A Novel tDCS Sham Approach Based on Model-Driven Controlled Shunting

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Introduction

Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique able to transiently modulate brain activity, is used in many neurological and psychiatric disorders. However, to ensure adequate understanding of the observed effects, researchers need to rely on valid and approved control placebo conditions, a fundamental requirement in randomized controlled trials. Traditional standard sham protocols consist on an initial ramp up of the current, followed by a short stimulation period (usually for 5-60 seconds) and a final ramp down (Axelrod et al., 2015) (i.e., Fade In of current, brief real Stimulation, Fade-Out; commonly known as "FISSFO" protocol), an approach thought to cause sensory stimulation similar to real tDCS without affecting cortico-spinal excitability (Gandiga et al., 2006). However, profound limitations exist in current placebo (sham) protocols that limit blinding, especially in non-naïve subjects. In the present study, we investigate a novel approach to sham stimulation based on controlled shunting of currents via a model-based quantification of transcutaneous and transcranial effects. Specifically, the novel active/sham tDCS solution (ActiSham) benefits from the use of an optimization algorithm allowing tDCS montages to be tailored in such a way that zero or very low magnitude electric fields are delivered on the brain, while medium to high intensity currents are maintained in at least some scalp electrodes, thus eliciting scalp sensations necessary for blinding.

Methods

Particpants. 14 healthy right-handed naïve subjects (25.4 years ± 2.1; 5 males) were recruited. tDCS sessions lasted 15 minutes, with electrode types, scalp montages and stimulation intensities customized for each tDCS protocol (Figure 1-A).

MEP Acquisition and Analysis. For each session, 20 TMS pulses were delivered at 7 different time points: Pre-10; Pre-5; Pre-0; Post-0; Post-5; Post-10; Post-15 minutes in respect to the tDCS intervention (Figure 1-A). Surface electromyography (EMG) responses were obtained via 9 mm diameter surface Ag–AgCl electrodes, attached to the right first dorsal interosseous (FDI) muscle. The average MEPs amplitude obtained at Pre-tDCS was used as Baseline to look at tDCS-induced modulatory effects. Peak-to-peak amplitudes of post-tDCS measurements were normalized to the average of the baseline MEPs amplitudes to ease comparisons A Repeated Measures Analysis of Variance (ANOVA) model was ran, including factors *Stimulation* (two levels: Bifocal-Sham, ActiSham) and *Time* (five levels: Baseline, Post-0, Post-5, Post-10, Post-15), as well as their interaction. Significant interactions (p<.05) were further explored via post-hoc multiple comparisons, with Bonferroni correction and considering the factor *Time* within each condition.

tDCS Protocols. For canonical Bifocal-tDCS (active or sham), stimulation was delivered through traditional 5x7 cm rectangular sponge electrodes. For Multichannel stimulation conditions (real and ActiSham), current was instead delivered using circular Ø 20 mm PISTIM electrodes (Figure 1-B and Figure 2).

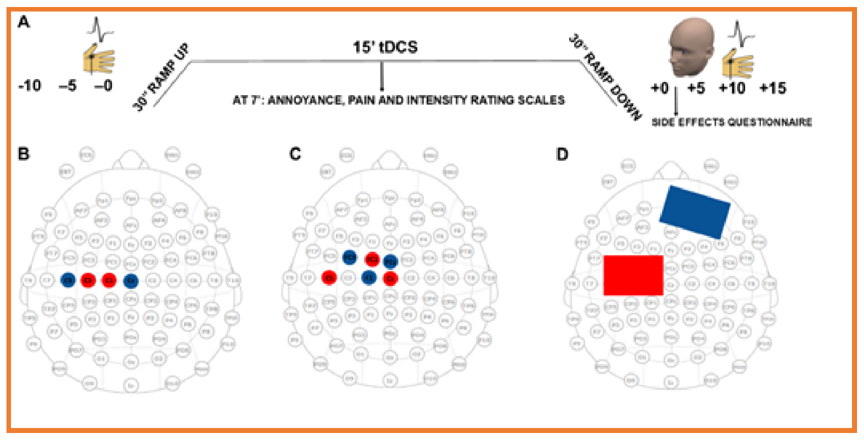

Figure 1. Study design. (**A**) Active stimulation was delivered for 15 minutes, (30 sec of ramp up/down). Corticospinal excitability of FDI muscle was measured via TMS at Pre-10, Pre-5, Pre-0, Post-0, Post-5, Post-10, Post-15). Halfway through the protocol subjects were asked to rate stimulation-related annoyance and pain levels. tDCS montages for Multifocal-tDCS (**B**), ActiSham (**C**), Bifocal-tDCS and Bifocal-Sham (**D**) are shown.

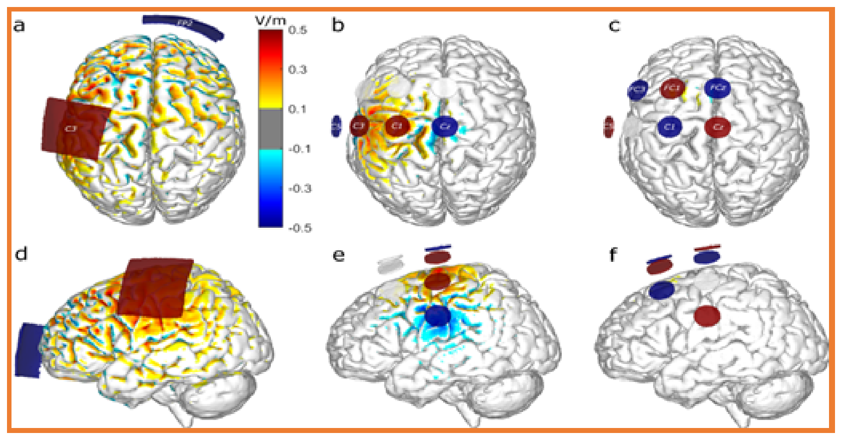

Figure 2. Induced E-field. Normal component of the electric field (En, in V/m) induced in the GM surface by: (**a, d**) Bifocal-tDCS montage with 35 cm2 sponges located over C3 and FP3 (I=±2.0 mA); (**b, e**) optimized 4-channel montage with PISTIM electrodes; (**c, f**) ActiSham 6-channel montage. Anodes are shown in red, cathodes in blue, inactive

Scalp sensations and Blinding. Participants' blinding was assessed at Post-0. A binomial test was used to control for possible response biases, testing participant responses against chance level (p<0.05). Seven minutes into stimulation, subjects were asked to rate how *painful, annoying and intense* electrical stimulation was on a visual analogue scale from 1 to 100. To further quantify specific subjective sensations and investigate the presence of side or adverse effects, a questionnaire (Fertonani et al., 2010) was administered at Post-0 in each session assessing sleepiness, difficulties in concentrating and headache on top of classical sensations (i.e. tingling, burning, itching, etc.), for a total of twelve items on a 1 to 5 Likert-scale. Scalp sensations and adverse effects between conditions were compared conducting paired T tests. Participants were further asked to point with their fingers the scalp location in which they felt stimulation the most, and to rate whether the perceived effect was focal or distributed on the scalp. The reported hotspots were then marked by the experimenter on a graphical representation of the 10/20 EEG system. Data were imported in MATLAB 2018b (MathWorks, MA, USA) in the form of a 180-by-180 pixels matrix, assigning a value of 1 in each pixel surrounding the electrode indicated by the subjects as the site of perceived stimulation, and 0 otherwise. A smoothed thermal map was obtnaied, representing the frequency of reported scalp sensation for each scalp region with an approximately 0.5 cm.

ActiSham optimization. An algorithm was run with the target of a near zero electric field on the left motor cortex and a further condition for blinding: the minimal current in some electrodes was required to be of the same magnitude as in the real tDCS condition. The electrodes for sham condition were selected from a pool of closely spaced positions surrounding the M1 mask. The target E-field over the target region was set to be 0.001 V/m as opposed to 0.25 V/m in the active condition (Figure 3).

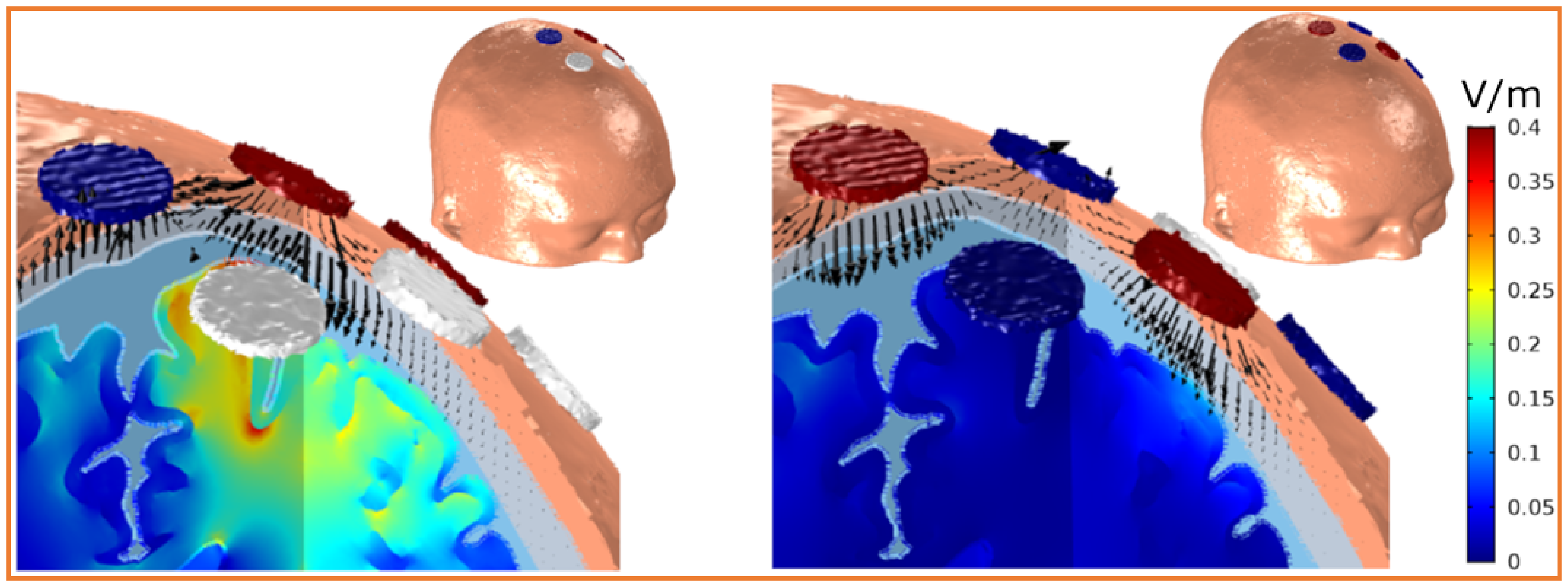

Figure 3. Physics of shunting. E-field magnitude and direction in the tissues beneath the electrodes in the two optimized montages used in this study: active 4-channel montage (left) and ActiSham 6-channel montage (right). ActiSham takes advantage of current shunting through the scalp to place the electrodes and decrease the E-field in the target M1 area. The magnitude of the E-field (in V/m) is, therefore, much higher in the active montage, despite similar injected currents in the two montages (see Table 2).

Results

Scalp sensations and Blinding: Significantly greater annoyance was reported during Bifocal-tDCS (mean score: 29.14, SD: 23.01) compared to Bifocal-Sham (mean score: 8.85, SD: 14.76; t= 2.436, p<.05). A general trend towards higher perceived stimulation intensities and pain perception was reported for Bifocal-tDCS compared to Bifocal-Sham (p= .054). Similarly, a trend for higher pain perception was found for Bifocal-tDCS compared to Bifocal-Sham (p= .063) (Figure 5). Binomial tests revealed a significant difference in participants' rating between real and sham Bifocal-tDCS (p<.004), but not between Multifocal-tDCS and ActiSham (p<0.1) (Figure 5). Diffuse sensations at the level of the whole scalp were more commonly reported during Bifocal-Sham, whereas more focal sensations were reported during Bifocal-tDCS and for both Multifocal conditions, especially in the area below the anode (C3 in the 10/20 reference EEG system).

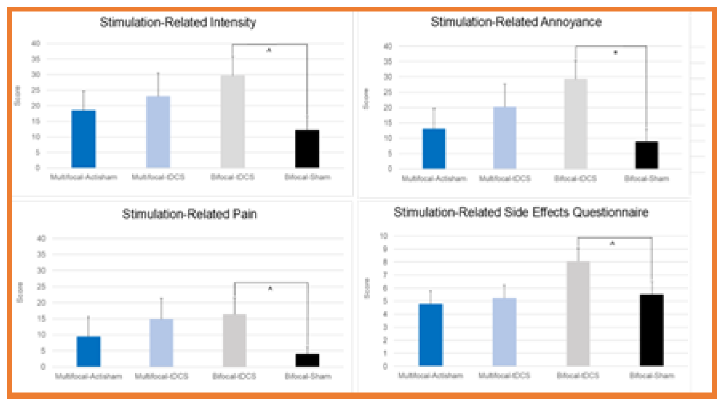

Figure 4. Discomfort and scalp sensations. Somatosensory sensations are shown for each condition separately. The intensity, annoyance and pain levels evoked by tDCS were rated during tDCS on a 1 to 100 scale. Additional scalp sensations (e.g., itching, burning, skin redness) were assessed offline after stimulation cessation, and summarized in the right-down panel. Note: * = p<.05; ^ = trend towards significance, p<.1.

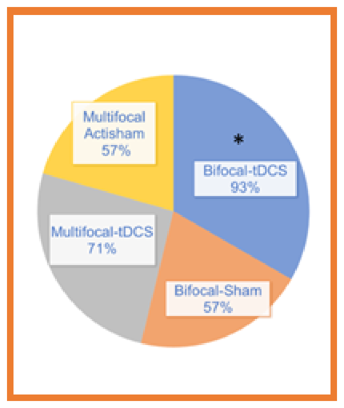

Figure 5. Blinding. Participants' accuracy in detecting real stimulation across the four conditions. A significant difference was observed between real and sham Bifocal-tDCS (p<.05).

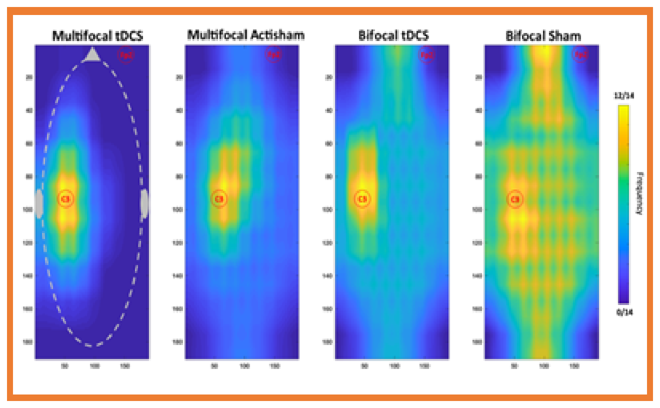

Figure 6. Scalp localization of tDCS-induced scalp sensations. Similar scalp locations were reported for Bifocal-tDCS and real/ActiSham Multifocal-tDCS. Bifocal-Sham displayed a more widespread scalp localization, also involving the position of the cathode (Fp2 electrode location).

MEPs modulation. The ANOVA showed a main effect of STIMULATION, with higher MEPs amplitude for Bifocal-Sham compared to ActiSham ($F_{(1,13)}$= 6.67, p=.023). Post-hoc analyses displayed significant changes in MEPs amplitudes during Bifocal-Sham, with higher MEPs at Post0 compared to Baseline ($t_{(1,13)}$=-3.82, p=.028) (Figure 7). The two conditions also differed between each other at Post-15 ($t_{(1,13)}$=-4.32, p=.014). No significant modulation of MEPs amplitude was observed during ActiSham.

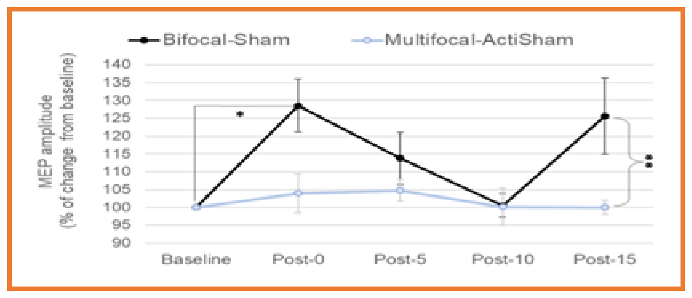

Figure 7. Corticospinal excitability changes in Sham conditions. A significant increase in MEPs was observed after Bifocal-Sham at Post-0 compared to Baseline (*=p=.028). The two conditions also differed between each other at Post-15 (**=p=.014). Bars represent +/- 1 Standard Error of Mean.

Conclusions

Compared to traditional Bifocal montages, ActiSham seems to induce somatosensory effects similar to those elicited by real Multifocal-tDCS, both in terms of intensity and scalp localization, with an overall improvement of participants' blinding. Sham solutions based on model-driven controlled shunting might represent a feasible solution to ameliorate blinding in future clinical trials and research studies.

Relevant Bibliography

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