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Effects of High-Definition and Conventional tDCS on Response Inhibition

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ABSTRACT

Background: Response inhibition is a critical executive function, enabling the adaptive control of behavior in a changing environment. The inferior frontal cortex (IFC) is considered to be critical for response inhibition, leading researchers to develop transcranial direct current stimulation (tDCS) montages attempting to target the IFC and improve inhibitory performance. However, conventional tDCS montages produce diffuse current through the brain, making it difficult to establish causality between stimulation of any one given brain region and resulting behavioral changes. Recently, high-definition tDCS (HD-tDCS) methods have been developed to target brain regions with increased focality relative to conventional tDCS.

Objective: Remarkably few studies have utilized HD-tDCS to improve cognitive task performance, however, and no study has directly compared the behavioral effects of HD-tDCS to conventional tDCS.

Methods: In the present study, participants received either HD-tDCS or conventional tDCS to the IFC during performance of a response inhibition task (stop-signal task, SST) or a control task (choice reaction time task, CRT). A third group of participants completed the same behavioral protocols, but received tDCS to a control site (mid-occipital cortex). Post-stimulation improvement in SST performance was analyzed as a function of tDCS group and the task performed during stimulation using both conventional and Bayesian parameter estimation analyses.

Results: Bayesian estimation of the effects of HD- and conventional tDCS to IFC relative to control site stimulation demonstrated enhanced response inhibition for both conditions. No improvements were found after control task (CRT) training in any tDCS condition.

Conclusion: Results support the use of both HD- and conventional tDCS to the IFC for improving response inhibition, providing empirical evidence that HD-tDCS can be used to facilitate performance on an executive function task.

Introduction

The human brain is capable of rapidly implementing a vast array of behavioral responses, yet this ability would be ill-suited to the real world without the capacity to stop responses that become irrelevant or inappropriate following changes in the environment [1]. This process, known as *response inhibition*, is critical to the executive control of behavior, and research aimed at identifying its neural substrates has received growing attention in recent years [2,3]. Functional magnetic resonance imaging (fMRI) studies have identified a consistent network of brain regions that are engaged during response inhibition tasks, including pre-supplementary motor area (preSMA), inferior frontal cortex (IFC), and the subthalamic nucleus (STN) of the basal ganglia [4–7]. The present study focuses on the IFC, which has been suggested to represent the key "brake" node in the response inhibition network, implementing the signal required to inhibit the performance of a planned response [2,3].

Neuropsychological evidence has consistently linked inhibitory control function to regions of the prefrontal cortex [8,9]. Supporting the view that the IFC is necessary for response inhibition, studies in patients with prefrontal brain lesions have shown that damage to this region impairs one's ability to refrain from either initiating a prepotent behavioral response [10] or stopping an ongoing response [11]. Furthermore, a causal role of the IFC in

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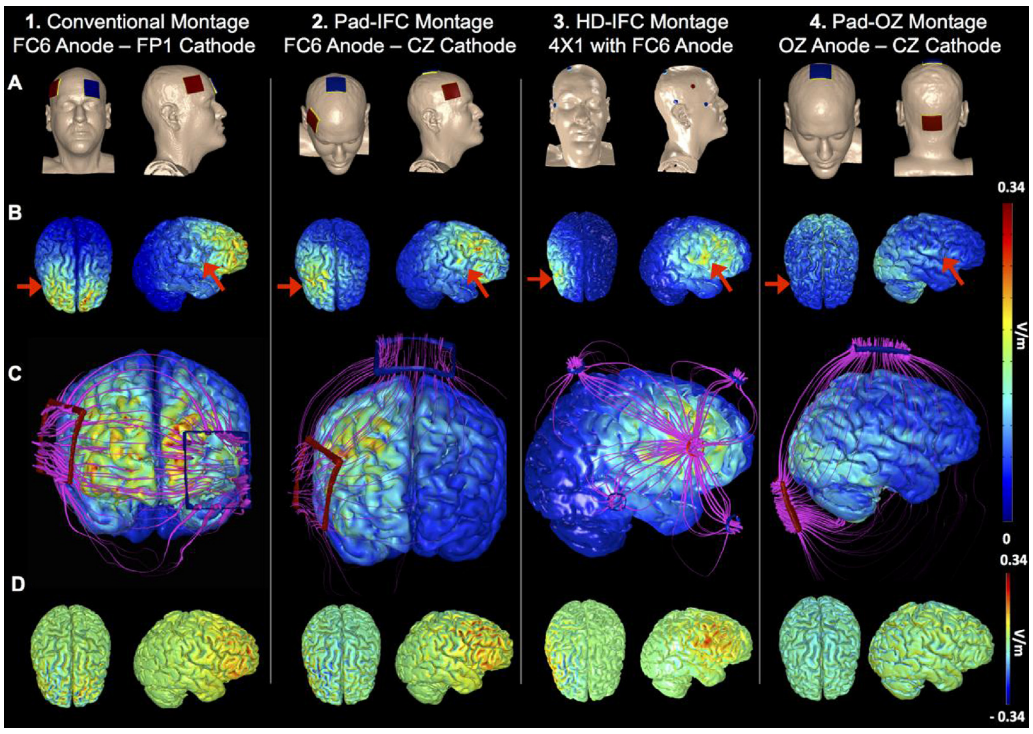

Figure 1. Computational neurostimulation models predict patterns of excitation induced by each of the tDCS montages (columns 1–4). A) Montages used in computational forward modeling displaying position of tDCS electrodes (red is anode and blue is cathode). B) Plot of electric field magnitude on cortical surface (scale 0: blue to ≥0.34 V/m: red). Red arrows approximately mark the IFC target region. Note the different brain current flow patterns and targetings predicted from montages in columns 1–4. C) Violet streamlines representing current flow through gray matter in each of the four montages. D) Plot of radial electric field component distribution across cortical surface with inward (nominally excitatory) current positive and outward (nominally inhibitory) current negative (scale ≤0.34: blue, 0: green, ≥0.34: red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

response inhibition has been reaffirmed by using transcranial magnetic stimulation (TMS) to disturb IFC function and impair response inhibition [12,13]. Since disturbed IFC recruitment during response inhibition is a hallmark of several psychiatric and neurological disorders [14–16], studies that aim to promote regional activity in this area of the brain may offer promising new developments in the treatment of these conditions.

One promising method for enhancing regional brain activity is transcranial direct current stimulation (tDCS [17]). In conventional tDCS protocols, a mild electrical current (≈1–2 mA) is passed between two large electrode pads (≈25–35 cm^2) placed in different arrangements on the scalp (electrode montage). One of the electrodes is an anode and the other is a cathode, and >10 minutes of tDCS delivery has been found to increase the excitability of cortical structures near the anode for as long as 90 minutes post-stimulation [18,19]. Critically, this enhanced neuronal excitability has been associated with improvements in cognitive functions associated with structures nearer to the anodal electrode site. For example, tDCS with the anodal pad placed over the parietal cortex has been associated with improved performance on spatial attention and numerosity tasks [20–23], whereas stimulation with the anode over prefrontal cortex has been shown to modulate planning [24], decision-making [25,26], social reasoning [27], and working memory [28,29]. Of particular relevance to the present study, researchers have started to investigate prefrontal tDCS as a tool for improving response inhibition.

Specifically, recent studies have demonstrated improved response inhibition following conventional tDCS with an anode placed over right IFC or pre-supplementary motor area (preSMA) and the cathodal electrode placed on the opposite side of the head [30–33]. Given the well-established role of right IFC and preSMA in response inhibition [2,3], the studies' authors argued that enhanced excitability at the structures underneath the anodal pad drove the observed behavioral improvement. However, computational neurostimulation[1] studies have suggested that pad tDCS produces diffuse current through the brain including both cortical and deep structures (Fig. 1.1–2,4; [34–36]). This diffuse pattern of current flow is supported by evidence from combined tDCS/fMRI studies [37,38], thereby making it difficult to establish causality between modulated activity at the nominal target site and resulting behavioral changes [39–41].

In an effort to improve the spatial focality of tDCS, researchers have recently developed high-definition tDCS (HD-tDCS) delivery systems [34,35]. Typically, HD-tDCS involves passing a small direct electrical current (again, typically 1–2 mA) through a 4×1 montage of stimulating electrodes (1 cm diameter), with a single anodal electrode placed over the target brain region, and four return electrodes arranged in a ring surrounding the anode, each receiving 25% of the return current. Computational neurostimulation studies suggest that the focality of HD-tDCS is far superior to conventional tDCS, with current flow restricted to the circumscribed ring (Fig. 1.3) [35,42]. The efficacy of HD-tDCS for inducing neurophysiological changes has been established in research on human motor system activity, by applying anodal stimulation over the primary motor cortex and demonstrating subsequent increases in corticospinal excitability [43,44].

Although such findings in the domain of motor excitation have been established and replicated, similar effects in non-motor domains

[1] "Biologically plausible models and/or neural networks that simulate the consequences of neurostimulation." [39]

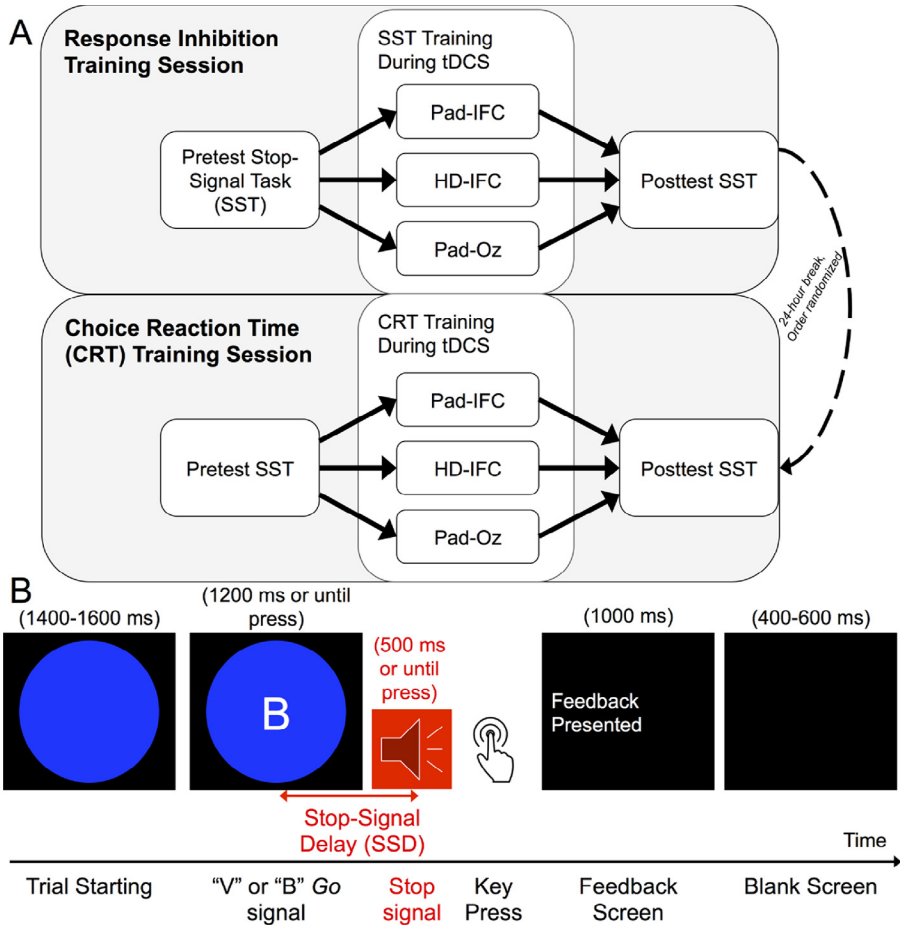

Figure 2. (A) Schematic of the study design. (B) Schematic of the response inhibition task (stop-signal task, SST). The control task (choice reaction time task, CRT) was identical to the SST, but did not include any stop signal trials.

remain unreported. To our knowledge, only one study to date has examined the impact of HD-tDCS on neuropsychological task performance [45], with results demonstrating that HD-tDCS led to significant improvements on a variety of cognitive tasks (in comparison to stimulation in a control region). Furthermore, no studies have directly contrasted the cognitive effects of conventional and HD-tDCS in the same experimental paradigm. Given the potential spatial advantage of HD-tDCS for targeting brain regions relative to conventional tDCS, as well as the translational potential of both approaches in improving cognitive performance, there is a need to compare the impacts of the two stimulation techniques on cognitive functioning.

In order to address this need, we directly compared the effects of HD-tDCS and conventional tDCS on response inhibition in a group of healthy adult participants. Participants were randomly selected to receive either HD-tDCS or conventional tDCS to IFC during a response inhibition training task (Fig. 2A). Both HD- and conventional tDCS montages were designed to maximize current flow to the IFC (Fig. 1.2–3). A third group of participants received conventional tDCS targeting a mid-occipital control site (Fig. 1.4). Inclusion of an active tDCS control condition ensured the relative target specificity of any behavioral effect observed following HD- or conventional tDCS over the IFC [46]. Finally, in addition to the response inhibition task, participants completed a control training task unrelated to response inhibition (choice reaction time task, CRT, Fig. 2A [47]), during a separate testing session. As in the experimental training session, participants performed the control training task during stimulation, enabling us to determine whether *task context* during tDCS influences subsequent behavioral effects. Our central hypothesis was that both HD-tDCS and conventional tDCS would facilitate response inhibition training relative to mid-occipital stimulation, without influencing performance after training on the control task. Most importantly, the inclusion of both HD- and conventional tDCS in the same experimental paradigm allowed for the first direct comparison, to our knowledge, of the effects of these two techniques on a cognitive task.

Materials and methods

Participants

Fifty-two individuals participated in the experiment for financial remuneration and were divided into three tDCS conditions: (1) conventional tDCS targeting the IFC (pad-IFC), $n = 16$; (2) HD-tDCS to IFC (HD-IFC), $n = 16$; and (3) conventional tDCS targeting the mid-occipital control site (pad-Oz), $n = 20$. Both gender (pad-IFC, $p = 0.69$ female; HD-IFC, $p = 0.62$ female; pad-Oz, $p = 0.75$ female; $X^2 = 0.66$, $p = 0.72$) and handedness (pad-IFC, $p = 0.94$ right-hand dominant; HD-IFC, $p = 0.88$ right-hand dominant; pad-Oz, $p = 0.95$ right-hand dominant; $X^2 = 4.51$, $p = 0.34$) were closely matched between tDCS groups, but there was a marginal difference in age between groups [pad-IFC, $M = 26.44$, $SD = 1.05$; HD-IFC, $M = 26.38$, $SD = 3.36$; pad-Oz, $M = 23.65$, $SD = 4.38$; $F(2,49) = 2.66$, $p = 0.08$]. Age, however, was not significantly associated with the primary outcome

measure during either of the experimental sessions (SST session gain score: $r = -0.01$, $p = 0.93$; CRT session gain score: $r = 0.16$, $p = 0.27$), suggesting that it was unlikely to mediate any observed effects.

Six subjects were observed to be 3 "median absolute deviations" from the rest of the sample on their pretest–posttest gain scores (see **Behavioral task materials and procedures**), and were removed prior to the inferential analyses [48]. The data reported herein are based on the remaining sample of 46 participants (pad-IFC, $n = 15$; HD-IFC, $n = 15$; pad-Oz, $n = 16$). After outlier removal, the groups were matched with respect to participants' years of age [pad-IFC, $M = 26.13$, $SD = 4.67$; HD-IFC, $M = 26.13$, $SD = 3.34$; pad-Oz, $M = 23.44$, $SD = 4.24$; $F(2,43) = 2.23$, $p = 0.12$], gender (pad-IFC, $p = 0.67$ female; HD-IFC, $p = 0.67$ female; pad-Oz, $p = 0.75$ female; $X^2 = 0.34$, $p = 0.84$), and handedness (pad-IFC, $p = 0.93$ right-hand dominant; HD-IFC, $p = 0.87$ right-hand dominant; pad-Oz, $p = 0.94$ right-hand dominant; $X^2 = 4.17$, $p = 0.38$). All participants were screened to ensure the final sample included only neurologically healthy individuals without any contraindications to tDCS. Recruited participants signed written informed consent statements before completing the study, and all experimental protocols were reviewed and approved by a local institutional review board.

Study design

The study employed a pretest–posttest design, repeated over two sessions (Fig. 2A). On the first session, participants completed a pretest response inhibition assessment, then received one of three tDCS conditions (pad-IFC, HD-IFC, or pad-Oz) during an extended response inhibition training session, followed by a posttest inhibition assessment identical to the pretest. The second session was equivalent to the first, with the exception that participants completed a choice reaction time task (CRT) while receiving tDCS. The order of the two sessions (inhibition task or CRT) was randomly assigned across participants.

Transcranial direct current stimulation (tDCS)

Electrode montage design and computational models

In previous studies on tDCS and response inhibition, the anodal electrode has typically been placed over the right IFC with the cathode placed on the contralateral orbital region ([30,31]; Fig. 1A, column 1), which may deliver more diffuse bilateral current through the prefrontal cortex. To deliver more focal stimulation, we designed a conventional tDCS montage with the anodal electrode over the IFC and the cathodal electrode over a closer, more innocuous cortical target (vertex; Fig. 1A, column 2 [47]). For the HD-IFC condition, HDTargets™ software (Soterix Medical, New York, NY) was used to design an optimal HD-tDCS montage for targeting IFC (Fig. 1A.3). Lastly, for the active control site montage (pad-Oz), we designed a montage with the cathodal electrode at the same electrode site as the pad-IFC condition, and an anode placed over a posterior target (mid-occipital cortex; Fig. 1A.4) that would be less likely to influence activity at the IFC than the pad-IFC condition.

Prior to beginning the experiment, computational neurostimulation models were used to predict current flow patterns induced by each of the selected montages, as well as the montage used in previous tDCS/response inhibition studies (Fig. 1). Specifically, we used high-resolution finite-element-method (FEM) computational models to calculate tDCS-induced cortical fields in order to predict the spatial extent of the stimulation montages, using modeling methods as described previously [35]. Briefly, a volumetric mesh was created using MRI scans of a template head, which was segmented into layers (with conductivity in S/m) corresponding to gray matter (0.276), white matter (0.126), cerebrospinal fluid (1.65), skull (0.01), fatty tissue (0.025), eyes (1.65), skin (0.465), and air (1×10^{-15}). The physical placement and dimensions of the electrodes (5.99×10^7 S/m) and saline-soaked sponges (1.4 S/m) were imported into the model, and the resulting volumetric meshes were imported into an FEM solver (COMSOL, Burlington, MA, USA). The model predicted the electric field magnitude on the cortical surface (Fig. 1B), trajectories of current flow through cortical gray matter (Fig. 1C), and the radial electrical field component distribution (Fig. 1D). These modeling procedures have been used extensively in previous studies to visualize the focality of HD- and conventional tDCS [43,44,49]. The results of these simulations confirmed initial predictions: i) the montage used to target IFC in previous tDCS/response inhibition studies (Fig. 1, column 1 [30,31]) induced more widespread bilateral current than the pad-IFC montage (Fig. 1, column 2), ii) pad-IFC and HD-IFC montages both delivered current to the IFC target, with pad tDCS delivering more diffuse current than HD-tDCS (Fig. 1, column 3), and iii) the pad-Oz montage provided an ideal active control montage as minimal current was expected to reach the IFC (Fig. 1, column 4).

tDCS materials and procedures

Stimulation sites for both conventional and HD-tDCS protocols were identified using an EasyCap (EasyCap, Herrsching, Germany) electrode cap modified according to standard 10% landmarks. Stimulation was delivered using the Soterix LTE-tDCS stimulator, and HD-tDCS was delivered using the Soterix 4×1 multichannel stimulation interface (Soterix Medical, Inc., New York, NY). In each condition, tDCS was delivered at 1 mA for 20 minutes, which previous studies have reliably found to improve cognitive performance [50–53]. The LTE-tDCS device has a built-in ramp down function that decreases stimulation intensity if electrode-to-skin contact quality is poor, but this feature was not engaged during active tDCS delivery for any of the participants.

For the two conventional montages (pad-IFC, pad-Oz), ≈25 cm^2 conductive rubber insets and 35 cm^2 saline-soaked electrode pads were used to deliver tDCS. For the pad-IFC group, the electrodes were placed at FC6 and Cz, with the anodal lead connected to the FC6 site and the cathodal lead connected to the Cz electrode. The setup for the pad-Oz group was identical except the anodal electrode was placed at Oz. In the HD-tDCS condition, electrode holders were inserted at the following locations: FC6, F10, CP2, TP8, and F2. With the cap in place, the experimenter applied ≈15 ml of electrolytic gel and placed a 1 cm diameter circular electrode at each site [54]. The montage was arranged such that 100% of the 1 mA current was being delivered through an anodal electrode at FC6, and 25% of the current was being returned through each of the four cathodal electrodes (i.e. F10, CP2, TP8, and F2). The tDCS device included a feature to decrease stimulation output whenever electrode impedance was high; this did not occur during any of the experimental sessions.

Behavioral task materials and procedures

The present experiment measured response inhibition using the stop-signal task (SST Fig. 2B [55,56];), programmed in PsychoPy2 version 1.81 [57]. The SST is a reliable and valid method for assessing rapid-response impulsivity by providing an indirect measurement of the "stop process" duration [58,59], or the amount of time it takes each subject to inhibit an ongoing prepotent response. Specifically, on the majority of SST trials (75%), participants responded to viewing the letters 'V' or 'B' on a screen by pressing the corresponding key on a keyboard as quickly and accurately as possible ("Go" trials). However, on the minority of trials (25%), a 900 Hz tone was presented shortly after the cue (the "stop signal"), instructing participants to cancel their planned response. During the pretest and posttest runs of the SST (Fig. 2A), subjects completed 128 total experimental trials, including 96 "Go" trials and 32 "stop-signal" trials.

During the combined tDCS/SST training session, subjects performed 192 experimental trials, including 144 "Go" trials and 48 stop-signal trials. At the start of each SST run, the stop signal was presented 250 ms after the response cue. This interval, known as the stop-signal delay (SSD), was shifted 50 ms later following each successful stop and 50 ms earlier after each unsuccessful stop, such that the overall probability of successful inhibition was ≈0.50 [60]. The key measure of response inhibition in the SST is the stop-signal reaction time (SSRT), wherein the average delay of the presentation of the stop signal is subtracted from the average reaction time on correct "Go" trials [55,61]. The SSRT provides an indirect measurement of the amount of time required by each subject to successfully inhibit their planned response, with shorter SSRTs indicating superior response inhibition. Importantly, the three tDCS groups (pad-IFC, HD-IFC, and pad-Oz) were matched with respect to SST performance at the beginning of the experiment [pad-IFC: $M = 342$ ms, $SD = 46$ ms; HD-IFC: $M = 349$, $SD = 32$; pad-Oz: $M = 348$, $SD = 34$; $F(2,43) = 0.14$, $p = 0.87$, $\eta^2 = 0.01$], thereby ensuring that potential group differences in pretest–posttest performance would be specific to the intervention. Because the primary aim of the present study was to measure response inhibition improvement following the combined tDCS/SST training session, the principal outcome measure ("SST gain score") was calculated by subtracting pretest SSRT (prior to the SST training session) from posttest SSRT (immediately following the SST training session).

During the control task (CRT) training session, subjects performed 192 "Go" trials, and were instructed ahead of time that they would not be exposed to any stop-signal trials. Pretest–posttest SSRT changes after the CRT session ("CRT gain score") were also analyzed, to determine whether the training task influenced the behavioral outcome of the tDCS intervention. CRT gain scores were calculated using the same approach as described above to calculate SST gain scores.

Bayesian parameter estimation

The *a priori* prediction in the present study was that the two IFC stimulation montages would facilitate response inhibition training relative to the pad-Oz montage. Additionally, given the promise of HD-tDCS for targeting cortical sites with increased spatial resolution relative to conventional tDCS [35,43], it was imperative to evaluate whether the HD-IFC and pad-IFC stimulation montages had comparable impacts on response inhibition. Whereas classical statistical testing would enable us to accept or reject the null hypothesis that two tDCS groups were statistically equivalent, this approach would provide minimal insight into the certainty with which a null effect could be claimed [62–64]. Therefore, a Bayesian parameter estimation approach was applied, using the "Bayesian estimation supersedes the t-test" (BEST) package [63,64] implemented in R version 3.2 [65]. This approach allowed for the estimation of credible distributions of the means, standard deviations, and effect sizes of each tDCS group contrast, thus enabling statistical judgments regarding the strength of the evidence in favor of either the alternative hypothesis (i.e. that two tDCS groups were *not* equivalent) or the null hypothesis (i.e. that two tDCS groups were equivalent [66,67]).

Briefly, in Bayesian estimation, the goal is to re-allocate credibility to a distribution of possible parameter values (mean and standard deviation) that are consistent with the observed data. In the present study, we first established a noncommittal set of initial credibility values for the study parameters (*prior distribution*), inputted the observed SST gain scores, and utilized a Markov Chain Monte Carlo method (MCMC) to generate a large number of samples consistent with the observed data in order to re-allocate credibility to the parameter values (*posterior distribution*). The difference between groups was estimated by subtracting the distributions of means and standard deviations between the pad-IFC and the pad-Oz groups, between the HD-IFC and pad-Oz groups, and finally between the HD-IFC and pad-IFC groups. Next, 90%-high density intervals (90%-HDI) were calculated to determine whether those differences were credibly below zero. Ultimately, decisions about these contrasts were made using a region of practical equivalence (ROPE) decision approach [63,64,68]. Specifically, from the posterior distributions of the parameter values, we computed the distribution of effect sizes[2] and defined the ROPE between $d = -0.1$ and $d = 0.1$, to denote a statistically meaningless effect [64,69]. For each Bayesian group contrast, the proportion of effect sizes falling outside of the ROPE represented the likelihood of an observed effect of $d \geq 0.1$. Conversely, the percentage of effect sizes that fell within the ROPE quantified the evidence in support of the null hypothesis that there was no meaningful difference between the groups [67]. Lastly, the same series of comparisons was performed on CRT gain scores, in order to determine whether pad-IFC and HD-IFC stimulation would improve response inhibition in the absence of tDCS-enhanced SST training.

Results

Stop-signal reaction times

The primary measure used to index response inhibition performance was the stop-signal reaction time (SSRT), which estimates the amount of time subjects take to successfully inhibit an inappropriate planned response. The experiment was a 2 (time: pretest, posttest) × 2 (session: CRT, SST) × 3 (tDCS: pad-IFC, HD-IFC, pad-Oz) design. SSRTs were thus analyzed via three-way mixed ANOVA, which revealed a significant main effect of time [$F(1,43) = 7.42$, $p = 0.009$, $\eta^2 = 0.14$] due to significantly slower SSRTs at pretest ($M = 335$ ms, $SD = 30$ ms) than at posttest [$M = 324$, $SD = 31$; $t(45) = -2.71$, $p = 0.009$, $d = -0.40$]. None of the other main effects or interaction terms were significant (all $ps > 0.1$). Of particular relevance to the present hypotheses, the three-way interaction term did not reach statistical significance [$F(2,43) = 1.98$, $p = 0.15$, $\eta^2 = 0.08$]. However, the lack of a significant three-way interaction effect was not surprising, as the experiment included two tDCS montages targeting the same cortical site (pad-IFC and HD-IFC), which were expected to induce comparable behavioral effects. Because the present study was specifically designed to explore the potential influences of tDCS method (i.e. HD versus conventional) and stimulation task on response inhibition performance, a series of planned comparisons on the SSRT gain scores (between the tDCS conditions) was performed, despite the lack of a significant interaction in ANOVA results. Comparisons were analyzed via a series of one-tailed *t*-tests, as prior literature regarding the effects of tDCS on response inhibition uniformly demonstrates a directional effect, with stimulation leading to enhanced SSRT [30–33].

The observed SST and CRT gain scores are depicted in Fig. 3. Independent *t*-tests on SST gain scores revealed significant performance improvements following SST training in both the pad-IFC [$M = -27$, $SD = 47$; $t(29) = 1.89$, $p = 0.03$, $d = 0.68$] and HD-IFC [$M = -22$, $SD = 32$; $t(29) = 1.82$, $p = 0.04$, $d = 0.65$] groups relative to the pad-Oz (control) group ($M = -1$, $SD = 31$; Fig. 3). In contrast, tDCS to IFC did not significantly impact CRT gain scores relative to pad-Oz stimulation [pad-IFC: $M = -1$, $SD = 44$; HD-IFC: $M = -9$, $SD = 39$; pad-Oz: $M = -10$, $SD = 33$; pad-IFC vs. pad-Oz: $t(29) = -0.60$, $p = 0.72$, $d = 0.21$; HD-IFC vs. pad-Oz: $t(29) = -0.04$, $p = 0.52$, $d = -0.01$; Fig. 3].

In the first Bayesian parameter contrast, SST gain scores were compared between the pad-IFC group and the pad-Oz group (Fig. 4).

[2] $Effect\ Size = \frac{(\mu_1 - \mu_2)}{\sqrt{(\sigma_1^2 + \sigma_2^2)/2}}$.

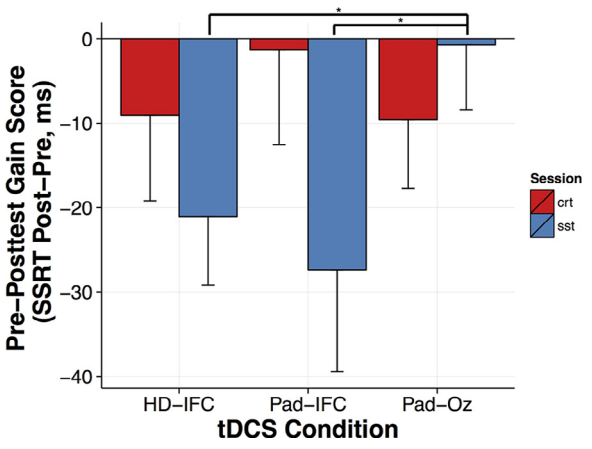

Figure 3. Figure depicting the pretest–posttest gain scores in stop-signal reaction time (SSRT) by tDCS intervention and training protocol. Planned independent sample *t*-tests revealed that both pad-IFC and HD-IFC stimulation enhanced response inhibition following SST training (*: $p = 0.03$ and $p = 0.04$, respectively).

Model checks revealed that the Bayesian estimation algorithm (MCMC) had achieved convergence, as the "potential scale reduction factor" (Rhat) was equal to 1 for all parameters [70]. Model parameter estimates provided evidence that there was a greater pretest–posttest improvement in response inhibition in the pad-IFC group ($M_1 = -28$, 90%-HDI = –49 to –6, Fig. 4A) than the pad-Oz group ($M_2 = 0$, 90%-HDI = –15 to 14, Fig. 4B; $M_{DIFF} = -28$, 90%-HDI = –54 to –2, Fig. 4C). The distribution of standard deviations was slightly higher in the pad-IFC condition, though this difference was not credibly different from zero (mode = 14, 90%-HDI = –6 to 37). Critically, the distribution of credible effect sizes did not include 0 (mode = –0.64, 90%-HDI = –1.35 to –0.02), and only 4.75% of the sampled effect sizes fell within the ROPE (Fig. 4D), providing support for a significant group effect. The same analysis on the CRT gain scores did not reveal any differences between the pad-IFC and pad-Oz groups (Supplementary Fig. S1). Lastly, the SST and CRT sessions were directly compared by subtracting the two mu parameter distributions, and found that 95% of the samples were less than zero. Therefore, this comparison provides credible evidence that the pad-IFC effect differed across the two tDCS sessions, affecting SST but not CRT session gain scores (Fig. 7).

Secondly, the same Bayesian estimation was performed, comparing the SST gain scores between HD-IFC and pad-Oz groups (Fig. 5). The model achieved convergence, as *Rhat* = 1 for all parameters. As in the pad-IFC/pad-Oz comparison, there was a greater improvement in response inhibition following HD-IFC stimulation ($M_1 = -22$, 90%-HDI = –37 to –7, Fig. 5A) relative to pad-Oz stimulation ($M_2 = 0$, 90%-HDI = –15 to 14, Fig. 5B; $M_{DIFF} = -21$, 90%-HDI = –42 to –1, Fig. 5C). The distribution of standard deviations was similar between the HD-IFC and pad-Oz conditions (mode = 0, 90%-HDI = –16 to 18). Also akin to the pad-IFC/pad-Oz comparison, the distribution of effect sizes (mode = –0.63, 90%-HDI = –1.31 to –0.02), and the percentage of effect sizes in the ROPE (5.11%) indicated that HD-IFC stimulation led to improved response inhibition relative to pad-Oz stimulation (Fig. 5D). In contrast, CRT gain scores did not credibly differ between the HD-IFC and pad-Oz groups (Supplementary Fig. S2). Although there was a clear difference in the Pad-IFC distributions between the CRT and SST sessions, when this difference was computed for the HD-IFC distributions only 86% of the samples fell below zero (Fig. 7).

In the critical third analysis, parameter values for the SST gain scores were directly compared between pad-IFC and HD-IFC groups (Fig. 6). The model achieved convergence with *Rhat* = 1 for all parameters. Interestingly, there was minimal statistical evidence for a difference between the two IFC stimulation conditions with the magnitude of response inhibition improvement similar across HD-IFC ($M_1 = -22$, 90%-HDI = –37 to –7, Fig. 6A) and pad-IFC stimulation ($M_2 = -28$, 90%-HDI = –50 to –7, Fig. 6B; $M_{DIFF} = 6$, 90%-HDI = –20 to 32, Fig. 6C). The percentage of effect sizes within the ROPE was relatively high (19.05%), suggesting that the two IFC stimulation groups were highly equivalent in terms of their SST gain scores (Fig. 6D). The same comparison on CRT gain scores supported similar equivalence between the two groups (Supplementary Fig. S3).

Control measures

"Go" trial reaction times

In addition to SSRTs, there are a variety of other performance metrics that can be analyzed from the stop-signal task (SST). Firstly, reaction times (RTs) from "Go" trials can be analyzed to index impulsive responding during the SST [71]. Therefore, if our tDCS intervention affected both SSRTs and RTs from pretest to posttest, this would suggest that the former effect was influenced by changes

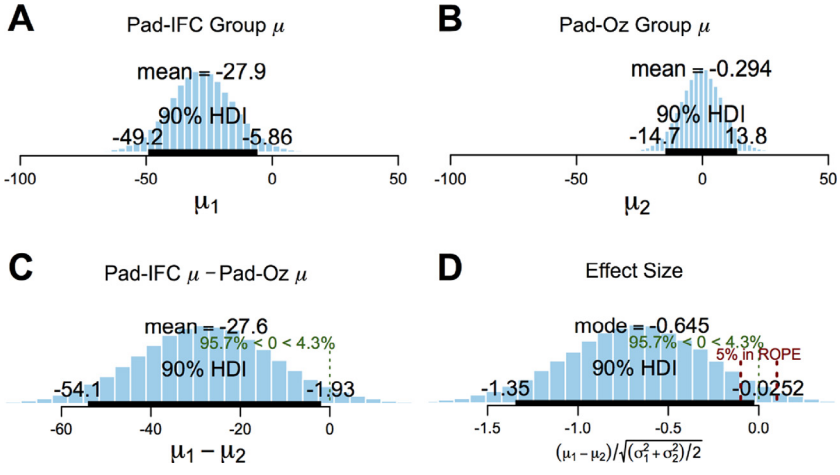

Figure 4. Bayesian parameter estimation results from the pad-IFC vs. pad-Oz SST gain score contrast. (A) Depicts the improvement in SSRTs in the pad-IFC condition, and (B) the lack of such improvement in the pad-Oz condition. (C) The pad-IFC group demonstrated greater pretest–posttest improvement than the pad-Oz group, and (D) the distribution of effect sizes had <5% of values within the region of practical equivalence (ROPE).

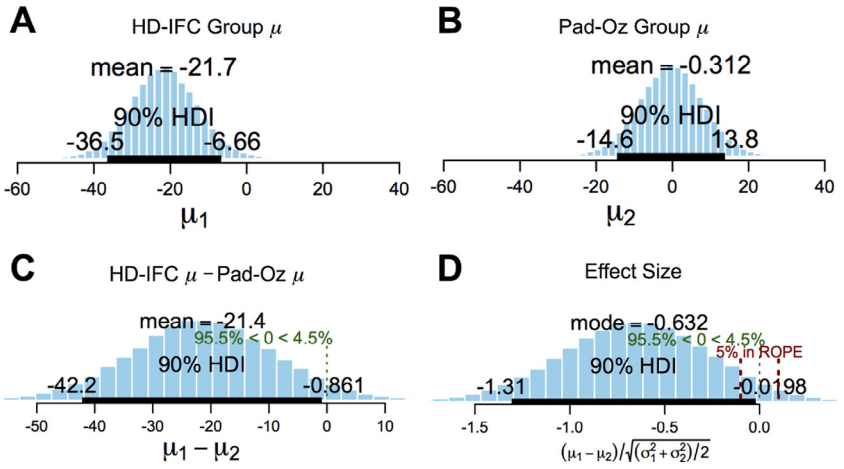

Figure 5. Bayesian parameter estimation results from the HD-IFC vs. pad-Oz SST gain score contrast. (A) Depicts a negative pretest–posttest shift in SSRTs in the HD-IFC condition, and (B) a lack of an SSRT improvement in the pad-Oz condition. (C) The HD-IFC group showed a greater improvement than the pad-Oz group, and (D) the distribution of effect sizes had 5% of values within the region of practical equivalence (ROPE).

in response impulsivity rather than inhibitory control *per se*. Accordingly, an ANOVA was used to analyze RTs, with results indicating that the main effects of time [$F(1,43) = 0.58$, $p = 0.45$, $\eta^2 = 0.01$] and session [$F(1,43) = 0.02$, $p = 0.89$, $\eta^2 < 0.001$] were not statistically significant. A trend towards a main effect of tDCS condition was observed, with higher RTs in the pad-IFC group ($M = 547$, $SD = 116$) than the other two tDCS groups [HD-IFC: $M = 483$, $SD = 94$; pad-Oz: $M = 468$, $SD = 74$; $F(2,43) = 2.92$, $p = 0.06$, $\eta^2 = 0.12$]. However, the marginal difference in "Go" trial RTs across tDCS groups did not interact with the time [$F(2,43) = 0.35$, $p = 0.70$, $\eta^2 = 0.02$] and session [$F(2,43) = 0.10$, $p = 0.90$, $\eta^2 = 0.005$] factors, and the three-way interaction term was not statistically significant [$F(2,43) = 0.50$, $p = 0.61$, $\eta^2 = 0.02$]. Therefore, the marginal trend towards generally slower RTs in the pad-IFC condition cannot account for any differences observed from pretest to posttest between tDCS conditions.

False alarm rate

The false alarm rate was defined as the probability of responding erroneously on "Stop" trials. The SST uses a staircase procedure to identify the stop-signal delay at which participants are ≈50% likely to successfully inhibit their planned responses on "Stop" trials [60,72]. Therefore, reduced false alarm rates in a particular experimental condition would suggest that participants in that group waited for the stop signal, rather than responding as quickly and accurately as possible. An ANOVA on false alarm rates did not find any statistically significant main effects [time: $F(1,43) = 1.63$, $p = 0.21$, $\eta^2 = 0.04$; session: $F(1,43) = 0.20$, $p = 0.66$, $\eta^2 = 0.004$; and tDCS: $F(2,43) = 1.59$, $p = 0.22$, $\eta^2 = 0.07$] or interactions [time*tDCS: $F(2,43) = 0.41$, $p = 0.67$, $\eta^2 = 0.02$; session*tDCS: $F(2,43) = 0.35$, $p = 0.71$, $\eta^2 = 0.02$; session*time: $F(2,43) = 1.00$, $p = 0.32$, $\eta^2 = 0.02$; time*session*tDCS: $F(2,43) = 0.18$, $p = 0.84$, $\eta^2 = 0.01$]. This analysis revealed that false

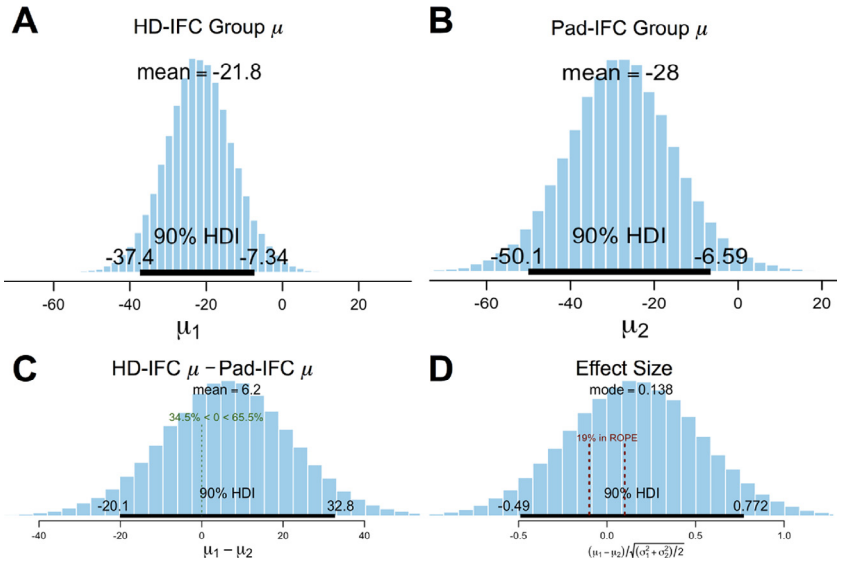

Figure 6. Bayesian parameter estimation results from the HD-IFC vs. pad-IFC SST gain score contrast. (A) Depicts the improvement in SSRTs in the HD-IFC condition, and (B) shows a similar improvement in the pad-IFC condition. (C) The difference between the two distributions was centered roughly at 0, and (D) the distribution of effect sizes had 19% of values within the region of practical equivalence (ROPE).

alarm rates were consistent between tDCS groups (pad-IFC: $M = 52\%$, $SD = 7\%$; HD-IFC: $M = 55\%$, $SD = 6\%$; pad-Oz: $M = 55\%$, $SD = 4\%$), thereby indicating that effects on the primary outcome measure (i.e. stop-signal reaction time) could not be accounted for by differential speed–accuracy trade-offs between groups.

Discussion

The present study compared the effects of conventional tDCS and HD-tDCS for targeting IFC in order to improve response inhibition. Response inhibition performance improved following stop-signal task (SST) training during both HD- and conventional tDCS targeting the right IFC, relative to conventional tDCS targeting a posterior control site. To our knowledge, these results provide the first evidence that HD-tDCS can improve response inhibition, or indeed, performance on any executive function task.

In addition to demonstrating the efficacy of HD-tDCS for improving response inhibition performance, the present study provides the first direct comparison between HD-tDCS and conventional tDCS on a cognitive task. Specifically, our results suggest that HD-tDCS and conventional tDCS (delivered to IFC) have statistically similar effects on response inhibition, as assayed through SST performance. Our observations of SST performance improvements following IFC stimulation are in accordance with substantial previous evidence that this region plays a significant role in enabling the successful inhibition of inappropriate behavioral responses [2,3,11].

Thus, the most straightforward interpretation of the present findings may be that the two IFC stimulation conditions (HD-tDCS, conventional tDCS) induced excitability changes directly to this region of the brain, making it unsurprising that both techniques had comparable effects on SST performance. Alternatively, if complex network effects of tDCS impact SST performance, it might be presumed that the markedly distinct patterns of electrical current flow delivered through HD-tDCS and conventional tDCS (Fig. 1B.1 *versus* 1B.2) would produce dissociable functional impacts on SST performance. While the present results seem to support the first interpretation, it is also theoretically possible that the similar behavioral response profiles of the two stimulation techniques were mediated by distinct underlying mechanisms (cf [73].). For example, although ventral portions of the IFC are reliably implicated in response inhibition *per se*, an adjacent dorsal sector of the IFC has been implicated in orienting attention towards the salient "stop" signal [13,74]. Whereas both IFC stimulation montages in the present study were expected to deliver current through both the ventral and dorsal sectors, computational analyses predicted that the pad-IFC montage would deliver its maximal current flow to a more dorsal region than the HD-IFC montage (Fig. 1.2–3). It is thus possible that HD-IFC stimulation improved response inhibition directly (i.e. via a ventral mechanism), whereas pad-IFC stimulation improved SST performance by facilitating attentional orientation to the inhibitory signal (i.e. via a dorsal mechanism). Future studies using tasks that dissociate the "attention-to-inhibition" and "inhibition *per se*" components of the SST would provide valuable clarification regarding the specific cognitive processes modulated by these two neurostimulation protocols.

Finally, the present results revealed that the effects of tDCS on response inhibition depend on the relevance of the task performed *during* stimulation. The prototypical experimental procedures in the tDCS literature tend to deliver stimulation "offline," or before the outcome variable is measured [19,75]. In contrast, several studies in the cognitive/behavioral domain have started to perform tDCS "online," during the performance of the experimental task [23,45,76]. The argument that "online" tDCS may be preferable to "offline" tDCS is based on the suggestion that neurons closer to firing threshold

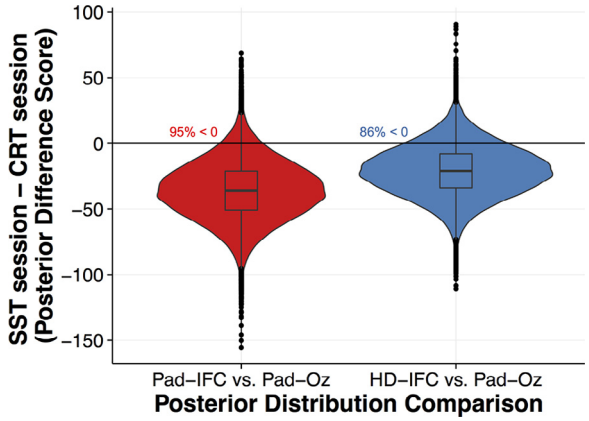

Figure 7. Violin/boxplot showing the effects of pad-IFC and HD-IFC stimulation as a function of session (i.e. SST session posterior distribution minus the CRT session). There was credible evidence for a difference in the pad-IFC effect between sessions, as 95% of the samples fell below zero. In contrast, the evidence for a session-wise difference in the HD-IFC effect was less robust, with only 86% of the samples below zero.

are more likely to be engaged by external electrical or magnetic stimulation [77–79]. The present results support the assertion that "online" tDCS delivery is preferable, as there were no reliable SST performance improvements following CRT training in any of the tDCS conditions (Supplementary Figs. S1,S2). The benefit of delivering tDCS during the performance of the SST was particularly robust for the pad-IFC condition (Fig. 7), suggesting that task context influences the cognitive effects of conventional tDCS. However, the difference in the HD-IFC effect across sessions was less pronounced (Fig. 7), suggesting that HD-tDCS may be less sensitive to the task performed during stimulation. Future studies are needed to clarify the relative importance of task context during tDCS.

The tDCS parameters used in the present study are consistent with those previously reported in the response inhibition literature to demonstrate increased task performance (i.e. <2 mA stimulation with an anode over the frontal cortex and a stop-signal task to measure response inhibition, 30–33). In contrast, to our knowledge there are no published reports demonstrating *impaired* response inhibition via tDCS, thus supporting our *a priori* hypothesis. Overall, the size of the observed effects was more modest than expected in comparison to prior research, which should be used to inform future studies employing similar designs.

The present study thus provides evidence supporting the efficacy of prefrontal HD-tDCS for producing significant improvements in response inhibition. In addition to inhibitory control performance, conventional tDCS targeting prefrontal cortex has been found to modulate performance on behavioral tasks linked to planning [24], decision-making [25], social reasoning [27], and working memory [28]. Given the similarity observed in the present study between effects induced by HD-tDCS and conventional tDCS, it is reasonable to suggest that high-definition montages might also prove useful for modulating additional neurocognitive functions. If future studies corroborate the efficacy of HD-tDCS for improving various cognitive functions, it will provide a promising technique for elucidating structure–function relationships with improved specificity relative to conventional pad tDCS [43,45]. Furthermore, because HD-tDCS appears to target cortical structures with improved spatial resolution relative to conventional tDCS, this technique could facilitate the tailoring of interventions to patient populations with specific neurocognitive impairments resulting from localized brain injury.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.brs.2016.04.015.

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