

Response Inhibition and Response Selection: Two Sides of the Same Coin

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Abstract

■ Response inhibition refers to the suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior. Studies using a range of methodological approaches have implicated executive control processes mediated by frontal-subcortical circuits as being critical to response inhibition; however, localization within the frontal lobe has been inconsistent. In this review, we present evidence from behavioral, lesion, neuroimaging, electrophysiology, and neurological pop-

ulation studies. The findings lay the foundation for a construct in which response inhibition is akin to response selection, such that pre-SMA circuits are critical to selection of appropriate behavior, including both selecting to engage appropriate motor responses and selecting to withhold (inhibit) inappropriate motor responses. Recruitment of additional prefrontal and posterior cortical circuits, necessary to guide response selection, varies depending on the cognitive and behavioral demands of the task. ■

INTRODUCTION

Within the realm of behavioral control, there has been much focus in the literature on response inhibition. The process is thought to be critical to suppression of inappropriate/unwanted actions that can interfere with attaining motor, cognitive, or socioemotional goals. It is therefore critical to the successful completion of many everyday tasks, such as stopping at traffic lights, preventing interruptive/impulsive verbal behavior, resisting eating all the candy in the bag, and waiting in line. Further, response inhibition is thought to be central in attentional control, in that inhibition of responses to distracting stimuli is important for staying focused and maintaining on-task behavior. In these contexts, impaired response inhibition has been hypothesized to contribute to several neuropsychiatric disorders, most notably, attention-deficit hyperactivity disorder (ADHD), prompting investigations into its neurological basis.

Lesion and functional magnetic resonance imaging (fMRI) studies have revealed frontal lobe involvement in response inhibition; however, localization and extent within the frontal lobe has not been consistent across these studies. Models have been proposed which highlight a single region/circuit as being critical to response inhibition in all contexts, with some recent emphasis on the right inferior frontal cortex (IFC) (for a review, see Aron, Robbins, & Poldrack, 2004). Other evidence, however, suggests that the role of the right IFC and other higher order prefrontal (as well as posterior cortical)

regions may be task dependent (Mostofsky, Schafer, et al., 2003).

In this article, we will review findings from behavioral, brain imaging, and lesion effects studies, and studies in neurologically diagnosed populations using the two tasks most often used to assess motor response inhibition, go/no-go and stop-signal. The evidence from these studies suggests that premotor regions of the medial wall of the frontal lobe play a central role in response inhibition. Based on the findings, we propose a theoretical construct in which response inhibition is viewed as a facet of response selection, such that response inhibition is an intentional process in which one actively selects to withhold a response while producing a goal-oriented one (not moving). As with response selection, response inhibition therefore depends on medial frontal premotor circuits critical for motor response preparation, with variable roles of involvement of prefrontal circuits (as well as posterior cortical regions) necessary for guiding response inhibition based on the cognitive/social context of the task (i.e., “task demand”).

As an important note, from a neuroanatomic perspective, much of the findings will be discussed in terms of systems at the cerebral cortical level. However, we recognize that these regions participate in specialized cortical-subcortical circuits that are comprised of looped interconnections with the basal ganglia-thalamus and cerebellum-thalamus (for a review, see Middleton & Strick, 2000) and that functions referenced to cortical areas (e.g., supplementary motor area, dorsolateral prefrontal cortex) may be addressing contributions at any level of the neuraxis within the circuits in which these cortical regions participate.

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RESPONSE SELECTION: NEURAL MECHANISMS AND RELATION TO RESPONSE INHIBITION

In order to facilitate goal-directed behavior, the proper motor actions in a given context need to be selected and then executed. Regions within the medial wall of the frontal cortex, in particular, the supplementary motor area (SMA) (see Figure 1), have been implicated in response preparation, selection, and execution. Single-cell recordings in monkeys performing a delayed reaction task reveal a distinction between the rostral portion of the SMA (“pre-SMA”) and the caudal portion of the SMA (“SMA proper”); neuronal activity is seen in the SMA proper only during the response; activity in the pre-SMA, however, is associated with both the delay period and the response, suggesting that the pre-SMA is involved in both preparation and selection of the response (Hoshi & Tanji, 2004; Matsuzaka, Aizawa, & Tanji, 1992). This observation is supported by neuroanatomic evidence. The SMA proper, but not the pre-SMA, projects to primary motor regions associated with response execution; the pre-SMA, on the other hand, is interconnected with prefrontal and nonprimary motor cortical regions, indicating that its role is upstream of motor execution, namely, in preparing and selecting motor actions (Rizzolatti, Luppino, & Matelli, 1996; Matsuzaka et al., 1992; Dum & Strick, 1991).

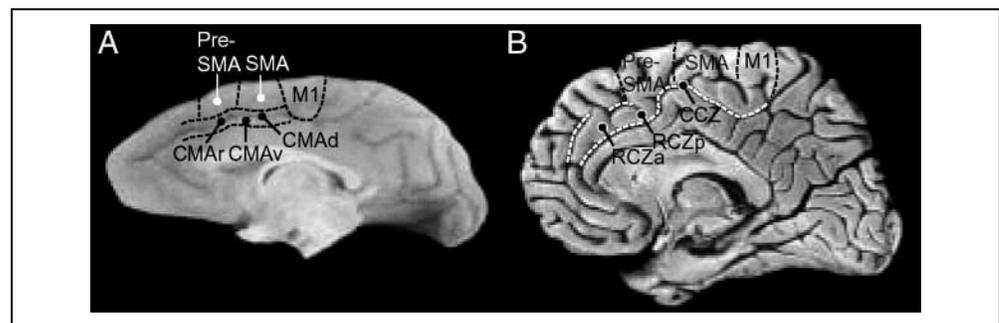
The role of the pre-SMA in response selection was highlighted in a recent study in rhesus macaque monkeys (Isoda & Hikosaka, 2007). Electrophysiologic recordings were taken from the pre-SMA during a response selection task requiring switching motor behavior from an automatic to a controlled response. Activation was seen in the pre-SMA whether or not the monkeys were successful in switching motor behavior; however, this activation was delayed when they were unsuccessful, suggesting it occurred too late to prevent selection of the incorrect response (see Figure 2). Additionally, when they applied microstimulation to the pre-SMA at the cue onset, successful switching was facilitated, suggesting

that early activation of the pre-SMA is critical to successful response selection.

Like response selection, response inhibition is an active process that involves suppression of a prepotent or competing response and switching to a controlled “response,” which in the case of response inhibition would be selecting not to move. Indeed, Isoda and Hikosaka (2007), in their experiments with rhesus monkeys, hypothesized that errors in response switching reflect a failure to inhibit the automatic response and/or to select the controlled, correct response. This hypothesis was examined by having the monkeys additionally perform a go/no-go task. In go/no-go tasks, there is a “go” stimulus (or stimuli) that requires executing a response, generally a button press, and a “no-go” stimulus (or stimuli) that requires withholding a response. As the no-go stimuli are generally infrequent and trials are typically presented rapidly, a prepotent tendency to respond is created which must be inhibited on presentation of a no-go stimulus. Findings from the go/no-go experiment revealed that of the pre-SMA “switch neurons” seen in the response switching experiment, some responded to go stimuli (“go type”), some to no-go stimuli (“no-go type”) and some to both (“dual type”). The activity of these pre-SMA “switch” neurons during the response switching task were then reclassified and reanalyzed, revealing that the no-go and dual-type neurons became active earlier than did the go-type neurons, suggesting that the pre-SMA “switch” neurons first inhibited the automatic response and afterward facilitated selection of a new, controlled response. It follows that the pre-SMA appears critical to successful response inhibition, in that neurons within this regions are involved in selecting to withhold the prepotent response and afterward in “selecting” to switch to a new motor response, in this case, selecting not to move.

There is also substantial evidence from lesion, electrophysiologic, and imaging studies of humans indicating that the pre-SMA is critical to response inhibition. Findings across several studies reveal that low-intensity electrical stimulation of the SMA facilitates response

Figure 1. Primary motor (M1) and premotor regions within the medial wall of the frontal lobe in (A) monkeys and (B) humans. Premotor regions include the cingulate motor areas and the supplementary motor area (SMA). The latter is divided into: (1) the rostral portion, referred to as the pre-SMA, which receives projections from prefrontal regions and is involved in response preparation and selection, and (2) the caudal portion, the SMA-proper, which projects to primary motor regions and is involved in response execution. CMAr = rostral cingulate motor area; CMAv = ventral cingulate motor area; CMAAd = dorsal cingulate motor area; RCZa = anterior rostral cingulate zone; RCZp = posterior rostral cingulate zone; CCZ = caudal cingulate zone. Replicated with permission from Picard and Strick (2003).



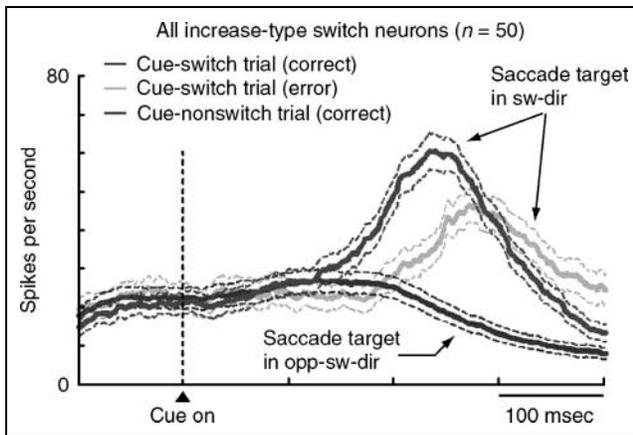


Figure 2. Graph showing single-cell recordings from the pre-SMA of macaque monkeys performing an oculomotor “switching” task, reported by Isoda and Hikosaka (2007). In the task, two different colored targets were presented on opposite sides of the screen, and a colored cue was presented in the middle, instructing the monkey which target to look at. The cue would remain the same for several successive trials and then would change colors so that the correct response would “switch.” Neurons in the pre-SMA, which demonstrated increased activity during switch trials (“increase-type switch neurons”), were active for both correct and incorrect switch trials; however, activation was delayed when switching was unsuccessful, suggesting that it occurred too late to facilitate successful switching and that early activation of the pre-SMA is critical for suppressing the incorrect response and selecting the appropriate response. sw-dir = switch direction (for switch trials); opp-sw-dir = opposite switch direction (for nonswitch trials). Replicated with permission from Isoda and Hikosaka (2007).

inhibition, causing suppression of motor activity, including that related to speech (Chauvel, Rey, Buser, & Bancaud, 1996; Fried, 1996; Lim et al., 1994); in one of these studies, inhibitory activity was more specifically localized to the pre-SMA (Lim et al., 1994).

Inhibitory-associated activation of the pre-SMA is a common finding among fMRI studies using the go/no-go task (Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Mostofsky, Schafer, et al., 2003; Durston, Thomas, Worden, Yang, & Casey, 2002; Liddle, Kiehl, & Smith, 2001; Rubia, Russell, et al., 2001; Kiehl, Liddle, & Hopfinger, 2000; Humberstone et al., 1997), and two meta-analyses have demonstrated significant concurrence in the pre-SMA across fMRI go/no-go studies (Simmonds, Pekar, & Mostofsky, in press; Buchsbaum, Greer, Chang, & Berman, 2005). Further, fMRI studies of the go/no-go task have been able to distinguish localization of activity related to habitual motor (go) response in the posterior SMA (“SMA proper”) with that related to successful inhibition (no-go) in the pre-SMA (Simmonds et al., 2007; Mostofsky, Schafer, et al., 2003; Humberstone et al., 1997). Pre-SMA activation is also observed during anti-saccade and antipointing tasks which, like the go/no-go task, also require inhibition of a prepotent response (Connolly, Goodale, Desouza, Menon, & Villis, 2000).

fMRI examination of response inhibition has also made use of the stop-signal task. In the traditional design of the

stop-signal task, there is a background choice reaction time task (“go”), in which the subjects select one of two responses; infrequently during the task, a signal is presented at a varying delay after a go stimulus, in which the participants are instructed to suppress the response-in-progress (“stop”). fMRI studies of stop-signal tasks reveal inhibitory-associated activation in the pre-SMA (Aron & Poldrack, 2006; Ramataur, Slagter, Kok, & Ridderinkhof, 2006; Rubia, Russell, et al., 2001), and one study demonstrated that individuals with better inhibitory performance activated the pre-SMA to a greater degree than individuals with poorer inhibitory performance (Li, Huang, Constable, & Sinha, 2006).

Although inhibitory-associated fMRI activation is commonly seen in the pre-SMA during response inhibition tasks, it is not seen in every study. A potential explanation for this is the particular fMRI contrasts selected. For example, in go/no-go studies using event-related designs, some studies report inhibitory-associated activation by directly contrasting no-go trials with go trials (Wager et al., 2005; Durston et al., 2002; Watanabe et al., 2002; Liddle et al., 2001), whereas others contrast no-go trials with rest or an implicit task baseline (Mostofsky, Schafer, et al., 2003; Kiehl et al., 2000; Humberstone et al., 1997). One study examined both of these contrasts, finding robust activation in the pre-SMA for the contrast of “no-go versus baseline” that was not present in the contrast of “no-go versus go” (Liddle et al., 2001). Go/no-go studies have shown that, when contrasted with the task baseline, no-go activation is seen in the pre-SMA; however, go activation contrasted with the task baseline is seen in both the SMA and the pre-SMA (Mostofsky, Schafer, et al., 2003; Liddle et al., 2001; Kiehl et al., 2000; Humberstone et al., 1997), which is also reflected by the presence of both “go action” and “no-go action” neurons in the pre-SMA (Isoda & Hikosaka, 2007). By contrasting no-go and go trials, activity in the pre-SMA would be masked. Consistent with this, findings from a meta-analysis of go/no-go studies, in which those using the no-go versus go contrast were excluded, revealed high concurrence of activation in the pre-SMA across studies (Simmonds et al., in press).

Human lesion studies provide further evidence for the role of the pre-SMA in response inhibition. Although many lesion studies using the go/no-go task used few subjects and were unable to make precise frontal localizations, the two studies with the largest numbers of subjects (Picton et al., 2007; Drewe, 1975) found that increased commission errors (when subjects respond to no-go stimuli) were associated with lesions in the pre-SMA. Additionally, a recent study demonstrated that lesions to the pre-SMA impair inhibitory performance in the stop-signal task (Floden & Stuss, 2006).

The connections of the pre-SMA demonstrate that it is well situated to rapidly suppress motor actions. The pre-SMA receives afferent connections from frontal and parietal association areas, including the right IFC and the

right dorsolateral prefrontal cortex (DLPFC), and projects to nonprimary motor but not to primary motor regions (Rizzolatti et al., 1996; Dum & Strick, 1991); hence, it may play a mediating role between integrating information from cognitive association areas and preparing for/selecting a motor response, including selecting to withhold a response. Furthermore, projections from the pre-SMA to the basal ganglia, which are associated with long-range inhibitory connections (Mink, 1996), may play a critical role in response selection and inhibition. In particular, there are selective connections between premotor and motor regions, which include the pre-SMA, and the subthalamic nucleus. Given their rapid conduction time, these “hyperdirect” projections from the pre-SMA to the substantia nigra pars reticulata through the subthalamic nucleus (Inase, Tokuno, Nambu, Akazawa, & Takada, 1999; Luppino, Matelli, Camarda, & Rizzolatti, 1993) may be particularly important in selecting appropriate behavior (including inhibiting inappropriate responses). Consistent with this are recent imaging findings in humans suggesting that the subthalamic nucleus may be important in response inhibition (Aron & Poldrack, 2006).

BEHAVIORAL EVIDENCE FOR LINK BETWEEN RESPONSE INHIBITION AND RESPONSE SELECTION

In addition to electrophysiological, imaging, and lesion findings, there is strong evidence of behavioral measures linking response selection and inhibition. In any type of reaction time task, an important measure of the consistency and efficiency of responding is reaction time variability. With respect to response inhibition, reaction time variability has particular behavioral relevance, as it has been shown that variability correlates with inhibitory performance such that poorer inhibitory performance is associated with less efficient response selection; this has been shown in adults (Bellgrove, Hester, & Garavan, 2004) and typically developing children (Simmonds et al., 2007; Klein, Wendling, Huettner, Ruder, & Peper, 2006; Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006). This contrasts with reaction time, which has been shown to have little or no correlation with inhibitory performance (Simmonds et al., 2007; Bellgrove et al., 2004). In addition, response time variability has been shown to correlate with inhibitory-associated activation in the pre-SMA such that greater pre-SMA activity is associated with lower variability (Simmonds et al., 2007), indicating that the pre-SMA may mediate the link between efficient response selection and better inhibitory performance.

The behavioral link between response selection and inhibition is further evidenced by disorders that present deficits in both domains. One notable example of this is ADHD, where deficits in response inhibition (Nigg, 1999; Barkley, 1997) and response selection (Flapper, Houwen,

& Schoemaker, 2006; Mostofsky, Newschaffer, et al., 2003; Rubia, Taylor, et al., 2001) are consistently observed. Children with ADHD show abnormal performance in both the go and no-go/stop processes of response inhibition studies, demonstrating both increased errors of commission and increased reaction time variability (Wodka et al., 2007; Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001; Nigg, 1999; Rubia, Oosterlaan, Sergeant, Brandeis, & van Leeuwen, 1998). In a meta-analysis of response inhibition studies in ADHD, deviation from control data had a large effect size for both response inhibition ($d = 0.58$) and reaction time variability ($d = 0.72$) (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). Additionally, across both ADHD and typically developing groups, correlations have been seen between inhibitory performance and response time variability (Klein et al., 2006; Verté et al., 2006; Nigg, 1999). Smaller premotor volume has been observed in boys with ADHD (Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002) and examination of cortical thickness in ADHD revealed significant thinning principally localized to a region of the superior medial frontal cortex consistent with the pre-SMA (Figure 3) (Shaw et al., 2006). Further, fMRI examination of response inhibition in ADHD has revealed decreased activation in the pre-SMA compared to controls (Suskauer et al., in press; Tamm, Menon, Ringel, & Reiss, 2004; Rubia et al., 1999).

A few studies have used electrophysiological measures to directly examine the link between response selection and response inhibition (Isoda & Hikosaka, 2007; Burle, Vidal, Tandonnet, & Hasbroucq, 2004; De Jong, Coles, & Logan, 1995). Burle et al. (2004) reported on both simple reaction time task with a single response and a go/no-go task with choice responding (right or left hand). During no-go trials, a positive wave appeared over the primary motor cortices, indicative of inhibition; a similar positive wave was seen during go trials over the ipsilateral (noninvolved) motor cortex, consistent with the need to suppress the incorrect response. In the simple reaction time task, however, the positive wave over the ipsilateral motor cortex was not observed, as this was not a potential response that needed to be suppressed. They proposed that the inhibition and selection seen in the go/no-go task were mediated by the SMA because, as with the ipsilateral motor cortex, a positive wave was observed in the SMA during a choice reaction time task with multiple responses (Vidal et al., 2003), but not during a simple reaction time task with a single automatic response (Burle et al., 2004).

Although most studies directly examining the link between response inhibition and response selection find that the processes are mediated by similar mechanisms, one study suggested otherwise, concluding that response inhibition is an “all-or-none” phenomenon in which all motor execution circuits are “shut down” via a “peripheral mechanism,” while response selection is mediated by motor execution circuits via a “central mechanism” (De Jong et al., 1995). The investigators recorded the “lateralized readiness potential,” a measure of the

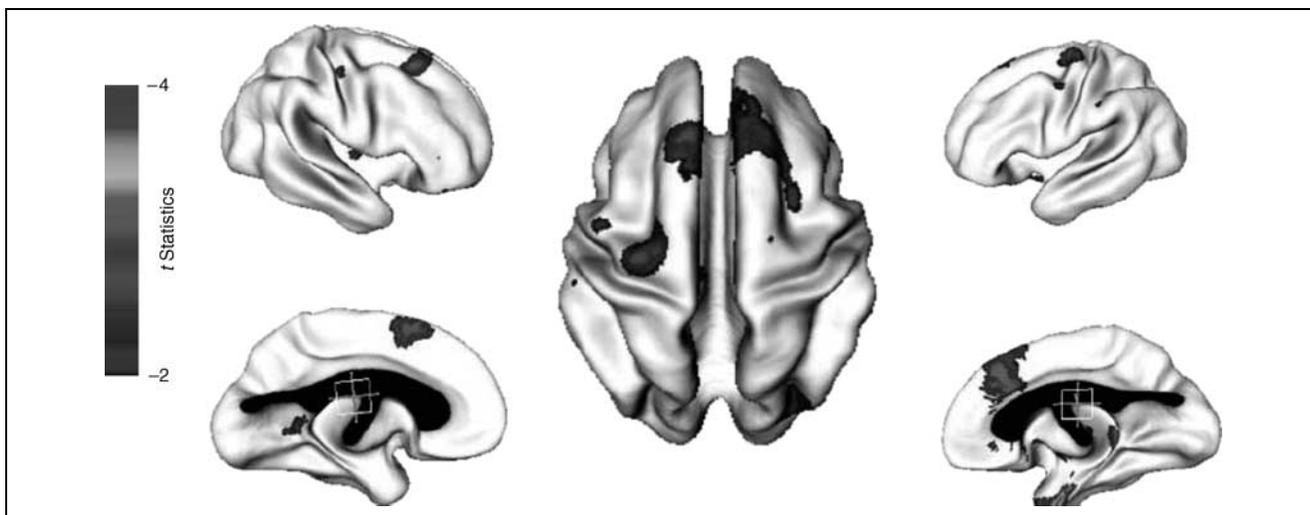


Figure 3. Cortical thickness map from Shaw et al. (2006) showing significant differences between children with ADHD and typically developing controls. After controlling for IQ and mean cortical thickness, differences were predominantly seen in the medial wall of the frontal lobe, including localization consistent with the rostral portion of the supplementary motor area (pre-SMA). Replicated with permission from Shaw et al. (2006).

electrophysiological difference between the potentials of the contralateral and ipsilateral primary motor cortices, during performance of a modified stop-signal task in which there were three possible responses to the stop signal: inhibit all hand responses (stop-all), inhibit responses for one hand (selective-stop), and inhibit hand response while changing to a response with both feet (stop-change); they found that the stop-change condition did not use the “peripheral” mechanism. However, their findings may have been confounded by use of the foot response for the stop-change condition; the lateralized readiness potential has the opposite polarity for foot and hand responses (Carrillo-de-la-Pena, Lastra-Barreira, & Galdo-Alvarez, 2006; Brunia, 1980) and this may have obscured the use of the “peripheral” mechanism in the stop-change task. Although the authors did not discuss a neural basis for the “peripheral” mechanism, it appears likely that it would involve the pre-SMA, given its role in preparing for and selecting, but not executing, responses.

TASK-DEPENDENT NATURE OF THE NEURAL CORRELATES OF RESPONSE SELECTION AND INHIBITION

As discussed, there is much evidence highlighting the central role of the pre-SMA in response selection and inhibition. Beyond the overlapping contribution of the pre-SMA to both response selection and response inhibition, however, both processes also appear to be associated with variable recruitment of prefrontal and posterior cortical regions that differs depending on the cognitive/behavioral demands of the task (Mostofsky, Schafer, et al., 2003). In the case of response selection, support comes from the observation that selection of

one of multiple motor responses is essential to nearly all fMRI tasks, the findings from which encompass a range of varying prefrontal and posterior cortical activation. For instance, working memory tasks typically involve selecting to push one of two buttons; nevertheless, the associated findings of prefrontal and posterior cortical activation from such studies are typically discussed in the context of the working memory demands necessary to guide the response selection, rather than response selection itself.

In contrast, tasks putatively designed to assess response inhibition tend to be discussed in terms of response inhibition itself, rather than the additional cognitive demands of the task. fMRI studies of the go/no-go task have consistently revealed frontal lobe activation; however, localization and extent of frontal activation varies across these studies, with activation most often localized to the right IFC (BA 45/47) (Durstun et al., 2002; Rubia, Russell, et al., 2001; Garavan, Ross, & Stein, 1999; Konishi et al., 1999), the right DLPFC (BA9/46) (Garavan et al., 1999, 2006; Bellgrove et al., 2004; Hester et al., 2004; Garavan, Ross, Kaufman, & Stein, 2003; Garavan, Ross, Murphy, Roche, & Stein, 2002), and the pre-SMA (BA 6/8) (Simmonds et al., 2007; Garavan et al., 2006; Mostofsky, Schafer, et al., 2003; Liddle et al., 2001; Rubia, Russell, et al., 2001; Kiehl et al., 2000; Humberstone et al., 1997).

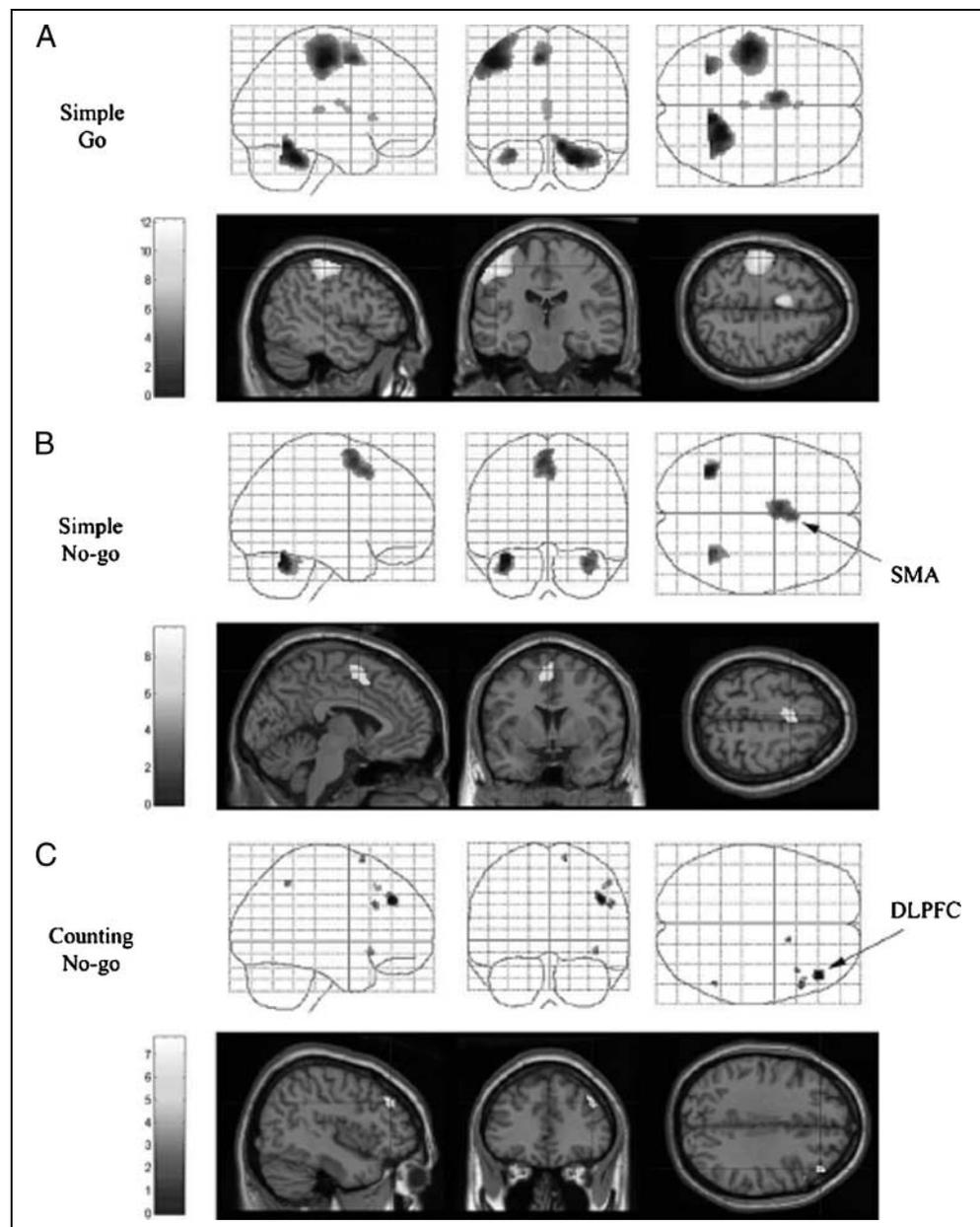
It may be that the variation in localization of frontal activation across go/no-go studies is due to differences in task design. This hypothesis was examined in a study of healthy adult subjects performing two different go/no-go tasks: a “simple” go/no-go task, in which the cognitive load of the task was minimized by using well-ingrained, habitual stimulus–response associations (green = go; red = no-go) and a “counting” go/no-go task with a high

working memory load (Mostofsky, Schafer, et al., 2003). For the counting task, the same stimuli were used as in the simple task, but the red stimulus could be either a go stimulus, if preceded by an even number of green stimuli, or a no-go stimulus, if preceded by an odd number of green stimuli; this task therefore required manipulation of the stimulus–response association for red stimuli in working memory on a trial-by-trial basis. For the simple task, no-go activation was localized to the pre-SMA (Figure 4A). In contrast, no-go activation in the “counting” go/no-go task was also observed in the right DLPFC, indicating that this region is recruited under circumstances when manipulation of information in working memory is necessary to guide response inhibition; however, no-go activation in the “counting” task was also seen in the pre-SMA, indicating

that the pre-SMA may be involved in response inhibition, irrespective of task demands (Figure 4B).

No-go activation in prefrontal, as well as posterior cortical, regions varies across fMRI studies and, as indicated by the “simple” and “counting” go/no-go tasks discussed above, this variation appears to depend on task demand. The context of response inhibition in “real life” settings often involves complex judgments based on a range of cognitive and behavioral information. For instance, as one pulls up to a yellow light, the decision to inhibit pushing harder on the gas pedal may involve processing and manipulating information regarding the distance from the light, the speed at which one is going, the presence of other cars/people, and one’s emotional judgment about how important it is to reach their

Figure 4. Glass-brain and sectional maps from Mostofsky, Schafer, et al. (2003) depicting the fMRI results of the “simple” and “counting” go/no-go tasks. The simple task utilized well-ingrained stimulus–response associations (green = go; red = no-go), whereas in the counting task, red was either go if preceded by an even number of greens or no-go if preceded by an odd number of greens. For the simple task, no-go activation in the frontal lobe was localized to the pre-SMA; in the counting task, activation was also seen in the right dorsolateral prefrontal cortex. Replicated with permission from Mostofsky, Schafer, et al. (2003).



destination as soon as possible. Guidance of response inhibition in this context would likely necessitate interaction between several cortical regions.

In the laboratory environment, assessment of response inhibition generally involves tasks in which the cognitive complexity is limited to having to maintain “rules” (generally involving novel stimulus response associations) necessary for selecting whether to engage in or withhold a response. For some tasks there is an additional need to manipulate information in working memory. There is strong evidence for a dorsal/ventral dissociation within the prefrontal cortex, whereby ventral prefrontal regions (IFC) are involved in maintenance of information, whereas dorsal prefrontal regions (DLPFC) are involved in manipulation of information in working memory (for reviews, see Courtney, 2004; D’Esposito, Postle, & Rypma, 2000).

Recruitment of the DLPFC in guiding response inhibition is reflected in the “simple” and “counting” go/no-go tasks discussed above (Mostofsky, Schafer, et al., 2003), where the counting task, which required manipulating information in working memory, showed increased activation in the right DLPFC. Similar findings were seen in another commonly used go/no-go task in which the letters “X” and “Y” are alternately presented, and the no-go stimulus occurs when there is a two-letter repeat. Hence, each trial required an update in stimulus–response associations (e.g., after presentation of an “X,” “X” becomes no-go and “Y” becomes go, and vice versa). All studies using this task have reported activation in the right DLPFC (Hester et al., 2004; Garavan et al., 1999, 2002, 2003) and an analysis of this task across 71 subjects showed robust activation in the right DLPFC (Garavan et al., 2006).

Studies reporting no-go activation in the IFC have used such stimuli as numbers (Fassbender et al., 2004), letters (Garavan et al., 1999, 2006), cartoon characters (Durstun et al., 2002), or an array of colored shapes (Booth et al., 2003, Konishi et al., 1999) with arbitrary stimulus–response associations, unlike those in the “simple” go/no-go task discussed above which utilized well-ingrained stimulus–response associations (green = go; red = no-go) (Mostofsky, Schafer, et al., 2003); all of these may have increased the need for establishing and maintaining novel stimulus–response associations. A meta-analysis including such studies revealed a region of concurrence in the right IFC, in addition to concurrence in the pre-SMA (Buchsbaum et al., 2005). The use of a design in which inhibition of a response is based on novel rules maintained in working memory is common to go/no-go studies; involvement of the right IFC in go/no-go tasks may be related to maintaining information about stimulus–response associations, to guide selection to withhold the response.

Right inferior parietal (BA 40) activation is typically observed in conjunction with right IFC activation. Corbetta and Shulman (2002) proposed that right inferior

parietal and prefrontal regions form a network specialized in the detection of behaviorally salient stimuli, and are particularly engaged when the stimuli are infrequent, unexpected, and require greater effort to change the behavior. It has also been shown that right inferior parietal regions deactivate during nonbehaviorally relevant stimuli (Shulman, Astafiev, McAvoy, d’Avossa, & Corbetta, 2007), potentially acting as a filter in order not to attend to irrelevant stimuli, and the same may hold for the rest of the network, including the right IFC. This is consistent with findings of activation in the right IFC and the right inferior parietal cortex during oddball tasks, irrespective of whether they require selection or inhibition of a motor response (Braver, Barch, Gray, Molfese, & Snyder, 2001).

This also raises the issue of whether right IFC findings in the go/no-go task may be due to oddball, expectancy, or behavioral relevance effects, rather than response inhibition per se. A number of event-related fMRI studies directly contrast no-go trials with go trials (Wager et al., 2005; Durstun et al., 2002; Watanabe et al., 2002; Liddle et al., 2001). One study that reported on both the contrasts of “no-go versus go” and “no-go versus task baseline” found right IFC activation only in the “no-go versus go” contrast (Liddle et al., 2001); as discussed, this may be due to oddball effects (Braver et al., 2001) or attentional filtering mechanisms attributed to the right inferior parietal cortex (Shulman et al., 2007).

Among fMRI studies of the stop-signal task, activation in the right IFC is a common finding (Aron & Poldrack, 2006; Li et al., 2006; Rubia, Russell, et al., 2001). This finding is more consistent than in the go/no-go task and may be reflective of differences between the two tasks. The stop-signal task is generally more difficult than the go/no-go task, as indicated by high commission error rates, generally around 50%. In the go/no-go task, the stimulus appears before the response begins and may be less taxing on prefrontal/parietal networks involved in the detection of behaviorally relevant stimuli. Response inhibition associated with the stop-signal task, on the other hand, appears to be more stimulus-driven; a response must be initiated before the onset of the stop signal, and thus, may necessitate a greater need for the detection of stimuli to guide selecting whether to execute or withhold a response.

Findings from lesion studies also suggest that the right IFC may be particularly relevant in stop-signal response inhibition. One lesion study using the stop-signal task found that performance was impaired specifically with damage to the right IFC (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003), although not to the pre-SMA. At first glance, this apparently contradicts another stop-signal study which found that inhibitory performance was impaired with pre-SMA lesions (Floden & Stuss, 2006); however, the superior frontal gyrus region of interest used by Aron et al. (2003) in their lesion-based study encompassed regions outside of the SMA/pre-SMA, including lateral portions of the superior frontal

gyrus, which have not been implicated in response inhibition; had they limited this region to the SMA/pre-SMA, they may have found an impairment similar to that seen with the right IFC.

Recently, Chambers et al. (2006) did a “temporary lesion” study of the stop-signal task using repetitive transcranial magnetic stimulation (rTMS), targeting the right IFC, the right DLPFC, and the right angular gyrus (AG). They used a background choice reaction time task, where the participants responded to one letter with their right hand and the other letter with their left hand; the stop signal was a red box presented around the letter. They found that rTMS to the right DLPFC and right AG did not significantly alter performance; however, rTMS to the right IFC significantly impaired inhibition performance. The absence of focus upon the pre-SMA is unfortunate, although we speculate that rTMS to the pre-SMA would also impair response inhibition. Of note, stimulation of the right IFC impaired response inhibition for both the right and left hands.

The importance of this finding was clarified in another recent study from the same group in which patients with schizophrenia were examined (Bellgrove et al., 2005). There was an increased stop-signal reaction time (SSRT), a measure of inhibitory performance, for the undifferentiated early-onset schizophrenia group, but it was specifically lateralized to left hand responses. As the study of Chambers et al. (2006) demonstrated that lesions to the right IFC impaired response inhibition for both hands, the authors concluded that this lateralized deficit in response inhibition could not be mediated by the right IFC, instead suggesting the involvement of premotor regions such as the pre-SMA as the cause of this deficit. The hypothesis that lesion of the pre-SMA contributes to lateralized impairments in response inhibition could be tested by applying rTMS separately to the right and left pre-SMA during performance of the stop-signal task. The midline location of the pre-SMA, however, could make it difficult to direct stimulation in a distinctly lateralized fashion.

The differential contribution of the pre-SMA and right IFC to response inhibition could also be examined during fMRI using a modified stop-signal task; instead of inhibiting a response with the signal, an additional response is added. If no right IFC activation is seen in response to the noninhibitory yet behaviorally relevant signal, this would suggest that the right IFC does, in fact, play a specific role in response inhibition that is not common to response selection; however, if right IFC activation is seen, it would suggest that the role of the right IFC is not specific to response inhibition, but rather is in orienting attention to behaviorally relevant stimuli.

Finally, it is important to note that recruitment of frontal regions outside of the right IFC and DLPFC to guide response inhibition may also relate to task demands. In particular, activation in the anterior cingulate cortex (ACC) appears to occur with tasks such as Stroop interference, in which resolving a stimulus–response

conflict is necessary to guide response selection (Bush et al., 1998). Electrophysiological findings in monkeys show that although the responses of neurons in the pre-SMA and the ACC during a delayed reaction task are very similar, pre-SMA firing was more associated with the stimuli, whereas ACC firing was more associated with reward (Akkal, Bioulac, Audin, & Burbaud, 2002); this suggests that the ACC may serve an error-monitoring function (Rushworth, Walton, Kennerley, & Bannerman, 2004), providing performance feedback to the pre-SMA.

CONCLUSION

In this article, we presented evidence supporting a theoretical construct in which motor response selection and response inhibition are viewed as being “two sides of the same coin.” The pre-SMA appears to be an essential part of the circuits mediating both of these processes. As such, distinctions between response selection and response inhibition may not be discernable at a neural systems level, but rather may manifest as differences in the timing/localization of neurons recruited in the pre-SMA and other overlapping regions in circuit with the pre-SMA (e.g., interconnected regions in the basal ganglia).

In addition, as with response selection, recruitment of prefrontal regions necessary to guide response inhibition appears to vary depending on the demands of the task; for instance, if manipulation of stimulus–response associations in working memory is required, the DLPFC is recruited, and if maintenance of stimulus–response associations in working memory is required, the IFC is recruited. Additionally, the right IFC and the right inferior parietal cortex seem to play an important role in the orienting of attention to behaviorally relevant stimuli, and they may work together with the pre-SMA to guide response inhibition under conditions where rapid detection of stimuli is necessary to guide response inhibition. There are a number of other contexts that may necessitate recruitment of other regions; this may include the orbito-frontal cortex, when emotional cues are required to guide response inhibition, or the ACC, in situations where error-monitoring is particularly important.

This construct provides a framework for understanding neural system deficits underlying a number of psychiatric disorders; the most relevant of these may be ADHD, in which response inhibition has been suggested as a fundamental deficit (Nigg, 1999; Barkley, 1997). Response inhibition deficits in ADHD have been documented across multiple domains, including skeletomotor, oculomotor, and cognitive domains, where inhibition is guided by a rule held in working memory; crucial but more difficult to study in laboratory conditions is socio-emotional disinhibition, which is the most clinically relevant finding in ADHD, contributing to impulsive behavior. However, deficits in ADHD are not limited to response inhibition, as deficits in motor response

preparation and selection have been noted as well (Castellanos et al., 2005; Mostofsky, Newschaffer, et al., 2003; Mostofsky et al., 2001; Rubia, Taylor, et al., 2001). It may be that abnormality in pre-SMA circuits is central to impaired response inhibition across domains of function; alternatively, it is possible and likely that abnormalities in prefrontal circuits contribute to impaired response inhibition in more complex contexts involving control of cognitive and socioemotional function. These competing hypotheses could be examined in ADHD using an fMRI experimental design previously applied to adults (Mostofsky, Schafer, et al., 2003), in which response inhibition is examined using two different go/no-go paradigms with distinct task demands. Understanding the neural basis of response inhibition and how it is impaired in neurological populations, including ADHD, may then help guide research into treatments for these populations.

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