Running title: rTMS over pre-SMA improves response inhibition

Theta burst magnetic stimulation over the pre-supplementary motor area improves motor inhibition

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Abstract

Background: Stopping an ongoing motor response or resolving conflict induced by conflicting stimuli are associated with activation of a right-lateralized network of inferior frontal gyrus (IFG), pre-supplementary motor area (pre-SMA) and subthalamic nucleus (STN). However, the roles of the right IFG and pre-SMA in stopping a movement and in conflict resolution remain unclear. We used continuous theta burst stimulation (cTBS) to examine the involvement of the right IFG and pre-SMA in inhibition and conflict resolution using the conditional stop signal task.

Methods: We measured stop signal reaction time (SSRT, measure of reactive inhibition), response delay effect (RDE, measure of proactive action restraint) and conflict induced slowing (CIS, measure of conflict resolution).

Results: Stimulation over the pre-SMA resulted in significantly shorter SSRTs (improved inhibition) compared to sham cTBS. This effect was not observed for CIS, RDE, or any other measures. cTBS over the right IFG had no effect on SSRT, CIS, RDE or on any other measure.

Conclusions: The improvement of SSRT with cTBS over the pre-SMA suggests its critical contribution to stopping ongoing movements.

Keywords: response inhibition; conflict resolution; cognitive control; pre-SMA; theta burst stimulation

Introduction

From a review of several strands of evidence from animal, imaging, clinical studies and behavioural and electrophysiological investigations of the impact of surgery on movement disorders, it has been suggested that the fronto-striato-subthalamic-pallidal networks mediate goal-directed (volitional, effortful inhibition to achieve a goal) and habitual (automatic) inhibition in the motor and non-motor domains [1]. The stop signal task [2] has been extensively employed for assessment of inhibition of ongoing motor responses. Imaging studies demonstrate that in a conditional stop signal task, successful inhibition and conflict resolution both recruit the 'braking' network of right hemispheric cortical and subcortical areas, including the inferior frontal gyrus (IFG), pre-supplementary area (pre-SMA), primary motor cortex (M1), caudate, subthalamic nucleus (STN) and the globus pallidus interna (GPi) [3–9]. Yet, there is little agreement about the specific roles these areas play during inhibition and conflict resolution and whether or not their contribution is causal or not.

The IFG and STN are considered two key nodes of the stopping network, since activation of these areas during successful inhibition are significantly correlated with each other and also with the measure of reactive inhibition, the stop signal reaction time (SSRT) [4]. Subsequent studies [8,10,11] using transcranial magnetic stimulation (TMS) and imaging show direct involvement of the pre-SMA in inhibition, although its involvement in related functions of action monitoring [12] and conflict resolution during action selection [13] have also been proposed. Based on the available evidence, the pre-SMA seems to play a role both in inhibition and in conflict resolution.

Previous studies (see Table 1 for a summary) using the stop signal task in healthy participants have shown that repetitive TMS (rTMS) over the IFG [14–17] impairs motor inhibition, but others reported no effects [18]. Alternatively, bilateral tDCS over the IFG affected

proactive control of behaviour [19] but produced no changes in reactive inhibition [20]. Similarly, the findings with regard to the effects of rTMS over the pre-SMA are also inconsistent, as improved [8,10,11] but also impaired inhibition [21] have been reported, while others noted involvement of the pre-SMA in conflict resolution [13].

We used the conditional stop signal task, which allows assessment of two types of inhibition, reactive inhibition triggered by stop signals, and proactive inhibition measured as prospective action restraint in anticipation of stop signals as well as conflict resolution (measured as the slowing induced by 'to be ignored' stop signals) with the same task. The novel aspect is our aim to investigate the differential contributions of the pre-SMA and IFG to two types of response inhibition as well as conflict resolution. We used continuous theta burst stimulation (cTBS), because of its demonstrated longer-lasting effects achieved with a short stimulation procedure (40secs) [22]. Based on previous studies showing improved behavioural effects after TMS (see Table 1), we hypothesized that, if the pre-SMA is involved in both inhibition and conflict resolution, then cTBS over the pre-SMA would improve measures of inhibition and conflict resolution, whereas cTBS over the IFG would only affect measures of inhibition.

[Table 1 about here]

Methods

19 healthy right-handed volunteers (10 male), aged 22-38 years (M = 29.36, SD = 4.6) participated, all of whom met the safety criteria for TMS [23]. The study was approved by the Joint Ethics Committee of the UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery. Informed consent was obtained from all participants.

Design

Each participant performed the conditional stop signal task three times with a different cTBS target: right IFG, pre-SMA, or sham over right M1, on three separate occasions/days in a counterbalanced order. There was at least a one-week interval between each of three assessments.

Conditional stop signal task

The conditional stop signal task [4,24,25] allows measurement of (i) how successfully and quickly a participant can inhibit a response when a stop signal is presented (reactive inhibition) and (ii) the extent that participants engage in proactive inhibition i.e. slowing their responses in anticipation of a stop signal (proactive inhibition) (iii) the extent of slowing of response initiation under conditions of conflict or "conflict induced slowing". On Go trials, a go signal (left or right pointing green arrow) was presented on a computer screen and participants had to respond accurately and as fast as possible using their index and middle fingers of their dominant hand to press left or right keys on a keypad respectively in response to the left and right pointing arrows. On Stop trials (25% of all trials), participants were instructed to stop their response when a stop signal (a red cross) was presented after a variable stop signal delay (SSD) following the go signal; applicable only if the stop signal was presented following an arrow in the direction assigned as 'critical' (see Figure 1). When a stop signal was presented following an arrow in the direction assigned as 'non-critical' participants were instructed to ignore the stop signal and respond to the go stimulus. For half of the participants a left pointing arrow and for the other half a right pointing arrow was assigned as the 'critical' direction. There were three blocks of trials consisting of 32 Stop and 96 Go trials per block (128 total trials per block). The

number of left and right pointing arrows was equal and in every four trials, there was one Stop trial and three Go trials.

[Figure 1 about here]

On Stop trials, the green arrows were replaced by a red cross at some stop signal delay (SSD) after the green arrow. Successful inhibition of a response made the red cross stay on the screen during the limited hold. However, if a participant responded within the limited hold period, the arrow disappeared, leaving the background screen and the null period. The SSD value for the Stop trials was sampled from one of four staircases, changing dynamically throughout the task based on the participant's behaviour. Successful inhibition of a response on a 'critical' Stop trial made inhibition more difficult on the next Stop trial by increasing the SSD by 50 ms. However, if the response was not successfully inhibited, then inhibition became easier by decreasing the SSD by 50 ms. Staircases of four step-up and step-down algorithms (100, 150, 200, and 250 ms) were used in this way to ensure convergence to *P*(inhibit) of 50% by the end of the three blocks. Therefore, each staircase (100, 150, 200, and 250 ms) moved four times within each block for the Stop trials of the 'critical' direction. SSDs for the Stop trials in the 'non-critical' direction were yoked to the 'critical' direction values. Participants were instructed to respond as quickly and accurate as possible to go trials and try to stop on 'critical' stop trials. Then, the active motor threshold (AMT) was obtained followed by 20 practice trials.

The stop signal task measures are described in Table 2. The standard Race Model [26] was applied to compute the SSRT by subtracting the average SSD from the mean correct 'critical' Go RT [27]. One of the main measures of interest was 'conflict induced slowing' (CIS) measured as the difference score between the 'non-critical' Stop trials and the 'non-critical' Go trials. Context-specific and strategic form of action restraint was calculated using the Response

Delay Effect (RDE) as the difference in RTs between the 'critical' and 'non-critical' Go RTs, which is the measure of proactive inhibition on this task. Finally, to determine if cTBS had any differential effects on the slowest and fastest part of the SSRT distribution, we examined how the fastest, middle and slowest SSRTs were influenced by cTBS by analyzing the cTBS effect on the 3 SSRT quartiles (25^{th}, 50^{th} and 75^{th}). For the quartile analysis we obtained the three sections of the distribution for every RT measure (critical Go RT, critical StopRespond RT, non critical GoRT, non critical StopRespond RT and SSD) and in turn derived the difference scores (SSRT, CIS and RDE) for these. Hence, three separate values for each quartile (25^{th}, 50^{th}, 75^{th}) were inserted in the analysis of each measure. Comparisons were type I error-corrected [28] and non-parametric tests were used to compare error data.

TMS and MRI procedures

A Magstim stimulator (Magstim, Whitland, UK) was employed to stimulate the target cortical sites. Based on previous studies [22], we used a stimulation output intensity of 80% of each individual's active motor threshold (AMT) for the hand (for IFG) or leg (for pre-SMA).

To obtain stimulation thresholds for the IFG condition, we used a 7-cm figure of eight-coil placed tangentially over the participant's scalp with the handle pointing 45 degrees backwards and laterally over the right motor cortex. Using single pulses over the right hemisphere, we registered motor evoked potentials (MEPs) from the left first dorsal interosseous (FDI) to localize the right hand motor area, starting at a point 2 cm anterior and 4 cm lateral to Cz. The stimulation coil was moved in steps of .5 cm to find the 'hot spot', marked over a swimming cap with a pen. The AMT was defined as the minimal stimulus intensity required to produce MEPs of $\geq$ 200 μV amplitude in $\geq$ 5 of 10 consecutive pulses. Participants were asked

to squeeze a ball between their forefinger and thumb to activate their FDI at approximately 10% of maximum force.

Because of the pre-SMA's deeper and more medial location, the stimulus intensity used for cTBS was estimated relative to the active threshold of a lower leg muscle (tibialis anterior) which is located at approximately the same depth from the scalp in the midline [29]. Because pre-SMA has a midline cortical position, with single pulses over the leg area of primary motor cortex, we registered MEPs from both right and left leg tibialis anterior muscles, so as to detect only left leg MEPs from right leg motor area. Using a large double cone coil we localized the left leg motor area starting at a point 2 cm posterior to Cz. The rationale for using a cone shaped TMS coil was to ensure that stimulation reached the pre-SMA which is a deeper structure [30,31]. Other smaller coils give larger focality over larger coils but this advantage diminishes with increasing target depth as in our case. The stimulation coil was moved in steps of .5 cm to obtain the 'hot spot', marked over a swimming cap with a pen. To obtain the AMT, participants were asked to contract their left foot to activate their left tibialis anterior by dorsiflexing the ankle.

The target sites were localized in two different ways. For 4 participants, the right IFG stimulations site was localized over F6 in the 10-20 electro-encephalography system [32] and the pre-SMA site was localized at a point 6 cm anterior to the right foot motor area [29]. For 10 participants localization was confirmed using the Brainsight frameless stereotaxy system (Rogue Research, Canada) with a Polaris (NorthernDigital, Canada) infrared tracking system to measure the position of anatomical landmarks on each participant's head. For each participant's magnetic resonance image (MRI) scan, several anatomical landmarks were marked (tip of nose, bridge of nose, nose gap, left and right intra-trageal notches). Another infrared tracker was placed over the

TMS coil to identify the scalp point where the target was selected in the MRI image and to mark the point on the cap. Each participant's MRI was compared to a normalized space so that TMS coordinates used were identified in a standard space (mean right IFG, x = 43, y = 29, z = 15.4; right pre-SMA, x = 6.6, y = 26.4, z = 44). Coordinate values were set according to Brodmann areas for the right IFG (BA44/45) and for the right pre-SMA (BA6) based on functional activation co-ordinates [4]. The M1 location was the 'hot spot' with the greatest and most consistent MEPs.

We used theta burst stimulation, a TMS protocol where each train of stimulation consists of repeated burst of 3 pulses at 50Hz, which is known to deactivate the stimulated neurons for a period of 40 minutes [22] when applied continuously. Every TBS burst was repeated at a 5Hz rate resulting in 200 bursts with a total of 600 pulses at 80% of the AMT of each participant, following safety guidelines [33]. For pre-SMA stimulation, the coil was placed tangentially and for the IFG vertically (with the current going in the ventral to dorsal direction) to the selected spot. For sham M1 stimulation, the coil was tilted vertically over the right M1 with a 90-degree inclination making sure the magnetic field was not pointed towards the participant's scalp.

Results

Five participants were excluded from the analysis (two reported uncomfortable sensory feelings while undergoing cTBS over the IFG; three did not engage adequately with the task as shown by outlier values more than 2.5 standard deviations above the mean for percent correct inhibition and thus did not achieve the requisite 50% inhibition). A final sample of 14 participants was included in the analysis.

[Table 2 about here]

'Critical' trials

The dynamic adjustment of SSD converged on probabilities of inhibition that were close to 50% (Table 2) and these percentages did not differ significantly between conditions [$F_{(2, 26)}$ = .30, p = .74].

To establish whether RTs differed significantly across trial types on the 'critical' direction for the cTBS conditions, an ANOVA was performed on mean 'critical' RT with Trial Type (Go vs. StopRespond) and stimulation Site (pre-SMA vs. IFG vs. Sham M1) as within-subject variables. This analysis revealed a significant Trial Type x Site interaction [$F_{(2,26)}$ = 3.51, p = .04] (see Figure 2a). The main effects of Trial Type and Site were not significant (Fs < 1). Paired t-tests revealed faster StopRespond RTs for the pre-SMA (M = 369.14, SD = 32.9) compared to the Sham (M = 390.01, SD = 42.2; $t_{(13)}$ = - 2.08, p = .05). Comparisons of StopRespond RTs between pre-SMA and IFG (M = 383.30, SD = 50.7) [$t_{(13)}$ = 1.16, p = .26] or IFG and Sham (t<1) were not significantly different. Paired t-tests on 'critical' Go RTs, showed that none of the differences were significant (see Table 2). Importantly, the 'critical' StopRespond RTs (Stop trials on which participants failed to inhibit and responded) marks the speed of failed inhibition and thus represents the racing process between go and stop, with faster StopRespond RTs after pre-SMA stimulation than in the Sham condition.

[Figure 2 about here]

The SSD is adjusted by the staircase tracking procedure but this adjustment is dependent on each participant's actual behaviour and efficiency in achieving motor inhibition. Those who achieve 50% inhibition with longer (harder) or shorter (easier) SSDs differ in the efficiency of

motor inhibition. An ANOVA was performed on mean SSD with stimulation Site (pre-SMA vs. IFG vs. Sham M1) as the within-subject variable. The effect of stimulation site was not significant [$F_{(2,26)} = 2.89$, $p = .08$], suggesting that there were no significant differences in mean SSD between the three target sites (Table 2).

A one-way ANOVA on mean SSRT with Site as a within-subjects variable, revealed a significant effect of Site [$F_{(2,26)} = 6.86$, $p = .004$]. Post-hoc paired *t*-tests showed significantly faster SSRTs with cTBS over the pre-SMA relative to Sham M1 [$t_{(13)} = 4.5$, $p = .001$] and IFG conditions [$t_{(13)} = -2.68$, $p = .01$, Table 2], indicating that pre-SMA cTBS improved/ speeded up stopping (Figure 2b). Mean SSRTs for the IFG and Sham conditions were not significantly different ($t < 1$). To examine which part of the SSRT distribution (fast, middle or slow part), was affected by pre-SMA cTBS relative to the other stimulation conditions, we divided the SSRT into 3 quartiles, 25th, 50th and 75th. A one-way ANOVA was conducted for each SSRT quartile and showed a main effect of TMS condition on the slowest SSRT quartile [$F_{(2,26)} = 3.55$, $p = .04$], while the effect on the middle and fast parts of the SSRT distribution were not significant [$F = 1.71$ and $F = .32$ respectively]. Further comparisons revealed that this effect was due to cTBS over the pre-SMA resulting in significantly shorter/faster SSRTs ($M = 347.15$, $SD = 40.7$) in the slowest quartile of the distribution compared to IFG [$M = 384.97$, $SD = 71.3$, $t_{(13)} = 2.58$, $p = .02$] and sham cTBS [$M = 378.59$, $SD = 71.3$, $t_{(13)} = 2.26$, $p = .04$] (Figure 3). Thus, the slowest part of the SSRT distribution, was preferentially and differentially speeded up by pre-SMA cTBS relative to IFG or sham stimulation.

[Figure 3 about here]

'Non-critical' trials

An ANOVA was performed on mean 'non-critical' RT with Trial Type and Site as within-subject variables. A significant main effect of Trial Type [$F_{(1,26)} = 61.08$, $p < .001$] was found due to slower 'non-critical' StopRespond RTs compared to 'non-critical' Go RTs, indicative of the 'conflict induced slowing' effect. The main effect of Site and the Site x Type interaction were not significant (Fs < 1).

[Figure 4 about here]

A one-way ANOVA on the mean CIS difference scores was performed with Stimulation Site as a within-subjects variable. This analysis revealed that Stimulation Site did not significantly affect CIS [$F_{(2, 26)} = .24$, $p = .78$] (Table 2, Figure 4b). This suggests that neither the contribution of the pre-SMA nor the IFG are critical for conflict resolution.

Finally, a one-way ANOVA on mean RDE scores was performed with Stimulation Site as a within-subjects variable. This analysis revealed that the Stimulation Site did not significantly affect RDE [$F_{(2, 26)} = .57$, $p = .57$].

Discussion

We investigated the effect of cTBS over the right IFG and pre-SMA on reactive and proactive inhibition and conflict resolution measures relative to sham stimulation. We found significantly faster SSRTs- i.e. improved/faster inhibition of the motor response- following cTBS over the pre-SMA compared to sham cTBS. This effect was evident for the slowest part of the SSRT distribution, which became significantly faster with cTBS over the pre-SMA relative to

cTBS over the IFG or sham stimulation. Stimulation over the right IFG did not influence SSRT. Importantly, conflict resolution was unaffected by cTBS over either the right IFG or pre-SMA, which did not influence the RDE measure of proactive inhibition either. Our results provide novel evidence on the role of the pre-SMA in inhibitory control.

Motor inhibition

Imaging suggested that the pre-SMA is part of the brain "inhibitory network" [3,8,10,11,34] and here we provide direct 'causal' evidence to indicate that the pre-SMA is a structure with a primarily inhibitory function. Amongst the various processes by which the pre-SMA is considered to exert top-down control [34–37], our results suggest a predominant role in reactive motor inhibition, without a significant contribution to conflict resolution (see next section for interpretation). Previous imaging evidence shows activation of the pre-SMA during performance of the go no-go [38,39], or stop signal tasks [3–5,7,9,21]. Greater pre-SMA activation has been associated with: (i) faster SSRTs [6], and (ii) stronger effective connectivity with the right caudate [40] and right IFG [37], related to gray matter densities [41]. Our results showing that continuous cTBS of the pre-SMA improves/speeds up motor inhibition is consistent with previous findings [6]. It is possible that this improvement in the speed of motor inhibition with pre-SMA cTBS is achieved either via its hyperdirect pathway connections with the STN [34] or via its direct pathway connections with the striatum [42].

A role for the pre-SMA in motor inhibition can now be considered as well-established. It appears that experimental manipulation of its normal activity by means of brain stimulation alters the functioning of the right hemispheric inhibitory network, but based on our behavioural results and combined TMS and imaging data [8,10,11], it seems that the brain adapts to this

'perturbation' of the right hemispheric inhibitory network in such a way that motor inhibition improves. The seemingly 'paradoxical' enhancement of motor inhibition may be related to compensation from distant sites with connectivity to the right pre-SMA across the left hemisphere network (i.e. left pre-SMA, left IFG), perhaps by a behavioural shift from controlled and selective inhibition to more fast and global inhibition as suggested by Aron and Verbruggen [43]. This interpretation is supported by results showing increased activity following TMS over homologous regions in the left hemisphere "inhibitory network". After 1Hz rTMS of the pre-SMA, connectivity between the left IFG and STN was strengthened [10]. Similarly, the left pre-SMA showed increased activation following TMS over the right pre-SMA and new functional connections linked the left IFG with the left pre-SMA [8]. However, our TMS coil and stimulation protocol do not guarantee that we successfully targeted the right pre-SMA alone but could potentially have influenced the medial section including the left pre-SMA. Hence, it is possible that our results reflect a combination of right and to some extent left pre-SMA stimulation.

In line with the above evidence from combined TMS and imaging for a shift in the inhibitory network, we speculate about the possible mechanisms for our observed findings. One is that pre-SMA stimulation intensified the activation of other neural circuits for stopping. A clue as to how this might have happened comes from the observation that cTBS over the pre-SMA affected the distribution of SSRTs: the mean SSRT was shorter after cTBS because there were fewer trials in which the SSRT was much longer than the mean. This suggests that cTBS had tightened the distribution of SSRTs, effectively reducing the "noise" in withholding a prepared response. This is likely to be mediated via the pre-SMA connections to the striatum, a pathway shown to mediate fast and urgent behaviours [42] and is in line with recent findings showing

striatal changes after inhibitory rTMS over the pre-SMA [21]. Thus, our findings support an inhibitory function of the pre-SMA that when perturbed using stimulation paradigms, drives distant and interconnected regions to manifest its behavioural effects.

cTBS is often labeled "inhibitory" on the basis of experiments on the motor cortex [22]. However, even in the motor cortex, the effects are highly variable [44], and in other regions, such as the primary sensory cortex, the effects have been better described as changing levels of neural "noise" [45]. In the sensory cortex, it was speculated that cTBS reduced the effectiveness of feedforward inhibitory circuits that were essential in sharpening the temporal profile of sensory inputs needed to perform a temporal discrimination task, effectively introducing noise into a detection task [44]. The present study does not involve detection of low-level inputs. Instead, it required the rapid withholding of a prepared response to a well-defined input (the stop signal). Reducing inhibitory control in this case would enhance signal amplitude and improve performance in a manner equivalent to reducing "noise", hence the observed effect of speeding of response inhibition with cTBS over the pre-SMA. It is possible that this "noise" reduction operated at both the level of the perceptual and motor systems.

Some previous TMS studies investigating the role of the pre-SMA or IFG in response inhibition are not consistent with our results. Other studies used cTBS over the pre-SMA and found no significant change in SSRTs [17,18]. Verbruggen et al [17] used a figure-of-eight coil and the stimulation applied was based on hand motor thresholds. Here, we used a cone-shaped coil and stimulation based on foot motor thresholds that involve higher intensities than hand regions to obtain consistent MEPs. Therefore, it is possible that the cTBS used by Verbruggen et al [17] was not as efficient as ours in actually stimulating the pre-SMA, particularly since we stimulated with a cone-shaped coil that reaches deeper structures in the brain. Other rTMS

protocols (such as inhibitory quadruple TMS) over the pre-SMA reported worse response inhibition [21], perhaps because of a stronger physiological effect (due to larger pulse trains) as compared to here.

The current results did not reveal any effect of cTBS over the IFG in proactive or reactive inhibition or in conflict resolution. The left IFG has shown causal relevance to stopping behaviours in patients with lesions [46] and also increased BOLD activity in healthy participants during action restraint on a go-nogo task [47] or tasks requiring inhibitory control for interference resolution [48]. Some imaging evidence with the stop signal task has considered the right IFG as a key node in the inhibitory network [49]; whereas other imaging studies attributed a role in attention rather than inhibition to the IFG [50]. Thus, a contribution from the left IFG may partly explain our negative results after cTBS over the right IFG.

Conflict resolution

In addition to inhibition, the pre-SMA has been implicated in several other cognitive control mechanisms, such as switching, updating or initiation of actions [8,51–54]. It is not surprising that brain networks involved in inhibition, namely the pre-SMA and the STN, also operate during conflict resolution and switching, as shown previously [4,7], although other studies show greater anterior cingulate cortex (ACC) activity in conflict resolution [55,56]. In fact, Casey and colleagues [57] use the term the ‘anterior system’ involving the ACC, and considered this responsible for conflict resolution while performing the flanker interference task. Other tasks commonly used to assess conflict resolution are the Flanker, the Simon or the Stroop tasks, which in imaging studies have been shown to engage medial frontal areas including the ACC and the pre-SMA [58,59]. Conflict between competing actions has also previously implicated the pre-SMA [60–62]. To causally influence conflict resolution, it is possible that

more extensive stimulation of the full SMA complex, including both the SMA and pre-SMA [63], is required.

Conclusions

We show that the pre-SMA plays a critical role in response inhibition as cTBS over this area improved SSRT. Our results did not reveal any role for the pre-SMA or IFG in conflict resolution.

There is evidence that SSRTs are delayed in impulsive individuals [64]. Our behavioural results showing that cTBS over the pre-SMA speeded up SSRTs have potential implications for future rehabilitation programs for patients with impaired decision-making and impulsivity, such as those with compulsive eating or shopping, pathological gambling or frontal-like disinhibited behaviours. Specifically, disorders with altered pre-SMA activity (both at rest and task-related) may benefit from similar pre-SMA cTBS as the one used here as previously suggested [65,66].

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References

[1] Jahanshahi M, Obeso I, Rothwell JC, Obeso JA. A fronto-striato-subthalamic-pallidal network for goal-directed and habitual inhibition. Nat Rev Neurosci 2015;16:719–32. doi:10.1038/nrn4038.

[2] Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: a model and a method. J Exp Psychol Hum Percept Perform 1984;10:276–91.

[3] Aron AR, Poldrack R a. Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 2006;26:2424–33. doi:10.1523/JNEUROSCI.4682-05.2006.

[4] Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack R a. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci 2007;27:3743–52. doi:10.1523/JNEUROSCI.0519-07.2007.

[5] Duann J-RR, Ide JS, Luo X, Li CSR. Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. J Neurosci 2009;29:10171–9. doi:29/32/10171 [pii]10.1523/JNEUROSCI.1300-09.2009 [doi].

[6] Chao HHA, Luo X, Chang JLK, Li C-SSR. Activation of the pre-supplementary motor area but not inferior prefrontal cortex in association with short stop signal reaction time – an intra-subject analysis. BMC Neurosci 2009;10:75:75. doi:10.1186/1471-2202-10-75.

[7] Kenner NM, Mumford J a, Hommer RE, Skup M, Leibenluft E, Poldrack R a. Inhibitory motor control in response stopping and response switching. J Neurosci 2010;30:8512–8. doi:30/25/8512 [pii]10.1523/JNEUROSCI.1096-10.2010 [doi].

[8] Obeso I, Cho SS, Antonelli F, Houle S, Jahanshahi M, Ko JH, et al. Stimulation of the pre-SMA influences cerebral blood flow in frontal areas involved with inhibitory control of action. Brain Stimul 2013;6:769–76. doi:10.1016/j.brs.2013.02.002.

[9] Ray Li CS, Yan P, Sinha R, Lee TW, Li CS, Yan P, et al. Subcortical processes of motor response inhibition during a stop signal task. Neuroimage 2008;41:1352–63. doi:S1053-8119(08)00484-9 [pii]10.1016/j.neuroimage.2008.04.023 [doi].

[10] Herz DM, Christensen MS, Bruggemann N, Hulme OJ, Ridderinkhof KR, Madsen KH, et al. Motivational tuning of fronto-subthalamic connectivity facilitates control of action impulses. J Neurosci 2014;34:3210–7. doi:10.1523/jneurosci.4081-13.2014.

[11] Zandbelt BB, Bloemendaal M, Hoogendam JM, Kahn RS, Vink M. Transcranial Magnetic Stimulation and Functional MRI Reveal Cortical and Subcortical Interactions during Stop-signal Response Inhibition. J Cogn Neurosci 2013;25:157–74. doi:10.1162/jocn_a_00309.

[12] Bonini F, Burle B, Liégeois-Chauvel C, Régis J, Chauvel P, Vidal F, et al. Action monitoring and medial frontal cortex: leading role of supplementary motor area. Science 2014;343:888–91. doi:10.1126/science.1247412.

[13] Duque J, Olivier E, Rushworth M. Top–Down Inhibitory Control Exerted by the Medial Frontal Cortex during Action Selection under Conflict. J Cogn Neurosci 2012:1–15. doi:10.1162/jocn.

[14] Dippel G, Beste C. A causal role of the right inferior frontal cortex in implementing strategies for multi-component behaviour. Nat Commun 2015;6:6587. doi:10.1038/ncomms7587.

[15] Chambers CD, Bellgrove MA, Gould IC, English T, Garavan H, McNaught E, et al. Dissociable mechanisms of cognitive control in prefrontal and premotor cortex. J Neurophysiol 2007;98:3638–47. doi:00685.2007 [pii]10.1152/jn.00685.2007 [doi].

[16] Chambers CD, Bellgrove MA, Stokes MG, Henderson TR, Garavan H, Robertson IH, et al. Executive "brake failure" following deactivation of human frontal lobe. J Cogn Neurosci 2006;18(3):444–55.

[17] Verbruggen F, Aron AR, Stevens MA, Chambers CD. Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. Proc Natl Acad Sci U S A 2010;107:13966–71. doi:1001957107 [pii]10.1073/pnas.1001957107 [doi].

[18] Lee HW, Lu M-S, Chen C-Y, Muggleton NG, Hsu T-Y, Juan C-H. Roles of the pre-SMA and rIFG in conditional stopping revealed by transcranial magnetic stimulation. Behav Brain Res 2016;296:459–67. doi:10.1016/j.bbr.2015.08.024.

[19] Cunillera T, Brignani D, Cucurell D, Fuentemilla L, Miniussi C. The right inferior frontal cortex in response inhibition: A tDCS-ERP co-registration study. Neuroimage 2016;140:66–75. doi:10.1016/j.neuroimage.2015.11.044.

[20] Dambacher F, Schuhmann T, Lobbestael J, Arntz A, Brugman S, Sack AT. No effects of bilateral tDCS over inferior frontal gyrus on response inhibition and aggression. PLoS One 2015;10:1–12. doi:10.1371/journal.pone.0132170.

[21] Watanabe T, Hanajima R, Shirota Y, Tsutsumi R, Shimizu T, Hayashi T, et al. Effects of rTMS of pre-supplementary motor area on fronto basal ganglia network activity during stop-signal task. J Neurosci 2015;35:4813–23. doi:10.1523/JNEUROSCI.3761-14.2015.

[22] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6. doi:S0896627304008463 [pii]10.1016/j.neuron.2004.12.033 [doi].

[23] Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol 2001;112:720.

[24] De Jong R, Coles MG, Logan GD. Strategies and mechanisms in nonselective and selective inhibitory motor control. J Exp Psychol Hum Percept Perform 1995;21:498–511.

[25] Obeso I, Wilkinson L, Casabona E, Bringas ML, Álvarez M, Álvarez L, et al. Deficits in inhibitory control and conflict resolution on cognitive and motor tasks in Parkinson's disease. Exp Brain Res 2011;212:371–84. doi:10.1007/s00221-011-2736-6.

[26] Logan GD, Cowan WB. On the ability to inhibit thought and action: a theory of an act of control. Psychol Rev 1984;91:295–327.

[27] Band GP, van der Molen MW, Logan GD. Horse-race model simulations of the stop-signal procedure. Acta Psychol 2003;112:105–42.

[28] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 1995;57:289–300.

[29] Hadland KA, Rushworth MF, Passingham RE, Jahanshahi M, Rothwell JC. Interference with performance of a response selection task that has no working memory component: an rTMS comparison of the dorsolateral prefrontal and medial frontal cortex. J Cogn Neurosci 2001;13:1097–108. doi:10.1162/089892901753294392.

[30] Guadagnin V, Parazzini M, Fiocchi S, Liorni I, Ravazzani P. Deep Transcranial Magnetic Stimulation: Modeling of Different Coil Configurations. IEEE Trans Biomed Eng 2016;63:1543–50. doi:10.1109/TBME.2015.2498646.

[31] Deng Z-D, Lisanby SH, Peterchev A V. Coil design considerations for deep transcranial magnetic stimulation. Clin Neurophysiol 2014;125:1202–12. doi:10.1016/j.clinph.2013.11.038.

[32] Aziz-Zadeh L, Cattaneo L, Rochat M, Rizzolatti G. Covert speech arrest induced by rTMS over both motor and nonmotor left hemisphere frontal sites. J Cogn Neurosci 2005;17:928–38. doi:10.1162/0898929054021157 [doi].

[33] Wassermann EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K, et al. Use and safety of a new repetitive transcranial magnetic stimulator. Electroencephalogr Clin Neurophysiol 1996;101:412–7.

[34] Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a Cognitive Control Network Using Diffusion-Weighted Magnetic Resonance Imaging (MRI) and Functional MRI. J Neurosci 2007;27(14):3743–52.

[35] Obeso I, Robles N, Muñoz-Marrón E, Redolar-Ripoll D. Dissociating the role of the pre-SMA in response inhibition and switching: A combined online and offline TMS approach. Front Hum Neurosci 2013. doi:10.3389/fnhum.2013.00150.

[36] Cai W, Oldenkamp CL, Aron AR. A proactive mechanism for selective suppression of response tendencies. J Neurosci 2011;31:5965–9. doi:31/16/5965 [pii]10.1523/JNEUROSCI.6292-10.2011 [doi].

[37] Xu B, Sandrini M, Wang W, Smith JF, Sarlls JE, Awosika O, et al. PreSMA stimulation changes task-free functional connectivity in the fronto-basal-ganglia that correlates with response inhibition efficiency 2016;0:1–14. doi:10.1002/hbm.23236.

[38] Humberstone M, Sawle G V, Clare S, Hykin J, Coxon R, Bowtell R, et al. Functional magnetic resonance imaging of single motor events reveals human presupplementary motor area. Ann Neurol 1997;42:632–7. doi:10.1002/ana.410420414 [doi].

[39] Mostofsky SH, Schafer JGB, Abrams MT, Goldberg MC, Flower A a., Boyce A, et al. fMRI evidence that the neural basis of response inhibition is task-dependent. Brain Res Cogn Brain Res 2003;17:419–30. doi:S0926641003001447 [pii].

[40] Jahfari S, Waldorp L, van den Wildenberg WPM, Scholte HS, Ridderinkhof KR, Forstmann BU. Effective Connectivity Reveals Important Roles for Both the Hyperdirect (Fronto-Subthalamic) and the Indirect (Fronto-Striatal-Pallidal) Fronto-Basal Ganglia Pathways during Response Inhibition. J Neurosci 2011;31:6891–9. doi:31/18/6891 [pii]10.1523/JNEUROSCI.5253-10.2011 [doi].

[41] van Gaal S, Scholte HS, Lamme VA, Fahrenfort JJ, Ridderinkhof KR. Pre-SMA graymatter density predicts individual differences in action selection in the face of conscious and unconscious response conflict. J Cogn Neurosci 2011;23:382–90. doi:10.1162/jocn.2010.21444 [doi].

[42] Forstmann BU, Dutilh G, Brown S, Neumann J, von Cramon DY, Ridderinkhof KR, et al. Striatum and pre-SMA facilitate decision-making under time pressure. Proc Natl Acad Sci U S A 2008;105:17538–42. doi:0805903105 [pii]10.1073/pnas.0805903105 [doi].

[43] Aron AR, Verbruggen F. Stop the presses: dissociating a selective from a global mechanism for stopping. Psychol Sci 2008;19:1146–53. doi:PSCI2216 [pii]10.1111/j.1467-9280.2008.02216.x [doi].

[44] Hamada M, Murase N, Hasan A, Balaratnam M, Rothwell JC. The Role of Interneuron Networks in Driving Human Motor Cortical Plasticity 2012. doi:10.1093/cercor/bhs147.

[45] Rocchi L, Casula E, Tocco P, Berardelli XA, Rothwell J. Somatosensory Temporal Discrimination Threshold Involves Inhibitory Mechanisms in the Primary Somatosensory Area 2016;36:325–35. doi:10.1523/JNEUROSCI.2008-15.2016.

[46] Swick D, Ashley V, Turken AU. Left inferior frontal gyrus is critical for response inhibition. BMC Neurosci 2008;9:102. doi:1471-2202-9-102 [pii]10.1186/1471-2202-9-102 [doi].

[47] Hirose S, Chikazoe J, Watanabe T, Jimura K, Kunimatsu A, Abe O, et al. Efficiency of go/no-go task performance implemented in the left hemisphere. J Neurosci 2012;32:9059–65. doi:10.1523/jneurosci.0540-12.2012.

[48] Nelson JK, Reuter-Lorenz P a., Persson J, Sylvester CYC, Jonides J. Mapping interference resolution across task domains: a shared control process in left inferior frontal gyrus. Brain Res 2009;1256:92–100. doi:S0006-8993(08)02912-0 [pii]10.1016/j.brainres.2008.12.001 [doi].

[49] Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: One decade on. Trends Cogn Sci 2014;18. doi:10.1016/j.tics.2013.12.003.

[50] Sharp DJ, Bonnelle V, De Boissezon X, Beckmann CF, James SG, Patel MC, et al. Distinct frontal systems for response inhibition, attentional capture, and error processing. Proc Natl Acad Sci U S A 2010;107:6106–11. doi:1000175107

[pii]10.1073/pnas.1000175107 [doi].

[51] Mostofsky SH, Simmonds DJ. Response inhibition and response selection: two sides of the same coin. J Cogn Neurosci 2008;20:751–61. doi:10.1162/jocn.2008.20500 [doi].

[52] Criaud M, Boulinguez P. Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review. Neurosci Biobehav Rev 2013;37:11–23. doi:10.1016/j.neubiorev.2012.11.003.

[53] Obeso I, Robles N, Marron EM, Redolar-Ripoll D, Marrón EM, Redolar-Ripoll D. Dissociating the Role of the pre-SMA in Response Inhibition and Switching: A Combined Online and Offline TMS Approach. Front Hum Neurosci 2013;7:150. doi:10.3389/fnhum.2013.00150.

[54] Rae CL, Hughes LE, Weaver C, Anderson MC, Rowe JB. Selection and stopping in voluntary action: a meta-analysis and combined fMRI study. Neuroimage 2014;86:381–91. doi:10.1016/j.neuroimage.2013.10.012.

[55] Blasi G, Goldberg TE, Weickert T, Das S, Kohn P, Zoltick B, et al. Brain regions underlying response inhibition and interference monitoring and suppression. Eur J Neurosci 2006;23:1658–64. doi:10.1111/j.1460-9568.2006.04680.x.

[56] Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. Psychol Rev 2001;108:624–52.

[57] Casey BJ, Thomas KM, Welsh TF, Badgaiyan RD, Eccard CH, Jennings JR, et al. Dissociation of response conflict, attentional selection, and expectancy with functional magnetic resonance imaging. Proc Natl Acad Sci U S A 2000;97:8728–33. doi:97/15/8728 [pii].

[58] Ullsperger M, von Cramon DY. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. Neuroimage 2001;14:1387–401. doi:10.1006/nimg.2001.0935 [doi]S1053-8119(01)90935-8 [pii].

[59] Peterson BS, Kane MJ, Alexander GM, Lacadie C, Skudlarski P, Leung HC, et al. An event-related functional MRI study comparing interference effects in the Simon and Stroop tasks. Brain Res Cogn Brain Res 2002;13:427–40. doi:10.1016/S0926-6410(02)00054-X.

[60] Rushworth MF, Hadland KA, Paus T, Sipila PK. Role of the human medial frontal cortex in task switching: a combined fMRI and TMS study. J Neurophysiol 2002;87:2577–92.

[61] Taylor PC, Nobre AC, Rushworth MF. Subsecond changes in top down control exerted by human medial frontal cortex during conflict and action selection: a combined transcranial magnetic stimulation electroencephalography study. J Neurosci 2007;27:11343–53. doi:27/42/11343 [pii]10.1523/JNEUROSCI.2877-07.2007 [doi].

[62] Soutschek A, Taylor PCJ, Müller HJ, Schubert T. Dissociable networks control conflict during perception and response selection: a transcranial magnetic stimulation Study. J

Neurosci 2013;33:5647–54. doi:10.1523/JNEUROSCI.4768-12.2013.

[63] Spieser L, van den Wildenberg W, Hasbroucq T, Ridderinkhof KR, Burle B. Controlling Your Impulses: Electrical Stimulation of the Human Supplementary Motor Complex Prevents Impulsive Errors. J Neurosci 2015;35:3010–5. doi:10.1523/JNEUROSCI.1642-14.2015.

[64] Logan GD, Schachar RJ, Tannock R. Impulsivity and Inhibitory Control. Psychol Sci 1997;8:60–64.

[65] Obeso I, Cerasa A, Quattrone A. The effectiveness of transcranial brain stimulation in improving clinical signs of hyperkinetic movement disorders. Front Neurosci 2016;9. doi:10.3389/fnins.2015.00486.

[66] Luber B, Lisanby SH. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). Neuroimage 2013. doi:10.1016/j.neuroimage.2013.06.007.

Figure captions

Figure 1. *A, The conditional stop signal task. Participants were required to respond to the go signal that was either a right or left pointing arrow. On 'critical' stop trials, the go signal was followed by the appearance of a stop signal (red cross) which appeared after a variable delay (stop signal delay) following the go signal and participants were instructed to inhibit their response. On 'non-critical' stop trials, participants were instructed to ignore the stop signal and to continue to respond to the go signal; B, trial types for both critical and non-critical directions with description of what participants need to do; C, 'virtual' location of cTBS targets.*

Figure 2. *A, Mean 'critical' Go and Stop Respond reaction times in milliseconds; B, Mean stop signal RT (SSRT) in milliseconds plotted separately for each of the theta burst stimulation conditions: inferior frontal gyrus, sham motor cortex and pre-SMA. Error bars represent standard errors and an asterisk indicates a significant comparison, $p < .05$.*

Figure 3. *The stop signal RT (SSRT) in milliseconds plotted separately for each quartile , 25^{th}, 50^{th} and 75^{th}, for each theta burst stimulation condition: inferior frontal gyrus, sham motor cortex and pre-SMA. Error bars represent standard errors and an asterisk indicates a significant comparison, $p < .05$.*

Figure 4. *A, Mean 'non-critical' Go and Stop Respond RTs in milliseconds; B, Mean conflict induced slowing (CIS) difference score in milliseconds plotted separately for each of the theta burst stimulation conditions: inferior frontal gyrus, sham motor cortex and pre-SMA. Error bars represent standard errors.*