Executive "Brake Failure" following Deactivation of Human Frontal Lobe

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Abstract

■ In the course of daily living, humans frequently encounter situations in which a motor activity, once initiated, becomes unnecessary or inappropriate. Under such circumstances, the ability to inhibit motor responses can be of vital importance. Although the nature of response inhibition has been studied in psychology for several decades, its neural basis remains unclear. Using transcranial magnetic stimulation, we found that temporary deactivation of the pars opercularis in the right inferior frontal gyrus selectively impairs the ability to stop an initiated action. Critically, deactivation of the same region did not affect the ability to execute responses, nor did it influence physiological arousal. These findings confirm and extend recent reports that the inferior frontal gyrus is vital for mediating response inhibition. ■

INTRODUCTION

The ability to apply executive control over actions is essential for normal human activities. Executive functions enable us to plan, execute, and update behavior in response to an environment of continual change (Heyder, Suchan, & Daum, 2004; Logan, 1994). In particular, unexpected events frequently require us to cancel intended actions. Without the ability to inhibit and update motor activities, many aspects of everyday living would become impossible, such as driving a vehicle, undertaking sporting activities, and engaging in social interactions. The importance of motoric inhibition as a core executive function is highlighted by the broad range of psychiatric conditions that are characterized by inhibitory deficits; among others, these include obsessive–compulsive disorder (Enright & Beech, 1993), attention deficit hyperactivity disorder (ADHD) (Aron, Dowson, Sahakian, & Robbins, 2003), and schizophrenia (Badcock, Michie, Johnson, & Combrinck, 2002).

Although the cognitive mechanisms underlying response inhibition have been studied in experimental psychology for many years (Logan, 1981, 1994), key questions remain concerning its underlying neural mechanisms. Most cognitive neuroscientists agree that the human prefrontal cortex is responsible for executive control, but it is contentious whether discrete prefrontal regions are specialized to carry out domain-specific functions (Aron, Robbins, & Poldrack, 2004; Duncan & Owen, 2000; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Goldman-Rakic, 1987). Some studies have suggested that different prefrontal regions share control over a range of cognitive processes, including those involved in the inhibition and selection of responses (Duncan & Owen, 2000). Others, however, have argued that mechanisms of response inhibition are governed by a discrete network of brain regions in the parietal and prefrontal cortex (Morita, Nakahara, & Hayashi, 2004; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Rubia, Smith, Brammer, & Taylor, 2003; Garavan, Ross, & Stein, 1999). Neurophysiological studies in macaques, for instance, have revealed contributions of ventral prefrontal cortex to the suppression of manual and saccadic responses (Hasegawa, Peterson, & Goldberg, 2004; Sakagami et al., 2001). In humans, neuroimaging studies have revealed selective activation of the inferior frontal gyrus (IFG), middle frontal gyrus (MFG), and inferior parietal cortex of the right hemisphere during inhibition of an intended action (Rubia et al., 2003; Swainson et al., 2003; Garavan et al., 1999; Konishi et al., 1999; Kawashima et al., 1996). Furthermore, a recent neuropsychological study showed that lesions of the right IFG were predictive of inhibitory deficits in patients with brain damage (Aron, Fletcher, et al., 2003).

Despite making a vital contribution to the cognitive neuroscience of response inhibition, previous neuroimaging and neuropsychological studies nevertheless have fundamental limitations. In particular, neuroimaging techniques cannot distinguish between neural activity

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that is *necessary* for a behavior and neural activity that is merely *associated* with the behavior. Therefore, it remains unclear whether the neural activation observed in previous studies reflects mechanisms that are vital for response inhibition (Garavan et al., 1999). In contrast, neuropsychological investigations can reveal which neural regions are necessary for specific behaviors. However, because such studies rely on patients with permanent brain lesions, definitive conclusions regarding the role of specific areas may be limited by the brain's capacity to functionally reorganize following injury (Rorden & Karnath, 2004; Wall, Xu, & Wang, 2002).

The technique of transcranial magnetic stimulation (TMS) provides a unique opportunity to address these limitations (Chambers, Payne, Stokes, & Mattingley, 2004; Chambers, Stokes, & Mattingley, 2004; Robertson, Theoret, & Pascual-Leone, 2003; Walsh and Cowey, 2002). During TMS, a time-varying magnetic field is discharged over the scalp, causing temporary disruption of underlying neural activity. As a reversible interference technique, TMS can establish which cortical regions are vital for specific functions in the healthy brain, thus complimenting neuroimaging and neuropsychological methods.

We used TMS to test the hypothesis that discrete regions of the right hemisphere selectively govern response inhibition in the healthy brain. Participants undertook a ''stop-signal'' task, which measured their ability to execute and inhibit motor responses (Figure 1A; Logan, 1994). On each trial, participants identified a target (''go'') stimulus as rapidly as possible (X or O) using the index finger of their left or right hand. On 25% of trials, a ''stop'' signal was presented, instructing participants to withhold their response. To manipulate the difficulty of successfully inhibiting, the stop signal was presented randomly at various delays after the go signal. Previous studies have shown that the probability of inhibition is closely related to this ''stop-signal delay'' (SSD) (Figure 1B; Logan, 1981, 1994). Furthermore, because this measure of inhibition is dependent on speed of responding, the SSD was adjusted according to each participant's mean reaction time (RT) (Figure 1C; Badcock et al., 2002).

Experiment 1 established psychophysical thresholds of response inhibition for the left and right hands. Experiment 2 investigated the effects of deactivating discrete regions of the right prefrontal and parietal cortex on inhibitory performance. Participants undertook the stop-signal task after receiving 15 min of TMS to the right IFG (pars opercularis), MFG, or angular gyrus (AG) (Figure 2A; Table 1). TMS protocols of similar duration have been shown to suppress cortical excitability, thus temporarily deactivating the stimulated region (Siebner & Rothwell, 2003; Hilgetag, Theoret, & Pascual-Leone, 2001). To maximize the sensitivity of our TMS protocol to changes in inhibitory performance, stop signals were presented at SSDs that yielded 25–75% correct inhibitions, as calculated in Experiment 1. Each experimental session involved stimulation of a different anatomical region (IFG, MFG, AG), or a sham control condition. To measure any effects of cortical reorganization over time, participants received two consecutive blocks of TMS per session, each followed by the stop-signal task (Figure 2B, black shading). If inhibitory brain networks are able to compensate for the deactivation of a primary region, then we expected cortical deactivation to be less effective following a second period of TMS. Finally, to determine whether a reduction of physiological arousal could explain any impairments of response inhibition, pupil diameter was recorded throughout the experiment.

METHODS

Experiment 1: Stop-Signal Task

Seventeen right-handed volunteers were recruited (8 men, 9 women, aged 18–27 years). Visual stimuli were presented against a uniform gray background on a gamma-corrected Phillips Brilliance CRT monitor (19 in.; 1280 × 1024 resolution; 100-Hz refresh rate). Each trial commenced with the onset of a black fixation cross (0.6° × 0.6°; 100%). The visual target was a black ''X'' (2.6° × 2.6°) or ''O'' (2.6° diameter), presented at fixation (Figure 1A). A red box surrounding the target indicated a stop trial (3.9° × 3.9°). White noise was delivered throughout testing via two speakers positioned on either side of the visual display. Participants also wore foam earplugs to mask ambient noise.

Inhibition functions were obtained over four to five sessions of behavioral testing by use of an iterative method of constants. The first two sessions involved SSDs of mean RT − 50, − 150, − 250, and − 350 msec. The remaining two to three sessions included SSDs at the 25th, 45th, 55th, and 75th SSD percentiles, calculated through sigmoidal regression of the results obtained in Sessions 1 and 2. Psychophysical functions were obtained with the three-parameter sigmoidal equation:

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

Inhibition percentiles were obtained by solving for the x values of 25, 45, 55, and 75 in the restructured equation:

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

Participants completed as many sessions as necessary to achieve a reliable inhibition function. The adjusted R^2 for the sigmoidal regressions averaged .91 across participants.

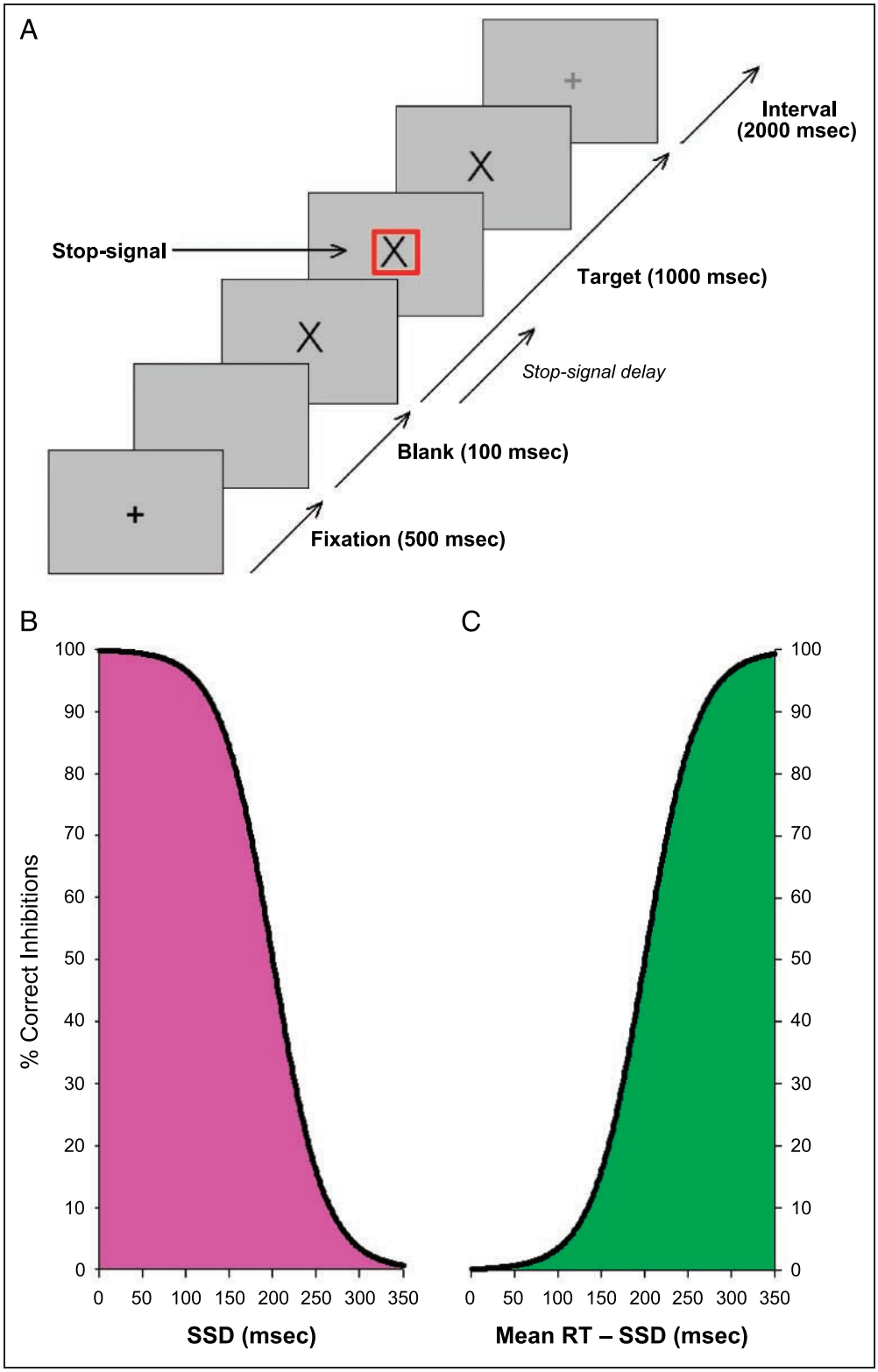


Figure 1. The stop-signal task used to measure response inhibition. (A) A typical display sequence is shown for a "stop" trial. On each trial, participants identified a "go" signal (X or O) as rapidly as possible using their left or right hand. On 25% of trials, a "stop" signal (red box) appeared around the target for 400 msec, signaling participants to withhold their response. The stop signal could appear at various delays following the onset of the go signal. In the example shown, the participant correctly inhibits, and the go signal remains visible for 1000 msec. On trials where participants responded, the go and stop signals disappeared and were replaced by the intertrial interval (gray cross). In all experiments, the assignment of target (X or O) to hand (left or right) was counterbalanced between participants. (B) The predicted effect of the stop-signal delay (SSD) on inhibition performance. At short SSDs, the stop signal occurs soon after the onset of the go signal, and participants are able to inhibit easily (e.g., SSD of 50 msec; magenta-shaded area). As the SSD is increased, participants are less likely to successfully inhibit because the go process is closer to completion (e.g., SSD of 250 msec; Logan, 1994). (C) Inhibition performance in the stop-signal task depends on the participant's reaction time (RT). To account for variation in response speed, the SSD was calculated with respect to each participant's mean RT, and updated every 64 trials within testing blocks. The pattern of inhibition performance yielded through adjusted SSDs is the mirror reverse of (B): As the SSD approaches the participant's mean RT, the likelihood of successful inhibition is reduced (green-shaded area).

Experiment 2: Stop-Signal Task following Transcranial Magnetic Stimulation

Sixteen right-handed volunteers were recruited, all of whom had participated in Experiment 1 (8 men, 8 women, aged 18–27 years). To ensure the measurement of threshold-level inhibition performance, SSDs were presented randomly at the 25th, 45th, 55th, and 75th percentiles (mean RT − SSD) obtained from each participant in Experiment 1. Participants wore foam

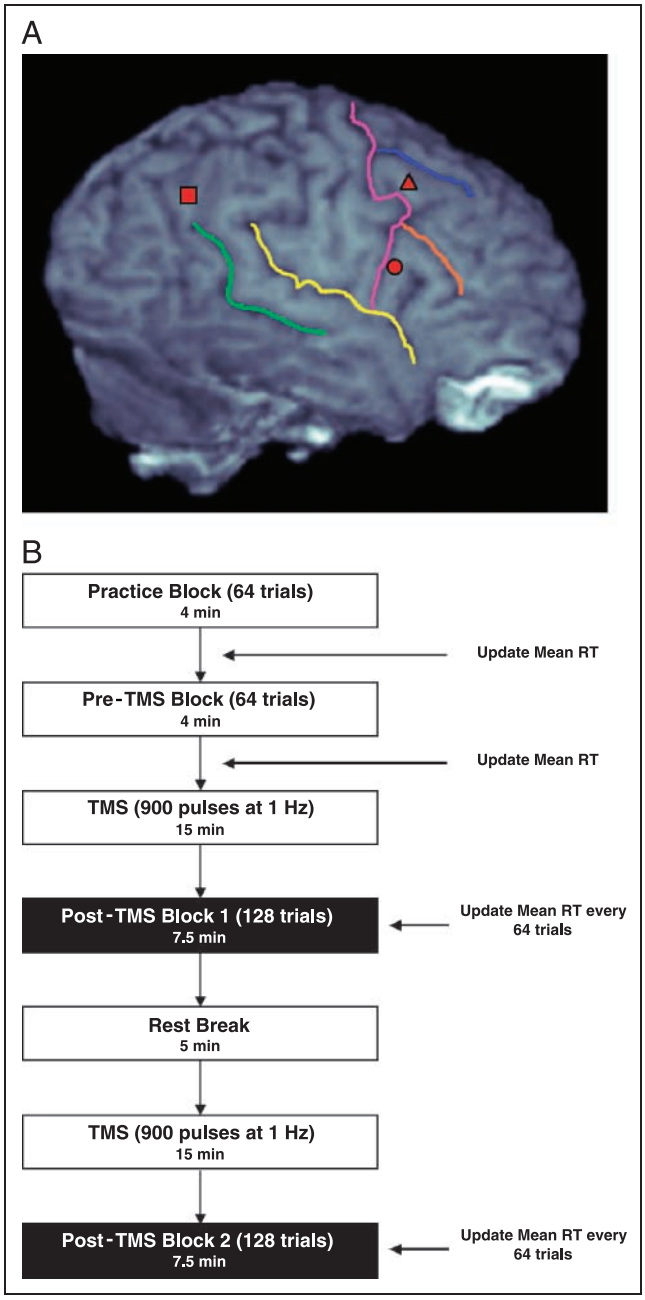


Figure 2. Magnetic stimulation sites and testing protocol in Experiment 2. (A) Brain regions in the right hemisphere that were stimulated with TMS, shown for one participant. TMS was delivered to the inferior frontal gyrus (pars opercularis; circle), middle frontal gyrus (triangle) and angular gyrus of the parietal lobe (square). Cortical sites were localized in each participant using sulcal landmarks from individual magnetic resonance (MR) scans. The location of the TMS coil was then projected to the scalp using TMS/MR coregistration (see Methods for details). Magenta line = precentral sulcus. Blue line = superior frontal sulcus. Orange line = inferior frontal sulcus. Yellow line = lateral sulcus. Green line = superior temporal sulcus. (B) The time course of each testing session in Experiment 2. Sessions began with a practice block and pre-TMS block of trials, which were used to obtain and update estimates of mean RT. Participants then received 15 min of repetitive TMS followed by an experimental block of 128 trials (post-TMS Block 1). After a short rest break, this TMS protocol was repeated over the same anatomical site (post-TMS Block 2). The order of TMS conditions (sham, IFG, MFG, AG) between sessions was counterbalanced across 16 participants.

Table 1. Mean and Standard Deviation of Normalized Coordinates (Millimeters) for Each Anatomical Location, According to the Montreal Neurological Institute Brain Atlas

Brain Site	*Mean (x)*	*Mean (y)*	*Mean (z)*	*SD (x)*	*SD (y)*	*SD (z)*
IFG	61	21	13	2.9	5.1	4.8
MFG	48	27	43	4.6	4.9	5.6
AG	53	−60	50	4.9	6.3	3.1

earplugs and were delivered white noise throughout the experiment.

TMS/Magnetic Resonance Coregistration

Prior to Experiment 2, magnetic resonance (MR) brain scans were obtained from each participant using a GE Signa 3T system (1.3 × 1.3 × 1.3 mm; sagittal acquisition). To enable TMS/MR coregistration, participants were scanned with contrast markers (vitamin E capsules) attached to known scalp locations (Chambers, Payne, et al., 2004; Chambers, Stokes, et al., 2004). Anatomical sites for TMS were then localized on the basis of individual neuroanatomy. The IFG site was defined as the dorsal midpoint of the pars opercularis, between the lateral sulcus and inferior frontal sulcus (IFS), and directly anterior to the precentral sulcus. The MFG site was defined as the dorsal midpoint of the MFG, between the IFS and superior frontal sulcus. The AG site was defined as the dorsal termination of the superior temporal sulcus, which bifurcates the AG in the inferior parietal lobule.

Average normalized coordinates for each site according to the Montreal Neurological Institute atlas are shown in Table 1. Scalp locations for TMS were calculated using a magnetic tracking device (miniBird 500; Ascension Tech, Burlington, VT) and MR coregistration software (MRIReg).

TMS Parameters

TMS was delivered using a Magstim Rapid system (2.2 T, Magstim Company, Whitland, UK) and 70-mm figure-of-eight induction coil, fixed in position by a holding clamp and tripod. The intensity of TMS was calibrated according to the maximum level of comfortable stimulation, expressed as a proportion of motor threshold, and adjusted for differences in scalp–cortex distance between brain regions (Stokes, Chambers, Gould, Henderson, Janko, Allen, & Mattingley, 2005). This protocol yielded an average TMS output of 92% distance-adjusted motor threshold. Consecutive testing sessions were separated by at least 24 hr.

Sham Control Condition

The sham configuration provides a control condition in which the TMS coil is oriented away from the scalp, mimicking the sensory artifacts that accompany magnetic discharge without stimulating the cortex. Results in the sham condition were collapsed across separate blocks in which the coil was placed over the parietal or prefrontal cortex. The order of sham placement (parietal, prefrontal) within sessions was counterbalanced between participants.

Eye Tracking

Gaze was monitored online with an ASL-504 remote infrared eye tracker (ASL, Bedford, MA). Trials in which participants blinked or gaze deviated more than 5° from fixation were discarded. Pupil diameter in the right eye was sampled every 20 msec (50 Hz) with a spatial resolution of 0.104 mm. Eye tracking ceased when the participant executed a response. On trials in which participants responded (correct responses, failed inhibitions), analysis of pupil diameter was limited to the first 900 msec of eye samples. Beyond 900 msec postfixation onset (300 msec posttarget onset), the variance of the mean pupil diameter increased substantially across participants due to the increased likelihood of a response.

RESULTS

Experiment 1: Behavioral Patterns of Response Inhibition

Prior to administering TMS, we confirmed the validity of the stop-signal task by establishing psychophysical patterns of response inhibition in each participant. As shown in Figure 3A, reducing the stop signal delay relative to each participant's mean RT improved inhibition performance in both the left and right hands. Furthermore, as expected, participants responded significantly faster with their right hand (357 msec) than with their left hand (380 msec; $p < .05$). This execution advantage for the right hand was mirrored by a corresponding inhibitory advantage. As indicated by the drop lines in Figure 3A, participants required the stop signal to be presented significantly sooner in time relative to their mean RT to successfully inhibit with their left hand compared with their right hand. Quantitative analysis of this effect is shown in Figure 3B. Paired t tests revealed significant inhibitory advantages for the right hand at SSDs that yielded 45% (mean advantage = 6 msec; $p = .03$), 50% (mean advantage = 7 msec; $p = .01$), 55% (mean advantage = 8 msec; $p = .02$), and 75% correct inhibitions (mean advantage = 11 msec; $p = .03$).

In addition to demonstrating the accuracy of response inhibition, Figure 3B indicates the latency of the inhibition process, a term referred to as stop signal reaction time (SSRT). The 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 $-$ $SSD_{50\%}$; Badcock et al., 2002; Logan, 1994). The 50% point is theoretically important because it represents maximal competition between the go and stop processes. As indicated by performance at the 50% percentile in Figure 3B, participants exhibited a significantly faster SSRT with their right hand (201 msec) than with their left hand (208 msec).

Overall, the results of Experiment 1 confirm the validity of the stop signal task as a sensitive measure of response inhibition. Furthermore, the presence of hand differences in both inhibition and execution performance underlines the importance of calibrating psychophysical thresholds of response inhibition separately for the left and right hands.

Experiment 2: Effects of Cortical Deactivation on Response Inhibition and Execution

In Experiment 2, participants completed the stop-signal task following 15 min of repetitive TMS. Threshold levels of response inhibition were ensured by including SSDs that yielded 25–75% correct inhibitions for each hand in Experiment 1. To determine the effects of TMS on inhibition and execution performance, a variety of behavioral measures were analyzed. Execution ability was determined through analysis of mean RT and response accuracy on go trials. Inhibitory ability was examined by analyzing the latency and accuracy of withholding responses on stop trials. Because a successful inhibition has no observable latency, SSRT was used to estimate the speed of the inhibition process (Logan, 1994). The accuracy of inhibition was determined through analysis of the percentage of correct inhibitions.

Figure 4 reports inhibitory performance in the left and right hands following sham TMS, or deactivation of the IFG, MFG, or AG. Figure 4A and C indicate results following the first period of disruption (Block 1); b and d show the results following the second period of disruption (Block 2). A two-way ANOVA of inhibition accuracy in Block 1, with factors of TMS Condition and Response Hand, revealed a significant main effect of TMS Condition, $F(3,45) = 3.6$, $p = .02$ (Figure 4A). Analysis of simple main effects demonstrated a significant reduction in the percent of correct inhibitions following deactivation of the IFG relative to sham, in both the left and right hands (both $p < .05$; stars in Figure 4A). No significant differences in inhibition accuracy were observed between TMS Conditions of MFG and sham, AG and sham, or between IFG, MFG, and AG (all $p > .28$). Analysis of inhibition accuracy in Block 2 revealed no significant effect of TMS Condition on behavior, $F(3,45) = 0.28$, $p = .84$ (Figure 4B).

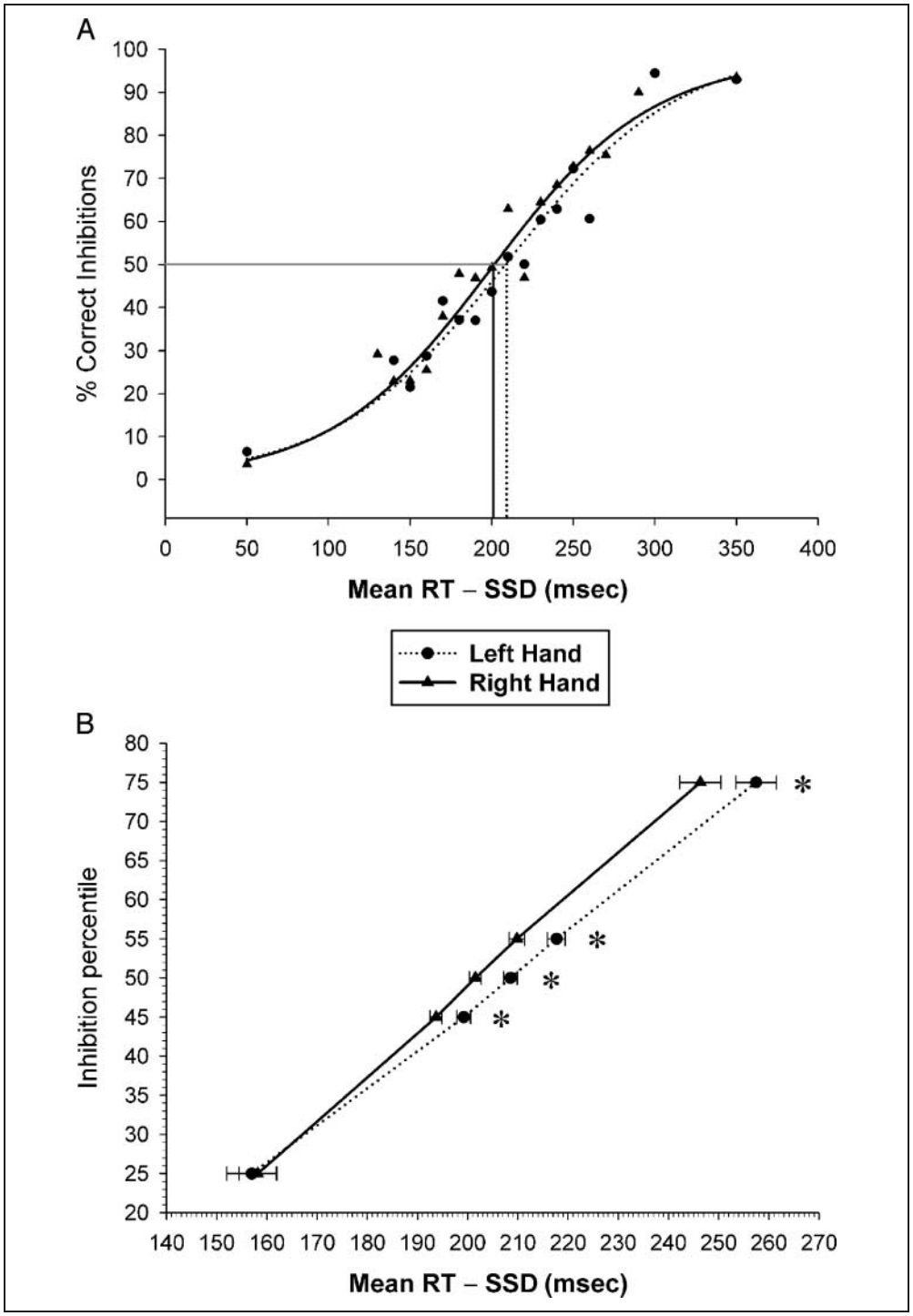


Figure 3. Behavioral results of the stop-signal task without TMS (Experiment 1). (A) Inhibitory performance averaged across 17 right-handed participants. Psychophysical inhibition functions were calculated using a three-parameter sigmoid for the left (circles/solid lines) and right (triangles/dotted lines) hands. As expected, participants inhibited more effectively at shorter SSDs (larger values of mean RT − SSD) than at longer SSDs. Drop lines for left and right hands denote the SSDs that corresponded to 50% inhibition performance. Note that the function for the right hand is shifted slightly in the negative direction, indicating improved inhibition. (B) The SSDs required to yield percentile levels of inhibition in Experiment 1, plotted for the left and right hands. Data were calculated by fitting three-parameter sigmoidal regressions to each participant's inhibition function and solving for the 25th, 45th, 50th, 55th, and 75th percentiles. Error bars are ±1 *SEM*.

Figure 4C reports the average latency of response inhibition in Block 1, as a function of TMS Condition and Response Hand. A two-way ANOVA of mean SSRT revealed a robust main effect of TMS Condition, $F(3,45) = 14.8$, $p < .00001$. As indicated by stars in Figure 4C, this effect was driven by impaired inhibitory performance of the left and right hands following TMS of the IFG, compared with each of the sham, MFG, and AG conditions (all $p < .015$, Bonferroni corrected). Critically, deactivation of the MFG and AG yielded no significant effects on inhibition performance relative to sham (all $p > .8$). Similarly, analysis of SSRT in Block 2 revealed no significant main effect of TMS Condition, $F(3,45) = 1.7$, $p = .17$ (Figure 4D). These results demonstrate a significant effect of IFG deactivation on the latency of response inhibition.

Figure 5 reports execution performance of the left and right hands following sham TMS, or deactivation of the IFG, MFG, or AG. As in Figure 4, left and right panels illustrate the results following Block 1 or Block 2 of TMS,

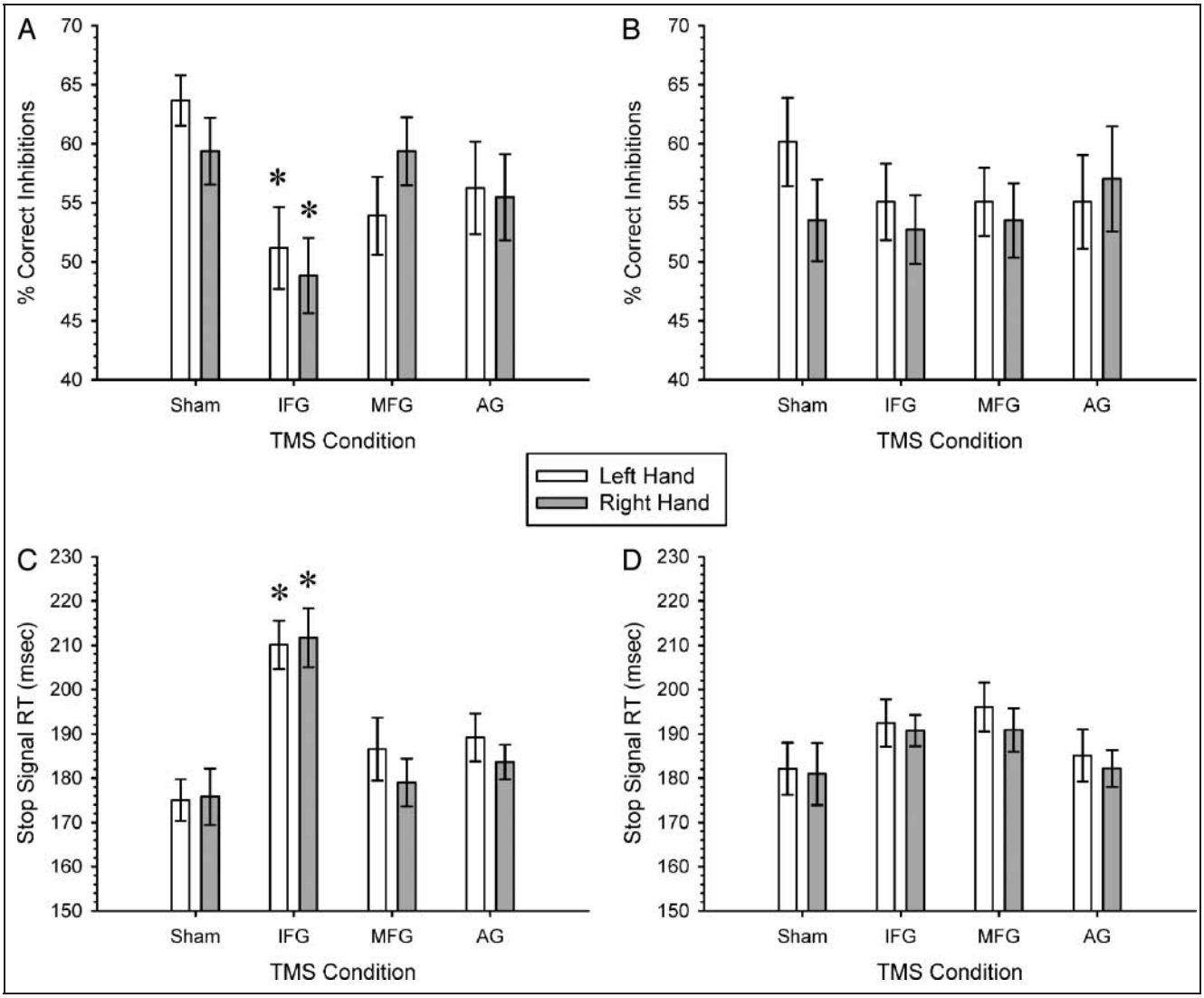


Figure 4. Inhibition performance in Experiment 2, averaged across 16 participants. (A, B) The percent of correct inhibitions following Block 1 (A) and Block 2 (B) of TMS, plotted by TMS Condition and Response Hand. As indicated by stars in (A), deactivation of the IFG significantly reduced inhibitory performance relative to the sham condition, but only following Block 1. (C, D) Mean stop-signal reaction time (SSRT) following Block 1 (C) and Block 2 (D) of TMS. Consistent with the accuracy results, deactivation of the IFG in Block 1 significantly slowed SSRT relative to the sham condition. Error bars in all panels are ±1 *SEM*. Stars indicate a significance difference in performance between the respective TMS condition and the sham control ($p < .05$).

respectively. Figure 5A and B present the mean RT on Go trials, whereas c and d show the mean percent of assignment errors (responses with the wrong hand on go trials). Separate two-way ANOVAs, with factors of TMS Condition and Response Hand, revealed no significant effects of TMS Condition on go RT or the rate of assignment errors in either Block 1 or Block 2 (all $F < 2.3$, all $p > .1$).

Experiment 2: Relationship between Inhibitory Deficits and Arousal

As shown in Figure 4, analysis of the behavioral results revealed a selective deficit of inhibition performance following the first period of IFG deactivation. To what extent might this observed deficit have arisen due to TMS-induced depression of arousal? (Karatekin, 2004; Niehaus, Guldin, & Meyer, 2001) To answer this question, we compared average pupil diameter in Block 1 between TMS of the IFG and the sham control condition (Figure 6). Crucially, no significant effects of TMS on pupil diameter were observed for trials in which participants correctly inhibited (Figure 6A), failed to inhibit (Figure 6B), or responded correctly on go trials (Figure 6C). Furthermore, although pupil diameter increased as expected throughout the course of each trial (Karatekin, 2004), TMS of the IFG did not alter the change in pupil diameter over time (Figure 6D–F).

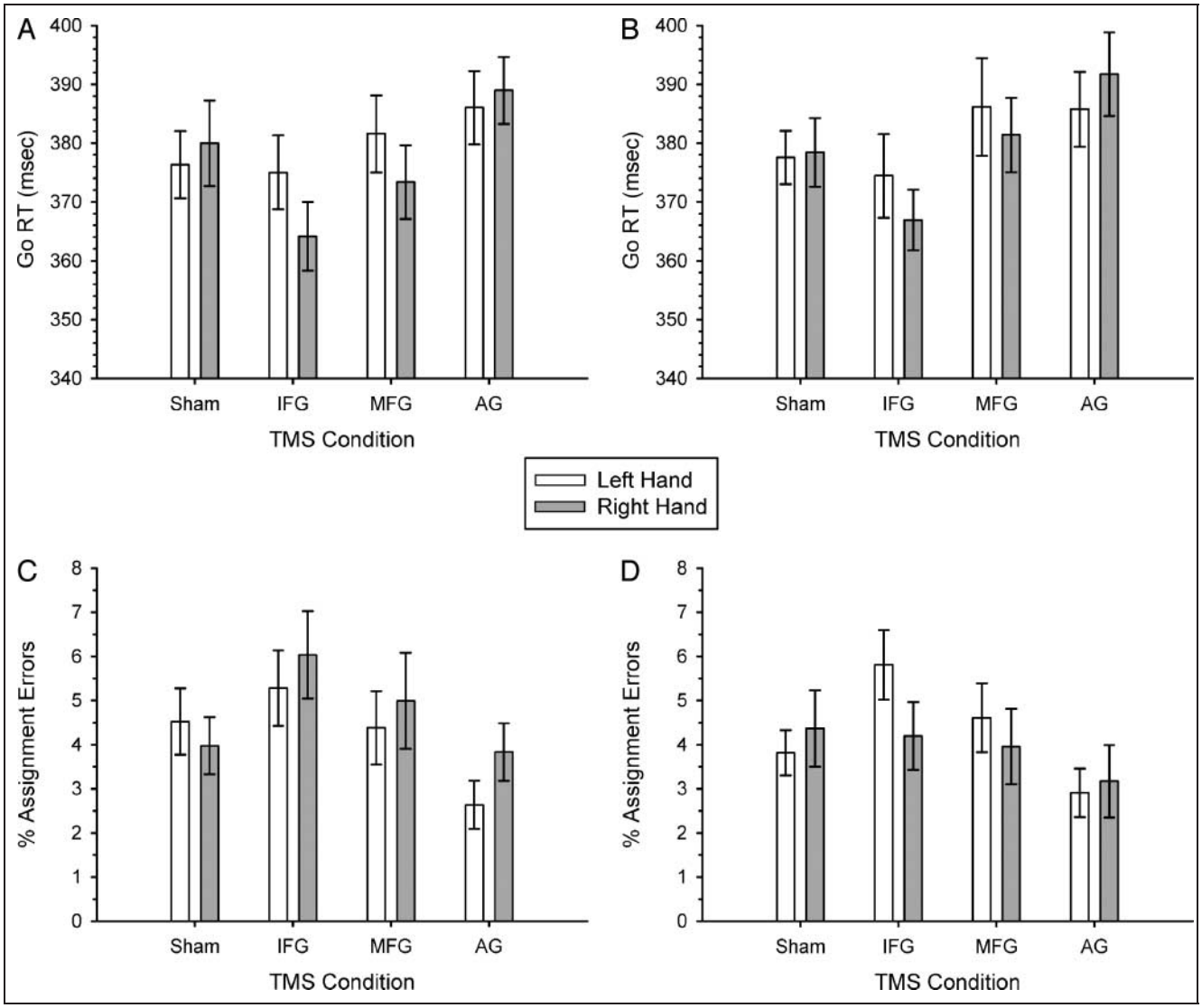


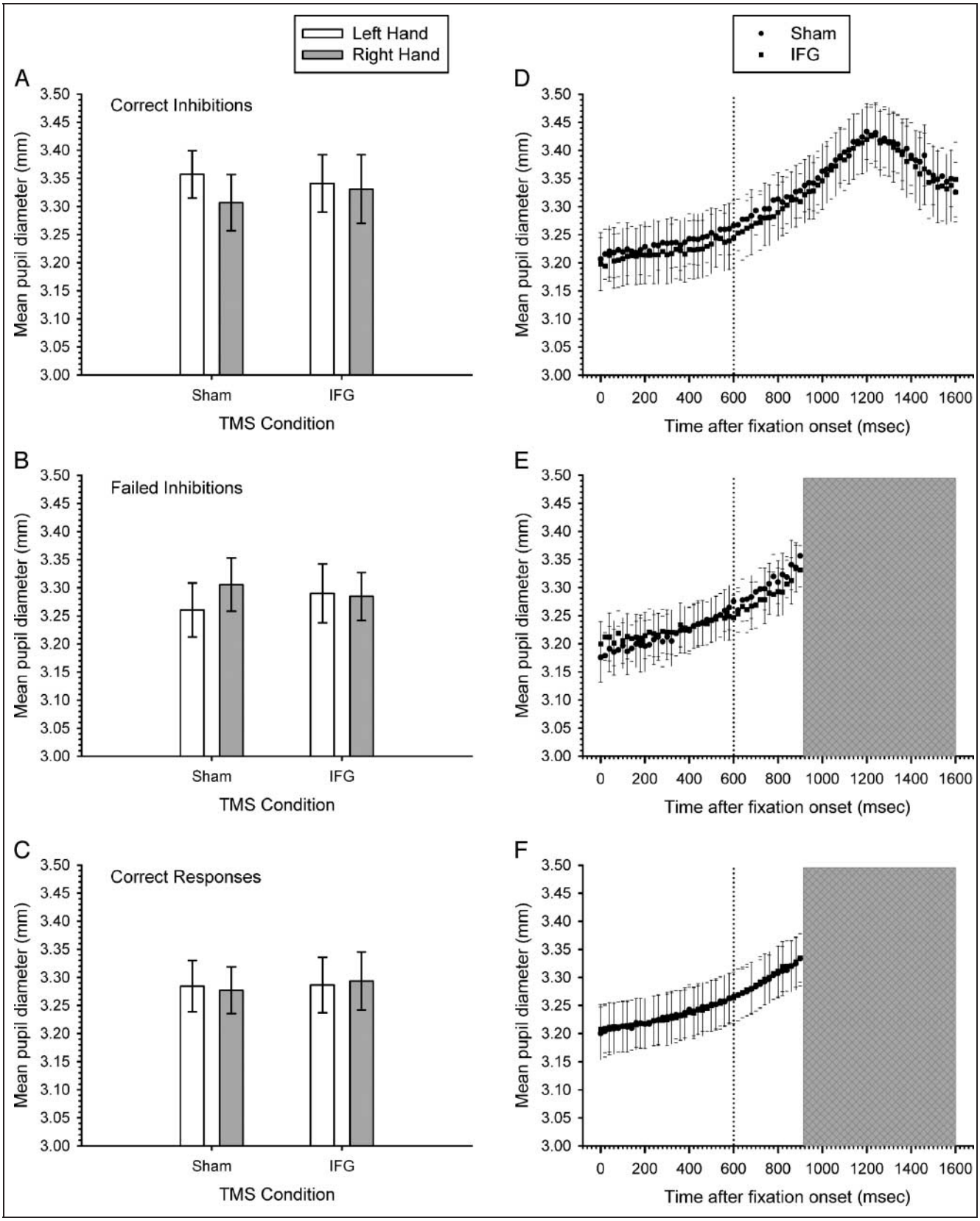
Figure 5. Execution performance in Experiment 2, averaged across 16 participants. (A, B) Mean RT on Go trials following Block 1 (A) and Block 2 (B) of TMS, plotted as a function of TMS Condition and Response Hand. (C, D) The mean rate of assignment errors following Block 1 (C) and Block 2 (D) of TMS. No effects of TMS on response speed or accuracy were observed. Error bars in all panels are ±1 *SEM*.

These results indicate that the impairment of response inhibition in Block 1 cannot be explained by diminished arousal.

DISCUSSION

This study investigated the critical role of the right prefrontal and parietal cortex in response inhibition using repetitive TMS. Results showed that temporary deactivation of the IFG in the right hemisphere impaired inhibitory control of the left and right hands. Critically, TMS of the MFG and AG did not significantly alter inhibitory performance; nor did TMS of any regions significantly affect the speed or accuracy of responses on go trials. This dissociation of effects between stop and go trials enables us to eliminate various alternative explanations of the present results. It is possible, for instance, that a deficit of response selection, response execution, or sustained attention could yield an inhibitory deficit (Sergeant, 2000). Note, however, that impairment of these functions would also be expected to cause a slowing of correct responses on go trials or an increase in the rate of assignment errors (responses with the wrong hand). Because neither result was observed, our findings suggest that deactivation of the IFG selectively impaired mechanisms responsible for inhibiting or overriding prepotent responses.

Taken together, our results are consistent with the emerging view that executive control of response inhibition is mediated by ventral regions of the human prefrontal cortex (Aron et al., 2004; Hasegawa et al., 2004; Morita et al., 2004; Aron, Fletcher, et al., 2003; Hazeltine, Bunge, Scanlon, & Gabrieli, 2003; Rubia et al., 2003; Swainson et al., 2003; Durston, Thomas,


Left Hand
Right Hand
A
Correct Inhibitions
Mean pupil diameter (mm)
3.50
3.45
3.40
3.35
3.30
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3.10
3.05
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Sham
IFG
TMS Condition
B
Failed Inhibitions
C
Correct Responses
Sham
IFG
D
E
F
0
200
400
600
800
1000
1200
1400
1600
Time after fixation onset (msec)

Worden, Yang, & Casey, 2002; Sakagami et al., 2001; Garavan et al., 1999; Konishi et al., 1999; Kawashima et al., 1996). Furthermore, the present study provides several unique insights into the cortical basis of inhibitory processing. First, because TMS selectively impaired response inhibition for both hands, our results indicate that the right IFG fulfils an executive role in controlling inhibition in both cerebral hemispheres. Importantly, however, our results need not imply that the IFG is the sole mediator of response inhibition. The human IFG is richly interconnected with a range of cortical and subcortical structures, including prefrontal regions in the opposite hemisphere, the anterior cingulate, and the striatum (Vink et al., 2005; Durston et al., 2003). Consequently, deactivation of the IFG is likely to influence processing in a variety of remote neural regions that also contribute to executive functions. Given the improbability of any executive function being mediated solely by a single cortical subregion (Duncan & Owen, 2000), we favor the view that the IFG is one critical component within an inhibitory network. To further elucidate the dynamics of this network, future studies could combine TMS and neuroimaging to examine the effects of IFG deactivation on neural activity in remote structures.

Second, our findings suggest that activation of the MFG and parietal cortex observed in previous neuroimaging studies is unlikely to reflect processing that is singularly critical for response inhibition (Garavan et al., 1999; Kawashima et al., 1996). Instead, this activity may reflect auxiliary processing within the prefrontal network. Alternatively, subsidiary activations revealed in fMRI studies may reflect the execution of cognitive processes that are activated in synchrony with response inhibition but are not necessary for inhibitory control. This interpretation is consistent with a prominent review of neuroimaging studies by Duncan and Owen (2000). Through meta-analysis, these authors discovered that many prefrontal regions are activated during a variety of executive functions, including response inhibition, response selection, and working memory. However, rather than indicating a generalized cognitive system, much of this coactivation may reflect the ecological likelihood that executive demands in one subsystem (e.g., working memory) are likely to require processing in another (e.g., response selection). Consequently, only a portion of these activations may be critical for mediating specific behaviors, as suggested by the present findings and those of Aron et al. (2004) and Aron, Fletcher, et al. (2003).

Third, our results showed that the effects of IFG deactivation on response inhibition were specific for Block 1 and did not arise in Block 2. This finding implies that although the IFG is critical for inhibitory processing, the cortical network that governs inhibition is able to functionally reorganize within approximately 30 min after disruption, allowing critical processing within the IFG to be directed elsewhere (Siebner & Rothwell, 2003). Based on previous studies, inhibitory mechanisms may be reallocated to the right MFG, parietal cortex, or homologous structures in the left hemisphere (Hester, Murphy, & Garavan, 2004). Hester et al. (2004) have shown that increasing the difficulty of response inhibition yields additional activation of structures in the left and right dorsolateral prefrontal cortex. Given that TMS increased the difficulty of response inhibition in the present study, it is possible that these regions were recruited in our participants to compensate for deactivation of the right IFG. Future studies could investigate this question by varying the site of deactivation between blocks of TMS. If repetitive TMS can induce reorganization of executive processing, then ancillary brain regions should become vital for inhibitory control only following deactivation of a critical region.

Finally, our results show that neural mechanisms of response inhibition and autonomic arousal can be effectively decoupled. Even though deficits of arousal, such as in ADHD and schizophrenia, are commonly accompanied by inhibitory pathology (Sergeant, 2005; Granholm & Verney, 2004; Hermens et al., 2004; Aron, Dowson, et al., 2003; Badcock et al., 2002), the present findings indicate that impairments of inhibitory processing need not be associated with deficits of autonomic arousal. This dissociation of TMS effects implies that the neural systems mediating inhibition and arousal are at least partially distinct.

The present findings open several avenues for further investigating the neural basis of response inhibition. For instance, given known behavioral interactions between selection and inhibition of motor responses (Verbruggen, Liefooghe, & Vandierendonck, 2004), it will be important for future studies to determine whether specific prefrontal regions that are known to govern response selection, such as the left dorsal premotor cortex (Praamstra, Kleine, & Schnitzler, 1999), are also necessary for inhibitory control. Furthermore, the increasingly feasible combination of simultaneous TMS and neuroimaging presents a unique opportunity to elucidate the architecture of critical and noncritical

Figure 6. The effect of IFG deactivation on arousal in Experiment 2. (A–C) Average pupil diameter following TMS of the IFG compared to the sham condition. Data are plotted by target stimuli assigned to the left (white bars) and right (gray bars) hands. Results for the three most common response types: correct inhibitions (A), failed inhibitions (B), and correct responses (C). (D–F) Average change in pupil diameter throughout the course of each trial, after sham stimulation (circles) or deactivation of the IFG (squares). Results are collapsed across response hand and plotted separately for correct inhibitions (D), failed inhibitions (E), and correct responses (F). The vertical dotted line in each panel indicates the onset of the target stimulus (X or O). As indicated by the hatched areas in (E) and (F), results for failed inhibitions and correct responses are truncated at 900 msec because eye tracking ceased when the participant responded. Error bars in all panels are ±1 *SEM*.

processing within the prefrontal cortex. A related objective for TMS studies will be to disrupt multiple prefrontal regions simultaneously. Unlike single-coil stimulation, multicoil TMS can reveal whether brain areas that are unnecessary for inhibitory processing under normal circumstances become vital during the simultaneous deactivation of a primary region. Our results illustrate that the IFG of the right hemisphere is one such region that is crucial for inhibiting inappropriate action.

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