

The right inferior frontal cortex in response inhibition: A tDCS–ERP co-registration study



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ABSTRACT

In any given common situation, when an individual controls him/herself or obeys and stops a current action when asked to do, it is because the brain executes an inhibitory process. This ability is essential for adaptive behaviour, and it is also a requirement for accurate performance in daily life. It has been suggested that there are two main inhibitory functions related to behaviour, as inhibition is observed to affect behaviour at different time intervals. Proactive inhibition permits the subject to control his behavioural response over time by creating a response tendency, while reactive inhibition is considered to be a process that usually inhibits an already initiated response. In this context, it has been established that inhibitory function is implemented by specific fronto-basal-ganglia circuits. In the present study, we investigated the role of the right inferior frontal cortex (rIFC) in response inhibition by combining into a single task the Go-NoGo task and the Stop-Signal task. Concurrently, we applied transcranial direct current stimulation (tDCS) over the IFC and recorded electroencephalography (EEG). Thus, we obtained online EEG measurements of the tDCS-induced modifications in the IFC together with the participant's performance in a response inhibition task. We found that applying bilateral tDCS over the IFC (right anodal/left cathodal) significantly increased proactive inhibition, although the behavioural parameters indicative of reactive inhibition were unaffected by the stimulation. Finally, the inhibitory-P3 component reflected a similar modulation under both inhibitory conditions induced by the stimulation. Our data indicates that an online tDCS–ERP approach is achievable, but that a tDCS bilateral montage may not be the most efficient one for modulating the rIFC.

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Introduction

In any given common situation, when a person either controls him/herself or obeys and stops a current action when asked to do so, it is because the brain executes an inhibitory process. Because the behavioural inhibitory process permits control over inappropriate or unwanted responses, it is considered to be a key aspect of executive functions that are fundamental in daily life (Miyake et al., 2000). A single functional inhibitory process, however, may not suitably explain all inhibitory function effects on behaviour, as inhibition is observed to affect behaviour at different time intervals, integrating a global with a more selective mechanism (Aron and Verbruggen, 2008). For instance, a person can be cautious (i.e., inhibited) to not precipitate when performing a task that demands precise movements (proactive inhibition), or a person can be asked to immediately stop performing a move to avoid a possible

erroneous or dangerous effect (reactive inhibition). Therefore, while proactive inhibition permits the subject to display incremental attentional control over selective signals over a longer time frame by creating a response tendency, reactive inhibition is understood to be a process that usually interferes with an already initiated response (Aron, 2011).

The two more common paradigms employed to study response inhibition are the Go-NoGo task (GNG) and the Stop-Signal task (SST), which have been considered to similarly assess the inhibitory function (Huster et al., 2013). These two tasks, however, differ in their critical underlying cognitive processes. In a GNG task, participants are required to respond quickly to some stimulus (Go) and refrain from others (NoGo), whereas in the SST, participants are required to stop an already initiated response when the stop-signal is presented. Thus, while the inhibitory process engaged in the GNG task is driven by a consistent stimulus-response mapping, and importantly, can be sustained for a prolonged period of time (i.e., a response strategy used for a long lasting task), successful stop inhibition in SST may rely on a reactive process (Verbruggen and Logan, 2009). Only a few studies have directly compared the GNG and the SST, and predominantly, they have focused

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on searching for commonalities instead of singularities in terms of cognitive function (Enriquez-Geppert et al., 2010).

It has been well established that inhibitory function is implemented by specific fronto-basal-ganglia circuits (Aron et al., 2004, 2014). Functional neuroimaging studies have shown that both NoGo and Stop trials activate principally the right inferior frontal cortex (rIFC), presupplementary motor area (preSMA), and basal ganglia (subthalamic nucleus – STN) (Aron and Poldrack, 2006). The rIFC and the preSMA are believed to work in combination and to be the critical cortical areas for controlling and stopping behaviour (Alexander et al., 1990; Aron et al., 2007). Both cortical regions are strongly connected to the basal ganglia, which is of crucial importance for movement cancellation (Mink, 1996). The basal ganglia can be parcelled out into two different circuits, which might be differentiated depending on whether they are proactive (“indirect pathway”, via striatum) or reactive (“hyperdirect pathway”, via STN) (Aron, 2011; Jahfari et al., 2011). Importantly, the two inhibitory processes are governed by the rIFC, which may be responsible for initiating the movement suppression (Aron, 2011).

Recently, several studies have provided direct evidence of the importance of the rIFC for stopping behaviour using transcranial magnetic stimulation (TMS) (Chambers et al., 2006, 2007) and transcranial direct current stimulation (tDCS) (Cunillera et al., 2014; Ditye et al., 2012; Jacobson et al., 2011, 2012; Stramaccia et al., 2015). Hence, it has been shown that both TMS and tDCS can be used to interact with a specific brain region that is considered to be involved in a given cognitive function, as in the case of the rIFC in terms of response inhibition.

In the current study, we aimed to disentangle the role of the rIFC in proactive and reactive inhibition by studying the electrophysiological signatures of response inhibition using an experimental task in which we adapted a choice-reaction GNG task to incorporate a variant of the SST. Importantly, online, we manipulated the excitability of the rIFC through tDCS. This approach permitted us to evaluate the immediate changes on the neural excitability of the target area (i.e., rIFC) that occur during the tDCS and to investigate how task performance and its related electrophysiological markers are affected (Miniussi et al., 2013).

Because response inhibition is a covert process that produces no overt behaviour for measurements, the event-related brain potentials (ERPs) technique is well situated to investigate it. Electrophysiological studies conducted on healthy adults have revealed two candidates markers of response inhibition with frontocentral topography (i.e., the N2 and P3 ERP components). The N2 component (Gemba and Sasaki, 1989; Kok, 1986; Pfefferbaum et al., 1985; Sasaki et al., 1993) was first interpreted as a correlate of response inhibition, but more recently, it has been reinterpreted in terms of cognitive control and conflict processing (Donkers and van Boxtel, 2004; Huster et al., 2013; Nieuwenhuis et al., 2003). The N2 is followed by a positive deflection known as the NoGo Stop-P3 (hereafter, inhibitory-P3) (Falkenstein et al., 1995, 1999; Pfefferbaum et al., 1985). However, similar ERP patterns have been found using both GNG and SST tasks, suggesting similar underlying neurophysiological mechanisms (van Boxtel et al., 2001; Enriquez-Geppert et al., 2010). Although none of the ERP components are unequivocally qualified as an indicator of the inhibitory process, there is a growing agreement amongst studies that the inhibitory-P3 is well situated to be considered an index of the inhibitory function (Wessel and Aron, 2015; Smith et al., 2013). Supporting data come from studies showing that the amplitude of the inhibitory-P3 increases for successful in comparison to failed Stop trials (Dimoska et al., 2003; Greenhouse and Wessel, 2013; Kok et al., 2004; Ramautar et al., 2004; Smith et al., 2010; Wessel and Aron, 2015) or when inhibition is made more demanding (Bruin et al., 2001; Smith et al., 2007). Moreover, a delay in the peak of the P3 has been observed in NoGo trials for slow responders compared with fast ones (Smith et al., 2006).

Despite the large body of evidence showing the relation between the modulation of the P3 and successful response inhibition, it is still

disputed whether inhibitory-P3 is a direct reflection of the response inhibition process (Dimoska et al., 2003; Naito and Matsumura, 1996; Bruin et al., 2001) or if it just indicates the evaluation of the inhibitory process itself or its outcome (Huster et al., 2013). This last interpretation is in line with the most classical view, derived from extensive research conducted on the P3 from other domains (Polich, 2007), which postulates that P3 is related to evaluative and updating processes associated with the stimulus at hand. In some ERP studies, an attempt has been made to localise the neural generators of the inhibitory-P3. Results revealed that in NoGo and Stop trials, inhibitory-P3 seems to originate from a major generator in the IFC (Enriquez-Geppert et al., 2010).

Although the main focus of the current study was to investigate the role of the rIFC in reactive and proactive inhibition, the involvement of conflict in the inhibitory function was also studied. Similar to other executive functions, the inhibitory process is supposed to be influenced by variations in task difficulty (Verbruggen et al., 2014), although research on this topic is scarce (Band et al., 2003; Benikos et al., 2013; Gajewski and Falkenstein, 2013; Jodo and Kayama, 1992). Recently, different studies have assessed this question by manipulating task difficulty (minimizing the probability of the appearance of NoGo or Stop trials), and they observed a reduction of the amplitude of the NoGo-P3 in the highest task difficulty condition (Benikos et al., 2013; Gajewski and Falkenstein, 2013). The importance of monitoring for environmentally relevant and irrelevant information for stop-signals highlights the significance of signal detection, and more specifically, allows for consideration of the output of the sensory detection process for stopping behaviour (Verbruggen et al., 2014).

In summary, in this study, we sought to investigate the role of the rIFC in proactive and reactive inhibition using an online tDCS-ERP approach; concurrently, we intended to elucidate the effects of cortical excitability induced by tDCS on the ERP markers of these inhibitory functions. Furthermore, we manipulated the discriminability of the stimuli by making it easy or hard for participants to differentiate between the Go and NoGo stimulus to investigate the influence of conflict on the inhibitory function.

At the behavioural level, we hypothesise that if both inhibitory processes are governed by the rIFC, an increase in both proactive (increase of RT and/or reduction of commission and omissions) and reactive [reduction of the stop signal reaction time (SSRT)] inhibitory processes should be observed. At the electrophysiological level, although no clear predictions can be made due to the lack of previous results obtained with this combined tDCS-ERP approach, we expect that if the rIFC is differently involved in proactive and reactive inhibition, the modulation of the neural excitability produced by tDCS would lead to a dissociation of the inhibitory-P3 in the NoGo and Stop trial. Finally, and considering previous results (Benikos et al., 2013; Gajewski and Falkenstein, 2013), we expect a modulation of the N2 for the hard discriminability condition in comparison with the easy one. Similarly, if the inhibition function is affected by response conflict, we expect to observe a modulation of inhibitory-P3, which is associated with the discriminability of the stimuli to be inhibited.

Method

Participants

There were twenty-three participants [14 females, 9 males; age ($M \pm SD$), 25.0 ± 3.6 years; age range = 20–32 years] in the experiment, and all participants were paid. All the participants had normal or corrected-to-normal visual acuity and no history of neurological or psychiatric disorders. The study was approved by the Ethics Committee of IRCCS Centro San Giovanni di Dio, Fatebenefratelli, and written informed consent, according to the Declaration of Helsinki, was obtained from all participants before the experiment. All participants were right-handed, as assessed by the Edinburgh handedness questionnaire, and prior to the experimental session they were informed on what

they were going to do, but they were naïve about the precise purpose of the study and stimulation type. Data from 10 participants were excluded from the analysis due to saturation of the signal during the EEG recording in the anodal session (2 participants), highly noisy EMG signal (2 participants), failure to perform properly the task (1 participant whose SSRT value was less than 4 SD from the mean), or the low number of EEG epochs in some conditions (5 participants; below 15). The final sample of 13 participants had a mean age of 25.2 ± 3.3 years (6 females, 7 males; age range = 20–29 years).

Stimuli and procedure

Go-NoGo–Stop-Signal task (GNG–SST)

We implemented a design in which we adapted a choice-reaction GNG task (Osman et al., 1992) that incorporated a variant of the SST

(Logan et al., 1984). We manipulated the difficulty in perceiving the Go and NoGo stimuli and further evaluated the role of the reactive inhibitory process. Thus, two letter-digit pairs in the Courier New font served as stimuli (0.8° of visual angle), with one easily discriminated pair (letter V and number 5) and another hard-to-discriminate pair (letter I and number 1). One stimulus at a time was presented on the left or right side of a central fixation cross, requiring either left or right hand responses with the corresponding index finger (see Fig. 1A). The two response hands and the two types of discriminable items (easy/hard) were equally frequent and randomly presented within each block of the experiment. The stop-signal was a red frame (0.9° of visual angle) that was presented after a variable delay in the same location of the last Go stimuli, prompting participants to inhibit the Go response in those trials. The delay was adapted to each participant's behaviour using a staircase-tracking algorithm (Band and van Boxtel, 1999), with a dynamic tracking procedure that yielded an overall ratio

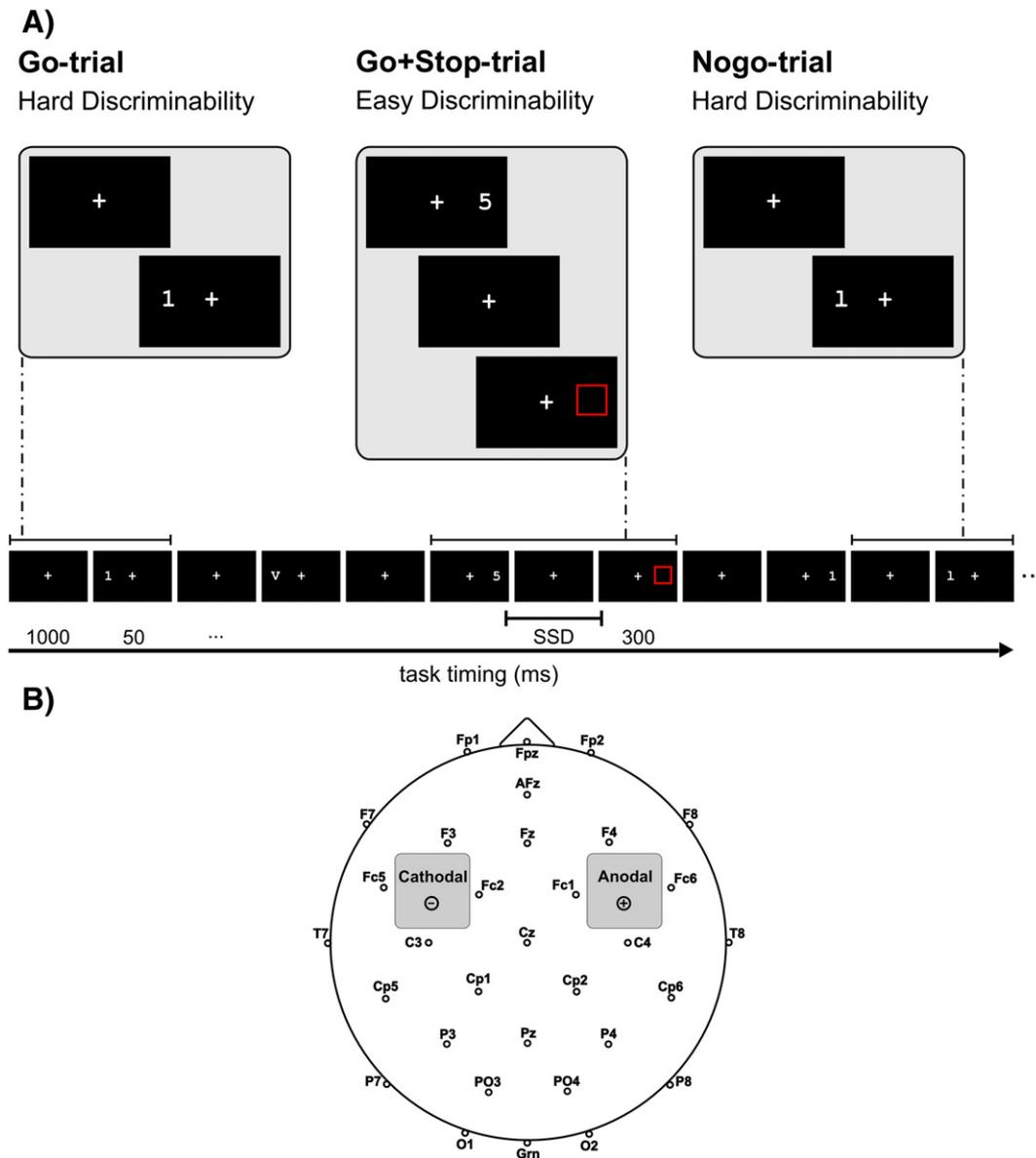


Fig. 1. A. Illustration of the combined Go-NoGo task (GNG) and the Stop-Signal task (SST) designed for the current study. The participants were instructed to respond to letters or numbers, in two separated and consecutive blocks, with the right or left hand depending on the side of the appearance of the Go-stimuli. One stimulus at a time, either on the left or the right side of a central fixation cross, was presented in each trial. In this example, different conditions are shown in the upper row of the Figure for the “go for numbers”. In the task the comparisons were made on easy or hard pairs, with the two stimuli to be compared presented in sequence. In the left row, participants are asked to respond to the side of appearance of the number 5 and 1 (easy and hard discriminability, respectively). The middle row shows an example of the Stop trial for the easy discrimination condition. The stop signal delay (SSD) was adapted (± 25 ms) after each Stop trial by means of a staircase-tracking algorithm. The right row corresponds to a NoGo-trial (letter “I”) in the hard discrimination condition. Amongst a total of 452 trials composing the task, 50% corresponded to Go, 25% to NoGo, and 25% to Stop trials. **B.** The location of the tDCS electrodes is illustrated on the lower part of the figure.

of p (response|stop-signal) of 0.5. The stop-signal delay (SSD) was set to 250 ms at the beginning of the two blocks and was adjusted separately for the easy and hard discriminability conditions. After a successful response inhibition, the SSD was increased by 25 ms, and after an unsuccessful inhibition, the SSD was reduced by 25 ms, thereby making the inhibition easier or harder, respectively, in the next Stop trial. Afterwards, the SSRT was first calculated individually for each block and condition and then averaged for each condition.

The participants were instructed to respond to letters or numbers in two separated and consecutive blocks that were counterbalanced across all participants. The Go stimuli were presented for 50 ms, whereas the duration of the stop-signal was always 300 ms. Stimulus onset asynchrony was fixed to 1000 ms. The total number of trials was 432 in each block, for which 50% of the trials corresponded to Go responses, 25% to NoGo responses and 25% to Go + Stop responses. The following constraints were introduced into the task: i) no more than three consecutive stimuli appeared on the same side, ii) two consecutive stop trials never occurred, and iii) the same type of stimuli (either letters or numbers) was not presented more than three consecutive trials in a row.

Procedures

Each subject participated in two online task-tDCS-ERP experimental sessions (sham vs. anodal tDCS) that were counterbalanced across the participants and conducted at least 1 week apart. The experiment began with a practice block that consisted of 64 trials to familiarise the participants with the task. To guarantee that the participants began the task aware of the difference between “l” and “1”, the practice block was repeated until the number of false alarms (FAs) and omissions was equal to or less than 10.¹ In the second session, a single practice block was administered with the sole purpose of reminding the participants of the task procedure. During the task and after every 29 trials, a short break of 5 s was included to allow the participants to have a short pause, and after 144 trials, a 10 s break was given. The online task-tDCS-ERP experiment session lasted for approximately 20 min, in which the EEG was recorded while the stimulation was on and the subject was performing the task.

tDCS

The location of the tDCS electrodes was established in accordance with the 10–20 EEG system. The anodal electrode was placed on the crossing point between the T4-Fz and F8-Cz positions, whereas the cathodal electrode was placed on the crossing point between the T3-Fz and F7-Cz positions, corresponding to the location right and left IFC on the scalp, respectively, (Cunillera et al., 2014; Jacobson et al., 2011) (see Fig. 1B). We created specific “cuts” in the electrode cap for placement of the tDCS electrodes. Moreover, we used self-adhesive insulation tape on the cap over the border of the cuts between the cap and the skin to minimise the spreading of the conductive medium used for tDCS electrodes.

In the anodal condition, a direct current of 1.5 mA was delivered with battery-driven stimulators (BrainStim, EMS, Bologna, Italy) through a couple of conductive-rubber electrodes inserted in sponges that were soaked with saline solution (9 cm², current density 0.16 mA/cm²) for 20 min with a ramping period of 10 s both at the beginning and at the end of the stimulation. Moreover, to obtain better adherence of the whole tDCS electrode and scalp, we used a tubular net-shaped elastic bandage in mesh tissue for the electrode fixation.

In the sham condition, the intensity of the current was the same, but the duration of the stimulation was limited to the duration of the current being ramped up and down (20 s) at the beginning and the end of the 20-min period. By following this protocol in the sham tDCS

session, we ensured that the participants felt the same sensations that they felt in the anodal stimulation session.

Importantly, the participants were not informed about the different stimulation protocols until the end of the entire experiment, and they could not distinguish between the anodal and the sham tDCS, as assessed by subject responses on a questionnaire completed at the end of each session (Fertonani et al., 2015) (nonparametric Wilcoxon rank sum tests all $ps > 0.1$).

Electrophysiological recordings

EEG equipment (BrainAmp 32 MRplus, BrainProducts GmbH, Munich, Germany) was used to record the ERPs, using sintered Ag–AgCl ring electrodes mounted in an elastic cap and located in standard positions (Fp1/2, Afz, Fpz, Fz, F7/8, F3/4, Fc1/2, Fc5/6, Cz, C3/4, T7/8, Cp1/2, Cp5/6, Pz, P3/4, P7/P8, PO3/4, O1/2, M1), as depicted in Fig. 1B. The ground electrode was placed in the Oz position. The electrode impedance was kept below 5 kOhm. The right mastoid served as a reference for all electrodes. The recordings obtained from the left mastoid electrode (M1) were used offline to re-reference the scalp recordings to the average of the left and the right mastoids [i.e., including the implicit reference (right mastoid) into the calculation of the new reference]. The electrophysiological signals were filtered with a bandpass of 0.1–1000 Hz (half-amplitude cutoffs) and digitised at a rate of 5000 Hz using a 16 bit A/D-converter. Horizontal and vertical eye movements were monitored with two bipolar electrodes placed at the infraorbital ridge and the outer canthus of the right and left eyes. The EMG activity was recorded from both hands using a bipolar montage placed on the first dorsal interosseous (FDI) and abductor digiti brevis (ADM) muscles using sintered Ag–AgCl electrodes. In each stimulation session, the task began 2 min after the EEG recording started, providing the necessary time for the EEG signal to stabilise.

EEG preprocessing

All EEG analyses were conducted using routines taken from the EEGLAB (version 9.046) Toolbox (Delorme and Makeig, 2004) and custom routines from MATLAB 2010b. After the EEG data were imported into MATLAB, the signal was sampled down to 500 Hz and then filtered with a band-pass filter with cut-off values ranging from 0.5 to 40 Hz. Furthermore, a high-pass filter with cut-off value of 10 Hz was applied to the two EMG channels. EEG signals from electrodes that were affected by tDCS during small sections of the experiment (i.e., electrodes with no signal) were interpolated using a linear combination of the potentials of the 4 nearest electrodes. Note that the interpolation was only used for graphical display of the topographic images, and this electrode signal was never considered in the statistical analysis. These EEG no-signal electrodes were recorded only in the anodal tDCS sessions for some participants (one electrode for 7 participants and two electrodes for 1 participant) and were always one of the electrodes surrounding the tDCS (i.e., F3/4, Fc1/2, Fc5/6, C3/4). For illustrative purposes only, the grand average ERPs were filtered using a 12 Hz low-pass filter.

ERPs analyses

We conceived the study with the aim of conducting standard ERP analysis on the tDCS-ERP data also to see the advantages of this novel multimodal approach. Thus, stimulus-locked ERPs for correct artefact-free trials (minimum of 15 trials, averaged per participant and condition) were averaged over epochs of 1100 ms, including a 100 ms pre-stimulus baseline. This process was performed separately for each condition. Trials with a base-to-peak electro-oculogram (EOG) amplitude of more than 75 μ V were automatically rejected offline. For the NoGo and Stop conditions, single-trial data from correct inhibited trials with

¹ The practice block was repeated for eight participants and repeated twice for the other two participants.

baseline shift exceeding 50 μV in the EMG channels were automatically rejected offline.

The analysis focused on the N2 and P3 components. Time windows (TW) for the measurement of the N2 and P3 mean amplitudes were defined separately for the Go, NoGo and Stop (correct and incorrect) events based on the peak latencies and visual inspections of the components located in the grand average waveforms at Cz or Pz electrodes. For the Go events, the N2 was measured at the 225–325 ms TW, whereas the P3 mean amplitude was measured within two consecutive TWs (300–400 ms, and 400–600 ms) that encompassed the P3 in that condition. For the NoGo events, the N2 was measured in the 275–375 ms TW, whereas for the P3, a different TW was defined for the easy (300–500 ms) and hard (400–600 ms) discriminability conditions. Finally, for the Stop conditions (correct and incorrect), measurements were determined within a 100 ms and a 50 ms TW for the N2 and P3, respectively, centred on the peak latencies of these components at Cz.

The mean amplitude values for the N2 and P3 at the different conditions were submitted separately to repeated measures ANOVA with three within-subjects factors: tDCS-session (two levels: sham vs. anodal), discriminability (two levels: easy vs. hard), and topography [three levels: anterior (Fz electrode), central [Cz electrode], and posterior (Pz electrode)]. The trial-type factor (Go vs. NoGo or NoGo vs. Stop) was analysed when the focus was on between-trial comparisons. Finally, follow-up analyses were conducted to test specific comparisons made between the sham and anodal conditions. For all statistical effects involving two or more degrees of freedom in the numerator, the Greenhouse–Geisser epsilon was used to correct for possible violations of the sphericity assumption (Jennings and Wood, 1976). The unadjusted degrees of freedom and adjusted p -values after the correction are reported.

Results

Behavioural results

For all analyses, the same two factors were introduced in separated repeated measures ANOVAs, with two within-subjects factors: tDCS-session (sham vs. anodal) and discriminability (easy vs. hard).

The participants inhibited their behavioural responses in approximately half of the stop trials in both tDCS-sessions, indicating a correct implementation of the tracking algorithm [$p(\text{response}|\text{stop-signal})$, sham-easy: $50.7 \pm 3.3\%$; sham-hard: $49.0 \pm 3.1\%$; anodal-easy: $48.6 \pm 3.2\%$; anodal-hard: $47.0 \pm 2.9\%$]. For the anodal session and hard condition, the $p(\text{response}|\text{stop-signal})$ was significantly less than expected (50%) [$t(12) = -3.6$; $p < 0.01$]. The ANOVA results revealed a main effect for the tDCS session, indicating that the participants inhibited their responses in a significantly larger number of trials in the anodal session compared to the sham tDCS-session [$F(1,12) = 8.0$; $p < 0.02$]. A main effect of discriminability was also observed [$F(1,12) = 10.7$; $p < 0.01$], which indicated a propensity toward responding to more trials for the easy condition than for the hard condition.

The main results are summarised in Table 1. The integration method was used to analyze the SSRT (Logan, 1981). The ANOVA results revealed a non-significant effect for both the tDCS-session [$F < 1$], and for discriminability [$F(1,12) = 2.3$; $p > 0.1$]. Comparable results were obtained when analysing the SSRT using the mean method (see Table 1).

When analysing the RT for Go trials, a strong main effect of discriminability was found [$F(1,12) = 22.7$; $p < 0.001$], which indicated that this manipulation worked as expected. Importantly, a significant main effect of tDCS-session was observed for Go RT [$F(1,12) = 16.1$; $p < 0.01$]. The interaction was not significant ($F < 0.2$).

The analysis of FAs revealed only a main effect of discriminability [$F(1,12) = 42.9$; $p < 0.001$; tDCS-session: $F < 1$; tDCS-session by

Table 1

The values of all different behavioural parameters analysed in the task are shown, separated for the easy and hard discrimination conditions and the sham and anodal tDCS sessions. For the Go trials, three mean values are presented for easy and hard discrimination conditions: RTs, percentage of correct responses and omissions. False alarms represent errors in NoGo trials. The mean Stop-Signal delay (SSD) refers to the average (SSD) in the two blocks (go for letters, go for numbers), computed with different staircases (see the Method section). The stop signal reaction time (SSRT) values presented were computed for each participant and condition using both the integration and the mean methods. Standard deviation = S.D.; degree of freedom = d.f.

		Sham ms (S.D.)	Anodal ms (S.D.)	t -value (d.f. = 21)	p -value
GO-RT	Easy	461 (50)	493 (53)	-3.17	<0.01
	Hard	494 (45)	529 (38)	-4.37	<0.01
SSD	Easy	252 (62)	280 (62)	-2.12	=0.06
	Hard	287 (63)	328 (55)	-3.31	<0.01
SSRT (integration meth.)	Easy	209 (20)	213 (19)	-0.52	>0.6
	Hard	207 (28)	201 (28)	0.79	>0.4
SSRT (mean meth.)	Easy	203 (24)	207 (21)	-0.64	>0.5
	Hard	202 (30)	191 (37)	1.15	>0.2
		% (S.D.)	% (S.D.)		
Go-correct	Easy	97.9 (1.9)	97.7 (2.5)	0.25	>0.8
	Hard	89.2 (8.6)	88.1 (8.4)	0.52	>0.6
False alarms	Easy	2.6 (2.6)	1.6 (1.9)	1.46	>0.01
	Hard	17.1 (10)	15.6 (11.6)	0.40	>0.7
Omissions	Easy	2.0 (1.8)	2.2 (2.5)	-0.26	>0.8
	Hard	10.8 (8.7)	11.8 (8.5)	-0.45	>0.6

discriminability: $F < 0.1$). Finally, the analysis of omitted responses also revealed only a main effect of discriminability [$F(1,12) = 23.1$; $p < 0.001$; tDCS-session and tDCS-session by discriminability: $F < 0.3$].

In summary, we found that in the current study, the anodal stimulation modulated behaviour by significantly slowing down the participants' RTs in the Go trials, but non-significant results were found for the SSRT.

ERP results

Results are reported separately for the N2 and the inhibitory-P3 components. All electrophysiological responses corresponding to Go, NoGo, and Stop trials and for anodal and sham conditions, as well as for the easy and hard discriminability conditions, can be viewed in Fig. 2.

N2 component

Go trials

The ANOVA results revealed no significant difference for the N2 component for the tDCS-session or discriminability factors ($F < .1$). The interaction tDCS-session \times discriminability reached the level of significance [$F(1,12) = 5.5$, $p < 0.04$], but a further t -test conducted to decompose the interaction failed to show significant differences between the anodal and sham tDCS-sessions (all p -values > 0.2).

NoGo trials

We found a modulation of N2 component through the stimuli discriminability, as revealed by the discriminability \times topography interaction [$F(2,24) = 6.7$, $p < 0.01$]. Thus, a reduction in the amplitude of the N2 for the hard discriminability condition was observed over the central area (Cz electrode) [easy vs. hard: $t(12) = 2.6$; $p < 0.03$]. No significant differences were observed for the N2 in NoGo trials involving the tDCS-session factor (all p -values > 0.2).

Correct and Incorrect inhibited Stop trials

Only the discriminability factor was found to modulate the N2 for correct and incorrect inhibited trials [correct: $F(1,12) = 8.4$, $p < 0.02$; incorrect: $F(1,12) = 6.9$, $p < 0.03$].

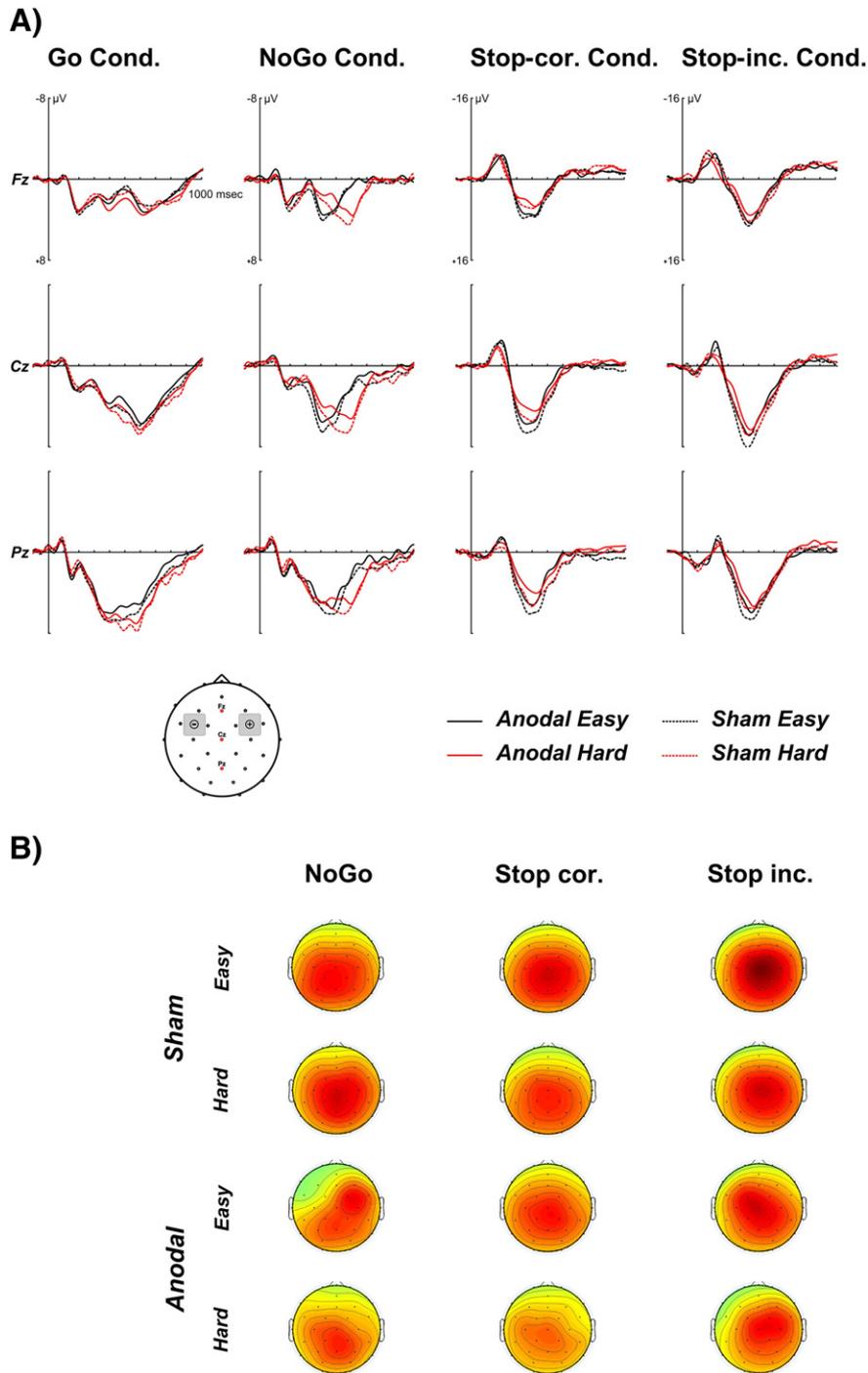


Fig. 2. A. Grand average ERPs for Go, NoGo, correct inhibited Stop, and incorrect inhibited Stop trials at midline electrode locations (Fz, Cz, and Pz) for the easy and hard discriminability conditions (black and red lines, respectively) and for the anodal (solid lines) and sham (dashed lines) stimulation sessions. The effect of anodal tDCS on the rIFC is reflected by reduced amplitude of inhibitory-P3 in both the NoGo and Stop trials. **B.** Isovoltage mapping with spherical spline interpolation depicts the scalp distribution of the inhibitory-P3 components for the different conditions and stimulation sessions. Note that a similar morphology of the inhibitory-P3 is observed for NoGo and Stop trials.

Go vs. NoGo trials

The ANOVA results revealed a trial-type × topography interaction [$F(2,24) = 25.1, p < 0.001$]. Further analyses were conducted to decompose this interaction. The N2 was larger in NoGo trials than in Go trials at the frontal regions [Fz: $F(1,12) = 18.7, p < 0.01$; Cz: $F(1,12) = 6.9, p < 0.03$] and reversed on posterior regions [Pz: $F(1,12) = 10.5, p < 0.01$]. Interestingly, a trial-type × discriminability interaction was observed [$F(1,12) = 12.6, p < 0.01$], indicating that the largest difference between the Go and NoGo trials was found in the hard condition [easy

discriminability: $t(12) = 3.2; p < 0.01$; hard discriminability: $t(12) = 4.3; p = 0.001$].

Inhibitory-P3 component

Go trials

As seen in Fig. 2A, a P3 component was evoked by Go stimuli. In the first time window entered for the analysis (300–400 ms), this P3 was observed to be similar in both tDCS-sessions ($F < 0.1$), and for hard

and easy discriminability conditions ($F < 0.2$). In the 400–600 ms time range, however, a significant tDCS-session \times topography interaction was observed [$F(2,24) = 5.6, p = 0.01$]. The interaction indicated that the differences between the anodal and sham trials were larger at the posterior sides and reversed at the frontal sides, although no significant difference was found [anodal minus sham, at Fz: $0.6 \mu\text{V}, t(12) = 1.2; p > 0.2$; Cz: $-0.7 \mu\text{V}, t(12) = -1.1; p > 0.3$; Pz: $-0.8 \mu\text{V}, t(12) = -1.8; p > 0.09$].

NoGo trials

ERPs elicited by the correct inhibited trials on NoGo trials elicited a robust P3 component that was delayed in the hard discriminability condition. The ANOVA results revealed that the inhibitory-P3, with a central maximum, decreased in amplitude in the anodal stimulation session [tDCS-session $F(1,12) = 7.1, p < 0.03$; Fig. 3]. The difference between the anodal and sham conditions was significant for all electrodes [topography: Fz: $t(12) = -2.1; p = 0.05$; Cz: $t(12) = -2.7; p < 0.02$; Pz: $t(11) = -2.5; p < 0.03$].

Correct inhibited Stop trials

The ERPs elicited by the correct inhibited Stop trials elicited a robust P3 component with a central maximum. This P3 was larger for the easy discriminability condition than it was for the hard condition [$F(1,12) = 7.7, p < 0.02$], and importantly, it was reduced for the anodal session compared to the sham stimulation session [tDCS-session $F(1,12) = 8.9, p < 0.02$]. The interaction tDCS-session \times topography was also significant [$F(2,24) = 6.0, p = 0.01$]. The difference between the anodal and sham conditions was significant at the central and posterior electrodes [Fz: $t(12) = -0.9; p > 0.3$; Cz: $t(12) = -2.9; p = 0.01$; Pz: $t(12) = -4.0; p < 0.01$; Fig. 3].

Incorrect inhibited Stop trials

A non-significant trend was observed for P3 in terms of the discriminability factor [$F(1,12) = 4.0, p = 0.07$], but no differences were found for the tDCS-session [$F(1,12) = 2.2, p > 0.1$].

Correct vs. incorrect inhibited Stop trials

The comparison between the correct and incorrect inhibitions Stop events revealed no differences between these trials [$F(1,12) = 2.9, p > 0.1$], although a significance trend was observed for the trial-type \times topography interaction [$F(2,24) = 3.1, p = 0.06$]. A further analysis, collapsing the discriminability and tDCS-session factors, revealed a significant trend for the inhibitory-P3, indicating that it was larger for incorrect than for correct inhibited Stop trials at Cz [$t(12) = -2.1; p = 0.06$; see Fig. 3]. Finally, the ANOVA results revealed a significant difference for the discriminability factor [$F(1,12) = 8.4, p < 0.02$], indicating a diminished P3 in the hard discriminability condition.

NoGo trials vs. correct inhibited Stop trials

To further investigate a possible differentiation of the inhibitory function in proactive and reactive inhibitions, the mean amplitude of the P3 elicited in the NoGo and correct inhibited Stop trials was entered into a new analysis. First, the ANOVA results revealed a main effect of Trial-type [$F(1,12) = 27.7, p < 0.001$], indicating a clear larger P3 in the Stop trials compared to the NoGo trials. In line with the results of the NoGo and Stop trials (conducted separately), when considering the analyses of these two type of inhibitory trials together, the tDCS-session factor was clearly significant [$F(1,12) = 9.5, p < 0.01$]. In addition, the discriminability factor was significant, indicating a general reduction of the inhibitory-P3 for the hard condition [$F(1,12) = 5.1, p = 0.04$]. Furthermore, a crucial difference was found when considering topographical similarities between the inhibitory-P3 elicited in the NoGo and Stop trials. Here, the significant interaction, trial-type \times tDCS-session \times topography [$F(2,24) = 7.0, p < 0.01$] and trial-type \times topography [$F(2,24) = 5.3, p < 0.03$], indicated that the anodal stimulation modulated the inhibitory-P3 differently depending on the trial-type. A further analysis conducted separately at Fz, Cz, and Pz electrodes revealed that the significant trial-type \times tDCS-session interaction was only found at Pz [$F(1,12) = 12.4, p < 0.01$].

Discussion

The current research aimed to study the role of the rIFC in response inhibition with a multimodal approach (i.e., combining online tDCS and EEG while the participants performed a mixed GNG and SST) using standard ERP analysis. On the one hand, anodal tDCS applied on the rIFC was found to modulate RTs (the participants slowed down their responses in the Go trials), which we interpret as increased behavioural control (increased proactive inhibition). Anodal stimulation with the current sample and tDCS montage was not observed to be effective in modulating reactive inhibition, as indicated by the non-significant effect of stimulation for the SSRT. On the other hand, the ERP results revealed that tDCS reduced the amplitude of the inhibitory-P3 in NoGo and Stop correct inhibited trials. Finally, response conflict, implemented in the task by manipulating the difficulties in discriminating the stimuli, was found to modulate the N2 and the inhibitory-P3, showing the importance of considering the monitoring of response conflict while studying the inhibitory function.

In the following section, we further discuss the implications of our results regarding the different contributions of the present data to the involvement of the IFC in i) the inhibitory function, ii) the ERP markers of response inhibition, and iii) the influence of response conflict in the inhibitory function. Finally, we finish with an outline of the limitations of our study by considering the tDCS-ERP approach and the standard ERP analyses that we employed to study the inhibitory function.

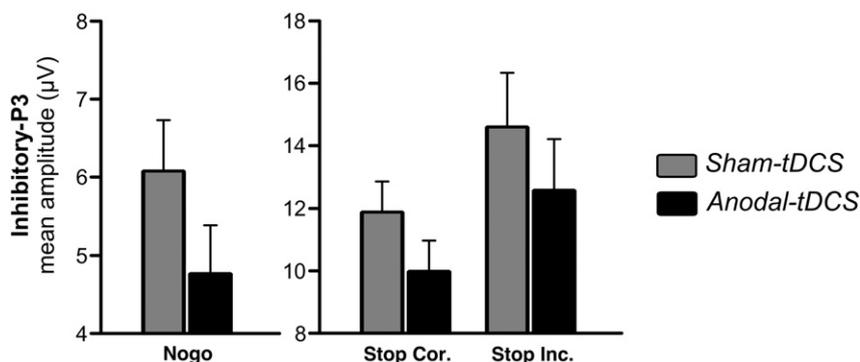


Fig. 3. The bar plots illustrate the effect of anodal and sham tDCS [mean amplitude values (μV)] for the NoGo and Stop conditions in the Cz electrode. The discriminability factor is collapsed in the figure. All differences between the anodal and sham sessions presented in the figure were significant ($p < 0.05$).

The rIFC in proactive and reactive inhibition

The main indicator of enhanced proactive inhibition in the present study was found in the significant increase of RT for anodal tDCS applied on the rIFC, which replicated previous results (Cunillera et al., 2014). However, the null effect on reactive inhibition in the current study, as reflected by a similar SSRT in both stimulation sessions, does not align with previous results (Cunillera et al., 2014; Chambers et al., 2009; Jacobson et al., 2011; Stramaccia et al., 2015). In a previous behavioural experiment using an identical task and tDCS procedure, we did observe a decrease in the SSRT caused by the injection of anodal current on the rIFC. A speculative explanation for the null effect of tDCS on the SSRT in the present study may be related to the specificities of our tDCS design. Thus, we opted for an online design in which the task duration was aligned to the stimulation time. Different studies have obtained significant results, by stimulating a target area, using offline measurements (Jacobson et al., 2011; Stramaccia et al., 2015). In support of this interpretation, Sehm et al. (2013) reported an effective modulation of the primary motor cortex (M1) measured after the bilateral tDCS stimulation was over – but not during the stimulation – as indicated by the intracortical functional connectivity values obtained with fMRI. Finally, it is likely that the bilateral montage that we used could have had a negative impact on the pursued effects mediated by the reference electrode (Brunoni et al., 2012), as the injection of cathodal current on the left IFC may have led to antagonistic effects on the contralateral cortex (see Antal et al., 2004; Accornero et al., 2007; Nitsche and Paulus, 2000). Regardless, the present experiment does not question the importance of the rIFC in stopping behaviour in the reactive inhibition, which has been confirmed by previous studies using TMS (Chambers et al., 2006, 2007) and tDCS (Cunillera et al., 2014; Jacobson et al., 2011; Stramaccia et al., 2015). Finally, it is worth mentioning that in a recent study the authors proposed that the inhibitory function may be dissociable into two networks (Hughes et al., 2014), with the rIFC been involved in reactive inhibition (phasic function), and the right dorsolateral prefrontal cortex (rDLPFC) supporting proactive inhibition (tonic function) (see also Penolazzi et al., 2014). Therefore, given also the low spatial resolution of tDCS, it is possible that the discrepancy with our previous results may implicate that these two areas associated with the inhibitory function were simultaneously stimulated in our previous study, while in the current one, the anodal current reached the rDLPFC more than the rIFC.

Our observation of a similar modulation (induced by tDCS) of the inhibitory-P3 elicited in NoGo and Stop trials aligns with the interpretation that the rIFC is a crucial region for inhibition in general, although considering together behavioural and ERP results, we may not have succeeded in modulating the activity of the rIFC enough to distinguish between reactive and proactive processes. When considering the fact that at the behavioural level (the SSRT), reactive inhibition was unaffected by tDCS, the interpretation of the modulation of the inhibitory-P3 seems consistent with the account that postulates that the P3 is indicative of the evaluation of the inhibitory process (Huster et al., 2013) or the context updating account (Donchin and Coles, 1988; Polich, 2007), which states that the P3 indicates a reconfiguration of attention and a revision of a created representation of a task goal. However, the fact that tDCS did not affect the P3 in incorrectly inhibited Stop trials is difficult to explain by the evaluative or the context updating account. Future tDCS investigations may further address this question by using different tDCS montage that ensure a more effective modulation of the rIFC and tasks in which distinct inhibitory loads are manipulated or with a between blocks design that would permit the separation of proactive and reactive inhibitory processes in the same task.

The N2 and inhibitory-P3 components

To the best of our knowledge, this study is the first study in which the inhibitory function is investigated with a paradigm that combines

a highly demanding attentional task with the need to stop, commanded by external or internal cues.

Our ERP findings align with the predominant assumption of the role that N2 and P3 ERP components play in response inhibition tasks (Huster et al., 2013). Thus, we found that the N2 was modulated by response conflict in NoGo trials but was unaffected by tDCS, supporting the idea that its major neural generator may be on the cingulate cortex (anterior and medial), outside the influence of the tDCS in the current study (Botvinick et al., 2004; Folstein and van Petten, 2008; Nieuwenhuis et al., 2003; Yeung and Nieuwenhuis, 2009). The inhibitory-P3 tDCS was found to reduce the component amplitude in NoGo and successful inhibited Stop trials, supporting both the importance of the IFC in response inhibition and the fact that the inhibitory-P3 is directly related to the suppression of an overt motor response (Huster et al., 2013). The fact that during unsuccessful inhibited stop trials tDCS had no effect on the P3 is also in line with studies showing that rIFC is less activated in unsuccessful stop trials (Aron and Poldrack, 2006).

Additionally, we investigated how tDCS applied on the IFC modulated inhibitory-P3 in NoGo and Stop trials. Our results indicate that tDCS had a different effect on these two types of trials, but differences were only observed on posterior regions, while the major generators of the inhibitory-P3 are estimated in the anterior cingulate cortex and IFC (Crottaz-Herbette and Menon, 2008; Enriquez-Geppert et al., 2010). It has been stated that a different inhibitory load is involved in a correct performance of NoGo and Stop trials (Johnstone et al., 2007; Enriquez-Geppert et al., 2010). Accordingly, it is possible that these unequal inhibitory loads may explain the difference observed for the inhibitory-P3 in those trials. Thus, tDCS may have had the largest effect on those trials demanding the highest inhibitory load, and consequently, differences were not detected at the proximal frontal region, but were detected at the distal posterior region.

In general, we observed that the stimulation induced a reduction of inhibitory-P3. Although results of multimodal tDCS-ERP co-registration are scarce, recently, Lapenta et al. (2014), using an offline tDCS-ERP approach in a GNG task, found that stimulating the dorsolateral prefrontal cortex (right anodal/left cathodal) resulted in a reduction of the N2 together with an enhancement of the NoGo-P3 amplitudes. However, they did not find any effect of tDCS on behavioural performance, which blurred the interpretation of such effects. In other studies that combined transcranial electrical stimulation [using either direct (tDCS) or alternate (tACS) current applied on different scalp regions] with ERP measurements, a modulation of the task-related P3 has been reported (Helfrich et al., 2013; Keeser et al., 2011; Zaehle et al., 2011), although the direction of the effect on the P3 is not consistent throughout these studies and, therefore, is difficult to interpret.

It is well established that in the SST, the inhibitory-P3 is clearly increased for successful trials compared to unsuccessful inhibited trials (Dimoska and Johnstone, 2008; Dimoska et al., 2006; Kok et al., 2004; Ramautar et al., 2004, 2006), a result of an inhibitory process. We did not find a large difference between correct and incorrect Stop trials for the P3, although this difference was observed in the expected direction. However, this lack of a clear significant difference cannot be understood as a failure of the inhibitory function, as the subjects were able to correctly inhibit approximately 50% of the Stop trials. As previously stated, it is possible that participants relied heavily on a proactive inhibition function to solve the task and that the role of reactive inhibition was secondary and not enough to be reflected on the inhibitory-P3 elicited when the responses on Stop trials were inhibited.

Conflict and inhibition

The conflict theory states that response conflict arises when incompatible representations are simultaneously activated (Botvinick et al., 2001). In the current study, we found that RT increased and the amplitude of the NoGo-N2 decreased when incrementing the task difficulty. Assuming that conflict occurs at the level of response representations

and under conditions in which the bias toward the Go responses is increased, the diminished N2 in NoGo trials may indicate a reduced response conflict when evaluating the NoGo stimuli. The N2 has been postulated to originate principally in the cingulate cortex (Folstein and van Petten, 2008) and to be elicited under conditions in which a low frequency response is required (Gajewski and Falkenstein, 2013; Huster et al., 2013). Thus, conflict arises when a behavioural response goes against our expectations. Overall, in our task, the participants faced each trial with an equal probability to respond to than to inhibit the response (50%). The N2 was found to be larger for NoGo than for Go trials, as previously reported (e.g., see Nieuwenhuis et al., 2003), and this difference was increased for the easy discriminability condition. We did not find an effect of tDCS on the N2 when stimulating the IFC, indicating that monitoring response conflict may be sustained by other areas rather than the IFC, most likely the cingulate cortex (Folstein and van Petten, 2008).

While response conflict is primarily related to the frequency of the stimuli (with lower frequency implicating a larger conflict), the present results indicate that conflict may also be influenced by stimuli identification process, as indicated by the reduced amplitude of the inhibitory-P3 that we observed only in the Stop trials and for the hard discriminability condition. The importance of monitoring for environmental relevant and irrelevant information for Stop signals involves the significance of signal detection, and more specifically, the output of the sensory detection process for stopping behaviour (Verbruggen et al., 2014).

Multimodal tDCS-ERP approach

By overcoming the encountered intrinsic difficulties of combining two apparently conflicting techniques (recording electrical brain activity from the scalp while simultaneously injecting current on the same surface), we have proven that the combination of task, tDCS and EEG in a simultaneous recording is possible, although at the moment an offline design may have been more suitable and desirable considering the noise introduced by the tDCS in the online approach that limited us to conduct the analyses on a larger set of electrodes. However, as far as we know, there are no studies directly comparing online vs. offline tDCS during EEG recording.

In the current experiment, we have succeeded in enhancing control processes (proactive inhibition) by stimulating the rIFC with anodal current, thereby demonstrating supporting information in the role of the rIFC in response inhibition. As tDCS has been described to act upon brain function by modulating resting membrane potentials (Kuo and Nitsche, 2012; Miniussi et al., 2013), thereby affecting spontaneous cortical activity, we hypothesise that a reduction of the inhibitory-P3 may reflect a modulation of the excitability of the IFC, or by extension, of the activity of a more extensive network (Bortoletto et al., 2015) in which the IFC is a critical area. However, the neural mechanisms underlying the modulation of the P3 are beyond the scope of the study. Finally, we cannot rule out the possibility that, although the selected electrodes for the analyses seemed to not be affected by the intrinsic tDCS noise, an artifact produced by the tDCS could have partially affected our results.

Limitations of the study

We limited our investigation to the analysis of ERPs, taking advantage of the fact that the noise introduced in the EEG signal by the two tDCS electrodes did not apparently affect the ERP results conducted on the selected electrodes for the study, and under the premise that noise uncorrelated with the signal may have been largely cancelled out when averaging ERP epochs (Talsma and Woldorff, 2005). However, tDCS-induced noise in our EEG data limited us from using a methodological approach that involves an extensive set of electrodes covering the scalp (e.g., Independent Component Analysis), and forced us to reject data from a large number of participants. Likewise, due to the

reduced sample size of the study, our results should be interpreted with caution, although the study was mainly focused on the P3 components, which is a robust and consistent waveform that does not need a large signal-to-noise ratio (Cohen and Polich, 1997; Luck, 2005). Finally, to proceed with a 100% online approach, we limited the duration of the EEG recording to the duration of the tDCS, which was limited to 20 min for safety reasons (Nitsche and Paulus, 2011). All in all, using the online approach was challenging, but without EEG data from studies comparing online vs. offline tDCS, we cannot evaluate the advantages and disadvantages of one procedure over the other.

Conclusions

We investigated the involvement of the rIFC in response inhibition using a tDCS-ERP methodological approach, which permitted us to modulate the cortical excitability of rIFC while measuring the electrophysiological markers and behavioural performance derived from the experimental task. For such a purpose, we designed a mixed GNG and SST, assuming that the inhibitory function may be divided into proactive and reactive inhibitory processes, with both processes sustained by the activity of the rIFC. We found that by applying anodal current on rIFC, we increased proactive inhibition. The behavioural parameters indicative of reactive inhibition were unaffected by the stimulation, although the inhibitory-P3 components reflected a clear modulation induced by the stimulation. Together, our data support the hypothesis of a general role of the rIFC in the inhibitory function, but, this time, we could not prove a clear dual inhibitory function of the rIFC.

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