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Modulating inhibitory control with direct current stimulation of the superior medial frontal cortex

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ABSTRACT

The executive control of voluntary action involves not only choosing from a range of possible actions but also the inhibition of responses as circumstances demand. Recent studies have demonstrated that many clinical populations, such as people with attention-deficit hyperactivity disorder, exhibit difficulties in inhibitory control. One prefrontal area that has been particularly associated with inhibitory control is the pre-supplementary motor area (Pre-SMA). Here we applied non-invasive transcranial direct current stimulation (tDCS) over Pre-SMA to test its role in this behavior. tDCS allows for current to be applied in two directions to selectively excite or suppress the neural activity of Pre-SMA. Our results showed that anodal tDCS *improved* efficiency of inhibitory control. Conversely, cathodal tDCS showed a tendency towards *impaired* inhibitory control. To our knowledge, this is the first demonstration of non-invasive intervention tDCS altering subjects' inhibitory control. These results further our understanding of the neural bases of inhibitory control and suggest a possible therapeutic intervention method for clinical populations.

Introduction

Efficient and timely control over behavioral urges is vital to the executive control of voluntary action, and inhibitory control in the context of prepotent actions is critical in a variety of scenarios. Oft mentioned examples of such behavior include driving towards a crossroads, where the choice of executing or withholding an action (acceleration or braking) must be made in a very brief period of time. This behavior can be investigated experimentally using stop-signal tasks that have been shown to reliably estimate the response time of an internally generated act of control (Logan, 1994).

Stop-signal task

The stop-signal task is widely used to investigate the processes of motor inhibition (Boucher et al., 2007; Chen et al., 2008, 2009; Chao et al., 2009; Li et al., 2006a, 2008a; Logan et al., 1997; Logan and Cowan, 1984; Logan et al., 1984; Schachar et al., 1993; Schachar et al., 1995; Schachar and Logan, 1990). This task consists of 'go' and 'stop' trials. In the go trials, subjects are required to respond to a stimulus as soon as possible. In the stop trials, an additional stop signal is displayed to instruct the subject to withhold response. The interval between the go and stop signal is known as the stop signal delay (SSD), which is estimated by considering the distribution of go reaction times and the probability of responding correctly in those trials with a stop signal. This estimation effectively predicts the time required to inhibit a planned response, called the stop-signal reaction time (SSRT).

The neural correlates of inhibitory control

When performing a manual inhibitory control task, the signal from the retina is projected from the visual areas to brain regions that are related to inhibitory control, such as frontal eye fields (FEF, Curtis et al., 2005; Hanes and Schall, 1996; Muggleton et al., 2010), supplementary eye fields (SEF, Isoda and Hikosaka, 2007; Stuphorn et al., 2000; Stuphorn and Schall, 2006), and anterior cingulate cortex (ACC, Chevrier et al., 2007; Ito et al., 2003). Information converges at the primary motor cortex (M1), which executes motor commands by transmitting them to the spinal cord and muscles. M1 is therefore considered to be a part of the 'final common path' for voluntary action (Sherrington, 1906). More important, M1 also receives input from the pre-supplementary motor area (Pre-SMA), which is involved in initiating self-paced actions (Deiber et al., 1999; Jenkins et al., 2000)

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and mediating motor inhibition that is required for voluntary muscle relaxation (Toma et al., 1999). Neuroimaging studies have shown stronger activation of the Pre-SMA for self-paced actions than for externally triggered actions. Such a function has been confirmed by patient studies, where patients with Pre-SMA lesions showed primed speeded motor responses regardless of the relevance of the primes to the targets (Sumner et al., 2007). In contrast, speeded responses were only observed when the mask was compatible with the targets in a healthy control group (Eimer and Schlaghecken, 1998). This suggests that a normally functioning Pre-SMA should suppress automatic responses to environmental stimulation, and those patients with Pre-SMA damage are therefore hyper-responsive. Indeed, Ball et al. (1999) found that Pre-SMA decreases its activity level in response to activation of the primary motor cortex before voluntary movements (Ball et al., 1999). In the context of the stop-signal task, Li et al. (2006a) systematically investigated the neural correlates of motor inhibition with the stop-signal task and found a linear correlation between the BOLD activation of Pre-SMA and SSRTs. They found that greater activation in Pre-SMA led to shorter SSRTs, suggesting an efficient stop-signal processing. In contrast, IFG did not show this association (Chao et al., 2009), although it is also considered as the cortical site for inhibitory motor control (Aron and Poldrack, 2006; Rubia et al., 2003; Rubia et al., 2005; Verbruggen and Logan, 2008). These results suggest that Pre-SMA mediates motor inhibition (Aron et al., 2007b; Aron and Poldrack, 2006; Kenner et al., 2010; Nachev et al., 2005). Recently, Chen et al. (2009) used TMS to probe the functional role of Pre-SMA in the stop-signal paradigm. They observed elevated SSRTs and increased error rates when TMS was delivered over Pre-SMA. Their results implied that Pre-SMA plays a direct and causal role in response inhibition and response selection.

Modulation of neural activity using tDCS

Although elevated SSRTs and increased error rates were observed as a consequence of TMS stimulation of Pre-SMA, it is unclear whether the underlying neurons were facilitated or inhibited by TMS (Chen et al., 2009). Thus, the present study employed transcranial direct current stimulation (tDCS) to disambiguate the role of Pre-SMA and its vicinity (for simplicity, Pre-SMA will be used to denote Pre-SMA and its vicinity throughout the text) in the stop-signal task. tDCS is a technique that can either facilitate or suppress cortical excitability by using anodal or cathodal electrical stimulation. This modulation was first introduced in animal studies, where subthreshold DC stimulation increased cerebral excitability beneath anodal stimulation by depolarizing cell membranes and increasing firing rates, while cathodal stimulation resulted in the opposite effect by hyperpolarization and decreasing firing rates (Bindman et al., 1964; Creutzfeldt et al., 1962; Nitsche et al., 2009b; Nitsche et al., 2009b; Purpura and McMurtry, 1965; Scholfield, 1990). Neural excitability has also been observed using functional near infrared optical brain imaging (fNIR) with increasing oxyhemoglobin (HbO_2), indicating extra oxygen delivery and a raised CBF signal after anodal stimulation (Merzagora et al., 2010). Nitsche and Paulus (2001) also found consistent results by measuring human motor-evoked potentials (MEP). Higher MEPs were elicited after anodal stimulation than cathodal stimulation, indicating that neural excitability in the primary motor cortex was varied by tDCS. Therefore, the current study used anodal and cathodal tDCS to respectively facilitate or inhibit neural activity in Pre-SMA in order to investigate the functional role of the Pre-SMA in motor inhibition.

Materials and methods

Participants

Fourteen students (aged 20 to 26 years, mean 22.1, 8 males, 6 females and all right handed) from the National Central University took part in the Pre-SMA tDCS experiment. An additional group of fourteen volunteers (aged 18 to 27 years, mean 21.79, 8 males and 6 females) participated in the left primary motor cortex tDCS experiments (M1 tDCS) that served as a control condition. All gave informed consent prior to participation. The experiments were approved by local ethical committee.

Apparatus

Testing took place in a sound attenuated room. Stimuli were presented on a 19-inch CRT screen using a video resolution of 800×600 pixels and a vertical refresh rate of 100 Hz. Subjects sat 70 cm in front of the screen, which was positioned at an eye level. The task was programmed using E-prime running on a Pentium IV PC, which controlled the presentation of the stimuli as well as recording response information. tDCS was delivered with a Magstim Eldith DC-stimulator and a pair of electrodes housed in 4×4 cm saline-soaked sponge coverings. The center of the stimulation electrode was placed over the target site (Pre-SMA or M1). The reference electrode was placed over the left cheek of the subject. In the tDCS conditions the current was applied for 10 min with an intensity of 1.5 mA.

Procedure

Stop-signal task

In the stop-signal task, the stop signal delay (SSD) is the most critical independent variable and it is manipulated by adjusting the time between the onset of the go stimulus and the stop signal. The noncancelled rate denotes the error rate when the stop signal is presented but subjects fail to inhibit their responses. The outcome of the race between the go and the stop processes is reflected by the inhibition function, which describes the probability of responding for a given a stop signal delay in accordance with the race model of Logan and Cowan (1984). The stop signal reaction time (SSRT) represents the latency of the stop process and it is another dependent variable in the task. The SSRT can be estimated from the observed distribution of RTs in no-stop signal trials in combination with the inhibition function (Logan, 1994). In the current study, SSRTs for each SSD were estimated using the integration method, and one summary SSRT was calculated by averaging the three SSRTs acquired from the three SSDs in our experiments (Logan, 1994; Band et al., 2003).

In the present study, each trial of the stop-signal task began with a 500 ms central fixation dot. Following the offset of this dot, a white target dot was presented to the left or right of the fixation at 9° eccentricity on the horizontal meridian (see Fig. 1). On 75% of the trials (go trials) subjects were required to make a key-press response indicating whether the dot was presented on the left or right with their left and right index fingers, respectively. On 25% of the trials (stop trials), the central fixation dot reappeared and served as a signal to withhold responses to the peripheral target.

Baseline parameters

In order to reduce the number of trials in the formal experiments, each subject's Mean RT for go trials and critical SSD were acquired with three pre-tDCS sessions (see Fig. 2). Every subject started with a session of the choice RT task (50 trials). Subjects were asked to respond to a target which appeared in the left or the right visual field with their corresponding index fingers. They were encouraged to make the responses correctly and as quickly as possible. The purpose of this session was to obtain each subject's mean go RT and standard deviation in the absence of stop signals. Each subject's mean go RTs plus two standard deviations was set as his/her time limit for go RT trials in the subsequent sessions. If the subject did not respond quicker than this time restriction on a go trial, the trial was counted as a non-responding error and a warning beep would sound. This procedure has been demonstrated to effectively limit the strategy of

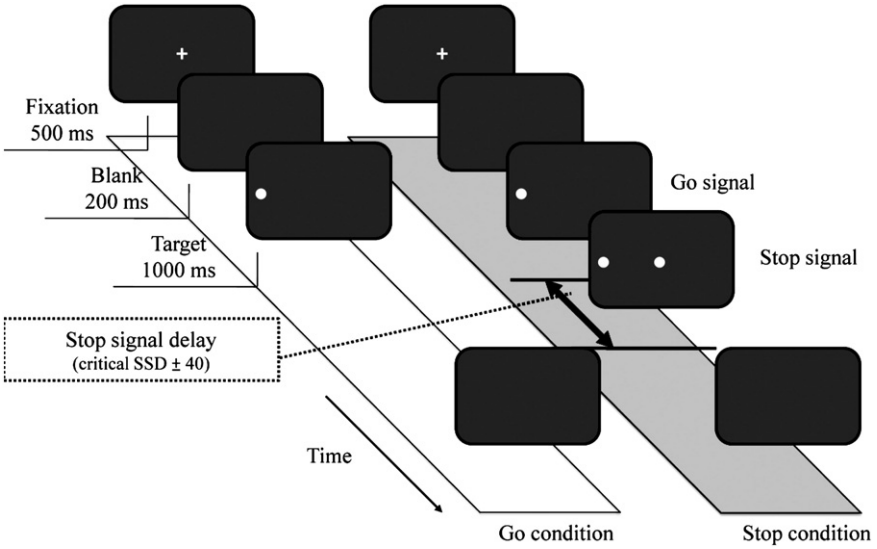

Fig. 1. Stop-signal task procedure. The stop signal was presented on 25% of trials.

intentionally slow responses that participants sometimes use to avoid errors (Chen et al., 2008, 2009; Muggleton et al., 2010).

A practice session of 24 go trials and 8 stop trials was conducted following the choice RT session. The SSD was fixed at 170 ms in the stop trials in this session. The experimental trials were identical in structure apart from the SSD, as were the subsequent formal TMS session trials. After subjects performed the go time-restricted session and the practice session, they were required to carry out a critical SSD session (see Fig. 2). The purpose of this session was to estimate every subject's SSD at which their noncancelled rate would be around 50%. This session also helped decrease the number of trials in the formal tDCS sessions. A tracking procedure was used to acquire the critical SSD. According to the results of our pilot experiments, the initial SSD was set at 170 ms. The SSD of each subject was adjusted until the subject's accuracy on stop-trials reached 50%. The program monitored subjects' performance in blocks of 32 trials. If the subject's noncancelled rate was lower than 37.5%, the SSD was increased by 40 ms. Conversely, if the noncancelled rate was higher than 62.5%, the SSD was decreased by 40 ms. A critical SSD could subsequently be computed that represented the time delay required for the subject to achieve a 50% success rate in withholding a response in the stop trials. Each subject's critical SSD was determined when their noncancelled rate was within 37.5%–62.5% for two consecutive blocks.

tDCS blocks

Subjects were randomly assigned to one of the two tDCS groups: Pre-SMA tDCS or the M1 tDCS group. After the pre-tDCS sessions (i.e. acquisition of baseline parameters: Go RT, practice and critical sessions), subjects received tDCS over one of the target sites (i.e.: Pre-SMA or M1) according to their group. Subjects then carried out the formal stop signal task (see Fig. 2). The main bodies of the Pre-SMA tDCS and M1 tDCS experiments consisted of three conditions; two of these involved tDCS (anodal and cathodal stimulations) and one with no tDCS, which served as one of the control conditions. In other words, each subject from both groups received three conditions (i.e. anodal, cathodal, and no-tDCS). The time interval between each condition was least at 24 h. Three SSDs were presented to each subject based on their individual critical SSDs: critical SSD, 40 ms less than the critical SSD, and 40 ms more than the critical SSD. For example, if a

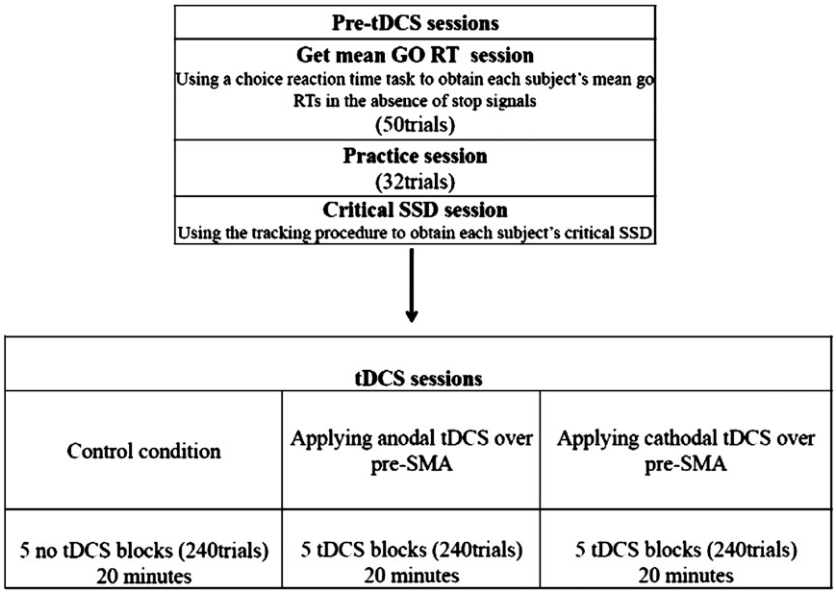

Fig. 2. The procedure for the experimental sessions.

subject's critical SSD was 130 ms (acquired in the critical SSD session), the other two conditions were 90 ms and 170 ms. Five experimental blocks were presented for each condition, and each block included 48 trials, lasting approximately 4 min; the occurrence and order of the three stop signal presentation conditions were randomized within each block. For each tDCS site an ABBA design was used to control for sequence effects. Subjects only received one tDCS session on the first day and received the second tDCS session on the next day. Subjects were randomly assigned to receive either anodal or cathodal tDCS for their first tDCS session (see Fig. 2).

tDCS parameters and site localization

Since tDCS requires two electrodes that simultaneously stimulate one brain region and inhibit another, the left cheek was selected as the region for the 'reference' electrode, based on previous reports (Nitsche and Paulus, 2001; Nitsche et al., 2003a; Nitsche et al., 2003b). Three conditions were analyzed: Pre-SMA anodal/left cheek cathodal, left cheek anodal/Pre-SMA cathodal, and a control group with no tDCS stimulation. The stimulation site for the Pre-SMA was localized with the EEG 10-20 system, with the center of the tDCS electrode placed over the site of Fz. The accuracy of this localization method was confirmed in 6 subjects using magnetic resonance image (MRI)-guided frameless stereotaxy system (Brainsight, Rogue Research, Montreal, Canada). Briefly, identification of the Pre-SMA site on the structural scans was achieved by the following procedure. Individual MRIs were normalized against a standard template using the FSL software package (FMRIB, Oxford). This produced a matrix of values describing the transformation from the structural scan to the normalized brain. This was then reverse-applied to the coordinates of Pre-SMA (−4, 32, 51; Li et al., 2006a; see Fig. 3) to obtain the location of the site in the original structural scan for each subject. The location was then marked on the MRI scan in the Brainsight system.

After the Pre-SMA location had been identified in each subject's structural MRI scan, a Polaris infra-red tracking system (Northern Digital, Waterloo, Canada) was then used to co-register the positions of anatomical landmarks on each subject's head, which were also visible on each MRI scan (bridge of nose, nose tip, left and right intra-tragal notches). Another infra-red tracker was placed on a pointer to identify the scalp point over the identified Pre-SMA site.

In addition to the no-tDCS control condition, we also applied tDCS over the primary motor cortex (M1) to better control for physical sensations, if any, that may be associated with tDCS. M1 has been investigated in many tDCS studies (Nitsche and Paulus, 2000; Nitsche et al., 2003a; Nitsche et al., 2003b; Reis et al., 2009) and tDCS has been shown to affect the motor-evoked potential (MEP) from M1, MEP is a sensitive index to measure the tDCS modulation of M1. Nitsche et al. (2003a) found that M1 tDCS affects reaction times in an implicit motor learning task. However, the current study focuses on inhibitory control and mostly utilizes behavioral indexes (i.e. go RT, SSRT and SSD), therefore a weak functional influence of M1 on inhibitory control is expected, except for any non-experimental factors such as fatigue (Gandiga et al., 2006), nor any effect from the current flowing through the brain (Priori et al., 2009) that the M1 tDCS condition acts as a control for. For the localization of the primary motor cortex, we used transcranial magnetic stimulation (TMS) to functionally localize each subject's M1. Based on previous studies (Wassermann et al., 1996; Kozel et al., 2000), the initial left M1 was marked as 5 cm left relative to the vertex. After we marked the left M1, a figure-of-eight coil was used to stimulate that point initially. The experimenter then moved the coil around that point to search for the 'hot spot' which was defined when the largest visible twitch in the right hand thumb and index finger was observed. In the tDCS conditions, the center of the tDCS electrode was placed over the target site (Pre-SMA or M1). The reference electrode was placed over left cheek of the subject. The current was applied for 10 min with an intensity of 1.5 mA. Based on the safety criteria proposed by Nitsche et al. (2003c), both current density and stimulation strength are important in determining the safety limits of stimulation. In the present study, both indexes are below the safety criterion. The criterion for current densities is 25 mA/cm^2 (McCreery et al., 1990). In our protocol, the current density was 0.0937 mA/cm^2, well below the criterion. With regard to stimulation strength, tissue damage has been detected at a minimum total charge of 216 C/cm^2 (Yuen et al., 1981). The total charge in our current experiment was 0.0056 C/cm^2, which is also below the safety criterion. Therefore, the parameters in the present study were in accordance with the literature and safe for the participants.

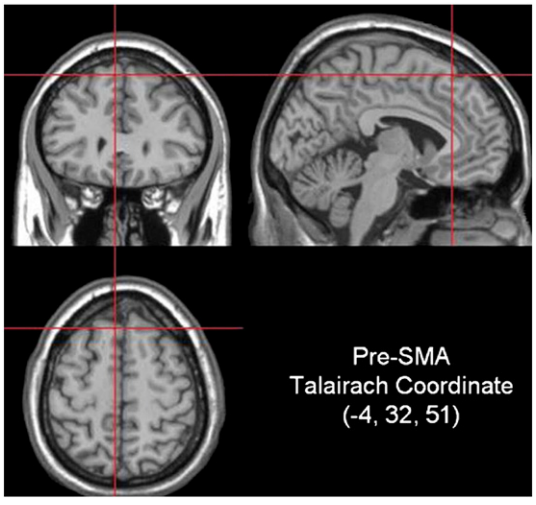

Fig. 3. The pre-SMA stimulation site shown in one participant. The location corresponding to the standard coordinates of −4, 32, 51.

Results

Results summary

The primary finding was that noncancelled response rates were significantly modulated by tDCS delivered over Pre-SMA. Specifically, these rates were reduced by anodal stimulation and increased by cathodal stimulation. No effects on go RT, noncancelled RT or SSRT were observed. Below we detail the results for all conditions.

Pre-SMA tDCS condition

Repeated measures analysis of variance (ANOVA) was carried out for correct go RT, noncancelled go RT, noncancelled rate and SSRT with factors of Pre-SMA tDCS condition (anode, cathode and no tDCS), and response hand. As there was no significant effect of response hand ($t(13) = 1.259$ and $P > 0.05$) (see Supplementary Information A for a comparison of the performance of the two hands), data were collapsed for this factor and the analysis was repeated with it omitted. Since many tDCS studies have demonstrated that anodal tDCS has excitatory effects and cathodal tDCS has inhibitory effects (e.g.: Nitsche et al., 2003a; Nitsche et al., 2003b; Fecteau et al., 2007a; Fecteau et al., 2007b; Hecht et al., 2010), we use one tailed corrected t-tests in the post hoc analysis as specified by the *a priori* directionally-specific predictions.

Go RTs (correct responses)

There were no significant effects of tDCS condition on go RTs (Anode tDCS: 321.41 ± 15.31, Cathode tDCS: 317.4 ± 16.55, no tDCS: 323.77 ± 13.24, $F_{(2,6)} = 0.161$, MSE = 904.192, and $P > 0.05$).

Go RTs (noncancelled responses)

To reiterate, noncancelled go RTs are mean go reaction times when responses were not inhibited appropriately. There was no significant

effect of tDCS on go RTs for these responses (Anode tDCS: 284.37 ± 15.24, Cathode tDCS: 288.55 ± 13.68, no tDCS: 294.94 ± 8.82, $F_{(2,26)} = 0.383$ and $P > 0.05$).

Noncancelled rates

Fig. 4 (a) shows the noncancelled rates. Significant differences were observed among the noncancelled rates for the three tDCS conditions ($F_{(2,26)} = 4.864$ and $P < 0.05$). The mean noncancelled rate in the anodal tDCS condition (0.4 ± 0.04) was significantly lower than the cathodal tDCS condition (0.53 ± 0.04, $t_{(13)} = -3.722$ and $P < 0.01$) and also lower than in the no tDCS condition (0.48 ± 0.05, $t_{(13)} = -2.018$ and $P < 0.05$).

Inhibition function

Fig. 4 (b) shows the inhibition function for the different tDCS conditions. The noncancelled rate was significantly increased with the increment of SSDs ($F_{(2,26)} = 145.306$ and $P < 0.01$). The main effect of the tDCS condition was significant ($F_{(2,26)} = 4.831$ and $P < 0.05$). *Post-hoc* analyses showed that anodal tDCS significantly decreased the noncancelled rate in comparison to cathodal tDCS ($t_{(13)} = -3.722$ and $P < 0.01$) and no tDCS ($t_{(13)} = -2.018$ and $P < 0.05$) conditions. The interaction between the SSD factor and the tDCS conditions factor was not significant ($F_{(4,44)} = 0.557$ and $P > 0.05$).

Stop signal reaction times

Fig. 4 (c) shows the mean SSRTs for the different tDCS conditions. There were no significant differences across the different conditions ($F_{(2,26)} = 0.562$ and $P > 0.05$). The SSRT from the anodal tDCS condition (176.07 ± 8.06 ms) was not significantly shorter than SSRT from the cathodal tDCS condition (177.518 ± 7.71, $t_{(13)} = -.383$ and $P > 0.05$) or the no tDCS condition (180.81 ± 8.18, $t_{(13)} = -.917$, $P > 0.05$).

M1 tDCS condition

Repeated measures ANOVA was carried out for correct go RT, noncancelled go RT, noncancelled rate, and SSRT with factors of M1 tDCS condition (anode, cathode and no tDCS). Since the results of left and right responses had no difference under both tDCS and no tDCS conditions (anodal tDCS: $t(13) = 0.248$ and $p > 0.05$; cathodal tDCS: $t(13) = 1.231$ and $p > 0.05$; and no tDCS : $t(13) = 0.787$ and $p > 0.05$), data from both hands were combined for subsequent analyses.

Go RTs (correct responses)

There were no significant effects of tDCS condition on go RTs (anodal tDCS: 342.72 ± 11.594, cathodal tDCS: 327.4 ± 13.284 and no tDCS: 339.17 ± 13.725, $F_{(2,26)} = 2.048$, $P > 0.05$).

Go RTs (noncancelled responses)

There was no significant effect of tDCS on go RTs for these responses (anodal tDCS: 307.27 ± 9.03, cathodal tDCS: 296.56 ± 8.89 and no tDCS: 298.779 ± 9.028, $F_{(2,26)} = 1.386$, $P > 0.05$).

Noncancelled rates

Fig. 5 (a) shows the noncancelled rates. There were no significant effects among the noncancelled rates for the three tDCS conditions ($F_{(2,26)} = 0.585$ and $P > 0.05$).

Inhibition function

Fig. 5 (b) shows the inhibition function for the different tDCS conditions. The noncancelled rate was significantly increased with the increment of SSDs. ($F(2,26) = 104.003$ and $p < 0.001$). The main effect of tDCS condition was not significant ($F_{(2,26)} = 0.993$ and $P = 0.384$). The interaction between the SSD factor and the tDCS conditions factor was not significant ($F_{(4,52)} = 0.38$ and $P > 0.05$).

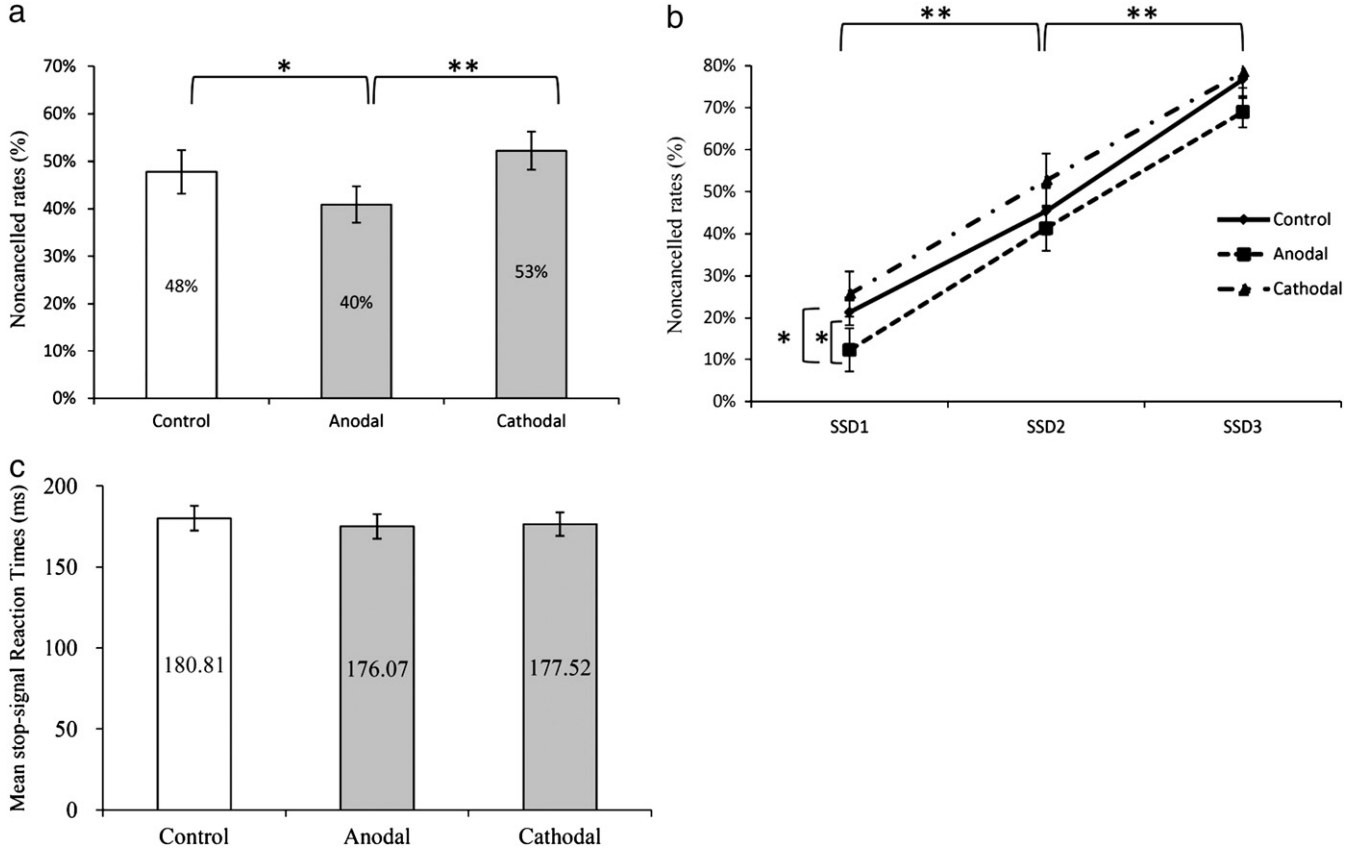

Fig. 4. Pre-SMA tDCS condition (a) Noncancelled rates for each condition (*p<0.05 and **p<0.001). (b) Inhibition functions for each SSD (**p<0.01). (c) Stop-signal reaction times for each condition. Each error bar shows the standard error of the mean.

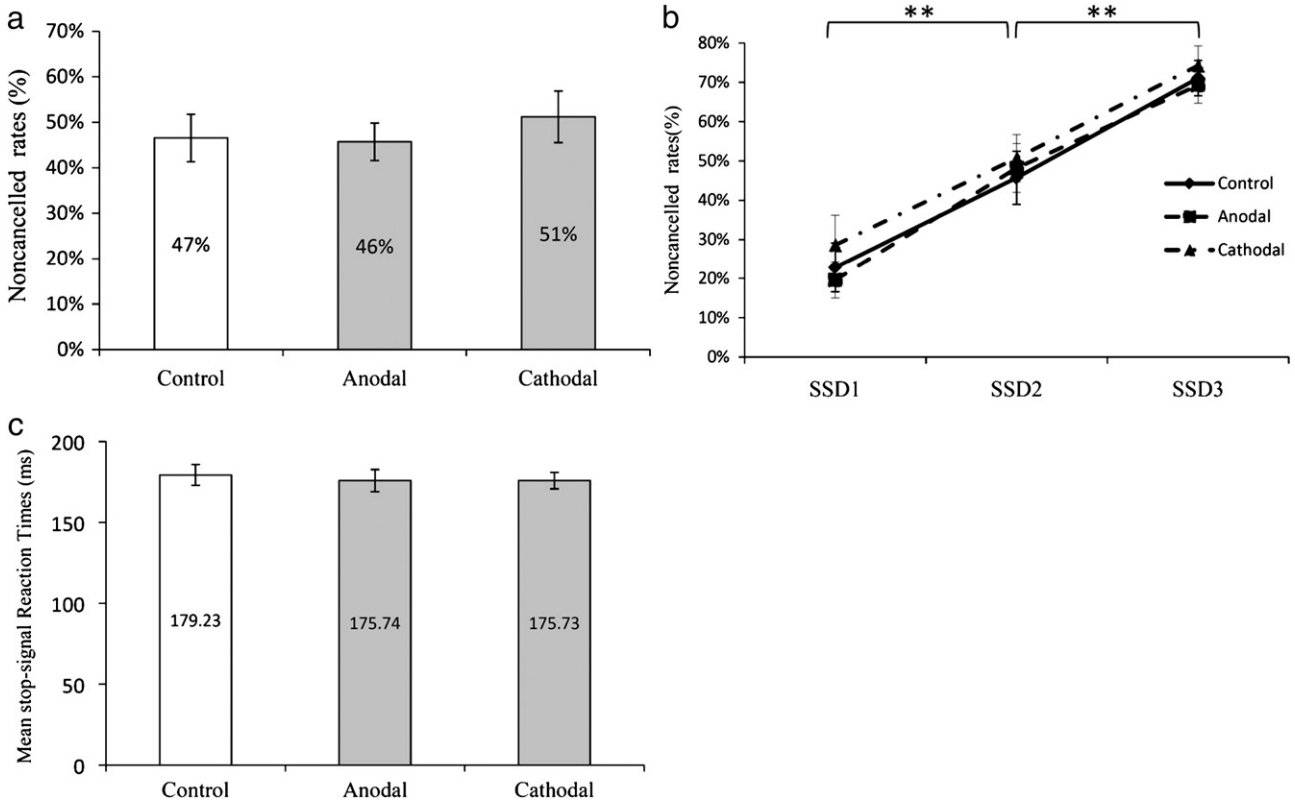

Fig. 5. M1 tDCS condition (a) Noncancelled rates for each condition. (b) Inhibition functions for each condition. (c) Stop-signal reaction times for each condition. Each error bar shows the standard error of the mean.

Stop signal reaction times

Fig. 5 (c) shows the mean SSRTs for the different tDCS conditions. There were no significant differences across different conditions ($F_{(2,26)} = 1.386$ and $P > 0.05$).

Discussion

Several studies have suggested a role for Pre-SMA in the control of voluntary action (e.g.: Li et al., 2006a; Nachev et al., 2008). A recent TMS study has also confirmed a causal role for Pre-SMA in inhibitory control (Chen et al., 2009). These investigations have shown that temporary interference with Pre-SMA activity can impair performance of inhibitory control tasks. In order to further investigate the underlying neural activities behind the critical role of the Pre-SMA in inhibitory control, the present study employed tDCS that can independently excite or inhibit Pre-SMA activity. Our hypothesis was that excitatory (anodal) tDCS over Pre-SMA would facilitate inhibitory control and that inhibitory (cathodal) tDCS would impair performance. Such effects would not only confirm the critical role of Pre-SMA in the inhibitory control network (e.g.: Miniussi et al., 2008), but, importantly, demonstrate an improvement in inhibitory control under the anodal tDCS condition. This tDCS-induced improvement may be a fruitful as an initial step towards developing clinical treatments to enhance inhibitory control.

We found that the effects of inhibitory (cathodal) tDCS replicated previous TMS findings by impairing performance on the task. The pattern was similar to TMS findings in the sense that there was marked failure to inhibit responses when a stop signal was presented (an elevated noncancelled rate). Additionally, facilitatory effects were observed as a consequence of applying excitatory (anodal) tDCS over the Pre-SMA. Decreased noncancelled rates suggested improvement in inhibiting responses when a stop signal was presented. Such improvement or decrement in noncancelled rates implied that neuronal excitability was modulated by tDCS, as many studies have suggested (Bindman et al., 1964; Creutzfeldt et al., 1962; Purpura and McMurtry, 1965; Scholfield, 1990; Nitsche et al., 2009a; Chouinard and Paus, 2010). These findings also suggest a critical role for Pre-SMA in suppressing unwanted actions and facilitating desired ones as seen in a recent microstimulaton study (Isoda and Hikosaka, 2007). Together, such effects on noncancelled rates provide direct evidence showing that the region containing Pre-SMA is important in inhibitory control.

The current study used the same paradigm as used with TMS by Chen et al. (2009) to investigate the functional role of Pre-SMA. In their study, longer SSRTs and larger noncancelled rates were observed after online Pre-SMA TMS. The current cathodal tDCS condition showed the same pattern in noncancelled rates but not in terms of effects on SSRTs. The lack of effect in SSRTs may be due to the restriction of the experimental design. Based on the current experimental design, SSRT was estimated by recruited data, such as: go RT distribution, SSD, and noncancelled rate. Each subject has three SSDs: critical SSD, 40 ms less than the critical SSD, and 40 ms more than the critical SSD. During 40 ms less than the critical SSD condition (i.e. the easiest condition to stop go response), we observed that the noncancelled rate was zero in 4 out of 14 subjects. Hence, SSRT of these 4 subjects could not be estimated under this condition. Such indirect index (i.e. SSRT) may be largely affected by other dependent variables. It might be the reason why SSRT could not represent tDCS effect. However, noncancelled rate was directly obtained by subject response. The direct index might represent tDCS effect. Therefore, the significant tDCS treatment was observed in noncancelled rate. In addition, the go RT and SSD were tested before tDCS. After the tDCS interference, the same parameters were used in formal test due to the time limitation of tDCS effect. The possibility that could not be excluded is that tDCS might change SSD. The unchanged SSD might affect the estimation of SSRT. Both accounts might explain the lack of effect of SSRT, and significant effect on noncancelled rate.

It is also possible that training induced ceiling effect, therefore, no RT modulation was observed after tDCS. The training-induced ceiling

effect activates maximum individual ability level. Each subject performed three experimental conditions that might result in significant practice effects on RT, possibly leading to no significant RT differences being observed. Another possibility is the variability between individuals. Comparing the mean SSRT from the current study with Chen et al. (2009), mean SSRT here (anodal = 176.07 ms; cathodal = 177.51; and no tDCS = 180.81) was faster than mean SSRT (Pre-SMA TMS = 210.5; vertex TMS = 193.5; and no TMS = 196.9) in Chen et al. (2009). Although no statistical index can be provided due to different sample sizes, mean SSRT may provide another potential explanation that subjects in the current study had better inhibitory control than subjects in the Chen et al. (2009) experiment. Thus, the variability between different groups of subjects may also explain why no RT modulation was observed under different tDCS conditions.

In addition, the different findings on the two dependent variables (i.e. noncancelled rates and SSRT) suggest that TMS and tDCS may result in different modulation on neurons even though both are active interference techniques. TMS may result in modulation of neuronal thresholds, or a change in synaptic efficiency, and these mechanisms are generally expressed as a form of functional plasticity or metaplasticity (Siebner and Rothwell, 2003; Siebner et al., 2009; Silvanto et al., 2007a; Silvanto et al., 2007b). In contrast, tDCS changes neuron excitability. Anodal and cathodal stimulations show polarity-specific depolarizing or hyperpolarizing effects on neuron firing rates (Bindman et al., 1964; Creutzfeldt et al., 1962; Purpura and McMurtry, 1965; Scholfield, 1990; Nitsche et al., 2009b). In addition, with regard to focality, tDCS stimulates a relatively large area (1600 mm^2) in contrast to TMS (25 mm^2) (Priori et al., 2009). Thus, there is the possibility that tDCS stimulation affected other nearby regions such as the SMA. Imaging studies have demonstrated a functional role for SMA in complex sequences of finger movements (Roland et al., 1980; Goldberg, 1985; Verwey et al., 2002; Serrien et al., 2002; Steyvers et al., 2003). However, the current experiment required only simple one-button responses, which is unlikely to be heavily dependent upon SMA functioning. Furthermore, even if tDCS did stimulate SMA in the present study, changes in RTs and accuracy would also be expected for the go condition, instead of merely affecting noncancelled rates. Thus, it seems unlikely that a lack of specificity can account for the effects on the noncancelled rates.

Previous fMRI experiments have indicated that greater Pre-SMA activity is associated with more efficient inhibitory control as indicated by shortened SSRTs (Li et al., 2006a; Chao et al., 2009). Moreover, the direct anatomical and functional connections between Pre-SMA and the basal ganglia (both caudate and STN) have been linked to a braking system for prepotent responses of the type observed in the current study (Aron et al., 2007a; Aron et al., 2007b; Aron and Poldrack., 2006; Madsen et al., 2010; Duann et al., 2009; Haggard, 2008; for a review see Nachev et al., 2008). This connection is further supported by several EEG studies which have also demonstrated activation of Pre-SMA prior to the initiation of a planned action (e.g.: Brinkman and Porter, 1979; for a review see Nachev et al., 2008; c.f.: Swann et al., 2009) and that the amplitude of the lateralized readiness potential from the primary motor cortex is correlated with the efficiency of inhibitory control (Dimoska and Johnstone, 2007). This evidence confirms a critical role for Pre-SMA within a neural network for inhibitory control in the stop-signal paradigm. It is important to note that a remote effect of tDCS on the regions neighbouring the stimulation site is also possible. This remote effect can be mediated via cortico-cortical and cortico-subcortical connections. Anodal stimulation induces more widespread increases in rCBF in remote brain regions whereas cathodal stimulation would have the opposite effect (Lang et al., 2005). Thus, although the current study confirms a critical role for Pre-SMA and its vicinity in inhibitory control, it does not mean that Pre-SMA is the only neural locus for such inhibitory processes, and should not be taken as evidence ruling out other regions such as IFG, basal ganglia, ACC, and SMA in the neural network.

Several studies have indicated that the cingulate cortex is connected to Pre-SMA and motor cortex. A simple effect of alertness and arousal might occur due to the current spread from Pre-SMA and motor cortex to cingulate cortex. If this was driving the effects seen, the same level of alertness and arousal should be reflected on all dependent variables. However, the present results showed that only noncancelled rate, a specific index of inhibitory control, was affected. In addition, performance on this measure was only affected in the Pre-SMA tDCS condition but not the M1 tDCS condition.

Indeed, Pre-SMA is not the only region that has been implicated to play a key role in inhibitory processes. Other brain regions including FEF (Hanes and Schall, 1996; Curtis et al., 2005; Muggleton et al., 2010), SEF (Stuphorn et al., 2000; Stuphorn and Schall, 2006; Isoda and Hikosaka, 2007; Chen et al., 2009), ACC (Ito et al., 2003; Chevrier et al., 2007), and IFG (Aron et al., 2003; Leung and Cai, 2007) have also been reported to be involved in the cognitive processes required for the stop-signal task. However, the precise role of each region, as well as their interactions with each other in the context of inhibitory control, remains to be investigated. For example, the basal ganglia/subthalamic route has been proposed to mediate action inhibition (Isoda and Hikosaka, 2008). However, this pathway was ruled out by Mars et al. (2009) using paired-pulse transcranial magnetic stimulation. Mars et al. (2009) found that the M1 induced motor-evoked potential (MEP) was affected 6 ms following the conditional pre-SMA TMS. The duration is too short to pass through basal ganglia/subthalamic route. However, Neubert et al. (2010) provided new evidence that M1 induced MEP is not only affected 6 ms after by conditional pre-SMA TMS, but also 12 ms after conditional pre-SMA and conditional rIFG TMS. This raises the possibility that information relating to action inhibition may indeed pass through the basal ganglia/subthalamic route. Additionally, IFG has been demonstrated to be necessary in the stop-signal paradigm (Chambers et al., 2006, 2007) due to its function in inhibitory motor control (Aron and Poldrack, 2006; Rubia et al., 2003; Rubia et al., 2005; Verbruggen and Logan, 2008). The interactions between rIFG with M1 were further investigated with using paired-pulse transcranial magnetic stimulation. At 175 ms after a visual cue, rIFG inhibits M1 corticospinal activity during action reprogramming (Mars et al., 2009; Neubert et al., 2010). But a fMRI study did not observe any correlation between IFG activation and SSRTs (Chao et al., 2009). In contrast, Li et al. (2006a) observed a linear correlation between the BOLD activation of Pre-SMA and SSRTs. They found that greater activation in the Pre-SMA led to shorter SSRTs, suggesting more efficient stop-signal processing. Converging evidence from other paradigms also suggests a critical involvement of Pre-SMA in inhibitory control. Rushworth et al. (2002) applied TMS over Pre-SMA to demonstrate the role of the area in task switching. They showed that the involvement of Pre-SMA in their task was temporally precise and related to the time of switching (Rushworth et al., 2002; Taylor et al., 2007). Similar results with Pre-SMA TMS experiments in the stop signal task have been reported by Chen et al. (2009). They also applied temporally precise TMS over the left Pre-SMA by delivering one pulse concurrent with the appearance of the GO signal and another one at 100 ms after its appearance. They demonstrated that the TMS pulses impaired inhibitory control and that the involvement of the Pre-SMA was early, consistent with a role in conflict resolution rather than error monitoring.

Conclusion

Despite evidence from magnetic stimulation experiments and lesion studies showing impaired inhibition when Pre-SMA activity is disrupted, no study has demonstrated that human inhibitory control can be improved with increased Pre-SMA activity. To the best of our knowledge, this study is the first to demonstrate both inhibition and facilitation effects by stimulating this area in healthy participants. The finding that it is possible to improve and impair inhibitory control

using anodal and cathodal tDCS is important, as it suggests that this type of stimulation may offer a potential clinical intervention for individuals exhibiting difficulties with inhibitory control. This includes a range of neuropsychiatric conditions, including but not limited to ADHD (e.g. Durston, 2008, 2010; Li e al., 2006b, 2008b; see Schachar and Logan, 1990, for an example in the stop-signal tasks), autism (Kana et al., 2007), and obsessive–compulsive disorder (Chamberlain et al., 2005). This is an area that may be fruitful for future research both in terms of stimulation effectiveness as well as development for longer-term clinical applications. In sum, by showing effects of anodal and cathodal tDCS over Pre-SMA in stop-signal performance, the current study further confirms that Pre-SMA has a unique role in mediating inhibitory control with the noncancelled rate either increased or reduced by facilitatory or inhibitory tDCS.

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