Please, don't do it!

Fifteen years of progress of non-invasive brain stimulation in action inhibition

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Abstract

The ability to inhibit prepotent responses is critical for survival. Action inhibition can be investigated using a stop-signal task (SST), designed to provide a reliable measure of the time taken by the brain to suppress motor responses. Here we review the major research advances using the combination of this paradigm with the use of non-invasive brain stimulation techniques in the last fifteen years. We highlight new methodological approaches to understanding and exploiting several processes underlying action control, which is critically impaired in several psychiatric disorders. In this review we present and discuss existing literature demonstrating i) the importance of the use of non-invasive brain stimulation in studying human action inhibition, unveiling the neural network involved ii) the critical role of prefrontal areas, including the pre-supplementary motor area (pre-SMA) and the inferior frontal gyrus (IFG), in inhibitory control iii) the neural and behavioural evidence of proactive and reactive action inhibition. As the main result of this review, the specific literature demonstrated the crucial role of pre-SMA and IFG as evidenced from the field of noninvasive brain stimulation studies. Finally, we discuss the critical questions that remain unanswered about how such non-invasive brain stimulation protocols can be translated to therapeutic treatments.

Keywords: Action inhibition; stop-signal task; transcranial magnetic stimulation; transcranial direct current stimulation; Action Inhibition Network.

1. Introduction

The control of voluntary action involves a series of different processes that need to be harmoniously orchestrated, such as choosing from a range of possible actions as well as inhibiting responses as circumstances demand. The ability to inhibit prepotent ongoing actions is crucial to prevent potentially harmful behavioral outcomes. The ability to inhibit prepotent responses can be investigated experimentally using a stop-signal task (SST), designed to provide a sensitive measure of the time taken by the brain to inhibit or suppress inappropriate motor responses (Lappin & Eriksen, 1966; Logan, Cowan, & Davis, 1984; Vince, 1948). It requires participants to respond to a go stimulus and to abort the ongoing response when a stop signal is presented. To measure the participant's performance on the SST, the stop signal reaction time (SSRT), an index of inhibition, is computed based on Logan and Cowan's notion (Logan et al., 1984). Logan and Cowan proposed the existence of a race between a go process, triggered by the presentation of the go stimulus, and a stop process, triggered by the presentation of the stop signal.

When the stop process terminates before the go process, the response is inhibited, but when the go process terminates before the stop process, the response is activated. Thus, unpredictable stop signals require withholding the response when a go response has already been initiated. The stopping process needs to be estimated from a stochastic model, the so-called 'race model' (Logan et al., 1984), which estimates the SSRT from the distribution of 'go' reaction times and the observed probability of responding on 'stop' trials for a given stop-signal delay. This measure is an indicator of inhibitory control, with a lower value indicating a more rapid ability to respond to a stop signal (Cai et al., 2015). The time between presentation of the go stimulus and presentation of the stop signal is termed the 'stop signal delay' (SSD). Critically, the motor inhibition will be successful only when the SSD is short enough to allow inhibitory processes to stop the ongoing motor program, while an increased SSD will result in an increased likelihood of failure to inhibit the response to the go stimulus. SSD can be fixed or dynamically modified trial-by-trial based on the participant's performance (Verbruggen & Logan, 2009). However, estimated SSRT gives the

measure of the duration of the inhibitory process by revealing the time necessary for successful motor inhibition (Logan et al., 1984).

Recent theories (Aron, 2011; Braver, Gray, & Burgess, 2007) propose that inhibitory control can be divided into proactive mechanisms (response slowing in anticipation of a stop-signal) and reactive mechanisms (outright stopping in response to a stop-signal, measured by means of the SSRT). An example of these mechanisms includes the possibility to brake roughly if a person gets in your way while you are driving your car, as a reaction to the rapid and unexpected change in the context (reactive inhibition). However, one could also pre-emptively act so as not to drive too fast, as the probability of encountering a bypassing pedestrian in the street is often high, and therefore this approach would almost guarantee a successful outcome (proactive inhibition and working memory). Typically, proactive inhibitory control is measured by the increase in reaction times in the go trial when the probability of a stop-signal is high (Cai et al., 2015; Meyer & Bucci, 2016; Zandbelt, Van Buuren, Kahn, & Vink, 2011) or by an index of the proactive inhibitory control, named 'preparatory cost' (PC) (Cai et al., 2015). Crucially, a low preparatory cost indicates a weaker anticipation of a stop-signal, while a higher preparatory cost indicates better proactive inhibitory control.

Several brain areas have been associated with the mechanisms underlying inhibitory control, with a network including left and right inferior frontal gyrus (IFG) (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Chevrier, Noseworthy, & Schachar, 2007; Leung & Cai, 2007; Zhang, Geng, & Lee, 2017), dorsolateral prefrontal cortex (dlPFC) (Bari & Robbins, 2013; Leung & Cai, 2007), anterior cingulate (ACC) (Ito, Stuphorn, Brown, & Schall, 2003; Zhang et al., 2017), pre-supplementary motor area (pre-SMA) (Bari & Robbins, 2013; Leung & Cai, 2007), supplementary motor area (SMA) (Bari & Robbins, 2013; Li, Huang, Constable, & Sinha, 2006; Zhang et al., 2017), bilateral superior temporal gyri (Zhang et al., 2017), parietal cortex (Bari & Robbins, 2013; Leung & Cai, 2007; Zhang et al., 2017), insula (Bari & Robbins, 2013; Leung & Cai, 2007; Zhang et al., 2017), basal ganglia (Bari & Robbins, 2013; Chevrier et al., 2007; Zhang et al., 2017), cerebellum (Clark, King, & Turner, 2020), frontal eye fields (FEF) and supplementary eye field

(SEF) (Dillon & Pizzagalli, 2007; Hanes & Schall, 1996; Leung & Cai, 2007; Stuphorn & Schall, 2006; Stuphorn, Taylor, & Schall, 2000), all implicated by a range of studies (see Zhang et al., 2017 for meta-analysis). The critical and specific role of each of these areas in action inhibition is still debated. Recent studies, for instance, have demonstrated that lesions to IFG cause a deficit of response inhibition, as measured using tasks that require the suppression of an initiated manual response (Aron et al., 2003) or the suppression of a reflexive saccade (Hodgson et al., 2007). In addition, human patient studies revealed that damage to another section of the prefrontal cortex, the right superior frontal regions (including pre-SMA and SMA), raised SSRT in the SST (Floden & Stuss, 2006 for a review see Mostofsky & Simmonds, 2008). In support of the critical role of pre-SMA in action control, several studies with macroelectrode stimulation in epilepsy patients show that pre-SMA stimulation leads to the arrest of ongoing vocal or manual movements (Lüders et al., 1988; Mikuni et al., 2006; Swann et al., 2012) and a single case report of a patient with a lesion of the pre-SMA extending to cingulate and superior frontal gyri also showed a behavioral stopping deficit for a stop-change task (Nachev, Wydell, O'Neill, Husain, & Kennard, 2007). From all this evidence, it seems clear that dorsomedial damage impairs stopping; however, lesions were not restricted to the pre-SMA, preventing the possibility to draw any conclusions. Indeed, macrostimulation of both the pre-SMA and the right IFG can induce motor arrest (Fried et al., 1991; Lüders et al., 1988), and stimulation of the pre-SMA evoked responses in the right IFG, corresponding well to a white-matter connection, and also the stopping-related task evoked responses (Swann et al., 2012). As suggested by the multiple domain hypothesis of response inhibition (Rubia et al., 2001), distinct parts of the frontal lobes may be responsible for different aspects of inhibitory control, for instance the recruitment of the dlPFC seems to be relevant under conditions in which greater cognitive demand (i.e., more working memory load) is necessary to guide response inhibition (Criaud & Boulinguez, 2013; Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010; Mostofsky et al., 2003). Indeed, although the modulation of behavior when expecting a stopping stimulus (proactive inhibition) is a proposed function linked to the pre-SMA (Aron, 2011;

Boulinguez, Ballanger, Granjon, & Benraiss, 2009; Chikazoe et al., 2009; Forstmann et al., 2008; Jahfari et al., 2010; Zandbelt & Vink, 2010), some hypotheses posit the dlPFC as a candidate for proactive inhibition due to the working memory component in such behavior (Criaud & Boulinguez, 2013; Jahfari et al., 2010; Mostofsky et al., 2003). Importantly, monkey evidence recorded firing in the pre-SMA during both stop trials and non-stop trials (Stuphorn & Emeric, 2012). Firing peaks during non-stop trials suggested that the pre-SMA could induce proactive inhibition throughout phasic firing due to its reactive function. In addition, switching from repetitive to new movements became worse by disrupting pre-SMA activity (Rushworth, Hadland, Paus, & Sipila, 2002). Thus, the pre-SMA appears to be recruited during both response inhibition and action switching.

Critically, all the aforementioned studies employed functional magnetic resonance (Aron et al., 2003; Bari & Robbins, 2013; Chevrier et al., 2007; Clark et al., 2020; Dillon & Pizzagalli, 2007; Hanes & Schall, 1996; Ito et al., 2003; Leung & Cai, 2007; Li, Huang, et al., 2006; Stuphorn & Schall, 2006; Stuphorn et al., 2000; Zhang et al., 2017) or patients with brain lesions (Aron et al., 2003; Floden & Stuss, 2006; Fried et al., 1991; Hodgson et al., 2007; Lüders et al., 1988; Mikuni et al., 2006; Nachev et al., 2007; Swann et al., 2012). Although neuroimaging studies provide evidence that links areas in the brain to task performance, this approach is unable to provide a causal link showing which areas play an essential role. Similarly, human patient studies cannot avoid associated limitations as a result of neural plasticity or reorganization. A way to solve this issue, is to use non-invasive brain stimulation (NIBS) techniques to selectively manipulate in healthy participants single cortical components of the action inhibition network (AIN) to investigate their - specific - contribution in the several processes underlying action control (i.e., inhibition, selection, competition and switching of actions). Recently, there has been a growing interest in the application of different non-invasive brain stimulation techniques to induce neuroplasticity and to modulate cognition and behavior (Huang et al., 2017). In this review, we report and compare, whenever possible, the main results of action inhibition studies that undertook to investigate the

critical role of the key nodes of the AIN by means of NIBS using an SST paradigm. In particular, only peer-reviewed published studies in English language were included. Studies were required to report experimental designs on healthy volunteers, using TMS (we excluded studies testing motor evoked potentials) or tDCS in human participants with a control condition (sham stimulation, active control stimulation or baseline performance). Only studies implementing the stop-signal task and reporting stop-signal reaction time (SSRT) as outcome were included. Our aim is to understand the crucial role of cortical brain regions of the AIN in motor action suppression and to disclose which are the most efficient NIBS protocols.

TMS is a non-invasive neural modulation technique with valuable potential in both neuroscience (Bergmann, Karabanov, Hartwigsen, Thielscher, & Siebner, 2016) and clinical studies (Lefaucheur et al., 2014). In particular, it has been shown that repetitive TMS (rTMS) can temporarily modify brain function for minutes to hours (Hamada et al., 2007; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Iyer, Schleper, & Wassermann, 2003; Jung, Shin, Jeong, & Shin, 2008). Stimulations at low (≤1 Hz) and high (≥5 Hz) frequency can decrease or increase neuronal excitability, respectively. Among rTMS protocols, theta-burst stimulation (TBS) can produce long after-effects (>20 min) using relatively short-term stimulation (typically, 40– 190 s) at a higher frequency (50 Hz) (Huang et al., 2005). In particular, continuous TBS (cTBS; 40 s train of uninterrupted TBS is given for a total 600 pulses) is supposed to suppress cortical excitability, while intermittent TBS (iTBS; 2 s train of TBS is repeated every 10 s for a total of 190 s and 600 pulses) is thought to facilitate it (Huang et al., 2005). While using tDCS, direct electric current, passing through two saline soaked sponge electrodes placed over the participant's skull, is applied to modulate human brain excitability (George & Aston-Jones, 2010). Through this type of stimulation, feeble electric currents (1-2 mA) are conducted through two electrodes (anode and cathode), which increase or decrease neuron activity by changing the membrane potential (Nitsche & Paulus, 2000). Although the exact functioning of tDCS is not entirely clear, it is well established that several minutes of stimulation with the anode placed over a target area increases its cortical

activity, whereas placing the cathode sustainably reduces it. Thus, tDCS could increase or decrease neuron activity and also modulate behavior, and the effects depend on the duration and the current density of the stimulation (Nitsche et al., 2008).

The endeavor to understand the neural circuits of action inhibition in humans originated approximately 15 years ago; here we review the major advances, highlighting new methodological approaches to understanding and exploiting several processes underlying action control. In particular, we critically examine different non-invasive brain stimulation protocols in SST and the specific results obtained, aiming at trying to delineate and suggest important factors that can contribute to modulate inhibition performance. Hence, our goal is to provide fundamental implications of clinical relevance for the recent enhancing in the understanding of psychiatric disorders and thus improving relative treatments in this area of research. A summary of the experimental results, methods and stimulation protocols adopted in each NIBS study is reported in Table 1 and Table 2, while Figure 1 and 2 show the stimulation site in each NIBS-SST experiment.

2. Transcranial Magnetic Stimulation and action inhibition

Although the cognitive mechanisms underlying response inhibition have been studied for several years (Logan, 1981, 1994), the neural mechanism subtending this process is still a matter of debate. The most accredited theory proposes that the human prefrontal cortex is responsible for executive control, but it is contentious whether discrete prefrontal regions are specialized to carry out domain-specific functions (Aron, Robbins, & Poldrack, 2004; Duncan & Owen, 2000; Goldman-Rakic, 1987; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). Results from several studies suggested that prefrontal regions share control over a range of cognitive processes, including those involved in the inhibition and selection of responses (Duncan & Owen, 2000). Others, however, have argued that mechanisms of response inhibition are governed by a discrete network of brain regions in the parietal and prefrontal cortex (Aron et al., 2003; Garavan, Ross, & Stein, 1999; Morita, Nakahara, & Hayashi, 2004; Rubia, Smith, Brammer, & Taylor, 2003). A way to solve this

issue is to use TMS in healthy volunteers to temporarily interfere with the activity of a selective region of the prefrontal cortex to assess its causal role in a discrete function. In 2006, Chambers and colleagues undertook to test the hypothesis that discrete regions of the right prefrontal and parietal cortex (e.g., IFG and middle frontal gyrus- MFG or angular gyrus -AG) selectively govern response inhibition in the healthy brain. To investigate this issue, the authors asked participants to undergo an SST after receiving different sessions of 15 min (1 Hz) of offline rTMS at an average of 92% resting motor threshold (rMT) to the right IFG, MFG, or AG. In the SST, participants had to identify a target go stimulus as rapidly as possible. In 25% of the trials, a stop signal was presented, instructing participants to withhold their response. To manipulate the difficulty of successfully inhibiting, the stop signal was presented randomly at various delays after the go signal. Moreover, to maximize the sensitivity of their TMS protocol, stop signals were presented at SSDs that that yielded 25–75% correct inhibitions. Finally, to measure possible effects of cortical reorganization over time, participants received two consecutive blocks of rTMS per session, each followed by the SST, and pupil diameter was recorded throughout the experiment as an index of physiological arousal. Results showed that rTMS over rIFG impact the response inhibition performance (i.e., lower percentage of correct inhibitions and longer SSRT) compared to sham, in both the left and right hands selectively in the first block after rTMS, while in the second block after rTMS no significant effects of rTMS on behavior were found. Moreover, no significant effects of rTMS were observed on go-RT or on error rates nor in the change of pupil diameter over time, excluding that diminished arousal over time may explain the lack of significant effect in the second block. To conclude, these data successfully demonstrated the critical role of the rIFG in inhibiting or overriding prepotent responses of both hands. However, such data do not imply that IFG is the sole mediator of response inhibition, since this brain region is richly interconnected with a range of cortical and subcortical structures (Durston et al., 2003; Vink et al., 2005), which can be affected by the deactivation of the IFG and may contribute to action control. Moreover, the rTMS effect over IFG was selectively observed in the first block and it tended to disappear during the second block.

These results suggest that the AIN is able to functionally reorganize, directing elsewhere the critical process ascribed to IFG (Siebner & Rothwell, 2003), such as to the right MFG, parietal cortex, or homologous structures in the left hemisphere (Hester, Murphy, & Garavan, 2004). The following year, the same research group (Chambers et al., 2007) investigated whether a range of inhibitory behaviors including response inhibition and response selection may be subtended by a common neural substrate. To test this hypothesis, participants were tested in their ability to overcome competing response tendencies (i.e., flanker task), and in the ability to withhold an initiated action (i.e., SST) after two separate sessions (20 min each) of offline 1 Hz rTMS at an average of 92% rMT over left and right IFG and dorsal premotor cortex (dPMC). The combined flanker/SST required participants to identify the direction of the central arrow as rapidly and accurately as possible with their left or right hand, ignoring the distractors and withholding their response when the stop signal occurred. Results from this behavioral data revealed that the ability to inhibit a prepotent response (in the SST) is closely related to the degree of competition between responses (in the flanker task SSRT reduced significantly when incongruent distractors flanked the central arrow target, relative to conditions in which the flankers were congruent or neutral). The rTMS data showed that the rTMS over rIFG slowed SSRT on incongruent trials relative to both sham and dPMC conditions (but see Yang, Khalifa, & Völlm, 2018 for null results on SSRT after the excitatory stimulation of the rIFG; 45 trains of 10-Hz rTMS stimulation session at 100% of the rMT consisted of 900 pulses in total with a 2-s duration of each train and a 10-s interval between each train). No effects were found in congruent trials, demonstrating that rTMS over the rIFG selectively increased SSRT in trials in which a suppression of a competing response is required. Moreover, analysis on go trials showed that performance tended to improve after stimulation of right dPMC compared with the sham and rIFG stimulation conditions. Data from the experiment in which IFG and dPMC were stimulated in the left hemisphere showed no significant effect of the rTMS either in the SSRT or in the go trials analysis. To sum up, these data confirm previous findings (Aron et al., 2003; Chambers et al., 2006; Hodgson et al., 2007) on the causal role of the right (and not the left)

IFG in stop-signal inhibition, selectively when response selection was placed under competition (i.e., incongruent flanker trials). Therefore, the rIFG appears to be especially crucial for erasing responses under conditions of increased response competition, even though rIFG stimulation did not alter the effect of competition on response execution. The rTMS over rIFG may have delayed the release of an inhibitory trigger or reduced the speed of the stopping process once triggered, possibly due to the existence of direct connections between the IFG and the subthalamic nucleus of the basal ganglia (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron & Poldrack, 2006; Nambu, Tokuno, & Takada, 2002). Moreover, stimulation of the right dPMC tended to enhance execution performance in all conditions, facilitating RT of both hand responses regardless of the degree of competitive response selection. This result is in contrast with results obtained in previous rTMS studies of response selection (Koski, Molnar-Szakacs, & Iacoboni, 2005; Praamstra, Kleine, & Schnitzler, 1999; Schluter, Rushworth, Passingham, & Mills, 1998), possibly due to several methodological differences such as the behavioral paradigms, rTMS protocols, and site localization. However, the observed double dissociation of the rTMS effects between the rIFG and right dPMC leads authors to the conclusion that response inhibition and execution rely on distinct neural processes despite activating a common cortical network. From this evidence, it seems clear that the rIFG has a predominant inhibitory role in updating behavior; however, other theorists posit that this area may have a role in attention, mediating detection of stimulus change (Sharp et al., 2010), whereas other brain regions, such as the pre-SMA, are effectively involved in action inhibition or in both processes (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). Alternatively, the rIFG could have a general role in updating action plans (Mars, Piekema, Coles, Hulstijn, & Toni, 2007). The key difference between the inhibition and updating accounts is that the inhibition account assumes that rIFG is selectively crucial for stopping, whereas the updating account assumes that rIFG is crucial for different forms of updating (including stopping). To investigate whether the rIFG effectively has a role in updating behavior, Verbruggen and colleages (2010) employed cTBS over rIFG, over the more dorsal right inferior frontal junction (rIFJ) and over pre-SMA or sham in

separate sessions, and tested participants in a context cueing paradigm. In this paradigm, which is able to dissociate several control processes involved in updating behavior, the identity of a cue indicated different task contexts (ignore, dual, and stop). When the cue changed color, participants initiated a manual response. In a minority of trials, the cue turned bold after a variable delay: in the signal-ignore trials, participants had to ignore the change and execute the response; in the dual-signal trials, participants had to execute an additional response by pressing an alternative key; and in stop-signal trials, participants had to try to withhold the response. Importantly, to disentangle visual-detection account and the action-updating account, the colored cue turned bold for 250 ms after a variable delay (Stimulus Onset Asynchrony - SOA). In signal-ignore and dual-signal trials, SOAs were fixed (100, 250, or 400 ms); in stop-signal trials, SOA was dynamically adjusted. Results showed that cTBS over the rIFG and rIFJ impaired performance in both stop and dual tasks compared to sham, suggesting that both areas are not selectively crucial for inhibitory control. In contrast to the results from cTBS over rIFG in which the dual-task effect did not interact with SOA, a strong interaction with SOA was found for the rIFJ stimulation. These results indicate that rIFG has a crucial role in action control, updating action plans, while rIFJ has a role in detecting visual changes of stimulus features. No effects were found when cTBS was applied over pre-SMA. These data demonstrated that rIFG is critical for stopping a response, but also that the cognitive role of rIFG is not purely one of inhibitory control (see data from dual-task) but seems to be not attentional (see data on the lack of interactions with SOA).

In 2015, Dippel & Beste tested the effect of an iTBS over the rIFG (together with cTBS over the rIFG and sham) and investigated the possible role of IFG in multi-component behavior. To test this issue, participants performed an SST in which the ongoing action was occasionally interrupted following delivery of a stop stimulus, while an alternative response had to be executed upon the presentation of an auditory stimulus. The auditory stimulus was presented either simultaneously or following the stop stimulus, so that when presented simultaneously, participants could process the two actions either serially or in parallel, while when the auditory signal followed the stop, it was

only possible to process the two actions in a serial manner. Results showed that iTBS over the rIFG induced a more efficient strategy of task goal activation, while cTBS of the rIFG induced a less efficient strategy of task goal activation compared with sham TBS (i.e., cTBS slowed the RT to the change stimulus, whereas the iTBS protocol increased it), while no effect on SSRT were found. It is important to mention that the present study is not completely comparable to the classical SST and therefore results may be ascribed to the use of a modified version of SST. However, these results are consistent with studies suggesting that the rIFG is unlikely to reflect a specific module for inhibitory demands but is instead also part of other cognitive domains (Erika-Florence, Leech, & Hampshire, 2014).

The first study that employed rTMS for investigating the critical role of pre-SMA in action inhibition was carried out by Chen, Muggleton, Tzeng, Hung, & Juan in 2009. Pre-SMA represents an important hub in the action inhibition network since it has direct connections to both the rIFG and the subthalamic nucleus, which are considered to be the main neural substrates for inhibitory control (Aron et al., 2007); however, its critical role in this process had never been tested. Chen and coworkers therefore decided to test the critical role of pre-SMA by using an online 10 Hz rTMS protocol (i.e., while participants are doing the SST). The SST required participants to make a key-press response when a dot was presented on the left with the left finger, or with the right index finger when the dot was presented on the right. In stop trials, a central fixation dot reappeared and acted as an instruction to withhold responses to the peripheral target. In the rTMS blocks, at the onset of the go signal, two TMS pulses with an inter-pulse interval of 100 ms at 60% of the maximum stimulator output (MSO) were delivered over the pre-SMA or vertex (i.e., the active control site) in separate sessions. rTMS over pre-SMA elongated the SSRT compared to vertex stimulation and without TMS. Since Chambers and colleagues in 2006 found differences in SSRT selectively in the first block, an additional analysis took into consideration data from separate sub-sessions. Results showed that the pre-SMA TMS effect seems more substantial in the first sub-session (i.e., longer SSRT in the first compared to the second sub-session). Indeed, no main effect

for stimulation sites was found in the second sub-session. These data demonstrate the critical role of pre-SMA in the inhibitory control for both hands, in line with previous fMRI data (Li, Huang, et al., 2006), which found that activation of the pre-SMA was correlated with shorter SSRTs, suggesting that greater activity in pre-SMA is indicative of more efficient inhibitory control. The fact that the effects are visible only during the first session may suggest that the role of pre-SMA is dependent on familiarity with the task or that its functional weight in inhibitory control may change over time. Although informative, the effect of the elongated SSRT when the TMS was applied before the stop signal left open two alternative hypotheses: the TMS may have disrupted the stopping preparation or the stopping process itself. To investigate the issue further, another study (Cai, George, Verbruggen, Chambers, & Aron, 2012) tested the role of the right pre-SMA in modulation of response tendencies versus implementation of the stopping process by using a conditional SST. In this task, participants were asked to cancel their response selectively whenever the arrow go signal turns red and points in the critical direction. During the task, dual TMS pulses were delivered over right pre-SMA or vertex at 125/150 ms or at 175/200 ms after the go signal, while no pulses were delivered on the remaining half of the trials. Results showed that SSRT on TMS trials in the pre-SMA session was significantly longer than SSRT in the vertex TMS condition or in trials without TMS, in line with previous findings (Chen et al., 2009). However, such effect of SSRT increase could relate to a disruption in setting up the stopping rule or to disruption in implementing stopping, and therefore, in a second experiment, the authors employed a selective SST, which involves a trial-by-trial changing stopping rule and allows to dissociate setting up the stopping rule from implementing stopping (Aron & Verbruggen, 2008). Specifically, the selective SST has a foreknowledge period (maybe stop right hand), a delay, a go stimulus (move both hands together) and, then, in some trials a stop signal requiring the participant to stop the cued hand and continue with the other is presented. The stop signal is not informative of which hand to stop; therefore, the participant needs to encode the cue presented in the foreknowledge period. To interfere with the period corresponding to setting up the selective stopping rule, dual pulses were delivered at 100/125

ms or at 150/175 ms after the offset of the task cue, while at 125/150 or 175/200 ms after the onset of the stop signal or after the average SSD in go trials to interfere with the period corresponding to implementing the stopping process. No pulses were administered in the remaining trials. In trials in which TMS was delivered over pre-SMA, SSRT was significantly longer than SSRT in trials without TMS or when the vertex was stimulated. In both experiments, no significant effect of the TMS over pre-SMA was found in other behavioral indices, ruling out possible distraction or discomfort effects. These data suitably demonstrated that TMS over the right pre-SMA specifically disrupted the implementation of stopping process, since the stimulation after the stop signal was too late to affect setting up the stopping rule. A later study (Obeso, Cho, et al., 2013) combined the cTBS (20 s block consisted of 3 pulses at a rate of 50 Hz repeated every 200 ms at 80% of the active MT; AMT) over pre-SMA or sham with the H2 15O positron emission tomography (PET) scans during the SST and provided evidences on the causal role of the pre-SMA in reactive inhibition (reduced SSRT relative to sham, as found in a subsequent study which found this effect to be specific for cTBS over pre-SMA and not IFG; Obeso et al., 2017). Moreover, cTBS had an impact on the regional cerebral blood flow (rCBF) in several frontal areas, such as in the left pre-SMA, left IFG, right premotor and right inferior parietal cortex, suggesting that the stimulation may have a major impact not only locally in the underlying cortex but also distally in interconnected areas, which may also be critical in the observed results or may represent a compensatory activation against the TBS-induced "disruptive" effect. In the same year, the same research group undertook to further investigate whether pre-SMA has a role in action inhibition (both reactive and proactive) and/or in the switching of actions, and whether this area acts in concert with the rIFG (Obeso, Robles, Muñoz-Marrón, & Redolar-Ripoll, 2013). Participants were involved in a modified version of the SST in which they have to respond to the arrow's directions (go trials), and to stop any movement when the arrow was followed by an infrequent cross. In the switch condition, the arrow turns blue, requiring switching to a new movement. Before the task, cTBS over the rIFG or sham were applied. To see the influence of rIFG in pre-SMA functioning, following cTBS, participants

performed the stop switching task while receiving single TMS pulses (100 ms after stimulus; 60% of the MSO) over the right pre-SMA or vertex. Results on stopping processes showed that online TMS pulses over the right pre-SMA (after sham cTBS but not after cTBS over IFG) altered the stopping process (i.e., prolonged SSRT), and the preparation to inhibit an action (i.e., reduced response times needed to adapt between different task conditions during proactive inhibition), but no such worsening was observed in switch trials, when participants received online TMS pulses over both IFG and pre-SMA, suggesting the lack of a critical role of these two regions at least in the tested temporal window (i.e., 100 ms). To conclude, these data confirmed the crucial role of pre-SMA in reactive and proactive inhibition. Moreover, it is obvious that the successful inhibition of an action requires the suppression of activity in the primary motor cortex; however, the way in which action inhibition commands reach M1 is still a matter of debate. In 2013 Zandbelt, Bloemendaal, Hoogendam, Kahn, & Vink undertook to investigate how the regions of the AIN interact to exert inhibitory control over M1 and whether these regions have a causal involvement in proactive and reactive inhibition. Each participant underwent three separate rTMS-fMRI sessions, in which they received rTMS stimulation over the rIFC, over the pre-SMA (i.e., supplementary motor complex; SMC) and sham. rTMS consists of 20 trains of 30 6-Hz pulses at 90% of rMT with an intertrain interval of 25 sec, followed by 600 1-Hz pulses at 110% of rMT. Immediately afterwards, participants were asked to perform the stop-signal anticipation task in the scanner. Importantly, to test both proactive and reactive inhibition, the stop-signal probability was manipulated across trials. Typically, as stop-signal probability increases, participants proactively slow down responding to increase inhibition accuracy when a stop-signal occurs. Results showed that rIFC and pre-SMA stimulation did not influence proactive inhibition (i.e., no changes in RT were detected) but only reactive inhibition. Indeed, participants became faster in reactive stopping (i.e., shorter SSRT) after both rIFC and pre-SMA stimulation. Interestingly, this effect was associated with increased M1 deactivation. Furthermore, rIFC and pre-SMA stimulation increased right striatal activation, implicating an involvement of fronto-striatal pathways in reactive

inhibition. Finally, rIFC stimulation altered pre-SMA activation, while pre-SMA stimulation did not alter rIFC activation, indicating that rIFC lies upstream from pre-SMA.

Although converging evidence of these NIBS studies suggests a causal role of rIFC in successful response inhibition, most of the above-mentioned studies focused exclusively on the SST as a measure of action cancellation, without assessing the critical role of the rIFC in action restraint. Thus, to fill this gap, Dambacher and colleagues in 2014 measured action restraint with a go/no-go task and action cancellation in an SST, after separate sessions of cTBS (at 100% of the AMT) or sham stimulation of the right anterior insula (rAI), right superior frontal gyrus, and pre-SMA. Results showed higher false alarms rates in inhibition trials in the go/no-go task and SST after rTMS over rAI, demonstrating that the stimulation reduced both the ability to restrain and cancel responses, while disruption of the right superior frontal gyrus specifically impaired the ability to restrain from responding (higher false alarms rates in inhibition trials selectively in the go/no-go task), while leaving the ability for action cancellation largely intact. Inhibitory processes were not affected by the stimulation applied to the right middle frontal gyrus and pre-SMA. These findings emphasize the role of IFG for global inhibition, whereas superior frontal regions seem to be specifically relevant for successful action restraint.

To examine the causal links between several regions of the action inhibition network, such as the frontal regions and basal ganglia, in 2015 Watanabe and coworkers measured human fMRI activity during SST before and after excitatory/inhibitory rTMS of the pre-SMA. To induce long-lasting changes in brain activity, the authors used quadripulse rTMS (QPS), the effects of which are supposed to continue for a relatively long time after the stimulation (from 30 min to 2 h; Hamada et al., 2007). The QPS consisted of a train of four monophasic magnetic pulses, delivered with four magnetic stimulators connected to a specially designed combining module at 90% of AMT. The inter-burst interval was set at 5 s. One rTMS block had 360 consecutive bursts, each of which comprised four magnetic pulses separated by interstimulus intervals of 5 or 50 ms, for excitatory or inhibitory rTMS respectively. Each participant underwent an SST performed in an fMRI scanner

before and after a session of rTMS (excitatory, inhibitory of the pre-SMA or sham). Excitatory rTMS significantly decreased SSRT compared to the sham condition, while inhibitory rTMS significantly increased SSRT. Indeed, such behavioral changes were correlated with neural changes in striatum (STR) and globus pallidus pars interna (GPi), which were affected by the stimulation of the pre-SMA. In contrast, such causal effects were not observed in the activity and functional interactions involving the right IFC and the subthalamic nucleus (SN), suggesting that the rTMS over the pre-SMA affected the indirect pre-SMA–STR–GPi pathway by possible top-down regulation from the pre-SMA to the GPi via STR during successful response inhibition. In an attempt to further investigate this point and to exclude the possible role of attentional capture of the stop signal presentation, Lee and colleagues (2016) investigated the causal relations of the pre-SMA and the rIFG in a conditional SST by combining cTBS and a continue condition task, which requires the same motor response as in a go trial but captures attention as in a stop trial, since participants were requested to respond to a continue signal with a go response rather than a stop response. The analysis took into account individual differences in the degree of slowing in continue trials (high versus low) and showed that the selective disruption of right pre-SMA activity significantly influenced the continue process only in the low-slowing group, whereas disruption of the rIFG did not lead to any significant changes in performance irrespective of the degree of slowing. The authors concluded that the pre-SMA plays a critical role in response slowing in continue trials during conditional stopping, and it is likely that its efficiency in updating motor planning and reinitiating an inhibited response was associated with the amount of slowing, as previously suggested by fMRI data (Sharp et al., 2010). In the same year, Xu and colleagues investigated the effect of online single pulses of TMS at different intensities (i.e., high =120%, medium = 80%, and low = 40% of the individual rMT) over the pre-SMA during fMRI within the fronto-basal-ganglia network and the relation of these changes to the response inhibition performance. The authors found that TMS induced a BOLD signal increase within the fronto-basal-ganglia inhibitory network. In particular, the high-intensity TMS changed the BOLD signal in the

right pallidum and left caudate, which also correlated specifically with the SSRT performance (i.e., increased in connectivity and decreased in SSRT). These results suggest that the widespread effect of pre-SMA TMS, at least at the suprathreshold level, was immediate and related to the task-free neural activity associated with response inhibition.

To go a step further in establishing the temporal and causal interplay between the pre-SMA and the rIFG, Allen, Singh, Verbruggen, & Chambers (2018) combined the high temporal and reasonable spatial resolution of magnetoencephalography (MEG) with TMS to elucidate the temporal dynamics of the interplay between the IFC and the pre-SMA in an SST. Indeed, very few studies have addressed this issue, and only one study on a single subject, has used intracranial recording to demonstrate that activity related to stopping in the pre-SMA can precede IFC activation (Swann et al., 2012). Allen and colleagues employed the same SST in both MEG and TMS sessions. As TMS was functionally guided according to the MEG results, participants underwent the TMS session on a separate day, after their MEG session. Single pulses of TMS were delivered at 110% of each participant's rMT and the timing of the TMS pulse was dependent upon an individual participant's tROI, which represents the limited period during which either the pre-SMA or the IFC can exert an influence, being situated between the onset of the stop signal and the action. Data showed larger SSRT during active TMS relative to sham, but no differences were found across temporal stimulation conditions (i.e., the temporal order in which TMS was applied to the regions, initial pre-SMA TMS or initial IFC TMS), demonstrating that the application of TMS to both regions disrupted stopping, consistent with the critical role of both the pre-SMA and IFC in inhibitory control. Importantly, however, the temporal order in which TMS was applied to the regions made no difference to the disruption of stopping, in contrast with the idea that information is transmitted from the pre-SMA to the right IFC, and that the pre-SMA may therefore be the cortical source of the stop signal. These results were additionally supported by MEG data, which suggested that the time course of activity originating from the two regions during response inhibition is roughly simultaneous, possibly mirroring high levels of mutually interdependent activity. Granger causality

tests suggested that while neither region has been shown to initiate or precipitate a cascade of events in the response inhibition process, it is possible that there is an ongoing drive from pre-SMA to IFC during the interplay between the regions during stopping. Hence, the authors concluded that a pre-SMA to IFC drive may correspond to a proactive state of preparation, as opposed to a specific direction of influence in the actual stopping of an action. The effectiveness of different TBS protocols was tested in a recent study (Ji et al., 2019) which tested their efficiency in affecting the response inhibition ability by interfering with the pre-SMA activity. Changes in performance in an SST were assessed comparing inhibition performance in two sessions performed pre and post different TMS protocols (i.e., 5-Hz, 25-Hz at 110% of the rMT, intermittent (i) TBS at 70% of the rMT, and sham stimulation). Results showed performance improvement (i.e., shorter SSRT) in the iTBS session compared to sham, while no effects were observed in the 5-Hz and 25-Hz rTMS protocols. This effect, however, only occurred during the second session of the SST after iTBS. However, the effect of iTBS was not reproduced if participants only received sham or iTBS. Therefore, further investigation is needed to account for the high intersubjective variability.

So far, NIBS studies have mainly tested the crucial role of the pre-SMA and rIFG in action control, while, to the best of our knowledge, only one study undertook to investigate the critical role of the FEF in action control (Muggleton, Chen, Tzeng, Hung, & Juan, 2010). Interestingly, a single unit recordings study in monkeys (Thompson, Biscoe, & Sato, 2005) found that manual responses are associated with inhibition of FEF movement neurons when the task does not require a saccade to be made, suggesting that the FEF might serve a general function related to inhibitory control in the absence of the involvement of eye movements. By applying TMS over the FEF during an SST, Muggleton and colleagues (2010) found that TMS over the FEF had no effect on response generation (indexed by go-RT) but disrupted inhibitory control (i.e., longer SSRT compared to control vertex stimulation and no TMS). This data suggested that the FEF may play a role in inhibiting actions that do not require eye movements. Finally, Osada and colleagues in 2019 investigated the crucial role of the posterior parietal cortex, which has reciprocal projections with

the prefrontal cortex (Cavada & Goldman- Rakic, 1989), in action inhibition. The authors found that the stimulation over the intraparietal sulcus (IPS) (single pulses of TMS delivered at 120% rMT), disrupted performance in the SST (i.e., longer SSRT) when stimulation was applied 30–0 ms before stopping.

In summary, the FEF and IPS, like the IFG and pre-SMA, are involved in successful inhibitory performance with TMS delivered over this area, resulting in elevated SSRT and indicative of altered inhibitory control.

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3. Transcranial direct current stimulation and action inhibition

A way to gain further evidence about the neural network implied in the action inhibition is the use of tDCS. Thus, the application of tDCS to the AIN would be a useful adjuvant intervention modality for modulation of response inhibition and its related dynamic behavioral changes. One of the first hypotheses of using this protocol in the SST framework was that excitatory tDCS, with the anode placed over the pre-SMA, would facilitate inhibitory control and that inhibitory tDCS, with the cathode placed over the pre-SMA, would impair performance. Such effects would not only confirm the critical role of the pre-SMA in the inhibitory control network, but, importantly, may demonstrate that a behavioral improvement in inhibitory control is possible by means of the

excitatory stimulation of this area. Such tDCS-induced improvement may be fruitful as an initial step towards developing clinical treatments aiming at enhancing inhibitory control (Schroeder, Schwippel, Wolz, & Svaldi, 2020).

In the seminal study of Hsu and coworkers (2011), participants performed an SST before and after tDCS administration (1.5 mA, 10 min). Two groups of participants were tested: one group underwent tDCS with the anode and cathode placed over the left pre-SMA (tDCS-pre-SMA) or as sham in separate sessions, while another group was stimulated with the anode and cathode placed over the left primary motor cortex (tDCS-M1) or as sham. The results showed that excitatory tDCS selectively over the pre-SMA improved the efficiency of inhibitory control (i.e., reduced errors). Conversely, inhibitory tDCS of the pre-SMA activity showed a tendency towards impaired inhibitory control. Thus, the main finding of the study was that selective error rates in the stop signal trials were significantly modulated by the tDCS polarity: they were reduced by excitatory stimulation and increased by inhibitory stimulation, confirming the critical role of the pre-SMA in inhibitory control (see also Liang et al., 2014 for similar findings after excitatory stimulation of the pre-SMA activity and Yu, Tseng, Hung, Wu, & Juan, 2015, who also demonstrated that excitatory tDCS-induced BOLD increases in the ventromedial prefrontal cortex (vmPFC), which was positively correlated with participants' improvement in stopping efficiency). No effects on RT or SSRT were observed either in the tDCS-pre-SMA or in the tDCS-M1 group (for similar results see Bender, Filmer, & Dux, 2017; Reinhart & Woodman, 2014).

The lack of significant results in the SSRT may be due to the fact that the authors set the SSD based on the participants' responses, and thus SSD made the task too simple, preventing SSRT estimation in some participants.

To further investigate the role of the pre-SMA, in a later study (Kwon & Kwon, 2013) the authors examined whether tDCS over the pre-SMA and M1 alters the SSRT using the SST. Participants were tested in two separate sessions, before and after tDCS administration (1 mA, 10 min) with the anode placed over the pre-SMA, or over the primary motor cortex (M1) as active control condition,

or sham stimulation. Findings demonstrated significant reductions in the SSRT and longer RT after pre-SMA stimulation compared to both M1 and sham stimulations (see Kwon et al., 2013 for a decrease of the SSRT after and during tDCS with the anode placed over M1). No significant effect after administration of the tDCS was found in the go trials. These data suggested that excitatory tDCS administered over the pre-SMA resulted in enhancement of the inhibitory control.

Within the AIN, response inhibition has also been localized in the IFG, based on both functional brain imaging and lesion-based approaches (Aron et al., 2003; Chevrier et al., 2007; Leung & Cai, 2007; Zhang et al., 2017). In the seminal study by Jacobson, Javitt, & Lavidor (2011), the authors used the SST to investigate whether the rIFG is crucial for action inhibition, by applying excitatory and inhibitory tDCS (1 mA, 10 min). Participants underwent different tDCS conditions: anode placed unilaterally over the rIFG, cathode placed unilaterally over the rIFG, bilateral anode/cathode placed over the rIFG and sham. Furthermore, in a control task, participants were required to discriminate visual shapes similar to those presented in the SST; however, no stop signal was given and, in a control experiment, the right angular gyrus was stimulated as control site (rAG). The authors found that the activation of the rIFG by unilateral excitatory stimulation significantly improved response inhibition relative to a sham condition (i.e., reduced SSRT; which was also recently confirmed in a study demonstrating strengthened behavioral response inhibition to external food images compared to sham after excitatory rIFG stimulation; Chen, Jackson, Dong, Zhang, & Chen, 2019), whereas excitatory stimulation of both the rIFC and rAG did not affect RT in the go trials of the SST and control task. Furthermore, the SST was not affected by tDCS delivered over the control site (rAG). The authors only found a near-significant effect for bilateral stimulation and suggested that the left IFG (lIFG) may also be involved in response inhibition. Indeed, only when the activity of the rIFG was facilitated (by unilateral excitatory stimulation) did the participants show reduced SSRT compared to the bilateral stimulation in which the rIFG was facilitated and lIFG was inhibited.

In addition, when only the rIFG was inhibited (by placing the cathode unilaterally), participants showed longer SSRT compared with the bilateral stimulation condition in which the rIFG was inhibited and the lIFG was facilitated. These findings suggest a critical role of both the right and left IFG in action control.

In the following year, Ditye, Jacobson, Walsh, & Lavidor (2012) investigated the effects of tDCS placing the anode over the rIFG in combination with a behavioral training using an SST. This study aimed to investigate the additional role of repetitive behavioral training combined with tDCS over the rIFG. The authors investigated the effect of the training integrated with rIFG-tDCS on behavioral inhibition and specifically tested whether i) multiple-session training is effective in improving the ability to inhibit responses and ii) the stimulation of the rIFG would further induce/facilitate training-induced improvements. Participants were randomly assigned to an excitatory tDCS group or to a control group without tDCS. Prior to performing the task, the experimental group received excitatory tDCS (1.5 mA, 15 min) over the rIFG. Importantly, tDCS was delivered every day (over a total of 5 days), except on the last day, because the fifth day was aimed to investigate the sustainability of the effects of tDCS, 24 h after stimulation had stopped. Results suggested that behavioral training effectively improved the ability to inhibit responses and that the combination of SST training with tDCS generated a greater effect than multiple-session training alone. The only significant difference across groups was found at day 3 and 4 (i.e., reduced SSRT in the group with the anode placed over the rIFG) but not at day 5, suggesting that the beneficial effect of tDCS is rather short-lived. An important limitation of this study is the lack of a placebo stimulation group, preventing the possibility to rule out unspecific effects of brain stimulation.

To sum up, the rIFG and pre-SMA have been the main focus of these attempts to modulate response stopping by means of NIBS. However, other cortical areas such as the dorsolateral prefrontal cortex (dlPFC) have been found to be implicated in inhibitory control (Bari & Robbins, 2013; Leung & Cai, 2007). Therefore, to investigate the crucial role of the right dlPFC (rdlPFC), Stramaccia and

coworkers (2015) delivered tDCS (1.5 mA, 20 min) over two target areas: the rIFG and rdlPFC. The participants, divided into five experimental groups based on whether their tDCS stimulation was with the anode placed over the rIFG or the rdlPFC, with the cathode placed over the rIFG or the rdlPFC, or sham. The SST was performed 15 min after the tDCS stimulation (delayed task). Results revealed reduced SSRT in the group with the anode placed over the rIFG relative to sham (but see Stramaccia, Penolazzi, Altoè, & Galfano, 2017). This finding suggests that the rdlPFC does not have a crucial role in response stopping. It is worth noting that this response stopping improvement is unlikely to result from a general cognitive enhancement, since no significant effects were found in the go trials. Indeed, such improvement is more likely to reflect increased inhibitory performance, due to the selective results on SSRT. However, this null result would not necessarily imply that the rdlPFC plays no role in inhibitory processing, but it is possible that the rdlPFC stimulation is short-lasting and hence not evident in the delayed protocol used in this study. Null effects after tDCS in SSRT were also found when placing the anode over the orbitofrontal cortex (OFC) (Ouellet et al., 2015), demonstrating that inhibitory motor control is primarily mediated by non-OFC regions (e.g., pre-SMA, IFG and FEF). In the study by Mansouri and colleagues (2017), participants performed an SST while they listened to high-tempo music, low-tempo music, or background-noise. SST was performed before and after tDCS (1.5 mA, 10 min) with the anode over the ldlPFC or sham. Practice led to a decrease in SSRT and an increase in RT, which was found to be significant only in the low-tempo music condition and for the background-noise condition (sham stimulation). The authors suggested that practice-related changes in response inhibition may be attenuated by high-tempo music. Indeed, such attenuation was restored by the excitatory stimulation of the ldlPFC, demonstrating that the tDCS modulatory effect was dependent on the background music (i.e., high-tempo music), which may improve the inhibitory performance.

To further investigate the role of dlPFC in the action inhibition Friehs and Frings (2018) used an SST and stimulated the rdlPFC in a pre-post experimental design employing excitatory tDCS (0.5 mA, 19 min). The authors contrasted the effect of an excitatory stimulation with sham and they

expected to observe an increase in inhibitory functions after tDCS with the anode placed over the rdlPFC, as evidenced by a reduction in SSRT. At the beginning participants performed a pre-test SST block; subsequently half the sample underwent the excitatory tDCS stimulation, whereas the other half received a sham stimulation. Afterward, participants were tested in a post-test SST. The results showed that applying tDCS with the anode placed over the rdlPFC relative to sham reduced SSRT and omission errors. Importantly, since RT were not affected by the stimulation, possible speed-up of responses due to the stimulation can be excluded. Although Stramaccia et al., 2015 were not able to point out the involvement of dlPFC, this study suggests a possible role of the rdlPFC in cognitive inhibition processes and further emphasizes that inhibitory control is a malleable mechanism. A similar and subsequent study (Friehs & Frings, 2019) used the same experimental design placing the cathode over the rdlPFC (0.5 mA, 19 min) to potentially hamper the response inhibition process as measured by the SST. Results showed that the inhibitory tDCS decreased performance by increasing SSRT, without affecting omission errors in stop trials and go-RT. Taken together, these results support the idea of a critical role of the dlPFC in response inhibition and suggest that polarity-dependent modulation of the response-inhibition process is possible with excitatory stimulation boosts inhibition, whereas inhibitory stimulation diminishes it, although to a lesser degree, in line with previous findings over pre-SMA (Hsu et al., 2011).

Finally, a recent work (Fehring et al., 2019) investigated whether excitatory tDCS effects in action inhibition depend on the level of learning in a cognitive task. To this aim, participants completed the SST either before and after tDCS stimulation (1.5 mA, 10 min) with the anode placed over the ldlPFC or sham tDCS stimulation was delivered in two distinct sessions, separated by a one-week washout period. This experimental design was implemented to test within-session learning (changes in performance on the same day) and across-sessions learning (changes in performance after one week). Results showed that excitatory tDCS had an across-week effect on behavioral measures (i.e., longer go-RT and shorter SSRT), suggesting that the impact of the tDCS was dependent on the level of experience learning. When excitatory stimulation was delivered in the first week (before the

occurrence of across session learning), shorter SSRT was observed in the post-tDCS testing (within-session learning), however when it was delivered in the second week, the magnitude of within-session learning was significantly attenuated (i.e., no effect on SSRT was observed). Taken together, these results suggested that plastic changes induced by learning may have altered the susceptibility of the prefrontal cortex to be further modulated by tDCS. However, such practice-related learning seems to saturate or attenuate the plasticity of the neurocircuitry; and therefore, attenuates tDCS differences across sections delivered in separate weeks.

In summary, according to several studies, tDCS administered with the anode placed over the IFG, pre-SMA, dlPFC and M1 reduced SSRT, improving behavioural performance. However, it is important to consider that all these studies investigated the critical role of each of these components independently, therefore, information about the neural interplay among these areas remains obscure. As mentioned in the introduction, inhibitory control can be divided into proactive mechanisms (response slowing in anticipation of a stop-signal) and reactive mechanisms (outright stopping in response to a stop-signal). Therefore, an important issue concerns the relationship between proactive and reactive inhibitory control, and whether the same neural substrate subserves both mechanisms.

To assess the causal role of the rIFG and IPL, which was found to be more strongly activated in the stop than go trials (Congdon et al., 2010; Hughes et al., 2014), in proactive and reactive inhibitory control, Cai and colleagues in 2015 asked participants to complete an SST after the administration of tDCS (1.5 mA, 15 min) with the anode placed over the rIFG, rIPL or the visual primary cortex (V1) as active control condition in a within-subjects design. To index proactive inhibitory control, the authors employed the preparatory cost (PC) index, which was calculated including only correct go trials by subtracting the mean RT of the first two post-stop go trials from that of the later post-stop go trials (i.e., higher PC indicates better proactive inhibitory control). Instead, reactive inhibitory control was indexed by SSRT. Compared to the V1 stimulation, excitatory stimulation of the rIFG facilitated both proactive and reactive control (i.e., after rIFG stimulation larger PC and

greater reduction of SSRT was found, see Li et al., 2019 for similar results on SSRT). No significant results were obtained by stimulating the IPL. Moreover, since there was a significant negative correlation between the PC index and the SSRT, the authors conducted a mediation analysis to examine whether the tDCS effect on reactive control was mediated by proactive control. The results showed no significant mediation effect, and the effect of stimulation condition on the SSRT change was still significant after adding the mediator. Thus, the results suggest that the tDCS effect on reactive inhibitory control was not mediated by facilitation of proactive inhibitory control. Another work investigated the role of the rIFC in the proactive and reactive inhibitory process (Cunillera, Fuentemilla, Brignani, Cucurell, & Miniussi, 2014) using a combination of go/no-go and SST. TDCS (1.5 mA, 18 min) with the anode placed over the rIFC or sham were delivered in a within-subjects design. The task consisted in a choice-reaction go/no-go task in which there were two variant perceptual complexity conditions, based on the visual discriminability of the stimuli. Results showed shorter SSRT in the excitatory rIFG condition relative to sham, reflecting a behavioral inhibitory improvement. Moreover, excitatory tDCS slowed down the RT, and reduced error rates when the stimuli discriminability was easier. These results indicate a possible increase in task control, which was interpreted as a proactive inhibitory process. A subsequent work (Cunillera, Brignani, Cucurell, Fuentemilla, & Miniussi, 2016) used the same task in a within-subject design in which online tDCS (1.5 mA, 20 min) with the anode placed over the rIFC or sham stimulation were delivered during the SST. The authors found a significant increase in RT for excitatory tDCS of the rIFC activity relative to sham, which was interpreted as increased proactive inhibition. However, in contrast to the previous result of the same authors (Cunillera et al., 2014), excitatory stimulation was not observed to be effective in modulating reactive inhibition, as indicated by the lack of significant effect in the SSRT. A possible explanation for the null effect of tDCS may be related to the different protocol of tDCS used between these studies (i.e., online vs offline stimulation). An additional study (Castro-Meneses, Johnson, & Sowman, 2016) compared reactive inhibition across manual and vocal effector systems (i.e., key pressing and vocal responses, respectively), examined

the effects of tDCS (1.5 mA, 15 min) with the anode placed over the right prefrontal cortex (rPFC) and looked at the relationship between reactive and proactive inhibition. Results showed that both vocal and manual reactive inhibition was faster (i.e., shorter SSRT) during and immediately after excitatory tDCS relative to sham. Moreover, a greater level of proactive inhibition (i.e., calculated by subtracting the mean of the go-RTs of the relevant stop condition from the mean of the go-RTs of the irrelevant stop condition; see Chikazoe et al., 2009) enhanced the reactive inhibition (i.e., when more proactive inhibition is implemented, SSRT gets shorter), supporting the hypothesis that the rPFC is part of a core network for reactive inhibition and supports the previous contention that proactive inhibition is possibly modulated via pre-activating the reactive inhibition network.

In an attempt to improve the spatial focality of tDCS, a recent study (Hogeveen et al., 2016) used high-definition tDCS (HD-tDCS) or conventional tDCS in two separate groups of participants to stimulate the rIFC during an SST or during a control task (choice reaction task; CRT). A third group of participants completed the same behavioral protocol but received conventional tDCS to a control site (mid-occipital cortex). The study employed a pretest–posttest design, repeated over two sessions. Thus, in the first session, participants completed the SST, then they underwent one of the three tDCS conditions while doing the same task, followed by another SST. The second session was equivalent to the first, with the exception that participants completed a choice reaction time task (CRT). SSRT analysis revealed significant performance improvements (i.e., shorter SSRT) in inhibitory control in both the conventional and the HD-tDCS group compared to the control group (mid-occipital cortex stimulation). The results suggest that HD-tDCS and conventional tDCS (delivered over rIFC) have statistically similar effects on response inhibition.

Finally, in a recent study by Sandrini and colleagues (2020), participants performed an SST before (on a first day) and after (day 2) tDCS with the anode placed over the rIFC (1.5 mA, 20 min) or sham in separate groups of participants. The study design included a resting-state functional magnetic resonance imaging (rsfMRI) before and after tDCS, and an event-related fMRI (efMRI) during the SST immediately following the post-tDCS rsfMRI on day 2.

Consistent with previous findings (Jacobson et al., 2011; Stramaccia et al., 2015), results (calculated on the difference in SSRT between session 2 and session 1) showed a significant difference between the excitatory and sham tDCS groups, with shorter SSRT found in the group with the anode placed over the rIFC relative to the sham group. In addition, no significant differences were observed between groups in RT. Regarding the fMRI results, rsfMRI revealed a significant increase in the functional connectivity between the rIFC and caudate, and between the rIFC, right pre-SMA, right inferior parietal cortex (rIPC), and rdlPFC after excitatory tDCS. Moreover, efMRI results showed that the excitatory tDCS strengthened the functional connectivity between the right pre-SMA and subthalamic nuclei during stop responses, suggesting that the stimulation of the rIFC induces neural modulation in several brain regions, such as the rIFC, rdlPFC, right pre-SMA, basal ganglia, and their interconnected brain regions (e.g., rIPC).

To conclude, the aforementioned tDCS studies suggested that proactive and reactive action inhibition mechanisms are partially independent and the existing studies converge in suggesting the crucial role of the rIFG in both reactive and proactive action control while, to the best of our knowledge, to date no studies have undertaken to specifically test the role of the pre-SMA in the proactive and reactive mechanisms by using tDCS.

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Conclusions

Action control represents a complex mechanism that subserves several different processes such as inhibition, selection, competition and switching of actions with a composite network of prefrontal areas (AIN) that have a role in orchestrating such processes. Indeed, deficits in performance in action control have been seen in various psychiatric disorders, including attention-deficit hyperactivity disorder and conduct disorder (Schachar & Logan, 1990; Schachar, Tannock, & Logan, 1993; Schachar, Tannock, Marriott, & Logan, 1995). It has also been shown to be altered in cocaine dependent men (Li, Milivojevic, Kemp, Hong, & Sinha, 2006), autism (Kana, Keller, Minshew, & Just, 2007) and obsessive compulsive disorder (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005), while impulsive-violent offenders show elevated SSRT (Chen, Muggleton, Juan, Tzeng, & Hung, 2008). Therefore, disclosing the specific and critical role of the different components of the AIN represents a crucial challenge to pave the way for designing novel NIBS therapeutic interventions aimed at enhancing the ability to improve cognitive control and inhibit potentially dangerous actions. Here we have reviewed the major research advances using the combination of SST with the use of NIBS over the last fifteen years (Juan & Muggleton, 2012). Although sometimes controversial, results suggest that both the pre-SMA and IFG (especially the right) may play a crucial role in (reactive and proactive) control of actions. The most controversial findings derived from studies assessing the proactive inhibitory control. Such inconsistency may be ascribed to the different paradigms used to investigate this process, relative to the consistency in the paradigms used to measure the reactive inhibitory (usually by means of classical SST). FEF represents an additional critical area, at least in reactive action control that does not require eye movements, while dlPFC was found to be critical in the proactive (but not reactive) control of action. An unresolved issue is whether the left IFG plays a crucial role in action inhibition since, to the best of our knowledge, only few studies employed NIBS to test its critical role (Chambers et al., 2007; Jacobson et al., 2011) and they reported partially contradicting results. Therefore we believe that the most parsimonious account is to suggest that both the right and left IFG are probably involved in response inhibition (in line with fMRI data of bilateral activations); however, future

studies should directly investigate the critical role of the left IFG involvement in response inhibition.

To conclude, it seems that pre-SMA and IFG do not play a selective role in inhibitory control but in a range of inhibitory behaviors including response inhibition, selection and competition. One potential limitation of the NIBS techniques is that the magnetic/electrical field falls off very rapidly with distance from the TMS coil/tDCS electrodes, meaning that superficial areas of cortex are easy to stimulate, but those deep in a sulcus or far from the scalp surface are more complicated to stimulate (Siebner, Hartwigsen, Kassuba, & Rothwell, 2009). Consequently, some of the AIN components cannot be investigated by NIBS, such as the subcortical structures (e.g., basal ganglia), thus their crucial role remains obscure. Moreover, it needs to be taken into account that tDCS have been found to produce spatially widespread electric fields (EF) on the cerebral cortex, hence, individual modeling is required to plan EF doses when focal montages are used (Mikkonen, Laakso, Tanaka, & Hirata, 2020). Beside this limitation, several progresses have been achieved in the last fifteen years in healthy participants, however future studies should assess not only the critical role of the single nodes of the AIN but also their interactions by studying their effective connectivity (Zanon, Borgomaneri, & Avenanti, 2018) and/or their causal interactions (Chiappini et al., 2020; Fiori et al., 2017, 2016). All this information is fundamental to carefully assess the clinical and applied potentialities of NIBS in clinical populations (Plewnia, Schroeder, & Wolkenstein, 2015).

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Declaration of Interests

The authors declare no competing interests

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Figure legend

Please use color for both:

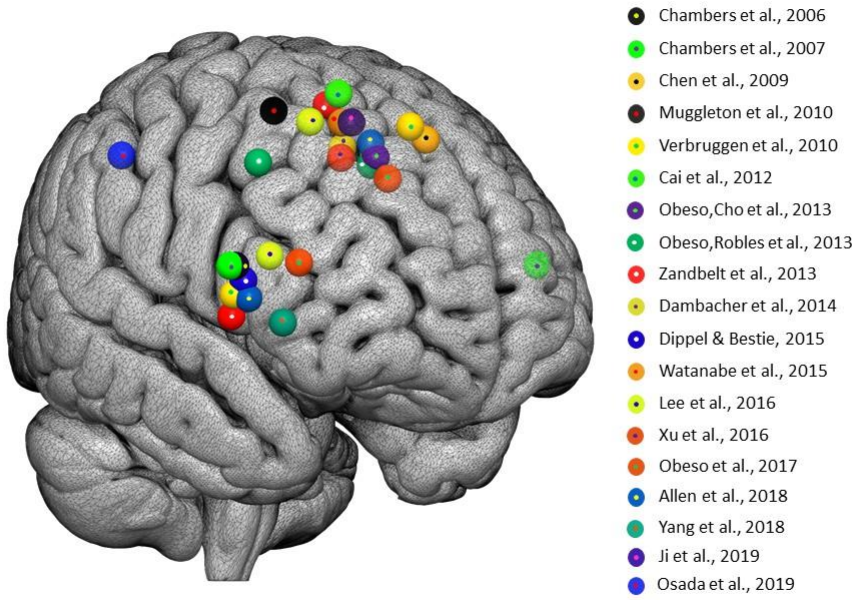

Figure 1. Talairach coordinates of the targeted cortical sites in the TMS studies employing SST reconstructed using Surf Ice (https://www.nitrc.org/projects/surfice).

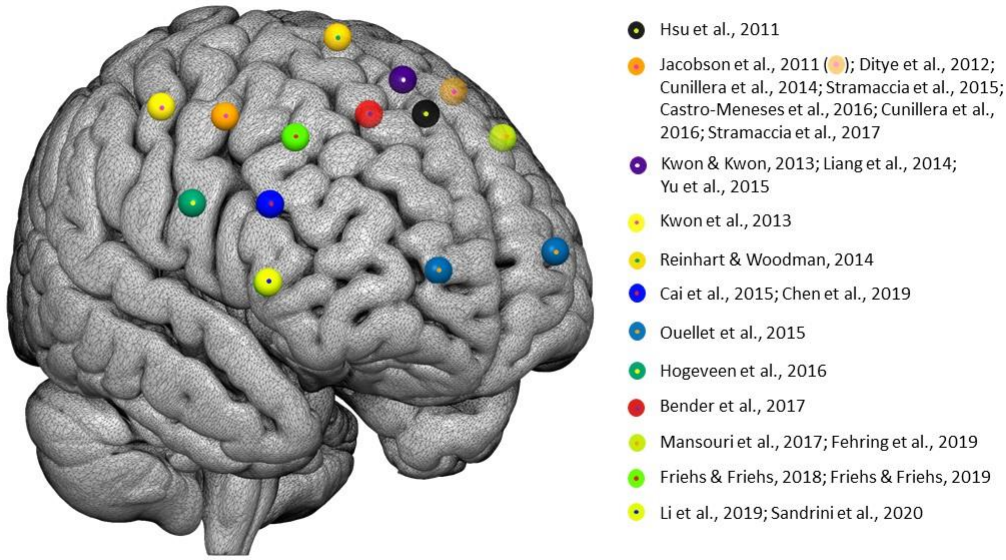

Figure 2. Electrodes placement for stimulation in the tDCS studies employing SST were converted into Talairach coordinates (Koessler et al., 2009) and the targeted cortical sites were reconstructed using Surf Ice (https://www.nitrc.org/projects/surfice).

Study	*Stimulation*	*Talairach Coordinates (x, y, z)*	*n*	*Frequency*	*Duration*	*Intensity*	*Online/ Offline*	*Task*	*Main findings on inhibitory control*
Chambers et al. (2006)	rTMS	rIFG: 58, 20, 15	16	1 Hz	15 min	92% rMT	offline	SST	Increased SSRT
Chambers et al. (2007)	rTMS	rIFG: 60, 20, 15 lIFG: -64, 18, 14	16	1 Hz	20 min	92% rMT	offline	Flanker-SST	Increased SSRT after rIFG stimulation
Chen et al. (2009)	rTMS	pre-SMA: -4, 32, 51	9	10 Hz	2 pulses	60% MSO	online	SST	Increased SSRT
Muggleton et al. (2010)	rTMS	FEF: 33, 9, 59	9	10 Hz	2 pulses	65% MSO	online	SST	Increased SSRT
Verbruggen et al. (2010)	cTBS	rIFG: 55, 16, 7 pre-SMA: 4, 36, 55	18	50 Hz	40s	70% rMT	offline	Dual SST	Increased SSRT after rIFG stimulation
Cai et al. (2012)	dual-pulse TMS	pre-SMA: 10, 11, 64	16	/	2 pulses	110% rMT	online	conditional SST	Increased SSRT
Obeso,Cho et al. (2013)	cTBS	pre-SMA: 6, 22, 46	16	50 Hz	20s	80% AMT	offline	SST	Reduced SSRT
Obeso, Robles et al. (2013)	cTBS or single-pulse TMS	pre-SMA: 6, 20, 44 rIFG: 53, 24, 44	16	50 Hz /	40s	80% AMT 60% MSO	offline online	modified SST	Increased SSRT with single-pulse TMS over pre-SMA

Zandbelt et al. (2013)	rTMS	rIFC: 53, 13, 1 rSMC: 8, 4, 61	21	6 Hz + 1 Hz	20 min	90% rMT + 110% rMT	offline	modified SST	Reduced SSRT after rIFC and rSMC rTMS
Dambacher et al. (2014)	cTBS	pre-SMA: 3, 5, 49	11	50 Hz	40 s	100% AMT	offline	SST and Go/no-Go	No difference in SSRT
Dippel & Bestie (2015)	cTBS and iTBS	rIFG: 54, 19, 11	18	50 Hz	40 s	70% rMT	offline	Stop-change task	No difference in SSRT
Watanabe et al. (2015)	Quadri-pulse rTMS	pre-SMA: 6, 10, 56	9	200 Hz 20 Hz	30 min	90% AMT	offline	SST	Reduced SSRT (excitatory rTMS) Increased SSRT (inhibitory rTMS)
Lee et al. (2016)	cTBS	pre-SMA: 20, 10, 56 rIFG: 42, 17, 18	24	50 Hz	40s	40% MSO	offline	conditional SST	No difference in SSRT
Xu et al. (2016)	single-pulse TMS	pre-SMA: 10, 12, 46	17	/	1 pulse	40% rMT + 80% rMT + 120% rMT	offline	SST	Increased connectivity within the inhibitory network which correlated with reduced SSRT
Obeso et al. (2017)	cTBS	pre-SMA: 6, 27, 40 rIFG: 41, 28, 16	14	50 Hz	40s	80% AMT	offline	conditional SST	Reduced SSRT after cTBS over pre-SMA
Allen et al. (2018)	single-pulse TMS	pre-SMA: 6, 20, 50 rIFC: 53, 20, 6	17	6 – 130 Hz	1 pulse	110% rMT	online	SST	Increased SSRT
Yang et al. (2018)	rTMS	rIFG: 50, 31, -1	20	10 Hz	9 min	100% rMT	offline	SST	No difference in SSRT

Ji et al. (2019)	rTMS rTMS iTBS	pre-SMA: 6, 10, 56	38	5 Hz 25 Hz 50 Hz	18 min 16 min 39 min	110% rMT 110% rMT 70% rMT	offline	SST	Reduced SSRT after iTBS
Osada et al. (2019)	single-pulse TMS	IPS: 43, -43, 47	22	/	1 pulse	120% rMT	online	SST	Increased SSRT

Table 1. Summary of TMS findings in inhibitory control investigations. Studies that reported coordinates based on the Montreal Neurological Institute were converted into Talairach coordinates through the application of the Yale BioImage Suite Package (Lacadie, Fulbright, Rajeevan, Constable, & Papademetris, 2008).

Study	*Stimulation*	*Stimulation Reference*	*Localization*	*n*	*Intensity*	*Duration*	*Electrodes' size*	*Online/ Offline*	*Task*	*Main findings on inhibitory control*
Hsu et al. (2011)	Anodal / Cathodal	Left cheek	pre-SMA: -4, 32, 51	28	1.5 mA	10 min	16 cm^2	offline	SST	No difference in SSRT after anodal or cathodal
Jacobson et al. (2011)	Anodal / Cathodal	Left orbito-frontal cortex	rIFG: crossing point between T4-Fz and F8-Cz lIFG: the crossing point between T3-Fz and F7-Cz	22	1 mA	10 min	25 cm^2	offline	SST	Reduced SSRT after anodal Increased SSRT after cathodal
Ditye et al. (2012)	Anodal	Left orbito-frontal cortex	rIFG: crossing point between T4-Fz and F8-Cz	22	1.5 mA	15 min	35 cm^2	offline	SST	Reduced SSRT
Kwon & Kwon (2013)	Anodal	Left supraorbital area	pre-SMA: 4 cm anterior to Cz	40	1 mA	10 min	35 cm^2	offline	SST	Reduced SSRT
Kwon et al. (2013)	Anodal	Left supraorbital area	M1: C4	40	1 mA	10 min	35 cm^2	online / offline	SST	Reduced SSRT
Cunillera et al. (2014)	Anodal	Left IFC	rIFC: crossing point between T4-Fz and F8-Cz	22	1.5 mA	18 min	9 cm^2	offline	SST and Go/no-Go	Reduced SSRT
Liang et al., (2014)	Anodal	Left cheek	pre-SMA: Fz	18	1.5 mA	10 min	16 cm^2	offline	SST	Reduced SSRT

Reinhart & Woodman (2014)	Anodal / Cathodal	Right cheek	medial-frontal cortex: FCz	18	1.5 mA	20 min	19 cm^2	offline	SST	No difference in SSRT
Stramaccia et al. (2015)	Anodal / Cathodal	Left supraorbital area	rIFG: crossing point between T4-Fz and F8-Cz	115	1.5 mA	20 min	16 cm^2	offline	SST	Reduced SSRT after anodal
Cai et al. (2015)	Anodal	Left cheek	rIFG: crossing point between F4 and F8	22	1.5 mA	15 min	25 cm^2	offline	SST	Reduced SSRT
Ouellet et al. (2015)	Anodal	Right and left OFC	OFC: Fp1 and Fp2	45	1.5 mA	30 min	35 cm^2	offline	SST	No difference in SSRT
Yu et al. (2015)	Anodal	Left cheek	pre-SMA: Fz	23	2 mA	20 min	16 cm^2	offline	SST	Reduced SSRT
Cunillera et al. (2016)	Anodal	Left IFC	rIFC: crossing point between T4-Fz and F8-Cz	13	1.5 mA	20 min	9 cm^2	online	SST and Go/no-Go	No difference in SSRT
Castro-Meneses et al. (2016)	Anodal	Left cheek	rPFC: crossing point between T4-Fz and F8-Cz	14	1.5 mA	15 min	25 cm^2	online / offline	SST	Reduced SSRT
Hogeveen et al. (2016)	HD-tDCS or Anodal	Vertex: Cz	rIFC: FC6	46	1 mA	20 min	25 cm^2	offline	SST	Reduced SSRT
Bender et al. (2017)	Anodal / Cathodal	Right mastoid	pre-SMA: 2, 15, 51	18 36	0.7 mA	9 min 13 min	25 cm^2	offline	modified SST	No difference in SSRT

Mansouri et al. (2017)	Anodal	Right supraorbital area	ldlPFC: F3	73	1.5 mA	10 min	10 cm^2	offline	modified SST	Reduced SSRT
Stramaccia et al. (2017)	Anodal / Cathodal	Left supraorbital area	rIFG: FC4	72	1.5 mA	20 min	16 cm^2	online	SST	No difference in SSRT
Chen et al. (2019)	Anodal	Left cheek	rIFG: crossing point between F4 and F8	57	1.5 mA	20 min	25 cm^2	offline	modified SST	Reduced SSRT
Friehs & Frings (2018)	Anodal	Left deltoid muscle	rdlPFC: F4	59	0.5 mA	19 min	9 cm^2	offline	SST	Reduced SSRT
Friehs & Frings (2019)	Cathodal	Left deltoid muscle	rdlPFC: F4	45	0.5 mA	19 min	9 cm^2	offline	SST	Increased SSRT
Fehring et al. (2019)	Anodal	Right supraorbital area	ldlPFC: F3	73	1.5 mA	10 min	10 cm^2	offline	SST	Reduced SSRT
Li et al. (2019)	Anodal / Cathodal	Right shoulder	rIFG: F8	24	2 mA	12 min	12 cm^2	online	SST	Reduced SSRT after anodal
Sandrini et al. (2020)	Anodal	Left supraorbital area	rIFC: 53, 28, 3	30	1.5 mA	20 min	25 cm^2	offline	SST	Reduced SSRT

Table 2. Summary of tDCS findings in inhibitory control investigations.