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J Neurophysiol 98:3638-3647, 2007. First published Oct 17, 2007; doi:10.1152/jn.00685.2007

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Dissociable Mechanisms of Cognitive Control in Prefrontal and Premotor Cortex

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Submitted 21 June 2007; accepted in final form 13 October 2007

Chambers CD, Bellgrove MA, Gould IC, English T, Garavan H, McNaught E, Kamke M, Mattingley JB. Dissociable mechanisms of cognitive control in prefrontal and premotor cortex. *J Neurophysiol* 98: 3638–3647, 2007. First published October 17, 2007; doi:10.1152/jn.00685.2007. Intelligent behavior depends on the ability to suppress inappropriate actions and resolve interference between competing responses. Recent clinical and neuroimaging evidence has demonstrated the involvement of prefrontal, parietal, and premotor areas during behaviors that emphasize conflict and inhibition. It remains unclear, however, whether discrete subregions within this network are crucial for overseeing more specific inhibitory demands. Here we probed the functional specialization of human prefrontal cortex by combining repetitive transcranial magnetic stimulation (rTMS) with integrated behavioral measures of response inhibition (stop-signal task) and response competition (flanker task). Participants undertook a combined stop-signal/flanker task after rTMS of the inferior frontal gyrus (IFG) or dorsal premotor cortex (dPM) in each hemisphere. Stimulation of the right IFG impaired stop-signal inhibition under conditions of heightened response competition but did not influence the ability to suppress a competing response. In contrast, stimulation of the right dPM facilitated execution but had no effect on inhibition. Neither of these results was observed during rTMS of corresponding left-hemisphere regions. Overall, our findings are consistent with existing evidence that the right IFG is crucial for inhibitory control. The observed double dissociation of neurodisruptive effects between the right IFG and right dPM further implies that response inhibition and execution rely on distinct neural processes despite activating a common cortical network.

INTRODUCTION

Neural mechanisms of cognitive control are essential to coordinate, execute and update behavior. A crucial feature of successful updating is the ability to inhibit thoughts and actions that are no longer appropriate or relevant. A large body of neuropsychological evidence has identified the human prefrontal cortex (PFC) and basal ganglia as especially crucial for response inhibition (see Aron et al. 2004; Hodgson et al. 2007 for recent reviews). Recent studies, for instance, have demonstrated that lesions to the inferior frontal gyrus (IFG) can cause a deficit of response inhibition, as measured using tasks that require the cancellation of an initiated manual response (Aron et al. 2003) or the suppression of a reflexive saccade (Hodgson et al. 2007). Importantly, Aron et al. further showed that the magnitude of this deficit in the stop-signal paradigm can be

predicted uniquely by the extent of damage to the right IFG but not the nearby middle frontal gyrus (MFG) or superior frontal gyrus (SFG).

Despite the general agreement in the neuropsychological literature that the PFC is crucial for response inhibition, key questions remain concerning the specificity of the underlying control mechanism. In particular, some patient studies have shown that impairments of inhibition are more likely after lesions of the right medial SFG (Floden and Stuss 2006) or left supplementary motor/dorsal premotor cortex (dPM) (Picton et al. 2007), whereas other evidence suggests that inhibitory processes may be largely spared in many frontal patients (Dimitrov et al. 2003). These inconsistencies between reports may have arisen due to differences in lesion focality, symptomatic co-morbidity, and the reorganizational capacity of intact brain regions (Rorden and Karnath 2004). Moreover, the behavioral tasks used to measure response inhibition differ widely between many studies, and it remains unclear whether such tasks (e.g., stop signal; go/no-go; anti-saccade, etc.) engage a common regulatory system or whether inhibitory behavior is supported by several distinct functions.

Compared with the large number of studies that have addressed the neural basis of response inhibition using single behavioral measures (Aron and Poldrack 2006; Aron et al. 2003; Bellgrove et al. 2004; Chambers et al. 2006; Garavan et al. 1999; Hasegawa et al. 2004; Matsubara et al. 2004), relatively few have examined whether a common neural system mediates inhibition over a range of tasks. Two notable exceptions, however, identified a shared network of brain regions, including dorsolateral PFC, parietal, and premotor cortices that became active during the stop signal, go/no-go, flanker, and stimulus-response (S-R) compatibility paradigms (Rubia et al. 2001; Wager et al. 2005). These results are consistent with an influential meta-analysis of neuroimaging studies by Duncan and Owen (2000), which demonstrated that common regions of human dorsolateral PFC are recruited during a range of executive behaviors, including response inhibition, response selection, and working memory (see also Ridderinkhof et al. 2004). Based on these findings, it would be parsimonious to conclude that much inhibitory behavior is supported by a unitary or global cognitive mechanism.

If a single neural process mediates a range of inhibitory functions, then many of the same brain areas that are required

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for canceling a response should also be necessary for resolving competition *between* responses. Indeed, converging evidence from functional magnetic resonance imaging (fMRI), primate lesion studies, clinical work, and transcranial magnetic stimulation suggests that a variety of regions, including the dorso-lateral PFC, IFG, anterior cingulate, and dPM are involved in response selection and interference control (Bunge et al. 2002; Halsband and Passingham 1985; Hazeltine et al. 2000, 2003; Koski et al. 2005; Praamstra et al. 1999; Rushworth et al. 2002; Schluter et al. 1998; Schumacher et al. 2003). Several fMRI studies, for instance, have reported differential activity in these areas when a speeded response is executed in the presence of flankers that activate a competing response (Bunge et al. 2002; Hazeltine et al. 2000, 2003; Ullsperger and von Cramon 2001). Furthermore, Praamstra et al. (1999) reported that disruption of the human dPM increased the *cost* in reaction time (RT) associated with incompatible S-R mappings (e.g., responding with the right hand to a stimulus in the left visual field) while increasing the *benefit* associated with compatible mappings (see also Koski et al. 2005).

To what extent are neural interactions between different inhibitory functions reflected in behavioral performance? Several psychological studies have shown that the ability to inhibit a prepotent response depends on the degree of competition between response alternatives (Kramer et al. 1994; Ridderinkhof et al. 1999; Verbruggen et al. 2004, 2005). For instance, stop-signal inhibition is substantially impaired when the “go” response requires interference control, as probed through manipulations of S-R compatibility (Verbruggen et al. 2005) or presentation of flankers that correspond to a competing motor output (Verbruggen et al. 2004). This behavioral interaction implies that stop-signal inhibition and the resolution of response competition draw on a common cognitive, and perhaps inhibitory, resource. Interestingly, however, pharmaceutical administration of *methylphenidate* in attention-deficit-hyperactivity disorder (ADHD) selectively improves stop-signal inhibition without affecting performance on flanker or Stroop tasks (Scheres et al. 2003). Different inhibitory demands therefore appear to require processing in neurocognitive systems that are both interactive and dissociable.

In the present study, we used repetitive transcranial magnetic stimulation (rTMS) to test the hypothesis that different inhibitory demands require activity in common neural substrates. Previously, we have applied this technique to confirm observations from patient lesion studies (Aron et al. 2003, 2004), demonstrating that the right IFG is necessary for inhibiting a prepotent response in the stop-signal task (Chambers et al. 2006). Here we exploited this neurodisruption technique to establish whether the IFG is crucial not only for cancelling initiated responses but for resolving competition *between* responses and thus whether it hosts a more general inhibitory mechanism.

To probe the functional specialization of inhibitory control, we combined rTMS with a stop-signal/flanker paradigm, similar to that adopted by previous investigators (Verbruggen et al. 2004). This task measures the interaction between two cognitive functions: the ability to overcome competing response tendencies (flanker task component), and the ability to withhold an initiated action (stop-signal task component). In *experiment 1*, we sought to confirm the expected interaction between the ability to suppress a competing response and the ability to

cancel an initiated action (Kramer et al. 1994; Ridderinkhof et al. 1999; Verbruggen et al. 2004, 2005). In *experiments 2* and *3*, we then examined whether this association was reflected in the role of cortical areas that previous studies have implicated in inhibitory control. Participants undertook the same stop-signal/flanker task after low-frequency rTMS of the IFG or dPM in the right (*experiment 2*) or left (*experiment 3*) hemisphere. Previous studies have shown that this TMS protocol reduces cortical excitability for ~15–20 min, thus temporarily deactivating the stimulated region (Chen et al. 1997).

Based on this combination of rTMS and behavioral manipulations, we proposed three principal hypotheses. First, consistent with previous neuropsychological (Aron et al. 2003), rTMS (Chambers et al. 2006), and fMRI studies (Aron and Poldrack 2006; Garavan et al. 1999; Konishi et al. 1999; Menon et al. 2001; Rubia et al. 2001), stimulation of the IFG in the right hemisphere was expected to impair the ability to withhold a prepotent response in the stop-signal task. Second, if stop-signal inhibition and flanker inhibition require common neural processes, then rTMS of the IFG should also impair the ability to suppress a competing response in the flanker task. Third, based on previous studies of response selection and movement preparation, stimulation of the dPM in the left (Koski et al. 2005; Praamstra et al. 1999; Schluter et al. 1998) or right (Praeg et al. 2005) hemisphere was expected to impair the ability to suppress a competing response, and possibly cause a deficit of stop-signal inhibition (Picton et al. 2007).

METHODS

Participants, apparatus, and visual stimuli

In *experiment 1*, 23 neurologically healthy, right-handed adults were recruited (11 males, 12 females; aged 19–46 yr); 16 of these participants also completed *experiments 2* and *3*. All experimental protocols were approved by the Human Research Ethics Committee at the University of Melbourne. In all experiments, participants responded to visual stimuli using switches positioned under their left and right index fingers. To ensure accurate fixation and to provide a measure of arousal (pupil diameter), gaze was monitored on-line with an ASL-504 remote infrared eye-tracking system. Throughout testing, white noise was delivered via speakers located on either side of the visual display, and participants wore foam earplugs to attenuate ambient noise.

Visual stimuli were presented against a black background on a 19-in gamma-corrected monitor (Fig. 1A). The target stimulus was a white arrow presented at fixation, pointing to the left or right. The central arrow was always flanked by *congruent* distractors (4 arrows pointing in the same direction), *incongruent* distractors (4 arrows pointing in the opposite direction), or *neutral* distractors (4 bars without arrowheads). A red box presented around the stimulus display denoted a stop trial.

Experimental procedures

On each trial, participants identified the direction of the central arrow as rapidly and accurately as possible with their left or right hand. Participants were instructed to ignore the distractors, and to withhold their response when the stop signal occurred. Targets occurred with equal probability and stop signals were displayed randomly on 25% of trials.

Each trial commenced with the onset of central fixation, followed 500 ms later by the target stimulus (Fig. 1B). The target was presented

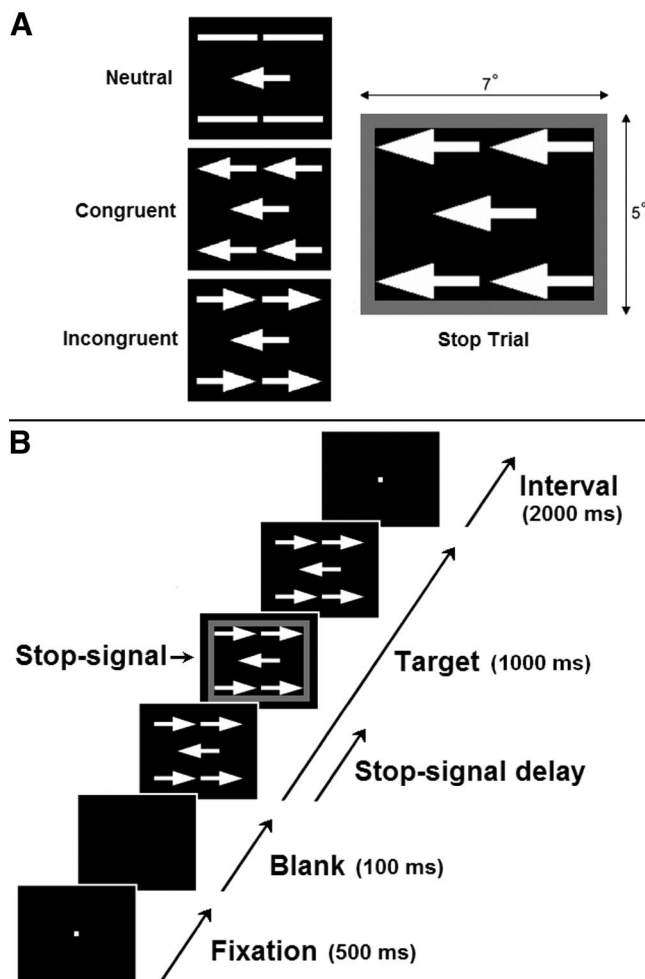


FIG. 1. Visual stimuli and displays employed in both experiments. *A*: target stimulus was a central arrow, flanked by distractors that were congruent, neutral, or incongruent with the correct response. All stimuli in this example correspond to left-hand responses. On a stop trial, a red box appeared around the target and flankers; this box is illustrated here in gray. *B*: typical display sequence in the combined flanker/stop-signal task. On each trial, participants responded as rapidly as possible with the hand indicated by the central target arrow. On a random 25% of trials, a stop-signal appeared, which instructed participants to cancel their response. To manipulate the likelihood of correctly inhibiting, the stop-signal occurred at various times after the onset of the target; this stop-signal delay was calibrated within subjects according to individual mean reaction times. Stimuli not shown to scale.

for 1,000 ms or until the participant responded, followed by an intertrial interval of 2,000 ms. On stop trials, the stop signal was displayed for 400 ms or until a response was registered. The stop signal was delivered randomly at one of three stop-signal delays (SSDs) after the onset of the go signal, calculated with respect to the participant's mean reaction time (MRT) on go trials. These SSDs included MRT – 250 ms, MRT – 200 ms, and MRT – 150 ms and were recalculated every 72 trials. The probability of inhibition is greater at short SSDs (*higher* values of MRT – x) and declines as the SSD increases (*lower* values of MRT – x) (Logan 1981, 1994). To control for within-subject differences in MRT, SSDs were calculated separately for each sub-condition of response hand (left, right) and flanker condition (congruent, neutral, incongruent). Thus each SSD had a different physical duration on congruent, neutral, and incongruent trials (and each sub-condition of response hand thereof). This calibration procedure ensured that variation in inhibition performance according to response hand or flanker condition was not confounded by corresponding variation in MRT.

In *experiment 1*, each participant completed 1,080 trials of the stop signal/flanker task over three sessions, yielding 30 trials per subcondition of SSD (MRT – 250 ms, MRT – 200 ms, MRT – 150 ms) and flanker condition (congruent, neutral, incongruent). In *experiments 2* and *3*, participants undertook the same task after six sessions of rTMS, including one session per anatomical site (left sham, right sham, left IFG, right IFG, left dPM, right dPM; see Fig. 2A). During “sham” TMS, the coil was oriented away from the scalp. Sham provided a control condition by mimicking some of the sensory artifacts that accompany TMS (e.g., the “clicking” sound) but without stimulating the cortex. Each testing session included two periods of rTMS (20-min each), followed immediately by a block of 216 trials (see Fig. 2B). Each block of 216 trials contained 54 stop trials (25%), and thus 6 stop trials per subcondition of SSD and flanker condition. The order of rTMS sites was counterbalanced across the sample using a Latin square design, and consecutive sessions were separated by ≥ 24 h.

TMS and MRI parameters

Prior to *experiment 2*, a T1-weighted MR scan was obtained from each participant using a GE Signa 3T system ($1.3 \times 1.3 \times 1.3$ mm, sagittal acquisition). To enable co-registration of cortical sites and scalp topography, participants were scanned with eight fiducial markers (vitamin E capsules) attached to the nasion, vertex, inion, prefrontal scalp, left/right tragi, and left/right temporal sites. Stimulation sites for rTMS were localized in each individual according to neuroanatomical landmarks (Fig. 2A). The IFG was defined as the dorsal midpoint of the pars opercularis, between the lateral sulcus and inferior frontal sulcus, anterior to the precentral sulcus (Chambers et al. 2006). The dPM was defined as the rostral midpoint of the rostral half of the precentral gyrus (i.e., anterior 75th quartile), at the junction of the superior frontal sulcus and precentral sulcus; this region corresponds to the premotor “upper limb” area in humans (Wise et al. 1997).

Average normalized coordinates for each site according to the Montreal Neurological Institute brain atlas are shown in Table 1. Cortical sites were calculated in slice and 3D-rendered brain scans using MRIcro imaging software (Rorden and Brett 2000). A magnetic tracking device (miniBird 500, Ascension Tech) and MR coregistration software (MRIreg) were used to coregister the neuroanatomical sites with the scalp surface.

Magnetic stimulation was administered via a MagStim Rapid system and 70-mm figure-eight, vacuum-cooled induction coil, fixed in position using a holding clamp and tripod. Prior to undertaking *experiments 2* and *3*, participants were screened for contraindications to TMS using a standard screening questionnaire. Exclusion criteria included, but were not limited to, a personal or family history of epilepsy, prior occurrence of seizure or stroke, previous head injury, any prior adverse effect to TMS, frequent or severe headaches, or prescription of psychiatric/neuroactive medication.

In *experiments 2* and *3*, rTMS was administered at 1 Hz within approved safety guidelines (Wassermann 1998) at the maximum level of output deemed comfortable by the participant. Stimulation of the IFG sites was generally the least comfortable due to activation of facial nerves; therefore each participant's “comfort threshold” was determined initially for the IFG sites. The lowest comfortable intensity was then matched across all remaining sites in each hemisphere as a percentage of the participant's resting motor threshold (MT). Across the sample, rTMS was administered at an average of 92% resting MT (mean stimulator output = $47 \pm 5.5\%$) as defined through a visually observed muscular contraction of the contralateral hand. The stimulation output was further corrected for differences in the scalp-cortex distance between brain sites, as we have described elsewhere (Stokes et al. 2005, 2007).

For each site, the coil was placed tangential to the scalp surface with the handle oriented toward the vertex. During sham rTMS, the

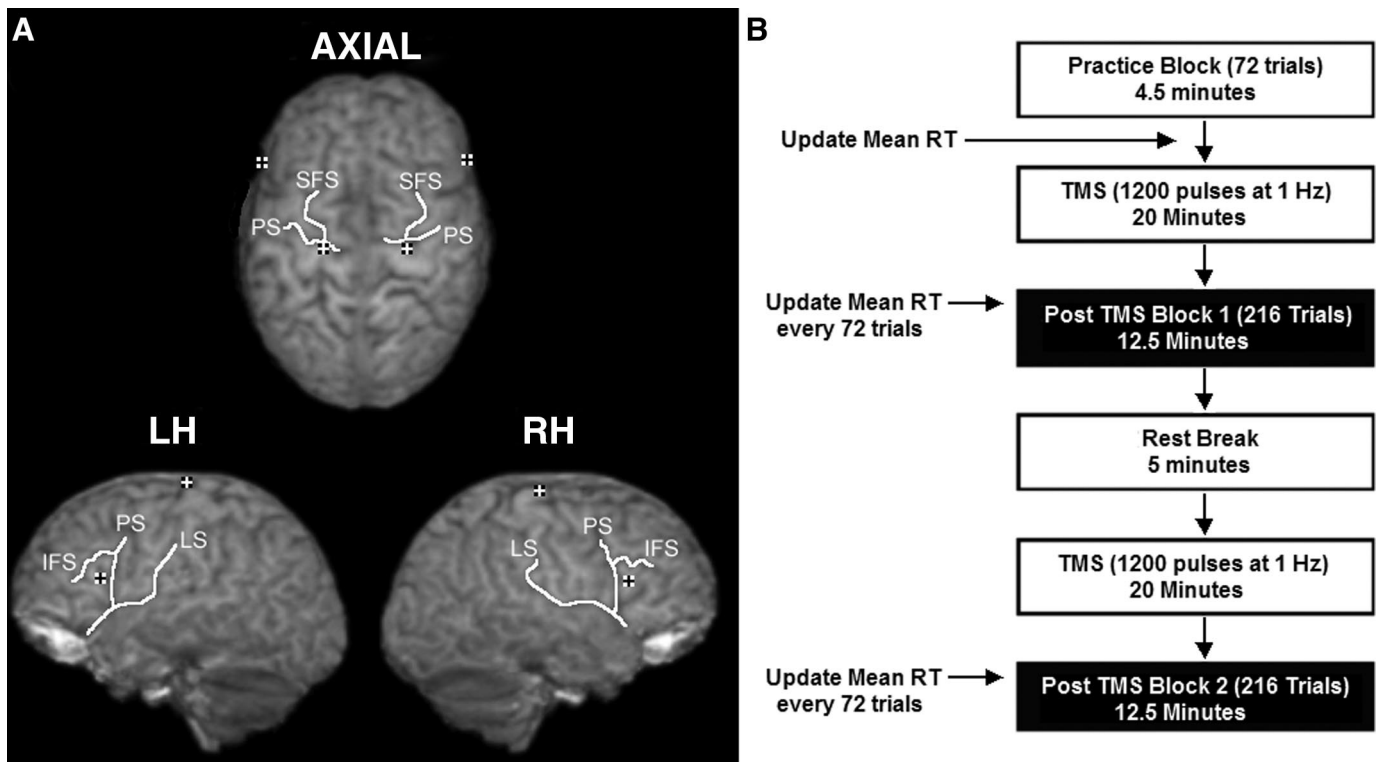


FIG. 2. Stimulated brain regions and testing schedule in *experiments 2* (right hemisphere) and *3* (left hemisphere). *A*: anatomical sites that were stimulated with repetitive transcranial magnetic stimulation (rTMS), shown in axial and sagittal planes for 1 participant. Each site was localized based on individual sulcal landmarks (see METHODS for details). LH, left hemisphere; RH, right hemisphere; black cross, inferior frontal gyrus; white cross, dorsal premotor cortex; LS, lateral sulcus; PS, precentral sulcus; IFS, inferior frontal sulcus; SFS, superior frontal sulcus. *B*: sequence of events that comprised each experimental session. Initially, participants undertook a practice block of 72 trials to acquire an estimate of mean RT for congruent, neutral and incongruent trials. Repetitive TMS was then delivered for 20 min. Immediately after the termination of rTMS, participants completed 3 blocks of 72 trials, taking ~12.5 min. This time period is within the interval where effects of rTMS are generally considered maximal (Chen et al. 1997). After a 5-min rest period, a 2nd period of rTMS was delivered for 20 min to the same cortical region after which participants undertook a further 3 blocks of 72 trials. To enable accurate calculation of SSDs, mean RT was updated after the practice block and at regular intervals throughout both post-TMS blocks.

coil was oriented perpendicular to the scalp and positioned at the approximate dorsolateral midpoint between the IFG and dPM sites.

Inhibition and execution measures

The time course of response inhibition was estimated through the calculation of stop-signal reaction time (SSRT). As described previously (Aron et al. 2003; Chambers et al. 2006; Logan 1981), SSRT represents the theoretical latency of inhibition by subtracting the SSD at which participants correctly inhibited on 50% of trials from their mean RT on go trials (mean RT - SSD_{50%}). This 50% threshold represents the point of maximal theoretical competition between execution and inhibition processes (Logan 1994). Consistent with our previous study (Chambers et al. 2006), we calculated the SSRT through sigmoidal regression of the percent of correct inhibitions (%CI) at SSDs of MRT - 150 ms, MRT - 200 ms and MRT - 250 ms;

TABLE 1. Means ± SD of normalized coordinates (mm) for each anatomical location, according to the Montreal Neurological Institute brain atlas

Brain Site	x	y	z
Right IFG	63 ± 2.6	21 ± 3.5	13 ± 3.1
Right dPM	31 ± 4.2	-8 ± 4.1	72 ± 2.1
Left IFG	-66 ± 2.6	20 ± 5.0	13 ± 4.5
Left dPM	-30 ± 4.8	-6 ± 5.2	73 ± 3.3

IFG, inferior frontal gyrus; dPM, dorsal premotor cortex.

these regression analyses were undertaken for each participant within the sub-conditions of flanker condition, coil hemisphere, rTMS site, and response hand. Psychophysical inhibition functions were obtained using the three-parameter equation

$$y = \frac{a}{1 + e^{-\left(\frac{x-x_0}{b}\right)}} \quad (1)$$

where a is the maximum possible performance (constrained to 100%), b is the slope parameter, and x_0 is the inflection point. The SSRT was then determined by solving for the x value of 50 in the restructured equation

$$x = -\left[b \times \ln\left(\frac{a}{y} - 1\right) - x_0 \right] \quad (2)$$

The precision of the SSRT estimate in this procedure depends on the goodness of fit yielded by the sigmoidal regression. Consequently, to maximize the sensitivity of group-level analyses, we weighted SSRT values linearly at each sublevel of subject × rTMS site × coil hemisphere × flanker condition according to the corresponding adjusted R^2 of the sigmoidal regression (median adjusted $R^2 = 0.94$; min adjusted $R^2 = 0.16$; max adjusted $R^2 = 1$). This procedure ensured a greater statistical contribution of more precise SSRT estimates.

Execution performance was measured primarily as the adjusted RT on correct responses (AdjRT). The AdjRT variable provides an overall index of execution performance that accommodates for response speed and response criterion (Chambers et al. 2004;

Townsend and Ashby 1983). For each condition, AdjRT was calculated as

$$\text{AdjRT}_{ij} = \frac{\overline{\text{RT}}_{ij}}{\text{PC}_{ij}} \quad (3)$$

where $\overline{\text{RT}}$ is the mean RT of correct responses for the i th participant in the j th condition, and PC is the proportion of correct responses within go trials for the i th participant in the j th condition. The mean RT on correct responses and percent of assignment errors (%AE: responses with the wrong hand) were also calculated and are reported in supplementary information.¹ After ANOVA analyses of inhibition and execution measures, all pair-wise comparisons between experimental conditions were undertaken with appropriate type I error correction (Bonferroni).

In addition to the execution measures described in the preceding text (RT, %AE, AdjRT), the behavioral cost in execution performance caused by incongruent flankers was also analyzed in *experiments 2* and *3*. In each case, this *incongruence cost* was calculated relative to the respective neutral flanker condition, collapsed across response hand (e.g., for AdjRT: incongruent AdjRT – neutral AdjRT). A deficit of competitive response selection was expected to manifest as an *increase* in the incongruence cost, consistent with a reduced ability to suppress a competing action plan.

RESULTS

Behavioral relationship between stop-signal inhibition and competitive response selection

Analysis of execution and inhibition measures in *experiment 1* confirmed the effectiveness of the flanker and stop-signal manipulations. Execution performance on go trials was examined through two-way repeated-measures ANOVA of mean AdjRT, including within-subjects factors of response hand (left, right) and flanker condition (congruent, neutral, incongruent). This analysis revealed significant main effects of response hand [$F(1,22) = 8.4, P = 0.008$] and flanker condition [$F(2,44) = 76.2, P < 0.001$] but no significant interaction [$F(2,44) = 1.4, P = 0.26$]. As expected for the right-handed individuals in this sample, analysis of simple main effects indicated a significant performance advantage for the right hand [433 ± 2.1 (SE) ms] compared with the left hand (446 ± 2.1 ms). A significant performance disadvantage was also observed on incongruent trials (484 ± 5.0 ms) relative to congruent (416 ± 2.6 ms) and neutral trials (418 ± 2.6 ms; both $P < 0.05$). No significant difference in AdjRT was observed between the congruent and neutral conditions. These results confirm the effectiveness of the task-irrelevant flankers in modulating response competition.

Inhibition performance was examined through separate analyses of the percent of correct inhibitions on stop trials (%CI) and the mean SSRT (see Fig. 3). For %CI, a three-way ANOVA with factors of response hand (left, right), flanker condition (congruent, neutral, incongruent), and SSD (MRT – 150, MRT – 200, MRT – 250) revealed the expected robust effect of SSD [$F(2,44) = 188.5, P < 0.0001$] and, crucially, a significant main effect of flanker condition [$F(2,44) = 9.1, P = 0.001$]. No other main effects or interactions were significant (all $P > 0.05$). As denoted by the square symbols in Fig. 3, analysis of simple main effects revealed that %CI was significantly lower on trials with incongruent flankers ($46.1 \pm 1.0\%$,

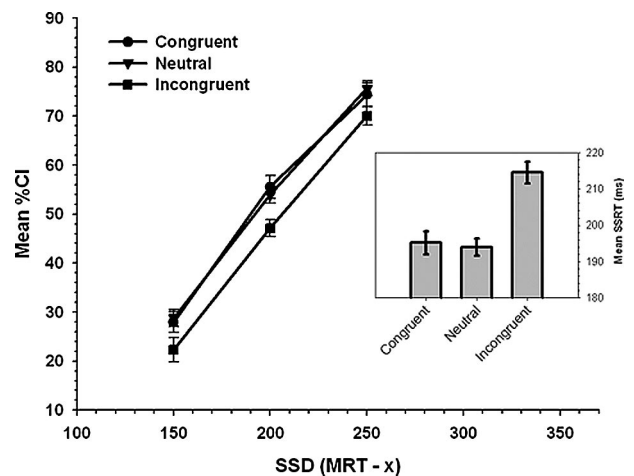


FIG. 3. Mean accuracy and latency of stop-signal inhibition obtained in *experiment 1*. ●, ■, ▼, and lines plot percent of correct inhibitions (%CI) as a function of stop-signal delay (SSD), calculated according to the mean RT (MRT) for congruent (●), neutral (▼) and incongruent trials (■). Larger values thus indicate *shorter* SSDs (MRT – x , where $x = 150, 200$, or 250). The mean %CI was significantly reduced on incongruent trials relative to congruent and neutral trials, which did not differ from each other. This performance cost was also reflected in the latency of inhibition (*inset*: ■), with the mean SSRT elevated significantly on incongruent trials compared with neutral and congruent trials. Error bars are ± 1 SE.

mean \pm SE) than on trials with either neutral ($52.8 \pm 0.75\%$) or congruent flankers ($52.6\% \pm 1.3\%$; both $P < 0.05$). No significant difference in %CI was observed between neutral and congruent conditions ($P > 0.95$).

These findings were mirrored in the analysis of inhibitory latency. A two-way ANOVA of SSRT with factors of response hand and flanker condition revealed a significant main effect of flanker condition [$F(2,44) = 10.9, P < 0.0001$], and no other significant effects (all $P > 0.05$). As indicated by the gray bars in Fig. 3, SSRT was significantly delayed on incongruent trials (214 ± 3.0 ms) relative to congruent (195 ± 3.1 ms) and neutral trials (194 ± 3.3 ms; both $P < 0.05$). No significant difference in SSRT was observed between the congruent and neutral conditions.

Experiment 2: effects of right hemisphere rTMS on stop-signal inhibition and execution

In *experiment 2*, inhibitory performance in the stop-signal task was analyzed following repetitive rTMS of the right hemisphere. Figure 4A illustrates the inhibitory latency (SSRT) after rTMS of the right IFG, right dPM, or right-hemisphere sham. A two-way repeated-measures ANOVA of mean SSRT was undertaken with factors of flanker condition and rTMS site (collapsed across response hand). Consistent with *experiment 1*, this analysis revealed a significant main effect of flanker condition [$F(2,30) = 12.9, P < 0.0001$], driven by differentially higher SSRT on incongruent trials. The main effect of rTMS site was not significant [$F(2,30) = 1.2, P = 0.33$]; however, a significant flanker condition \times rTMS Site interaction was detected [$F(4,60) = 3.0, P = 0.02$]. As shown by the asterisk in Fig. 4, stimulation of the right IFG significantly slowed SSRT on incongruent trials (223 ± 4.7 ms) relative to both sham (206 ± 5.0 ms) and dPM conditions (209 ± 4.6 ms; both $P < 0.05$). The same comparisons were not significant for congruent or neutral trials (all $P > 0.67$). These results indicate

¹ The online version of this article contains supplemental data.

Right Hemisphere TMS

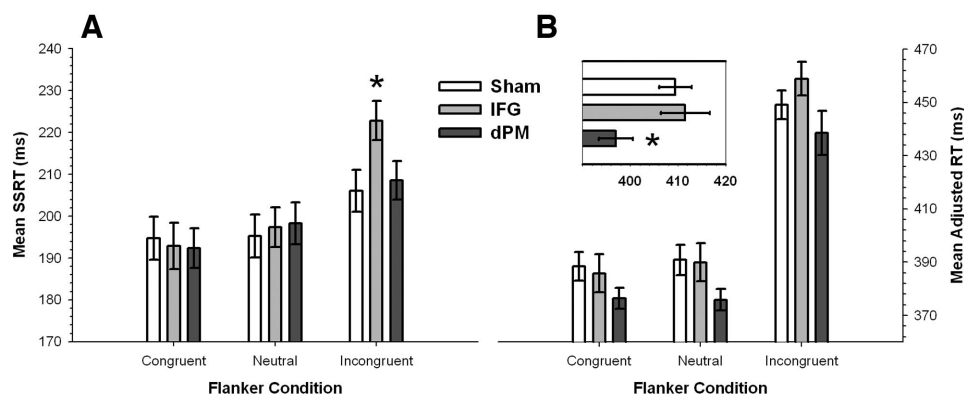


FIG. 4. Mean inhibition and execution performance in *experiment 2* after stimulation of the right hemisphere. *A*: consistent with *experiment 1*, stop-signal reaction time (SSRT) was significantly higher on incongruent trials relative to neutral and congruent trials. As indicated by the asterisk ($P < 0.05$), stimulation of the right inferior frontal gyrus (IFG) differentially increased SSRT on incongruent trials, relative to the sham and dorsal premotor cortex (dPM) conditions. This inhibitory deficit was not evident on neutral or congruent trials. *B*: mean execution performance, plotted according to the stimulated anatomical site (sham, IFG, dPM) and flanker condition (congruent, neutral, incongruent). Consistent with *experiment 1*, flanker congruency modulated execution performance in all conditions. Furthermore, stimulation of the right dPM (dark gray bars) improved performance relative to the sham and IFG conditions; this main effect is highlighted in the panel inset, collapsed across flanker condition. Error bars are ± 1 SE. See supplementary information for separate RT and error rate data.

that rTMS of the right IFG selectively increased SSRT on trials in which suppression of a competing response was also necessary.

Execution performance on go trials was examined through analysis of AdjRT, RT, and %AE. Figure 4*B* presents the mean AdjRT according to the flanker condition and rTMS site in the right hemisphere. A three-way ANOVA with factors of flanker condition, rTMS site, and response hand revealed a significant main effect of flanker condition [$F(2,30) = 52.5, P < 0.0001$], a significant main effect of response Hand [$F(1,15) = 4.9, P = 0.042$], and a marginal main effect of rTMS site [$F(2,30) = 3.0, P = 0.059$]. No interactions were significant (all $P > 0.05$). Analysis of simple main effects confirmed the global increase in AdjRT on incongruent trials (449 ± 5.4 ms) relative to congruent (384 ± 4.4 ms) and neutral trials (386 ± 3.6 ms; both $P < 0.05$), in addition to the expected AdjRT advantage for responses with the right hand (398 ± 4.4 ms) compared with the left hand (414 ± 4.0 ms). As shown in Fig. 4*B*, *inset*, performance tended to improve after stimulation of right dPM (397 ± 3.5 ms) compared with the sham (409 ± 3.4 ms; $P = 0.03$) and IFG conditions (412 ± 5.1 ms; $P = 0.06$). This reduction in AdjRT was similarly expressed in terms of

RT {main effect of rTMS site: [$F(2,30) = 2.9, P = 0.07$]} but was not significant for %AE (main effect of rTMS site: [$F(2,30) = 0.47, P = 0.61$]; see Fig. S1 in supplementary information}. Hence, stimulation of the right dPM did not cause a speed/accuracy trade-off. Furthermore, as shown in Fig. S2 (supplementary information), stimulation of the right dPM facilitated responses consistently in each hand.

Experiment 3: effects of left hemisphere rTMS on stop-signal inhibition and execution

In *experiment 3*, inhibitory performance in the stop-signal task was analyzed following repetitive rTMS of the left hemisphere. Figure 5*A* illustrates the mean inhibitory latency after rTMS of the left IFG, left dPM, or left-hemisphere sham. As with the analysis of the right-hemisphere sites, a two-way repeated-measures ANOVA of SSRT was undertaken with factors of flanker condition and rTMS site. This analysis revealed the expected significant effect of flanker condition [$F(2,30) = 21.5, P < 0.0001$]. However, neither the main effect of rTMS site [$F(2,30) = 2.4, P = 0.11$] nor the

Left Hemisphere TMS

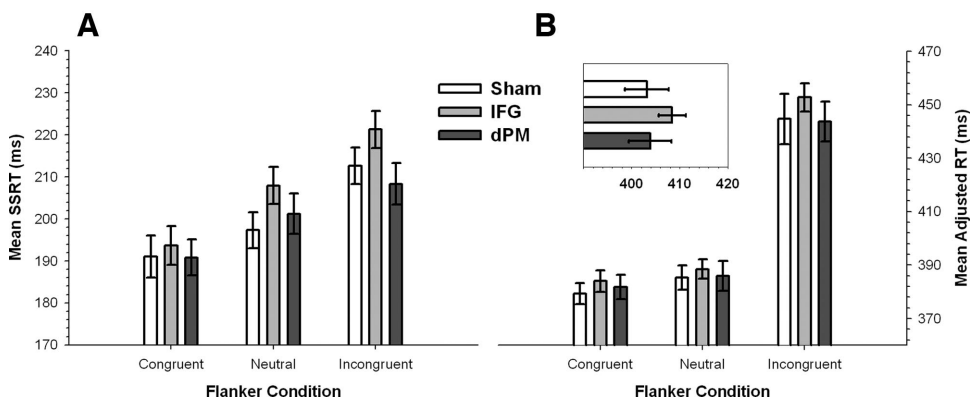


FIG. 5. Mean inhibition and execution performance in *experiment 3* after stimulation of the left hemisphere. *A*: neither the main effect of rTMS site nor the rTMS site \times flanker condition interaction were significant (both $P > 0.10$). *B*: mean execution performance, plotted according to the stimulated anatomical site (sham, IFG, dPM) and flanker condition (congruent, neutral, incongruent). Only a main effect of flanker congruency was observed; stimulation of the left IFG or dPM did not affect performance. Error bars are ± 1 SE. See supplementary information for separate RT and error rate data.

interaction between rTMS site and flanker condition were significant [$F(4,60) = 0.27, P = 0.89$].

As in *experiment 2*, execution performance on go trials was examined through analysis of AdjRT, RT, and %AE. Figure 5B reports the mean AdjRT according to the flanker condition and rTMS site after stimulation of the left hemisphere. Consistent with the right-hemisphere conditions, the main effect of flanker condition was again significant [$F(2,30) = 63.01, P < 0.0001$], and detected alongside a marginal effect of response hand [$F(1,15) = 4.5, P = 0.052$; right-hand advantage]. However, neither the main effect of rTMS site [$F(2,30) = 0.43, P = 0.63$] nor any interactions were significant (all $P > 0.05$). These null effects were similarly reflected in analyses of mean RT and %AE (see Fig. S3 in supplementary information).

Effects of cortical stimulation on response competition

To isolate possible effects of cortical stimulation on suppressing competitive response tendencies, we also analyzed the behavioral cost in execution performance caused by incongruent flankers. These analyses were undertaken for go trials and stop trials in which participants responded. In the former case (go trials), we thus probed the effect of rTMS on response selection in the *absence* of stop-signal inhibition; whereas in the latter case (stop trials: failed inhibitions), we examined whether the attempted cancellation of a prepotent response—and thus additional engagement of inhibitory mechanisms—altered the role of the stimulated cortex in mediating response selection.

For go trials, separate one-way ANOVAs of mean AdjRT, RT and %AE revealed no significant effects of rTMS site in either the left or right hemisphere (all $F < 2$, all $P > 0.16$). For stop trials, the same analyses were undertaken on RT only, as participants made an insufficient number of assignment errors on failed-inhibition trials to permit calculation of %AE or AdjRT. These analyses of RT were similarly nonsignificant in both the left and right hemispheres (all $F < 1$, all $P > 0.5$).

DISCUSSION

In this study, we investigated the critical role of the IFG and dPM in response inhibition, using rTMS and a combined stop-signal/flanker paradigm. *Experiment 1* revealed that the ability to inhibit a prepotent response in the stop-signal task is closely related to the degree of competition between responses in the flanker task. Specifically, stop-signal inhibition performance declined significantly when incongruent distractors flanked the central arrow target, relative to conditions in which the flankers were congruent or neutral. These results are consistent with previous observations (Kramer et al. 1994; Ridderinkhof et al. 1999; Verbruggen et al. 2004, 2005) and imply that flanker inhibition and stop-signal inhibition share a common cognitive resource. In *experiments 2* and *3*, participants completed the same behavioral task after rTMS of the IFG or dPM in the right or left hemisphere. Two principal results were obtained. First, stimulation of the right IFG impaired stop-signal inhibition but only when response selection was placed under competition (incongruent flanker trials). Second, stimulation of the right dPM tended to enhance execution performance in all conditions, facilitating RT of left and right hand responses regardless of the degree of competitive

response selection. We initially consider the implications of these two findings before turning to additional aspects of the data.

Role of the right IFG for cancelling a prepotent motor response

The observed impairment of stop-signal inhibition after rTMS of the right, but not left, IFG accords with converging fMRI (Aron and Poldrack 2006; Garavan et al. 1999; Konishi et al. 1999), neuropsychological (Aron et al. 2003; Hodgson et al. 2007), and rTMS evidence (Chambers et al. 2006), all of which indicate an inhibitory function of the right ventrolateral PFC. Our results confirm and extend these observations, showing that the right IFG appears to be especially crucial for cancelling responses under conditions of increased response competition (Fig. 4A) even though right IFG stimulation did not alter the effect of competition on response execution (Fig. 4B). These findings imply that stimulation of the right IFG may delay the release of an inhibitory trigger or reduce the speed of the stopping process once triggered. Furthermore, this observation is broadly consistent with the proposed role of the IFG as a “circuit breaker” (Corbetta and Shulman 2002), interrupting ongoing perceptual and motor processing to incorporate a behaviorally relevant event (in this case the stop signal). Recent studies have shown that a plausible inhibitory mechanism for this circuit breaker may lie in direct and hyperdirect pathways between the IFG and subthalamic nucleus of the basal ganglia (Aron and Poldrack 2006; Aron et al. 2007; Kühn et al. 2004; Nambu et al. 1997, 2002).

The selective inhibitory role of the right IFG on *incongruent* flanker trials implies that this area is not singularly critical for response inhibition under all circumstances. Instead the right IFG appears to be especially important for inhibition during the suppression of a competing response. It would be tempting to conclude from this finding that cancelling a prepotent response on an incongruent flanker trial represents an emphasized case of response inhibition (i.e., a “double inhibition”) and that the IFG is especially crucial for controlling behavior under these circumstances. Although appealing, this explanation is not consistent with all aspects of the present data. In particular, stimulation of the right IFG did not significantly influence the effect of incongruent flankers on execution performance, whereas a deficit under these conditions would be expected if the IFG were necessary for suppressing a competing action plan. The inhibitory function of the right IFG thus appears to depend on the degree of response competition without being necessary for *resolving* such competition. Thus although stop-signal and flanker tasks draw on a common cognitive resource (*experiment 1*) and co-activate a variety of common cortical substrates (Rubia et al. 2001; Wager et al. 2005), the present results suggest that the PFC accommodates multiple inhibitory subprocesses rather than a single regulatory system.

Superficially, this interpretation of the results seems inconsistent with existing evidence that disruption of the right IFG impairs stop-signal inhibition on a letter discrimination task *without* flankers (Chambers et al. 2006). In the current study therefore, one might have expected to observe a significant deficit of stop-signal inhibition on trials with neutral or congruent flankers, in addition to the observed impairment on incongruent trials. One explanation for this discrepancy may

lie in the different S-R relationships in these studies and corresponding variations in response competition. In particular, the letter discrimination task requires an arbitrary S-R mapping and is thus likely to engender greater competition for response selection than the strong and automatic S-R binding for arrow targets flanked by neutral or congruent stimuli (Ridderinkhof et al. 1995; Verbruggen et al. 2004). In contrast, arrow targets surrounded by *incongruent* flankers require active suppression of a competing response and may thus elicit a more comparable degree of response competition to an arbitrary S-R mapping.

Involvement of the right dPM in response selection

Contrary to expectations, stimulation of the left or right dPM did not impair performance in the stop-signal/flanker task. Instead stimulation of the right, but not left, dPM tended to speed RT generally, independent of the flanker condition or the hand of execution. These results differ from those obtained in previous rTMS studies of response selection (Koski et al. 2005; Praamstra et al. 1999; Schluter et al. 1998). For instance, Praamstra et al. reported that rTMS of the left dPM disinhibited S-R mapping independent of overall RT, whereas Schluter et al. showed that stimulation of the left, but not right, dPM slowed choice RT of both hands. In contrast, Koski et al. demonstrated that single-pulse TMS of the left dPM selectively facilitated right-hand responses, independent of the degree of response competition. In a recent study, O'Shea et al. (2007) further showed that repetitive 1-Hz stimulation of the left dPM can slow RT with the right hand and can also lead to adaptive reorganization of the right dPM to mediate response selection.

The variation between these findings (and with our own) may have arisen due to substantial differences in behavioral paradigms, rTMS protocols, and site localization. In particular, most of these previous studies employed an event-related rTMS protocol in which the technique is designed to interrupt preparatory or transient processing, rather than induce a sustained change in cortical excitability. Furthermore, we localized the dPM anatomically as the premotor "upper limb" area (Wise et al. 1997), whereas other studies used either scalp landmarks (Praamstra et al. 1999; Schluter et al. 1998), fMRI activations (Koski et al. 2005), or a combination of both approaches (O'Shea et al. 2007) to guide coil placement. Importantly, each of these methods may yield a slightly different anatomical locus within the dPM, and it remains for future studies to determine whether variation between results can be explained—at least in part—by the existence of functionally distinct subregions within this area.

One potential explanation for our observed facilitation effect is that the 1-Hz rTMS protocol suppressed cortical excitability in our *anatomically defined* dPM (Chen et al. 1997), releasing the motor system from sustained premotor inhibition (von Geissen et al. 1994). This explanation is broadly consistent with evidence that premotor rTMS can modulate RT (Koski et al. 2005) and the excitability of the primary motor cortex (M1) (Gerschlagler et al. 2001; Münchau et al. 2002; Siebner and Rothwell 2003). For three reasons, however, the observed facilitation effect seems to extend beyond changes in corticospinal excitability caused by activation of cortico-cortical connections between dPM and ipsilateral M1. First, disinhibition of the motor system would be expected to facilitate RT (as observed) while simultaneously increasing the rate of assign-

ment errors (%AE). This change in the response criterion (i.e., speed/accuracy trade-off) would be expected to emerge most clearly on incongruent flanker trials; however, it is notable that dPM stimulation did not significantly influence %AE in any of the flanker conditions. Second, sustained 1-Hz rTMS of the premotor cortex tends to decrease, rather than increase, the excitability of M1 neurons (Siebner and Rothwell 2003), which would be expected to *impair* rather than facilitate response execution. Finally, the effects of premotor rTMS on motor thresholds are usually expressed in contralateral motor effectors; thus an additional or alternative mechanism appears to be responsible for the bilateral effects reported here.

One such possibility is that rTMS of the right dPM released the left dPM from inter-hemispheric inhibition, leading to facilitation of RT in both hands. Although speculative, this explanation is consistent with evidence of transcallosal inhibitory connections between premotor and motor cortices (Bous-saoud et al. 2006; Marconi et al. 2003; Mochizuki et al. 2004) and with the observation that premotor TMS increases activity in the opposite dPM (Bestmann et al. 2005). This interpretation similarly accords with evidence that the left dPM is necessary for bilateral response selection (e.g., Schluter et al. 1998). Note, however, that if right dPM stimulation had facilitated RT by disinhibiting contralateral premotor cortex, we might have expected stimulation of the *left* dPM to also influence RT (e.g., a bilateral *slowing* of responses, as observed by Schluter et al.). Because this finding was not observed, we suggest that an explanation in terms of interhemispheric disinhibition should be considered with caution.

More broadly, these interpretations highlight the caveat that the behavioral changes caused by TMS can stem from modulation of activity in remote but connected structures (Siebner and Rothwell 2003). In the case of dPM stimulation, facilitation of RT can result not only from locally induced activity but from spread of induced current to adjacent structures within the same hemisphere, such as the frontal eye field (Grosbas and Paus 2003). Similarly, in the case of IFG stimulation, the deficit of stop-signal inhibition might arise from interference with the middle/superior frontal gyri (Floden and Stuss 2006; Garavan et al. 1999) or via connected subcortical regions such as the sub-thalamic nucleus (Aron and Poldrack 2006; Aron et al. 2007). Given the improbability that any single brain region exclusively mediates response inhibition, understanding the role of functional coupling within this network is likely to be crucial. In this regard, the increasingly feasible combination of concurrent TMS-fMRI provides a promising avenue for future studies of inhibitory control (Ruff et al. 2006).

No evidence for critical role of left IFG in response inhibition or response selection

Our results provide no indication that the left IFG is essential for either stop-signal inhibition or resolving competition between responses. This null result is broadly consistent with existing evidence for right-hemispheric dominance of inhibitory control (Aron et al. 2003; Garavan et al. 1999). However, our observation that left IFG stimulation was behaviorally ineffective contrasts with previous neuroimaging studies of cognitive control. In general, these studies have demonstrated task-related activity of the left PFC during response selection (Jiang and Kanwisher 2003), interactions between response

inhibition and working memory (Hester et al. 2004), and the control of interference within working memory (see Jonides and Nee 2006 for a recent review). The variation between these findings and our own may stem from a variety of sources, including paradigmatic differences, and the inferential bases of neuroimaging and neurodisruption techniques. In particular, neurodisruption techniques, such as TMS, are logically conservative and in most cases can reveal only whether a stimulated region is singularly critical for behavior (Chambers and Mattingley 2005). Consequently, the absence of a TMS-induced functional deficit need not indicate that the area is uninvolved; similarly, previous observations of activity in the left IFG during inhibition and conflict resolution need not indicate that such activity is necessary for behavior.

Conclusion

Taken together, the present results indicate that mechanisms of response inhibition and selection are functionally dissociable between the IFG and dPM of the right hemisphere. The findings of *experiment 2* reinforce a role of the right IFG in response inhibition, especially for the cancellation of a prepotent response measured in the stop-signal task. However, the right IFG does not appear to be essential for response execution; nor do our results provide evidence that this region is necessary for resolving competition between responses. In contrast, the right dPM appears to have an important role in bilateral response selection without being crucial for cancelling a prepotent response. Investigating in more detail the behavioral and neural interaction between these inhibitory mechanisms will be a key objective for future TMS, fMRI, and neurophysiological studies.

ACKNOWLEDGMENTS

We thank M. Rademacher for technical assistance and three anonymous reviewers for helpful comments on a previous version of the manuscript.

GRANTS

This work was supported by a grant from the Australian National Health and Medical Research Council to J. B. Mattingley and C. D. Chambers, the Australian Research Council Grant DP0770337 to M. A. Bellgrove and C. D. Chambers, and the Biotechnology and Biological Sciences Research Council, UK, David Phillips Fellowship held by C. D. Chambers.

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