Activation of Inhibition: Diminishing Impulsive Behavior by Direct Current Stimulation over the Inferior Frontal Gyrus

Liron Jacobson[1], Daniel C. Javitt[2], and Michal Lavidor[1,3]

Abstract

■ A common feature of human existence is the ability to reverse decisions after they are made but before they are implemented. This cognitive control process, termed response inhibition, refers to the ability to inhibit an action once initiated and has been localized to the right inferior frontal gyrus (rIFG) based on functional imaging and brain lesion studies. Transcranial direct current stimulation (tDCS) is a brain stimulation technique that can facilitate as well as impair cortical function. To explore whether response inhibition can be improved through rIFG electrical stimulation, we administered focal tDCS before subjects performed the stop signal task (SST), which measures response inhibition. Notably, activation of the rIFG by unilateral anodal stimulation significantly improved response inhibition, relative to a sham condition, whereas the same tDCS protocol did not affect response time in the *go* trials of the SST and in a control task. Furthermore, the SST was not affected by tDCS at a control site, the right angular gyrus. Our results are the first demonstration of response inhibition improvement with brain stimulation over rIFG and further confirm the rIFG involvement in this task. Although this study was conducted in healthy subjects, present findings with anodal rIFG stimulation support the use of similar paradigms for the treatment of cognitive control impairments in pathological conditions. ■

INTRODUCTION

A common feature of human existence is the ability to reverse decisions after they are made but before they are implemented. This cognitive control process, termed response inhibition, allows individuals to recover from potentially harmful situations before it is too late—for example, avoiding touching a hot stove when realizing it is too hot or not commenting negatively about a coworker who suddenly appears. Cognitive control, in general, and response inhibition, in particular, are impaired in several neuropsychiatric disorders, such as attention-deficit hyperactivity disorder (ADHD; Aron & Poldrack, 2005; Barkley, 1997), schizophrenia (Hoptman et al., 2004; Kiehl, Smith, Hare, & Liddle, 2000), and obsessive compulsive disorder (Rosenberg, Dick, O'Heam, & Sweeney, 1997), and appears to be critically dependent on the intact function of the right inferior frontal gyrus (rIFG; Aron, Robbins, & Poldrack, 2004; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003).

Response inhibition can be evaluated by the stop signal task (SST; Logan & Cowan, 1984). In the SST, there are two types of trials: go trials and stop trials. In the go trials, subjects are required to make a simple discrimination task within a prespecified time window; the go trials are more frequent, thus setting up a prepotent response tendency. The stop trials are less frequent and require subjects to refrain from making the response when a stop signal is randomly presented following the go signal (Verbruggen, Logan, & Stevens, 2008; Logan & Cowan, 1984).

When administered with a tracking procedure, task difficulty can be adjusted trial by trial by changing the delay between the go signal and the stop signal (stop signal delay, SSD). As the delay increases, the probability of successful inhibition decreases as critical neuronal systems become committed to the go decision (Li, Huang, Constable, & Sinha, 2006). The standard index for response inhibition level in the SST is the stop signal response time (SSRT), which is calculated as the difference between mean RT over go trials and the mean SSD over stop trials and so reflects the time duration needed to stop the response (Logan & Cowan, 1984). This index may have both clinical and conceptual relevance, as there is accumulative evidence that impulsive people have longer SSRTs (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005; Oosterlaan, Logan, & Sergeant, 1998; Logan, Schachar, & Tannock, 1997).

Cognitive control processes, in general, are attributed mainly to the pFC, which is a collection of interconnected neocortical areas that send and receive multisensory integrated information. Response inhibition has been localized more specifically to the rIFG, based on both functional brain imaging and lesion-based approaches. For example, in a recent fMRI study, Li et al. (2008) showed that

[1]Bar Ilan University, Ramat Gan, Israel, [2]The Nathan S. Kline Institute for Psychiatric Research, New York, [3]University of Hull

successful inhibition was associated with greater activation of multiple cortical areas, among others, the rIFG and middle frontal gyri. Rubia et al. (2001) also showed common activation foci across different stop task versions in bilateral but predominantly right hemispheric inferior pFC. Similarly, patients with rIFG, but not left IFG (lIFG), lesions show a selective deficit in response inhibition as measured by the SST (Aron et al., 2003).

A second set of evidence linking rIFG to response inhibition comes from studies utilizing TMS. Magnetic stimulation over the cortex can disrupt ongoing activity and produce a temporary "lesion" to test potential and causal structure–function relationships (Walsh & Cowey, 2000). Studies employing temporary deactivation using TMS over the rIFG indeed found impaired inhibitory control (Verbruggen, Aron, Stevense, & Chambers, 2010; Chambers et al., 2006), supporting the potential role of the rIFG in response inhibition. However, although TMS was successful in establishing interference stimulation protocol that impaired cognitive control (Figner et al., 2010; Muggleton, Chen, Tzeng, Hung, & Juan, 2010), its use also raised some concerns. The same repetitive stimulation protocol resulted in facilitative effects in several reported studies (Bloch et al., 2010; Cho et al., 2010). The inconsistent effects and other practical limitations of TMS such as mobility and subjects' comfort mean that it might not be the ideal tool for developing enhancement stimulation protocols. Bearing this in mind, we aim here to test the possibility of enhancing cognitive control by applying noninvasive transcranial stimulation over the rIFG, taking advantage of a different technique where a weak direct current is applied (transcranial direct current stimulation, tDCS).

tDCS utilizes persistent direct current injection into the brain as opposed to the phasic electrical responses initiated by the TMS coil. Currents are typically applied for up to 30 min (Bolognini, Fregni, Casati, Olgiati, & Vallar, 2010; Ohn et al., 2008), permitting brain stimulation throughout a cognitive paradigm. tDCS is applied using scalp electrodes with the electrical current passing between a positively charged anode and a negatively charged cathode.

Because flow of current is directional, anodal and cathodal stimulation may have different effects on brain activity. In general, anodal activation causes an enhancement of cortical excitability both during stimulation and lasting for a few minutes thereafter (Nitsche & Paulus, 2000). At least when applied over motor cortex, cathodal activity appears to have an opposite effect. For example, Nitsche and Paulus (2000) reported that stimulation with the anodal electrode over the motor cortex increases motor excitability, whereas stimulation with the cathodal electrode decreases motor excitability. Several tDCS studies employed pFC stimulation and evaluated the effect using various cognitive control tasks (Kang, Baek, Kim, & Paik, 2009; Beeli, Koeneke, Gasser, & Jancke, 2008; Fecteau, Knoch, et al., 2007; Fecteau, Pascual-Leone, et al., 2007) and response inhibition tasks (Beeli, Casutt, Baumgartner, & Jancke, 2008). However, one of the most common and well-established response inhibition task, the SST, was never tested with tDCS applied over rIFG.

The present study evaluates the ability of tDCS, when applied over rIFG, to facilitate response inhibition without affecting other aspects of motor performance. We hypothesized that tDCS effect will be selective, affecting response inhibition, but not overall response time in the SST or response time in a simple discrimination task not requiring response inhibition.

In addition to testing this primary hypothesis, several ancillary hypotheses were tested. First, whereas anodal stimulation to date was shown to be effective in a variety of motoric as well as cognitive paradigms, cathodal stimulation has been primarily effective in motor paradigms. The present study allows the evaluation of both anodal and cathodal stimulation effects on performance in a cognitive task.

Second, although the role of rIFG in response inhibition is well established, the role of lIFG is less so. However, several recent studies have suggested that lIFG may also contribute to this process (Swick, Ashley, & Turken, 2008; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). In the present study, bilateral stimulation approaches were used and compared with both unilateral and sham stimulation conditions; the direction of current flow was opposite in the two hemispheres, leading to anodal flow in rIFG when lIFG received cathodal flow, in one bilateral condition, and cathodal flow in rIFG when lIFG received anodal flow, in the second bilateral condition. We hypothesized that cathodal flow in the lIFG would counteract the facilitating effects of anodal flow in rIFG.

Finally, to exclude nonspecific effects of tDCS, we performed a control experiment in which anodal stimulation was applied to a different brain region, the right angular gyrus (rAG), which is reportedly uninvolved in response inhibition (Chambers et al., 2006).

METHODS

Subjects

Twenty-two subjects participated in the study. Eleven of them (eight women and three men) with a mean age (*SD*) of 28.3 years (6.8 years) participated in the main part of the study, and additional 11 subjects (eight women and three men; matched for age) participated in the control condition part. The participants were all right-handed, without any known neurological or psychiatric conditions. All were naive to the nature of the experiment and gave a written informed consent before taking part in the study, which was approved by the Bar Ilan institutional review board committee. Inattention and impulsivity were assessed via the Adult ADHD Self-report Scale, and only participants with an average scores of 17 and below were included, as this is threshold score for ADHD (Reuter, Kirsch, & Hennig, 2006), mean inattention score was 12.8, and mean impulsivity score was 13.5.

Procedure

Each session began with 10 min of stimulation in one of the tDCS conditions, followed by SST and a control task in counterbalanced order (Figure 1).

tDCS

A direct current of 1 mA for 10 min was induced by two saline-soaked surface sponge electrodes (5 × 5 cm) and delivered by a battery-driven, constant-current stimulator (Rolf Schneider Electronics, Gleichen, Germany). Previous studies have shown this intensity of stimulation to be safe in healthy volunteers (Iyer et al., 2005).

SST

We used the STOP-IT program by Verbruggen et al. (2008), which adjusts the SSD after every stop-signal trial. The task starts with SSD of 250 msec, following successful stopping, SSD increases by 50 msec increments, after unsuccessful stopping, SSD decreases by 50 msec increments. The tracking procedure yielded an overall ratio of *p(response/stop signal)* of .5. An auditory "beep" was used as a stop signal and was randomly presented in 25% of the trials. The task consisted of 128 trials, which were divided into two blocks with a 10-sec break between them. Each session started with four practice trials, although the experimenter made sure that participants understood the task and added practice trials when needed. A fixation sign (+) and visual stimuli were presented at the screen center, in a white font on a black background. The distance between participants and the screen was about 65 cm, and stimulus size was 1.5 cm^2. Occasionally, a stop signal sound (750 Hz, 75 msec) was presented shortly after stimulus onset in the primary task. The response keys were the right mouse button for circles and the left mouse button for squares. The visual stimulus remained on the screen for 1250 msec, and the ISI was 2000 msec.

Control Task

A control task was used to test whether tDCS affects the ability to inhibit responses specifically, rather than a general effect of functioning. The control task required visual discrimination of shapes similar to those presented in the SST; however, no stop signal was given (all the operational data are the same as the SST).

Main Experiment

In the first part of the main experiment, 11 participants underwent three counterbalanced tDCS conditions, which were administered at intervals of about 1 week. The tDCS conditions were Unilateral AnodalR, Unilateral CathodalR, and Sham.

In *Unilateral AnodalR*, the anode electrode was placed over the rIFG, and the cathode electrode was placed over the contralateral orbito-frontal cortex.

In *Unilateral CathodalR*, the cathode electrode was placed over the rIFG, and the anode electrode was placed over the contralateral orbito-frontal cortex.

We used the orbito-frontal cortex for the reference electrode relying on Swick et al. (2008), who reported that patients with orbito-frontal cortex lesions showed intact performance in a response inhibition in the go/no-go task.

In *Sham*, the electrodes were placed at the same position as the Unilateral AnodalR stimulation; however, the current intensity was turned off automatically after 30 sec. Therefore, during sham stimulation, the subjects felt the initial itching sensation in the beginning but received no current for the rest of the stimulation period (Fecteau, Knoch, et al., 2007).

After the completion of the three counterbalanced sessions of the main experiments, we recruited the original subjects to complete two more stimulation session: Bilateral AnodalR/CathodalL and Bilateral CathodalR/AnodalL.

In *Bilateral AnodalR/CathodalL*, the anode electrode was placed over the rIFG, and the cathode electrode was placed over the lIFG.

In *Bilateral CathodalR/AnodalL*, the cathode electrode was placed over the rIFG, and the anode electrode was placed over the lIFG.

Localization was established using 10–20 EEG system, of which the lIFG was identified as the crossing point between T3-Fz and F7-Cz (Monti et al., 2008) and the rIFG was identified as the crossing point between T4-Fz and F8-Cz. Left orbito-frontal cortex electrode was positioned above the left eyebrow.

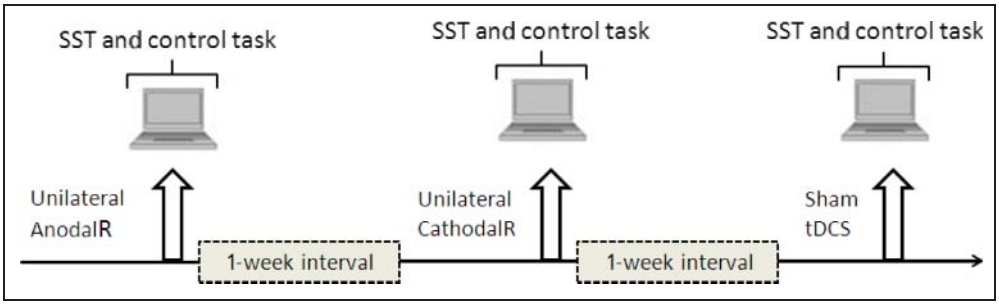

Figure 1. Illustration of the main part of the experimental procedure.

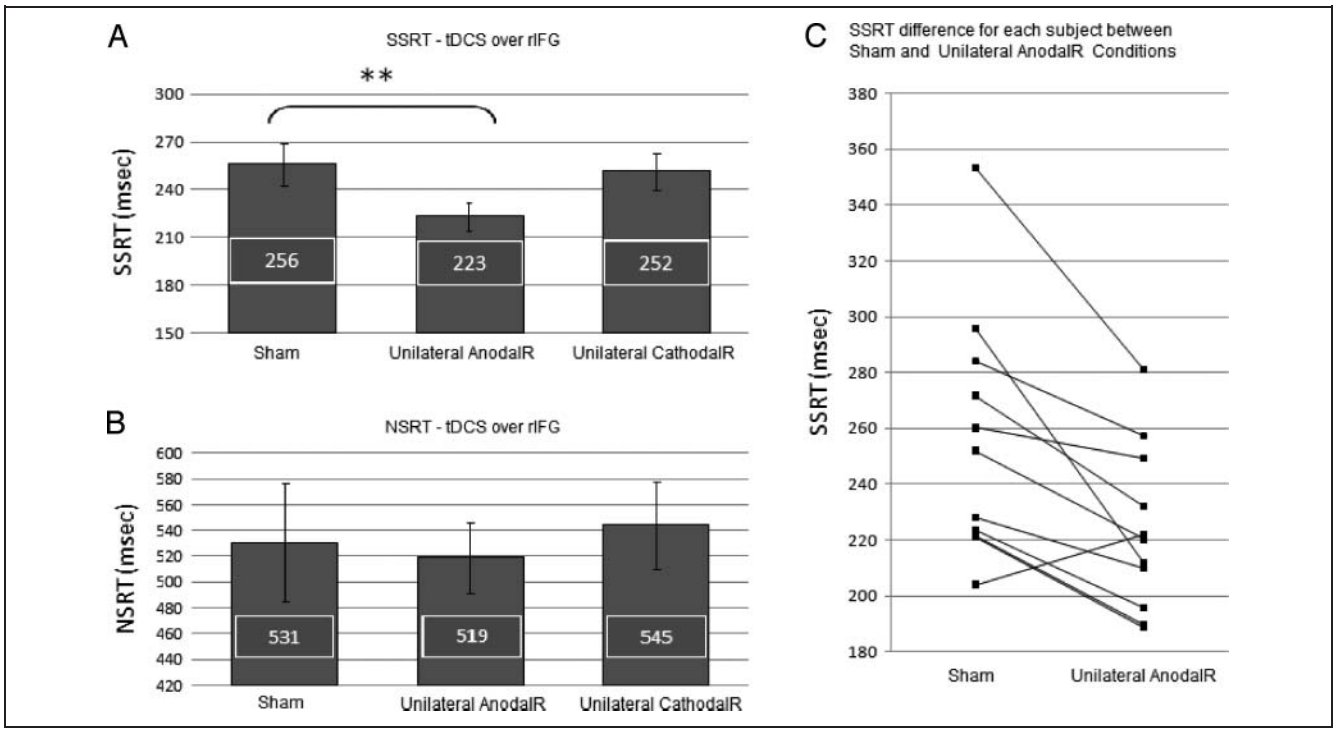

Figure 2. Mean (*SEM*) SSRT and NSRT values for the two unilateral conditions and Sham. (A) Comparison between unilateral simulation conditions (Unilateral AnodalR, Unilateral CathodalR, Sham) of the mean SSRT for 11 subjects. Unilateral AnodalR differed significantly from Sham condition. (B) Comparison between unilateral stimulation conditions of the mean NSRT for 11 subjects. This nonsignificant effect of tDCS on general RT indicates Unilateral AnodalR tDCS effect was specific to response inhibition rather than causing a general cognitive improvement. (C) The improved inhibition control (SSRT) in the Unilateral AnodalR stimulation compared with Sham in the SST plotted for each subject. Shorter SSRT indicates better ability to inhibit responses, which was found in 10 of the 11 subjects. Only one subject showed the opposite pattern of SSRT, without tDCS-generated improvement; however, because he had the best performance in the Sham condition, this might be due to a ceiling effect.

Control Experiment

In a control experiment, 11 subjects, none of whom participated in the main experiment, were tested following anodal and sham tDCS over the rAG. Similar to the main experiment, stimulation sessions were conducted 1 week apart and were counterbalanced.

In *Anodal rAG*, the anode electrode was placed over the rAG, and the cathode electrode was placed over the contralateral orbito-frontal cortex.

In *Sham*, tDCS was turned off automatically after 30 sec (the electrodes were placed at the same position as the Anodal rAG stimulation).

The control site, the rAG, was marked over P4 (Fuggetta, Pavone, Walsh, Kiss, & Eimer, 2006).

RESULTS

Inhibition Measurement

We used a tracking procedure that enabled us to find the temporal threshold interval required for successful inhibition in about 50% of the trials (SSD), which we relied on in calculating the SSRT, which reflects the covert latency of the stop process and calculated by subtracting the mean SSD from the mean RT in the go trials (trials with no stop signal; NSRT). Shorter SSRT represents better inhibition abilities.

A repeated measures ANOVA for SSRT in the three unilateral tDCS conditions revealed a significant stimulation Effect ($F(2, 8) = 7.53$, $p = .012$), a subsequent post hoc comparison revealed that only the Unilateral AnodalR condition significantly differed from sham ($t(10) = 3.92$, $p = .003$, Bonferroni correction; Figure 2A). The same stimulation protocol with these subjects did not generate a significant effect either for Response time in the go trials of the SST ($F(2, 8) = .93$, $p = .430$; Figure 2B) or for response time in the control task ($F(2, 8) = 1.01$, $p = .407$). Subjects completed the SST in 5.33 ± 0.07 min (range = 5.27–5.48) and the control task in 5.14 ± 0.37 min (range = 4.22–5.41; the two durations did not significantly differ; $t(10) = 1.63$, $p = .14$). The significant anodal effect in the SST was found for 10 of the 11 subjects (χ^2 (1) = 7.36, $p < .01$; Figure 2C), and the mean improvement in SSRT was about 13%. Cohen's d, which was calculated as mean sham SSRT minus mean unilateral AnodalR SSRT divided by pooled *SD*s, was 0.81.

Regional Selectivity

To verify regional selectivity of the stimulation, effects over rIFG were compared with those over a control region, rAG

using a mixed design analysis with SSRT as a dependent variable, stimulation condition (Anodal vs. Sham) as a within-subject variable, and a stimulation site (rIFG vs. rAG) as a between-subject variable. This analysis yielded a significant Condition × Site interaction ($F(1, 20) = 11.87, p = .003$): Although in the rIFG stimulation condition there was a significant improvement of 32.5 msec in the SSRT ($t(10) = 3.92, p = .003$) for the Unilateral AnodalR condition compared with Sham condition (Figure 2A), there was no significant difference between SSRT under Anodal (SSRT = 251 ± 45 msec) versus Sham (SSRT = 227 ± 40 msec) for rAG with, if anything, a tendency toward worsening of response (diff = +24, $t(10) = 1.69, p = .12$). We assume the differences between Sham stimulation over rIFG to the Sham stimulation over rAG are because of random selection differences.

Bilateral Stimulation

Repeated measures for SSRT in the five tDCS conditions (Unilateral AnodalR, Unilateral CathodalR, Bilateral AnodalR/CathodalL, Bilateral CathodalR/AnodalL, and Sham) yielded near-significant results ($F(4, 6) = 3.42, p = .075$). The near-significant results and their directions imply there might be a trend to suggest the involvement of lIFG as well (Figure 3). It is important to note that the additional two bilateral conditions were applied always at the end of the three main stimulation conditions; therefore, direct comparisons of all stimulation conditions should be interpreted with caution as results might reflect session order effects.

Assuming that anodal tDCS enhances cortical excitability and cathodal tDCS inhibits cortical excitability (Nitsche & Paulus, 2000), note that when only the rIFG was facilitated (Unilateral AnodalR), subjects showed reduced levels of SSRT (mean = 223) compared with the Bilateral AnodalR/CathodalL condition (mean = 230) of which the rIFG was facilitated and the lIFG was inhibited. In addition, when only the rIFG was inhibited (Unilateral CathodalR), subjects showed increased levels of SSRT (mean = 252) compared with the Bilateral CathodalR/AnodalL condition (mean = 237) of which the rIFG was inhibited and the lIFG was facilitated.

DISCUSSION

Response inhibition is a critical component of cognitive control in both normal and pathological conditions (Miller & Cohen, 2001; Barkley, 1997). Response inhibition may be disrupted by lesions of the rIFG (Aron et al., 2003) or by local application of disruptive stimulation techniques over IFG such as TMS (Verbruggen et al., 2010; Chambers et al., 2006). tDCS is a more recently developed brain stimulation technique that has the ability to facilitate cortical function when applied anodally over focal brain regions. The present study is the first to demonstrate a significant beneficial effect of anodal tDCS applied over rIFG on response inhibition as assessed by the SST. As such, the study has implications for both functional anatomy of cognitive control processes, in general, and for development of new treatments for pathological cognitive control conditions, in particular.

In the present study, we utilized the SST, a well-established task for response inhibition (Logan & Cowan, 1984). The SST is widely used, although there are some reported limitations of this task such as poor ability to measure interference control (Barkley, 1997). In the SST, response inhibition is captured by SSRT, which represents latency of effective stop signals relative response latency in the absence of a stop signal (NSRT). The SSRT measure successfully distinguished between people with ADHD and controls (Liotti et al., 2005).

As per our a priori hypothesis, we demonstrated that anodal stimulation applied over the rIFG led to significant reduction in SSRT (Figure 2A) but had no effect on either NSRT in the SST (Figure 2B) or on response time in a control task that used SST stimuli but did not employ

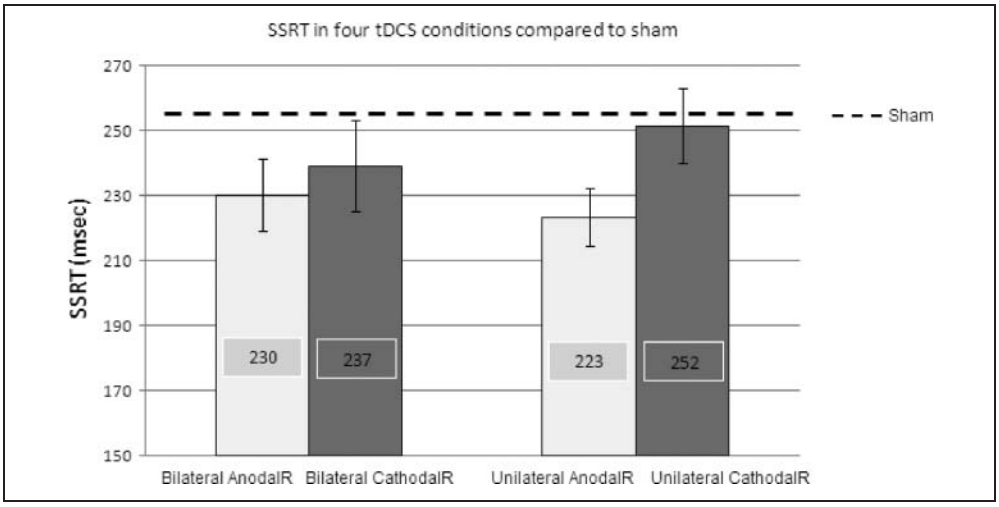

Figure 3. Mean (*SEM*) SSRT values for five stimulation conditions: two bilateral, two unilateral, and sham (dashed line).

the response inhibition task. In addition, stimulation over rAG, an area known to be without involvement in the SST (Chambers et al., 2006), did not affect response inhibition, demonstrating regional selectivity of the effect. On a single-subject level, 10 of the 11 subjects had shorter SSRTs during anodal compared with sham stimulation. Across subjects, anodal results were highly significant ($p < .001$) relative to sham stimulation and were of moderately large effect size. Thus, these results both support theories of brain mechanisms underlying response inhibition and provide a potential method for behavioral modification. The study adds to a growing list of cognitive control measures that may be influenced with focal tDCS stimulation (Kang et al., 2009; Beeli, Casutt, et al., 2008; Beeli, Koeneke, et al., 2008; Fecteau, Knoch, et al., 2007; Fecteau, Pascual-Leone, et al., 2007) but is the first to specifically target rIFG.

The results suggest that stimulation of rIFG generates significant changes in response inhibition in an easy and painless protocol. This is not to say that the rIFG is exclusively involved in response inhibition; it is part of a wider network of regions, for example, ACC (Garavan, Ross, Murphy, Roche, & Stein, 2002; Kiehl et al., 2000), and other cortical as well as subcortical regions (Aron & Poldrack, 2006; Li et al., 2006).

In addition to assessing effects of unilateral tDCS over rIFG, the present study also evaluated recent suggestions that lIFG may contribute along with rIFG to response inhibition. Although most evidence to date links mainly the rIFG to response inhibition (Verbruggen et al., 2010; Li et al., 2008; Chambers et al., 2006; Aron et al., 2003), several studies have suggested a potential additional role of lIFG (Swick et al., 2008; Bunge et al., 2002) to response inhibition.

In the present study, bilateral stimulations were applied by passing current between left and right infero-lateral prefrontal scalp regions in both anodal and cathodal directions. This produces opposite polarity stimulation of rIFG and lIFG as current flows lateral-medial on one side while flowing medial-lateral in the opposite hemisphere and is possible by using a single stimulator. An alternative approach would have been to use bilateral anodal or cathodal stimulation linked to a common midline frontal electrode, which would have produced same polarity stimulation of rIFG and lIFG. Such an approach, however, requires paired stimulators and was not performed. Although we only find a near-significant effect for bilateral conditions, we did see a trend, which may imply lIFG is also involved in response inhibition; on the basis of the assumption that anodal tDCS enhances cortical excitability and cathodal tDCS inhibits cortical excitability (Nitsche & Paulus, 2000), we found that when only the rIFG was facilitated (Unilateral AnodalR), subjects showed reduced levels of SSRT compared with the Bilateral AnodalR/CathodalL condition of which the rIFG was facilitated and the lIFG was inhibited. This finding may suggest that inhibition of the lIFG disrupts the ability to inhibit response. In addition, when only the rIFG was inhibited (Unilateral CathodalR), subjects showed increased levels of SSRT compared with the Bilateral CathodalR/AnodalL condition of which the rIFG was inhibited and the lIFG was facilitated. The most parsimonious account for this pattern is that both the rIFG and lIFG are involved in response inhibition; however, future studies should investigate the lIFG involvement in response inhibition, for example, by applying unilateral anodal stimulation over lIFG.

In general, although cathodal stimulation has been shown to be effective in worsening motor performance when applied over motor cortex, its ability to impair performance of cognitive tasks has been less consistent. In fact, most of the literature involving tDCS with cognitive functions and nonmotor cortical areas did not find a significant effect for cathodal tDCS (Floel, Rosser, Michka, Knecht, & Breitenstein, 2008; Priori et al., 2008; Iyer et al., 2005). In particular, some studies actually found an excitation rather than an inhibition effect for cathodal tDCS (Sparing et al., 2009; Monti et al., 2008; Marshall, Molle, Siebner, & Born, 2005), similar to the patterns reported here. This may reflect issues with geometry of the electrical field (Priori et al., 2008) but, alternatively, could indicate greater bilateral interaction in cognitive regions and ability for contralateral compensation. Such compensation is not possible in motor regions where cortical motor projections are almost always contralateral but may be possible in cognitive control regions from which outflow is typically bilateral.

In conclusion, this is the first demonstration of the utility of tDCS over rIFG to enhance cognitive control, in general, and response inhibition, in particular. In addition to supporting a specific role for rIFG in response inhibition, this study could constitute a critical step toward the use of tDCS as a therapeutic tool in the treatment of impairments in cognitive control in conditions such as ADHD or schizophrenia. Future studies in pathological conditions, as well as normative populations, are warranted, especially to investigate the long lasting after effect of tDCS.

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Reprint requests should be sent to Michal Lavidor, Department of Psychology, Bar Ilan University, Ramat Gan, Israel, or via e-mail: Michal.lavidor@gmail.com.

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