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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.

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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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[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

temporary perturbation of neural activity in the two regions. TMS has been shown to impair performance on a stop-signal task as indicated by an elevated SSRT when it was applied over the pre-SMA [10,37] and over the rIFG [8,7]. Specifically, we wanted to compare the TMS effect on performance in the high- and low-slowing participants. Since these two groups did not differ in inhibition failure rate, differences due to pre- and post-response processing were controlled for. Considering that the high-slowing group can be distinguished from the low-slowing group behaviorally by their longer continue–go RT and neurally by the greater pre-SMA activity on continue trials, we expected pre-SMA stimulation to make the high-slowing group more impulsive and thus show a reduced continue RT relative to the sham condition but no change in performance for the low-slowing group. An alternative hypothesis is that pre-SMA stimulation would prolong the low-slowing group's continue RT because they show a better capacity for task updating and switching and are thus more amenable to the influence of TMS. A differential group response as hypothesized after pre-SMA stimulation would provide evidence that this region is involved in the inhibitory processing during response slowing. Given that continue trials and go trials are similar in the required response but different in the magnitude of attentional capture, we expected a similar level of impairment in continue RT between groups after rIFG stimulation, which would be indicative of its role in attentional capture. Since Sharp et al. [45] did not find activations of the right pre-SMA and rIFG to correlate with participants' SSRT, we did not expect TMS to have behavioral effect on stop trials.

2. Methods

2.1. Participants

Twenty-four healthy right-handed undergraduate and graduate students (18 males, mean age = 23 ± 2 years) from National Central University, Taiwan, participated in this experiment. All participants had normal or corrected-to-normal visual acuity. The experiment was approved by the Institutional Review Board. Informed consent was obtained from all participants prior to the experiment. Participants received monetary reward for participation in the experiment.

2.2. Apparatus

A Pentium III computer with a NVIDIA PRO TNT 32-MB graphics card controlled the stimulus display and recorded participants' response. All stimuli were presented in the center of a 19-inch color CRT (View Sonic Professional Series P95+) computer screen using Matlab (r2009a; Psychology Software Tools Inc., Pittsburgh, 2002). The resolution of the monitor was 1024 × 768 pixels and the vertical refresh rate was fixed at 100 Hz, permitting display times to be varied in steps of approximately 10 ms. The presentation of the stimuli was synchronized with the refresh rate of the monitor. The stimuli were presented at a visual angle of approximately 1.5° and a viewing distance of approximately 70 cm with the participant's head stabilized by a chin rest.

2.3. The conditional stop-signal task

The conditional stop-signal task consisted of three types of trials: go, stop and continue. A go trial began with a 500 ms central fixation cross, followed by a 200 ms blank screen. The go stimulus was then presented for 1000 ms, which was followed by a blank-screen intertrial interval (ITI) ranging between 500 and 1000 ms. All stimuli were presented at the center of the screen. The go stimulus was either three "less than" symbols («<) indicating a leftward direction or three "greater than" symbols (»>) indicating a rightward direction. Participants were required to respond to a leftward-pointing go stimulus by pressing the letter X on a standard QWERTY keyboard with their left index finger and to a rightward-pointing go stimulus by pressing the letter M with their right index finger. Participants were instructed to respond to the go stimulus as quickly and accurately as possible.

The stop signal was a red dot that appeared above the location of the go stimulus. The stop-signal delay (SSD) was initially set at 170 ms, which would be dynamically adjusted on a trial-by-trial basis based upon a participant's performance. The SSD of the next stop trial was increased by 40 ms after successful stopping and decreased by 40 ms after unsuccessful stopping. A minimum and a maximum SSD were set so that the stop signal always occurred at least 50 ms and also no longer than 290 ms after the onset of a trial to ensure it appeared well within a participant's go reaction time (RT) so as to avoid intentional waiting.

The continue signal shared all the properties of a stop signal except that it was in green and was presented below the location of the go stimulus. The signal delay used for a continue trial was the same as the SSD of the most recent stop trial, and it was not adjusted according to a participant's performance on a continue trial. Participants were instructed to respond to the go stimulus when a continue signal was presented as quickly as they could without sacrificing accuracy.

The distribution of go, stop and continue trials was 60%, 20% and 20%, respectively. These three types of trials were randomly presented such that there was one stop trial and one continue trial in every five trials. The leftward and rightward go stimuli were equally distributed.

A number of feedback mechanisms were in place. For the go trials, to avoid strategic slowing in order to achieve a higher success rate in stopping, a participant would receive both auditory and visual feedback if their go RT was 2 SDs greater than their baseline go RT. They would hear a 2000 Hz beep for a duration of 200 ms and see a warning message on screen to remind them not to purposely wait. Auditory and visual feedback was also provided when a wrong response or no response to the go stimulus was detected. For the continue trials, the same auditory and visual feedback was provided when participants gave an incorrect response or no response. For the stop trials, participants would hear a beep when they failed to inhibit a response to the stop signal.

A participant's mean go RT and continue RT were calculated by first removing trials with no response or incorrect responses. In addition, trials with latencies that were 2 standard deviations away from a participant's mean go RT or continue RT were also excluded from analysis. Estimation of the stop-signal reaction time (SSRT) was calculated using the distribution of go RT and the probability of responding given a stop signal delay (SSD) according to Logan and Cowan's [53] horse-race model. A participant's SSRT was estimated using the mean method, whereby the SSRT was estimated by subtracting the SSD from the mean go RT when the tracking procedure yielded a p(response|signal) of 0.50 [50]. The mean method for SSRT estimation is considered most reliable when used with the tracking procedure [50] and also requires less stop-signal trials to obtain robust findings [4].

2.4. Procedures

The experiment used a within-subjects design and consisted of three sessions: pre-SMA stimulation, rIFG stimulation, and sham. The three TMS sessions were carried out on three separate days, with an interval of at least five days between conditions, and the order was counterbalanced across participants. Identical materials, stimuli and procedures were used in all conditions, so the only difference in the three experimental sessions was the TMS condition.

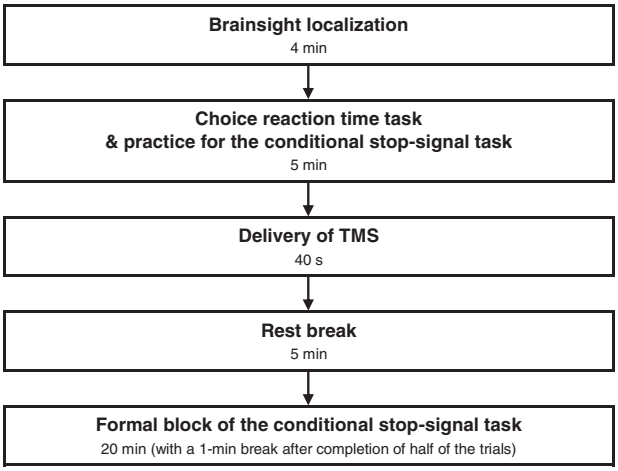

Fig. 1. The procedures of an experimental session.

In an experimental session (see Fig. 1), a participant first entered the laboratory for Brainsight localization. Each participant then completed 60 trials of a choice reaction time task to measure their baseline go RT and 30 practice trials for the conditional stop-signal task. They were then given 40 s of TMS and then rested for 5 min Hubl et al. [54]. After the remain-seated rest, the formal block began. The formal block included a total of 300 trials, and participants were given a short period of rest (no longer than 1 min) after they completed half of the trials. During the practice and formal blocks, the main lights of the laboratory were turned off, leaving a dim light behind the computer screen. The experimenter remained in the laboratory with the participants but on the other side of the curtain while they performed the task.

2.5. TMS parameters and site localization

Offline continuous theta burst stimulation (cTBS) was delivered using a Magstim Super-Rapid Stimulator connected to a figure-of-8 coil with a diameter of 70 mm. Each train of cTBS consisted of three pulses given at 50 Hz every 200 ms for 40 s, resulting in 600 pulses in total. A single threshold of 40% of the maximal stimulator output (2 T) was used based on past studies showing reliable TMS effects across a wide range of tasks [30,9]. This protocol has been demonstrated to produce temporary disruptive suppression of motor evoked potentials when delivered over the primary motor cortex for up to 60 min [22].

The coordinates of the right pre-SMA and rIFG were chosen based on Sharp et al.'s [45] neuroimaging results where the peaks of activation of the right pre-SMA and rIFG were obtained during the conditional stop-signal task. The peak of activation of the right pre-SMA (MNI: $x = 20$, $y = 6$, $z = 62$) was obtained from the contrast of correct stop versus correct continue trials. The peak of activation of the rIFG (MNI: $x = 44$, $y = 18$, $z = 16$) was obtained from the contrast of correct stop versus correct go trials (see Fig. 2). The coordinates were transformed into the Brainsight coordinate system (Rogue Research, Montreal, Canada) using the FSL software package (FMRIB, Oxford, UK), which were then determined using Brainsight with reference to each participant's T1 anatomical brain MRI image previously obtained. A Polaris infra-red tracking system (Northern Digital, Waterloo, Canada) was used to coregister the positions with a participant's structural image. For the sham condition, the coil was placed vertically over the vertex at 90° to the skull to mimic the sound of pulses and create a sensation on the scalp as in the right pre-SMA and rIFG stimulation conditions without stimulating the cortex.

2.6. Statistical analysis

Several sets of ANOVAs were designed to investigate the effect of applying TMS over the pre-SMA and rIFG on participants' response inhibition during conditional stopping. Since all participants' accuracy in all trial types of the three TMS conditions was over 95%, the ANOVAs were mainly performed on the RT data. Normality was met in all RT measures in all TMS conditions. Sphericity was met for continue–go RT and SSRT but was violated for go RT and continue RT, so degrees of freedom for go RT and continue RT were corrected using the Greenhouse–Geisser estimates of sphericity. Post-hoc pairwise comparisons were performed with Holm–Bonferroni correction to control for family-wise error rate. A first set of within-subjects ANOVAs were run to assess the main effect of TMS on participants' performance on all measures. We performed another series of 2 (trial type) × 3 (TMS condition) within-subjects ANOVAs to investigate whether participants'

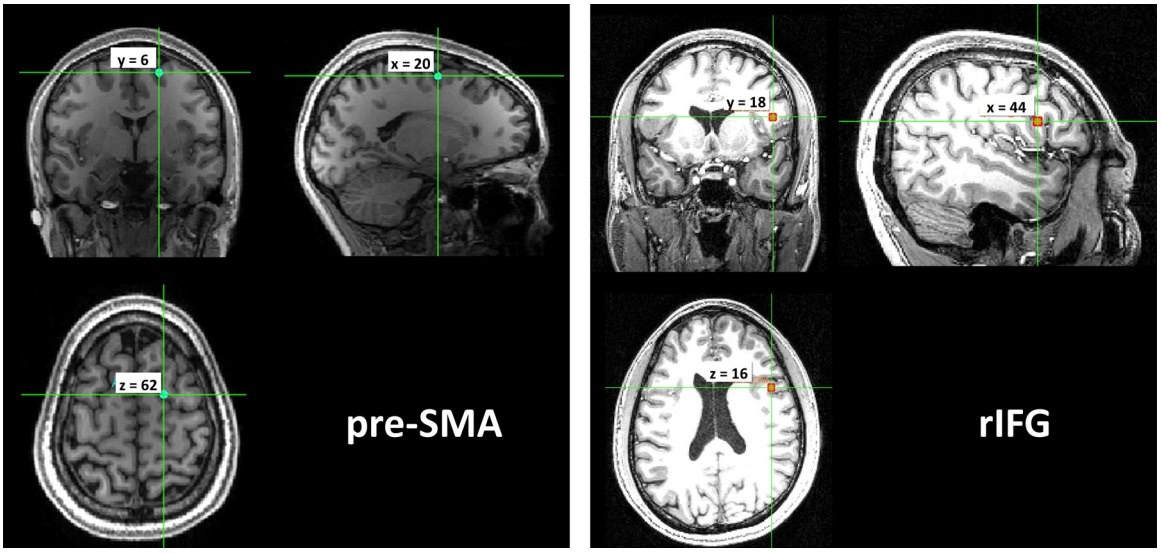

Fig. 2. Coordinates of the right pre-SMA and rIFG used for cTBS. The coordinates of the right pre-SMA (MNI: $x = 20$, $y = 6$, $z = 62$) and rIFG (MNI: $x = 44$, $y = 18$, $z = 16$) were based on the peaks of activation in Sharp et al.'s [45] neuroimaging results. The peak of activation of the right pre-SMA was obtained from the contrast of correct stop versus correct continue trials. The peak of activation of rIFG was obtained from the contrast of correct stop versus correct go trials.

performance on go trials and continue trials differed in terms of accuracy and RT. To further delineate the causal roles of the pre-SMA and rIFG in response inhibition, we also contrasted the performance of participants with a low degree of slowing (i.e., a smaller difference between continue RT and go RT) to those with a high degree of slowing (i.e., a larger difference between continue RT and go RT) across different TMS conditions by using the median continue–go RT obtained from the sham condition. These two groups of participants did not differ in age (22.58 versus 22.67 years), gender composition (9 males versus 10 males), or performance on any go and stop measures across conditions (all F values < 2 and $ps > 0.18$). We then performed a 2 (group) × 3 (TMS condition) mixed-design ANOVA with continue RT group as the between-subjects factor, TMS condition as the within-subjects factor, and participants' continue–go RT as the dependent variable.

To further probe the between-group differences in temporal dynamics of slowing in continue trials, the underlying RT distributions were analyzed by using delta plots [14]. To obtain the delta plots, RT was computed for each participant for each go and continue trial in the three TMS conditions. Go and continue RTs of the correct responses for each participant were rank ordered for each condition, respectively, and then divided into four quartiles. Mean RT was calculated separately for each quartile in each condition. Delta plots for RT were constructed by plotting the continue–go RT (i.e., the delta value) as a function of overall RT (the average of the mean go RT and mean continue RT) per quartile. Slopes were also computed for the delta plot segments connecting the data points of consecutive quartiles (Q1–2, Q2–3, and Q3–4). The slope of a line segment was defined as the difference in mean continue–go RT of two consecutive quartiles divided by the difference in mean overall RT of the two quartiles. A first mixed-design ANOVA was conducted on the mean continue–go RT, with TMS condition and quartile as the within-subjects factors and group (low- versus high-slowing) as the between-subjects factor. A second mixed-design ANOVA was conducted on the slopes of the delta plot segments (Q1–2, Q2–3, and Q3–4) for RT, with TMS condition and segment as the within-subjects factors and group as the between-subjects factor. Distributions of the RT and slope data were approximately normal. Violations of sphericity were corrected by adjusting the degrees of freedom in the ANOVAs using the Greenhouse–Geisser correction. Holm–Bonferroni correction was applied for post-hoc pairwise comparisons.

3. Results

3.1. Comparison of performance in the three TMS conditions

Table 1 summarizes the results for the conditional stop-signal task in the three TMS conditions. There was no significant main effect of TMS on participants' performance on any of the measures, Wilks' $\Lambda = 0.798$, $F(12, 82) = 0.82$, $p = 0.632$.

3.2. Comparison of performance on go and continue trials

On the assumption that the continue signal indicates a continuation of the ongoing action, it should not affect participants' accuracy and RT relative to their go performance. However, although we found that participants' accuracy did not significantly differ in either of the trial types or TMS conditions (all F values < 0.18 and $ps > 0.75$), their RTs in go trials and continue trials were highly significantly different, $F(1, 23) = 100.91$, $p < 0.001$, partial $\eta^2 = 0.814$. As shown in Table 1, mean RTs for continue trials in all three TMS conditions were approximately 23–28 ms slower than RTs for go trials (all pairwise comparisons showed $ps < 0.001$). The within-subjects effect of TMS condition ($F(2, 46) = 0.490$, $p = 0.616$, partial $\eta^2 = 0.021$) and the interaction effect ($F(2, 46) = 1.46$, $p = 0.242$, partial $\eta^2 = 0.060$) were not significant. These results indicate that, regardless of the TMS conditions, participants performed on continue trials as accurately as on go trials but also consistently more slowly than go trials.

3.3. Comparison of performance between the high- and low-slowing groups

As shown in Fig. 3, the continue–go RT of the high-slowing group was longer than that of the low-slowing group in all the three TMS conditions, $F(1, 18) = 23.38$, $p < 0.001$, partial $\eta^2 = 0.515$. The within-subjects main effect of TMS condition was not significant, $F(2, 44) = 1.88$, $p = 0.165$, partial $\eta^2 = 0.079$, but there was a significant group × TMS condition interaction, $F(2, 44) = 7.51$, $p = 0.002$, partial $\eta^2 = 0.254$, suggesting that the two groups responded to TMS differently. Post-hoc pairwise comparisons showed that, for the low-slowing group, the continue–go RT of the pre-SMA stimulation condition significantly increased relative to the sham condition ($p < 0.001$), whereas the high-slowing group showed no significant difference between conditions (all $ps > 0.10$). The contrast between pre-SMA and rIFG stimulation was not significant in either group. Since it has been shown above that participants' go process was not affected by TMS, the group comparison indicates that it is the continue process that took longer for the low-slowing participants after pre-SMA stimulation, but the continue process was not affected by rIFG stimulation in either group.

We further explored the within-group differences in distributional properties of continue–go RT by using delta plots. Delta plots can be used to reveal differences in individual efficiency in response inhibition and in the level of inhibitory strength [39,40]. The analysis indicated that the slopes between the three conditions were similar across all RT segments in the two groups (TMS condition × quartile × group interaction: $F(1.59, 34.96) = 0.07$, $p = 0.899$, partial $\eta^2 = 0.003$). As shown in Fig. 4, the delta plots are positive-going. There was no slowing in either group in the fastest RT segment, but the amount of slowing increased as a linear function of participants' overall RT. There was, however, a significant three-way interaction in participants' continue–go RT, $F(2.93, 64.52) = 3.58$, $p = 0.019$, partial $\eta^2 = 0.140$. The univariate results showed that TMS significantly affected the low-slowing group, $F(1.34, 14.69) = 8.59$, $p = 0.007$, partial $\eta^2 = 0.438$, with post-hoc comparisons showing a significant difference only between the pre-SMA stimulation and sham conditions, $p < 0.000$. The main effect of TMS on the high-slowing group was not significant, $F(2, 22) = 2.43$, $p = 0.111$, partial $\eta^2 = 0.181$. There was no TMS × quartile interaction effect in either group ($Fs < 2.10$, $ps > 0.065$), indicating that the effect of TMS on slowing was similar in the different RT segments. Overall, the results of the delta-plot analysis were consistent with the analysis above using the mean continue–go RT and revealed an increase in slowing in the low-slowing group when pre-SMA activity was temporarily disrupted.

4. Discussion

The present study investigated the causal involvement of the right pre-SMA and rIFG in response inhibition, particularly during incomplete or partial inhibition when stopping is conditional. By comparing how participants responded to go and continue signals in the stop-signal task, we found that, as expected, participants did not respond to a continue signal the same way as to a go signal. As reported in Sharp et al.'s [45] study, participants consistently took longer to respond to a continue signal than to a go signal. Importantly, we also found that this fundamental difference between go and continue RTs was not affected by TMS. This delay in response

Table 1
Results for the conditional stop-signal task in the three TMS conditions.

	pre-SMA stimulation	rIFG stimulation	Sham
Mean accuracy on go trials (%)	98.66 (1.59)	98.63 (1.16)	98.66 (1.20)
Mean accuracy on continue trials (%)	98.89 (1.53)	98.61 (2.23)	98.68 (1.55)
Mean accuracy on stop trials (%)	50.90 (1.55)	50.83 (1.77)	50.76 (2.08)
Mean go RT (ms)	369.11 (27.59)	366.63 (25.01)	370.33 (30.42)
Mean continue RT (ms)	396.53 (29.52)	389.57 (32.19)	393.60 (39.80)
Mean continue–go RT (ms)	27.42 (10.36)	22.94 (14.47)	23.27 (17.83)
Mean SSD (ms)	139.28 (30.15)	136.47 (27.28)	146.39 (38.99)
Mean SSRT (ms)	229.83 (16.73)	230.15 (18.10)	223.94 (20.00)

Note: RT = reaction time; SSD = stop signal delay; SSRT = stop-signal reaction time. Standard deviations are shown in brackets.

in the continue trials indicates that the processing involved in continuing was not the same as going in the go trials.

The appearance of a continue signal has been argued to lead to either pausing or slowing of the initiated go response. As previously discussed, Sharp et al. [45] attributed this response delay to incomplete inhibitory processing triggered by the appearance of the unexpected continue signals. van de Laar et al. [48] also argue that there is incomplete inhibition involved in the continue trials, but it is due to the early processing and discrimination of the signal, which then led to a reinitiation of the go response. Bissett and Logan [6] propose that this delay in response reflects a change in participants' strategy use for conditional stopping as a result of the discrimination between a stop and a continue signal required during a continue trial. As a signal occurs, some participants may first

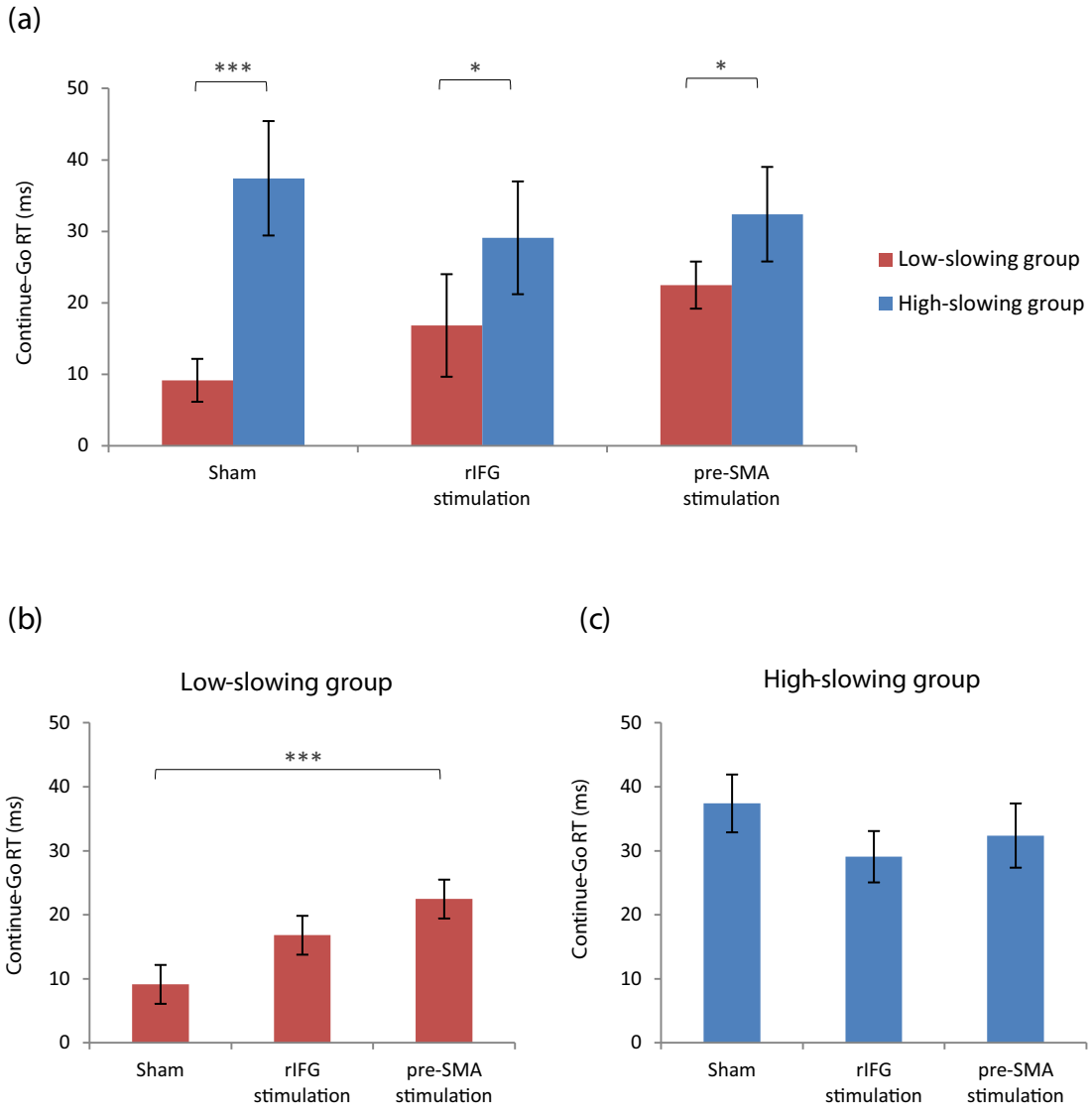

Fig. 3. Panel (a) shows the between-group comparison in the three TMS conditions. Error bars denote 95% confidence intervals. Panels (b) and (c) show the within-group differences in continue–go RT for the low- and high-slowing groups in the three TMS conditions. Applying TMS over the right pre-SMA significantly increased the low-slowing group's continue–go RT (i.e., their degree of slowing) relative to the sham condition ($p < 0.001$). Error bars denote 95% within-subjects confidence intervals computed in accordance with Cousineau [12].

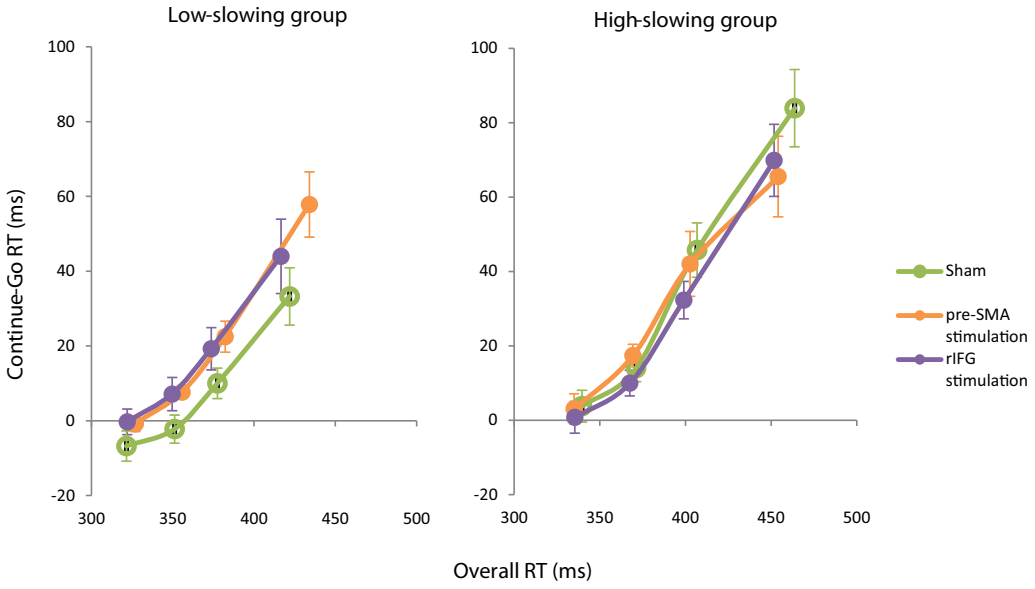

Fig. 4. Delta plots showing the within-group differences in continue–go RT for the low- and high-slowing groups in the three TMS conditions. Error bars denote 95% within-subjects confidence intervals computed in accordance with Cousineau [12].

pause their go response to discriminate the signal and then restart the go process if it is a continue signal, whereas in some other participants, the discrimination process does not lead to a pause but rather a slowing in the go process.

Adopting the distinction between low-slowing and high-slowing participants used in Sharp et al.'s [45] study, we found significant group differences in their response latency on continue trials in the sham condition, indicating that some individuals did require more time than others to respond in the face of a continue signal. Given that only activation of the right pre-SMA but not rIFG differentiated the two groups in Sharp et al.'s study after controlling for attentional capture, and that the observed pre-SMA activity during the continue trials was believed to be associated with the cost of response slowing, we expected that pre-SMA TMS should lead to differential group responses while disruption of the rIFG should equally affect both groups of participants. Interestingly, we found that the high-slowing group showed no significant changes in continue RT when either pre-SMA or rIFG TMS was applied. The low-slowing group, on the other hand, showed significant slowing in the continue trials after pre-SMA TMS was applied but their performance was not affected by rIFG TMS. In short, only disruption of right pre-SMA activity significantly influenced the continue process of the low-slowing group.

It is important to highlight that the behavioral and neural differences in the two groups were only manifested in the contrast of continue versus go trials, but they did not significantly differ in accuracy on continue trials or in any other go and stop measures, which indicates that this distinction between high- and low-slowing participants was unique only in their response latency during the continue trials. Therefore, what precisely differs in the processing between continue and go trials and between continue and stop trials, and how this processing differs between the high- and low slowing group are the key factors that drive the between-group differences.

Because the continue trials were intended to be a high-level baseline to contrast performance with stop trials given that the two types of trials involve similar levels of attentional processing but different required responses [45], the processing components of both the continue and stop trials are essentially identical. In either trial, the participant first processes the go signal until they are interrupted by the appearance of a continue or a stop signal. At this point, the presence of this signal is detected, and the participant has to discriminate whether it is a continue or a stop signal, which then activates the corresponding response, resulting in response execution or inhibition (cf. [48]). Although Sharp et al.'s results suggest that the same region of the pre-SMA activated during complete inhibition in the stop trials was also activated during partial inhibition in the continue trials, this study found that suppressing right pre-SMA activity did not lead to differential group response in the stop trials. Therefore, the observed between-group difference in response to pre-SMA TMS did not seem to be due to participants' differences in inhibitory processing.

It also seems unlikely that the between-group differences are attributable to the different preparatory processes involved in the continue and go trials. As opposed to the go processing involved in the choice reaction time task where preparation to stop is not necessary (i.e., go response is certain), the go trials in the stop-signal task invoke preparation to inhibit in anticipation of a stop signal (i.e., go response is uncertain), as shown by the longer time required to execute a go response in the latter type of go trials. This preparatory process in uncertain-go trials resembles the processing involved in a continue trial. In addition, Chikazoe et al. [55] fMRI data also revealed that the latter type of go processing recruited most of the inhibition-related frontoparietal regions (including the pre-SMA and IFG) that were also recruited in response inhibition (see also Ref. [26]), and they argue that the preparation cost may reflect components such as attention, uncertainty and anticipation rather than participants' waiting strategy. If it were the extent of preparation to inhibit that differentiated the high- and low-slowing group in the continue trials, similar results would have been expected in the go as well as the stop trials, but this was not the case.

Compared with both the uncertain-go and stop trials, one major component process that is distinctive in the continue trials is the reinitiation of an action that has been partially inhibited as a result of the sudden appearance of the continue signal. This reinitiation of action is not required either in the go trials because the go response is not interrupted or in the stop trials because no execution of response is needed. Updating action planning [46], switching [41], and reselecting and reinitiating an inhibited response [13] have been shown to be associated with the pre-SMA. In Sharp et al.'s [45] results, the low-slowing participants did not show signifi-

cant difference in pre-SMA activation for continue versus go trials, which suggests that the pre-SMA was similarly recruited in both conditions. It could be viewed that these participants were more efficient in the update of their action planning and in the reinitiation of the go response shortly after partially inhibiting their response due to the sudden signal. They were able to cope with the additional cognitive processing during the continue trials without substantially slowing down their response or further activating the pre-SMA as in the case of the high-slowing group. This may potentially explain why compromising the integrity of right pre-SMA processing in the low-slowing group led to substantial response slowing upon presentation of the continue signals. In other words, many of the low-slowing participants had become high-slowing after pre-SMA TMS was applied. In contrast, because response slowing was already fundamental for those high-slowing participants to perform successfully on a continue trial, applying TMS to these participants did not appear to lead to further slowing in performance.

Intriguingly, disruption of the rIFG did not lead to significant changes in behavioral performance on the continue trials. As reasoned by Sharp et al. [45], the continue trials provide a high-level baseline to contrast performance with stop trials, and greater activation of only the rIFG but not the right pre-SMA observed on continue trials in their results lend support to their argument that its involvement is in attentional capture of the unexpected continue signals. Because rIFG recruitment on the continue trials presumably should be comparable in both the high- and low-slowing groups given the same level of attentional capture they experienced, we expected a deterioration in performance in both groups after rIFG stimulation in our study. However, this prediction was not borne out in our data. A previous TMS study using the context-cueing paradigm [49] also reported that rIFG stimulation did not influence the cost associated with response slowing on signal-ignore trials. Noteworthily, although our results showed no significant rIFG TMS effect in either group on their RT or accuracy on continue trials, the within-subjects contrast of continue–go RT between the pre-SMA and rIFG stimulation conditions in the low-slowing group was not significant. From our delta-plot analysis of the continue–go RT distributions, the curve for rIFG TMS of the low-slowing group did show a tendency of deviation from the baseline condition, but applying TMS led to much greater variability of effect in all RT segments in the rIFG stimulation condition than in the other two conditions. These results suggest a putative role of the right pre-SMA in response slowing but no conclusive evidence for functional differentiation between the right pre-SMA and rIFG in this process. Further research is necessary to confirm this finding by increasing the sample size of study.

The absence of TMS effects on SSRT, as we hypothesized, provides evidence that the sub-regions of the right posterior pre-SMA and rIFG identified by Sharp et al. [45] are recruited in response inhibition but their activity was nonessential to outright stopping performance. Future research may fruitfully test the idea of essential and nonessential activations during response inhibition further by employing both neuroimaging and stimulation techniques to study the patterns of activity in different sub-regions of the pre-SMA and IFG.

5. Conclusion

The present study built on Sharp et al.'s [45] neuroimaging results and applied offline theta-burst TMS to investigate the subtle differences in involvement of the right pre-SMA and rIFG during a conditional stop-signal task. We observed that there were clear individual differences in the amount of slowing in response caused by the additional processing of the infrequent continue signals. By comparing two groups of participants who differed only in the amount of slowing on continue trials but not in any other go or stop measures, we found that temporary suppression of right pre-SMA activity prolonged the RT on continue trials of those who exhibited low slowing but not those with high slowing, whereas no significant effect on performance was found after rIFG stimulation. These results replicate Sharp et al.'s [45] findings and provide new causal evidence that the right posterior pre-SMA is associated with response slowing during conditional stopping. More importantly, the differential group response in the pre-SMA TMS condition suggests that it could be the right pre-SMA's efficiency in updating motor planning and reinitiating a partially inhibited response that was associated with the amount of slowing in response to continue trials.

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