# Inhibitory Control is Slowed in Patients with Right Superior Medial Frontal Damage

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## Abstract

■ Inhibitory control is an essential part of behavior. Comprehensive knowledge of the neural underpinnings will shed light on complex behavior, its breakdown in neurological and psychological disorders, and current and future techniques for the pharmacological or structural remediation of disinhibition. This study investigated the neural mechanisms involved in rapid response inhibition. The stop signal task was used to estimate inhibitory speed in a group of neurologically normal control subjects and patients with discrete frontal lobe lesions. Task procedures were controlled to rule out probable confounds related to strategic changes in task effort. The findings indicate that the frontal lobes are necessary for inhibitory control and, furthermore, that the integrity of the right superior medial frontal region is key for rapid inhibitory control under conditions controlling for strategically slow responses, forcing reliance more on a rapid, ''kill-switch'' inhibitory system. These results are interpreted within an anatomical framework of corticospinal motor control. ■

## INTRODUCTION

Response inhibition is a cardinal element of efficient behavioral control. A range of tasks, populations, and methods has been used to investigate response inhibition. Impaired inhibitory control is associated with the functional disturbances found in disorders involving known or suspected frontal lobe dysfunction such as attention deficit/hyperactivity disorder (Schachar, Mota, Logan, Tannock, & Klim, 2000) and traumatic brain injury (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). Early neuropsychological studies of go/no-go tasks demonstrated deficits in patients with frontal lobe damage (i.e., Decary & Richer, 1995; Leimkuhler & Mesulam, 1985; Drewe, 1975), but the precise neuroanatomical correlates have not been extensively studied in patients. Several recent functional neuroimaging studies suggest that sites on the medial and lateral aspects of the right frontal lobe participate in networks underlying response inhibition (i.e., Garavan, Ross, Murphy, Roche, & Stein, 2002; Menon, Adleman, White, Glover, & Reiss, 2001; Rubia et al., 2001). Converging evidence from lesion studies, controlling for response speed and assessing patients with focal and defined frontal lesions, is needed to verify the *necessary* role of these regions and the nature of their contributions to inhibitory processing. To address these issues, we administered a carefully controlled response inhibition procedure known as the *stop signal task* to patients with well-documented focal frontal lesions.

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The stop signal task is unique among response inhibition tasks in that it provides an estimate of inhibitory speed (Logan & Cowan, 1984). The task is a choice reaction time (RT) procedure where, on a fraction of trials, a stop stimulus signals the subject to inhibit an already initiated response (see Figure 1). The onset asynchrony of the stop signal (stimulus onset asynchrony [SOA]) is varied to increase or decrease the likelihood of successfully stopping, and the observed inhibition success rate at each SOA is used to estimate RT to the stop signal (or stop signal RT [SSRT]). The task has demonstrated sensitivity to inhibitory control problems in children diagnosed with attention deficit/hyperactivity disorder (Schachar et al., 2000) and its treatment with methylphenidate (Tannock, Schachar, & Logan, 1995). We reasoned that the task would also be sensitive to inhibitory deficits in patients with focal frontal lobe lesions. We specifically hypothesized that in the experimental condition that controls for strategic changes in response speed, reduced inhibitory control would be related to damage at right medial and/or lateral sites but not other frontal lesion locations.

There is some limited evidence that inhibitory speed on the stop signal task is impaired after frontal lobe damage (although see Dimitrov et al., 2003). Rieger, Gauggel, and Burmeister (2003) found that right or bilateral frontal lobe lesions or basal ganglia damage produced slower SSRTs, but they did not attempt to identify more specific anatomical correlations. Another study in patients with lesions of the right frontal lobe (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003)

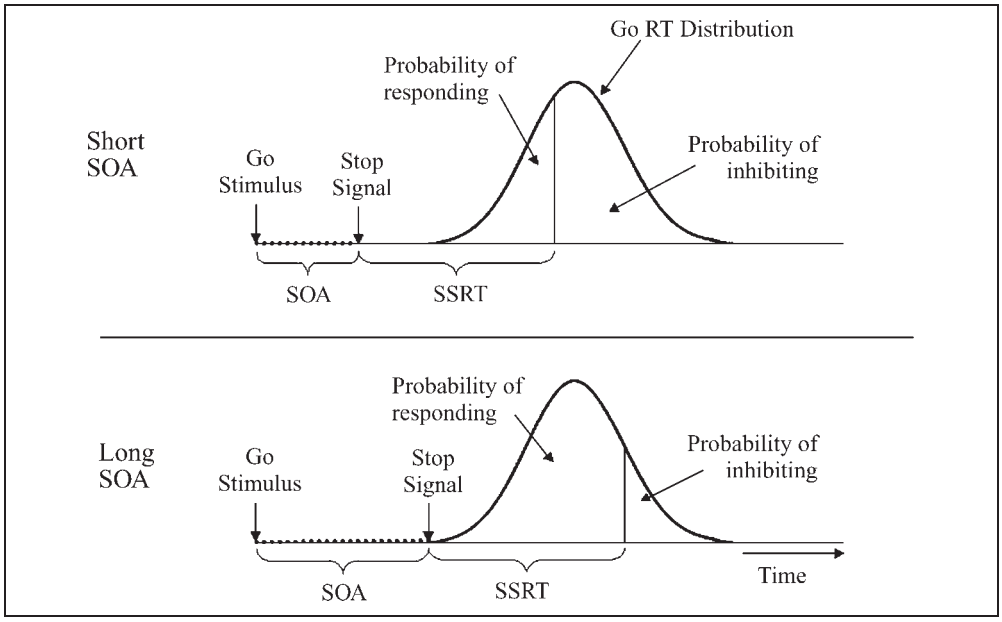


**Figure 1.** The stop signal task reflects a race between a go process and a stop process. Stop signal delay length (SOA) biases the competition by determining the ''head start'' for go processing. For example, a .4 probability of responding given SOA means that 40% of go responses are faster than the total stopping time (SOA + stop signal RT [SSRT]). Go RTs are rank-ordered and the 40th go RT minus the SOA gives the estimated SSRT (Logan & Cowan, 1984).

reported that slow SSRTs were related to lesions in the inferior frontal gyrus, which has been implicated repeatedly in functional neuroimaging studies of go/no-go and stop signal tasks (Brass, Derrfuss, & von Cramon, 2005; Menon et al., 2001; Rubia et al., 2001). These same imaging studies also demonstrate consistent activations in superior medial regions, including anterior cingulate, supplementary motor area (SMA), and pre-SMA. In fact, Aron et al. (2003) found a correlation between anterior cingulate lesions and slow inhibitory speed. However, they also reported that when inferior frontal lesions were factored into the analysis, the influence of anterior cingulate lesions was not significant.

Recent work by Garavan et al. (2002) offers a possible explanation for the conflicting imaging and lesion findings regarding the role of superior medial regions. Using functional magnetic resonance imaging and electroencephalography during performance of go/no-go tasks, they showed that right lateral frontal and parietal activation were related to successful stopping on relatively ''easy'' inhibition conditions (i.e., relatively slower RTs, or go RTs, possibly reflecting weaker response set). In contrast, a superior medial region involving the posterior portion of the anterior cingulate cortex and pre-SMA was more active for successful stop trials when go RTs were fast leading up to the stop trial, suggesting a rapid ''kill-switch'' type of inhibitory control. From this, they proposed two networks that participate in inhibition under different conditions. Correlations with absentmindedness scores on the Cognitive Failures Questionnaire (Broadbent, Cooper, Fitzgerald, & Parkes, 1982) suggested that high absentminded subjects tended to rely on the fast medial inhibitory system, whereas low absentminded subjects relied more on a strategic lateral inhibitory system.

In the stop signal task study of Aron et al. (2003), the frontal lobe group had significantly longer go RTs than controls and it is possible that patients deliberately slowed their response times to avoid making errors on stop trials. The observations of Garavan et al. (2002) would suggest that inhibition under these conditions (strategically slowed response speed) would rely on more lateral frontal regions rather than medial regions. A control condition measuring go RT without additional stop trials is necessary to evaluate baseline response speed to confirm that subjects are performing the choice RT task as quickly as possible. Prior work on the psychometric properties of the stop signal task has shown that when subjects delay responses in anticipation of the rare stop signals, estimates of inhibitory speed are artificially inflated (van den Wildenberg, van der Molen, & Logan, 2002). To circumvent this potential obstacle, the current study included a control condition to verify that subjects continued to perform the task at baseline speeds.

## METHODS

### Participants

Participants were 23 patients (17 men, 19 right-handed; age, 50.6 years, *SD* = 12.7 years; education = 14.3 years, *SD* = 2.4 years) with single focal frontal lobe lesions (7 vascular, 10 tumor/epilepsy resections, 6 traumatic focal contusions without evidence of diffuse injury; mean chronicity = 32, *SD* = 22 months) (see Stuss, Alexander, et al., 2002, for rationale on inclusion of these patient groups) and 19 age- and education-matched control subjects (11 men, 14 right-handed; age, 49.5 years, *SD* = 11.6 years; education = 14.6 years, *SD* = 1.9 years). One patient with a left lateral lesion arising from a vascular

insult was excluded because he failed to show any stopping behavior throughout the task, which precludes estimation of inhibitory speed. Exclusion criteria included impaired/uncorrected vision/hearing, history of psychiatric disorder, substance abuse, or neurological disorder unrelated to lesion, estimated full-scale IQ <90, and diet-controlled diabetes.

### Lesion Analysis

Lesions were documented from anatomical scans performed in the course of clinical care and depicted on a standard anatomical template based on the cytoarchitectonic divisions of Petrides and Pandya (1994). The full procedure is described in detail elsewhere (Stuss, Alexander, et al., 2002). Lesion locations were coded as present or absent in seven regions for each hemisphere: dorsolateral (4 [lateral], 6A [lateral], 8Ad, 8Av, 9 [lateral], 46, 9/46D, 9/46V), ventrolateral (4 [ventral], 6B, 44, 45A, 45B, 47/12 [lateral]), polar (10), superior medial (6A [medial], 8B, 9 [medial]), inferior medial (14 [medial], inferior 24, 25, 32), dorsal anterior cingulate (superior 24, 32), and orbitofrontal (11, 13, 14, 47/12 [orbital]). Lesion location, etiology, chronicity, and size are displayed in Table 1.

### Stop Signal Task

Stimuli and instructions were programmed by using Mel v 2.01 for DOS and presented on an IBM-compatible

**Table 1.** Lesion Characteristics

| *Subject No.* | *Laterality* | *Pol* | *Orb* | *IM* | *AC* | *SM* | *DL* | *VL* | *NF* | *Etiology* | *Chronicity (months)* | *Lesion Size (% Whole Brain)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | *Frontal* | *Nonfrontal* |
| 517 | Bilateral | 0 | 0 | 0 | B | B | B | 0 | 0 | Tumor | 33 | 9.09 | |
| 500 | Bilateral | B | R | B | R | R | R | R | 0 | CVA | 51 | 6.47 | |
| 520 | Bilateral | B | B | B | R | B | R | B | 0 | Trauma | 59 | 4.33 | |
| 526 | Bilateral | B | B | B | L | 0 | 0 | 0 | 0 | Trauma | 5 | 3.32 | |
| 528 | Bilateral | B | B | 0 | 0 | 0 | R | R | R | Trauma | 12 | 2.37 | 0.40 |
| 529 | Bilateral | B | B | R | 0 | 0 | 0 | L | 0 | Trauma | 24 | 1.42 | |
| 515 | Bilateral | 0 | 0 | 0 | 0 | B | 0 | 0 | 0 | Tumor | 82 | 1.36 | |
| 531 | Bilateral | B | B | R | 0 | 0 | 0 | 0 | R | Trauma | 20 | 1.31 | 0.21 |
| 522 | Bilateral | 0 | 0 | B | 0 | 0 | 0 | 0 | 0 | CVA | 41 | 0.33 | |
| 523 | Right | R | R | R | R | R | R | R | R | CVA | 48 | 12.67 | 0.22 |
| 527 | Right | R | 0 | R | 0 | R | 0 | 0 | 0 | Trauma | 10 | 2.05 | |
| 507 | Right | 0 | 0 | 0 | R | R | R | 0 | 0 | Epilepsy | 34 | 1.19 | |
| 518 | Right | 0 | 0 | 0 | 0 | 0 | 0 | R | 0 | Tumor | 59 | 0.68 | |
| 535 | Right | 0 | 0 | 0 | R | R | 0 | 0 | R | CVA | 17 | 0.24 | 0.06 |
| 508 | Right | 0 | 0 | 0 | R | R | 0 | 0 | 0 | Tumor | 19 | 0.20 | |
| 506 | Left | 0 | 0 | 0 | 0 | 0 | L | L | 0 | Epilepsy | 39 | 3.07 | |
| 504 | Left | 0 | 0 | 0 | 0 | 0 | L | L | 0 | Tumor | 72 | 2.08 | |
| 505 | Left | L | L | L | 0 | 0 | 0 | 0 | 0 | Epilepsy | 20 | 1.66 | |
| 509 | Left | 0 | 0 | 0 | 0 | 0 | L | L | 0 | Tumor | 32 | 1.44 | |
| 525 | Left | 0 | L | 0 | 0 | 0 | 0 | L | 0 | Trauma | 8 | 0.91 | |
| 502 | Left | 0 | 0 | 0 | 0 | L | L | 0 | 0 | Epilepsy | 12 | 0.57 | |
| 533 | Left | 0 | 0 | 0 | 0 | 0 | L | 0 | L | CVA | 40 | 0.21 | 0.02 |
| 534 | Left | 0 | 0 | 0 | 0 | 0 | L | 0 | 0 | CVA | 10 | NA | |

Pol = polar (10); ORB = orbitofrontal (11, 13, 14, 47/12 [orbital]); IM = inferior medial (14 [medial], inferior 24, 25, 32); AC = dorsal anterior cingulate (superior 24, 32); SM = superior medial (6A [medial], 8B, 9 [medial]); DL = dorsolateral (4 [lateral], 6A [lateral], 8Ad, 8Av, 9 [lateral], 46, 9/46D, 9/46V); VL = ventrolateral (4 [ventral], 6B, 44, 45A, 45B, 47/12 [lateral]); NF = nonfrontal; B = bilateral; R = right; L = left; CVA = cerebrovascular accident.

desktop computer. Subjects were seated directly in front of the monitor at a distance of approximately 0.5 m. In the initial control condition, subjects received 40 choice RT trials requiring keypress responses to the letters X and O to evaluate baseline go RT to control for strategic slowing in subsequent blocks. Subjects were then informed that the task would be repeated but that an auditory cue would occasionally occur after a letter and that responses to that letter should be withheld if possible. Subjects performed four experimental blocks of 55 trials, each involving 15 (27%) random stop trials. Ten stop signals occurred at each of six fixed SOAs: 75, 150, 225, 300, 375, and 450 msec poststimulus. We adopted a fixed SOA procedure in light of computational studies of the psychometric properties of the stop signal task (Band, van der Molen, & Logan, 2003), which indicate that titrating SOA procedures are more susceptible to artifact introduced when subjects fail to initiate inhibitory processing (i.e., no stopping behavior is attempted).

SSRTs were calculated from the observed data at each SOA according to the method described in Logan and Cowan (1984). Briefly, the stop signal task is thought to reflect the race between a ''go'' process and a ''stop'' process. On a stop trial, a response is executed if the total time to receive and respond to the stop signal exceeds the go RT. Therefore, for each subject, the probability of responding given a stop signal was calculated for each SOA ($p_r|\text{SOA}$). This was multiplied by the total number of correct go trials to give the percentage of trials ($n$) where the stop process is slower than the go process. Go RT values were then rank ordered and the $n$th fastest go RT selected. For example, a .4 probability of responding given $\text{SOA}_1$ means that 40% of go RTs are faster than the total stopping time. The $n$th go RT minus the SOA equals the estimated SSRT at that SOA. Therefore, go $\text{RT}_{40} - \text{SOA}_1 = \text{SSRT}_1$. SSRT estimates were averaged for all SOAs (where $0 < p_r|\text{SOA} < 1$) for each subject.

Reaction time feedback for correct go trials was presented after each block to discourage subjects from delaying responses in the attempt to avoid responding on stop trials. Comparison of go RTs in the experimental and control conditions verified that all subjects maintained consistent go RTs or ''response readiness'' during stop blocks.

## RESULTS

### Inhibitory Speed

When ranked according to SSRT, seven patients showed SSRTs longer than 1.5 *SD* above the control mean. Five of the seven had damage to the right superior medial region ($\chi^2 = 4.0$, $p < .05$). The other two patients had either left dorsolateral damage or left orbital and polar damage. Maximal lesion overlap in slow-SSRT patients occurred in the region that likely corresponds to the SMA and pre-SMA (see Figure 2). Mean SSRT (see Table 2) for all nine patients with right superior medial damage was significantly longer than control subjects, $t(26) = 2.1, p < .05$. For all other frontal regions, slowed SSRTs were present in less than half the subjects with

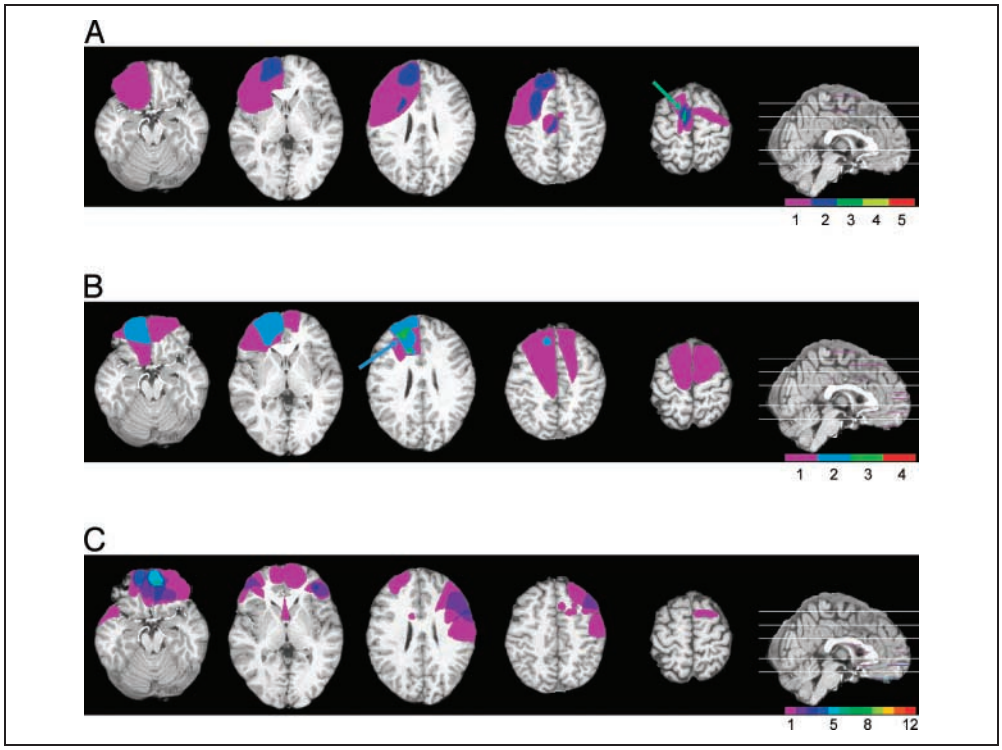


**Figure 2.** Density maps for lesion locations. (A) Patients with right superior medial damage with slow inhibitory speed ($n = 5$). (B) Patients with right superior medial damage with inhibitory speed similar to controls ($n = 4$). (C) Patients with lesions outside the right superior medial area and speed similar to controls ($n = 13$). Purple represents a single subject, whereas red represents overlap of all subjects in map. Note that maximal overlap in right superior medial patients with slow SSRT (green arrow) is posterior and superior to the maximum overlap of right superior medial patients with SSRTs within 1.5 *SD* of control mean (blue arrow).

**Table 2.** Reaction Time (RT) and Errors for Stop Signal Task

| | *Simple Go RT* | | *Go RT* | | *SSRT* | | *% Go Errors* | |
|---|---|---|---|---|---|---|---|---|
| *Group* | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* |
| Frontal RSM | 532.8 | 124.8 | 549.6 | 116.9 | 308.7 | 81.2 | 3.1 | 2.7 |
| Frontal non-RSM | 503.1 | 76.1 | 509.6 | 109.7 | 274.0 | 99.2 | 2.4 | 3.9 |
| Control | 502.6 | 105.2 | 493.4 | 74.9 | 246.9 | 67.9 | 1.9 | 1.8 |

RSM = right superior medial.

lesions in that region. For example, five patients had damage to the right inferior frontal gyrus but only one demonstrated slowed SSRTs. SSRT was unrelated to lesion etiology, chronicity, and all demographic variables.

### Choice RT Performance

Patients and control subjects showed equivalent go RT, $t(39) < 1$, in the control condition. The encouragement to maintain baseline speeds during experimental trials was effective; go RT during stop blocks did not differ from baseline levels for patients or controls (both $t < 1$). Moreover, the subgroup of patients with right superior medial damage did not differ from controls in baseline go RT, $t(26) < 1$, and go RT did not differ from baseline levels during stop blocks, $t(8) < 1$. This rules out the possibility that a delayed responding strategy contributed to observed increases in SSRT. Go RT correlated with age ($r = .57$, $p < .001$) but not lesion size ($r = .12$, $p = ns$), or SSRT ($r = .13$, $p = ns$). Rate of response errors on trials without a stop signal did not differ between groups ($F < 1$).

## DISCUSSION

The current study is the first demonstration that damage to right superior medial frontal regions (specifically, SMA and pre-SMA) impairs inhibitory control in the stop signal task. In contrast to prior work (Aron et al., 2003), lesions of the right lateral region did not contribute to inhibitory speed (SSRT). On the surface, these two studies completely contradict each other. We would argue, however, that the current results are complementary and provide a key differentiation in the processes that underlie performance in response inhibition tasks. The design of our task was unique in that subjects were not able to strategically slow go RTs, and our results conform to the findings of Garavan et al. (2002), which suggested that inhibition in the context of speeded go RTs relies more on a rapid, kill-switch inhibitory system that involves superior medial regions. The anatomical connectivity of this region provides the anatomical substrates to accomplish such processing; major corticospinal projections originate in this region, providing a route for rapid control over motor effectors (Dum & Strick, 1991).

In contrast, when the task does permit a slowed go RT strategy (as the procedure of Aron et al., 2003, might have done), a more controlled response readiness process related to right lateral may dictate inhibitory speed. In a recent review, Aron, Robbins, and Poldrack (2004) discussed a number of attention tasks, including their stop signal task, that recruit the right inferior frontal gyrus in a more strategic type of inhibitory control, and our own work has suggested a right lateral involvement in response readiness over a number of task contexts (i.e., Stuss et al., 2005; Stuss, Binns, Murphy, & Alexander, 2002). The anatomical connections of this right lateral region with the SMA (Dum & Strick, 2002) and the basal ganglia (Alexander, DeLong, & Strick, 1986) also suggest a response biasing role rather than a direct access to motor effectors capable of interrupting an initiated response. Thus, we would argue that, together, the results support the suggestion that *both* superior medial and lateral regions of the right frontal lobe appear to participate in response inhibition depending on task requirements.

The probability of observing slow inhibitory control on experimental tasks following damage to these regions is also dependent on the method used to analyze lesion locations. Volumetric analysis is an excellent technique for detecting relationships between the severity of impairment and the size of the lesion within a set of predefined regions. The trade-off is that anatomical regions must be relatively large in order to keep the number of statistical comparisons (independent correlations for each region) small to avoid problems with statistical power. We have found in our earlier work that volume measures do not allow identification of critical areas within large regions and, in fact, result in lower sensitivity to brain–behavior correlations. This is particularly true in the case of small sample sizes such as ours where volume analysis may confound lesion size with lesion location. Our approach is to use a priori criteria for identifying poor performance in individual patients (i.e., cutoff scores) and only then investigate whether meaningful relationships exist with more focused lesion locations. Using this technique, we were able to identify a role for SMA and pre-SMA, separate from other

structures on the medial and lateral surface. In the study of Aron et al. (2003), these medial regions were incorporated into a much larger area involving substantial real estate on the lateral surface. It is therefore possible that the SMA and pre-SMA were in fact contributing to performance on their task, but that this was obscured by the inclusion of irrelevant areas within the same region of interest.

Although the SMA is intimately involved in general planning of movement, slowed inhibition of already initiated responses does not appear to be a result of a general motor slowing. Patients with SMA lesions demonstrated go RTs equivalent to control subjects. Moreover, correlational analyses support the dissociation of go RT and SSRT; although age correlated with go RT, neither showed any relationship to SSRT in the patients or controls, suggesting that these are independent processes. The lack of association between go RT and SSRT is one of the fundamental assumptions of the SSRT calculation. Aron et al. (2003) argued that go RTs probably had no impact on long stopping times in right inferior frontal patients because go RTs did not correlate with inferior frontal lesion volumes. However, a baseline measure of go RT speed would be necessary to validate this suggestion. Choice go RT can be slowed after damage to a number of frontal sites and under different conditions (Stuss, Binns, et al., 2002), and, without a baseline measure, it is difficult to determine whether slow go RTs in any particular subject reflected a strategic delay of go RTs or a genuine RT impairment.

At the same time, the absence of slowed go RTs in the current sample of patients was somewhat surprising. Our previous choice RT studies in patients with frontal lobe damage show differences in go RTs (Stuss, Binns, et al., 2002). However, others have demonstrated that go RT slowing in frontal patients is related to the complexity of stimulus–response mapping (Godefroy, Cabaret, Petit-Chenal, Pruvo, & Rousseaux, 1999). It may be the case that the simple two-choice task was too simple to reveal differences in go RTs.

Go RTs for both patients and controls were longer in the current study than that of Aron et al. (2003). This is most likely a function of differences in the choice RT tasks. Subjects in their study responded to arrows that pointed in the direction of the correct response (i.e., left arrow for left button press). The current study used consistent mappings of nondirectional stimuli (i.e., X for left button press). Decades of Stroop and Simon tasks (for a review, see MacLeod, 1991) demonstrate facilitation (faster RT) when stimulus and response are inherently related rather than arbitrary. What is more difficult to determine is whether the relationship between stimuli and responses also influenced estimates of SSRTs in the study by Aron et al. The inhibitory speeds reported in that study are much faster than those reported here or in prior work using the stop signal task (i.e., Dimitrov et al., 2003; Rieger et al., 2003; Williams, Ponesse, Schacher, Logan, & Tannock, 1999). The reason for this remains unclear.

As a final note, an interesting, although speculative, alternative explanation for the conflicting findings in our study and those of Aron et al. (2003) lies in the fact that long SSRTs can arise from problems other than simple inhibitory slowing. For example, one might fail to initiate a ''stop'' response for one of several reasons: impaired stimulus discrimination, difficulty in processing two stimuli occurring close in time, or poor switching between task sets or responses, all of which have been associated with right lateral frontal function (Aron, Monsell, Sahakian, & Robbins, 2004; Marcantoni, Lepage, Beaudoin, Bourgouin, & Richer, 2003; Stuss, Binns, et al., 2002). Although it is impossible to differentiate slowed inhibition from failure to initiate inhibition on any single trial where a response is made following a stop signal, computational studies that simulate these processes separately have shown that a fixed SOA procedure is less sensitive to failures to trigger inhibitory processing than titration procedures (Band et al., 2003). If right lateral lesions prevent the initiation of inhibition for some noninhibitory reason, it may be that our stop signal procedure, selected to minimize the influence of failures to initiate inhibitory processing, thereby reduced the relevance of right lateral frontal regions. In contrast, stop procedures using a titration procedure are more sensitive to these other noninhibitory processes and therefore the contribution of right lateral regions is more salient. However, this remains speculative on the basis of the current findings. To begin to assess this possibility, it would be necessary to directly compare stop procedures while manipulating other task parameters, such as stimulus discriminability or response cueing. This was beyond the scope of the present study but may be a fruitful avenue of research to pursue.

## Summary

This study demonstrated that lesions of the right superior medial frontal lobe, particularly the pre-SMA and SMA, impair estimated inhibitory control speed on the stop signal task. Procedural comparisons with prior work suggest that this region is involved in contexts where strategic response modulation cannot be implemented to bolster inhibitory control. This study constitutes an important step toward understanding the anatomical basis of different components underlying behavioral control. It demonstrates how lesion studies with careful manipulation of task parameters can validate and clarify the nature of regional contributions to processing networks, offer vital insight into the necessary functional role of particular anatomical regions, and aid the interpretation of neuroimaging findings. Identifying the anatomical substrates underlying inhibitory control will also help to elucidate the neural basis of clinical syndromes that involve disinhibition.

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