artifact can contaminate signal in auditory-related cortices and other brain regions [3]. Methods attempting to control AEP artifact include post-processing procedures and sound masking methods using white noise or phantom TMS clicks [4,5]. One promising method of TMS auditory masking is the freely available TMS Adaptable Auditory Control software (TAAC) [6]. TAAC uses a mixture of real TMS clicks and white noise, providing masking superior to white noise alone.

A new experimental method, combining TMS with intracranial electrode recording (TMS-iEEG), allows for precise localization of physiologic responses to TMS and associated artifact. Preliminary studies support the safety and feasibility of this approach [7]. Here we discuss the intracranial TMS-evoked potential (iTEP) findings with and without TAAC sound masking in a patient implanted with iEEG electrodes for medically refractory epilepsy, including coverage of auditory and non-auditory regions. This provided a unique case to test the effectiveness of TAAC for reducing TMS-associated auditory artifact.

The patient was a 36-year-old right-handed female. She had onset of seizures at age 18 after suffering a traumatic brain injury in a motor vehicle accident. She underwent stereoencephalography monitoring for seizure localization and evaluation for epilepsy surgery.

Single pulse TMS was delivered at 100 % motor threshold to the right and left dorsolateral prefrontal cortex (DLPFC) using coordinates from Fried et al. [8]. TMS was delivered in four conditions (50 biphasic pulses per condition, 0.3 Hz): 1) sham TMS (coil flipped 180°) without sound masking, 2) sham TMS with TAAC sound masking, 3) active TMS without sound masking, and 4) active TMS with sound masking. The participant wore custom ear molds throughout for delivery of masking sound generated from a computer in the adjacent room. For sound masking conditions, the TAAC volume was adjusted to a threshold where the participant could no longer hear the acoustic clicks of the TMS coil. During no sound masking trials, the sound was turned off.

Data analysis was performed using customized MATLAB scripts (MathWorks, Inc., United States). Additional details of participant background, TMS, neuroimaging, electrode localization, data recording, and data processing including artifact removal, baseline correction, bipolar re-referencing, and detrending are described in the Supplementary Material.

iTEPs were obtained by averaging the iEEG activity recorded across trials within each condition, and a cluster-based permutation test [9] was used to examine the temporal differences between the sound masking and no masking conditions (two-tailed test, alpha 0.05, 1500 permutations, cluster threshold 10 consecutive milliseconds).

iEEG were obtained from 85 contacts recorded from the gray matter. A total of 39 pairs (31 right hemisphere, 8 left hemisphere) of bipolar contacts in the temporal and occipital regions were available for analysis, such that two adjacent contacts could be co-localized within the same gray matter region.

Fig. 1 shows the right hemisphere iEEG contacts and corresponding EPs during active left and right DLPFC TMS. Left hemisphere and sham TMS EPs are presented in Supplementary Figs. 1–4. Supplementary Figs. 5–8 present all bipolar EPs across all conditions. Auditory responsive channels were confirmed in a separate experiment using acoustic stimuli (Supplementary Fig. 9).

Abbreviations: AEP, auditory evoked potential; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; EP, evoked potential; iEEG, intracranial electroencephalography; iTEP, intracranial TMS-evoked potential.

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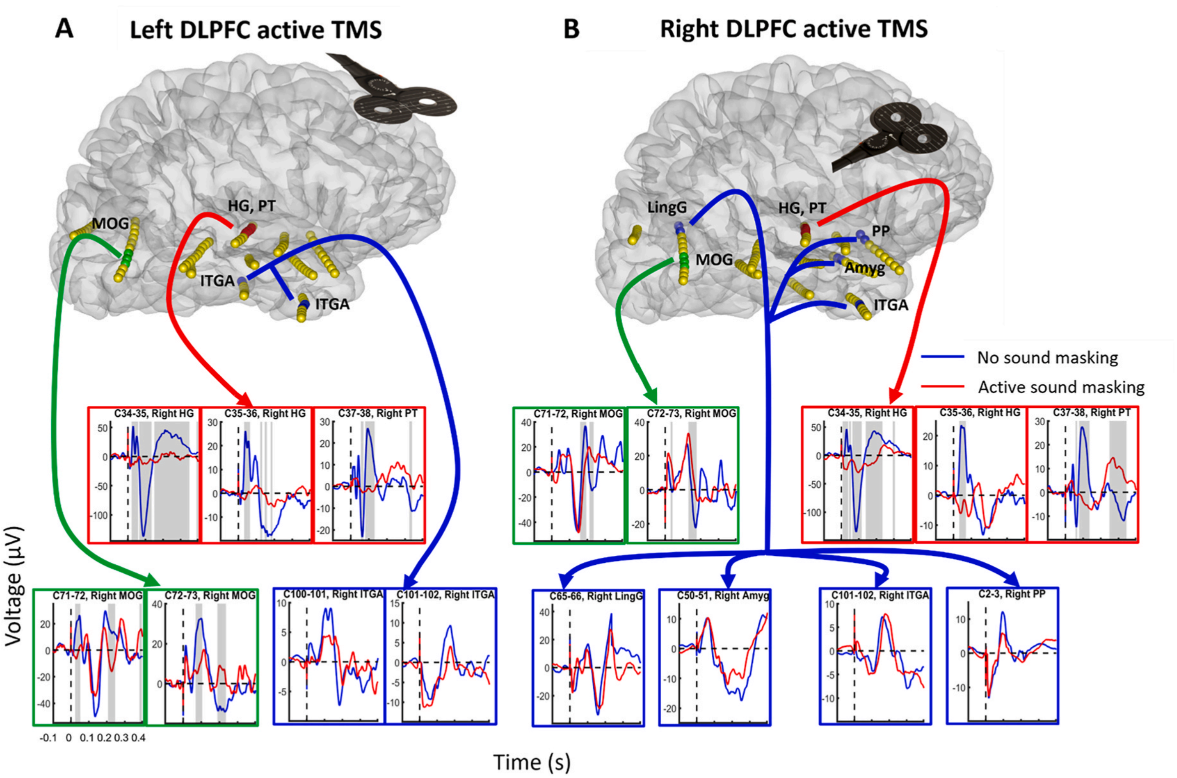

Fig. 1. (A) Lateral view of the brain showing iEEG contacts in the right hemisphere with their corresponding TMS evoked potentials during active left DLPFC TMS. (B) Lateral view of the brain showing iEEG contacts in the right hemisphere with their corresponding TMS evoked potentials during active right DLPFC TMS. The colors of contacts and frames of EPs indicate the regions of differences in AEPs between sound masking and no sound masking conditions. Gray shaded areas in EP figures indicate statistically significant time periods ($p < 0.05$) between no sound masking and active sound masking conditions. Red contacts indicate auditory-related regions with statistically significant differences between the conditions. Green contacts indicate non-auditory related regions showing statistically significant differences between conditions. Blue contacts indicate observable EPs are in both conditions with no significant difference. Yellow contacts indicate no observable EPs. Amyg, Amygdala; HG, Heschl's gyrus; ITGA, Anterior inferior temporal gyrus; LingG, Lingual gyrus; MOG, Middle occipital gyrus; PP, Planum polare; PT, Planum temporale. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Compared to no sound masking, TAAC sound masking consistently reduced AEPs in auditory-related regions in right Heschl's gyrus and planum temporale across both active and sham DLPFC TMS conditions. The primary exceptions to this were contacts during sham TMS in the left hemisphere, where no significant EP was identified with sparse cortical coverage. Moreover, sound masking reduced AEPs in the left superior temporal sulcus and middle temporal gyrus during active left and right DLPFC TMS, respectively.

In terms of non-auditory related regions, sound masking significantly reduced EPs in the right middle occipital gyrus during active DLPFC TMS. In other brain regions in which iTEPs were observed, sound masking either mildly changed or did not change the EP morphology. These included non-significant, but qualitatively different, morphology effects in the inferior temporal gyrus, fusiform gyrus, planum polare, amygdala, and lingual gyrus in the right hemisphere. This suggests that auditory artifacts impact a broad network of brain areas, and therefore auditory masking is key to interpret TMS effects beyond primary auditory regions. The interplay between auditory artifacts and neural responses in these regions warrants further investigation.

In summary, the direct electromagnetic effects of TMS are often contaminated by indirect auditory or somatosensory artifacts, particularly AEPs evoked by the TMS clicks. TAAC prevention of TMS-evoked AEPs has been demonstrated with scalp EEG in awake humans [6] and anesthetized primates [10]. Our results align with and extend these prior studies, employing a unique TMS-iEEG paradigm allowing for precise spatial localization of brain responses to TMS and auditory artifacts. Our results show that TAAC abolishes AEPs in sound-responsive electrodes, particularly in right Heschl's gyrus and planum temporale.

Our study contributes to the growing body of literature demonstrating safety and feasibility of TMS-iEEG. The ability to directly record intracranial signals allows for a more precise assessment of the impact of TMS and the effectiveness of artifact reduction strategies. TMS-iEEG could be used to validate other results and artifact-reduction strategies employed in TMS-scalp EEG studies.

Limitations of this study include findings based on a single patient with epilepsy and thus unclear generalizability. Larger studies are needed to confirm the present findings and to better understand the physiologic effects of sound masking on neuronal activity independent of TMS.

This work paves the way for future investigations of TMS neurophysiology in awake human participants with iEEG.

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review & editing. **Eric W. Tsang:** Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Joel Bruss:** Data curation, Methodology, Visualization, Writing – review & editing. **Simone Russo:** Conceptualization, Methodology, Supervision, Writing – review & editing, Software. **Phillip E. Gander:** Data curation, Investigation, Methodology, Supervision, Writing – review & editing. **Joel I. Berger:** Data curation, Investigation, Methodology, Writing – review & editing. **Kirill V. Nourski:** Validation, Visualization, Writing – review & editing. **Mario Rosanova:** Conceptualization, Methodology, Writing – review & editing. **Corey J. Keller:** Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing. **Hiroyuki Oya:** Data curation, Investigation, Methodology, Writing – review & editing. **Matthew A. Howard:** Resources, Supervision, Writing – review & editing. **Aaron D. Boes:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

SR is the Chief Medical Officer of Manava Plus. The other 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.

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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.2024.05.002.

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