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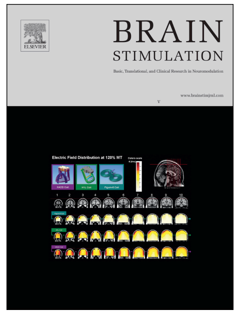

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Identifying neural targets for enhancing phonological processing with transcranial alternate current stimulation

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Language is organized in distributed networks in the human brain. Numerous previous neurostimulation studies have demonstrated the functional relevance of several regions in the left hemisphere for different aspects of language comprehension and production (e.g., [1] for review). In particular, the posterior part of the left inferior prefrontal cortex (IPC) has been identified as key region for processing the sound of words (i.e., phonological processing) [2]. Aside from probing the functional relevance of specialized language regions, there is increasing interest in enhancing language performance with neurostimulation to provide effective training and treatment protocols for language disorders [3]. Various neurostimulation protocols show promise but have inconsistent and variable effects across studies [4]. One reason for this inconsistency is the current lack of understanding of neurostimulation effects at the network level since most language studies focused on the behavioral level only. Some studies provide first evidence that participants with increased functional connectivity (FC) between the left IPC and the rest of the brain in the alpha frequency band during task-free states have better language abilities [5,6]. Consequently, increasing spontaneous alpha-band network interactions of the IPC may enhance language processing.

Transcranial alternate current stimulation (tACS) may be particularly suited for this purpose, as it allows targeting and modulating different brain rhythms of interest. Indeed, previous research has shown that alpha-tACS over the bilateral prefrontal cortex facilitates phonological decisions [7]. However, the neural correlates of such modulatory effects remain largely unclear. In particular, it remains unknown if the prefrontal cortex is the optimal target for enhancing phonological processing and if tACS modulates alpha-band oscillations and FC at the network level. Here, we address these questions based on a re-analysis of a previous dataset [7].

Details on the study sample and experimental procedures have been reported previously [7] and are provided in the Supplementary Information. In brief, subjects performed a phonological decision task on two- and three-syllable nouns after receiving tACS at 10 Hz, 16.6 Hz (control frequency) or sham stimulation over the bilateral prefrontal cortex. For the current analysis, we localized resting-state oscillations before and after stimulation with minimum variance beamformers and computed oscillation power as well as the absolute imaginary coherence as index of FC. The main analysis was done in the alpha (7.5-12.5 Hz) frequency band as this corresponds to the stimulated frequency, but to examine specificity, we additionally examined delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), and beta (12.5-20.5 Hz) frequency bands. At each voxel, we computed global FC as the mean FC with all other voxels, hence obtaining the graph theoretical measure of weighted node degree (WND).

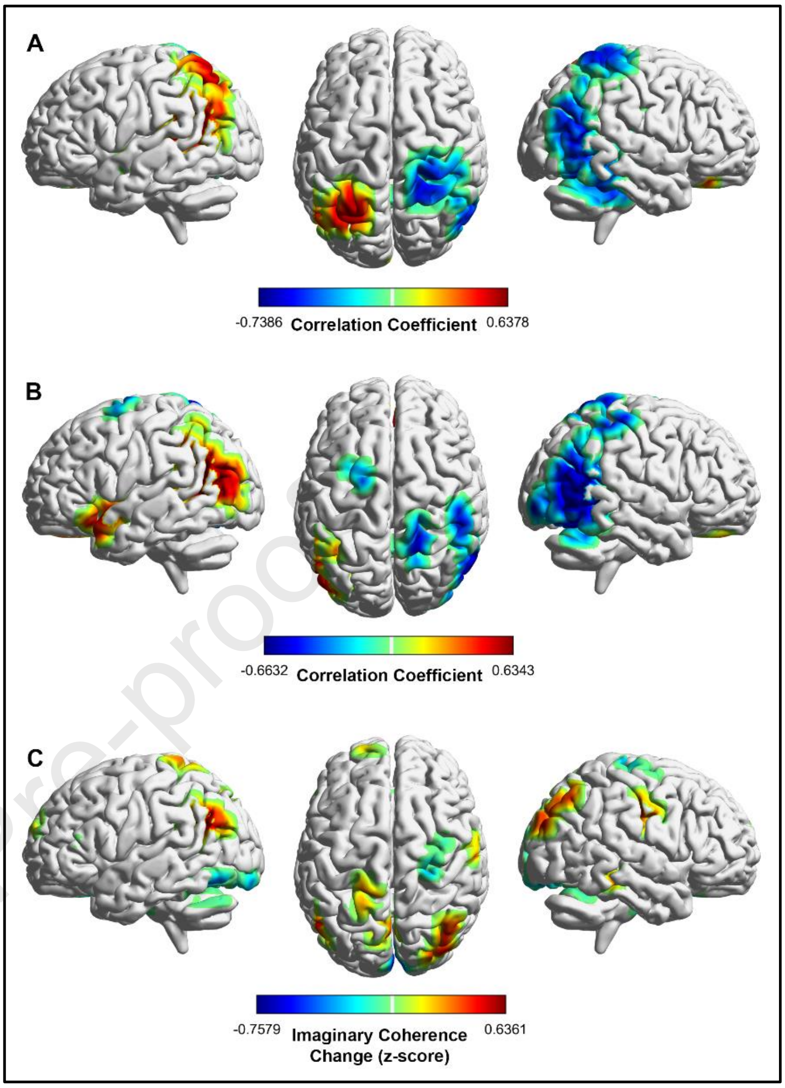

Fig. 1. Correlation between alpha-band FC and inverse reaction time. A. Correlation between pre-post differences and language improvement. B. Correlation between post-differences and language improvement. C. Changes in alpha-band WND after stimulation

We first asked which neural patterns were associated with better behavioral performance in the language task. Behavioral performance was quantified with the inverse of the reaction time (iRT). A correlation between resting-state FC and iRT revealed that the more alpha-band WND at left inferior parietal (r=0.45, p=0.027) and left temporo-parietal areas (r=0.50, p=0.013) increased after compared to before 10 Hz stimulation, the faster the phonological response speed (Fig. 1A). Similarly, greater levels of alpha-band WND at the same areas, measured *after* 10 Hz stimulation, were also correlated also with faster iRT (r>0.46, p<0.023, Fig. 1B). This suggests that temporo-parietal regions may play a role in behavioral improvements and, in particular, that alpha-band WND at these areas is a potentially behaviorally useful marker for tACS effects. Conversely, greater increases of WND at the homologous right temporo-parietal areas correlated with worse behavioral performance (r=-0.43, p=0.038). Changes in resting-state FC at the other frequency bands did not correlate with iRT (p>0.35), demonstrating the specificity of the observed effects.

In summary, we identify global interactions of the left temporo-parietal area with the whole brain as neural correlate of stimulation-induced performance increases. In line with our previous observations in healthy humans as well as stroke patients [5,6], abundant spontaneous network communication in the alpha-frequency range is associated with better performance. Our previous work suggests this to be a general mechanism beyond the language domain that also applies to motor, cognitive, and visual perception performance [8]. Coherent alpha activity could thus represent integration over different cortical areas [9], which likely represents a domain-global mechanism.

Next, we tested if 10 Hz tACS could induce changes in alpha-band WND. We indeed noticed an increase at the left posterior temporal lobe after 10 Hz tACS ($p<0.05$, uncorrected, Fig. 1C). Significant voxels corresponded to the left temporal parts of Brodmann area 40 of the Montreal Neurological Institute template. This increase did not survive correction for multiple comparisons in a whole-brain analysis, but was significant after small-volume correction in the left temporal Brodmann area 40 ($t_{23}=2.4$, $p=0.028$). Stimulation with 16.6 Hz ($p=0.11$) and sham stimulation ($p=0.45$) did not induce a significant change of alpha-band WND at this area.

No significant changes in oscillation power were observed after any stimulation condition in prefrontal or parieto-temporal brain areas at any frequency band ($p>0.17$). There was no correlation of oscillation power at any band with the inverse reaction time ($p>0.09$).

Collectively, our results show the relevance of remote stimulation effects. Contrary to our hypothesis, the region where FC was associated with behavioral improvements was not located in the prefrontal cortex. Indeed, we did not observe any modulatory tACS effects at the stimulation site but only at temporo-parietal areas. Notably, the modulatory effect was relatively small. The spatially distant effect may have been induced through fronto-parietal projections, which are known to contribute to working memory [10].

Our results thus suggest that global FC of temporo-parietal areas may be a better and potentially behaviorally useful marker for language performance and modulatory stimulation effects than local activity of prefrontal areas. Furthermore, the ability of tACS to enhance alpha-band network communication at the stimulation site is limited, at least if it is applied at prefrontal areas. Future studies should evaluate if we can obtain greater effects on neural communication and phonological processing with the electrodes placed above temporo-parietal areas.

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Conflicts of interest

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.

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