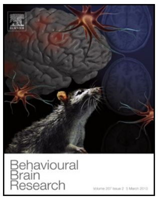
Behavioural Brain Research 296 (2016) 459–467

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr



Research report

Roles of the pre-SMA and rIFG in conditional stopping revealed by transcranial magnetic stimulation

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HIGHLIGHTS

- Disruption of pre-SMA activity impaired the continue process in low-slowing participants.
- Disruption of rIFG activity did not significantly affect response slowing.
- Pre-SMA's efficiency in reinitiating an inhibited response may be related to response slowing.

ARTICLE INFO

Article history:
Received 3 June 2015
Received in revised form 30 July 2015
Accepted 18 August 2015
Available online 21 August 2015

Keywords:
Inhibitory control
Conditional stop-signal task
Pre-supplementary motor area
Right inferior prefrontal gyrus
Transcranial magnetic stimulation

ABSTRACT

Although both the presupplementary motor area (pre-SMA) and the right inferior frontal gyrus (rIFG) have been demonstrated to be critical for response inhibition, there is still considerable disagreement over the roles they play in the process. In the present study, we investigated the causal relations of the pre-SMA and the rIFG in a conditional stop-signal task by applying offline theta-burst transcranial magnetic stimulation. The task introduced a continue condition, which requires the same motor response as in a go trial but captures attention as in a stop trial. We found great individual differences in the amount of slowing on continue trials. Temporary suppression of pre-SMA activity prolonged the continue RT in participants who slowed little in response to continue trials, whereas disruption of the rIFG did not lead to significant changes in performance irrespective of the degree of slowing. Our results contribute to the understanding of the role of the pre-SMA by providing causal evidence that it is involved in response slowing on 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.

1. Introduction

The ability to inhibit a prepotent motor response or interrupt a habitual action is an important function of executive control. Take driving as an example. When a driver sees a reckless person running the red light, the driver's ability to suppress the ongoing action of pressing the accelerator and hit the brake pedal instead becomes vital. A critical brain area for cognitive control that has been identified is the prefrontal cortex [15,32,39]. Two frontocortical areas, the pre-supplementary motor area (pre-SMA) and the right inferior prefrontal gyrus (rIFG), are consistently implicated in the withholding of motor responses (e.g., [2,16,29,45]). Despite their essential involvement in stopping, their precise roles in motor response inhibition remain largely equivocal.

The pre-SMA, which is located in the dorsomedial prefrontal cortex, has been suggested to be involved in inhibiting responses because of its roles in updating or change of action plans, switching between tasks, and switching between rules linking stimuli to responses [23,34,41,46]. The rIFG, which is located in the ventral prefrontal cortex, is also critical for successful response inhibition [1–3,17], but some have proposed that the primary role of the rIFG is in the attentional processing associated with inhibitory control, such as implementing signal detection or monitoring

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http://dx.doi.org/10.1016/j.bbr.2015.08.024

[11,18,26,36,45], or in the affective or motivational processing associated with inhibition successes and failures [29,38].

Three important issues have arisen in previous attempts to clarify the involvement of the pre-SMA and rIFG in response inhibition by using the stop-signal paradigm. The first relates to the methods used to isolate their roles. Previous fMRI studies tried to do so by contrasting participants' neural activity during successful and failed inhibition, which may have mainly controlled for differences in pre-response processing but not differences in signal monitoring and post-response processing such as emotional frustration associated with inhibition failures [29]. To address this issue, Li et al. [29] proposed the use of the contrast between short and long SSRTs as these two groups of participants showed no difference in inhibition failure rate. Their results revealed that a shorter SSRT was associated with greater activation primarily in the left superior frontal gyrus, but there was no group difference in activation in the IFG. In Li et al.'s [29] view, these results suggested that although both the pre-SMA and IFG are recruited in successful inhibition, only the pre-SMA is important for more efficient stopping. The IFG activation observed in previous studies that used the contrast of successful and failed inhibition may primarily reflect differences in attentional processing associated with inhibition successes and failures. However, Aron and Poldrack [2] employed the same contrast in their fMRI analysis but found the opposite results: participants with shorter SSRTs only showed significant activation within the rIFG but not the pre-SMA. Because the rIFG activation also correlated with activation in the right subthalamic nucleus (STN) and both predicted SSRT, they argued that the rIFG plays a role in inhibitory control by exciting the STN, which in turn suppresses thalamocortical output to block response execution. Nevertheless, evidence to date for IFG-STN connectivity and its specific role in response inhibition is equivocal [27,28,44,51].

The second issue relates to the design of the stop-signal task itself. On the one hand, the stop-signal task involves detection of a signal to stop, which may confound a role in target detection with a role in response inhibition [18]. On the other hand, the stop signal contains the properties of an unexpected abrupt onset because not only does it occur with low probability but its latency of occurrence is also adjusted dynamically on a trial-by-trial basis according to individual performance, so the processing that takes place in stop trials may also be related to attentional capture [45]. Sharp et al. [45] attempted to separate the cognitive processing involved in attentional capture and response inhibition by adding continue trials to the conventional stop-signal task. The continue trials were similar to the stop trials in that the number of trials and signal delay periods were identical, but participants were required to respond to a continue signal with a go response rather than a stop response. Because a continue trial included a visual cue that was intended to be an unexpected signal sharing all crucial properties of a stop signal but required no change of behavior, the processing involved in a continue trial could be used to contrast with that in a stop trial to distinguish between brain regions for attentional capture of a perceptual cue and those for outright stopping. Behaviorally, they found no significant difference in performance regardless of whether continue trials were included in the stop signal task, except that continue RT in the conditional stop-signal task was approximately 40 ms slower than go RT in the conventional stop-signal task. However, their neuroimaging results based on the contrast of correct stop versus correct continue trials revealed only right pre-SMA but no significant rIFG activation, suggesting that it was the right pre-SMA rather than the rIFG that was specifically supporting response inhibition. By further contrasting the activation patterns between participants who showed a high and a low degree of slowing in continue trials, they found that high-slowing participants showed more active right pre-SMA activation in continue trials than those with low slowing, but rIFG activation was not different between the two groups. Because this same region of the pre-SMA was also activated in the contrast of correct stop versus correct go trials, they argued that the observed response slowing in continue trials was due to incomplete inhibition triggered by the appearance of an unexpected event. Therefore, the contrast of neural activation between high- and low-slowing participants delineated a role for the right pre-SMA in both withholding and delaying a response and a role for the rIFG in attentional capture of low-frequency unexpected stimuli. Aron et al. [3] argue against the view that the rIFG is important for attentional detection rather than for inhibition by suggesting that all unexpected stimuli involve inhibition and that these stimuli lead to response slowing that has the same scalp electroencephalography signature as outright stopping (for a discussion of the rIFG's roles in response inhibition and attentional control, see Ref. [36]).

The third issue concerns the regions of the pre-SMA and rIFG that have been identified as the locus for response inhibition. While the rIFG activation obtained from the different contrasts in Aron and Poldrack's [2] study referred to above were in close proximity (MNI: $x = 44$, $y = 12$, $z = 8$ for the StopInhibit-Go contrast, and $x = 42$, $y = 26$, $z = 14$ for the short/long SSRT contrast), the activated area of the pre-SMA in Li et al.'s [29] study obtained from the short/long SSRT contrast (MNI: $x = -5$, $y = 29$, $z = 57$) was markedly different from the area obtained from the successful/failed inhibition contrast (MNI: $x = 18$, $y = 50$, $z = 42$). A different profile of pre-SMA activation (MNI: $x = 20$, $y = 6$, $z = 62$) was also reported in Sharp et al.'s [45] study. This region not only lies more posteriorly as compared to the anterior pre-SMA identified in Ref. [29], but its location is also more lateral and is bordering on the superior frontal gyrus. These anatomical variations suggest a possibility that different regions of the pre-SMA are involved in different stages and/or types of stopping, and the level of recruitment of these regions may vary accordingly. Indeed, a number of recent studies showed that the posterior pre-SMA can be delineated from the anterior pre-SMA in terms of both functional connectivity [52] and division [21], with the posterior part specifically related to response slowing and the anterior part to stop signal anticipation and proactive control. Furthermore, although the right pre-SMA and rIFG identified in Sharp et al.'s [45] study were based on the peaks of activation from the contrast of correct stop versus correct continue trials and from the contrast of correct stop versus correct go trials, respectively, the neural activity of these two regions did not correlate with participants' SSRT. These results may suggest that the two regions they identified presumably were recruited in the stop process but were nonessential to stop performance. The case of essential and nonessential pre-SMA activations can be demonstrated in Ref. [41], in which they found that the pre-SMA was recruited during task-set switching in both the response-switching and the visual-switching paradigms, but applying TMS over the pre-SMA compromised performance only during switching in the motor response modality, indicating that pre-SMA activation was essential for visuomotor intentional set shifts but nonessential for visual attentional set shifts.

These three issues illustrate that, in addition to using neural activation as an index, interference techniques such as TMS are instrumental in establishing the precise roles of the pre-SMA and rIFG in response inhibition. Previous brain stimulation studies have already demonstrated that both the pre-SMA and rIFG are causally involved in inhibitory control (e.g., [10,20,25,31,51]). The goal of the present brain stimulation study was to go beyond reconfirming their causal involvement to investigate the subtle differences in their functional roles by building on Sharp et al.'s [45] neuroimaging results. We applied reversible disruption to the right pre-SMA and the rIFG separately by using offline transcranial magnetic stimulation (TMS) to examine how participants' performance in the conditional stop-signal task would be affected as a result of the