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The importance of model-driven approaches to set stimulation intensity for multi-channel transcranial alternating current stimulation (tACS)

The use of multi-channel transcranial alternating current stimulation (tACS) is topical for its potential to modulate brain network connectivity [1–3]. Concurrently stimulating distinct cortical regions with weak sinusoidal alternating electrical currents using a multi-channel montage (known as multi-channel tACS) can effectively modulate the oscillatory phase synchrony and functional connectivity between targeted brain regions [2]. The idea of manipulating oscillatory phase synchrony between regions to facilitate brain network communication is underpinned by the communication-through-coherence hypothesis [4]. That is, effective communication occurs between neuronal populations when their peak excitability phases are aligned. To achieve oscillatory phase synchrony, multi-channel tACS is used to deliver alternating currents with a 0° relative phase difference (in-phase) to distinct cortical regions (typically two). This in-phase tACS protocol has been found to increase oscillatory phase synchrony between stimulated regions and has been associated with improvements in cognitive performance [2,3].

As with other brain stimulation techniques, one of the challenges inherent to tACS lies in the determination of stimulation parameters for the effective stimulation of targeted cortical regions. Notably, tACS intensities have received somewhat less attention when compared with other parameters such as electrode montage and channel configuration, e.g., Ref. [5]. If tACS is not applied at an optimal intensity with respect to induced electrical fields at the target sites, the stimulation may be ineffective in inducing oscillatory phase synchrony, which makes interpretation of results difficult and critically undermines the value of the study with respect to the synchronisation aspect. The majority of multi-channel tACS studies have used stimulation protocols with the same current intensity across stimulation sites. Studies targeting non-homologous stimulation sites should consider the anatomical features of each target site separately, and set current intensities accordingly because a substantial amount of the current delivered transcutaneously (such as during tACS) is attenuated by subcutaneous soft tissue and the skull [6], and electrode to target distance. Evidence shows that this attenuation differs between cortical areas with different anatomical characteristics, such as skull thickness [7]. Thus, the field strength for each target region needs to be carefully adjusted to produce sufficient current density to stimulate the underlying neural structure.

Reinhart and Nguyen [2] recently demonstrated the efficacy of multi-channel tACS to improve working memory in older adults by targeting the prefrontal and temporal regions with different stimulation intensities. Stimulation intensities were set based on current-flow models estimating comparable electric field strengths for prefrontal regions with 0.6 mA (peak to peak) and temporal regions with 1.0 mA (peak to peak). This work highlights the importance of current intensity selection in multi-channel tACS protocols, as well as advocating for a model-driven approach for stimulation intensity determination. Here we empirically demonstrate this crucial point by presenting the electric field simulations of a tACS protocol aimed to deliver in-phase stimulation to the pre-supplementary motor area (pre-SMA) and the right inferior frontal gyrus (rIFG). Electric field calculations were conducted with SimNIBS (v. 3.1.2) [8] using finite-element methods. The head model was derived from the MNI152 template brain using the “headreco” function in SimNIBS. Electrodes of 2 cm radius were placed in a 2×1 montage [2] surrounding each target region, and modelled as rubber layers (conductivity: 29.400 S/m) that are 2 mm thick, and with conductive gel (conductivity: 1.000 S/m) of 3 mm thickness underneath. We further computed the mean electric field strength for each target region. This was obtained by means of binary masks based on the Brainnetome atlas (>50% probability), with areas A45c, A45r, and A44v for rIFG and bilateral A8m for pre-SMA [9]. Fig. 1A shows the current-flow model with 1 mA peak-to-peak amplitude applied to both rIFG and pre-SMA: it is clear from the figure that the electric field is substantially weaker for pre-SMA than rIFG with these stimulation intensities. This indicates that the tACS protocol potentially exerts differential effects on the cortical activity of the two regions, which may, in turn, impact the extent of oscillatory phase synchrony between the stimulated regions. For example, in case of insufficient stimulation of one area, results may not reflect connectivity changes between the stimulated regions, but rather may predominantly represent the neurophysiological changes induced by the cortical region sufficiently affected by tACS; this would lead to the misinterpretation of the outcomes. Using current-flow models, we found that the adjustments in stimulation intensities reduced the disparity in field strengths between the two sites: as shown in Fig. 1B and C, the application of higher stimulation intensities to pre-SMA (1.6 mA and 2.0 mA) relative to rIFG (1.0 mA) reduced the disparity between the simulated electric field strength at the two sites. It is important to note, however, that higher field strengths are accompanied by poorer field focality to the target sites (see focality values Vol_{50} and Vol_{75} in Fig. 1). Therefore, it is imperative to also consider this strength-focality trade-off when determining stimulation intensity for different target sites. Moreover, higher stimulation

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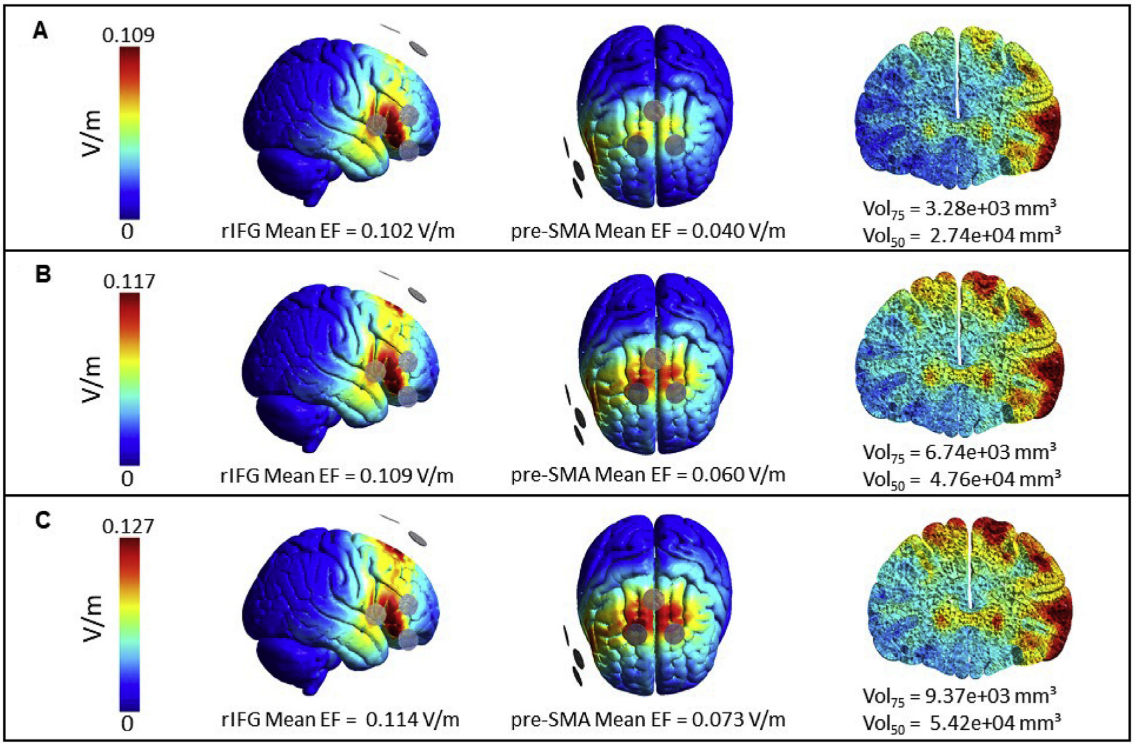

Fig. 1. Three current flow models of a multi-channel tACS protocol delivering in-phase stimulation to the pre-SMA and the rIFG. The stimulation intensities (peak-to-peak amplitudes) for pre-SMA were set to: (a) 1.0 mA; (b) 1.6 mA; (c) 2.0 mA. The current intensity for rIFG remained at 1.0 mA in all three models. Vol_{75} (mesh volume with field strength $\geq$ 75% of the 99.9th percentile) and Vol_{50} (mesh volume with field strength $\geq$ 50% of the 99.9th percentile) provide measures of focality. While the application of higher stimulation intensities to pre-SMA reduces the disparity in mean electric field strengths (mean EF) between rIFG and pre-SMA, field focality is reduced as well. The consideration of this strength-focality trade-off is hence important when determining stimulation intensities for tACS protocols.

intensity has a greater propensity for side effects such as phosphenes, which also has to be taken into account for determination of stimulation intensity.

In sum, we demonstrated the importance of intensity selection in multi-channel tACS and how current-flow models can assist in that selection to ensure a satisfactory balance between electric field strength and focality in the targeted regions. We acknowledge that the calculation of the induced currents is based on several assumptions, including previously established tissue and skull conductivities, that the quantitative reliability of respective models is still limited, and that physical validation studies are rare, which are limitations of current-flow models. However, the benefit of modelling current flow outweighs these limitations as shown in the present example. Accordingly, we suggest that studies targeting non-homologous regions should use current-flow models to determine stimulation intensities that provide comparable electric field strengths for the targeted stimulation sites. Moreover, validation studies of respective models are still warranted to enhance the validity of model-based determined stimulation parameters.

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Declaration of competing interest

Authors declare no conflict of interest.

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