22.

IS THERE AN INFERIOR FRONTAL CORTICAL NETWORK FOR COGNITIVE CONTROL AND INHIBITION?

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INTRODUCTION

Cognitive control is one of the cardinal functions of the frontal lobes. Among the core components of cognitive control are information updating, inhibition, and mental set-shifting. These allow us to select actions and control behavior in accordance with external environmental demands and internal goals. Changes in goals or circumstances often entail the reprogramming of actions, and this, in turn, often requires inhibition of movements or movement plans, resolution of response conflict, and initiation of alternative actions.

In this chapter, we discuss how executive control is exerted by different regions in the frontal lobes. There is a particular focus on inhibitory motor control. It has been suggested that the inferior frontal gyrus (IFG), particularly the right IFG (rIFG), and the pre-supplementary motor area (pre-SMA) play a major role in inhibitory control and the flexible adjustment of movement plans. Although inhibition is often thought to constitute the means by which executive control is exerted, it is not always clear how inhibitory control on a cognitive level can be related to physiological inhibition. In order to address these questions, we will review studies that looked at measures of brain activity during tasks that required inhibitory control. Moreover, we will also consider studies that have sought to investigate the consequences of changes in brain activity, as a result of either lesions or transcranial magnetic stimulation (TMS), for inhibitory control. A limited number of studies have also tried to disentangle how areas in the frontal lobes influence other areas during inhibitory control tasks, using functional connectivity analyses of functional magnetic resonance imaging (fMRI) data and paired-pulse TMS. These experiments suggest that executive control is partly accomplished via direct cortico-cortical interactions but also partly through a complex and distributed network of cortex-basal ganglia-cortex loops. Finally, an important theme is the claim that while these areas, particularly the IFG, exert inhibitory control over motor representations when expectations about the environment are violated, this is just one aspect of their broader function in cognitive control. An important aspect of their function includes exploiting environmental regularities, when they exist, in order to facilitate action selection.

FRONTAL LOBE INTERACTIONS WITH THE BASAL GANGLIA DURING COGNITIVE CONTROL

Several accounts of executive control have focused on the possibility that frontal cortex might exert cognitive control via frontal cortex-basal ganglia loops (Hazy, Frank, & O'Reilly, 2007; O'Reilly, 2006). The multisynaptic connection pathways from the cortex that pass through the basal ganglia and back to the cortex take several routes. The possibility that two of these are especially important for the inhibition of actions has received particular attention.

Cortical projections to the basal ganglia terminate mainly in the caudate and putamen. The projections originate in many areas in the cerebral cortex but especially from areas in the frontal lobes. Output from the basal ganglia originates in the internal segment of the globus pallidus (GPi) and terminates in thalamic nuclei, which then project to the primary motor cortex (M1), premotor areas, and prefrontal cortex (Nambu, 2008). These cortex-basal ganglia-cortex projections have been characterized in terms of a "direct" pathway and an "indirect" pathway (Figure 22–1). The direct pathway consists of inhibitory projections from the striatum to the GPi and substantia nigra pars reticulata (SNr), which in turn have inhibitory projections to the superior colliculus and the thalamus. The indirect pathway connects the striatum with the external segment of the globus pallidus (GPe) and the subthalamic nucleus (STN), which then projects to the GPi and SNr and to the thalamus. Another, "hyperdirect," pathway has been proposed, which consists of direct projections from the cortex

to the STN and thereafter via GPi to the thalamus (Aron et al., 2007b; Isoda & Hikosaka, 2008; Nambu, 2004).

These different loops have been thought to play different roles in motor control. Via the direct pathway target neurons in the output nucleus, GPi, are inhibited. As GPi has inhibitory connections to the thalamus, inhibition of GPi leads to excitation of thalamus and cortical areas and thus to the release of a selected motor program for execution. The indirect and hyperdirect pathways, however, have been particularly implicated in response inhibition because an increase in their activity leads to excitation of GPi and hence inhibition of thalamocortical projections. It has been proposed that cortical activity is controlled via these direct, indirect, and hyperdirect loops. The basal ganglia are hypothesized to play a crucial role in resolving competition between possible movement programs and allowing the initiation of the selected program while other programs are inhibited. Strong inhibitory baseline activity in the indirect pathway holds potential responses in check. A distinct movement plan is selected, and specific neuronal circuits within the direct pathway are activated to release their specific target neurons in the thalamus and M1 ("go signal" conveyed by the direct pathway), whereas all other potential responses remain inhibited via indirect pathway projections ("no-go signal" conveyed by the indirect/hyperdirect pathway).

It has been suggested that higher order executive control might be an evolutionary extension of the same cortex-basal ganglia functions, which convey go- and no-go signals (Aron et al., 2007b; Isoda & Hikosaka, 2008; Nambu, 2004), therefore guiding not only (1) motor initiation (go) and motor inhibition (no-go) in the motor system, but maybe also (2) updating (go) and maintenance (no-go) of working memory content and information in the prefrontal cortex. Hence, different executive control processes (inhibition, set-shifting, updating) may rely on these two fundamental neuronal mechanisms (go vs. no-go; Hazy et al., 2007). When to activate the go loops (i.e., when to initiate a movement, when to update information about a cue, etc.) and when to activate the no-go loops (inhibiting motor output, maintaining information) may be determined by the prior reward history, perhaps conveyed via the dopaminergic projections that modulate cortex-basal ganglia-cortex loops. Such a hypothesis would predict that, if IFG and pre-SMA are important for response inhibition, then they might also be implicated in a wider range of processes such as the reorienting of attention and the updating of working memory.

WHAT AND WHERE IS THE INFERIOR FRONTAL GYRUS?

Within the frontal cortex it is the IFG and, to a lesser extent the medial frontal cortex, that have been especially associated with the inhibitory aspects of cognitive control. While many studies agree that an important region in the medial frontal cortex is the pre-SMA, there is less consensus about the whereabouts of the IFG region that is implicated in cognitive control. The anatomically defined IFG is located ventral to the inferior frontal sulcus and dorsal to the lateral fissure. While the posterior border of the IFG is conventionally taken to be the inferior precentral sulcus, as discussed below, activity recorded in many studies of cognitive control and attributed to the IFG often extends more posteriorly.

The human IFG is subdivided into the pars opercularis, pars triangularis, and pars orbitalis, which approximately correspond with cytoarchitectonic areas 44, 45, and 12/47. Similar regions have been identified in the inferior convexity (areas 45 and 12/47) and in the fundus of the inferior limb of the arcuate sulcus (area 44) in the monkey (Brodmann, 1909; Petrides & Pandya, 1994, 2002; Walker, 1940). Subregions within IFG are interconnected with different posterior cortical areas in the temporal and parietal cortex; while both temporal and parietal cortex are interconnected with more anterior IFG, the pars opercularis region

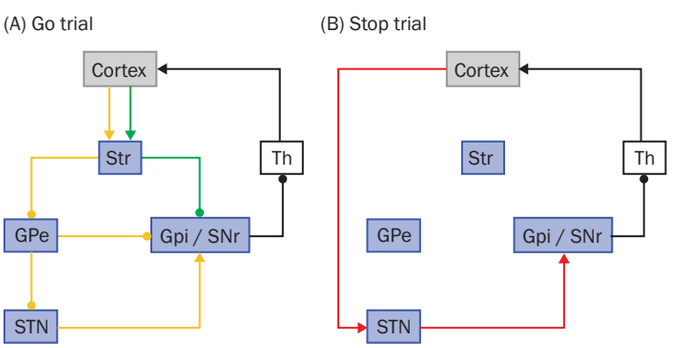

Figure 22–1 Different cortico-basal ganglia cortical routes might be associated with selection and promotion of a response on a go trial and inhibition of a response (a no-go trial). Cortical areas (such as rIFG, pre-SMA, and MI) are summarized as "cortex" in the gray box, basal ganglia structures in blue boxes, and thalamus in the white box. (A) This panel summarizes the direct and indirect pathways. (B) This panel summarizes the hyperdirect pathway. Arrows indicate excitatory (glutamatergic) connections; circles indicate inhibitory (GABAergic) connections. Red, green, and yellow lines denote the hyperdirect, direct, and indirect pathways, respectively. GPe, external segment of the globus pallidus; GPi/SNr, internal segment of the globus pallidus/substantia nigra pars reticulata; STN, subthalamic nucleus; Str, striatum; Th, thalamus.

in the posterior IFG resembles the adjacent ventral premotor cortex (PMv) in being interconnected with anterior inferior parietal cortex (Anwander, Tittgemeyer, von Cramon, Friederici, & Knosche, 2007; Aron, Behrens, Smith, Frank, & Poldrack, 2007a; Croxson et al., 2005; Ford, McGregor, Case, Crosson, & White, 2010; Petrides & Pandya, 2009; Rushworth, Behrens, & Johansen-Berg, 2005; Tomassini et al., 2007). It may be useful to think of IFG as having at least two component parts—an anterior prefrontal division with a granular cytoarchitecture and a more posterior premotor division with a dysgranular cytoarchitecture.

The rIFG region identified in many fMRI investigations of go/no-go tasks, stop-signal tasks, and similar response inhibition and set-shifting paradigms is extensive, and its posterior part includes a region that others have frequently identified with PMv. Table 22–1 summarizes 50 studies, mostly involving fMRI but also some TMS studies, that have sought to delineate brain areas involved in response inhibition (20 studies), action reprogramming and set-shifting (20 studies), and pure motor control (10 studies). The Montreal Neurological Institute (MNI) coordinates of rIFG peak activations/TMS sites are plotted on a standard MNI brain template (Figure 22–2). This meta-analysis focused on rIFG blood oxygenation level-dependent (BOLD) activation peaks/TMS sites; other areas (such as pre-SMA or left IFG) were not considered for this analysis. The less frequent occurrences of activation in the left IFG were ignored because the aim of the analysis was to assess the distribution of activations without any potentially confounding influence of the hemispheric differences in anatomy. Eight of the 20 peak activations associated with response inhibition, 12 of the 20 activations associated with action reprogramming and set-shifting, and all 10 peak activations associated with motor control lie within the 95th percentile of the activation likelihood estimation (ALE) for PMv determined by Mayka, Corcos, Leurgans, and Vaillancourt (2006). Moreover, the three means of these peak activations (20 for inhibition, 20 for set-shifting, and 10 for motor control) all lie within the 95th percentile of the PMv ALE map.

Although the role of PMv in many motor behaviors, such as grasping and other hand movements, has received particular attention, it is becoming clear that it is able to exert an inhibitory influence over M1 (Baumer et al., 2009; Buch, Mars, Boorman, & Rushworth, 2010; Davare, Andres, Cosnard, Thonnard, & Olivier, 2006). Together with dorsal premotor cortex (PMd), PMv provides one of the largest inputs into the hand representation in M1 (Dum & Strick, 2005). In turn, PMv itself receives inputs from other premotor areas and M1. but notably it is also the premotor area that receives the most direct monosynaptic input from ventral and other lateral prefrontal cortical areas (Dum & Strick, 2005). Therefore, PMv is ideally positioned to mediate the influence of prefrontal cortex on motor behavior.

By contrast, the medial frontal areas that have been associated with response inhibition have less direct access to the motor system. In general, medial frontal activation in fMRI studies of response inhibition lies anterior to the plane of the anterior commissure, placing it in the pre-SMA rather than in the more posterior SMA. Although it has been claimed that there is a rostrocaudal continuum of graded change in structure and function between pre-SMA and SMA (Nachev, Kennard, & Husain, 2008), there is evidence for an important change in anatomical connectivity between the pre-SMA and SMA (Johansen-Berg et al., 2004). Whereas the SMA makes a substantial contribution to the corticospinal tracts (~10%) and has reciprocal connections with M1, pre-SMA is more strongly interconnected with prefrontal cortex (Bates & Goldman-Rakic, 1993; Lu, Preston, & Strick, 1994; Luppino, Matelli, Camarda, & Rizzolatti, 1993). There is, however, evidence suggesting that both IFG and pre-SMA have connections with basal ganglia, including the STN, which might mean that they influence action inhibition via these routes (Aron et al., 2007a; Inase, Tokuno, Nambu, Azakawa, & Takada, 1999).

THE rIFG AND RESPONSE INHIBITION

The prominent identification of IFG with response inhibition is the result of a large number of fMRI studies that have interpreted BOLD signal changes found in the IFG, albeit in the context of a number of cognitive tasks, in terms of response inhibition. In one early event-related fMRI study Konishi, Nakajima, Uchida, Sekihara, and Miyashita 1998b) reported greater activity in a posterior part of the right inferior frontal sulcus on task trials that required no response (no-go trials) than on trials that required a response (go trials). A subsequent study found prominent no-go-related activity in the posterior part of the inferior frontal sulcus in the right hemisphere irrespective of whether subjects used their right or left hands (Konishi et al., 1999). In the same study, a similar area was found to be active during cognitive set-shifting in the Wisconsin Card Sorting Task (WCST; Figure 22–3). Activation that is related to set-shifting suggests that this area may have a broader role in a number of cognitive processes in addition to action inhibition (Duncan & Owen, 2000; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). The broader role of the IFG, beyond inhibition of motor responses, is a theme that we return to below.

An association between rIFG and inhibition of action was also present in the work of other researchers. Garavan, Ross and Stein (1999) asked their subjects to perform a response inhibition task similar to the go/no-go task and found inhibition-related activity in the right middle and inferior frontal gyri (as well as in the anterior insula and the inferior parietal lobe). Using a standard go/no-go task,

TABLE 22-1

MNI COORDINATE			BEHAVIORAL TASK, INTERPRETATION OF ACTIVATION, AND DESCRIPTION OF ACTIVATION LOCATION	AUTHORS
X	Y	Z		
44	12	18	SSRT-related activity in a **go/no-go task**, referred to as **IFC**	Aron and Poldrack (2006)
50	16	20	Activity related to inhibition and conflict in a **go/no-go task**, referred to as **IFC**	Aron et al., (2007a)
36	23	33	Activity related to inhibition in a **target-detection-response-inhibition task**, referred to as **IFG**	Garavan et al. (1999)
56	16	16	**Go/no-go task**, activity related to no-go trials compared to infrequent go-trials, referred to as **posterior IFG**	Chikazoe et al. (2009a)
46	16	16	Activity in a **modified SSRT** that was related to inhibition but not to preparation to inhibit (disjunction analysis)	Chikazoe et al. (2009b)
52	12	20	Segregation of two areas within IFG, activity in the middle part of area 44, referred to as **posterior IFG**, was associated with inhibition in an **antisaccade task**; activity in anterior area 44 was associated with negative feedback processing	Hirose et al. (2009)
49	26	27	Comparison of (1) preparation for to inhibit to wholly inhibiting a response in a **go/no-go task** and (2) wholly inhibiting a response to reprogramming a response in a **stimulus-response reversal task; IFG** was found to be active during both preparation to inhibit and response inhibition	Goghari and MacDonald (2009)
48	14	8	Correlation between RT distribution measures of response inhibition in a Simon task with individual patterns of brain function and structure in IFC measured with fMRI and (DTI), respectively	Forstmann et al. (2008a)
44	32	−4	**SSRT task** together with fMRI-based Granger causality analysis; activity reported in **IFC** and pre-SMA was associated with stopping but suggests that IFC detects stop signals and expedites response suppression via connections with the basal ganglia and pre-SMA	Duann et al. (2009)
48	14	32	**SSRT task**; the **IFG** was more active during successful stop trials compared to go trials and also during successful stop trials compared to unsuccessful stop trials	Boehler et al. (2010)
47	26	19	**SSRT task**; the **IFG** was more active during successful stop trials compared to unsuccessful stop trials; when subjects were rewarded for correct go trials, the IFG contrast (successful > unsuccessful) disappeared; moreover, subjects had longer SSRTs	Padmala and Pessoa (2010)
48	18	−6	The study combined data from five different fMRI studies of the **SSRT task**; SSRT, a behavioral measure of response inhibition, is positively correlated with BOLD activity in **rIFG/anterior insula**	Congdon et al. (2010)
50	−7	17	Modified **go/no-go task**; activity associated with successful stopping was found in **precentral gyrus/IFG**	Garavan et al. (2002)
43	22	21	**Go/no-go task**; activity in the posterior part of the right **inferior frontal sulcus** was associated with response inhibition, irrespective of the hand that had to be inhibited	Konishi et al. (1998a)
41	25	−2	Modified **SSRT**; brain activation correlating with successful inhibitory control was isolated in **inferior prefrontal cortex**	Rubia et al. (2003)
34	18	36	**Go/no-go task; IFC** is proposed as the key structure for making decisions not to move	Kawashima et al. (1996)

(*Continued*)

TABLE 22-1 (*Continued*)

MNI COORDINATE			BEHAVIORAL TASK, INTERPRETATION OF ACTIVATION, AND DESCRIPTION OF ACTIVATION LOCATION	AUTHORS
X	Y	Z		
42	18	−6	Modified **SSRT task**; a network including **IFC** was activated during inhibition of both manual and saccadic responses	Leung and Cai (2007)
46	18	8	**SSRT task** and a speech control task; manual response inhibition and inhibition of speech both engaged **right inferior frontal cortex** and pre-SMA, indicating that manual responses and speech acts share a common inhibitory mechanism	Xue et al. (2008)
61	21	13	**SSRT task**; repetitive TMS to the IFG impaired the subjects' ability to stop a prepared movement	Chambers et al. (2006)
40	30	26	Activation likelihood estimate (ALE) in a meta-analysis of 11 studies using the **go/no-go task** to investigate response inhibition in 212 subjects; activity in **middle frontal gyrus/IFG**	Simmonds et al. (2008)
41	26	21	**Task-switching paradigm**; activity in the **right lateral prefrontal cortex** was associated with task set and response reconfiguration	Brass et al. (2003)
45	12	24	**Visual detection task** in which subjects tended to favor a default when making difficult decisions; activity associated with difficult decisions and **rejection of the default** was found in IFC and the subthalamic nucleus	Fleming et al. (2010)
41	16	19	**Go/no-go task** and a **WCST**; a focus that showed transient no-go activity in the **posterior part of the inferior frontal sulcus**, irrespective of whether the subjects used their right or left hands, was also active during set-shifting	Konishi et al. (1999)
48	14	28	**WCST; posterior prefrontal cortex** together with other areas showed increased activity specifically during the reception of negative feedback, which signals the need for a mental shift to a new response set	Monchi et al. (2001)
44	11	32	**Stroop task**; cortical activation for the contrast of incongruent minus congruent trials in the **Stroop task** was found in posterior inferior frontal sulcus	Brass et al. (2005b)
38	19	11	In a **task-switching paradigm** the **right lateral prefrontal cortex** was involved in overcoming residual inhibition of a recently performed task	Dreher and Berman (2002)
36	15	30	Modified **go/no-go task**; activity in right dorsal prefrontal cortex was associated with withholding an immediate response in combination with task switching; the authors concluded that right dorsal prefrontal cortex could be involved in switching to a response suppression mode	Swainson et al. (2003)
44	10	34	Meta-analysis of frontal lobe and anterior insula activations in **task-switching, set-shifting, and nonprobabilistic S-R reversal paradigms**; consistent activation was found in the **inferior frontal junction**	Derrfuss et al. (2005)
47	8	30	**Task-switching paradigm, a manual Stroop task, and a verbal n-back task** in a within-session, within-group design; consistent involvement of the **inferior frontal junction** revealed	Derrfuss et al. (2004)
52	12	26	Eriksen flanker task; activity in the right inferior prefrontal cortex was associated with incongruent stimuli and interference control	Hazeltine et al. (2000)
44	23	28	Modified Eriksen flanker task; a region within the right IFG exhibited competition-related activation	Hazeltine et al. (2003)

39	15	22	**WCST**; activation of the posterior part of the bilateral inferior frontal sulci was associated with set-shifting	Konishi et al. (1998a)
60	18	2	Action reprogramming-related activation in IFG	Mars et al. (2007)
40	8	36	Task-switching activity in inferior frontal sulcus	Dove et al. (2000)
55	10	35	Decision uncertainty-related activity in IFG	Huettel et al. (2005)
36	16	4	Conjoint analysis of data from mixed design experiments using 10 different tasks and 183 subjects. The aim was to extract a core system for the implementation of task sets; the authors found (1) start cue-related activity, (2) sustained block activity, and (3) error-related activity in the posterior medial frontal cortex and the frontal operculum	Braver and Barch (2006); Dosenbach et al. (2006)
45	30	25	Decision-making task and fMRI effective connectivity-based analysis showing that pre-SMA detects motivationally salient stimuli and subsequently energizes IFG to increase executive control	Kouneiher et al. (2009)
44	12	32	Activity related to organization of action chunks, referred to as BA44	Koechlin and Jubault (2006)
42	18	−6	IFG activated when responses have to be inhibited in the SSRT task but also when responses have to be selected in an action selection task, when behaviorally relevant cues are detected in a signal detection task and even in a working memory task	Hampshire et al. (2010)
44	30	−6	Reversal learning task; activity in IFG associated with optimization of postreversal accuracy and hypothesized to play a role in inhibition of learned associations during reversal	Ghahremani et al. (2010)
58	13	19	Interaction with M1 at rest and during grasping, referred to as ventral premotor (PMv)	Davare et al. (2008)
60	16	23	Involved in precision grasping, especially in positioning of fingers on the object; PMv activation	Davare et al. (2006)
54	4	28	Presentation of actions and reading phrases relating to actions; PMv activation	Aziz-Zadeh et al. (2006)
41	5	3	Imitation inhibition task; PMv activation	Brass et al. (2005a)
54	8	22	Learning and practice of a bimanual motor skill; PMv activity decreased during the learning stage, possibly due to a decreasing necessity to inhibit preexisting response tendencies and the development of an internal feedforward-driven execution mode	Puttemans et al. (2005)
55	15	30	TMS study of inhibitory influences on the motor cortex when grasping movements had to be inhibited and reprogrammed; PMv activation	Buch et al. (2010)
52	8	20	**Manipulation and naming of simple and complex objects**; PMv active during object manipulation, recognition, and naming	Binkofski et al. (1999)
51	−1	35	Integration of information about the location of the target with information about the limb to be used during reaching movement; PMv activation	Beurze et al. (2007)
44	−7	46	Saccade or reach preparation; PMv active during both tasks	Beurze et al. (2009)
64	10	4	Observation of grasping movements (object grasping) and action end states (object placement); (1) grasping the object and (2) positioning the grasped object differently engaged PMv and PMd	Majdandzic et al. (2009)

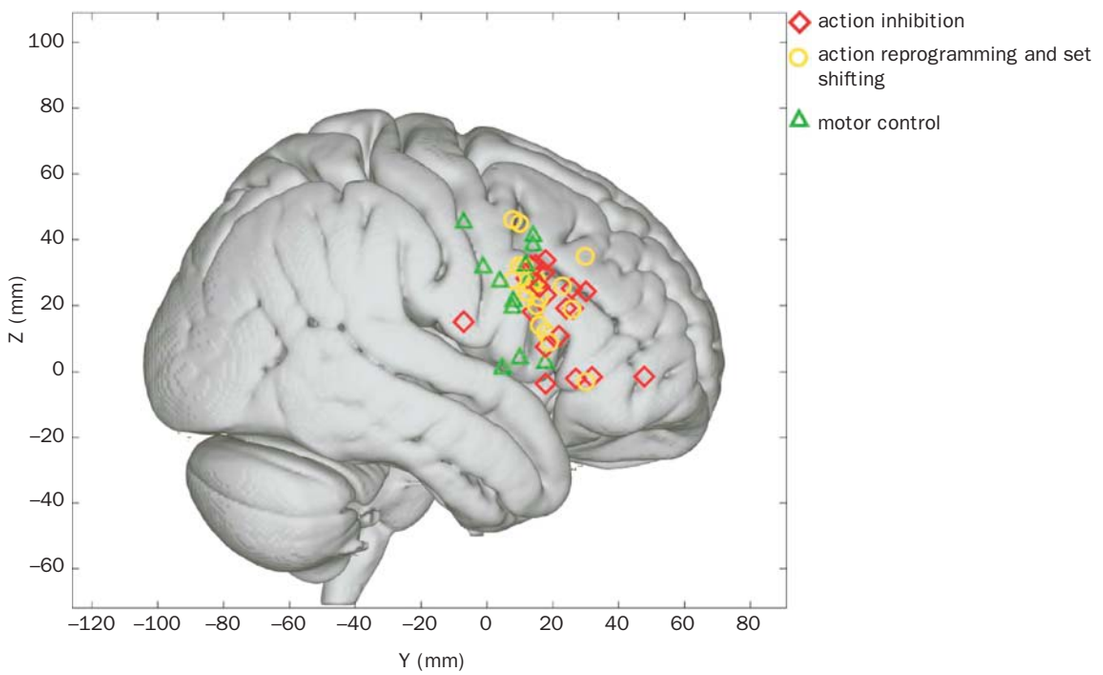

Figure 22–2 The IFG/PMv brain areas that have been related to action *inhibition* [mean (and standard error of MNI coordinates): $x = 46.25$ (1.4065); $y = 18.5$ (1.8517); $z = 15.6$ (2.839)], *action reprogramming and set-shifting* ($x = 44.25$ (1.3512); $y = 16.15$ (1.4837); $z = 21.35$ (2.9703)), and *motor control* ($x = 53{,}3$ (2.1861); $y = 7.1$ (2.2728); $z = 23$ (4.1285)]. Eight of 20 foci related to action inhibition, 12 of 20 foci related to action reprogramming and set-shifting, and all 10 motor control activations are within the 95th percentile of activation likelihood for the PMv (Mayka et al., 2006).

Garavan, Ross, Murphy, Roche, and Stein (2002) found activity related to inhibition in the right middle frontal, inferior precentral, and inferior prefrontal cortex. Activity related to errors was found in pre-SMA and anterior cingulate cortex (ACC). Using a modified stop-signal reaction time (SSRT) task (Figure 22–4). Aron and Poldrack (2006) showed inhibition-related BOLD activity in a network including rIFG and STN (Figure 22–5). Activity of rIFG and STN was correlated across subjects. Moreover, subjects who inhibited more quickly (shorter SSRTs) activated rIFG and STN more strongly. Leung and Cai (2007) conducted an fMRI study in combination with a stop-signal task and showed that IFG is activated during inhibition of both manual and saccadic responses. Aron and colleagues (2007a) have also used fMRI in combination with a SSRT task to identify brain areas active during stopping. They found pre-SMA, rIFG, and STN to be active during response inhibition. Activity of rIFG and STN was correlated with SSRT. Moreover, diffusion- weighted magnetic resonance imaging (DW-MRI) suggested the probable existence of connections between these areas. Such results have been taken as evidence that response inhibition is

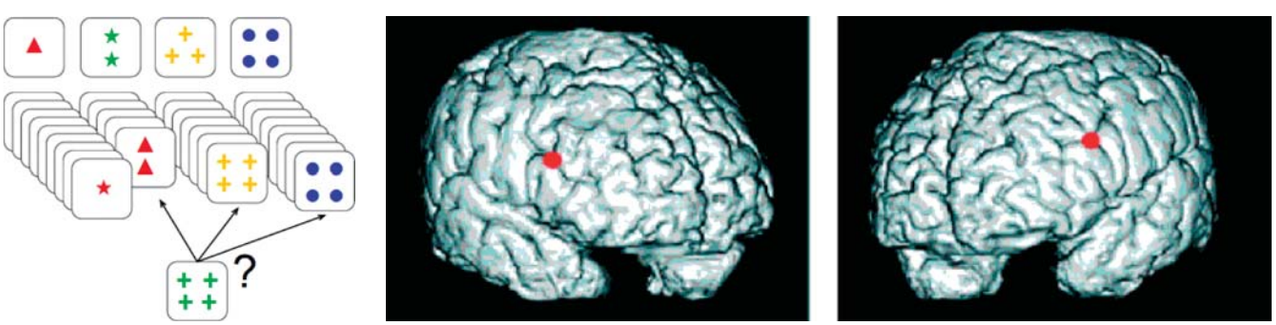

Figure 22–3 The WCST can be used to test perseveration and the ability to shift mental sets. Subjects are asked to sort a deck of cards. These cards show different numbers of different symbols in different colors and can be sorted based on one of three categories: color, shape, and number. However, the subjects are not told the sorting rule but have to deduce it themselves based on "right"/"wrong" feedback. Moreover, sorting rules change once the subject has sorted 10 cards correctly. Typically, patients with lesions to the prefrontal cortex have difficulty switching to a new sorting rule once they have discovered the initial rule. This perseveration of behavior has been interpreted as being caused by loss of inhibitory control that is carried out by areas in the frontal lobes (e.g., IFG). On the right side,activity in the left and right inferior frontal sulci time-locked to the attentional set-shift. Source: From Konishi et al. (1998a) with permission.

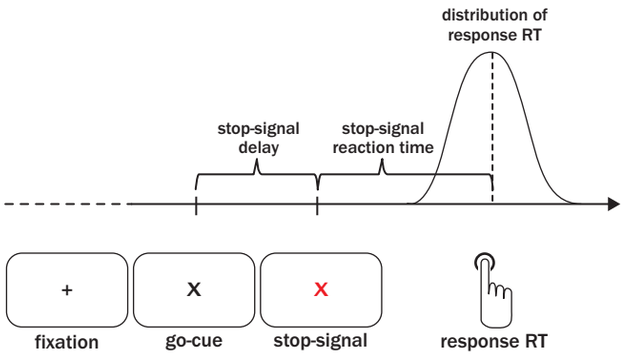

Figure 22–4 In stop-signal trials of the SSRT, the interval between the go cue and stop signal is varied so that the subject is successful in 50% of the stop trials. The interval, which allows the individual subject 50% performance accuracy in stop trials, is called "stop-signal delay" (SSD). The difference between SSD and median reaction time (RT) in go trials is called the "stop-signal reaction time" (SSRT). It is thought to be an index for the duration of the stopping process within the brain. This notion is based on the assumption that stop and go processes are independent processes. Response control has been modeled as a race between the stop and go processes, in which the relative finishing time of these two independent processes determines whether subjects will respond or stop (i.e., the winner takes all). Recent computational modeling, however, has allowed the two processes to interact (not to be fully independent) and has shown that an "interactive race model" best fits the neurophysiological and behavioral data if the stop and go processes are independent for most of their durations and interact strongly for a brief period in their final stages (Boucher et al., 2007; Verbruggen & Logan, 2009).

carried out via a hyperdirect pathway projecting from rIFG to STN (Nambu, Tokuno, & Takada, 2002). In addition, both areas were identified as likely to be connected to the pre-SMA (STN in 7 out of 10 subjects, rIFG in 8 out of 10 subjects). Those findings were interpreted in terms of pre-SMA monitoring response conflict, control demand or uncertainty, and subsequent recruiting of the rIFG-STN inhibitory control system. Swann and colleagues (2009) used electocorticography from subdural electrodes and found that successful stopping in a stop-signal task was associated with a greater rIFG response in the beta frequency band 100–250 ms after the stop signal occurred.

In an ALE meta-analysis, Simmonds, Pekar, and Mostofsky (2008) confirmed the existence of inhibition-related activation in IFG in a number of studies employing complex go/no-go tasks with higher working memory loads, but they also noted that activation is present in adjacent parts of the middle frontal gyrus. In another meta-analysis, Congdon and colleagues (2010) pooled data from five fMRI studies of the SSRT task. They found that activity in a network of brain regions including IFG, but also the precentral gyrus, caudate and putamen, ACC, and superior temporal gyrus, was associated with better stopping ability. Activity in a default-mode network was associated with poorer stopping ability across individuals.

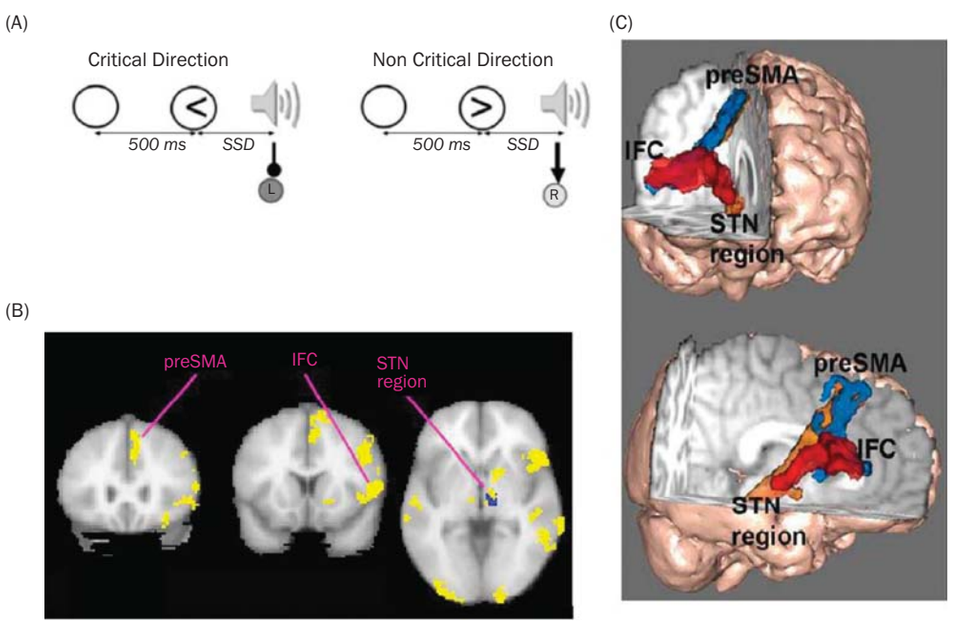

Figure 22–5 The modified stop-signal paradgim used by Aron and colleagues (2007): a conditional stop-signal paradigm. (a) A critical and a noncritical stop trial. On go trials, the subject has 1 s to press a left or right button in response to a leftward- or rightward-pointing arrow stimulus. On a stop trial, a tone is played at the stop signal delay (SSD) after the arrow stimulus. The SSD changes dynamically throughout the experiment. If the arrow stimulus is in the critical direction (in this case leftward) and a tone occurs, then the subject must try to inhibit the response, but if the arrow is in the noncritical direction (in this case rightward) and a tone occurs, this tone can be ignored and the subject must respond anyway. (b) Three-dimensional rendering of tracts defined by DW-MRI and tractotraphy between the right IFC, the right pre-SMA, and the right STN region. (c) Conjunction analysis between fMRI activation induced by two measures of response inhibition: (i) outright inhibition: StopRespond—Go (in the noncritical direction). This image shows loci where there is a parametric increase in activation with increasing reaction time (RT); (ii) conflict-induced slowing: on noncritical trials, separate regressors were created for trials with a stop signal (StopRespond) and trials without it (Go), each parametrically modulated by RT, and the two were compared (StopRespond_parametric—Go_parametric). Each individual group map was itself corrected for multiple comparisons. In the bottom right panel, the anatomical locus of the STN is indicated with a blue region of interest.
SOURCE: Adapted from Aron et al. (2007) with permission.

The IFG may not only mediate the inhibition of an action. It may also be needed if a person is to take an alternative, rather than the default option, during decision making. Fleming, Thomas, and Dolan (2010) suggest that a network including rIFG and STN is involved in overcoming the "status quo bias." When faced with the need to make complicated decisions, we often stick with the default option, even though this might sometimes be the wrong choice. Accepting the default option is suboptimal in that more errors are made when we stick to the status quo. Fleming and colleagues used a detection task in combination with fMRI and an effective connectivity analysis. They found that subjects tended to favor the default option when making difficult but not easy decisions. Activity in STN was increased and rIFG exerted an enhanced modulating influence over STN when the status quo was rejected in difficult decision trials.

LESIONS AND REPETITIVE TMS IN THE IFG

Studies of the effects of lesions in IFG have also been interpreted as supporting a role for this brain region in response inhibition. Iversen and Mishkin (1970) trained monkeys in a go/no-go task. After surgery, monkeys with lesions to the inferior frontal convexity, a region with resemblances to the anterior human IFG areas 45 and 47 (Croxson et al., 2005; Petrides & Pandya, 2002, 2009), made errors primarily on no-go trials. By contrast, control monkeys made similar numbers of errors in the go and no-go trials. In another study, Butter (1969) showed that monkeys with lesions to inferior areas of the frontal lobes performed more poorly than normal monkeys and monkeys with lesions to the dorsolateral prefrontal cortex in a reversal learning task. Similarly, Dias, Robbins, and Roberts (1997) showed that marmoset monkeys with lesions to the inferior convexity had difficulty shifting between stimulus dimensions on a monkey version of the WCST and attributed these shifting difficulties to the loss of inhibitory control. There have been no investigations of the role of the most posterior IFG areas and PMv in response inhibition in the monkey.

Patients with lesions in rIFG have been reported to show impaired stopping performance in the SSRT task (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003). Moreover, the SSRTs were positively correlated with the volume of brain damage in pars triangularis (BA45) and pars opercularis (BA44).

Even when the disruption to the IFG is only of the temporary kind induced by TMS, there is still evidence that response suppression is impaired. Chambers and colleagues (2006) found that temporary disruption of the pars opercularis with repetitive TMS (rTMS) selectively impairs the ability to stop an initiated action in an SSRT task. Disruption of the same region did not affect the ability to execute a response. Critically, TMS to the middle frontal gyrus and the angular gyrus did not significantly alter inhibitory performance. In a follow-up study, Chambers and colleagues (2007) showed that a virtual lesion of rIFG by rTMS impaired stop-signal inhibition especially under conditions of heightened response competition.

IFG: RESPONSE INHIBITION OR ATTENTIONAL CONTROL?

More recently, a number of investigators have begun to explore whether and how factors other than the requirement to suppress a response also influence IFG and pre-SMA activity. It is now clear that IFG activity is also modulated by other task factors, such as the nature of the motivational incentives that are being used. Padmala and Pessoa showed that participants performing an SSRT task exhibited longer SSRTs when they were rewarded for correct "going" (Padmala & Pessoa, 2010). One possibility is that the rIFG is a locus of integration for motivational and executive control processes. In another study, Hirose et al. (2009) tried to disentangle inhibition and feedback processing; both processes have been attributed to IFG. They found two distinct but very close areas within rIFG. An area often referred to as the "inferior frontal junction" (IFJ; Brass, Derrfuss, Forstmann, & von Cramon, 2005a), at the boundary of the inferior precentral sulcus and the inferior frontal sulcus, was active during feedback processing, whereas posterior IFG was active during inhibition.

In this context, there has been particular interest in the possibility that IFG activation might reflect the operation of attentional processes that are instigated by the presentation of the infrequent and salient stop cue rather than the subsequent process of response inhibition that is actually instructed by the stop cue. One way this has been addressed has been by measuring functional connectivity between brain areas using fMRI data and employing Granger causality analyses (Duann, Ide, Luo, & & Li, 2009). According to Duann and colleagues, rIFG is simply part of the ventral attention system, activated in response to the detection of a salient target stimulus, particularly when the stimulus is behaviorally relevant. Therefore, rIFG might respond specifically to no-go stimuli, because they constitute highly salient and relevant stimuli. Right IFG only serves to detect no-go signals and subsequently "energizes" pre-SMA, which then exerts inhibitory motor control via the STN (Duann et al., 2009). Sharp and colleagues (2010) came to a similar conclusion after using a stop-signal task designed to dissociate attentional capture, response inhibition, and error processing. The authors argued that IFG supports attentional capture, whereas pre-SMA inhibits the ongoing action.

By contrast, although they also relied on functional connectivity indices, Kounieher and colleagues came to the opposite conclusion about the order in which pre-SMA and IFG are active, at least during rule-guided decision making

and action selection (Kouneiher, Charron, & Koechlin, 2009). They argue that pre-SMA detects motivationally salient stimuli and subsequently energizes rIFG to increase executive control.

In summary, while initially there seems wide agreement that IFG and pre-SMA are active when cognitive control must be exerted and when responses must be inhibited, there is disagreement about exactly what role is played by IFG. It is possible that several component processes occur within different parts of the IFG. In a recent study, Chikazoe and colleagues (Chikazoe et al., 2009a) tried to dissociate activity related to stimulus saliency and activity related to response inhibition: they used a modified go/no-go task with frequent go, infrequent no-go, and infrequent go cues. Infrequent cues elicited activity in IFJ, anterior prefrontal sulcus, and posterior intraparietal sulcus. Response inhibition-related activity was found in posterior IFG, dorsolateral prefrontal cortex, ACC, and pre-SMA. The IFG might therefore contain at least two functionally distinct subregions: IFJ, which was activated when infrequent stimuli occurred, and posterior IFG, which was active when the subjects had to inhibit prepared movements. These areas were extremely close but nevertheless separable on an individual subject level.

In a recent study, Verbruggen, Aron, Stevens, and Chambers (2010) showed that disruption of rIFG with theta burst TMS impaired stop performance, suggesting that rIFG is critical for stopping a response. Moreover, disruption of the right IFJ slowed the detection of behaviorally salient cues, again suggesting that the right IFJ is crucial for the visual detection of infrequent changes in task-relevant stimulus features.

Part of the reason for a lack of consensus about the function of IFG may also be that, although many studies have used similar behavioral paradigms, such as the go/no-go task or the stop-signal task, there has been disagreement about which task and trial comparisons should be used to isolate neural processes related to inhibition. Often successful stopping is contrasted with unsuccessful stopping (Duann et al., 2009; Li, Huang, Constable, & Sinha, 2006; Rubia, Smith, Brammer, & Taylor, 2003). However, response inhibition is almost certainly present in both successful and unsuccessful stop trials, although it might be more pronounced, or at least faster, in successful stop trials. Sometimes stop trials (all stop trials or successful stop trials) are compared to go trials (e.g., Aron et al., 2007a; Pliszka et al., 2006; Ramautar, Slagter, Kok, & Ridderinkhof, 2006). But stop trials differ greatly from go trials in such important characteristics as their sensory stimulation and the frequency with which they occur.

IFG: PREDICTION AND REPROGRAMMING

Part of the appeal of attempting to identify the neural basis of response inhibition is that response inhibition appears, at least initially, to be a simple and unitary computational function. Whether it is realistic, however, to imagine that a single brain region might have evolved only to act as a brake on the activity of other regions is less clear. An alternative way to think about response inhibition is within the larger framework offered by predictive coding accounts of brain function (Friston, 2005; Rushworth, Mars, & Summerfield, 2009).

Recently, the notion that our brains are "proactive," that is, constantly making predictions about the environment and decision outcomes and revising future predictions in the light of the "prediction error"—the discrepancy between actual events and prior predictions (den Ouden, Daunizeau, Roiser, Friston, & Stephan, 2010; den Ouden, Friston, Daw, McIntosh, & Stephan, 2009; Friston, 2005; Rushworth et al., 2009)—has gained considerable ground. In the real world outside the psychology laboratory, people are faced with uncertainty and therefore rely on their predictions about future events, their own actions, and the actions' likely outcomes. In addition, they make predictions about the uncertainty or risk of their predictions (Preuschoff, Bossaerts, & Quartz, 2006; Preuschoff, Quartz, & Bossaerts, 2008). Executive and inhibitory control over action can be understood within this framework as a mechanism for exploiting such predictions in the guidance of behavior and for adjusting behavior when the predictions prove incorrect (Neubert & Klein, 2010).

According to this perspective, it might be thought that brain mechanisms will attempt to exploit statistical regularities in the environment in order to predict the actions that will be needed next. Actions could then be prepared in advance of their trigger cues and then made quickly and efficiently. If there was considerable certainty about the actions that will be needed, then there would be the potential for preparatory programming of actions. If, however, there was a prediction error and an unexpected event occurred, then the actions would have to be reprogrammed. An alternative possibility, therefore, is that IFG is part of a mechanism for making action predictions but also for detecting when there have been prediction errors and action reprogramming is needed.

Some evidence in favor of such an alternative account of IFG function comes from Chikazoe et al. (2009b), who used a modified stop-signal task with "uncertain" go cues (normal go cues that were in 20% of the trials followed by a stop signal) and "certain" go cues (go cues that were never followed by a stop signal). This enabled the authors to investigate the effect of the certainty with which the movement was prepared and the possible "precautionary" preparation of the need to inhibit a response. It was found that in situations where a go signal could potentially be followed by a stop signal (uncertain go), participants responded more slowly than on certain go trials. The areas more active for uncertain compared to certain go cues were the pre-SMA, IFJ, and insula. Compared to uncertain go

trials, successful inhibition was associated with more activity in the pre-SMA, the insula, and, among other areas, the posterior IFG.

It is now clear that IFG encodes information about at least some statistical regularities of the stimuli that subjects encounter. Vossel, Weidner, and Fink (2010) measured IFG activity in a combined oddball and location cueing paradigm and found that IFG activity on invalidly cued trials reflected the number of previous trials in which the cues had been valid. However, a negative modulation of the IFG BOLD signal, as a function of the number of previous valid cues, was also apparent on validly cued trials. In other words, IFG reflects not only the need to change or inhibit a response but also information about how necessary such response changes have been in the past. Huettel, Song, and McCarthy (2005) have also reported that activity in IFG, together with other frontal and parietal areas, increased with the uncertainty under which a decision was to be made.

Other studies have suggested IFG to be more generally involved in action reprogramming, attentional reorienting, information updating, task switching, and motor control. A study by Mars, Piekema, Coles, Hulstijn, and Toni (2007) investigated action reprogramming and tried to control for (1) the frequency of occurrence of the stimuli (as in Chikazoe et al., 2009a), (2) attention to action, and (3) the presence of an instructive and action-relevant stimulus. They found an area close to IFJ with activity that was associated with response inhibition and suggest that both IFG and pre-SMA might be better characterized as involved in response selection in the context of ongoing movement plans. One possibility is that the IFG, together with pre-SMA and other frontal and parietal areas, constitute a network that represents and rapidly updates inputs and responses that form the currently relevant task schema (Bode & Haynes, 2009; Brass et al., 2005a; Dosenbach et al., 2006; Hampshire et al., 2010). A number of other studies have also recently reported that IFG and pre-SMA are active not just when subjects have to stop themselves from making a response but also when they have to switch from one response to another (Goghari & MacDonald, 2009; Kenner et al., 2010). Verbruggen and colleagues (2010) also observed that rIFG disruption impaired action reprogramming.

PRE-SMA AND INHIBITION

Although pre-SMA activation has been reported in several studies in which subjects inhibit or change responses (Brass & von Cramon, 2002; Forstmann, van den Wildenberg, & Ridderinkhof, 2008b; Isoda & Hikosaka, 2007; Li et al., 2006; Mars et al., 2009; Nachev, Rees, Parton, Kennard, & Husain, 2005; Passingham, Stephan, & Kotter, 2002; Rushworth, Hadland, Paus, & Sipila, 2002; Sumner et al., 2007), it has long been clear that the pre-SMA is involved in other aspects of high-level movement control, such as action sequencing (Tanji, 2001) and task initiation and switching (Braver & Barch, 2006; Dosenbach et al., 2006). During action sequencing, it seems that the pre-SMA is most active during initiation of the sequence and at transition points between component parts of the sequence (Kennerley, Sakai, & Rushworth, 2004; Rushworth, Walton, Kennerley, & Bannerman, 2004; Shima, Mushiake, Saito, & Tanji, 1996).

Even though the medial frontal cortex and IFG are often coactivated, there has been particular interest in the role that the medial frontal cortex plays not just when an action has to be inhibited but also in situations in which stimuli in the environment might afford more than one action, which then compete for selection. According to one influential view, medial frontal cortex detects and monitors conflict between representations of actions that might be made and then subsequently recruits lateral prefrontal cortex areas to control the manner in which actions are selected on subsequent occasions (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Kerns et al., 2004; Miller & Cohen, 2001).

It is, however, clear that at least one area in the medial frontal cortex, the pre-SMA, exerts a relatively short-latency influence over action representations in M1. Direct evidence that this is the case comes from a study (Figure 22–6) in which TMS was applied to the pre-SMA at the same time that electroencephalographic (EEG) recordings were made from M1 (Taylor, Nobre, & Rushworth, 2007). The subjects were performing a "flanker" task in which they had to respond with left or right hand movements that were instructed by arrows pointing to the left or the right. Flanking arrows were also presented, and on "incongruent" trials these pointed in the opposite direction to the central arrow. In other words, on incongruent trials, the flanking arrows afforded conflicting responses. The conflict between response representations can be measured with an event-related potential (ERP) measure called the "lateralized readiness potential" (LRP) that indexes how much more active is one M1, the one that should execute the response indicated by the central arrow, than the other M1. The opposite M1 is more active on incongruent trials, suggesting that a conflicting response to the flanking arrows is prepared. Crucially, disruption of pre-SMA with TMS within less than 200 ms augmented the relatively greater activation of the M1 associated with the wrong response but only on incongruent trials. In other words, disruption of pre-SMA led to a failure to activate the correct response at the expense of the incorrect response on incongruent trials.

Despite some discrepant reports (Verbruggen et al., 2010), both lesions and TMS investigations have also implicated the pre-SMA in similar cognitive processes. Nachev and colleagues (Nachev et al., 2008; Nachev,

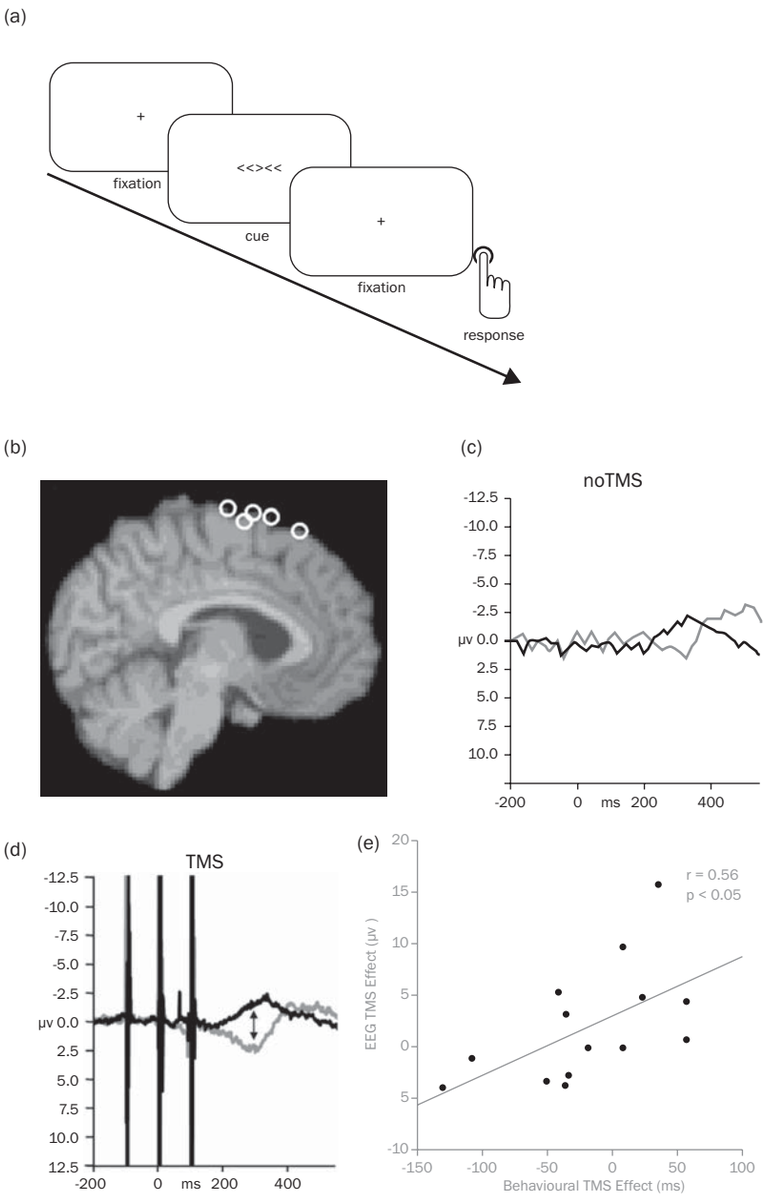

Figure 22–6 (a) In the Eriksen flanker task, the participant is asked to respond to a central stimulus (e.g., a rightward-pointing arrow with a right button press) flanked by distracting stimuli (e.g., leftward-pointing arrows) that are to be ignored when selecting a response. Trials are called "congruent" if all stimuli (the central stimulus and surrounding "distractors") cue the same response. Trials are called "incongruent" if the distractors cue a different response from the central stimulus. Subjects normally have a shorter RT and more accurate performance in congruent compared to incongruent trials. (b) Left pre-SMA TMS site. The circles represent the MNI coordinates at which TMS was applied over left pre-SMA in a subset of the subjects from Experiment 1 (mean $x = -5$, $y = 7$, $z = 73$). The circles are superimposed over the brain of an example subject that had also been registered in MNI space. The site is just left of the midline and over tissue normally assigned to the pre-SMA. (c) On no-TMS congruent trials (black) there was a clear negative deflection in the LRP (negative is plotted upward for the LRP) indicative of the preparation of correct responses, peaking at approximately 300 ms. On incongruent trials (gray) the waveform was instead displaced in the positive direction associated with the preparation of the wrong response. The negative deflection associated with the correct response was delayed. (d) When pre-SMA TMS was applied, there was a significant increase in the difference between the waveforms recorded on congruent and incongruent trials starting at 180 ms. This was due to pre-SMA TMS causing a positive deflection in the LRP on incongruent trials. (e) Positive correlation between pre-SMA TMS effects on behavior and the LRP. The effect of pre-SMA TMS on conflict resolution was calculated for both behavior and the LRP as $TMS_{incongruent\text{-}congruent}$-$noTMS_{incongruent\text{-}congruent}$. Subjects who showed the strongest effects of TMS on the behavioral measure of conflict also showed the strongest effects on the LRP measure of conflict.

SOURCE: Adapted from Taylor et al. (2007) with permission.

Wydell, O'Neill, Husain, & Kennard, 2007) reported deterioration of the ability to inhibit ongoing movement plans in a patient with a rare lesion involving the pre-SMA but sparing the supplementary motor area (SMA) proper. Rushworth and colleagues (2002) showed that online TMS over pre-SMA disrupted performance of a response-switching task. Chen, Muggleton, Tzeng, Hung, and Juan (2009) used online (rTMS) in combination with a stop-signal task and showed that TMS delivered over the pre-SMA impaired performance in stop-signal trials.

While the brain stimulation furnished by TMS, particularly rTMS, is likely to disrupt response inhibition, focal microstimulation of a small part of the pre-SMA might be expected to facilitate response inhibition. This is exactly what was reported by Stuphorn and Schall (2006), although they did not investigate the pre-SMA itself but rather an adjacent and interconnected region called the "supplementary eye field" (SEF; Wang, Isoda, Matsuzaka, Shima, & Tanji, 2005). They trained macaques to perform a saccadic SSRT task. In many instances, SEF microstimulation was associated with a higher probability of countermanding the saccade when the stop signal was presented even though it had no impact on go trial performance. Isoda and Hikosaka (2007, 2008) have reported related effects in an action-selection paradigm that was investigated while recording and microstimulating neurons in the pre-SMA itself. They trained macaques to make saccades to yellow or purple squares shown on the left or right of a central fixation point. The fixation point turned either yellow or purple and instructed the monkeys to make a saccade to the similarly colored peripheral square. Animals' reaction times (RTs) decreased when the central cue color remained the same over the course of several trials but increased on trials when the color switched. Again, Isoda and Hikosaka found that pre-SMA neurons often coded for one direction of response or the other (Figure 22–7), but in addition, the activity of a number of pre-SMA neurons changed on switch trials. Although pre-SMA microstimulation was found to affect RT on both switch and nonswitch trials, it only affected the likelihood of performing the correct action on switch trials.

INHIBITION OF M1

At a physiological level, inhibition might be expected to refer to the causal influence exerted by region A on region B, whereby region A decreases the excitability and output firing of region B. In contrast, in cognitive models of behavior, inhibition is described as"the suppression of previously activated cognitive contents, or processes, the clearing of irrelevant actions or attention from consciousness, and the resistance to interference from potentially attention-capturing processes or contents" (Aron, 2007, p. 216, 2nd column as taken from Harnishfeger, 1995). It has been unclear how well inhibition at the behavioral and cognitive levels corresponds to physiological inhibition.

In the case of the motor system, it is obvious what, at a neurophysiological level, must ultimately be inhibited if an action is to be stopped—the output firing and the excitability of the corticospinal tract. Corticospinal excitability can be studied by applying single pulses of TMS to M1. A single suprathreshold TMS pulse applied over M1 causes direct and transsynaptic excitation of corticospinal neurons, which in turn affect the corresponding spinal motoneuron pools, resulting in activity in the muscles of the body part associated with the part of M1 that was stimulated. Moreover, the balance of excitatory and inhibitory circuit activity within M1 can be studied by applying pairs of pulses to Ml. If the first pulse (often referred to as a "conditioning" pulse) that is applied is below the threshold for eliciting muscle activity, it may still have a modulating influence on the effect of a second suprathreshold "test" pulse in producing a motor evoked potential (MEP). The MEP induced by the M1 test pulse might be either facilitated or inhibited by the prior conditioning pulse, although the precise effect depends on the interpulse interval and the conditioning pulse intensity (Hallett, 2007; Reis et al., 2008; Rossini & Rossi, 2007; Wasserman et al., 2008). The impact of the conditioning pulse can be quantified by calculating the ratio between paired-pulse TMS MEP size (MEP recorded after conditioning and the test pulse) and single-pulse TMS MEP size (MEP recorded after the test pulse), with values smaller than 1 (or 100%) indicating inhibition and values bigger than 1 indicating facilitation.

Corticospinal excitability increases progressively in the 80–120 ms before movement onset (Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000). This increase is preceded by a "release" from previously higher levels of intracortical inhibition, as indexed by the conditioning influence of one M1 pulse on another pulse, which persists during action execution (Reynolds & Ashby, 1999; Stinear, Coxon, & Byblow, 2009). Corticospinal excitability and intracortical inhibition are also modulated in tandem with response signal expectancy and uncertainty (Bestmann et al., 2008; Sinclair & Hammond, 2008; van Elswijk, Kleine, Overseem, & Stegeman, 2007). Both corticospinal excitability and intracortical inhibition are also modified in a muscle-specific way during movement selection and initiation; MEPs were found to be suppressed in muscles not required for a task, and inhibition was found to be increased (Stinear et al., 2009; van den Hurk et al., 2007). In go/no-go paradigms, MEPs are facilitated in go trials 50 ms prior to movement onset and suppressed in no-go trials 250 ms after the no-go cue (Hoshiyama et al., 1997; Leocani et al., 2000). Such inhibitory effects appear to have no muscle specificity and were observed even in hand muscles close to, but not involved in, the prepared action. Intracortical inhibition has been shown to be enhanced in no-go trials and released in go trials (Coxon, Stinear, &

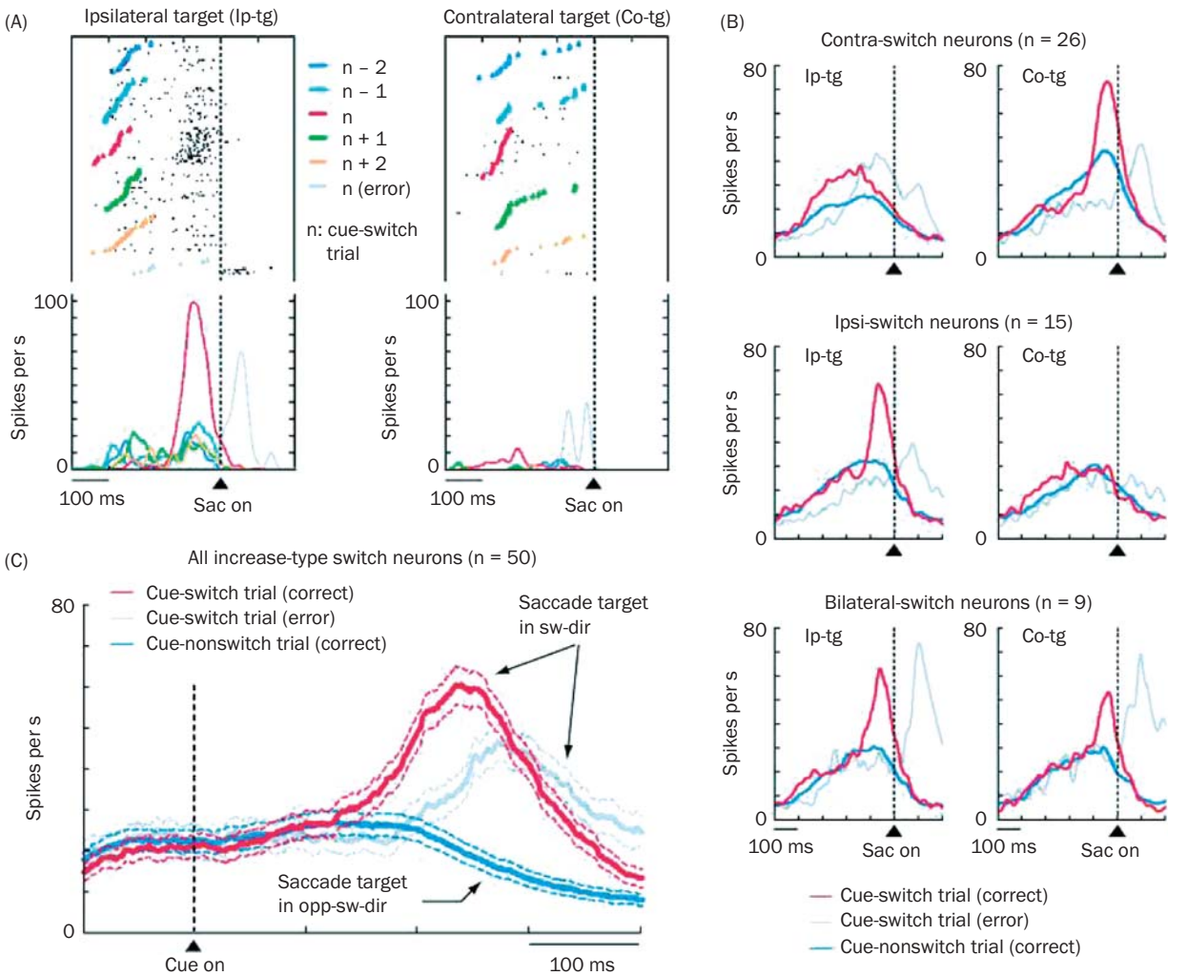

Figure 22–7 Switch-selective activity of pre-SMA neurons. (a) Activity of a single "ipsi-switch" neuron—a neuron with greater activity when saccades were made to the same side as the hemisphere in which recordings were made. Rastergrams and spike density functions (SDFs) are sorted according to the trial position in each block (n represents the cue-switch trials) and aligned with saccade onset. In rastergrams, black dots indicate the time of individual action potentials, and colored triangles indicate the time of cue onset; trials are arranged in order of saccadic RTs. Activity in switch-error trials is shown in gray. (b) Ensemble average SDFs for contra-switch neurons (top), ipsi-switch neurons (middle), and bilateral-switch neurons (bottom) shown separately for the correct cue-switch trials (red), correct cue-nonswitch trials (blue), and switch error trials (gray). All SDFs are aligned with saccade onset. (c) Ensemble SDFs (mean ± SD) for all increase-type switch neurons. The SDFs are aligned with cue onset. Note that the direction of the saccade target on the cue-switch trials, in a given panel, is opposite that of the saccade target for the cue-nonswitch trials with which they are compared in the same panel. SOURCE: Reprinted from Isoda and Hikosaka (2007) with permission.

Byblow, 2006; Sohn, Wiltz, & Hallett, 2002; Waldvogel et al., 2000).

These changes in M1 excitability and in intracortical inhibitory and excitatory circuits are likely to be influenced by input from other brain areas; there is certainly evidence that M1 corticospinal activity changes, and that it does so in a temporally specific and task-specific manner, when conditioning pulses are applied over premotor cortex during action selection (Boorman, O'Shea, Sebastian, Rushworth, & Johansen-Berg, 2007; Buch et al., 2010; Davare, Rothwell, & Lemon, 2006; Koch et al., 2006, 2010; Mars et al., 2009; O'Shea, Sebastian, Boorman, Johansen-Berg, & Ruthworth, 2007). In the next section, we describe experiments that investigated whether and how induced IFG and pre-SMA activity leads to changes in inhibition in M1 in during action reprogramming.

THE IFG–PRE-SMA NETWORK AND ITS ROLE IN SELECTION AND REPROGRAMMING OF ACTIONS

In a recent series of studies, Neubert and Mars used a combination of techniques to characterize the interactions of several cortical regions, including IFG, pre-SMA, and M1, during response inhibition and action reprogramming (Mars et al., 2009; Neubert, Mars, Buch, Olivier, & Rushworth, 2010) and to study the underlying anatomical

networks involved. Paired-pulse TMS was used to characterize the interactions between rIFG and pre-SMA with M1 during normal action selection and action reprogramming. Mars and Neubert and colleagues then used DW-MRI to investigate the anatomical networks that support these interactions. This combination of paired-pulse TMS and DW-MRI approach was aimed at addressing two issues. The first is the relationship between inhibition on a cognitive level and inhibition on a neurophysiological level. It is often argued that IFG or pre-SMA exerts an inhibitory influence over other brain regions, but it has been difficult to establish how this is to be understood in neurophysiological terms. Although it has been suggested that IFG might implement executive control by exerting inhibitory physiological influences over other brain areas, including M1, the degree to which inhibition of action at a behavioral level can be related to inhibition at a physiological level has been difficult to ascertain. The second issue is the anatomical routes mediating functional connectivity between IFG, pre-SMA, and M1 during action inhibition and whether these are simply cortico-cortical routes or whether they run via one of the basal ganglia pathways (Figure 22–1).

To investigate functional rIFG-M1 and pre-SMA–M1 connectivity, Neubert and Mars and colleagues (2009, 2010) used a paired-pulse TMS paradigm in combination with a simple action reprogramming task (Figure 22–8) adapted from the one previously used by Isoda and Hikosaka (2007, 2008; Figure 22–7). This task required participants to either execute a prepared response ("stay trials") or to reprogram the action by inhibiting a prepared response and executing another alternative response ("switch trials"). On some trials, a TMS test pulse was applied over M1 and the resulting MEP provided an index of corticospinal excitability. On other trials, the M1 TMS pulse was preceded by another prior TMS pulse to either the IFG or the pre-SMA. The first pulse altered the impact that the second pulse had; it either increased or decreased the impact of the second pulse. The influence of the first pulse over the second M1 TMS pulse changed, depending on the behavioral context, and indexed the nature of the underlying interactions between the two areas. The changes depended on the anatomical area over which the conditioning pulses where delivered, on whether the pulses were delivered on switch trials or on stay trials, and on exactly when the pulses to the two areas were delivered with respect to the cues that instructed movement.

Several important differences were found in the way pre-SMA and IFG influenced M1 corticospinal excitability. First, it was found that TMS delivered over the pre-SMA modulated the MEPs 125 ms after presentation of a switch stimulus, whereas TMS over rIFG modulated the amplitude of MEPs 175 ms after the switch stimulus (Figure 22–9). Hence, pre-SMA influence on M1 excitability occurred earlier in the time course of action reprogramming than rIFG influence on M1.

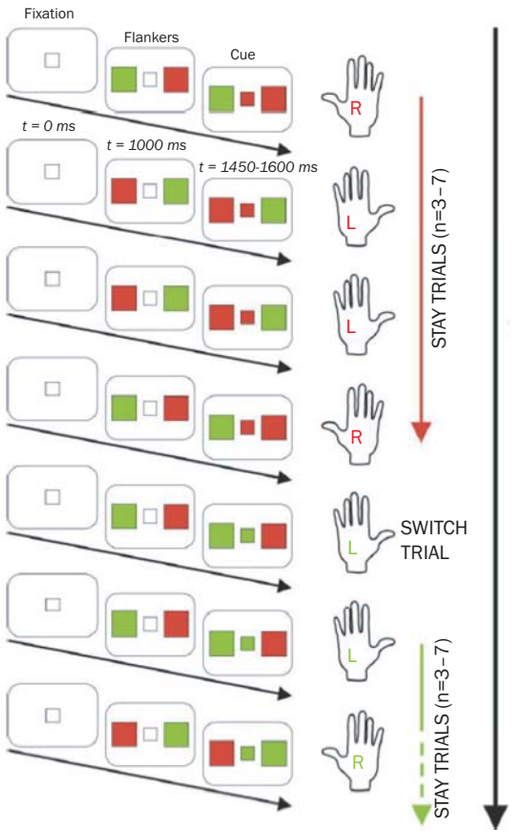

Figure 22–8 A response switching task developed by (Isoda & Hikosaka, 2007) was used in the paired-pulse TMS studies investigating rIFG/M1 and pre-SMA/M1 functional connectivity (Mars et al., 2009; Neubert et al., 2010). Each trial started with the presentation of two red and green flankers. A center cue taking the color of one of the flankers appeared 450–600 ms later. Participants had to respond with the index finger of the hand on the side of the congruent flanker color. The center cue took the same color for trains of three to seven trials. Hence, on each trial, participants could prepare a movement based on their knowledge of the identity of the center cue on the previous trial. However, after taking the same color for a series of trials (stay trials), the center cue color changed (switch trials). In stay trials the participants could exert the already prepared response. In switch trials participants had to inhibit the already prepared response and reprogram their action plans.

While both pre-SMA and rIFG exerted different patterns of influence over M1 corticospinal excitability during execution of prepared actions and during action reprogramming, it was notable that only IFG exerted a clear inhibitory influence during reprogramming on switch trials (Figure 22–9). Inferior frontal gyrus exerted an inhibitory influence over M1 in both hemispheres only during reprogramming, both over the M1 that controlled the hand that was to be stopped and the other M1. By contrast, pre-SMA stimulation led to facilitation of M1 corticospinal excitability during action reprogramming. There was some evidence that the representation of the action toward which subjects were switching was more facilitated than the representation of the action from which they were switching (Mars et al., 2009). In other words, pre-SMA TMS pulses

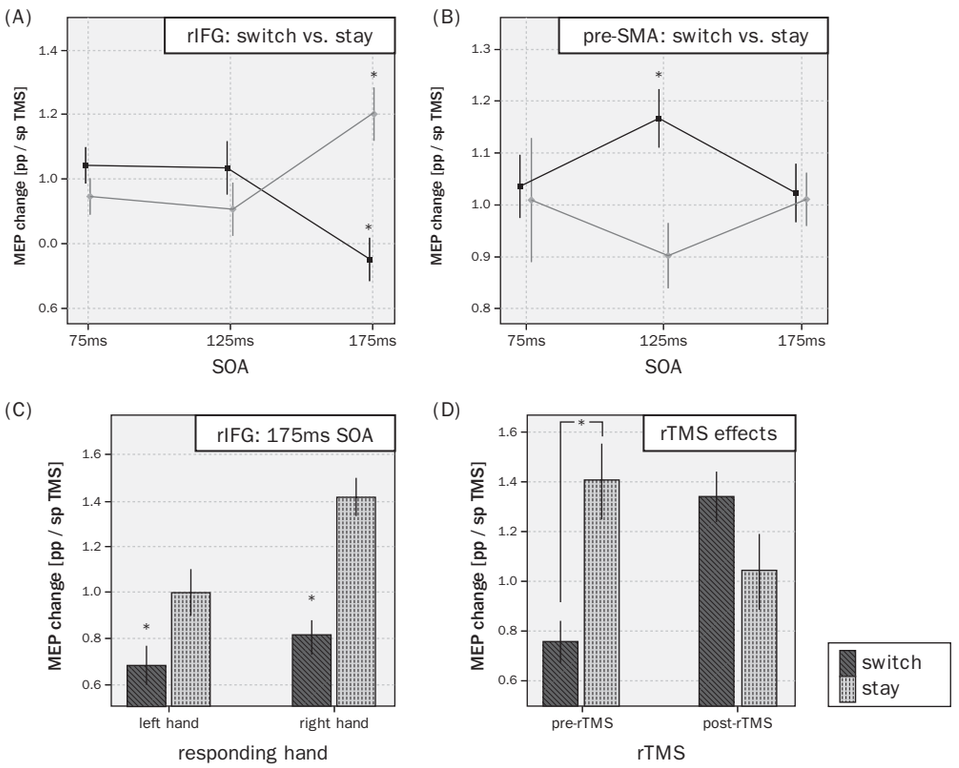

Figure 22–9 (a) Time course of rIFG/M1 interactions. Paired-pulse/single-pulse TMS MEP ratios are plotted for each stimulus-onset asynchrony (SOA) between central fixation color change and TMS delivery. Plotted MEP ratios are for switch (gray) and stay (black) trials pooled over both hands (both data from trials on which the hand that is contralateral to the M1 TMS coil responds and data from trials on which the hand ipsilateral to the TMS coil responds). (b) Time course for pre-SMA/M1 interactions shown using the same conventions. (c) Right: IFG/M1 interactions are shown separately for trials in which right and left hand responses were executed. The subjects' right hands were contralateral to the M1 over which one of the coil was placed, but similar inhibitory effects are seen on switch trials on which either hand is used to respond (black bars). The facilitatory effect of rIFG TMS (gray bars) was greater for the right hand (the hand contralateral to the M1 TMS). (d). Bar graphs shows rIFG/M1 interactions before (left) and after (right) 15 min of 1 Hz TMS over pre-SMA. The pattern of facilitatory and inhibitory rIFG effects on switch and stay trials (black and gray bars) was replicated prior to pre-SMA TMS (left) but not after pre-SMA TMS (right). Asterisks indicate significant modulations from the single-pulse baseline.

SOURCE: Adapted from Mars et al. (2009) and Neubert et al. (2010) with permission.

increased the corticospinal excitability of the M1 that controlled the hand that subjects were switching toward more and at a more precisely defined time point than it did in the M1 that controlled the hand that had been prepared and that subjects were no longer going to use to respond. The difference, however, was small.

Importantly, even IFG did not have only an inhibitory role. When subjects executed prepared actions, on stay trials as opposed to switch trials, IFG facilitated M1 corticospinal activity in a selective manner; it facilitated the prepared motor representation; it increased M1 corticospinal activity in the hemisphere contralateral to the movement that had been prepared because it had been made on previous trials.

Although, as mentioned above, there was no evidence that pre-SMA itself directly inhibited M1 corticospinal activity, it was found that the inhibitory influence of IFG during reprogramming on switch trials depended on the pre-SMA. When rTMS was directed over the pre-SMA, so as to disrupt its function, IFG no longer exerted the same clearly distinct inhibitory and facilitatory influences over M1 during reprogramming and prepared action execution (Figure 22–9).

Neubert, Mars, and colleagues then went on to correlate individual differences in paired-pulse TMS effect sizes with individual difference in fractional anisotropy (FA) in the DW-MRI scans. Fractional anisotropy is a measure of the degree to which the diffusion of water in a voxel in the brain is greater in one direction than in another. Water diffusion is known to be directionally dependent in brain white matter because it is less restricted along the neuron fiber axis than across it (Johansen-Berg & Rushworth, 2009). Previous studies have shown that FA shows topographically specific correlations with certain skills, such as reading ability, visuospatial attention, and mental object rotation (Bengtsson et al., 2005; Klingberg et al., 2000; Tuch et al., 2005; Wolbers, Schoell, & Buchel, 2006). Rather than correlating FA with a behavioral measure, Neubert, Mars, and colleagues correlated it with the MEP ratio as an index of the functional interactions between brain regions. The rationale behind the analysis is that

a stronger white matter tract, reflected in a higher FA value, results in a stronger influence of one brain region on another, reflected in a higher MEP ratio (i.e., stronger inhibition or facilitation of M1 by the frontal area).

Neubert, Mars, and colleagues found evidence for short-latency and long-latency influences on M1 being exerted by both pre-SMA and rIFG. The short-latency influences were apparent when the conditioning pulse over IFG/pre-SMA and the M1 test pulse were applied with an interpulse interval of 3–6 ms, while the long-latency influences were apparent with interpulse intervals of 9–18 ms (Figure 22–10). The short- and long-latency effects appeared to depend on different mechanisms because they were uncorrelated in size across individuals. Short-latency pre-SMA-M1 and rIFG-M1 functional connectivity was correlated with FA in dorsomedial and inferior frontal white matter, respectively, suggesting that short-latency connectivity was likely to be mediated by relatively direct cortico-cortical projections. By contrast, long-latency pre-SMA/M1 and rIFG/M1 interactions were correlated with FA in the white matter surrounding the basal ganglia adjacent to the GPi and STN (Figure 22–10).

CONCLUSIONS

The notion that frontal cortex exerts an inhibitory influence over more posterior brain areas seems to have an enduring appeal for cognitive neuroscientists and is frequently invoked as an explanation of the role of the frontal cortex in cognitive tasks (Anderson et al., 2004; Depue, Curran, & Banich, 2007; Tsushima, Sasaki, & Watanabe, 2006). Within the frontal cortex two regions, IFG and pre-SMA, stand out as being especially closely associated with the inhibition of actions. The critical IFG region may be quite posterior and close to, or a part of, PMv. Testing whether or not these areas actually exert an inhibitory influence over activity in other brain areas has only recently become possible, and it is now clear that IFG does indeed inhibit M1 when actions have to be stopped. However, it also exerts a pronounced facilitatory influence over M1 when prepared actions are to be executed. Although a normally functioning pre-SMA is needed for IFG to exert differential facilitatory or inhibitory influences over M1, depending on the current need for action reprogramming, it does not itself directly inhibit M1.

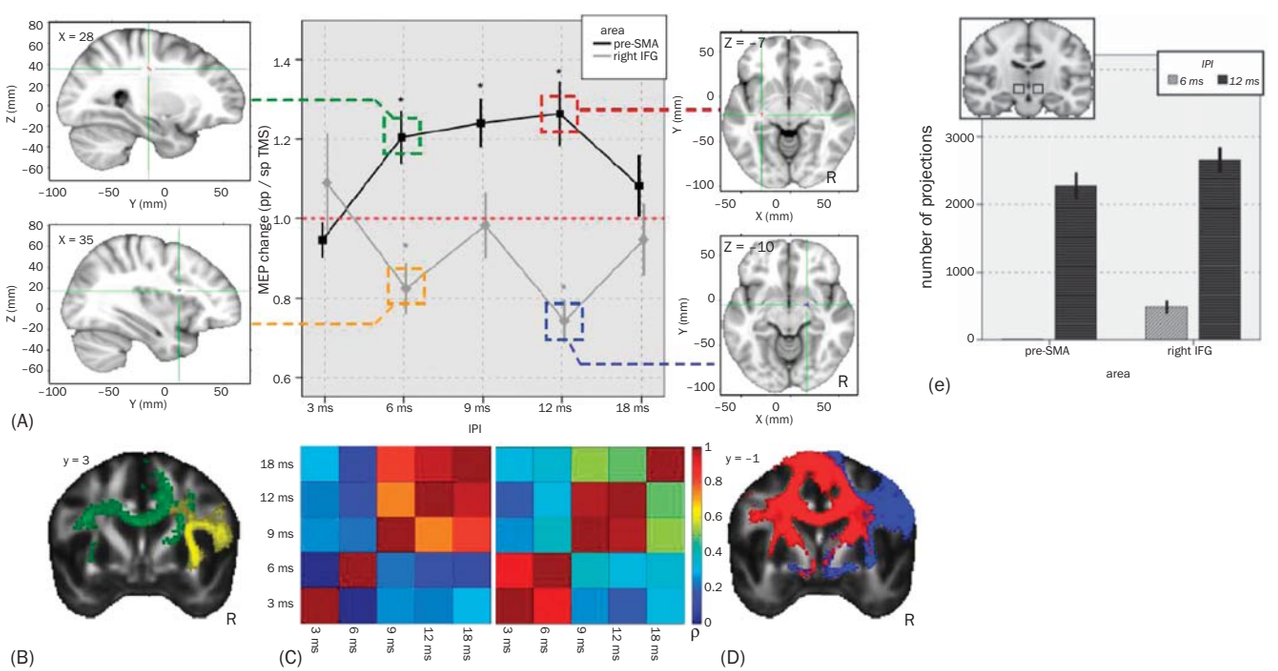

Figure 22–10 (a) Pre-SMA- M1 (black) and rIFG- M1 (gray) MEP ratios during action reprogramming at different TMS interpulse intervals (IPIs) plotted for right-hand responses only (asterisks indicate significant modulation from the single-pulse baseline). Clusters showing significant correlations between individual FA and MEP effect sizes are displayed on the MNI brain (pre-SMA, green 6 ms and red 12 ms; rIFG, yellow 6 ms and blue 12 ms). (b) Comparison of two connectivity networks derived from the pre-SMA (green) and the rIFG (yellow) at 6 ms ITI, showing dorsomedial cortical white matter. (c) Cross-correlation matrices for pre-SMA/M1 (left) and rIFG/M1 (right) functional connectivity effects at different IPIs. Paired-pulse–single-pulse TMS MEP effects are correlated across different IPIs and plotted with their Pearson correlation coefficient. The 6 and 12 ms effects are sufficiently uncorrelated to be separate regressors in a multiple regression model. (d) Comparison of two composite connectivity networks derived from pre-SMA (red) and rIFG (blue) at 12 ms IPL, showing white matter in the vicinity of the GPi and the STN. (e) The bars show the number of connections, estimated from probabilistic diffusion tractography, that passed through the STN ROIs (top). Tracts are derived from clusters of significant correlation between FA and TMS effect size in the same experiment shown in panel A (pre-SMA left, rIFG right) and the two different IPIs (light gray = 6 ms, dark gray = 12 ms). It can be seen that tracts were significantly more likely to pass through or near STN at the 12 ms IPI only.

Even in the case of the pre-SMA and IFG, it may be helpful to think of the action of these frontal areas not so much as a brake that might be exerted over processing occurring elsewhere in the brain but rather as part of a predictive coding mechanism in the action domain. The pre-SMA and IFG exploit statistical regularities and other information in the environment in order to prepare actions that are likely to be needed soon in addition to reprogramming actions when the predictions prove to have been in error.

DISCLOSURE STATEMENT

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