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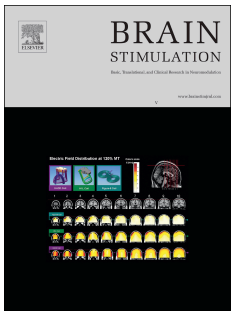

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A Novel tDCS Sham Approach Based on Model-Driven Controlled Shunting

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Abstract

Background: Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique able to transiently modulate brain activity, is surging as one of the most promising therapeutic solutions in many neurological and psychiatric disorders. However, profound limitations exist in current placebo (sham) protocols that limit single- and double- blinding, especially in non-naïve subjects.

Objective/hypothesis: To ensure better blinding and strengthen reliability of tDCS studies and trials, we tested a new optimization algorithm aimed at creating an "active" sham tDCS condition (*ActiSham* hereafter) capable of inducing the same scalp sensations perceived during real stimulation, while preventing currents from reaching the cortex and cause changes in brain excitability.

Methods: A novel model-based multielectrode technique —optimizing the location and currents of a set of small electrodes placed on the scalp— was used to control the relative amount of current delivered transcranially in real and placebo multichannel tDCS conditions. The presence, intensity and localization of scalp sensations during tDCS was evaluated by means of a specifically designed questionnaire administered to the participants. We compared blinding ratings by directly addressing subjects' ability to discriminate across conditions for both traditional (Bifocal-tDCS and -Sham, using sponge electrodes) and our novel multifocal approach (both real Multifocal-tDCS and ActiSham). Changes in corticospinal excitability were monitored based on Motor Evoked Potentials (MEPs) recorded via concurrent Transcranial Magnetic Stimulation (TMS) and electromyography (EMG).

Results: Subjects perceived Multifocal-tDCS and ActiSham similarly in terms of both scalp sensations and their localization on the scalp, whereas traditional Bifocal stimulation was rated as more painful and annoying compared to its Sham counterpart. Additionally, differences in scalp localization were reported for active/sham Bifocal-tDCS. As for MEPs amplitude, a main effect of stimulation was found when comparing Bifocal-Sham and ActiSham ($F_{(1,13)}$= 6.67, p=.023), with higher MEPs amplitudes after the application of Bifocal-Sham.

Conclusions: Compared to traditional Bifocal-tDCS, ActiSham offers better participants' blinding by inducing very similar scalp sensations to those of real Multifocal tDCS both in terms of intensity and localization, while not affecting corticospinal excitability.

Keywords

Transcranial Direct Current Stimulation, tDCS, Placebo, Sham, Blinding, Neuromodulation

Introduction

Non-invasive Brain Stimulation (NIBS) techniques are used to modulate brain activity in a safe and well-tolerated way [1]. In particular, Transcranial direct current stimulation (tDCS), uses low-intensity electrical currents to modulate cortical excitability in a polarity-specific manner [1]. Classical tDCS montages consist of two rectangular sponge electrodes with a contact area of ~25-35 cm^2, where electrical current between 0.5mA and 4mA flows from a positively charged electrode (anode) to a negative one (cathode)[2] passing through various tissue compartments including skin, muscle, bone, cerebrospinal fluid and brain. Due to its safety and relatively low-cost, tDCS experiments have been widely carried out to investigate human neurophysiology and to test its application as a new potential therapeutic solution for neurological and psychiatric conditions. To ensure adequate understanding of the observed effects, however, 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 [3–5], (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 [6]. However, both these assumptions (i.e., adequate blinding and absence of effects on the brain) are still under examination. FISSFO sham has been considered effective in providing a proper blinding when compared with real tDCS at 1mA for 20 minutes [6], becoming the standard for sham tDCS [7]. The rationale stems from participants’ reports in which the cutaneous perceptions that generally cue subjects on tDCS being effectively delivered (i.e., tingling or itching sensation), have been mostly reported during the first 30-60 seconds of stimulation to then gradually decrease, possibly due to habituation [4]. However, a recent investigation has revealed that even naïve subjects (N=192) are capable of distinguishing classic sham stimulation (FISSFO) from active tDCS when delivered at 1 mA for 20 minutes over the left dorsolateral prefrontal cortex (DLPFC) [8]. Prior experiments had already suggested blinding inefficacy when real tDCS is applied at 1.5-2 mA, even for only 10 minutes [9,10]. Accordingly, non-naïve subjects seem more

capable of distinguishing real from sham tDCS [11] and extreme individual variability has been reported with regard to sensibility to stimulation intensity and duration, with subjects being able to perceive tDCS even at very low intensity (i.e., 400 μA) [11].

On the other hand, additional sham protocols have been developed with modified durations of ramp up/down, or even delivering constant low intensity currents (0.016 or 0.034 mA) [7,12,13]. However, these approaches have not been properly tested on large sample of patients/subjects, with no data on the effects of such alternative sham protocols on the brain, while inconsistent results on many neurophysiological parameters have been documented when adopting such modified approaches [13].

Beyond the single or double blinding efficacy of FISSFO and related approaches [14], an element of interest is the question of whether tDCS effects are due to cortical interaction of the generated electric fields or from peripheral nervous system (PNS) stimulation. Since the ramp-up/ramp-down method for blinding decreases both cortical and peripheral stimulation, they cannot help disentangling cortical and peripheral effects. In addition, cortical effects of the brief period of real stimulation during sham protocols may not completely be excluded [15].

An additional challenge is the fact that the induced tDCS electric field is conditioned by the heterogeneity of cortical and non-cortical tissues, as well as by the complexity of cortical geometry [16]. In recent years, this has been addressed by the use of multichannel tDCS systems in combination with realistic finite element modeling of current propagation in the head derived from subject neuroimaging data (e.g. MRI, fMRI) [17,18]. The rationale for multifocal stimulation resides on both the need for more targeted stimulation of the cortex, as well as the notion that brain regions operate in networks and communicate with each other's through modulatory interactions [19–21]. Realistic physical models provide a crucial element for better experimental understanding and control of the electric fields generated by tDCS.

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 sham tDCS solution 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. Notably, this allows to maintain the stimulation ON for the entire duration of sham tDCS, therefore inducing scalp sensations similar to real tDCS, while avoiding known limitations of the FISSFO protocol. We hypothesize that such montage (Active Sham, *ActiSham* hereafter) (i) will generate scalp sensations similar to a Multifocal (real) tDCS montage based on the same electrodes' location and identical stimulation intensity/duration; and that (ii) ActiSham will not induce changes in cortico-spinal excitability (CSE), as assessed through Motor Evoked Potentials (MEPs) induced by Transcranial Magnetic Stimulation (TMS) as an index of corticospinal excitability. If successful, this and similar other approaches for improved sham stimulation could contribute to more efficient design of future tDCS research studies and clinical trials.

Methods

Study design

Fourteen subjects participated in 4 randomized tDCS stimulation visits, spaced 7±3 days to ensure no carryover effects. The tDCS conditions were: real Bifocal-tDCS, Bifocal-Sham, real Multifocal-tDCS and ActiSham. Each session lasted approximately 90 minutes during which participants seated in a comfortable chair with their eyes open. To measure changes in corticospinal excitability, single pulse TMS was applied over the left primary motor cortex (M1) at the beginning and the end of each stimulation session. Somatosensory sensations elicited by tDCS were addressed by means of ad-hoc questionnaires. See dedicated sections below for further details about tools and procedures.

Participants

Fourteen healthy right-handed naïve subjects (25.4 years ± 2.1; 5 males) were recruited at the University Campus of Siena, School of Medicine (Siena, Italy). Possible contraindications to either TMS or tDCS were assessed by means of a screening questionnaire [22]. Exclusion criteria included: history of seizures, head injury, pacemakers or other implanted medical devices, metallic objects in the head, hearing impairments, medications altering cortical excitability or other significant medical concerns. All participants gave written informed consent prior to participating to the study. The research proposal and associated methodologies were approved by the local ethical committee in accordance with the principles of the Declaration of Helsinki.

tDCS

tDCS sessions lasted 15 minutes, with electrode types, scalp montages and stimulation intensities customized for each tDCS protocol (Figure 1). Transcranial stimulation was delivered using a “Starstim 8” brain stimulator controlled via Bluetooth using a laptop computer (Neuroelectrics, Barcelona, Spain). For canonical Bifocal-tDCS (active or sham), stimulation was delivered through traditional 5x7 cm rectangular sponge electrodes, with a contact area of 35 cm^2

(SPONSTIM, Neuroelectrics, Barcelona, Spain). Before current delivery, electrodes were soaked with 15 ml of sterile sodium chloride solution (0.9%). For Multichannel stimulation conditions (real and ActiSham), current was instead delivered using circular Ø 20 mm PISTIM electrodes (Neuroelectrics, Barcelona, Spain) with an Ag/AgCl core and a gel/skin contact area of 3.14 cm^2. Electrodes were filled with a conductive gel before the tDCS intervention. To further improve current conductivity, the scalp was gently rubbed with an alcohol solution at the beginning of each session. Electrodes were inserted in a neoprene cap with available positions following the 10/20 EEG system.

In both Bifocal and Multifocal conditions, stimulation was aimed at modulating corticospinal excitability of the left motor cortex, with electrode placement guided by (i) a genetic algorithm in the case of Multifocal tDCS and (ii) the most commonly used tDCS montage for left M1 stimulation in the case of Bifocal tDCS (i.e. anodal stimulation over left motor cortex, cathodal stimulation over contralateral supraorbital region).

Traditional Bifocal-tDCS (active and sham)

Bifocal-tDCS and Bifocal-Sham were delivered at an intensity of 2000 µA on C3 (anode) and -2000 µA on Fp2 (cathode). Sham stimulation was delivered according to the FISSFO protocol.

Multichannel tDCS

Electrodes' position for real multichannel tDCS were tailored to provide the optimal distribution of current sources to match the desired electric field pattern on the left motor cortex [17]. Optimization was based on a standard template head model, Colin27. Based on the template's T1 MRIs (available at http://www.bic.mni.mcgill.ca/ServicesAtlases/Colin27), a head model was created as detailed in [16]. A target map of M1 was then created, comprising Brodmann areas 1-4 (on the left hemisphere) slightly edited manually to focus more on the upper limb representation. An optimization algorithm was then used to find the optimal multichannel montage to target M1 using PISTIM electrodes. In short, this algorithm uses a fast calculation of Multifocal-

tDCS electric fields (including components normal to the cortical surface) using an MRI derived six-layer finite element realistic head model [16]. Under the assumption that the effects of current stimulation are of first order due to the interaction of electric fields with populations of pyramidal cortical neurons, the optimization problem for tDCS is defined in terms of the component of the electric field normal (orthogonal) to the cortical surface. Solutions are found using constrained least squares comparing weighted target and normal electric field cortical maps to optimize current intensities.

The objective function of the optimization is the ERNI (Error with Respect to No intervention, in units of mV^2/m^2), as defined in [17]:

$$ERNI(\boldsymbol{x}) = \sum_{i=1}^{N} \frac{\left(w(\boldsymbol{r}_i) * E_n(\boldsymbol{x}, \boldsymbol{r}_i) - w(\boldsymbol{r}_i) * E_n^{Target}(\boldsymbol{r}_i)\right)^2 - \left(w(\boldsymbol{r}_i) * E_n^{Target}(\boldsymbol{r}_i)\right)^2}{\frac{1}{N}\sum_i w(\boldsymbol{r}_i)^2} \quad (1)$$

where each node i of the surface mesh of the cortical surface has coordinates r_i, and N is the total number of mesh nodes. Weights ($w(r_i)$) are defined for each of the target regions and they vary between one (minimum weight) and ten (maximum weight). The vector x represents the currents in each electrode.

To constrain electrodes number in the final montage and determine their location, a genetic algorithm that searches in montage configuration space is employed. Specifically, optimization is carried out using a genetic algorithm with solution populations consisting of individuals that encode for a particular montage and the optimal currents associated with it. Details, including the rules for genetic cross-over and mutation are described in [17]. Optimization constraints were set on the maximum current per electrode (2.0 mA) and total injected current (4.0 mA). Having tried montages from two to eight electrodes, we opted for the four-channel montage as it provided a very good fit (see Table 1) to the normal electric field (0.25 V/m) target map while keeping the electrodes close together, which is advantageous for the sham optimizations (closer electrodes increase current shunting), as described below.

All optimizations were performed in Matlab (R2018a) using custom scripts. Least-squares fits were performed with *fmincon* (constrained minimization, using the active-set algorithm, as described in https://www.mathworks.com/help/optim/ug/constrained-nonlinear-optimization-

algorithms.html). The genetic algorithm optimization was implemented using the *ga* function in Matlab (constrained GA optimization) with custom functions for mutation and cross-over.

To evaluate montage performance, we calculated the ERNI of the montage, the WCC (weighted cross-correlation between the target E_n field and the field induced by the montage) and the surface average of E_n in cortical regions of interest.

A comparison between this multi-channel solution and the traditional montage with two large "sponge" electrodes (over C3 and FP2, I=±2.0 mA) is shown in Figure 2. The multi-channel solution is clearly more focal than the conventional one, minimizing the E-field in non-motor areas over the left hemisphere and orbitofrontal areas in the right hemisphere (see Table 2 for a summary of the currents used).

Multichannel tDCS – ActiSham

For ActiSham, the optimization 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). To prevent the optimizer from returning the trivial solution (all currents set to 0 mA), we constrained one of the electrodes (henceforth referred to as "itchy" electrode) to have a current close to the maximum current in the active montage (1.7 mA). We then cycled through all possible positions for the "itchy" electrode, returning the solution that induced a lower average E_n-field in the target region. The minimization algorithm for the ActiSham montage can be described as follows:

1. Add a pool of neighboring electrodes to those in the active montage to create an expanded, dense montage over the target area. In the case at hand, eight electrodes (T7, C2, FT7, FC5, FC3, FC1, FCz, FC2) were added to the four (C5, C3, C1 and Cz) composing the active montage.
2. For each electrode (*E*) in this selection:

a. Constrain current of electrode *E* to an intensity able to guarantee itching sensation (e.g. 1.7 mA).
b. Optimize the currents of the (unfixed) extended montage with a null electric field target (here 0.001 V/m) with desired constraints (here a maximum of eight electrodes)
c. Calculate average E_n over the target region.

3. Return solution that has lower average E_n-field over the target region.

Mathematically the first optimization (step 2b) can be described as:

$$\boldsymbol{x}_s^* = \underset{\boldsymbol{x}=(x_{i,i\neq s}, x_s = I_{itchy})}{\arg\min} ERNI(\boldsymbol{x}, E_n^{Target} = 0.001\, V/m) \quad (2)$$

Where $\boldsymbol{x}$ is a vector with the currents in each electrode, s is the position corresponding to the fixed current electrode and I_{itchy} is the current value imposed in this electrode (1.7 mA in this case).

The second optimization (step 3) returns the best position for the itching-inducing electrode, s^*:

$$s^* = \underset{s\in S}{\arg\min} < E_n(\boldsymbol{x}_s^*) >_T \quad (3)$$

Where S is the set of all the positions available for the itching electrode and the operator $\langle\cdot\rangle_T$ denotes the surface integration over a target region (Motor cortex – M1 – in this case).

The maximum total injected current in this optimization was limited to the same value as used in the active montage. The montage induces an average E-field in the M1 and pre-motor areas much lower than the active condition (see also Table 1). The resulting montage employs 6 closely spaced electrodes located over the M1 area, with anodes and cathodes following a crisscross/interleaved pattern (Figure 3). This montage generates an average E_n-field in the target region and premotor areas much lower than the one induced in the active montage (0.001 V/m in ActiSham vs 0.156 V/m in the active montage, see Table 1 for a summary of electric field statistics).

Transcranial Magnetic Stimulation

TMS was delivered by means of a STM9000 magnetic stimulator (Ates-EBNeuro) connected to a figure-of-eight coil that was held tangentially over the left M1. The coil was

positioned at an angle of 45°to the scalp midline, with the induced current flowing in a posterior-to-anterior direction. Resting Motor Threshold (RMT) was defined as the minimum intensity necessary to elicit an evoked response of ~ 50 μV in the 50% of trials. An infrared camera (Polaris Vicra, NDI, Waterloo, Canada) with a neuronavigation software (BrainNET, EBneuro Ltd, Florence, Italy) was used to monitor the position of both TMS coil and participant's head in real time [23].

Electromyography Recordings

Surface electromyography (EMG) responses were obtained via 9 mm diameter surface Ag–AgCl electrodes, attached to the right first dorsal interosseous (FDI) muscle with the negative electrode positioned over the muscle belly, the positive electrode over the metacarpophalangeal joint of the index finger and the ground electrode placed on the subjects' wrist. The EMG activity was amplified, analogue band-pass filtered (3Hz to 1 kHz), and digitized (A/D rate 5 kHz) by a micro 1401 unit and Signal 2 software (Cambridge Electronic Devices, Cambridge, UK). For each session, 20 TMS pulses were delivered at 7 different time points, identified as Pre-10; Pre-5; Pre-0; Post-0; Post-5; Post-10; Post-15 minutes in respect to the tDCS intervention, for a total of 140 stimuli (Figure 1, panel A). The intensity of stimulation was set at 110% of RMT.

MEP Data Analysis

Raw MEPs for each subject, condition and time point were considered. MEPs amplitude (peak-to-peak) exceeding two standard deviations of average MEPs were identified as outliers at single subject level and removed prior to data analysis. The average MEPs amplitude obtained at Pre-10, Pre-5, Pre-0 was used as Baseline to look at tDCS-induced modulatory effects. Peak-to-peak amplitudes of post-tDCS measurements (Post-0, Post-5, Post-10 and Post-15) were normalized to the average of the baseline MEPs amplitudes to ease comparisons. Analyses were performed with the Statistical Package for Social Science (SPSS) version 16.0 (Inc. Released 2007, Chicago, SPSS Inc.).

Given the focus on assessing differences between two Sham tDCS approaches, and the number of conditions/time points, the analysis primarily focused on investigating changes in MEPs

after Bifocal-Sham and ActiSham. A Repeated Measures Analysis of Variance ($ANOVA_{RM}$) 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 STIMULATION*TIME. An alpha level of 0.05 was used. Significant interactions were further explored via post-hoc comparisons, with adjustment for multiple comparisons with Bonferroni correction and considering the factor “TIME” within each condition. The same analysis was carried out on MEP data collected before/after real Bifocal and Multifocal tDCS, to ensure the effectiveness of real tDCS protocols on corticospinal excitability.

Scalp Sensations, Safety and Adverse Effects

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 previously published questionnaire was administered at Post-0 in each session [15]. This questionnaire was modified by adding a few items 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 group average including data reported by each participant was then computed, obtaining a thermal map representing the frequency of reported scalp sensation for each scalp region with an approximately 0.5 cm resolution. The resulting map was smoothed to ease interpretation of spatial patterns. Given the

novelty of the ad-hoc approach for scalp localization, data were not analysed quantitatively but rather interpreted qualitatively.

Blinding

An attempt was made to maximize double blinding during stimulation, with two experimenters carrying out each tDCS session, one responsible for setting up the stimulation apparatus (e.g., cap, electrodes, device), one operating the stimulation software and thus aware of the specific tDCS protocol (real or sham). In this sense, investigators carrying out data analysis were blinded to the stimulation conditions and were provided with raw MEPs data for each group/condition. However, given the different electrodes used for Bifocal (sponges) and Multifocal (PIstim electrodes) stimulation, operators blinding was not possible across stimulation types. For this reason, investigators' blinding rate was not considered for the present investigation. Participants' blinding was assessed at Post-0 by asking participants: "*In your opinion, was the stimulation you just received real or simulated?*". A binomial test was used to control for possible response biases, testing participant responses against chance level ($p<0.05$).

Results

Scalp Sensations, Safety and Adverse Effects

In general, all stimulation conditions were well tolerated. 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). No other significant effects were found, but a general trend towards higher perceived stimulation intensities was reported for Bifocal-tDCS (mean score: 29.6, SD: 23.3) compared to Bifocal-Sham (mean score: 12.1, SD: 16.1; t= 2.116, p= .054). Similarly, a trend for higher pain perception was found for Bifocal-tDCS (mean score: 16.4, SD: 19.4) compared to Bifocal-Sham (mean score: 4.0, SD: 7.9; t= 2.032, p= .063).

Minor adverse effects usually associated with tES (i.e., itching, burning, skin redness) were observed during stimulation. Specifically, 85% of participants reported scalp hitching, 64% reported scalp pain, 28% reported neck pain, 92% reported scalp stinging, 85% reported scalp heating, 92% reported skin hitching, 7% reported metallic taste (only 1 subject after Bifocal-tDCS), 28% reported fatigue, 78% reported sleepiness, 21% reported concentration difficulties and 21% reported headache. Scalp redness was observed in 85% of the participants. For information on sensations in each specific condition see Table S1. No serious adverse effects were reported during/after stimulation [24]. Subsequent analyses did not reveal significant between-groups differences, even though a similar trend for greater effects during Bifocal-tDCS (mean score: 8.1, SD: 4.7) compared to Bifocal-Sham was observed (mean score: 5.5, SD: 3.5; t= 1.856, p=.086). In contrast, no significant effects or trends were found across Multifocal conditions. Multifocal-ActiSham and Multifocal-tDCS did not differ on Stimulation-Related Intensity (means: 18.42 and 23.00 and SD: 23.41 and 28.04, respectively; t= -.444, p= .66), Annoyance (means: 13.07 and 20.21 and SD: 24.71 and 27.47, respectively; t= -648, p= .52), and Pain (means: 9.42 and 14.85 and SD: 22.81 and 24.12, respectively ; t= -552, p= .59) levels (see Figure 4).

Scalp localization

As seen in 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). Multifocal-tDCS and ActiSham displayed a very similar scalp location, with ActiSham-related sensations being located slightly more anterior respect to real Multifocal-tDCS. Overall, greater similarity between multifocal conditions was found, together with a widespread localization for Bifocal Sham stimulation.

Blinding

Binomial tests were performed to assess blinding for each stimulation condition. Following data analysis, 93% and 71% of participants correctly detected the stimulation as "real" in the Bifocal-tDCS and Multifocal-tDCS conditions, respectively. Responses at chance level were instead collected following the administration of both sham protocols, such as that the 57% of subjects perceived the stimulation as real during both Bifocal-Sham and ActiSham. A significant difference in participants' rating was found between real and sham Bifocal-tDCS ($p<.004$), but not between Multifocal-tDCS and ActiSham ($p<0.1$) (Figure 6).

Modulation of MEPs

The $ANOVA_{RM}$ model 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.

As for corticospinal excitability modulation assessed during real tDCS, the $ANOVA_{RM}$ model showed a main effect of STIMULATION ($F_{(1,13)}= 7.35$, $p=.004$) and TIME ($F_{(1,\ 23)}= 5.74$, $p=.009$). Post-hoc analyses showed a significant change in MEPs amplitudes during Bifocal-tDCS right after

stimulation (i.e. Post0) ($t_{(1,13)}$=4.37, p=.003), as well as 10' after stimulation ($t_{(1,13)}$=3.92, p=.006), whereas Multifocal tDCS elicited a significant increase in MEPs size 10' after stimulation ($t_{(1,13)}$=-3.32, p=.013) (Figure S1).

Discussion

In the present study, we investigated a novel sham tDCS protocol aimed at improving known caveats of Sham tDCS stimulation [25–28]. We tested a novel tDCS solution based on a multielectrode montage and optimization algorithm which allow to control transcranial and transcutaneous shunting of currents, ensuring induction of scalp sensations similar to those experienced during real tDCS, however without injecting sufficient energy/current into the brain to modulate cortical excitability. Importantly, this approach allows to keep the stimulation ON for the entire session even during Sham stimulation, avoiding the limitation of classical ramp-up/down sham protocols and ensuring constant scalp stimulation as in real tDCS. Results suggest the feasibility of such approach, with preliminary data about potential improvement of participants' blinding obtained via Multifocal-tDCS and ActiSham, compared to canonical Bifocal-tDCS performed with rectangular sponge electrodes and following the FISSFO sham protocol.

Overall, the safety and feasibility of tDCS was confirmed [29] for both approaches, with only mild and transient side effects being reported by the participants. The initial hypothesis regarding the possibility to induce low intensity cortical electric fields was hereby confirmed by the absence of significant changes in MEPs amplitude following ActiSham stimulation, compared to the significant increase in MEPs seen after Bifocal-Sham tDCS. Preventing changes in cortical excitability is a pre-requisite for an effective sham condition, that was not fulfilled by Bifocal-Sham tDCS in the current study. Considering that great emphasis was placed in ensuring reliable coil placement over the FDI hotspot across conditions by means of stereotaxic neuronavigation, it is unlikely that the null effect of ActiSham on corticospinal excitability reflects coil displacement. One possibility is that even brief periods of stimulation, such as those matching the ramp up/down of the FISSFO protocol, might have still exerted a central –or peripheral— effect beyond transitory scalp sensations [15]. Indeed, trends towards a significant increase in MEPs amplitude have been reported after the administration of Bifocal Sham tDCS in previous studies [30,31], with participants reporting high individual variability and both increases or decreases in cortical excitability. Future investigations accounting for peripheral (PNS) vs central nervous system (CNS) -mediated tDCS

effects are needed to fully disentangle the mechanism behind sham Bifocal-tDCS modulation. Indeed, even though stimulation intensity is much lower for tDCS than peripheral stimulation (i.e., 2 mA in tCS *vs* 100 mA), effects on the peripheral nervous system (PNS) cannot be excluded. This is becoming more and more relevant considering recent evidence of similar-to-identical antidepressant effects of real and sham tDCS in patients with depression [12]. To control for PNS effects, possible solutions include (i) using stimulation protocols designed to have different CNS effects but similar impact on PNS, and (ii) testing tCS on subjects whose afferent PNS receptors are inhibited (with the application of a local anesthetic agent). The latter solution has been tested in two recent tDCS studies, with the aim, however, to reduce pain and discomfort on the skin and not to disentangle peripheral and cortical effects [32,33].

ActiSham seems to induce scalp sensations with a similar intensity to those elicited by Multifocal-tDCS. Most importantly, Bifocal-tDCS seems to induce stronger sensations compared to Multifocal-tDCS, possibly explaining the reduced efficacy of blinding for this condition, whereby participants could discriminate between real and sham protocols with an accuracy level approaching 100%. Even more interestingly, the localization of scalp sensations was different for ActiSham and Bifocal-Sham tDCS, with the latter inducing widespread, rather unspecific tingling/itching-like sensations all over the scalp compared to ActiSham and even real Multifocal or real Bifocal tDCS. This difference, even though only observed at a qualitative level, may represent a crucial aspect to improve blinding of future tDCS trials, possibly helping to mask the nature of stimulation for both participants and operators.

A few limitations of the present study must be mentioned. First of all, the different electrode arrays adopted for Multifocal-tDCS/ActiSham could have cued subjects (and operators) in correctly identifying real and sham conditions during Multifocal stimulation. Future investigations should adopt an ActiSham solution optimized to be delivered via the same electrode array used for real Multifocal-tDCS, still guaranteeing the same intensity of scalp sensation and no cortical stimulation. Future studies should also investigate the feasibility of applying ActiSham for other tDCS modalities, such as transcranial Random Noise Stimulation (tRNS) and transcranial Alternating Current Stimulation (tACS) [34,24], with the latter requiring additional attention due to stronger

frequency-specific tapping-like scalp sensations, as well as induction of strong visual sensations (i.e., phosphenes). For instance, in the case of tACS, we are working on extending our present segmentation and modeling pipeline to take into account anatomical detail in the eye region [35]. This will allow the montage optimization pipeline to correctly account for the E-field at the retina and output montages that achieve small retinal electric fields. Once the Active montage is defined, the average electric field on the retina, which will be small but non-zero, will be computed. The corresponding ActiSham and real Multifocal tACS montages will be optimized with the requirement of generating the same average retinal electric field as well as tactile sensations. Finally, the present study should be replicated on a larger sample, also extending MEP recording for longer time after stimulation.

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.

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Conflicts of Interest

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

Giulio Ruffini is a shareholder and works for Neuroelectrics, a company developing medical devices for non-invasive brain stimulation. Ricardo Salvador works for Neuroelectrics.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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FIGURE LEGENDS

Figure 1. Study design. (**A**) Active stimulation was delivered for 15 minutes, (30 seconds of ramp up and down). Corticospinal excitability was measured via TMS three times prior to stimulation (Pre-10, Pre-5 and Pre-0) and compared with post measurements collected up to 15 minutes after stimulation (Post-0, Post-5, Post-10, Post-15). Halfway through the protocol (i.e., at minute 7), 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 (E_n, 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 electrodes in white.

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).

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. Bars represent +/- 1 Standard Error of Mean. Note: * = p<.05; ^ = trend towards significance, p<.1.

Figure 5. 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).

Figure 6. Blinding. Participants' accuracy in detecting real stimulation across the four conditions. A significant difference was observed between real and sham Bifocal-tDCS, while in general both sham approaches were recognized as real stimulation at chance level. Note: * = p<.05.

Figure 7. Corticospinal excitability changes in Sham conditions. Changes in FDI MEPs are shown for Baseline and Post-tDCS measurements (Post-0, Post-5, Post-10 and Post-15). No significant changes were

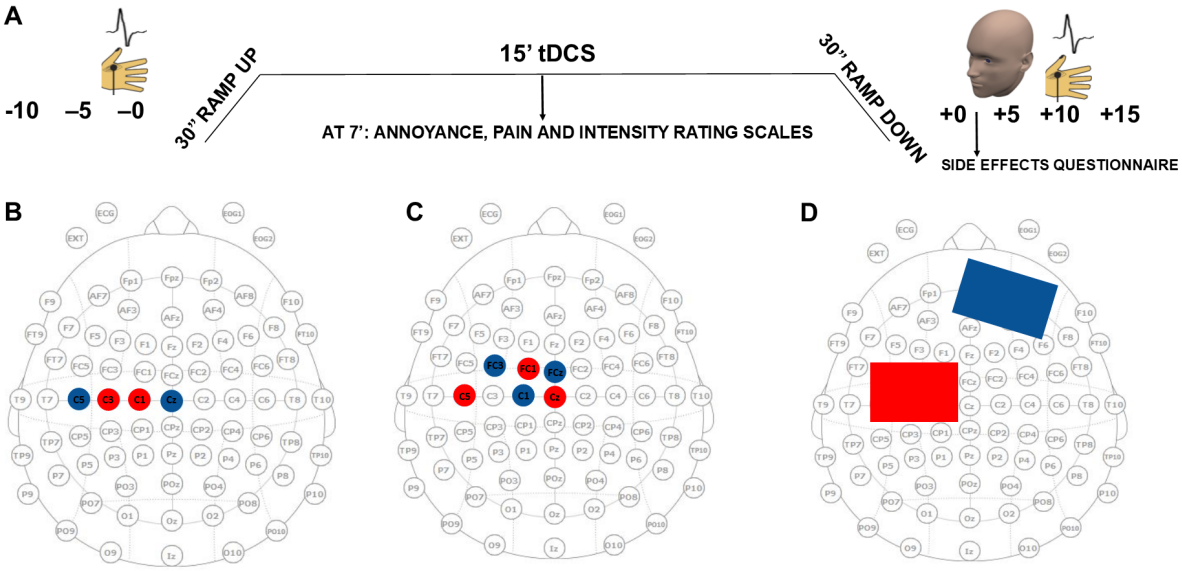
observed after Multifocal-ActiSham, whereas a significant increase in MEPs was observed after Bifocal-Sham at Post-0 compared to Baseline (*=p=.028). The two conditions also differed between each other at Post-15 (**=p=.014). Bars represent +/- 1 Standard Error of Mean.

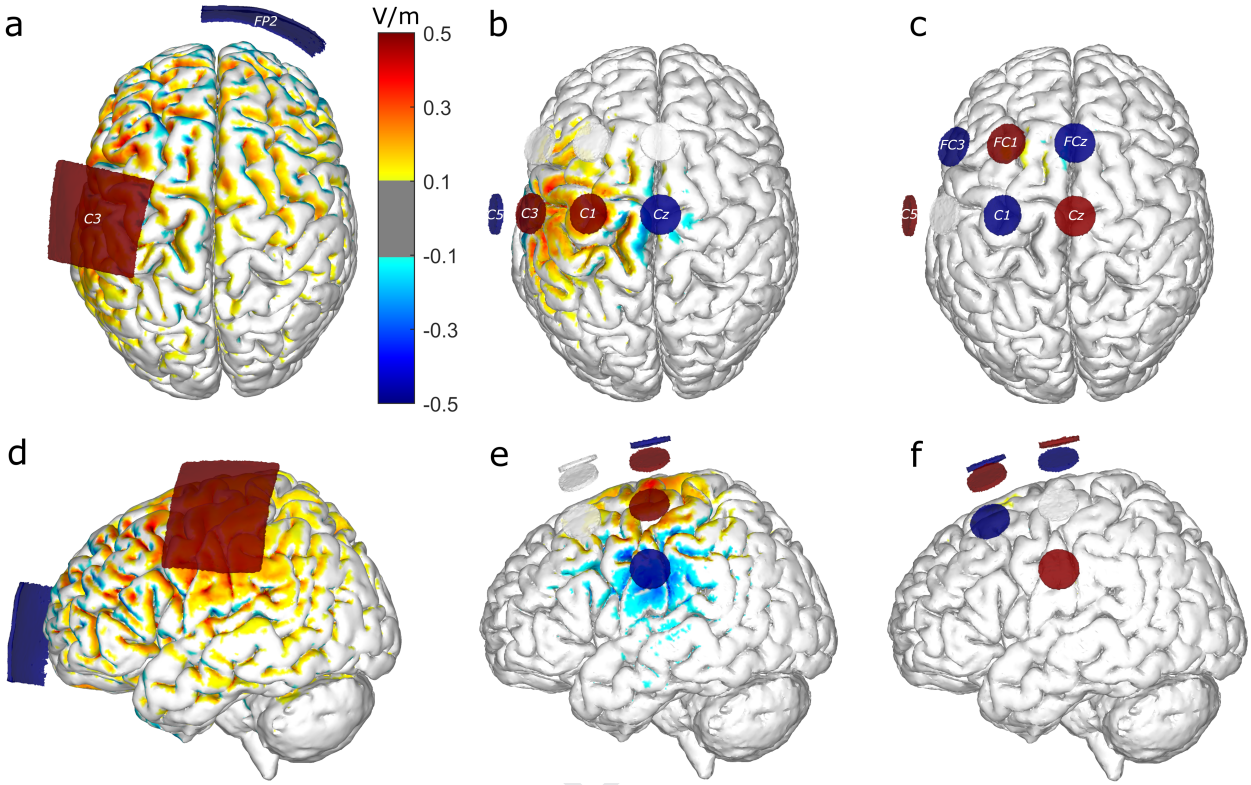
Table 1. E-field on target areas. Average values of normal electric field (E_n) on the target area (M1) as well as in pre-motor areas (pre-motor ventral or PMv, dorsal, PMd and supplementary motor area, SMA) as well as optimization statistics ERNI (error relative to no intervention) and WCC (weighted correlation coefficient). The ratio of average M1 electric fields in the tDCS and ActiSham condition is more than two orders of magnitude.

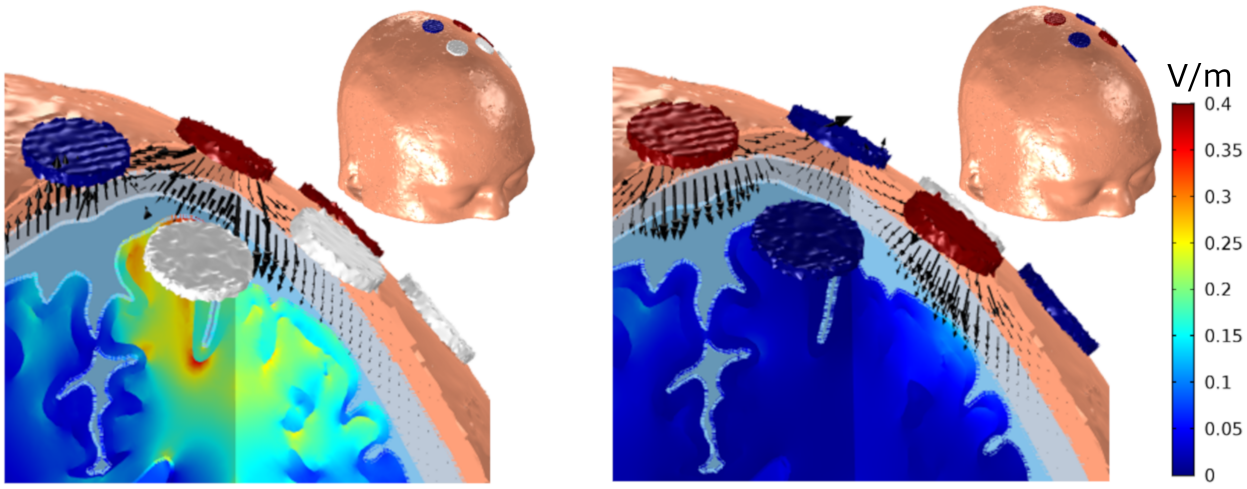
Table 2. Current per electrode for each montage. The last columns provide the maximum current per electrode and total injected current (all currents in µA).

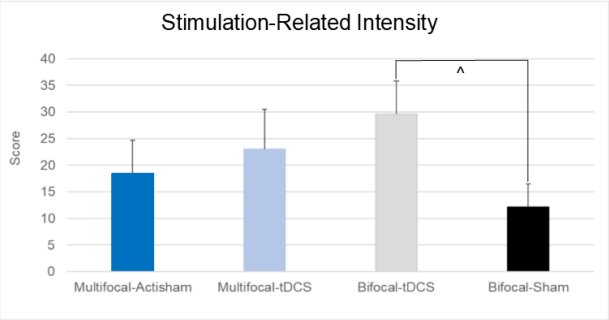
Condition	***Statistics***		***Average E_n (V/m)***			
	WCC	*ERNI (mV^2/m^2)*	*M1*	*SMA*	*PMv*	*PMd*
Multifocal-tDCS	0.79	1.63×10^4	0.156	0.026	-0.043	0.112
Multifocal-ActiSham	0.04	0.02×10^4	0.001	0.000	-0.003	0.001

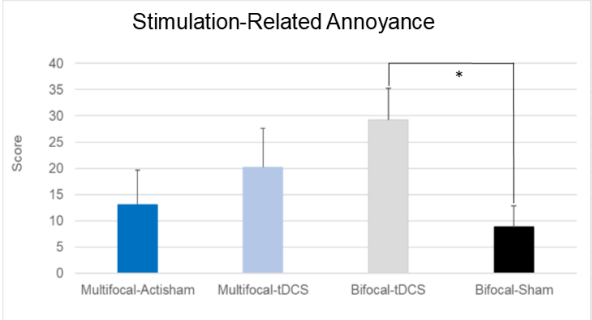
	Current (μA)									
Montages	**FC1**	**Cz**	**C5**	**FCz**	**FC3**	**C1**	**C3**	**FP2**	**Max Injected Current**	**Total Injected Current**
Multifocal-tDCS	0	-1432	-1750	0	0	1777	1405		1777	3182
Multifocal-ActiSham	1700	615	300	-1429	-781	-405			1700	2615
Bifocal-tDCS							2000	-2000	2000	2000
Bifocal-Sham							2000	-2000	2000	2000

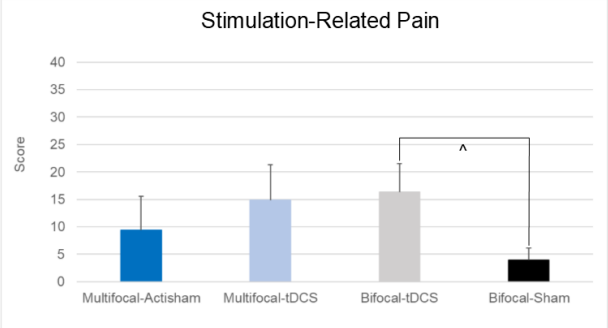


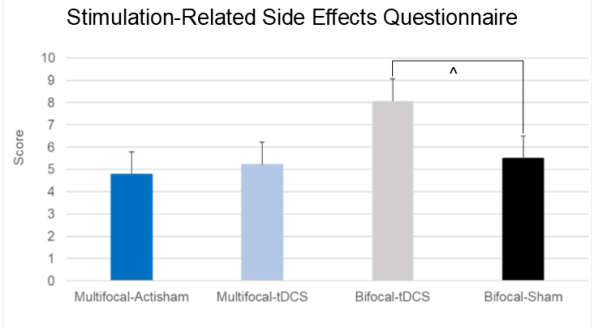


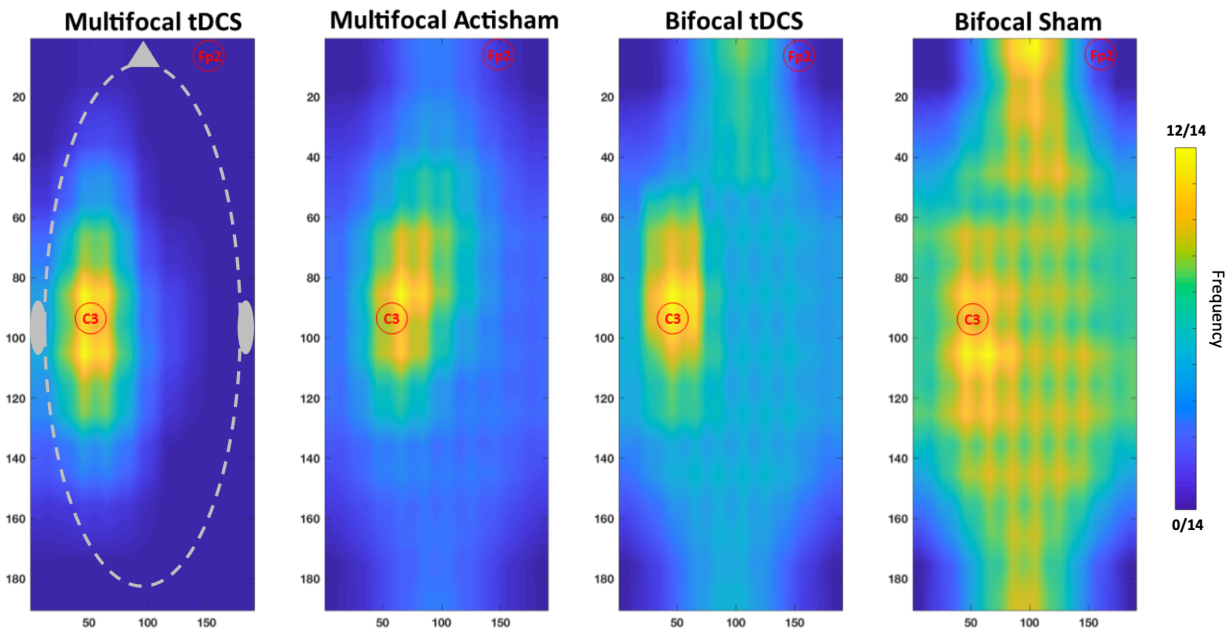


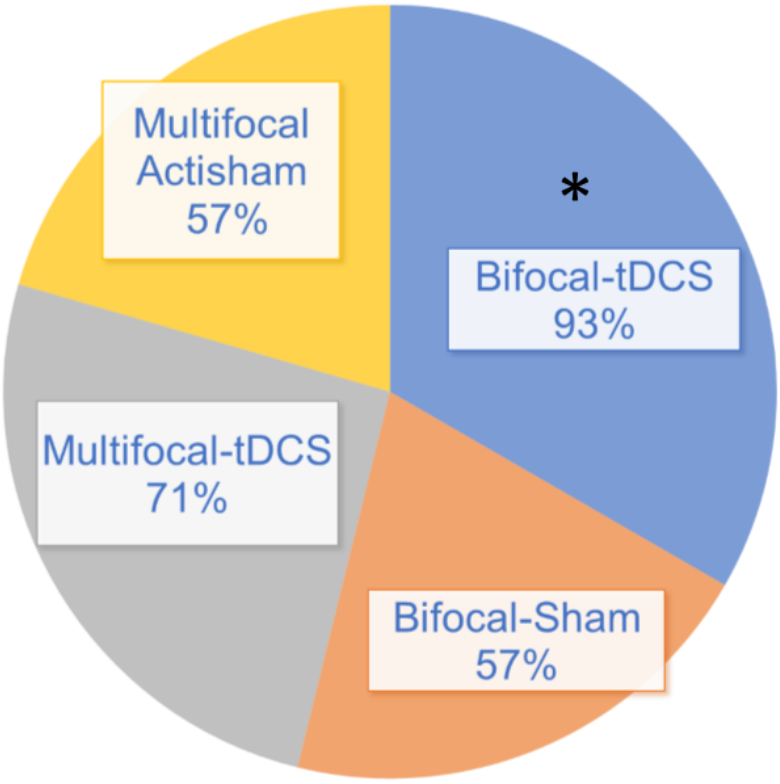


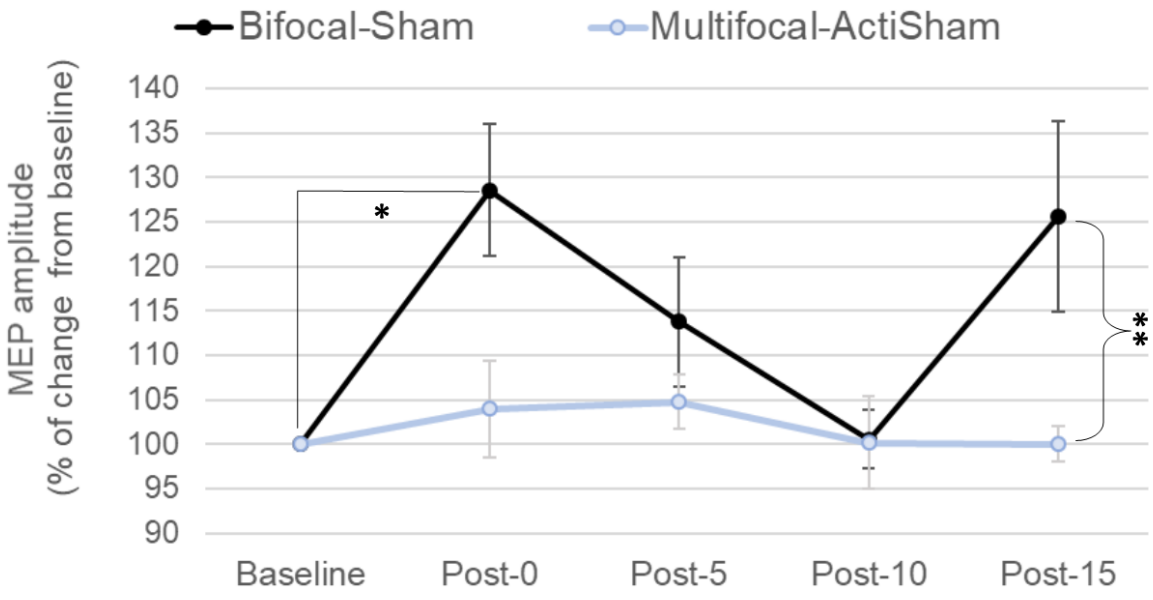









Multifocal
Actisham
57%
*
Bifocal-tDCS
93%
Multifocal-tDCS
71%
Bifocal-Sham
57%


Bifocal-Sham
Multifocal-ActiSham
MEP amplitude
(% of change from baseline)
140
135
130
125
120
115
110
105
100
95
90
*
**
Baseline
Post-0
Post-5
Post-10
Post-15

Highlights

- Canonical On/Off solutions for Sham tDCS do not allow proper blinding
- We tested an “Active-Sham” multi-electrode stimulation based on controlled current shunting
- Comparable scalp sensations were reported for Active-Sham and real Multifocal-tDCS
- A significant difference was observed between Bifocal Sham and Active-Sham conditions
- Active-Sham could improve blinding for both research and clinical trials

Conflicts of Interest

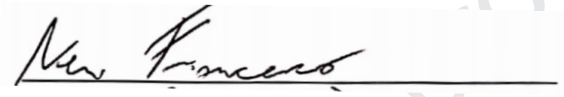
We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

Giulio Ruffini is a shareholder and works for Neuroelectrics, a company developing medical devices for non-invasive brain stimulation. Ricardo Salvador works for Neuroelectrics.

We confirm that the manuscript has been read and approved by all named authors and that there are not other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Signed by all authors as follows

Francesco Neri 

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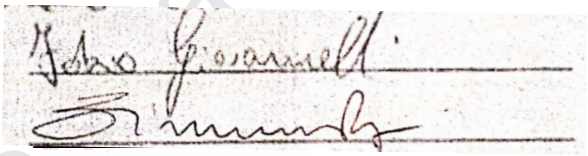
Fabio Giovannelli 

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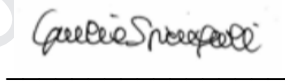
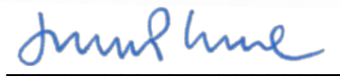
Giulia Sprugnoli 

Alessandro Rossi 

Alvaro Pascual-Leone 

Ricardo Salvador 

Giulio Ruffini 

Emiliano Santarnecchi