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Functional Topography for Stimulus-Driven Control of Response Inhibition in Human Inferior Frontal Gyrus

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Abstract of the Dissertation
Functional Topography for Stimulus-Driven Control of Response Inhibition in Human Inferior Frontal Gyrus
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The inferior frontal gyrus (IFG) has been widely implicated in inhibitory control of voluntary behaviors. The involvement of the IFG in response inhibition has been reported in many manual control studies and a few oculomotor control studies. However, behavioral data does not fully support a common mechanism of response inhibition but suggests different underlying neural mechanisms for response inhibition over different sensorimotor associations. Aside from response inhibition, the IFG has been associated with multiple cognitive functions, including rule representation and infrequent stimulus processing. Given that the IFG has different cytoarchitectonic subdivisions with different connections with other cortical and subcortical areas, it is likely that the different IFG subdivisions support various cognitive processes. Thus, it is unclear whether the IFG plays a common role in inhibitory control of behaviors and whether the activation of IFG on response inhibition is dissociable from those in rule representation and infrequent stimulus processing. In this dissertation, two functional magnetic resonance studies have been conducted to examine 1) the contribution of the IFG to response inhibition over different sensorimotor associations and 2) the functional topography of the IFG during rule-guided response control. The first study has shown that the bilateral posterior ventral IFG/insula is commonly activated in response inhibition over different sensorimotor associations but interacts with different sensory areas in processing different sensory stop signals. The more dorsal part of the IFG and middle frontal gyrus (MFG) are more involved in inhibition of oculomotor responses. The second study has shown that the left anterior IFG is particularly involved in rule representation, the right posterior ventral IFG/insula in triggering stop process, the right MFG/anterior dorsal IFG in general response control and the right posterior dorsal IFG in infrequent stimulus processing. These findings have demonstrated that the IFG is a functional heterogeneous structure and IFG subdivisions interact with groups of different cortical and subcortical regions while they serve different cognitive functions.

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List of Symbols

ACC: anterior cingulate cortex
AF: arcuate fascicle
BA: brodmann¡¯s area
CING F: cingulate fascicle
DLPFC: dorsolateral prefrontal cortex
DMPFC: dorsomedial prefrontal cortex
DTI: diffusion tensor imaging
ExtmC: external capsule fiber bundle
FEF: frontal eye field
FDR: false discovery rate
FWE: family-wise error
FG: fusiform gyrus
fMRI: functional magnetic resonance imaging
FOF: fronto-occipital fascicle
FPC: frontopolar cortex
IFC: inferior frontal convexity (non-human primates)
IFC: inferior frontal cortex (human/animal)
IFG: inferior frontal gyrus
IFJ: inferior frontal junction
IPL: inferior parietal lobule
IPS: inferior parietal sulcus
IT: inferior temporal (non-human primates)
ITG: inferior temporal gyrus
LPFC: lateral prefrontal cortex
M1: primary motor cortex
MFG: middle frontal gyrus
MT: middle temporal (non-human primates)
MTG: middle temporal gyrus
PFC: prefrontal cortex
PM: premotor cortex
Pop: pars opercularis
Por: pars orbitalis
PPC: posterior parietal cortex
Pre-SMA: pre-supplementary eye field
Prt: pars triangularis
SC: superior colliculcus
SEF: supplementary eye field
SFG: superior frontal gyrus
SFS: superior frontal sulcus
SII: second somatosensory area
SLF: superior longitudinal fascicle
SMA: supplementary eye field

SPL: superior temporal lobule
SSD: stop-signal delay
SSRT: stop signal reaction time
STG: superior temporal gyrus
STS: superior temporal sulcus
TL: temporal lobe (non-human primates)
TMS: tanscranial magnetic stimulation
UF: uncinate fascicle
VLPFC: ventrolateral prefrontal cortex

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1. Introduction

Response inhibition refers to a cognitive-motor process to suppress an impulsive response or cancel a planned action under certain contexts. It is part of the daily routine; for example, pedestrians stop by the curb when a car is approaching. The ability to inhibit responses improves throughout childhood and declines slightly through adulthood (Band et al., 2000; Schachar and Logan, 1990; Williams et al., 1999) and is associated with maturation of the prefrontal cortex (Casey et al., 1997; Tamm et al., 2002).

Frontal lobe damage could lead to deficiency in various cognitive and motor functions, such as cognitive control, decision making, rule learning, working memory and response inhibition (Badre et al., 2009; Clark et al., 2003; Demakis et al., 2004; Dimitrov et al., 1999; 2003). Earlier work on non-human primates has demonstrated that the damage to inferior frontal convexity (IFC) could lead to the disinhibition of perseverative behaviors (Fuster, 1997; Iversen and Mishkin, 1970). A recent clinical study has shown that patients with damage on the right frontal lobe have difficulty in inhibiting sequential actions in response to distractors (Niki et al., 2009). Previous studies have particularly implicated the critical role of the right inferior frontal gyrus (IFG) in manual response inhibition, showing that patients with damage in the right IFG and healthy adults with temporary disturbance in the right IFG by transcranial magnetic stimulations (TMS) have impaired ability of response inhibition (Aron et al., 2003, Chambers et al., 2006; 2007). Consistently, neuroimaging literatures have shown the common activation of the right IFG in different response inhibition tasks that require the inhibitory control of manual responses (Garavan et al., 1999; Konishi et al., 1999). Conversely, studies of nonhuman primates and humans have demonstrated that the frontal eye field (FEF) and the supplementary eye field (SEF) are involved in inhibition of oculomotor movements (Hanes et al., 1998; Stuphorn et al., 2000; Curtis et al., 2005). It seems that the manual and oculomotor systems have their own mechanisms for inhibiting movements. Nonetheless, recent neuroimaging studies have shown that the IFG is also activated during oculomotor response inhibition (Chikazoe et al., 2007; Heinen et al., 2006). Thus, the challenging question is whether the IFG plays a common role in response inhibition over different sensorimotor associations.

Also, there is no doubt that the IFG is engaged in various cognitive processes besides response inhibition. The IFG is composed of multiple subdivisions with different cytoarchitectonic features and connections with

other cortical and subcortical regions, suggesting its role in diverse cognitive and motor processes (Brodmann, 1909; Walker, 1940; Petrides and Pandya, 2001). In particular, neuroimaging studies have revealed that the left IFG is activated in rule representation (Bunge et al., 2003) and the right posterior dorsal IFG in infrequent stimulus processing (Chikazoe et al., 2007). It remains unclear whether and how the IFG subdivisions contribute to other cognitive processes during response inhibition. The functional dissociations between the IFG subdivisions are rarely tested in within-subject studies.

This dissertation aims at understanding 1) whether the IFG plays a common role in response inhibition over different sensorimotor associations and 2) the functional organization of the IFG in diverse cognitive processes involved in control of response inhibition.

2. Background

2.1. Inferior frontal gyrus anatomy

2.1.1. Topographic and cytoarchitectonic organization of inferior frontal cortex

The lateral surface of the frontal lobe can be grossly recognized as having three functional regions, including the primary motor cortex, premotor cortex, and prefrontal cortex (PFC) (Fuster, 1997). Topographically, lateral prefrontal cortex (LPFC) is located in the anterior part of the frontal lobe. It is anterior to primary motor cortex and premotor area, which are labeled as Broadmann's area (BA) 4 and 6, respectively. It has two main subdivisions: dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC). The VLPFC is also called inferior frontal cortex (IFC) in human or inferior frontal convexity (IFC) in non-human primates. It is mainly composed of the IFG. The IFG has three macroanatomical divisions: pars orbitalis (Por), pars triangularis (Ptr) and pars opercularis (Pop). The Por is located inferior and anterior to the horizontal ramus of the lateral fissure. The Ptr is located between the ascending ramus and the horizontal ramus of the lateral fissure. The Pop is located posterior to the ascending ramus of the lateral fissure. The Por, Ptr and Pop roughly correspond to the area 47, 45 and 44, respectively, according their cytoarchitectonic features. The LPFC receives multi-modal sensory information through reciprocal connections with the parietal, temporal and occipital cortex and influences motor output through connections with the premotor cortex (Fuster, 1997). In addition, the LPFC is connected with the thalamus and striatum (Alexander et al., 1986). The profuse connections provide the biological basis for communication between the LPFC and other brain regions and support multiple cognitive functions including working memory, rule learning and action control (see reviews by Fuster, 1989; Goldman-Rakic, 1987b; Miller and Cohen, 2001).

2.1.2. Corticocortical connections of inferior frontal cortex

Our knowledge about anatomical connections between the LPFC and other cortical regions mainly relies on non-human primate studies. There is limited knowledge about the cortical connections from human research because most of the fiber-tracking measurements (e.g. degeneration of axons and active transport of tracers), which are generally used in living animals, cannot be applied to living human subjects. The postmortem tracer method

can only track fibers for a limited distance. The diffusion tensor imaging (DTI) has been widely used in studying corticocortical connections in humans recently. Although it is good in tracking the major fiber tracts across cerebral cortices, the current DTI is not accurate in tracking smaller fibers within the cerebral cortex.

The PFC connects with other cortical and subcortical areas mainly through multiple major association fascicles, including uncinate fascicle (UF), external capsule fiber bundle (ExtmC), superior longitudinal fascicle (SLF) I, II and III, arcuate fascicle (AF), cingulate fascicle (CING F) and the fronto-occipital fascicle (FOF) (Ungerleider et al., 1989; Petrides and Pandya, 1984; 1988; 1994; 1999; 2002). The corticocortical connections to IFG regions are briefly summarized in the following paragraph, and are mainly based on a series of work by Petrides and Pandya (1984; 1988; 1994; 1999; 2002). Recent DTI studies (e.g. Anwander et al., 2006; Croxson et al., 2005) have shown major fiber tracts to IFG regions in humans that are mostly consistent with the findings in non-human primates.

Area 47 is a ventral part of the lateral frontal convexity in the monkey brain, which has similar cytoarchitecture of area 47 in the human brain. It is connected with the visual area of the IT and other projections are from the rostral STG, rostral multi-modal areas in the STS, and the rhinal and parahippocampal regions. It also has local connections with the DLPFC (areas 46, 9, 9/46v, 8B), VLPFC (area 45v), orbital PFC (areas 10, 11, 13, 14) and DMPFC (areas 9, 14, 24, 32).

Area 45 is the rostral bank of the lower limb of the arcuate sulcus in the monkey brain. It is connected with the IPL, IPS, the entire STG, the multi-modal areas in the upper bank of the STS, insula cortex, limbic regions, the somatosensory cortex and the visual area of the IT. It also has local connections with DLPFC (areas 8, 9, 9/46v, 46), VLPFC (areas 47/12, 44), orbital PFC (areas 10/11/13/14) and DMPFC (areas 6, 8B, 9, 24, 32).

Area 44 is a controversial area in the monkey brain. Pandya and Yeterian (1996) suggested that the caudal bank of the lower limb of the arcuate sulcus in monkeys corresponds to the human area 44. It is connected with the rostral and middle IPL, the second somatosensory cortex, and STS. It also has local connections with the DLPFC (area 9/46v), VLPFC (areas 47/12, 45), orbital PFC (area 13), ventral premotor cortex (area 6v), and DMPFC (area 24).

Since the dissertation focuses on the IFG, the anatomical connections to other prefrontal regions are briefly summarized in Appendix 3.

2.2. Inferior frontal gyrus functions

The inferior frontal gyrus has been associated with various cognitive functions, including response inhibition (e.g. Konishi et al., 1998), rule representation (e.g. Bunge et al., 2003), infrequent stimulus processing (e.g. Chikazoe et al., 2008), working memory (e.g. Goldman-Rakic, 1987b),

stimulus-driven attention (e.g. Corbetta and Shulman, 2002), verbalization (e.g. Grezes and Decety, 2001) and response imitation (e.g. Heiser et al., 2003). In the following chapters, we selectively review some cognitive functions associated with the inferior frontal gyrus.

2.2.1. Theories: functional organization of lateral prefrontal cortex

The LPFC has long been considered to be critical in coordinating various cognitive and motor processes to achieve behavioral goals. It remains unclear how the LPFC supports and manages multiple cognitive processes. Many theories about the functional organization of the PFC have been proposed in the past decades. Despite a large number of studies in the past decades, there is not a consensus on the functional organization of the LPFC. In this chapter, some theories will be selectively reviewed.

One central control theory: Duncan and Owen (2000) have considered the PFC as a nonspecific processor because there is a similar recruitment of the DLPFC, VLPFC and dorsal anterior cingulate cortex (ACC) in diverse cognitive tasks involving response conflict, task novelty, working memory and perceptual difficulty.

Material-dependent theory**:** Goldman-Rakic (1987b) suggested that the LPFC has an important role in working memory and it may be organized by the type of material. She and her colleagues found that the VLPFC mediates non-spatial/object working memory whereas the DLPFC mediates spatial working memory. However, there are contradictory findings. For example, Owen et al. (1998) showed that spatial and non-spatial working memory tasks activate similar regions within the human LPFC. Others have suggested a hemispheric material-dependent view with the left LPFC for processing verbal or non-spatial information and the right LPFC for processing non-verbal or spatial information (D'Esposito et al., 1998; Kelley et al., 1998).

Process-dependent theory: In contrast to the material-dependent theory, another group of studies suggested that the LPFC is organized by different cognitive processes. Smith and Jonides (1999) suggested that the LPFC (mainly IFG and pre-SMA and premotor area) in the left hemisphere is more for short-term storage of verbal material, the LPFC (mainly premotor cortex) in the right hemisphere is more for short-term storage of spatial information, and other prefrontal regions are involved in short-term storage of object information. Petrides (2000, 2005) proposed the theory that the LPFC is functionally organized along a rostral-caudal axis and a dorsal-ventral axis. Along the rostral-caudal axis, the caudal frontal regions were involved in fine motor control and direct sensorimotor mapping, the caudal LPFC was involved in regulating the selection among multiple learned stimuli-response associations, and the rostral LPFC was involved in more complex and abstract functions such as cognitive control. Along the dorsal-ventral axis, the mid-DLPFC was involved in monitoring and manipulating information in working memory and the mid-VLPFC in active judgments on information held working memory.

Process and material-dependent theory: Johnson et al. (2003) showed left PFC participates in refreshing verbal and pictorial information and right PFC is involved in recognizing a recently presented word or object. They suggested that the LPFC is organized by both the type of process and the type of material.

Control hierarchical theory: Fuster (2001) suggested a hierarchical system for processing sensory and motor information as well as executive memory. Koechlin et al. (2003) suggested that the LPFC is organized as a cascade of executive processing in response to stimuli, the present perceptual context and the temporal episode from premotor to anterior PFC. Badre and D'Esposito (2007) showed a hierarchical organization of action control along rostro-caudal axis in the frontal lobes. They found the caudal LPFC is more involved in selection of competing responses and the rostral LPFC in more abstract representation of action control, such as the competition among sets of contextual cue-to-dimension mappings. However, studies also showed that similar regions of prefrontal and parietal regions are involved in selection of rules and selection of actions (Rowe et al., 2008).

2.2.2. Response inhibition and inferior frontal gyrus

2.2.2.1. Definition of response inhibition

Voluntary control of behavior means that people or animals have the ability to initiate, change and cancel actions in accordance to their will. The ability to inhibit a response is the hallmark of voluntary action control. It refers to the cognitive-motor process to inhibit an inappropriate response or an impulse under a given situation. Response inhibition has been considered as one key component in executive function (Miyake et al., 2000). Inhibiting unwanted behavior and improper impulses is important for animal survival as well as routine human activities. Without inhibitory control, many aspects of everyday living would become impossible. Patients with Parkinson's disease, for example, suffer in daily life because of a deficit in initiating responses and inhibiting unwanted movements.

2.2.2.2. Stop-signal Paradigm

We use the stop-signal task to study response inhibition because this paradigm is a direct measure of inhibition of initiated responses. The inhibitory process can be quantified by using the stop-signal reaction time (SSRT). The stop-signal task consists of go trials and stop trials. In a go trial, participants are asked to make a response to a go signal in a go trial. In a stop trial, the go signal is followed by a stop signal. Participants are required to stop their responses. The interval between a go signal and a following stop signal is called stop-signal delay (SSD).

A race model has been proposed to understand cognitive-motor processes involved in the stop-signal paradigm(Logan and Cowan, 1984). The race model suggests that there are two independent processes in a stop trial, a go

process and a stop process. Whether a planned action can be inhibited depends on which process completes first. If a go process completes first, a planned action is executed. If a stop process completes first, a planned action is canceled. It is important to note that the stop process is not an isolated process. Instead, it can be considered as a sequence of interpreting a stop signal, initiating a stop process and stopping an initiated go process. Failure to inhibit a planned movement can result from the failure to complete any of these processes. In other words, an unsuccessful stop trial does not necessarily implicate the failure to interpret a stop signal to inhibit a stop process, but may simply show an unfinished stop process.

The race model can be used to estimate the SSRT, which is an estimation of reaction time to cancel an initiated response. A previous electrophysiological study has found that the firing rate of neurons in the FEF begin to drop while a stop signal is presented and a saccadic eye movement is successfully cancelled (Hanes et al., 1998). This finding validates that the estimated SSRT matches the neuronal activity associated with response inhibition.

2.2.2.3. The role of inferior frontal gyrus in response inhibition

A large number of literatures have found that the IFG is involved in response inhibition, including animal lesion studies (Butters et al., 1973; Eagle et al., 2008; Iversen and Mishkin, 1970), electrophysiological studies (Hasegawa et al. 2004; Sakagami et al., 2001), human patient studies (Aron et al., 2003; Godefroy and Rousseayx, 1996; Knight et al., 1999; Verfaellie et al., 1987), neuroimaging (Aron and Poldrack, 2006; Aron et al., 2007; Blasi et al., 2006; Booth et al., 2003; 2004; Cai and Leung, 2009; Chevrier et al., 2007; Coxon et al., 2009; Garavan et al., 1999; Goldstein et al., 2007; Hazeltine et al., 2000; 2003; Hare et al., 2005; Horn et al., 2003; Konishi et al., 1998;1999; Langenecker et al., 2003; Laurens et al., 2005; Leung and Cai, 2007; Liddle et al., 2001; Maguire et al., 2003; Menon et al., 2001; Nakata et al., 2007; Ramautar et al., 2006; Rubia et al., 2001; 2003; 2006; 2007; Shafritz et al., 2006; Wager et al., 2005) and TMS studies (Chambers et al., 2006; 2007).

2.2.2.3.1. Animal research

Early animal work from Iversen and Mishkin (1970) found that the monkeys with lesions of the inferior frontal convexity have difficulty in withholding responses to negative stimuli. The finding suggested the damage to the IFC impairs inhibition of preseverative responses. A recent study showed that a lesion in the orbitofrontal cortex in rats slow stop processes (longer SSRTs) without slowing go processes (Eagle et al., 2008). Electrophysiological literatures revealed that neurons around the caudal prinicipal sulcus including the IFC are activated during inhibition of saccadic eye movements (Hasegawa et al., 2004). Sakagami and his colleagues (2001) recorded neurons in the IFC of monkeys during a color/motion cued go/no-go

task. They found that neurons can code color-cued no-go responses, implicating its role in sensory guided response inhibition. Taken together, animal findings suggested that the inferior frontal convexity plays a critical role in response inhibition.

2.2.2.3.2. Human subject research

Human patients with prefrontal damage have difficulty in inhibiting inappropriate responses (Fuster, 1997; Knight et al., 1999). Recent studies of patients with frontal lesions and TMS studies of healthy adults emphasized a critical role of right IFG in response inhibition. Aron and his colleagues (2003) found that lesions in the right IFG cause more severe impairment in response inhibition than lesions in other prefrontal regions and that damaged volume in pars opercularis and triangularis is correlated with impaired behaviors (SSRTs). Significant temporary reduction on performance of response inhibition (SSRT) was also observed when the TMS was applied on the right posterior IFG (mainly pars opercularis) compared to other prefrontal regions (Chambers et al., 2006; Chambers et al., 2007). These findings suggested that the right IFG plays a critical role in response inhibition. In consistent, a large amount of neuroimaging literatures showed the activation of the right IFG in manual response inhibition using various tasks, including the go/no-go task (Garavan et al., 1999; Konishi et al., 1999) and the stop-signal task (Aron and Poldrack, 2006; Leung and Cai, 2007; Rubia et al., 2001; Rubia et al., 2003). It indicated that the right IFG may play a common role in manual response inhibition.

2.2.2.4. Other cortical and subcortical regions in response inhibition

Although the right IFG has been emphasized in human response inhibition, other prefrontal regions such as the pre-SMA and premotor cortex have been shown to be involved in manual response inhibition (e.g., Li et al., 2006) and frontal eye field and supplementary eye field are suggested for inhibition of eye movements in the majority of oculomotor literatures (e.g., Hanes et al., 1998; Curtis et al., 2005). The activation of the pre-SMA has also been reported in many response inhibition studies (Aron and Poldrack, 2006; Aron et al., 2007; Leung and Cai, 2007; Rubia et al., 2001). Recent studies have shown that the damage in the superior medial regions causes a deficit in withholding responses and also increases the reaction time for response execution (Folden and Stuss, 2006; Picton et al., 2007). In addition, a few studies found involvement of subcortical regions in response inhibition, including subthalamic nucleus (STN) (Aron and Poldrack, 2006) and caudate nucleus (Li et al., 2008b). In particular, Aron et al. (2007) proposed a network of the IFG, the pre-SMA and the STN in the right hemisphere for supporting manual response inhibition. Their diffusion tensor imaging (DTI) analysis suggested that these three regions are anatomically connected. In contrast, it has been suggested that the medial prefrontal-caudate and striato-thalamic circuits is involved in manual response inhibition using fMRI (Li et al., 2008b). Taken

together, previous findings were consistent in that a set of prefrontal and subcortical regions is involved in response inhibition. However, the exact role of the IFG and other cortical and subcortical regions in response inhibition remains unclear.

2.2.2.5. Response inhibition in different motor modalities

Voluntary control of manual and oculomotor movements has been widely investigated in behavioral and neuroimaging studies. Logan and Irwin (2000) have compared inhibition of eye and hand movements using the stop-signal task and found that the estimated SSRT was shorter overall for eye movements (shorter than 200ms) than for hand movements (longer than 200ms). This finding has been replicated in other studies (Boucher et al., 2007; Leung and Cai, 2007). Boucher and her colleagues (2007) have also found that the inhibition of eye movements and inhibition of hand movements are not fully dependent and the difference in eye SSRTs between auditory and visual stimuli is bigger than the difference in hand SSRTs. These findings suggest that there could be different processes underlying the inhibition of eye and hand movements. The SSRT difference between two motor modalities, however, is not sufficient to reject the assumption of a common inhibitory mechanism. The difference in SSRTs between inhibiting eye and hand responses may be due to physiological differences between the two muscle systems rather than differences in mechanisms of inhibitory control of responses between two motor systems. It is possible that the difference in SSRTs is due to the different complexities of the muscle control systems in different motor modalities.

In contrast to neuroimaging literatures of manual response inhibition, oculomotor literatures suggested a different set of cortical and subcortical regions in inhibiting eye movements, including the FEF, SEF and superior colliculus (SC), in electrophysiological studies (Hanes et al., 1998; Hasegawa et al., 1998; Pare and Hanes, 2003; Sato and Schall, 2003; Stuphorn et al., 2000; Stuphorn and Schall, 2006) and neuroimaging studies (Curtis et al., 2005; Heinen et al., 2006; Brown et al., 2006; Chikazoe et al., 2007). These findings suggested that different motor systems may have their own mechanisms in inhibiting movements.

Interestingly, recent studies have shown that the damage to the IFG can impair oculomotor response inhibition (Hodgson et al., 2007) and the IFG along with the FEF and SEF are involved in oculomotor response inhibition using an oculomotor version of go/no-go task (Brown et al., 2008; Heinen et al., 2006) and an antisaccade task (Chikazoe et al., 2007). Our previous study also reported the activation of the IFG in an oculomotor version of the stop-signal task (Leung and Cai, 2007). Besides, the common involvement or the IFG during response inhibition has been reported in other cross-modalities studies, showing the activation of the IFG in inhibition of manual and vocal

responses (Xue et al., 2008). Taken together, the IFG may play a common role in response inhibition in different motor modalities.

2.2.2.6. Response inhibition guided by different sensory stimuli

Sensory stimuli have an influence on response inhibition behavior, although it is inconsistent as to whether visual, auditory or other stimulus (e.g. tactile stimulus) is more efficient in stopping a planned response (Akerfelt et al., 2006; Boucher et al., 2007; Cabel et al., 2000; Colonius et al., 2001; van der Schoot et al., 2005). It is unclear whether the effect of sensory modality on response inhibition is caused by the cognitive mechanism of response inhibition or merely differences in the process of sensation and perception. Sakagami and his colleagues (2001) have found that neurons in the IFG of monkeys differentiate color stimuli that are no-go vs. go responses, but not motion stimuli. This suggests that the neurons of the IFG can selectively encode particular sensory information to guide response inhibition. To our knowledge, few neuroimaging studies have looked at the effect of sensory stimuli on response inhibition. To further understand the neural mechanism of response inhibition, it is necessary to investigate the neural substrates of response inhibition over different sensorimotor associations.

2.2.3. Rule representation and inferior frontal gyrus

2.2.3.1. Definition of rule

Most behaviors are guided by a set of constraints, which are so called rules. Rules can be simple and concrete, representing straightforward associations between previously experienced stimuli and potential responses and rewards; or, they can be more complex and abstract, defining an input pattern as a grammatical pattern, member of a category, or a regular sequence (Reber, 1989). In our daily life, following rules is important for selecting an appropriate course of actions and suppressing inappropriate responses in a given situation to achieve either internal or external goals. In most experimental settings, a behavioral response is guided by sensorimotor associations set by the experimenter, which is one type of rule.

2.2.3.2. The role of inferior frontal gyrus in rule representation

It has been found that the IFG is involved in rule-related processes in animal lesion studies (Bussey et al., 2001; Browning et al., 2006; Eacott and Gaffan, 1992; Gaffan and Harrison, 1989; Parker and Gaffan, 1998; Petrides et al., 1985b; Rushworth et al., 2005; Murray et al., 2000; Wang et al., 2000) and human neuroimaging studies (Brass and von Cramon, 2002; 2004; Bengtsson et al., 2009; Boettiger et al., 2005; Bunge et al., 2003; Chiu et al., 2009; Cools et al., 2002; 2004; Crone et al., 2006; Donohue et al., 2005; Hanakawa et al., 2006; Montojo and Courtney, 2008; Passingham et al., 2000; Reynolds et al., 2004; Rowe et al., 2008; Sakai and Passingham, 2006; Strange et al., 2001; Toni et al., 1999; 2001; 2002).

2.2.3.2.1. Animal research

Lesion studies of non-human primates suggested that the VLPFC but not the DLPFC is critical in learning arbitrary visuomotor associations. Several studies showed that the ablation of the DLPFC leads to mild deficit in learning of visuomotor associations (Gaffan & Harrison, 1989; Petrides, 1982). In contrast, the VLPFC (including orbital PFC) was critical in learning visuomotor associations. Bussey et al. (2001) trained four monkeys to learn different sets of visuomotor associations. After bilateral ablation of the VLPFC and orbital PFC, monkeys were unable to learn new conditional visuomotor associations within several sessions and had deficiency in the retention of familiar learned visuomotor associations. Rushworth et al. (2005) also showed that the VLPFC and ortibal PFC is critical to the use of conditional rule while selecting action in non-human primate lesion studies. Wang et al. (2000) found that monkeys with the DLPFC damaged by injection of the GABAergic antagonist had no obvious deficit in learning a novel visuomotor association, whereas monkeys with the VLPFC lesion had a dramatic deficit in learning a novel visuomotor association. Therefore, the VLPFC (including orbital PFC) was particularly implicated in visuomotor association learning.

Electrophysiological studies have revealed neurons in the LPFC can code stimulus-response associations (Asaad et al., 1998; 2000; Hoshi et al., 1998; Muhammad et al., 2006; Wallis et al., 2001; Wallis & Miller, 2003; White & Wise, 1999). Asaad et al. (1998) trained monkeys to associate two visuospatial cues with saccades to two different directions. They found that the activity of a group of neurons in the LPFC (area 46, 9/46, 45, and 47/12, around the sulcus principalis) reflects the association between the visual cue and the oculomotor response rather than responds selectively to either visual cue or the saccade direction. White and Wise (1999) also found that neurons in the LPFC (area 9, 8B, 46, 9/46, and 45, around the sulcus principalis, extending to the medial surface) showed varied activities corresponding to different rules. Wallis et al. (2001) recorded neurons in the LPFC (between the sulcus principalis and the sulcus or orbitalis, area 9, 46, 9/46, 45, 47/12, 11, 13, and 14) while monkeys performed tasks following the abstract rules (match and non-match) to make responses indicating whether two successively presented pictures were same or different. They found that the activity of some neurons was modulated by the abstract rule instead of the visual stimuli and motor responses. The aforementioned electrophysiological evidences indicated that the activity in the LPFC neurons reflects the meaning of learned stimulus-response associations.

There are several potential explanations for the conflicting findings between electrophysiological and lesion studies. Firstly, although neurons around the sulcus principalis show rule- or task-dependent activity, the activity of these neurons may not be necessary for learning or performing simple S-R task. Secondly, the conflicting findings could be due to task differences. In most lesion studies, monkeys were asked to follow a direct stimulus-response

association. For example, monkeys learned problems in which visual stimuli indicated whether the reward was to be found on the monkey's left or right (Gaffan & Harrison, 1989). In some electrophysiological studies, however, monkeys were asked to acquire abstract rules such as match/non-match (Asaad et al., 2000; Muhammad et al., 2006; Wallis et al., 2001; Wallis & Miller, 2003). Moreover, most of these tasks required a delayed response in the electrophysiological studies, so the instruction or the rule had to be held during the delay period after the cue disappeared. The short-term storage of information was required in order to memorize the current S-R association. Thus, the DLPFC may be involved in working memory and utilizing the complex and abstract rules, but it is not critical for action control based on the simple visuomotor association. Instead, the connection between the VLPFC and temporal cortex seems particularly important in learning simple visuomotor associations. In addition, lesions in the DLPFC impaired more severely in learning spatially cued associations than non-spatially cued associations (Gaffan & Harrison, 1989). It is consistent with the material specific hypothesis that the DLPFC is involved in spatially directed cognitive control.

2.2.3.2.2. Human subject research

Human patient studies and neuroimaging studies have examined various cognitive operations in rule-related behaviors, such as learning rules (e.g. sensorimotor associations) (e.g. Aron et al., 2004), retrieving learned rules (e.g. Bunge et al., 2003) and maintaining retrieved rule in a delay-response task (e.g. Montojo and Courtney, 2008).

2.2.3.2.2.1. Frontal damage and rule learning

Human patients with frontal lobe damage showed similar deficits in learning stimulus-response associations as non-human primates with lesions in the frontal lobe. Petrides (1982; 1985a) examined human patients with frontal lobe excision. He found that those patients suffered severe impairment in learning arbitrary associations between visual stimuli and hand responses. Dimitrov et al. (1999) also found that patients with lesions in the left frontal lobe have the worst performance on the cued and free recall conditions. Aron et al. (2004) found that a group of patients with either right frontal lesions (right IFG) or left frontal lesions (left MFG) had deficits in switching rules among tasks. Together, human patient literatures implicated the frontal lobe in rule processing.

2.2.3.2.2.2. Rule retrieval

Rule retrieval refers to a process of retrieving recently acquired or well-learned stimulus-response associations from long-term memory. It is more important when multiple rules are required in an experiment. The process of rule retrieval has been examined by comparing cortical activations involved in retrieving different types of rules. A neuroimaging study has

compared brain activations during processing complex and simple rules and found that the left anterior IFG is more active in retrieving complex rules than simple rule (Bunge et al., 2003). Donohue et al. (2005) have shown that the right anterior IFG is involved in retrieving new-leaned rules relative to well-learn rules and the left anterior IFG is generally involved in rule retrieval but is not influenced by either familiarity or success of retrieval. These findings suggested the role of the anterior IFG in effortful rule retrieval.

2.2.3.2.2.3. Rule maintenance

Rule maintenance refers to a working memory process that maintains the retrieved rule online during preparing or making response decisions. It has been suggested that the lateral PFC plays an important role in working memory (Funahashi et al., 1989; Goldman-Rakic, 1987b). A recent study (Montojo and Courtney, 2008) has compared neural activation for updating rule versus number and they have found that a set of prefrontal regions is involved in updating both kinds of information, including left IFG, left MFG, left IFJ, and pre-SMA, while the left IFJ shows higher activation for rule updating. Their findings suggest that rule and stimuli information are maintained in a common working memory system but that different types of information might be controlled independently.

A previous study has found that the left posterior IFG, frontopolar area and pre-SMA are activated and sensitive to rule type and the MFG is activated but not sensitive to the rule type in the post-cue delay epoch during which subjects are required to remind themselves of the task rule and prepare for coming trials (Bunge et al., 2003). Consistent with this finding, it has been shown that the IFJ (the junction of precentral sulcus and inferior frontal sulcus) and the pre-SMA are involved in task preparation during which subjects prepared to make responses to the stimulus with or without prior task instructions (Brass and von Cramon, 2002). This suggests that the IFJ and pre-SMA are involved in rule maintenance and response preparation. Consistent with Bunge et al.'s study, it has also been found that the MFG is highly activated but not sensitive to the rule type while sustaining the task rule (Sakai and Passingham, 2006). This suggests that the MFG is generally involved in holding information without differentiating rule specificity.

Taken together, previous findings suggested that the anterior IFG is involved in retrieving rules and the posterior dorsal IFG, MFG and pre-SMA are probably involved in maintaining rules.

2.3. Role of inferior frontal gyrus in other cognitive functions

2.3.1. Infrequent stimulus processing and inferior frontal gyrus

The brain activation involved in response inhibition has been mainly measured by contrasting response inhibition trials with response execution trials. In the stop-signal paradigm, since stop trials are much less frequent than

go trials, the interpretation of response inhibition in stop trials would require understanding of infrequent sensory signal processing, also called the oddball effect. In addition, the stop trial requires additional attention to process the stop signal, which is associated with the infrequent behavioral change. The contrasts of stop trials and go trials thus reflect not only infrequent response inhibition but also infrequent response-relevant stimulus processing.

Combined ERP and fMRI studies have implicated the association of the frontal and temporoparietal regions and an event-related potential component P300 in detecting infrequent stimuli (Bledowski et al., 2004; Linden et al., 1999). The posterior IFG, along with the temporoparietal regions, is activated in processing infrequent stimuli associated with or without responses (Downar et al., 2000; Downar et al., 2001; Huettel and McCarthy, 2004; Stevens et al., 2005) and is independent of the sensory modalities of the stimuli (Downar et al., 2000; Linden et al., 1999). A recent study has dissociated the response inhibition and sensory oddball effect by contrasting no-go trials and infrequent go trials with frequent go trials (Chikazoe et al., 2008). According to this study, the posterior IFG is activated during response inhibition and the IFJ is mainly activated during processing infrequent stimuli. Their findings thus indicate that activations of different parts in the IFG are probably associated with different cognitive control processes in the response inhibition task. It has been suggested that the right ventral frontoparietal network directs attention to response-relevant sensory stimuli (Corbetta and Shulman, 2002). Previous studies have found that the posterior dorsal IFG is more active in processing infrequent targets than infrequent distractors (Bledowski et al., 2004; Kiehl et al., 2001; Serences et al., 2005). It suggests that the posterior dorsal IFG is more involved when the infrequent stimulus is associated with behavioral responses.

2.3.2. Working memory and inferior frontal gyrus

Working memory refers to the process of temporally storing and manipulating information that was retrieved from long-term memory or just experienced. Among several working memory models, the most well-known one was originally proposed by Baddeley and Hitch (1974) and later revised by Baddeley (1986; 2000) that working memory consists of one executive control center and three slave systems, including the phonological loop, the visuospatial loop and the episodic buffer. Working memory is important to humans' daily activities. It has been considered to participate in various high-level cognitive functions, such as reasoning, planning and decision making. The delayed-response paradigm has been widely used to study working memory. In a typical delayed-response task, subjects are required to remember or manipulate the information associated with the sensory stimulus in a period of delay after the stimulus disappears. Neural activity during the delay period is considered as neural substrate associated with the process in maintaining and manipulating information.

Accumulating electrophysiological and neuroimaging evidences consistently suggested that the prefrontal cortex plays an important role in working memory (Fuster, 1997; Goldman-Rakic, 1987b). Funahashi et al. (1993) trained monkeys to make memory-guided saccades using two oculomotor delayed-response tasks, including pro-saccade and anti-saccade. They found that a majority of neural activity in the DLPFC during the delay epoch represents information for visual cue position instead of the direction of saccadic eye movements. Wilson et al. (1993) further revealed that the lateral prefrontal cortex can be functionally segregated by the maintained information that the dorsal prefrontal areas are involved in processing visuospatial information while the ventral prefrontal areas are involved in processing non-spatial/object information. Goldman-Rakic (1995) thus suggested that the DLPFC is mainly involved in spatial working memory and the VLPFC is mainly involved in non-spatial and object working memory. Human neuroimaging studies replicated the dorsal-ventral segregation of lateral prefrontal cortex in working memory supported by electrophysiological studies (see review by Ungerleider et al., 1998). For example, Courtney and her colleague (1996) showed that superior frontal sulcus is more involved in location working memory while the inferior frontal cortex is more involved in face working memory. However, inconsistent findings have also been reported that the spatial and non-spatial working memory may not be mediated by the DLPFC and VLPFC, respectively (Owen et al., 1998). They did not find the VLPFC is uniquely involved in non-spatial working memory, but the mid-DLPFC is commonly involved in spatial and non-spatial working memory. Instead, they suggested that the lateral prefrontal cortex plays an identical role in spatial and non-spatial working memory. Taken together, although there is inconsistent evidence to support the particular role of the VLPFC in the non-spatial or object working memory, the majority of literatures agree that the VLPFC is involved in working memory.

3. Specific aims and significance

It has been suggested that the right IFG is commonly involved in response inhibition (Garavan et al., 1999; Konishi et al., 1999), while electrophysiological literature have shown that the FEF and SEF play an important role in inhibition of oculomotor movements (Hanes et al., 1998). It remains unclear whether the right IFG serves as a common inhibitory mechanism in the voluntary control of behavior. Besides, the IFG supports other cognitive functions, such as rule representation and infrequent stimulus processing. It is possible that different parts of the IFG serve different cognitive functions.

3.1. Aim 1: Response inhibition over different sensorimotor associations

Although most literatures emphasized the FEF in inhibiting eye movements (Brown et al., 2006; Hanes et al., 1998) , a few recent studies found the activation of the IFG in inhibiting eye responses as well as in inhibiting hand responses (Chikazoe et al., 2007; Heinen et al., 2006; Leung and Cai, 2007). If the right IFG served as a common inhibitory mechanism in response inhibition, the activation of the right IFG should be independent of sensorimotor associations. We examined the common cortical activation involved in response inhibition of different sensorimotor associations (visual versus auditory stop signals and manual versus oculomotor responses) using fMRI. Modality-dependent and modality-independent effects of sensory input and motor output were investigated using paired comparison and conjunction analysis, respectively. Functional connectivity between cortical regions during response inhibition was examined using psychophysiological interaction (PPI) analysis to investigate the interaction between the posterior ventral IFG and sensory and motor areas during stimulus-driven response inhibition. We expected common involvement of the right posterior ventral IFG in response inhibition in all sensorimotor associations and dorsal-ventral segregation for motor modalities rather than sensory modalities.

3.2. Aim 2: Dissociation of response inhibition and rule representation

Neuroimaging studies have found that the left anterior IFG is active during rule retrieval and the left posterior dorsal IFG, MFG and frontopolar regions are active during rule maintenance (Bunge et al., 2003; Sakai and Passingham, 2006). The activation of the IFG in a response inhibition task could be associated with response inhibition and rule processes. We tested whether the common area defined by data from Aim 1, likely the posterior ventral IFG, is dissociable from the anterior IFG and posterior dorsal IFG that are involved in rule retrieval and rule maintenance by previous studies. One fMRI experiment was conducted to show the brain activation during three task epochs: cue, delay and response execution/inhibition and identify cortical areas contributing to the rule retrieval, rule maintenance and response inhibition processes, respectively. PPI analysis was also applied to examine the cortical functional connections during response inhibition and rule processes. We expected the activation of the left anterior IFG in rule retrieval, the left posterior dorsal IFG and MFG in rule maintenance, and the right posterior ventral IFG in response inhibition.

4. Study 1: Effect of response inhibition over different sensorimotor associations

4.1. Background and significance

It has been questioned whether there is common mechanism for inhibiting response across different sensorimotor systems. Studies have identified different SSRTs between inhibition of eye responses and hand responses (Boucher et al., 2007; Logan and Irwin, 2000) and between response inhibition guided by visual and auditory stop signals (Cabel et al., 2000), indicating that different sensorimotor control systems may have their own mechanism for response inhibition. However, it is unclear whether the difference in SSRTs among different sensorimotor associations is due to physiological differences among sensory and motor systems or different inhibitory control circuits.

It has been suggested that the right IFG plays a common role in response inhibition (Garavan et al., 1999; Konishi et al., 1998). Human patient study and TMS studies of healthy adults have shown that the damage or temporally disturbance on the right IFG is tightly associated deficit in response inhibition (Aron et al., 2003; Chambers et al., 2006; 2007). A large number of neuroimaging studies have emphasized the role of the right IFG in manual response inhibition using various tasks, including the go/no-go task (Garavan et al., 1999; Konishi et al., 1999) and the stop-signal task (Aron and Poldrack, 2006; Leung and Cai, 2007; Rubia et al., 2001; Rubia et al., 2003). A few recent studies have reported the IFG is involved in inhibitory control of responses in other motor modalities, including eye movements (Brown et al., 2008; Chikazoe et al., 2007; Heinen et al., 2006) and vocal responses (Xue et al., 2008). However, the majority of the electrophysiological literature has emphasized a different set of cortical and subcortical regions in inhibiting eye movements including the FEF, SEF and SC (Hanes et al., 1998; Hasegawa et al., 1998; Pare and Hanes, 2003; Sato and Schall, 2003; Stuphorn et al., 2000; Stuphorn and Schall, 2006). Moreover, Sakagami and his colleagues (2001) have found that some neurons in the IFG can selectively encode particular sensory information to guide response inhibition, suggesting that the neural activity in the IFG during response inhibition is sensory-dependent.

We previously investigated whether the IFG is commonly involved in inhibition of hand and eye movements (Leung and Cai, 2007). We found a major common activation in bilateral ventral IFG during inhibiting hand and eye

movements and some degree of segregation within the IFG for inhibiting hand versus eye responses. A more dorsal and posterior part of ventral IFG (mostly pars opercularis) showed stronger activity during canceling eye movements than hand movements, whereas a more ventral and anterior part of ventral IFG (pars orbitalis) showed the opposite pattern. However, since the same visual stop signal was used to trigger response inhibition in both tasks, it is unclear whether the common activation in the IFG can be attributed to the common visual stimulus processing. So, we further investigated the effect of sensory stop signals (color versus orientation stimuli) on response inhibition (Cai and Leung, 2009). We found the common activations in bilateral ventral IFG/insula during response inhibition guided by color and orientation stop signals. The activation in the ventral IFG was mainly located in the pars triangularis, close to the common activation during inhibition of manual and saccadic responses in the our previous finding (Leung and Cai, 2007). No significant sensory-dependent activation was observed in the IFG during response inhibition. In sum, our previous studies have shown that the ventral IFG is commonly involved in inhibiting both hand and eye responses and the engagement of the ventral IFG during inhibition of hand responses is not influenced by different visual stop signals. Our data has also shown that a more dorsal and posterior part of ventral IFG is more involved in inhibiting eye movements and a more ventral and anterior part of ventral IFG in inhibiting hand movements. One limitation in our previous studies is that error trials are not excluded because we are not able to record eye movements in the magnet during the scanning. Besides, it remains unexplored whether the activation of the IFG during response inhibition is fully independent of sensorimotor associations and how the IFG interacts with sensory and motor areas during response inhibition over different sensorimotor associations.

The main purpose of this experiment was to examine whether the IFG is commonly involved in inhibition of different motor responses with guidance of different sensory stimuli. To achieve this goal, we manipulated associations between different sensory stimuli (auditory versus visual) and different motor responses (hand versus eye). Eye movements were recorded during scanning in this experiment. Considering the go signal (appearance of stimuli in the left/right sides on the screen) might facilitate reflexive saccades in our previous study, the go signal was made as a directional sign and presented in the center in the current study. We also used a mix block and event-related design that each run includes all combinations of sensory stimuli and motor responses, instead of the design in the previous study that different tasks were conducted in different experimental runs. This should give us an equal BOLD signal baseline among different conditions.

4.2. Materials and methods

4.2.1. Subjects

Twenty-three healthy young adults (age range: 19 – 37 yrs, 12 females) were recruited from the Vanderbilt university campus and Nashville local area; none reported a history of neurological/psychiatric disorders or a history of drug abuse. All subjects had normal or corrected to normal vision. All subjects provided written consent, which is approved by the local Institutional Review Board. Four participants were excluded in the group analysis because of bad head motion during the scanning. Nineteen subjects were included in the final analysis.

4.2.2. Response inhibition task

The response inhibition task was a 2 (sensory modalities: visual versus auditory stop signal) x 2 (motor modalities: hand versus eye responses) design, including four different conditions: Hand-Auditory (HA), Hand-Visual (HV), Eye-Auditory (EA) and Eye-Visual (EV) (see figure 1). The task was a modified stop-signal task to minimize reflective saccadic eye movements in order to counterbalance with the hand responses. In each trial, a white diamond (fixation) was presented at the center and two dots (targets) were presented in the left and right side of the central fixation (4.4^{o} of eccentricity). Subjects were asked to look at the fixation center and put the right index finger between the left and right buttons during the time when they did not need to make any responses. After 200ms, the left or right part of the central diamond changed to black (a go signal). Depending on the initial block instruction, subjects were asked to press either the left or the right button using their right index finger in the hand task or make a saccadic eye movement to the left or the right dot according to the go signal. Occasionally (30%), a circle (a visual stop signal) or a beep (900Hz) (an auditory stop signal) was presented shortly after the go signal is presented. The stop signal lasted for 300ms. Subjects were told to make no response when either stop signal is presented. Four stop-signal delays (SSDs) were randomly assigned in the SS task for each condition. The SSDs for the hand tasks were 10, 110, 210 and 310 ms and the SSDs for the eye tasks were 10, 90, 180 and 270 ms. A successful go trial occurred when a response was made during a 1-sec time window for key pressing responses or saccadic responses, and a successful stop trial occurred when no button pressing response was made in hand response conditions or eyes are fixating the center in eye response conditions during a 1-s time window. The sequences of go and stop trials were randomly generated using the “optseq” algorithm, which was designed to increase the sensitivity of detecting BOLD signal change among task conditions (Dale, 1999) (http://surfer.nmr.mgh.harvard.edu/optseq).

Each experiment run included sixteen task blocks, two for each condition. The order of task blocks was counterbalanced. At the beginning of each block,

an instruction cue (“hand”/”eye” and “circle”/”beep”) was presented with a warning beep (500Hz) for 2 sec, followed by 15 continuous stop-signal task trials. The ITI was 1.7, 2.3 or 4.3 sec. The interval between two adjacent blocks was 16, 18 or 20 s.

4.2.3. Localizer task

Two localizer tasks were conducted to identify the brain areas involved in executing hand/eye movements and perceiving visual/auditory signals. Both localizer runs consisted of eight task blocks. In the eye/hand localizer task, the instruction was either “hand” or “eye”. The paradigm was similar to the response inhibition task but no stop-signal involved. The timing of the go signal and other trial events is the same as above. Subjects were asked to press either the left or the right button using their right index finger in the hand task or make a saccadic eye movement to the left or the right dot according to the go signal. In the visual/auditory localizer task, the instruction was either “beep” or “circle”. In the “beep” block, subjects were asked to press the left button whenever they heard a beep. In the “circle” block, subjects were asked to press the left button whenever they saw a circle in the center.

4.2.4. Procedure and apparatus

Each subject was trained before the scanning session. Subjects first practiced one run of each localizer task (5 minutes each). Afterward, they were trained to perform 3 runs of response inhibition tasks (7 minutes each). Speedy response was emphasized during the training and throughout the fMRI experiment. Subjects were required to achieve 90% accuracy for go trials and about 50% accuracy for stop trials in the hand response inhibition task. Eye movement was not monitored during the training session.

During the scanning session, each subject performed 8 runs of the response inhibition task and one run of each localizer task. Subjects did localizer tasks either in the beginning of the experiment or in the end of the experiment. The running order of tasks was counterbalanced across subjects.

Visual stimuli were rear-projected onto a screen positioned at the back of the magnet bore opening. Subjects viewed the visual stimuli through a mirror mounted on the head coil. Stimuli presentation was controlled and response data were collected with E-prime version 2.0.1.109 (Psychology Software Tools, Pittsburgh, PA) running on a personal computer (PC) with a Windows XP operation system. A response box interfaced with the PC through the parallel port was used for collecting manual responses.

4.2.5. Oculomotor recording and analysis method

A long range optic eye tracker (Applied Sciences Laboratories) was used to record eye positions in the scanner at 60 Hz. Since the camera was at the back of the magnet bore opening and the illumination beam went through the right side of the projection screen, only the right eye was monitored. Nine-point

calibration and drift correction was conducted at the beginning of the scanning and before each scanning run if necessary. Eye recording started at the beginning of each trial and ended at the end of each trial. Due to the limitation of the program, the performance of eye task was determined offline.

The original eye data included a set of parameters, including recording times, horizontal gaze coordinates, vertical gaze coordinates and event labels. The eye data was exported using EYENAL (Applied Sciences Laboratories). The saccadic eye movements were determined by a series of steps. First, fixations were identified using the criteria that at least six continuous data points are within a 0.5^{o} radius circle of the center of these data points. The onset and offset of a fixation were the time tag of the first and last data point during the fixation. A saccadic eye movement was defined as a movement between two continuous fixations. The onset of a saccade was the offset of the previous fixation. The offset of a saccade was the onset of the next fixation.

4.2.6. SSRTs estimation

According the Race Model (Logan and Cowan, 1984), the estimation of stop signal reaction time (SSRTs) was based on the inhibition function (the probability of responding when a stop signal is presented as a function of stop-signal delays) and distribution of the reaction time (RT) on go trials. SSRT was calculated using the integration method: SSRT=T-SSD, where T was the point when the integration of go RT equals the proportion of unsuccessful stop trials. To minimize the bias effect caused by the extreme SSDs (Band et al., 2003), only two central SSDs (out of four fixed SSDs) were used and the SSRT was averaged over SSDs after calculating those with integration method.

4.2.7. Image acquisition

All scans were carried on a Philips 3T Achieva scanner with an eight-channel SENSE head coil (Cleveland, OH). Head movement was minimized using foam padding and a tape across the forehead. We first collected a series of high-resolution structural 3D images (T1-weighted, 3D turbo field echo, 176 sagittal slices, slice thickness=1 mm, TR/TE=9.9/4.6 ms, matrix=256x256, FOV=25x25 cm). Ten series of functional images were acquired along to the anterior-posterior commissural (AC-PC) line using a standard T2*-sensitive gradient-recalled single shot echo planar pulse sequence (33 axial slices, 5mm thick, interleaved, TR/TE=2000/30 ms, Matrix=80x80, FOV=24x24 cm, Flip angle=79^{o}).

4.2.8. Image pre-processing

Images were first screened for obvious artifacts such as ghosting and motion. Runs with images showing large motion and artifacts were removed from further analysis. Image processing was carried out using Statistical Parametric Mapping version 2 (SPM2, Welcome Department of Imaging

Neuroscience, University College London, http://www.fil.ion.ucl.ac.uk/spm/). The first four images of each series of functional scans were discarded in each run to allow EPI signal to achieve equilibrium. Remaining images were corrected for differences in slice acquisition time and head motion. Functional series with images of greater than 3 mm of translational and 1.5^{o} of rotational motion were excluded from data analysis. A mean functional image volume was derived for each individual using the realigned images. The mean functional image was then normalized to the Montreal Neurological Institute (MNI) EPI template, using a 12-parameter affine registration followed by a series of nonlinear transformations (Friston et al., 1995). The normalization parameters were then applied to all the realigned functional images. Finally, all functional images were spatially smoothed with a Gaussian kernel of 8mm at full-width at half maximum (FWHM) and were high-pass filtered with a cutoff of 1/128 Hz.

4.2.9. Image data modeling

Functional Image data were modeled in two ways, by blocks and events. In block analysis, functional data were modeled by the cues and task blocks for the four task conditions. The individual block analysis results were mainly used for the functional connectivity analysis. The contrast maps of the block analysis were not major interested in this study (please see Appendix 4 for the block analysis result). In event-relate analysis, the trial vectors included go trials (G), successful stop trials (SS), unsuccessful stop trials (US) and undetermined trials for each condition. Undetermined trials referred to those stop trials in the eye task during which the saccadic eye movement cannot be determined because of blink or system noise. All vectors were convolved with a canonical hemodynamic response function (HRF) and then entered as regressors in the general linear model (GLM) (Friston et al. 1995). The vector of each epoch was constructed using the onset and duration of the vector as stated above. In conjunction and comparison analysis, in order to remove differences caused by the unequalled trial numbers between different conditions, we grouped all stop trials (AS) and conducted corresponding analysis.

4.2.10. Voxel-wise individual and group analysis

To eliminate artifacts caused by task-related motion, six motion parameters were entered as covariates. This procedure was demonstrated to increase the signal-to-noise ratio and improve task effects estimated using the GLM (Johnstone et al., 2006). Estimated parameters (beta values) were calculated and assigned to each voxel for each epoch or event for each task condition for each participant using the GLM (the first-level analysis). T tests were applied in the group level for contrasts of interests (the second-level analysis). A threshold of 0.05 (FWE corrected) was used to generate the contrast map from the block analysis and a threshold of 0.05 (FDR corrected) was used to generate contrast maps from the event-related analysis. To

identify common activations during response inhibition across different sensorimotor associations, the conjunction analytic procedures were applied to determine activations that are above threshold in different conditions (Friston et al., 2005; Nicholes et al., 2005). Since the activation of successful response inhibition in the HV condition was weaker than that in other conditions, the contrast maps of AS-G (all stop versus go trials) were reported in the result. Please see Appendix 5 for the conjunction result of SS-G (successful stop versus go trials) contrasts.

4.2.11. Functional connectivity analysis

Psychophysiological interaction (PPI) analysis was conducted to exam the functional connectivity of bilateral ventral IFG among different sensorimotor associations. Since each task block included both go trials and stop trials, the PPI analysis cannot identify the functional connectivity specifically for response inhibition at each condition. Instead, the PPI analysis in the current study reflected the covariation in activity in several brain regions for response control (mainly response inhibition) in one sensorimotor condition compared to another sensorimotor condition. We selected bilateral ventral IFG as the PPI seed because we want to see whether this region interacts with motor and sensory areas differently in response inhibition over different sensorimotor associations. The coordinates of the bilateral ventral IFG were identified individually using the contrast of all stop trials versus go trials. VOI were made as spheres with 8mm radius for each subject. The physiological component (Y series) was extracted from each VOI, corrected for variance associated with parameter of no interest and deconvolved by the HRF. The psychological component (P series) was made by convolving the contrast of each two task conditions with the HRF. We investigated the sensory effect by contrasting HA versus HV and EA versus EV and the motor effect by contrasting HA versus EA and HV versus EV. The psychological interaction component (PPI series) was made by reconvolving the multiplication of the physiological component and psychological component with the HRF. Then, PPI, Y and P series were used as predictors in the regression analysis. The PPI analysis reflects the correlation difference of one seed region with other brain regions between two psychological manipulations. The significant result may be caused by the co-activations between two “silence” regions. To remove this effect, we applied a mask using the contrast of AS versus G ($p<0.05$, uncorrected) in the group analysis level. The peak coordinate of each VOI for each subject was summarized and reported in Appendix 8.

4.3. Results

4.3.1. Behavioral results

A 2x2 ANOVA was conducted to test the main effect of motor and sensory modalities on behavioral performance. No significant main effect was observed on accuracy of go trials, reaction time of go trials and unsuccessful stop trials ($p>0.20$). The significant main effect of sensory modality was shown on accuracies of stop trials ($F[1,18]=51.18$, $p<0.001$) that stop trials with visual stop signals have higher accuracy than those with auditory stop signals in both motor modalities. The main effect of motor modality was significant on the SSRT ($F[1,18]=40.54$, $p<0.001$) that eye SSRTs are longer than hand SSRTs. In eye tasks, the SSRT for auditory stop signal (353±28 ms) was significantly longer than the SSRT for visual stop signal (298±31 ms) ($t[18]=5.25$, $p<0.001$) (see figure 2).

4.3.2. fMRI results

4.3.2.1. Activation during successful response inhibition

Group SS-G contrast maps showed great activations in bilateral MTG, STG, IPL, posterior ventral IFG/insula, right posterior dorsal IFG and left SFG in HA blocks; and bilateral IOG, MOG, FG, ITG, precuneus, right SPL and posterior ventral IFG/insula in HV blocks; bilateral MTG, STG, IPL, precuneus, posterior ventral IFG/insula, right posterior dorsal IFG, MFG and SEF in EA blocks; bilateral IOG, MOG, FG, ITG, IPL, SPL, posterior ventral IFG/insula, posterior dorsal IFG, MFG, SFG, pre-SMA and SEF in EV blocks ($p<0.05$, FDR corrected) (see figure 3).

4.3.2.2. Common activations during response inhibition

Hand response inhibition: Conjunction analysis of AS-G contrasts between HA and HV conditions showed common activation in bilateral MTG, posterior ventral IFG/insula, right posterior dorsal IFG, IPL, ACC and dorsal medial prefrontal cortex (DMPFC) ($p<0.05$, FDR corrected, see figure 4A).

Eye response inhibition: Conjunction analysis of AS-G contrasts between EA and EV conditions showed common activation in bilateral MTG, IPL, posterior ventral IFG/insula, dorsal IFG, MFG, posterior dorsal IFG, SFG, SEF, ACC and DMPFC ($p<0.05$, FDR corrected, see figure 4C).

Auditory guided response inhibition: Conjunction analysis of AS-G contrasts between EA and HA conditions showed common activation in bilateral STG, MTG, IPL, posterior ventral IFG/insula, SFG, right posterior dorsal IFG, ACC and DMPFC ($p<0.05$, FDR corrected, see figure 4B).

Visual guided response inhibition: Conjunction analysis of AS-G contrasts between EV and HV showed common activation in bilateral IOG, ITG,IPL/Precuneus, SPL, posterior ventral IFG/insula, right dorsal IFG, ACC and DMPFC ($p<0.05$, FDR corrected, see figure 4D).

Overall response inhibition: Conjunction analysis of AS-G contrasts across all conditions showed activation in bilateral posterior ventral IFG/insula, MTG, right dorsal IFJ, IPL, ACC and DMPFC ($p<0.05$, FDR corrected, see figure 4E).

4.3.2.3. Sensorimotor dependent activation during response inhibition

Although the bilateral posterior ventral IFG/insula was commonly activated in all conditions, the contrast map showed greater and more extensive activation in the IFG during inhibition of eye movements than during inhibition of hand movement. Paired comparison analysis showed that bilateral dorsal IFG were more activated in eye response inhibition than hand response inhibition ($p<0.05$, FDR corrected, see figure 5A). However, we did not find any IFG region shows greater activation during inhibition of hand movements than during inhibition of eye movements at the same threshold. A group of other prefrontal regions showed more extensive activation during inhibition of eye movements than during inhibition of hand movements, including bilateral MFG, SFS, and ACC ($p<0.05$, FDR corrected).

Paired comparison of SS-G contrasts showed that bilateral STG is more activated in HA and EA conditions than in HV and EV conditions, while bilateral FG, IOG and MOG extending to IPS are more activated in HV and EV conditions than in HA and EA conditions ($p<0.05$, FDR corrected). No sensory dependent activation was found in the lateral prefrontal cortex (see figure 5B).

4.3.2.4. Functional connectivity results

As expected, we found an increased functional connectivity between bilateral ventral IFG/insula and auditory regions (STG) in the EA condition compared to the EV condition ($p<0.05$, FDR corrected). The increased correlation between bilateral ventral IFG/insula and visual regions was found in the HV condition compared to the HA condition in a lower threshold, including fusiform gyrus and cuneus ($p<0.001$, uncorrected). Moreover, an increased functional connectivity was observed between the right ventral IFG/insula and areas in the tectum close to superior colliculus in the EV condition compared to the EA condition in a lower threshold ($p<0.001$, uncorrected). Figure 6 showed functional connectivity results at a relative low threshold ($p<0.001$, uncorrected). No significant correlation differences were found among bilateral ventral IFG/insula and other brain regions between HA and EA conditions and between HV and EV conditions.

4.3.2.5. Functional topography of brain regions involved in sensory processing and response control of different sensorimotor associations

Compared with the response inhibition tasks, two localizer tasks were conducted to identify cortical regions involved in processing sensory information and executing motor responses. Analysis showed that bilateral IOG, MOG and posterior temporal cortex are involved in processing visual

information, bilateral STG in processing auditory information, left M1 and SMA in executing manual responses and bilateral FEF, SEF and SPL in executing oculomotor responses ($p<0.05$, FDR corrected) (see figure 7). In contrast, a group of prefrontal, temporal and parietal regions are activated during response inhibition in different sensorimotor conditions (refer to 4.3.2.1).

4.4. Discussion

This study demonstrated a functional topography in the whole brain associated with sensory processing and response control of different sensorimotor associations. We found that bilateral posterior ventral IFG/insula along with MTG, right IPL and dorsal IFG are commonly involved in response inhibition over different sensorimotor associations. In addition, our results showed that more dorsal activation in the bilateral IFG along with the MFG during eye response inhibition than during hand response inhibition.

4.4.1. Common activation in posterior ventral IFG during response inhibition

Our data showed the common activation in bilateral posterior ventral IFG/insula in response inhibition over different sensorimotor associations, which is consistent with our previous findings that the activation of the bilateral posterior ventral IFG is independent of different motor responses (Leung and Cai, 2007) and different visual stop signals (Cai and Leung, 2009). The loci of bilateral posterior ventral IFG/insula in the current study were very close, within 9mm in all directions, to the loci of common areas identified in our previous study. It was also close to the right IFG associated with conditional stopping in previous studies, but more ventral to the IFC that is identified to connect with pre-SMA and STN (Aron et al., 2007).

Our functional connectivity analysis emphasized the increased interactions between bilateral ventral IFG/insula and auditory areas in response to the auditory stop signals than to the visual stop signal in the eye tasks. In a relatively lower threshold, the increased interactions between bilateral ventral IFG/insula and visual areas in response to the visual stop signal than to the auditory stop signal were observed in the hand tasks. The weak interaction between the ventral IFG/insula and visual region could be due to that the variation of the activity in visual regions between task blocks (e.g., EV vs. EA) is lower than that in auditory regions, since response execution was also triggered by the visual stimulus. The functional interaction between the bilateral ventral IFG/insula and sensory regions indicated the covariance between the IFG and other sensory areas in processing one type of sensory signal rather than in others. It suggests that the posterior ventral IFG/insula communicates closely with posterior association cortex in interpreting different sensory stop signals. It also suggested that the posterior ventral IFG/insula receives multisensory information from different sensory channels. Although

we did not find the significant covariance between the posterior ventral IFG/insula and motor areas (e.g. premotor and FEF) in one motor task compared with another one, we cannot exclude the possibility that the posterior ventral IFG/insula could interact with motor regions during response inhibition. The block contrasts in current experiment paradigm (e.g. HA versus EA and HV versus EV) mainly represented the difference in overall response control between two motor systems because each block includes go trials and stop trials. It was likely that the covariance between the posterior ventral IFG/insula and motor areas during response inhibition is underestimated in the PPI analysis with the current experiment design. It was also possible that the right posterior ventral IFG/insula is a “motor-independent” region. To solve this problem, future study could contrast the response inhibition task and a control task without response inhibition to identify the functional connectivity during response inhibition in different motor modalities.

4.4.2. IFG segregation between hand and eye response inhibition

Our previous study has shown the dorsal-ventral segregation of the IFG during response inhibition that the more dorsal part of the IFG is more involved in eye response inhibition while the more ventral part of the IFG is more involved in hand response inhibition (Leung and Cai, 2007). In this study, we also found more dorsal parts of IFG are more involved in inhibition of eye movements, and the loci of this activation are very close to those reported in our previous paper (8mm in all directions). Hasegawa and his colleagues (2004) found that neurons in the caudal end of the principal sulcus and the arcuate sulcus perhaps can code the signal for inhibition of eye movements. A few other neuroimaging studies also reported the activation of the IFG (dorsal and ventral) in oculomotor response inhibition (Heine et al., 2006; Chikazoe et al., 2007). Anatomical connection data from non-human primate studies supported that the IFG may play a role in controlling eye movements. Petrides and Pandya (1999; 2001) identified that the inferior frontal convexity is connected with area 8, which includes FEF. One recent anatomical study further showed that the area 45A is connected to the FEF and SEF and the connection between the area 45B and the FEF and the SEF is much stronger (Gerbella et al., 2009). The activation of dorsal IFG during inhibition of eye movements was very close to the area 45B. Taken together, our data suggested that the dorsal IFG plays a role in inhibiting eye movements.

However, this study did not replicate our previous finding that the more ventral IFG is more involved in inhibition of manual responses. This inconsistent finding could be attributed to differences in experimental design between two studies. Two points should be mentioned. One, participants generated and tried to inhibit voluntary saccadic eye movements in this study rather than more reflexive saccadic eye movements in our previous study, leading to more extensive activations in the prefrontal cortex. Two, this study used a mixed block and event design and each experimental run included all

different sensorimotor tasks, while the previous study used event-related design and each experimental run only had one sensorimotor response inhibition task. So participants were required to keep updating and remember the sensorimotor association associated with the current task during each task block in the current study, which could induce more activation in the posterior IFG because of verbalization or working memory. If it was mainly due to verbalization, the activation in the left hemisphere should be stronger than it in the right hemisphere. A previous meta-analysis study showed greater activation in the left IFG than in the right IFG during silent verbalization (Grezes and Decety, 2001). However, the hemisphere difference was not observed.

4.4.3. Cortical segregation between auditorily and visually guided response inhibition

We only found sensory-dependent activation in primary sensory cortex but not in lateral prefrontal cortex during response inhibition. Goldman-Rakic (1987a, 1987b, 1996) proposed “domain-specific” hypothesis that the prefrontal sub-regions are specialized to process different types of sensory information. She and her colleagues provided evidence that the dorsolateral prefrontal cortex is more involved in visuospatial working memory and the ventrolateral prefrontal cortex in object working memory (Goldman-Rakic, 1996; Romanski and Goldman-Rakic, 2002). They further investigated visual and auditory responsive neurons in the ventrolateral prefrontal cortex and found that auditory responsive neurons locate anterolateral to the visual responsive neurons but and some neurons in the ventrolateral prefrontal cortex are responsive to both auditory and visual stimuli (Romanski and Goldman-Rakic, 2002). These findings suggested that the ventrolateral prefrontal cortex process multisensory stimuli. However, we did not find the activation of the IFG is dependent on spatial/non-spatial (orientation/color) visual information during response inhibition in our previous study (Cai and Leung, 2009) and we did not find the activation of the IFG is dependent on visual/auditory information during response inhibition in this study. It is possible that the current functional MRI does not have enough spatial resolution to differentiate sensory-dependent activity during response inhibition. It is also possible that the posterior ventral IFG receives multisensory information to guide response inhibition or the current task does not require too much working memory.

4.4.4. Activation of other prefrontal regions during response inhibition

Besides bilateral posterior ventral IFG/insula, conjunction analysis also identified common activation in right dorsal IFG and ACC during response inhibition over different sensorimotor associations. Chikazoe et al. (2008) suggested that the activation of the right dorsal IFG (also called IFJ) in response inhibition tasks could be attributed to infrequent stimulus processing.

They manipulated infrequent stop signal and infrequent go signal and found the similar activation in the right dorsal IFG in response to the infrequent stop signal as well as the infrequent go signal. The similar analysis was conducted in our second study to separate infrequent stimuli processing from response inhibition. ACC has been associated with cognitive control and conflict monitoring (see review by Carter and van Veen, 2007). The common involvement of the ACC may represent a conflict-control process to manage the competing responses (go and stop) since all stop trials are included in the contrast of AS versus G. The activation of the ACC was not found in the conjunction analysis of successful response inhibition across different sensorimotor conditions (see Appendix 5).

Our result also showed the significant activation of the bilateral MFG during inhibition of saccadic eye movements rather than during inhibition of hand responses. Dorsolateral prefrontal cortex has profuse connection with prefrontal oculomotor regions, such as FEF and SEF (Petrides and Pandya, 1999; Wang et al., 2005). It has been suggested that the dorsolateral prefrontal cortex is involved in preparation of saccadic eye movements and saccade sequences, inhibition of unwanted reflexive saccadic eye movements, and memory-guided saccades (see review by Pierrot-Deseilligny et al., 2005). Therefore, the MFG may be particularly engaged in suppressing eye movements.

4.4.5. Sensorimotor effects on response inhibition

In contrast to previous findings (Logan and Irwin, 2000; Boucher et al., 2007), we found shorter SSRTs in the hand task than in the eye task and similar RT in go trials between the two motor modalities. Longer RTs and SSRTs in the eye task than the hand task were probably due to specific manipulation in the current experiment. Most eye response inhibition studies examined reflexive saccades using the peripheral stimuli. In the current task, however, the go signal was located in the center of the screen in order to match the hand and eye tasks and reduce the visual facilitation to reflexive saccadic eye movements. Subjects were required to generate voluntary saccades instead of reflexive saccades, which likely lead to longer reaction time.

The effect of sensory modality in the SSRTs was significant in the eye task but not in the hand task, which is consistent with previous findings (Boucher et al., 2007). Boucher et al. found that it is more difficult to inhibit a saccadic eye movement in response to an auditory stop signal than in response to a visual stop signal but the similar effect is not observed in inhibition of hand movements. Our PPI analysis revealed the significantly increased correlation between the ventral IFG/insula and auditory cortex in the EA condition compared to the EV condition, but the similar correlation difference pattern was not observed in the HA condition compared to the HV condition. It suggested that inhibiting eye movements in response to an auditory stop

signal probably requires extra effort to achieve the equivalent performance compared to other sensorimotor associations.

Compared with the auditory stop signal, the foveal visual stop signal facilitated response inhibition (higher stop accuracy for visual stop signal). In particular, the visual stop signal was more efficient in stopping eye movements than the auditory stop signal (EV has higher stop accuracy and shorter SSRT than EA), which is consistent with the previous finding (Cabel et al., 2000). Electrophysiological studies demonstrated that saccadic eye movements are mainly generated by movement neurons in FEF and superior colliculus (Hanes and Schall, 1996; Hanes and Pare, 1998). It has been shown that superior colliculus receives visual input (Frens and van Opstal, 1996). Therefore, it is possible that the facilitation of the visual stop signal on inhibition of eye movements relies on the superior colliculus. In consistent with this possibility, our PPI analysis exhibited the increased functional connectivity between the right ventral IFG/insula and superior colliculus in the EV condition than the EA condition.

In summary, this study identified the common activation in the bilateral posterior ventral IFG/insula along with right dorsal IFG, ACC and bilateral MTG during response inhibition over different sensorimotor associations. The motor-dependent activation was observed in the prefrontal cortex, showing that more dorsal part of bilateral IFG and MFG are more activated for oculomotor response inhibition than manual response inhibition. No sensory-dependent activation was observed in the prefrontal cortex. Therefore, we suggested that bilateral posterior ventral IFG/insula plays a common role in response inhibition independent of sensorimotor associations, most likely in interpreting stop signals and triggering stop processes, while the dorsolateral prefrontal cortex is important in inhibitory control of voluntary saccadic eye movements.

4.5. Limitations

There were three major limitations in this study. 1) The experiment design allowed separating sensory processing and motor control from response inhibition, but it cannot be excluded that the common activation among different sensorimotor associations may represent other cognitive processes, such as rule processing and infrequent stimulus processing. The next study was designed to separate rule representation and infrequent stimulus processing from the response inhibition. 2) We were unable to compare successful and unsuccessful inhibition of eye movements in the current dataset though the eye movements were recorded during the experiment. The total number of useful unsuccessful eye trials was not enough for statistical analysis. Because of the high stop accuracy, subjects failed in few stop trials (about 30%). And saccadic eye movements were difficult to determine in some eye trials because of blinks and increased system noise. The future study

should reduce the number of experimental conditions and increase the number of trials in each condition to attain enough useful eye trials. 3) Although we tried to balance behavior performance among different experimental conditions, it turned out that there is significant facilitation of visual stop signals compared to auditory stop signals. Ideally, the step-wised stop-signal paradigm should be used to assure that subjects could achieve about 50% stop accuracy in each condition. However, it was not trivial to determine the specific saccadic eye movement online given the current system noise.

5. Study 2: Dissociation of response inhibition and rule representation

5.1. Background and significance

As a type of executive function, response inhibition refers to a cognitive-motor process for inhibiting inappropriate or unwanted behavior. Earlier work on non-human primates has demonstrated that the damage to inferior frontal convexity could lead to the disinhibition of perseverative behaviors (Fuster, 1997; Iversen and Mishkin, 1970). Neuroimaging studies of human patients and TMS studies of healthy adults have emphasized the critical role of the right IFG in response inhibition (Aron et al., 2003; Chambers et al., 2006). However, there is no doubt that the IFG is engaged in various cognitive processes besides response inhibition.

The IFG is composed of multiple subdivisions with different cytoarchitectonic features and connections with other cortical and subcortical regions, suggesting its role in diverse cognitive and motor processes (Brodmann, 1907, 1909; Walker, 1940; Petrides and Pandya, 2001). In particular, neuroimaging studies have revealed that the left IFG is activated in rule representation (Bunge et al., 2003) and the right posterior dorsal IFG in infrequent stimulus processing (Chikazoe et al., 2007). It remains unclear whether and how the IFG subdivisions contribute to other cognitive processes during response inhibition. The functional dissociations between the IFG subdivisions are rarely tested in within-subject studies.

Most of response inhibition tasks, such as the go/no-go task and the stop-signal task, are composed of response execution and infrequent response inhibition trials. The contrast of infrequent inhibition versus frequent execution trials is widely used to identify the process of response inhibition (Garavan et al., 1999; Konishi et al., 1998; Rubia et al., 2001; 2003; 2007). It seems to us that this contrast reflects the mixture of response inhibition process and other cognitive processes, such as rule representation (stimulus-response associations) and infrequent stimulus processing. The goal of the current study is to dissociate the contribution of IFG subdivisions to rule representation and infrequent stimulus processing from response inhibition.

The goal of part of the dissertation is to identify the functional specificity and connectivity of IFG subdivisions using a Stop/Not-Stop task, which involves two types of visuomotor tasks (a stop-signal task and a not-stop task).

Subjects were presented with the exact same visual stimuli in both tasks. They were only required to inhibit their responses when stop signals were presented in the stop-signal task but not in the not-stop task. By comparing the activations across different stages of two tasks, we distinguished activations in different IFG subdivisions that could reflect different cognitive processes.

5.2. Material and Method

5.2.1. Subjects

Twenty-six healthy young adults (age range: 18 – 39 yrs, 11 females) were recruited from the university campus and the psychology subject pool, none reported a history of neurological/psychiatric disorders or a history of drug abuse. One participant was excluded from the group analysis because his/her stop accuracy was an outlier (3 standard deviations away from the mean) and two participants were excluded because of image artifacts. Twenty-three subjects were included in the final analysis. All subjects had normal or corrected to normal vision. All subjects provided written consent, which is approved by the local Institutional Review Board.

5.2.2. Stop/Not-Stop task

We designed the experiment aiming to differentiate activations in correspondence to rule and infrequent stimulus processing from response inhibition in the same experimental setting. We used a 2x2 design, with 2 types of visual cues (color and motion) and 2 types of visuomotor tasks (stop-signal task [SST] and not-stop task [NST]) (see figure 8) resulting in 4 task conditions (color-SST, color-NST, motion-SST, and motion-NST). Two types of visual cues were used to differentiate regions related to sensory processing from regions related to cognitive processes such as retrieval and maintenance of task rules. We chose to use color and motion cues because thy elicit responses in anatomically and functionally separable parts of the visual association cortex and similar parameters were used in previous studies of response inhibition in non-human primates (e.g., Sakagami et al., 2001). The two manual tasks are visually identical, with the same go and stop signals presented in random sequences. The corresponding response to the stop signal was rule dependent. We used a mixed event-related and block design. Each task block had three epochs: cue, delay and response. That is, cue and response epochs were separated by a delay in time as follows: a visual cue was presented at the beginning of the task block to indicate the current task rule (stop or not-stop). After a 6.5-sec delay (black screen), a warning signal was presented for 1 sec followed by a sequence of 9 go signals and on occasions (about 30% chance), followed by the stop signal. Depending on the initial visual cue, subjects would perform either the typical SST (rule 1: respond to the go signal and cancel the response upon the presentation of the stop signal) or the NST (rule 2: ignore the stop signal and continue to respond).

After the response epoch, there was a variable resting period (13.5, 15 or 18 sec) before the next visual cue for the next task block. Each stop signal (a circle) was presented for 300ms after the presentation of the go and subjects were asked to withhold their responses in the SST and continue to respond in the NST. For the SST, the interval between the go and stop signals, also called stop signal delay (SSD), was dynamically adjusted in steps of 50ms starting from 150ms for the purpose of achieving a stop accuracy of about 50%. If a subject failed on a stop trial, the SSD would be decreased by 50ms on the next stop trial. If a subject successfully inhibited a response on a stop trial, the SSD would be increased by 50ms on the next stop trial. The lower and upper limits of the SSDs were 0 and 600ms, respectively. A correct response was considered as a button press within 700ms after the onset of the go signal on a go trial or no button press within 1000ms after the onset of the go signal on a stop trial. For the NST, similar variations in SSD were used to simulate the SST, with SSD randomly varied in steps of 50ms ranging from 0 to 400ms. Variable trial durations (1, 1.5 or 2 sec) were used for both visuomotor tasks and counterbalanced across subjects.

The color cue was a matrix of black and color squares with huge change in the same range of blue or orange. The motion cue was a matrix of upward and downward moving black/grey squares. The associations between cue and task rule were randomly paired and counterbalanced across subjects.

5.2.3. Procedure and Apparatus

Each subject was trained a day or two before the scanning session. We first attained a baseline of visuomotor reaction time by recording speedy button press to the presentation of a visual stimulus (a triangular). Afterwards, each subject was trained to perform the SST and NST separately (10 minutes each). The training order of these two tasks was counterbalanced across subjects. Lastly, each subject was trained to perform the Stop/Not-Stop task for two runs (20 minutes total), during which the SST and NST blocks were mixed in each run. The reaction time in go trials and unsuccessful stop trials in SST and go trials and not-stop trials in NST in the not-mixed and mixed training runs were compared to evaluate reluctance in responding to the go signal for each individual. Subjects were required to achieve above 95% accuracy of go trials on go condition in SST and all trials in NST and around 50% accuracy on stop trials in SST. Speedy response was emphasized during the training and throughout the fMRI experiment. During the scanning session, subjects first practiced one run of the experimental task outside of the magnet and performed 6 runs of the experimental task during the scanning. Each run included 12 task blocks, thus there were 18 blocks for each task condition.

Visual stimuli were rear-projected onto a screen positioned at the back of the magnet bore opening. Subjects viewed the visual stimuli through a mirror mounted on the head coil. Stimuli presentation was controlled and response data were collected with E-prime version 2.0.1.109 (Psychology Software

Tools, Pittsburgh, PA) running on a personal computer (PC) with a Windows XP operation system (Pentium 4, Dell Dimension 5100, Dell Inc). A response box interfaced with the PC through the parallel port was used for collecting manual responses.

5.2.4. SSRTs estimation

According the Race Model (Logan and Cowan, 1984), the estimation of stop signal reaction time (SSRTs) was based on the inhibition function (the probability of responding when a stop signal is presented as a function of stop-signal delays) and distribution of the reaction time (RT) on go trials. In the tracking stop-signal task, we estimated the SSRT using two different ways. If the stop accuracy fell in the 95% confidence interval around 0.5 (0.5 is the theoretical mean of the stop accuracy in the tracking stop-signal paradigm), SSRT was calculated by subtracting the mean SSD from the mean go RT. If the stop accuracy fell out of the 95% confidence interval around 0.5, SSRT was calculated using the integration method: SSRT=T-SSD, where T was the point when the integration of go RT equals to the proportion of unsuccessful stop trials. To minimize the bias effect caused by the extreme SSDs (Band et al., 2003), only two or three central SSDs (about 25-30 trials for each) with the most observations were selected out (about 5-8 SSDs on average) and the SSRT was averaged over SSDs after calculating those with integration method.

5.2.5. Image Acquisition

All scans were carried on a Philips 3T Achieva scanner with an eight-channel SENSE head coil (Cleveland, OH). Head movement was minimized using foam padding and a tape across the forehead. We first collected a series of high-resolution structural 3D images (T1-weighted, 3D turbo field echo, 176 sagittal slices, slice thickness=1mm, TR/TE=9.9/4.6 ms, matrix=256x256, FOV=25x25 cm). A series of T1-weighted inplane structural images were then collected parallel to the anterior-posterior commissural (AC-PC) line (24 axial slices, slice thickness=5mm, TR/TE=300/5.0ms, Matrix=256x256, FOV=22x22 cm). Six series of functional images were acquired along the same AC-PC plane using a standard T2*-sensitive gradient-recalled single shot echo planar pulse sequence (24 axial slices, 5mm thick, interleaved, TR/TE=1500/30 ms, Matrix=64x64, FOV=22x22 cm, Flip angle=80^{o}, 309 volumes/session [463.5 sec]).

5.2.6. Image Pre-processing

Images were first screened for obvious artifacts such as ghosting and motion. Runs with images showing large motion and artifacts were removed from further analysis. Image processing was carried out using Statistical Parametric Mapping version 2 (SPM2, Welcome Department of Imaging Neuroscience, University College London, http://www.fil.ion.ucl.ac.uk/spm/).

The first four images of each series of functional scans were discarded in each run to allow T1 signal to achieve equilibrium. Remaining images were corrected for differences in slice acquisition time and head motion. Functional series with images of greater than 3 mm of translational and 1.5^{o} of rotational motion were excluded from data analysis. A mean functional image volume was derived for each individual using the realigned images. The inplane and high-resolution 3D anatomical images were segmented into grey and white matter and co-registered with the mean functional image. The segmented inplane image was then normalized to the Montreal Neurological Institute (MNI) grey matter template, using a 12-parameter affine registration followed by a series of nonlinear transformations (Friston et al., 1995).The normalization parameters were then applied to all the realigned functional images. Finally, all functional images were spatially smoothed with a Gaussian kernel of 8 mm at full-width at half maximum (FWHM) and were high-pass filtered with a cutoff of 1/128 Hz.

5.2.7. Image Data Modeling

Functional image data were modeled in two ways, by task epochs and by task events.

Epoch analysis: Functional data were modeled by the cue, delay and response epochs for the four task conditions. All epochs were convolved with a canonical hemodynamic response function (HRF) and then entered as regressors in the general linear model (GLM) (Friston et al. 1995). The vector of each epoch was constructed using the onset and duration of the epoch as stated above. The delay epoch was modeled by two vectors coding the first and second half of the delay following previous work on modeling sustained activity during the delay of delayed-recognition tasks (Zarahn et al., 1997). Since the cue vector and the first delay vector were only 1.5 seconds apart, the second delay vector was used to interpret brain activity during the delay. The design matrix thus included the following vectors for the 4 task conditions (color/motion SST/NST): cue, first half of delay, second half of delay and response. The warning signal was modeled as a separate vector independent of the task condition.

Event-related analysis: Since no effect of sensory cues was found in the response epoch, they were not modeled in the event-related analysis of response trials. The trial vectors included go trials in SST (SST-G), successful stop trials in SST (SST-SS), unsuccessful stop trials in SST (SST-US), go trials in NST (NST-G), and not-stop trials in NST (NST-NS). To test for response slowing, we distinguished the go trials preceded by a go trial (PG) by their RT. In SST, PG trials were divided by the mean RT of SST-US. In NST, PG trials were divided by the mean RT of NST-NS. Trials with short RT (SST-PG-SRT; NST-PG-SRT) and long RT (SST-PG-LRT; NST-PG-LRT) were modeled in both tasks.

5.2.8. Voxel-wise individual and group analysis

To eliminate artifacts caused by task-related motion, six motion parameters were entered as covariates. This procedure was demonstrated to increase the signal-to-noise ratio and improve task effects estimated using the GLM (Johnstone et al., 2006). Estimated parameters (beta values) were calculated and assigned to each voxel for each epoch or event for each task condition for each participant using the GLM (the first-level analysis). T tests were applied in the group level for contrasts of interests (the second-level analysis). Since IFG was the major region of interest, an anatomical mask obtained from the anatomical automatic labeling (AAL) atlas was applied to derive the IFG group analysis. In this dissertation, we reported the group maps with and without IFG masks. A threshold of 0.05 (FWE corrected) was used to generate the contrast map from the epoch analysis and a threshold of 0.05 (FDR corrected) was used to generate contrast maps from the event-related analysis.

5.2.9. Identification of activation foci

We first identified the activations in IFG related to response inhibition by contrasting the response epoch of SST versus that of NST. To further dissociate the cognitive and motor processes during the response epoch, we generated contrast maps of SST-SS versus SST-G, SST-US versus NST-NS and NST-NS versus NST-G from the event-related analysis. In order to determine the involvement of the different IFG activations during other epochs, we examined the contrast of SST versus NST and color versus motion cues for both the cue and delay epochs.

5.2.10. Region of interest analysis

One major goal of this study is to test whether the IFG subdivisions contribute to different cognitive processes involved in response inhibition tasks. We defined mainly functional IFG clusters as well as other cluster in prefrontal and other brain regions by contrasting SST versus NST at the response epoch. We then derived the activation values (betas) of these clusters for each epoch using Marsbar (Brett et al., 2002) (http://marsbar.sourceforge.net/). Three primary questions were addressed: 1) Are these clusters extracted from the response epoch contrast also activated during the cue or delay epoch? 2) Are they sensitive to the sensory cues or the task rules during the cue or delay epoch? 3) Do they show differential responses to different trial conditions: stop trials (SST-SS and SST-US) than not-stop trials (SST-G, NST-G and NST-NS)? We also calculated the correlation between the activation values of these functional clusters from the contrast of SST versus NST and response inhibition performance (i.e., SSRT).

To dissociate infrequent stimulus processing from response inhibition, we examined the activation by contrasting the NST-NS versus NST-G trials. Since

behavioral data showed longer RT on NST-NS trials compared to NST-G trials, we re-categorized go trials by their RTs (shorter [SRT] and longer [LRT] than US trials in SST and NS trials in NST, respectively) to test for response slowing effects. Furthermore, to minimize the effect of post-error slowing, only go trials after a correct go trial (PG) were selected in accordance to previous findings (Li et al., 2008a; 2009). We reported the betas and RTs of SST-PG-SRT, SST-US, SST-PG-LRT, NST-PG-SRT, NST-NS and NST-PG-LRT trials to see whether the pattern of activation is dependent on the infrequency effect or response slowing.

5.2.11. Functional connectivity analysis

Psychophysiological interaction (PPI) analysis was applied to differentiate the functional connectivity of clusters identified from the response epoch contrast. The center coordinates of clusters were determined individually using the contrast of SST versus NST. Spheres with 6mm radius were made for each individual as their voxels of interest (VOI) (6mm was determined by the half distance of between the centers of two closest group functional clusters). The physiological component (Y series) was extracted from each VOI, corrected for variance associated with parameter of no interest and deconvolved by the HRF. The psychological component (P series) was made by convolving the contrast of SST versus NST in the response epoch with the HRF. The psychological interaction component (PPI series) was made by reconvolving the multiplication of the physiological component and psychological component with the HRF. Then, PPI, Y and P series were used as predictors in the regression analysis. The peak coordinate of each VOI for each subject was summarized and reported in Appendix 9.

5.3. Results

5.3.1. Behavioral results

Figure 9 shows the reaction time (RT) results. Two-way ANOVA analysis showed no significant main effect of sensory cues for all the behavioral measurements for both SST and NST (all p's>0.5). There was no significant main effect of task rule for go accuracies (p's>0.3), but a significant main effect for go RT with responses to NST-G shorter than SST-G ($F[1,22]=128$, $p<0.001$). The average RT for NST-G was significantly shorter than that for NST-NS ($t[22]=4.11$, $p<0.001$). This effect, however, was not observed for the NST when performed separately from the SST during training, but for the NST during training mixed with SST ($t[22]=2.07$, $p<0.05$). Overall, RTs for SST-G, SST-US, NST-G and NST-NS were significantly shorter in runs with a single task than the runs with both tasks during training ($F[1,22]=30$, $p<0.001$).

5.3.2. Task and sensory-dependent activation across epochs

During the cue epoch, visual cues were presented and participants were assumed to recognize the visual stimuli and retrieve the corresponding task rules. Regions involved in processing specific visual stimuli or tasks rules were expected to show sensory-dependent (color versus motion) or task-dependent (SST versus NST) activations. No significant sensory-dependent activation was observed in the IFG. As expected, sensory-dependent activity was observed in the FG and MTG ($p<0.05$, FDR corrected). In contrast, task-dependent effect was observed in the left anterior IFG (anterior pars triangularis) and left anterior ventral IFG (pars orbitalis), showing greater activation to NST than SST ($p<0.001$, uncorrected; the cluster significance was close to FDR corrected threshold, $p=0.06$). The activation in the left anterior IFG was significantly above the baseline during the NST task cues whereas the activation in the left anterior ventral IFG was not above the baseline in each condition. Figure 10 showed corresponding contrast maps at threshold $p<0.001$, uncorrected.

During the delay epoch, participants were told to rehearse the relevant task rules. Regions involved in holding task rules were expected to show sustained activity during the delay. However, we did not observe any suprathreshold sustained task-dependent activation during the delay epoch. The weak activation during the delay epoch could be due to less demanded working memory load for remembering one task rule (Leung et al., 2004).

During the response epoch, participants were told to stop their planned response to the go signal infrequently in SST but keep making responses in NST. Results are shown figure 11. The right ventral IFG/insula (pars triangularis), posterior lateral ventral IFG (ventral pars opercularis), posterior dorsal IFG (dorsal pars opercularis), MFG/anterior dorsal IFG (dorsal pars triangularis), frontopolar cortex (FPC), bilateral FEF, IPL, SPL, right thalamus, left insula/ventral IFG, pre-SMA, cerebellum and tectum close to superior colliculus showed much stronger activation in SST than in NST ($p<0.001$, FWE corrected) (see figure 11).

To determine whether the regions identified from the contrast of SST versus NST in the response epoch contribute to other sensory and cognitive processes, we examined their activation during the cue epoch. ROI analysis showed suprathreshold activation in the cue epoch in the right posterior dorsal IFG, bilateral FEF, SPL and pre-SMA ($p<0.001$), but none of them are cue- and task-dependent in the cue epoch ($p>0.4$) (see Figure 11).

5.3.3. Activation pattern of clusters during response trials

We further examined activations in these clusters above defined by the contrast of SST versus NST in the response epoch during different types of response trials. Figure 12 A showed significantly greater activation on SST-SS, SST-US and SST-AS (all stop trials in SST) trials than SST-G trials and on NST-NS trials and NST-G in bilateral FG and MTG ($p<0.001$) and no

significant differences were observed among SST-SS, SST-US and SST-NS. Figure 12 B showed that significantly greater activation on SST-AS trials than SST-G trials, on NST-NS trials than NST-G trials, and on SST-AS trials than NST-NS trials in right MFG/anterior dorsal IFG, lateral posterior ventral IFG, ventral IFG/insula, FPC, bilateral IPL and SPL ($p<0.001$). Besides, right MFG, lateral posterior ventral IFG and ventral IFG/insula showed significantly greater activation in SST-US trials than SST-SS trials ($p<0.001$) whereas other clusters did not show significant difference between these two conditions. The significant correlation was observed between the SS-US betas of the right ventral IFG/insula and the SSRT ($r^2=0.3$, $p<0.006$, see figure 11I). Right posterior dorsal IFG showed greater activation in SST-SS trials than SST-G trials and in NST-NS trials than NST-G trials ($p<0.001$). However, no difference was found between SST-AS trials and NST-NS trials (see figure 12C).

5.3.4. Activation associated with failed inhibition effort

We contrasted the SST-US versus NST-NS with an attempt to reveal processes related to stop triggering. Participants were presented with same visual stimuli and responded on both SST-US and NST-NS trials. The key difference might have been that participants intended to inhibit their responses on SST-US trials though they failed. According the race model, the failed stopping does not necessarily indicate the absence of stop process rather a failure of completing the stop process before the go process. Thus, the contrast of SST-US trials versus NST-NS trials may reflect the process of triggering a stop process as well as error performance monitoring. We found that the activation in the right ventral IFG/insula, right anterior dorsal IFG extending to right MFG, right IPL and ACC is greater on SST-US trials than on NST-NS trials ($p<0.05$, FDR corrected, see figure 13). See Appendix 6 for other contrast maps with IFG mask in event-related analysis.

5.3.5. Activation associated with processing infrequent stimuli

The contrast of SST-SS versus SST-G was assumed to reflect a mixture of response inhibition and infrequent stimulus processing since the stop trials were infrequent. To dissociate these two processes, we compared NST-NS and NST-G trials. Since the NST-NS trials were less frequent than the NST-G trial and response inhibition was not demanded in the NST, the contrast of NST-NS versus NST-G would mostly reflect infrequent stimulus processing. This contrast revealed a greater activation in the right posterior dorsal IFG, FG, IOG and IPS during NST-NS trials relative to NST-G trials ($p<0.001$, FDR corrected, see figure 14).

5.3.6. Activation associated with response slowing

The behavioral results revealed that the average RT of NST-NS is longer than that of NST-G. Thus, the contrast of NST-NS versus NST-G may also

reflect response slowing besides infrequent stimulus processing. To dissociate response slowing from infrequent stimulus processing, we examined the effect of response slowing in SST-PG and NST-PG (only for go trials following go trials), in comparison with SST-US and NST-NS, on right posterior dorsal IFG (Figure 15A). The activation during NST-PG-LRT trials was greater than that during NST-PG-SRT trials ($p<0.005$) but the activation during SST-PG-LRT trials and during SST-PG-SRT trials were not significantly different ($p=0.17$). Activations during SST-US trials were greater than both short and long RT trials of SST-PG ($p<0.001$). Similarly, activations during NST-NS trials were greater than during the short and long TR trials of NST-PG ($p<0.001$). The numbers of each trial type are different but not correlated with infrequency.

5.3.7. Functional connectivity analysis

We further examined whether regions identified from the contrast of SST versus NST in the response epoch and the left anterior IFG identified from the contrast of NST versus SST in the cue epoch show differential pattern of functional connectivity during response epoch. Significantly increased functional interactions were found between left anterior IFG and the right MTG during SST compared to NST ($p<0.05$, FDR corrected, see Figure 16A). Right MFG/anterior dorsal IFG was significantly more correlated with supplementary area (SMA), right premotor cortex, putamen and left thalamus during the SST than during the NST ($p<0.05$, FDR corrected, see figure 16B). The right posterior dorsal IFG was mainly correlated with left putamen ($p<0.05$, FDR corrected, see figure 16C). The right FPC showed significant covariance with right ventral and dorsal IFG, bilateral putamen, SMA, left thalamus and right IPL ($p<0.05$, FDR corrected, see figure 16D). Although the PPI result of the right posterior ventral IFG/insula, right lateral posterior ventral IFG and pre-SMA did not reach the significance in the FDR level, it showed the similar functional connectivity pattern including putamen and SMA in a lower threshold ($p<0.001$, uncorrected, see Appendix 7).

5.4. Discussion

It has been suggested that the IFG plays an important role in response inhibition, while it has also been implicated in other cognitive processes, such as rule representation, infrequent stimulus processing and working memory. In this study, we demonstrated that IFG subdivisions are involved in different cognitive processes. We also revealed different functional coupling between IFG subdivisions and other cortical and subcortical regions during response inhibition. More specifically, we suggested that the right ventral IFG/insula and right MFG/anterior dorsal IFG contributes to response inhibition, the right posterior dorsal IFG contributes to infrequent stimulus processing, and the left anterior IFG contributes to rule representation.

5.4.1. Rule representation

The IFG has been implicated in learning and retrieving sensorimotor task rules. Bussey and his colleagues (2001) have found that the damage to the ventral and orbital prefrontal cortex impair the monkey's ability to rapidly learn new sensorimotor associations. An electrophysiological study of monkeys has shown that the neurons in the IFG can differentiate go/no-go responses in the color-cued condition, which implicates its role in stimulus-response association (Sakagami et al., 2001). Previous neuroimaging studies have also shown that the left IFG is involved in processing rule-related information. Bunge et al. (2003) have investigated cortical regions sensitive to task rules in the cue and delay epochs by manipulating the complexity of different task rules (abstract match/non-match rules versus a simple sensorimotor rule) and found greater activation in the left anterior IFG and left posterior dorsal IFG for the non-match task rule than the match task rule and the simple sensorimotor rule. Sakai and Passingham (2006) have also shown that the left anterior IFG and left posterior IFG are more activated in a semantic task than in a visual task. In consistent with previous findings, our data have showed that the left anterior IFG, mainly anterior pars triangularis, is sensitive to different task rules. It is interesting that the left anterior IFG is more activated for NST than SST. Although NST may seem less complicated than SST in the level of sensorimotor control, it involves an additional level of rules, such as ignoring the stop signal. Badre and D'Esposito (2007) have shown that the activation along the rostro-caudal axis of the frontal lobe may reflect hierarchical levels of cognitive control and the left inferior frontal sulcus and frontopolar cortex (FPC) may be involved in perceptual dimensional competition and context competition, respectively. The activation of the pars triangularis in our study is close to the FPC in their study. It is possible that this activation may reflect the representation of additional cognitive processes in NST.

It is arguable that the task-dependent activation of the left anterior IFG during the cue epoch could be explained as a resting-state effect since it is assumed that the NST is less demanding than the SST. However, this explanation is less possible. If one region represents a resting-state, the activation of NST versus SST should be sustained across three task epochs. The ROI analysis has shown the effect only in the cue epoch but not in the delay and response epochs. Instead, the activation of NST versus SST in the left anterior ventral IFG during the cue epoch may represent a resting state, given that the activation of this region at each condition is not suprathreshold and the greater activation of NST versus SST sustains across all epochs. A previous study has suggested that the left anterior ventral IFG is a part of default mode (Raichle et al., 2001).

In contrast to activation in the cue epoch, the left anterior IFG showed an opposite pattern in the response epoch that it has greater activations for the SST than for the NST. The PPI analysis revealed the significant covariance between the left anterior IFG and right MTG during the response epoch, which

is a unique functional connectivity pattern in comparison to other prefrontal regions. It further indicates that the left anterior IFG plays a role in rule processing. The connection between the ventrolateral prefrontal cortex and temporal cortex has been emphasized in rule learning. Animal lesion studies have demonstrated that the disconnection between the inferior frontal convexity and IT impairs the ability to learn new sensorimotor associations (Wang et al., 2000; Bussey et al., 2001; 2002).

5.4.2. Response Inhibition

A majority of neuroimaging studies have shown that the IFG is activated while a motor response is suppressed or cancelled. Some have further suggested that the IFG in the right hemisphere plays a dominant role in response inhibition rather than regions in the left hemisphere (Garavan et al., 1999; Konishi et al., 1999). Human patient studies and TMS studies have demonstrated that the dysfunction of the right IFG is tightly associated with the deficit in response inhibition (Aron et al., 2003; Chambers et al., 2006). Nonetheless, other studies have suggested that other cortical or subcortical regions play an important role in response inhibition, such as pre-SMA, striatum and subthalamatic nuclei (Aron and Poldrack, 2006; Li et al., 2006; Vink et al., 2005).

Our previous studies have shown that the bilateral posterior IFG is commonly involved in inhibition of movements in different motor modalities (eye versus hand) and the ventral IFG/insula is more activated during inhibition of manual responses than during inhibition of eye responses (Leung and Cai, 2007) and the activation of this region is not sensitive to different visual stop signals (color versus orientation) (Leung and Cai, 2007). In consistent with previous findings using the event-related design, the current study has shown that the right ventral IFG/insula extending to the right lateral posterior ventral IFG is more activated during the response epoch of SST than that of NST using the block design. The activation in the ventral IFG/insula was very close, 6mm in all directions, to the hand-specific response inhibition region defined in our previous studies. We also found the significant correlation between the activation of this region and the response inhibition performance (SSRT). Different to the right posterior dorsal IFG that is activated across three epochs, the right ventral IFG/insula does not show sustained activation in the cue and delay epochs. Also, the ROI analysis has found that the right ventral IFG/insula shows greater activation to SST-SS trials than NST-NS trials. Furthermore, the PPI analysis has revealed the functional coupling between this region and putamen during response inhibition, although the functional correlation does not reach the significance in the FDR level. All together, it suggests that the right ventral IFG/insula is probably more involved in inhibition compared to other regions.

Previous studies have found that the right ventral IFG/insula is activated in unsuccessful inhibition trial and suggested that it may be involved in triggering

a stop process rather than actually interrupting a go process (Aron and Poldrack, 2006; Cai and Leung, 2009). We further demonstrated this idea using the contrast of SST-US trials versus NST-NS trials that counterbalances both sensory stimuli and response execution. The key difference is that participants expended effort to cancel prepotent responses in SST-US trials but not in NST-NS trials. The race model has suggested two processes during a stop trial: a go process and a stop process (Logan and Cowan, 1984). The unsuccessful inhibition is due to the fact that the go process is completed before the stop process is completed. The contrast of SST-US trials versus NST-NS trials may reflect the unique process of triggering a stop process. Most likely, the right ventral IFG/insula is particular important for triggering a stop process.

Both the contrast map of SST-SS trials versus NST-NS trials and the contrast map of response epochs of SST versus NST have shown the activation of the right MFG/anterior dorsal IFG, which is located in the middle frontal gyrus and the anterior part of dorsal pars triangularis. The activation of this region is not correlated with the response inhibition performance. The ROI analysis has also demonstrated that the activation of this region cannot be attributed to infrequent stimulus processing. Interestingly, location of this activation is very close, 3mm in all direction, to the activation reported in a previous meta-analysis of go/no-go studies (Simmonds et al., 2008). It suggests that this region serves a common control mechanism shared by both go/no-go and our Stop/Not-stop tasks. The functional connectivity analysis has revealed that this region has significant covariance with putamen, right premotor cortex and SMA during the response inhibition. The SMA is part of the motor control circuit, which projects to the putamen in control of actions (see review by Alexander et al., 1986). It is more involved in complex than simple motor tasks, in internal than external motor initiation, and in motor preparation (see review by Tanji, 1996). Damage to the SMA could impair ability of action control (Gentilucci et al., 2000). It is also possible that this region may serve a general mechanism of cognitive control, such as orientation of attention to response-relevant external stimuli (Corbetta and Shulman, 2002).

5.4.3. Orientation to infrequent stimuli and response slowing

As mentioned above, one potential confound in the contrast of response inhibition trials versus response execution trials is that the contrast may reflect the infrequent stimulus processing instead of response inhibition because the response inhibition trials are much less frequent than response execution trials in the go/no-go task and the stop-signal task. One recent neuroimaging study has shown that the posterior dorsal IFG was activated primarily during processing infrequent stimuli rather than response inhibition in a go/no-go task (Chikazoe et al., 2008). In consistent with their findings, our current data has revealed that the right posterior dorsal IFG exhibit similar activation pattern in

the contrast of SST-SS trials versus SST-G trials as well as in the contrast of NST-NS trials versus NST-G trials. No significant difference has been found in the posterior dorsal IFG in SST-SS trials and NST-NS trials. It suggests that the right posterior dorsal IFG may be involved in infrequent stimulus processing rather than response inhibition.

The effect of stimulus-response infrequency is often accompanied with slower responses (i.e. Chikazoe et al., 2008). It is thus important to dissociate the effect of response slowing from infrequent stimulus processing. The bilateral IFG has been associated with post-stop error response slowing (Li et al., 2008b). However, one recent study did not find the involvement of the IFG in response slowing during post-go trials (Li et al., 2009). In contrast, we found that right posterior dorsal IFG is more activated in PG-LRT trials than PG-SRT trials. The contradictory findings between two studies could be attributed to different categorization methods. Li and his colleagues (2009) categorized PG trials with a decrease or increase in RT by comparing with PG trials that precede them. We distinguished PG trials by RTs to dissociate the response slowing from infrequent stimulus processing. In our study, however, the response slowing cannot explain the greater activation in NST-NS trials than NST-PG-LRT because the RT of NST-NS is shorter than the RT of NST-LRT. Taken together, this suggests that the right posterior dorsal IFG may be involved in response slowing but mostly in infrequent stimulus processing.

5.4.4. Other cortical and subcortical regions involved in response control

We found a group of cortical and subcortical regions are involved in response control (contrast of SST vs. NST blocks), including right FPC, pre-SMA, bilateral IPL, SPL and putamen. It has been suggested that the rostral lateral prefrontal cortex plays a more abstract role in cognitive control (Petrides, 2005). Koechlin et al. (2003) have studied the effective connectivity in the frontal lobe and found rostral lateral prefrontal cortex exerts control on caudal lateral prefrontal cortex and the rostral regions are engaged in selecting appropriate representations. Sakai and Passingham (2003; 2006) have revealed that the anterior PFC interacts with different caudal prefrontal regions depending on the nature of task. Our functional connectivity analysis have showed that the right FPC has significant covariance with regions in caudal and medial prefrontal cortex, parietal cortex and basal ganglia during response control, implicating its role in general control and coordination of different cortical and subcortical regions to achieve behavior goals.

The activation in dorsal-medial prefrontal cortex (DMPFC) has been reported in many response inhibition studies (e.g. Aron and Poldrack, 2006; Aron et al., 2007; Li et al., 2006). Furthermore, the connection between the pre-SMA and the inferior frontal cortex has been emphasized in response inhibition using diffusion tensor imaging (Aron et al., 2007) and Granger causality analysis (Duann and Li, 2008). We have identified the functional connection between the DMPFC and SMA, right premotor cortex, right dorsal

IFG and left putamen, although the correlation did not reach the significance in the FDR level. It has suggested that the DMPFC is interacted with other motor areas during response control. Interesting, the DMPFC have shown weaker activation during successful response inhibition than during unsuccessful response inhibition. Previous studies have suggested that the DMPFC is involved in error processing and response monitoring (Ullsperger and von Cramon, 2001). It is possible that the activation of the DMPFC during the response inhibition is associated with detecting response errors and monitoring for competitive go and stop processes.

The putamen is part of the motor control circuit (see review by Alexander et al., 1986). Previous studies have shown the involvement of the putamen during response inhibition (Aron and Poldrack, 2006; Vink et al., 2005). In the current study, we have found the putamen is more activated during successful response inhibition than during unsuccessful response inhibition and it is interacted with most of prefrontal regions that are important in response control. It suggests that the putamen may be particularly involved in directly stopping motor processes.

In conclusion, the current study identified functional heterogeneity of the IFG using Stop/Not-Stop task. This is the first study to dissociate rule representation, response inhibition and infrequent stimulus processing involved in a response inhibition task. We showed that the left anterior IFG is involved in task rule representation, the right ventral IFG/insula probably in triggering stop processes, the right MFG/anterior dorsal IFG in general response control, and the right posterior dorsal IFG in infrequent stimulus processing and probably response slowing. We also examined the functional connectivity of prefrontal regions during response inhibition and found a common functional coupling between prefrontal regions and putamen and SMA.

5.5. Limitations

The purpose of this study was to distinguish neural correlates underlying rule representation, working memory and infrequent stimulus processing from response inhibition. However, we did not find strong sustained activity during the delay epoch, which is probably due to lower demands on working memory during the delay epoch. A previous study showed that weak activation is associated with low working memory load task (e.g. Leung et al., 2004).

6. General discussion

The current findings demonstrated that the bilateral posterior ventral IFG/insula plays a common role in response inhibition. Consistent with our previous findings (Cai and Leung, 2009; Leung and Cai, 2007), we found that part of the activation of bilateral posterior ventral IFG/insula is independent of different sensorimotor associations during response inhibition. The correlation between the activation in the right posterior ventral IFG/insula and behavioral measure of response inhibition (SSRT) indicated that the right posterior ventral IFG/insula plays a particularly important role in response inhibition. However, we did not find greater activation of this region during successful response inhibition than unsuccessful response inhibition, suggesting that this region might not be involved in directly stopping a planned movement. The right posterior ventral IFG/insula showed the increased functional correlation with sensory areas and the relatively weak functional covariance with motor areas during response inhibition. All together, our data suggested that the right posterior ventral IFG/insula may play a role in the early stage of stopping behavior, most likely interpreting sensory stop signal and triggering the stop processing. The functional covariance between the right posterior ventral IFG/insula and the posterior sensory areas was consistent with the corticocortical connections between the caudal inferior frontal convexity and posterior association areas in non-human primates (e.g. Petrides and Pandya, 2002). However, we cannot exclude the possibility that the posterior ventral IFG/insula may play a more direct role in stopping motor responses. The functional interactions between the posterior ventral IFG/insula and motor areas might be underestimated in the current study because each block includes go trials and stop trials. It required further investigation in future studies. For example, future study could contrast the response inhibition task and a control task without response inhibition to identify the functional connectivity during response inhibition in different motor modalities.

Aron and Poldrack (2006, 2007) suggested a cortical-subcortical network particularly for manual response inhibition, including right inferior frontal cortex, pre-SMA and subthalamic nucleus. Duann and Li (2008) emphasized the functional connection between inferior frontal cortex and pre-SMA during response inhibition. However, we did not find the significant functional interaction between the IFG and pre-SMA during response inhibition in comparison to a control task without inhibition demand. Instead, we showed the weak covariance between the right IFG and SMA, premotor cortex and putamen. Our results indicated that the right IFG interacts with motor regions in controlling hand responses. The different findings might be due to the variance in different experiments and analyses. Aron et al. (2007) used diffusion tensor imaging to identify the anatomical connections among regions activated during response inhibition. It indicated that the right IFC and pre-SMA are connected in anatomy. Duann and Li (2008) used the Granger

causality analysis to identify the functional causality among regions involved in response inhibition. Granger causality analysis was to identify the direction of causality between regions using the temporal information in the data. Duann and Li's finding revealed that the activation of the IFC may lead to early activation of the pre-SMA. We used the PPI analysis to identify functional interactions between one seed region and other brain regions in one condition in comparison to another condition. In addition, the contrast of SST versus NST may represent the additional demand of general response control beside response inhibition. Therefore, findings from these three studies probably reflected different aspects in anatomical and functional connections of the inferior frontal gyrus during response inhibition.

We showed that the dorsolateral prefrontal regions are more involved in inhibition of eye movements than inhibition of hand movements, including bilateral dorsal part of the IFG and MFG. Non-human primates studies demonstrated the role of dorsolateral prefrontral regions in control of eye movements and the anatomical connection between dorsolateral prefrontal areas and eye areas in the frontal lobe, including FEF and SEF (Gerbella et al., 2009; Petrides and Pandya, 1999; 2001). Dorsolateral prefrontal regions received abundant projections from the parietal cortex via the dorsal visual pathway (Ungerleider and Mishkin, 1984). It had been shown that the dorsolateral prefrontal cortex may be particularly involved in processing visuospatial information (Goldman-Rakic, 1989), which is important in guiding eye movement. However, the right MFG was also involved in inhibition of hand movements when there are two competitive response control rules (SST versus NST) (The peak coordinates of activations in right MFG in both studies were very close, 6 mm in all directions). It has been suggested that the MFG plays a role in monitoring of information of working memory (Petrides, 2005). Probably, the dorsolateral prefrontal areas were involved in multiple cognitive-motor processes, such as monitoring and manipulating information and controlling responses (eye movements in particular).

We identified that the left anterior IFG is associated with rule representation. It was consistent with previous studies that showed the left anterior IFG probably play a role in retrieving task rules (Bunge et al., 2003). Besides, we found the functional interaction between the left anterior IFG and the right MTG during the response epoch, indicating that the left anterior IFG mainly communicates with posterior association areas during response inhibition. The functional covariance between the left anterior IFG and the right MTG during response inhibition was unique compared to functional connections of other prefrontal regions (e.g. right FPC, right MFG, right ventral IFG/insula) and motor regions (SMA and putamen) during response inhibition. It thus suggested the left anterior IFG is more involved in processing stop signals rather than response control. Previous anatomical studies revealed the profuse connections between anterior inferior frontal convexity and IT and rostral temporal lobe in non-human primates (Pandya & Yeterian, 1996;

Petrides & Pandya 2002). Animal lesion studies demonstrated the communication between the IFG and temporal lobe is critical in learning visuomotor associations (Browning et al., 2007; Eacott and Gaffa, 1992; Gaffan and Harrison, 1989; Wang et al., 2001). Our findings thus supported the role of the left anterior IFG in processing rule-related information.

We demonstrated that the right posterior dorsal IFG plays an important role in infrequent stimulus processing and probably response slowing, in consistent with previous studies (Chikazoe et al., 2008). Previous studies suggested that the right inferior frontal junction (the junction between the inferior frontal sulcus and precentral sulcus, which is next to the posterior dorsal IFG) is involved in different cognitive process, such as rule maintenance or task preparation (Brass and Cramon, 2002) and cognitive control (Brass et al., 2005; Derrfuss et al., 2005). It is possible that this region serves multiple cognitive processes. But it is also possible that previous studies underestimated the contribution of sensory processing to the activation in this region. In the current study, we found that the right posterior dorsal IFG is not only activated during the response epoch but also activated during the cue epoch, although the activation is not task-dependent during the cue epoch. It strongly suggested that the right posterior dorsal IFG is involved in processing sensory information.

Last but not least, this is the first study to dissociate cognitive functions of multiple prefrontal areas using both task-related activation patterns and functional connectivity. We identified that the right FPC has broad functional covariance with cortical and subcortical areas during response inhibition, including right IFG, premotor cortex, SMA, bilateral IPL, putamen and thalamus. It has been suggested that the lateral prefrontal cortex is organized as a functional hierarchical system and the anterior PFC plays a more abstract role in control of cognitive and motor processes (Badre, 2008; Koechin et al., 2003; Petrides, 2005). Sakai and Passingham (2006) revealed that the FPC interacts with the posterior areas differently depending on the task that subjects performed. In consistent with the hierarchical hypothesis, our finding indicated the right FPC may play a general role in coordinating multiple cortical and subcortical regions during stimulus-driven response control. In contrast, the right MFG and other regions in right ventral IFG showed major functional interaction with motor areas, such as SMA and putamen. It suggested that the right MFG and right ventral IFG regions may be involved in more direct control of response inhibition.

In conclusion, we demonstrated that the IFG is a functional heterogeneous structure. Our results suggested that the posterior ventral IFG/insula plays a common role (independent of sensorimotor associations) in response inhibition (probably interpreting sensory stop signal and triggering stop processes) by interacting with different sensory regions to guide response inhibition. The dorsal part of the IFG and MFG were more involved in inhibition of eye movements than inhibition of hand movement and the right MFG may

be more directly interacted with motor regions during response inhibition. The right posterior dorsal IFG was activated for infrequent stimulus processing and probably response slowing. The right FPC played a general role in coordinating other cortical and subcortical regions during response inhibition. The left anterior IFG was more involved in rule representation. Because the current study cannot effectively identify the activation associated with working memory, we were unable to dissociate the neural activity underlying working memory from other process. Also, the PPI analysis may underestimate the functional interaction between the posterior ventral IFG/insula and motor regions during response inhibition given the experimental design in the current study. Future studies should further identify the functional connection between the IFG and motor regions during response inhibition and separate working memory from response inhibition. Nonetheless, this was the first study that reveals the sensorimotor topography of the prefrontal cortex in stimulus-driven response inhibition and identifies functional differences among the IFG subdivisions as well as other prefrontal regions in a rule-guided response control task. These findings provide evidence on the functional topography of the IFG and other prefrontal regions during rule-guided executive control of behavior.

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Appendix 1 Figures

Figure 1: Response inhibition task paradigm (Study 1)

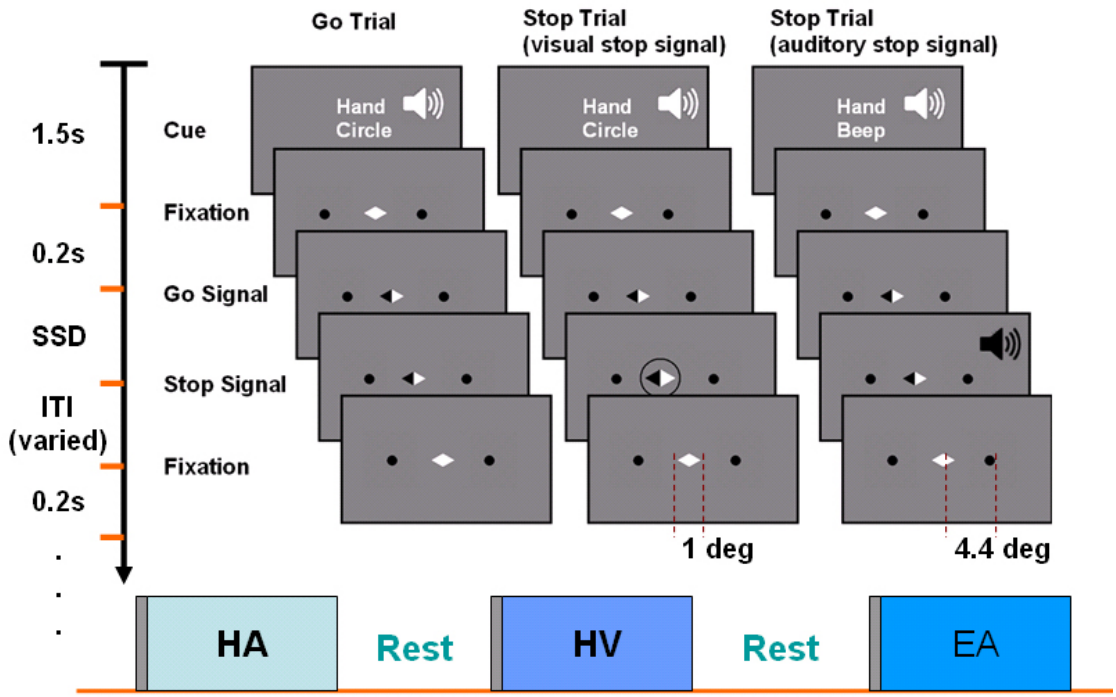


Figure 1: Response inhibition task. The response inhibition task included four different conditions: Hand-Auditory (HA), Hand-Visual (HV), Eye-Auditory (EA) and Eye-Visual (EV). At the beginning of each block, an instruction cue ("hand"/"eye" and "circle"/"beep") was presented with a warning beep (500Hz) for 2 sec, followed by 15 continuous stop-signal task trials. The ITI was 1.7, 2.3 or 4.3 sec. The interval between two adjacent blocks was 16, 18 or 20 s. In each trial, a white diamond (fixation) was presented at the center and two dots (targets) were presented in the left and right side of the central fixation (5^{o} of eccentricity). After 200ms, the left or right part of the central diamond changed to black (a go signal). Depending on the initial block instruction, subjects were asked to press either the left or the right button using their right index finger in the hand task or make a saccadic eye movement to the left or the right dot according to the go signal. Occasionally (30%), a circle (a visual stop signal) or a beep (900Hz) (an auditory stop signal) was presented shortly after the go signal is presented. The stop signal lasted for 300ms. Subjects were told to make no response when either stop signal is presented. Four SSDs were randomly assigned in the SS task for each condition. The SSDs for the hand tasks were 10, 110, 210 and 310 ms and the SSDs for the eye tasks were 10, 90, 180 and 270 ms.

Figure 2: Behavioral performance (Study 1)

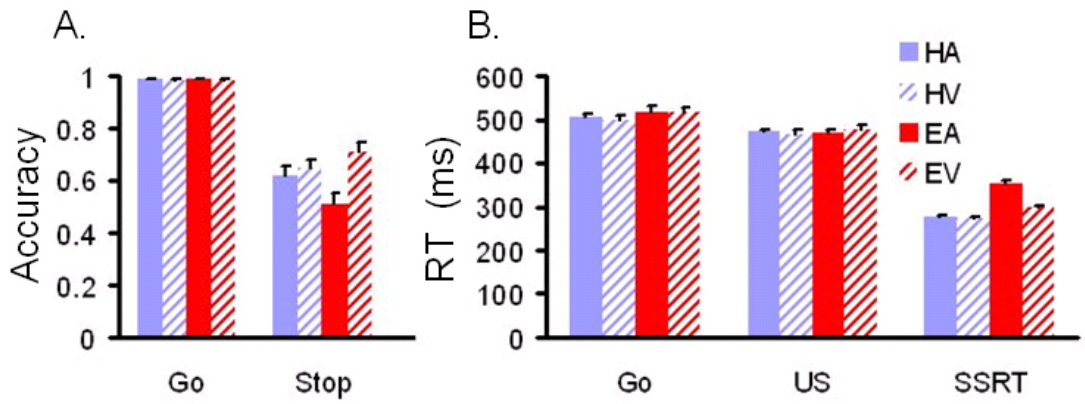


Figure 2: Behavioral performance. A: Accuracy of go and stop trials in each task condition. B: Reaction time of go and unsuccessful stop trials and SSRT in each task condition.

Figure 3: Successful response inhibition (Study 1)

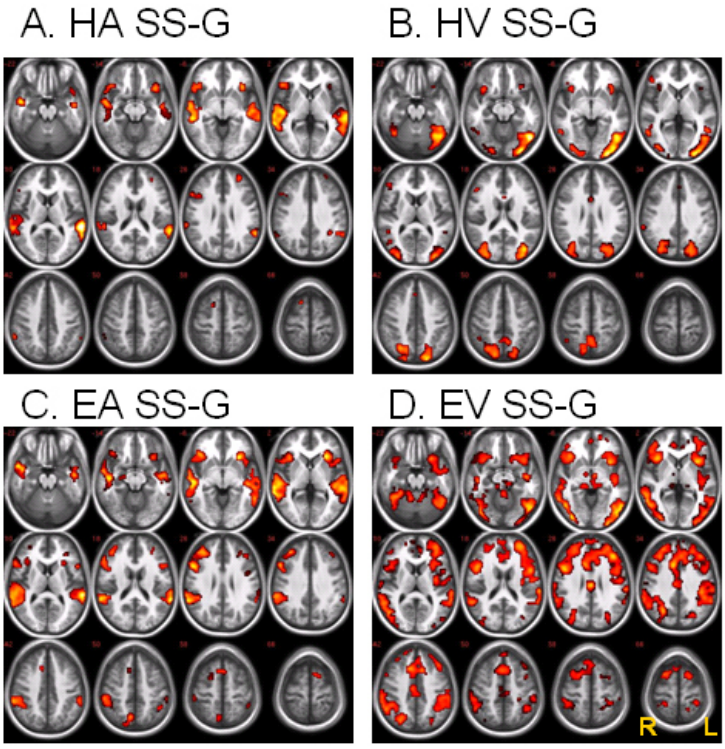


Figure 3: Successful response inhibition. (A) SS-G (successful stop vs. go) contrast map of the HA task showed suprathreshold activations during inhibition of hand movements cued by auditory stop signal. (B) SS-G contrast map of the HV task showed suprathreshold activations during inhibition of hand movements cued by visual stop signal. (C) SS-G contrast map of the EA task showed suprathreshold activations during inhibition of eye movements cued by auditory stop signal. (D) SS-G contrast map of the EV task showed suprathreshold activations during inhibition of eye movements cued by visual stop signal. All $p<0.05$, FDR corrected. The first letter ("R" and "L") of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Figure 4: Common activation in response inhibition (Study 1)

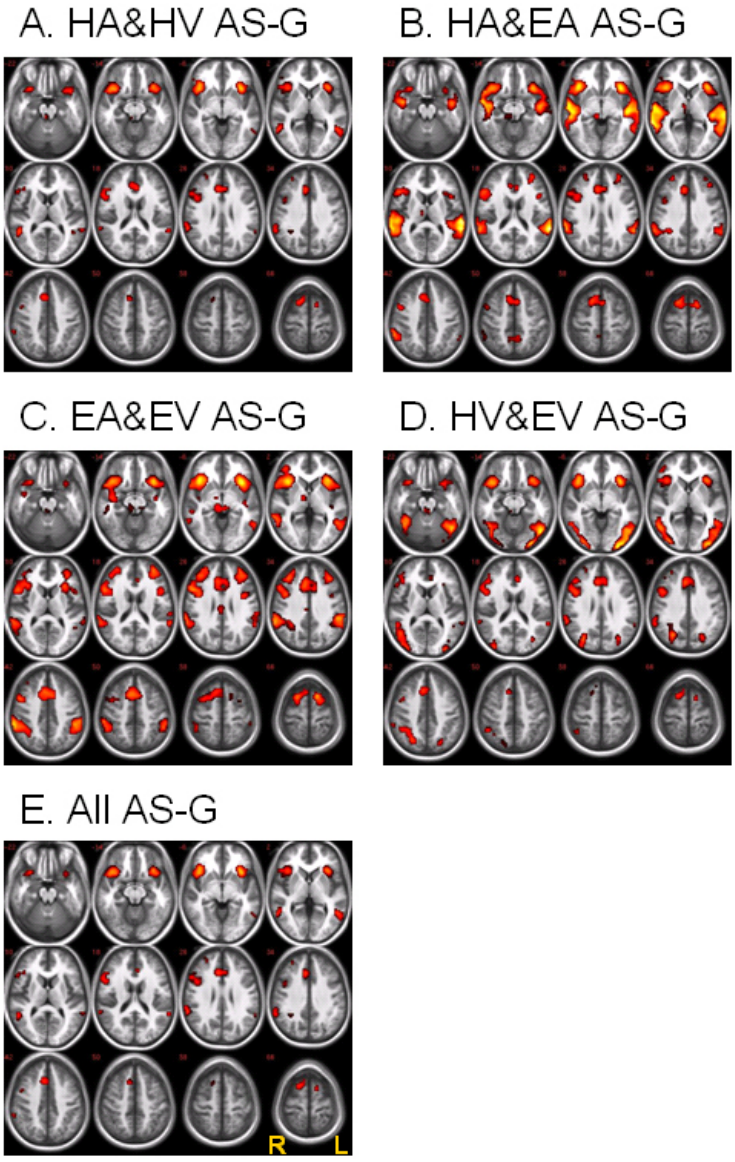


Figure 4: common activation in response inhibition. (A) Hand response inhibition: suprathreshold activations were identified in AS-G (all stop vs. go) contrasts in both HA and HV tasks. (B) Auditorily guided response inhibition: suprathreshold activations were identified in AS-G contrasts in both HA and EA tasks. (C) Eye response inhibition: suprathreshold activations were identified in AS-G contrasts in both EA and EV tasks. (D) Visually guided response inhibition: suprathreshold activations were identified in AS-G contrasts in both HV and EV tasks. All $p<0.001$, uncorrected. The first letter ("R" and "L") of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Figure 5: Differential activation during response inhibition (Study 1)

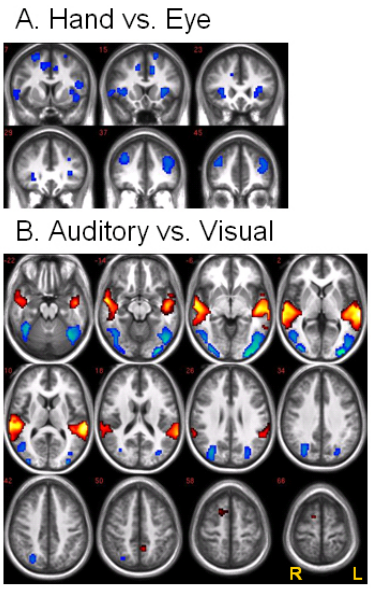


Figure 5: Differential activation during response inhibition. (A) Motor dependent activations during response inhibition: more dorsal part of the IFG and dorsal prefrontal regions were more activated during inhibition of eye movements than during inhibition of hand movements. Orange: hand>eye, Blue: eye>hand. (B) Sensory dependent activations during response inhibition: superior temporal gyrus was more activated during response inhibition cued by auditory stop signals than by visual stop signals, while fusiform gyrus, inferior occipital gyrus and inferior temporal gyrus were more activated during response inhibition cued by visual stop signals than by auditory stop signals. Orange: auditory>visual, Blue: visual>auditory. All $p<0.005$, FDR corrected. The first letter (“R” and “L”) of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Figure 6: Functional connectivity during response inhibition

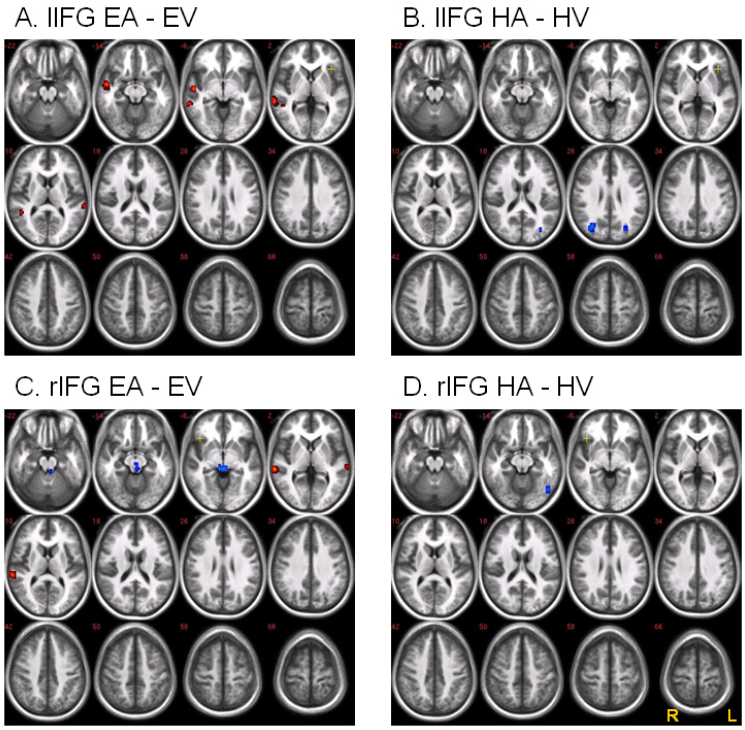


Figure 6: Functional connectivity during response inhibition. (A) Differential functional correlation with left IFG during eye response inhibition cued by auditory or visual stop signals. (B) Differential functional correlation with left IFG during hand response inhibition cued by auditory or visual stop signals. (C) Differential functional correlation with right IFG during eye response inhibition cued by auditory or visual stop signals. (D) Differential functional correlation with right IFG during hand response inhibition cued by auditory or visual stop signals. All $p<0.001$, uncorrected. The yellow cross represents the averaged MNI coordinates of left IFG (x=-36, y=23, z=-2) and right IFG (x=42, y=24, z=-3). Orange: auditory>visual, Blue: visual>auditory. The first letter (“R” and “L”) of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Figure 7. Functional topography of sensory and response control regions (Study 1)

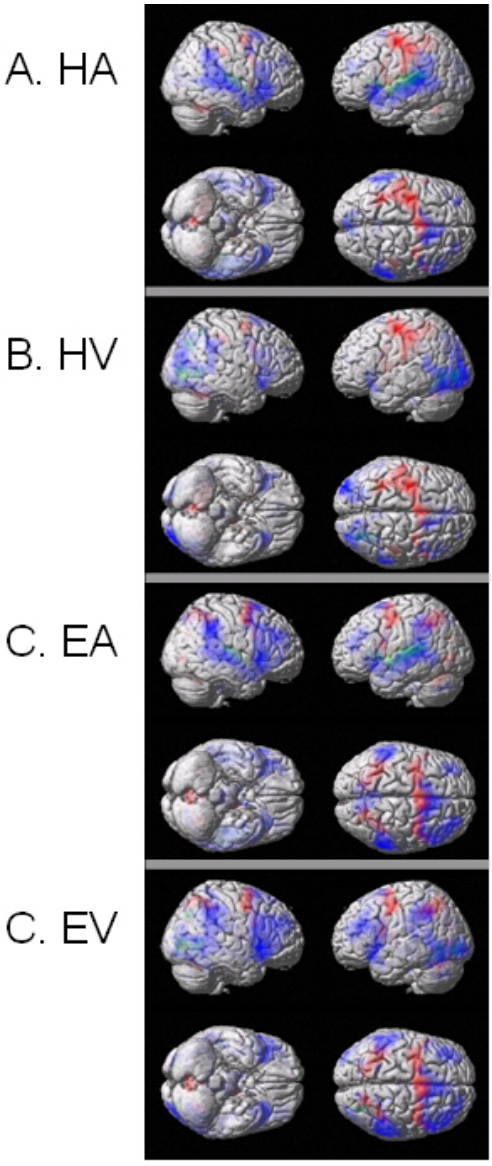


Figure 7. Functional topography of sensory and response control regions: (A) Suprathreshold activations during processing auditory signals (green), executing hand movements (red), and inhibition (AS-G contrast) of hand movements cued by auditory signals (blue). (B) Suprathreshold activations during processing visual signals (green), executing hand movements (red), and inhibition (AS-G contrast) of hand movements cued by visual signals (blue). (C) Suprathreshold activations during processing auditory signals (green), executing eye movements (red), and inhibition (AS-G contrast) of eye movements cued by auditory signals (blue). (D) Suprathreshold activations during processing visual signals (green), executing eye movements (red), and inhibition (AS-G contrast) of eye movements cued by visual signals (blue). All

$p<0.05$, FDR corrected.

Figure 8. Stop/Not-Stop task paradigm (Study 2)

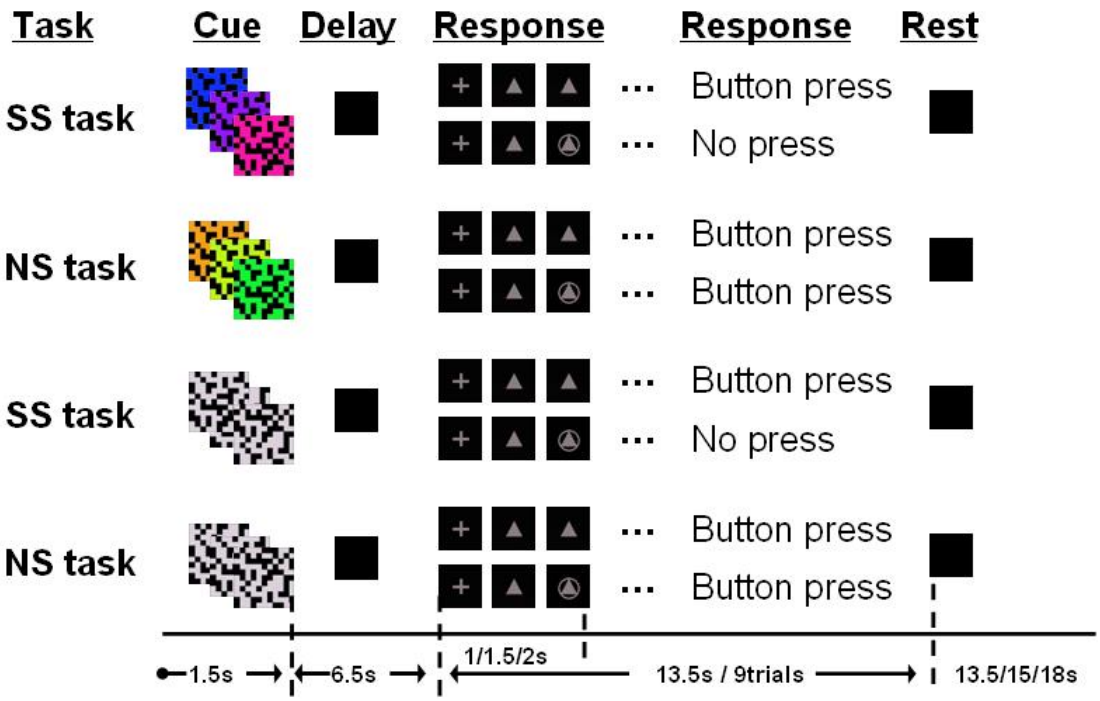


Figure 8: Stop/Not-Stop task. The Stop/Not-Stop task included 4 task conditions (color-SST, color-NST, motion-SST and motion-NST). Each task block had three epochs: cue, delay and response. A visual cue (color or motion) was presented at the beginning of the task block indicate the current task rule (SST or NST). After a 6.5-sec delay (black screen), a warning signal was presented for 1 sec followed by a sequence of 9 go signals and on occasions (about 30% chance), followed by the stop signal. After the response epoch, there was a variable resting period (13.5, 15 or 18 sec). Each stop signal (a circle) was presented for 300ms after the presentation of the go and subjects were asked to withhold their responses in the SST and continue to respond in the NST. For the SST, the SSD was dynamically adjusted in steps of 50ms starting from 150ms.

Figure 9. Behavioral performance (Study 2)

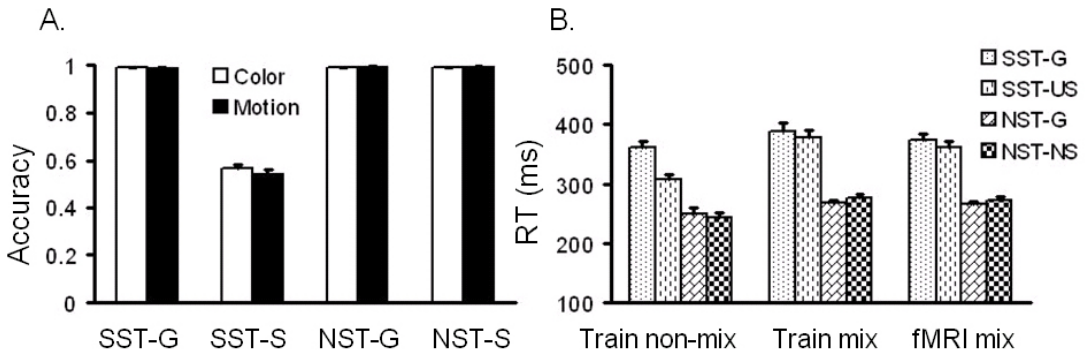


Figure 9: Behavioral performance. A: Accuracy of go and stop trials in SST and go and not-stop trials in NST. B: Reaction time of go and unsuccessful stop trials in SST and go and not-stop trials in NST.

Figure 10. Task- and cue-dependent activation during the cue epoch (Study 2).

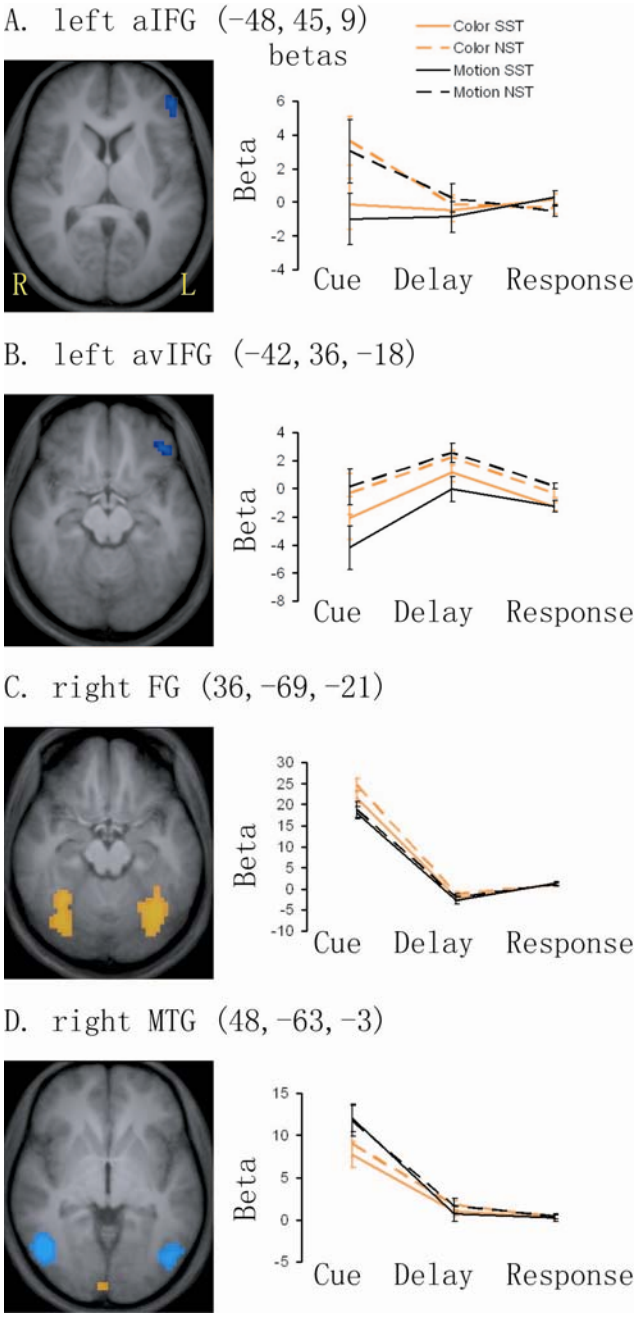


Figure 10. Task- and cue-dependent activation during the cue epoch. (A) Task effect (NST>SST) in left anterior IFG. (B) Task effect (NST>SST) in left anterior ventral IFG. (C) Cue effect (color>motion) in fusiform gyrus. (D) Cue effect (motion>color) in middle temporal gyrus. All p<0.001, uncorrected. Red: SST>NST; Blue: NST>SST; Yellow: color>motion; Indigo: motion>color. The first letter ("R" and "L") of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Figure 11. Task-dependent activation during the response epoch (Study 2)

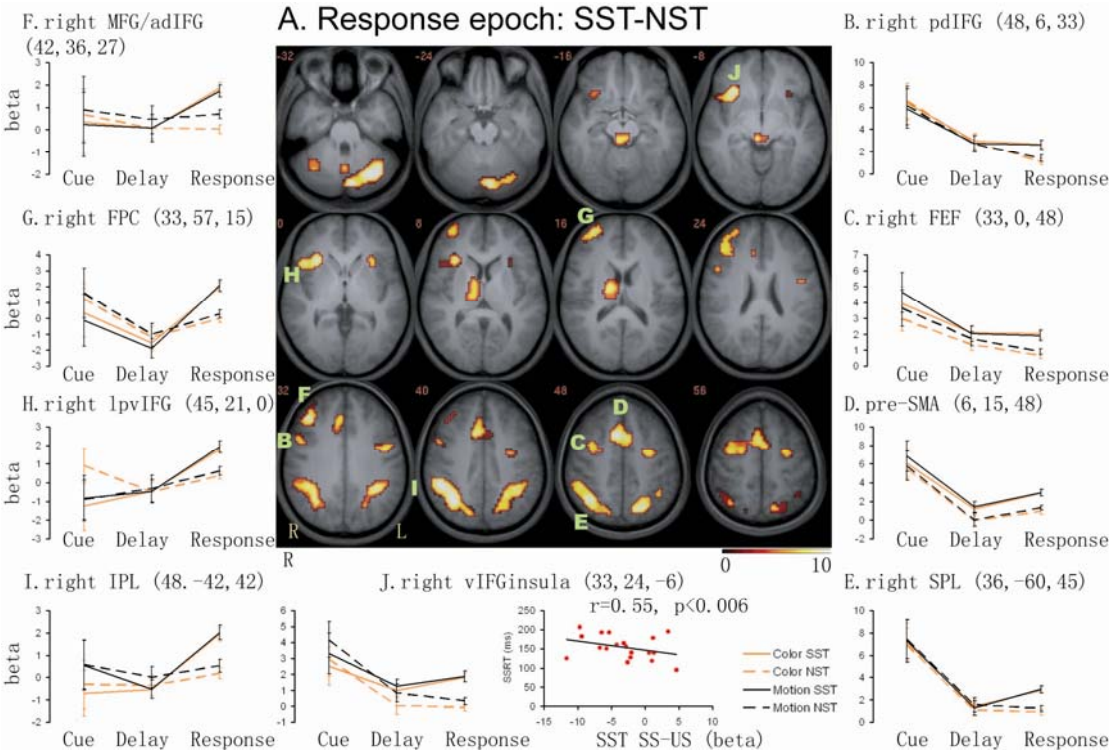


Figure 11. Task-dependent activation during the response epoch. (A) Suprathreshold activation of SST versus NST during the response epoch, p<0.001 FWE corrected. (B)-(J) Activations in right posterior dorsal IFG, right FEF, pre-SMA, right SPL, right MFG/anterior dorsal IFG, right FPC, right lateral posterior ventral IFG, right IPL and right ventral IFG/insula across cue, delay and response epochs. The first letter ("R" and "L") of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Figure 12. Activation pattern of clusters in response trials (Study 2)

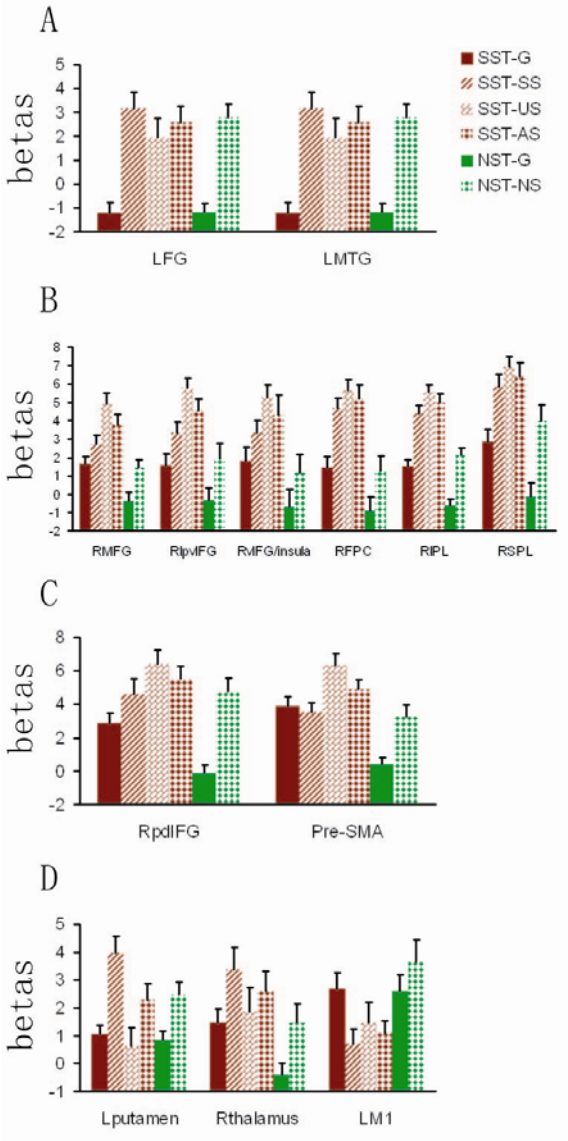


Figure 12. Activation pattern of clusters in response trials. (A) Average beta values of each type of trials in left fusiform gyrus and middle temporal gyrus. (B) Average beta values in right MFG, lateral posterior ventral IFG, ventral IFG/insula, FPC, IPL and SPL. (C) Average beta values in right posterior dorsal IFG and pre-SMA. (D) Average beta values in left putamen, right thalamus and left M1.

Figure 13. Unsuccessful response inhibition (Study 2)

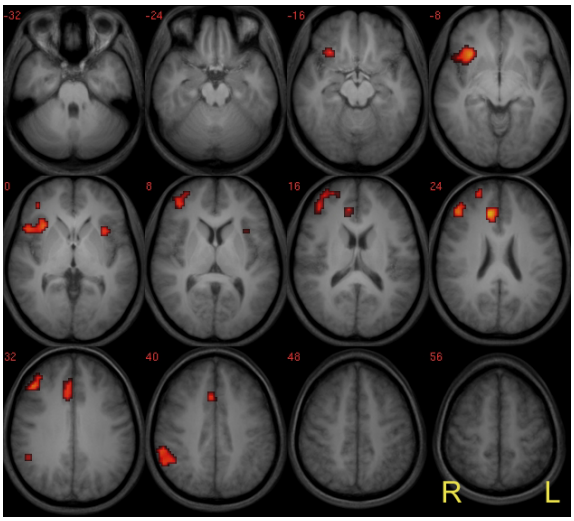


Figure 13. Unsuccessful response inhibition: SST-US - NST-NS (successful stop trials versus not-stop trials) contrast map showed suprathreshold activation during unsuccessful response inhibition, $p<0.05$, FDR corrected. The first letter (“R” and “L”) of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Figure 14. Infrequent stimulus processing (Study 2)

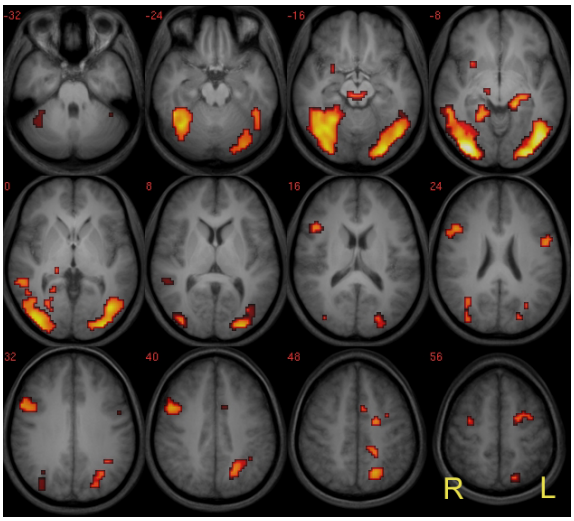


Figure 14. Infrequent stimulus processing: NS-G (not-stop trials versus go trials) contrast map showed suprathreshold activation for infrequent stimulus processing and probably response slowing, p<0.001 FDR corrected. The first letter (“R” and “L”) of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Figure 15. Infrequent stimulus processing and response slowing (Study 2)

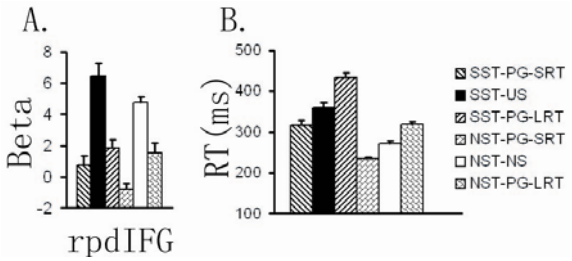


Figure 15. Infrequent stimulus processing and response slowing. (A) Average beta values of different types of trials in right posterior dorsal IFG. (B) Reaction times of different types of trials. Go trials were re-categorized by their reaction times (shorter [SRT] and longer [LRT] than US trials in SST and NS trials in NST, respectively). To minimize the effect of post-error slowing, only go trials after a correct go trial (PG) were selected.

Figure 16. Functional connectivity during response inhibition (Study 2)

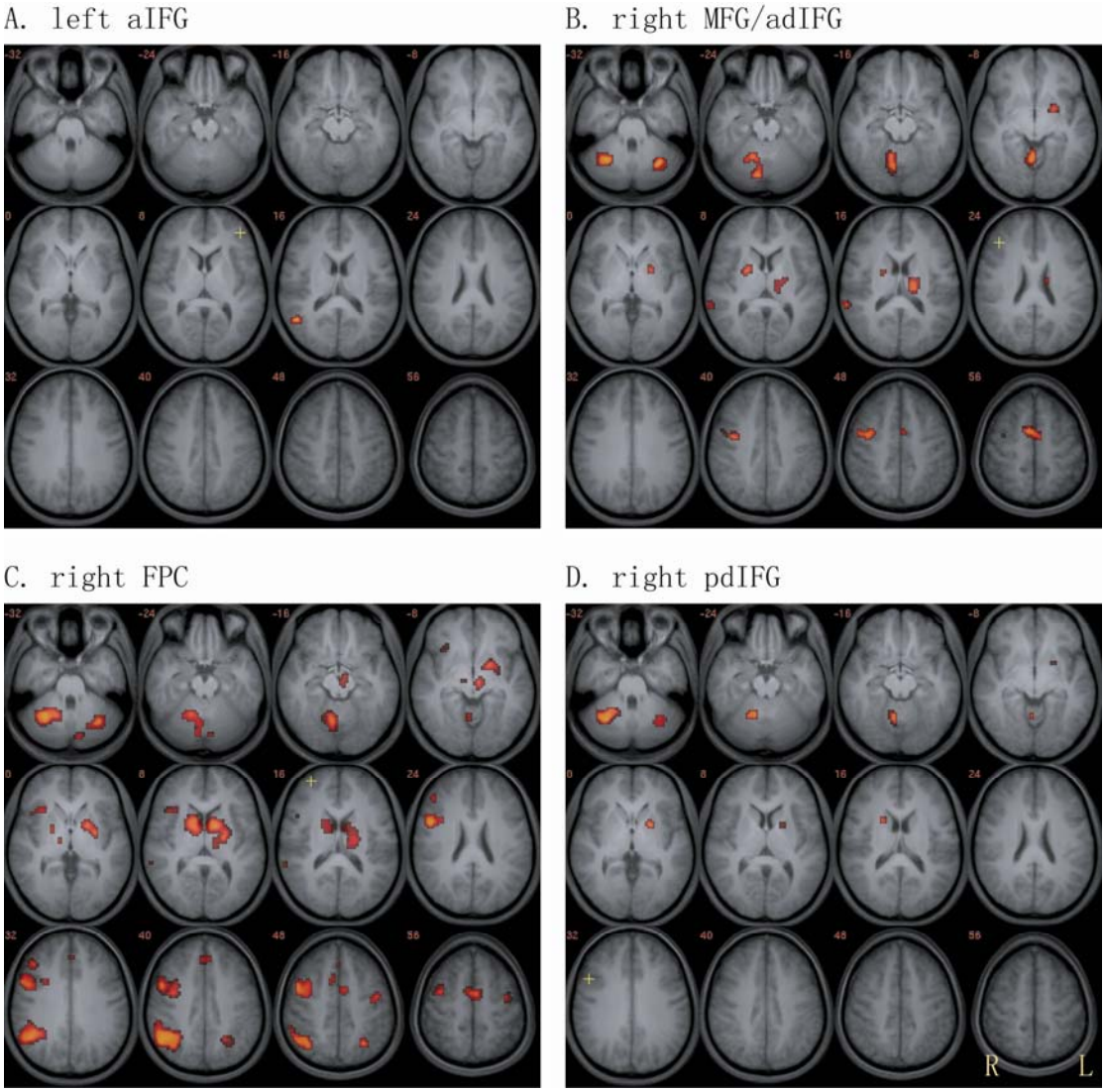


Figure 16: Functional connectivity during response inhibition. (A) Increased functional connectivity with left anterior IFG during the SST than during the NST. (B) Increased functional connectivity with right MFG/anterior dorsal IFG during the SST than during the NST. (C) Increased functional connectivity with right FPC during the SST than during the NST. (D) Increased functional connectivity with right posterior dorsal IFG during the SST than during the NST. All $p<0.05$, FDR corrected. The yellow cross represents the averaged MNI coordinates of left anterior IFG (x=-41, y=45, z=7), right MFG/anterior dorsal IFG (x=42, y=34, z=27), right FPC (x=33, y=56, z=15) and right posterior dorsal IFG (x=51, y=14, z=29). The first letter (“R” and “L”) of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Appendix 2 Tables

Table1: Successful Response Inhibition (Study 1)

Region	cluster size	Z	MNI Coordinates		
			x	y	z
EA:SS-G					
right MTG	702	6.08	51	-21	-9
		5.85	66	-33	0
right MTG/ITG		5.82	48	-15	-15
left MTG	445	5.96	-60	-36	6
		5.46	-45	-33	3
left STG		5.2	-66	-45	18
left ITG	60	5.3	-48	-9	-21
right MFG	113	5.07	36	42	30
		4.67	39	42	21
		4.24	45	30	30
left posterior ventral IFG/insula	24	5.03	-27	24	0
right posterior ventral IFG/insula	63	4.89	39	27	-6
		4.6	36	21	3
left IPL	9	4.28	-60	-45	33
		4.17	-60	-39	42
EV: SS-G					
left IOG	284	5.64	-33	-96	-3
left MOG		5.64	-57	-66	-6
left FG		5.51	-45	-66	-15
right IOG	296	5.43	33	-90	-3
right MOG		5.41	45	-66	-9
right FG		5.35	39	-81	-12
right posteroir ventral IFG/insula	85	5.41	36	21	0
left MFG	31	5.05	-39	33	24
right MFG	104	5.01	33	33	33
		4.68	27	45	30
right precuneus	27	4.94	27	-66	36
right MTG	11	4.67	48	-21	-15
		4.45	51	-33	-12
right IPL	41	4.63	54	-51	45
		4.35	63	-42	39
right IFJ	27	4.48	48	12	24

		4.42	45	18	18
right ACC	27	4.45	9	21	33
HA: SS-G					
left STG	337	6.58	-66	-39	9
		5.94	-60	-30	6
left STS		5.11	-54	-21	-9
right STS	402	5.92	48	-3	-21
right STG		5.68	66	-27	0
		5.45	51	-21	3
left posterior ventral IFG/insula	47	4.77	-39	18	-15
		4.69	-36	24	-6
right posterior ventral IFG	9	4.34	42	24	-3
HV: SS-G					
left FG	444	6.28	-48	-66	-15
left IOG		6.28	-30	-96	3
		6.13	-33	-90	-15
right MOG	54	5.23	33	-90	15
left precuneus	20	4.78	-21	-87	39
right IPL	26	4.58	30	-66	39
right AG		4.53	30	-72	33

All clusters reach the significance at $p<0.001$, FDR corrected.

Table2: Common activation during response inhibition (Study 1)

Region	cluster size	Z	MNI Coordinates		
			x	y	z
AS-G					
right posterior ventral IFG	480	5.96	42	18	-9
right posterior dorsal IFG		3.88	54	18	21
right posterior dorsal IFG		3.58	48	27	21
left posterior ventral IFG	243	5.93	-33	21	-6
right IPL	83	4.61	63	-42	24
right IPL		3.58	63	-39	42
right ACC	164	4.58	6	27	30
right pre-SMA		3.98	9	21	45
left ACC		3.75	-6	30	24
left MTG	67	4.45	-51	-54	3
right MTG	51	4.37	57	-57	3
right SFG	41	4.25	18	15	66
right SFG		3.24	9	12	69
right SFG		3.18	9	27	63
left STG	20	3.74	-63	-48	15
right MTG	9	3.49	33	-48	39
left SFG	9	3.43	-15	9	66
right MFG	12	3.39	30	48	33
SS-G					
right MTG	28	3.8	51	-51	6
right MTG		3.68	57	-54	0
right STG		3.25	54	-45	15
left posterior ventral IFG/insula	15	3.5	-36	18	-6
right posterior ventral IFG/insula	18	3.36	45	33	0
right posterior ventral IFG/insula		3.3	39	21	0
right posterior ventral IFG/insula		3.21	45	15	-6

All clusters reach the significance at $p<0.05$, FDR corrected.

Table3: Sensory- and motor-dependent activation during response inhibition (Study 1)

Region	cluster size	Z	MNI Coordinates		
			x	y	z
Auditory>Visual					
left STG	1274	7.83	-66	-27	3
left STG		7.33	-51	-18	-3
left STG		5.7	-66	-45	18
right STG	1083	7.18	63	-12	-3
right STG		7.06	66	-30	6
right STG		6.82	60	-6	-9
Visual>Auditory					
left MOG	1097	Inf	-36	-93	3
left IOG		7.22	-36	-90	-12
left FG		6.78	-33	-63	-18
right MOG	1094	6.59	36	-87	0
right MOG		6.22	36	-90	15
right cerebellum		6.12	33	-45	-24
right SPL	24	3.3	33	-51	54
left SPL	17	3.24	-27	-54	45
Medial Frontal Gyrus	32	3.23	0	48	15
Eye>Hand					
left IPL	286	6.45	-57	-30	48
left IPL		5.79	-48	-33	42
left IPL		5.54	-51	-36	54
right IPL	254	4.7	54	-30	45
right IPL		4.13	63	-36	42
right IPL		4.05	42	-39	51
left IFG	414	4.56	-33	36	12
left insula		4.51	-39	0	-6
left insula		4.13	-33	6	6
left ACC	49	4.15	-12	9	39
right MFG	89	4.02	36	39	33
right MFG		3.75	39	48	24
left SFG	42	3.89	-24	-3	66
right hippocampus	16	3.73	36	-21	-12
right SFG	54	3.71	18	-3	69

right SFG		3.2	24	9	63
left STG	16	3.55	-57	-9	3
left DMPFC	10	3.55	-15	24	-15
left SFG	10	3.53	-15	15	66
left thalamus	21	3.48	-15	-21	15
left cerebellum	14	3.48	33	-45	-30
right IFG/insula	51	3.34	36	15	6
right IFG/insula		3.22	30	21	6
left cerebellum	17	3.29	-24	-69	-33
left tectum	17	3.27	-18	-21	-3
left tectum		3.26	-12	-24	-12
right DMPFC	42	3.25	12	12	45
right ACC		2.92	9	18	30
right premotor	10	3.11	60	-15	15
right STG	19	3.1	60	12	0

A mask of the contrast of all stop versus go trials ($p<0.05$, uncorrected) was applied on this analysis. All clusters reach the significance at $p<0.05$, FDR corrected.

Table4: IFG Activations in Epochs (Study 2)

Region	cluster size	Z	MNI Coordinates		
			x	y	z
Cue: NST>SST					
left anterior ventral IFG*	9	3.61*	-42	36	-18
left anterior IFG*	13	3.35*	-48	45	9
Response: SST>NST					
right posterior ventral IFG/insula	108	7.63	33	24	-6
		6.21	33	24	12
right lateral posterior ventral IFG		7.17	45	21	0
right anterior dorsal IFG	128	7.55	42	36	27
right posterior dorsal IFG		5.97	51	12	30
		5.33	39	12	24
left posterior dorsal IFG	9	5.77	-45	3	27
Response: NST>SST					
left ventral IFG	99	7.45	-36	33	-15
left middle IFG	30	5.87	-48	27	6

All clusters reach significance at p<0.001, FWE corrected, except * indicating that the clusters reach p<0.06, FDR corrected.

Table5: IFG Activation in Response Trials (Study 2)

Region	cluster size	Z	MNI Coordinates		
			x	y	z
SST-US vs. NST-NS					
right posterior ventral IFG	22	4.48	33	24	-6
right anterior dorsal IFG	18	4.46	45	33	27
NST-NS vs. NST-G					
right posterior dorsal IFG	354	4.85	48	18	21
		4.67	45	9	36
		4.6	57	12	30
left posterior dorsal IFG	36	4.33	-51	6	24
left middle IFG	17	3.81	-36	18	9
		3.31	-36	27	6

All clusters reach threshold at $p<0.05$, FDR corrected.

Appendix 3

Corticocortical connections of other prefrontal regions

The DLPFC includes area 8, 9 and 46. Area 8 is caudal to area 9 and rostral to premotor cortex. Walker (1940) divided area 8 into two segments: area 8A in the concavity of the arcuate sulcus and area 8B dorsal to 8A. Pandya and Yeterian (1996) further divided area 8A into dorsal (8Ad) and ventral (8Av) parts. They also defined the ventral portion of 9 in the human brain and the caudal 46 in the monkey brain as area 9/46 because of their similar architectonic characteristics. Area 9/46 can be further divided into a dorsal part (area 9/46d) and a ventral part (area 9/46v).

Area 8B is connected with other cortical regions mainly via SLF I and less via FOF. It is connected with the SMA, caudal IPL, multi-modal areas in caudal superior temporal sulcus STS, rostral insular cortex, caudal dorsal cingulate (area 31), cingulate area (area 24, 23) and cingulate motor areas. It also has local connections with the premotor cortex (rostral area 6), DLPFC (areas 8Ad, 9/46d, 9, 46), DMPFC (area 8B, 9, 10, 32, 24) and a small portion in VLPFC (areas 45).

Area 8Ad is connected with other cortical regions via SLF II, FOF and AF. It is connected with IPL, IPS, caudal STG and multi-modal area in caudal STS. It also has local connections with the DLPFC (areas 8B, 9, 9/46) and VLPFC (areas 45A, 47/12).

Area 8Av is connected with other cortical regions via SLF II and FOF. It is connected with IPL and IPS, caudal STS, and middle temporal (MT). It also has local projections with the DLPFC (areas 8B, 8Ad, 46) and VLPFC (areas 45, 47/12).

Area 9/46 is connected with other cortical areas via SLF I, II and CING F. It is connected with second somatosensory area (SII), ventral somatosensory areas, SPLe, PPC, ventral medial parietal cortex, IPL, rostral multi-modal areas in STS, rostral STG and cingulate cortex. It also has local connections with dorsal premotor cortex (BA 6d), DLPFC (area 8B, 8Ad, 46), VLPFC (areas 45A) and DMPFC (areas 9, 24, 32).

Area 9 is connected with other cortical areas via CING F and ExtmC. It is connected with PCC, rostral multi-modal area in STS, STG, anterior and posterior cingulate cortex, and cingulate motor area. It also has local connections with the dorsal premotor cortex (BA 6d), DLPFC (areas 8B, 8Ad, 9/46d, 46), VLPFC (area 47/12), orbital PFC (area 11, 13, 14), and DMPFC (areas 8B, 9, 24, 32).

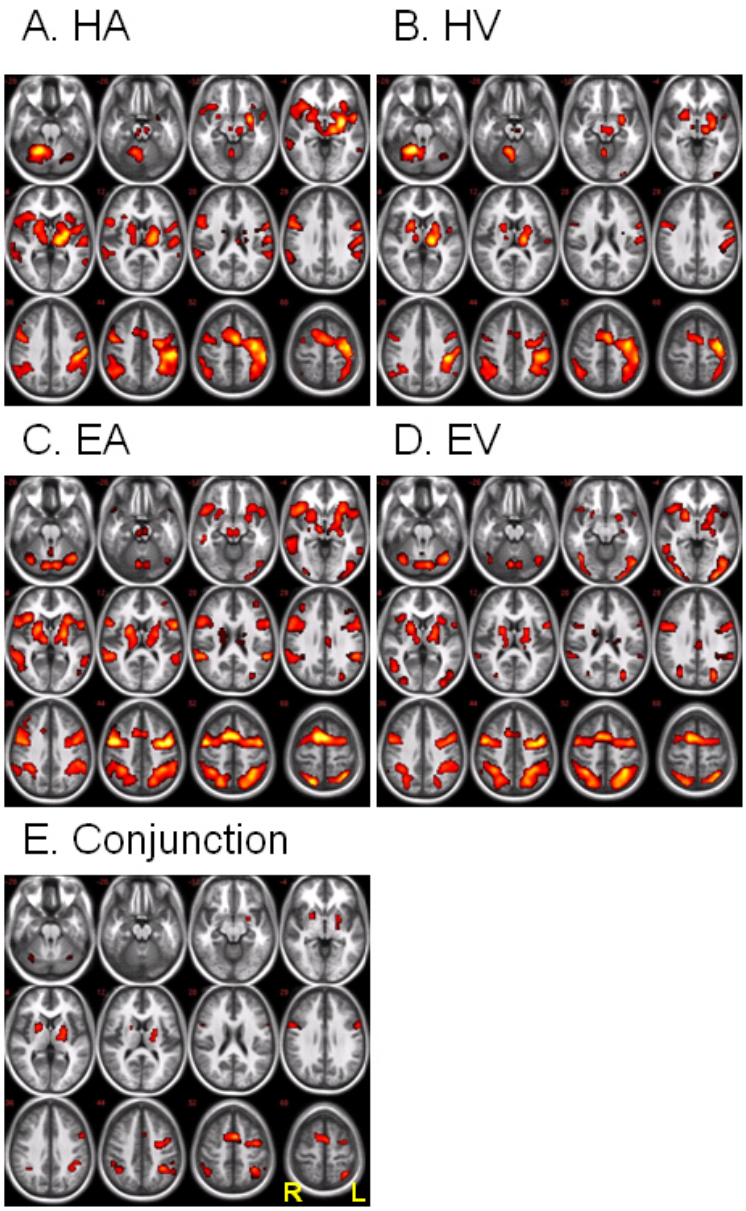
Area 46 is connected with PCC, STS and rostral STG. It also has local connections with other DLPFC areas (areas 8B, 8Ad, 9/46d, 9), VLPFC (45B, 47/12), orbital PFC (areas 10, 11) and DMPFC (areas 8B, 9, 10, 32).

Area 10 is connected with other cortical regions via CING F, ExtmC and UF. It is connected with rostral and posterior cingulate cortex, temporopolar proisocortex, amygdala, rostral STG and STS. It also has local connections

with dorsal premotor cortex (6d), DLPFC (area 9, 46, 9/46, 8Ad) and VLPFC (45, 47/12).

Appendix 4

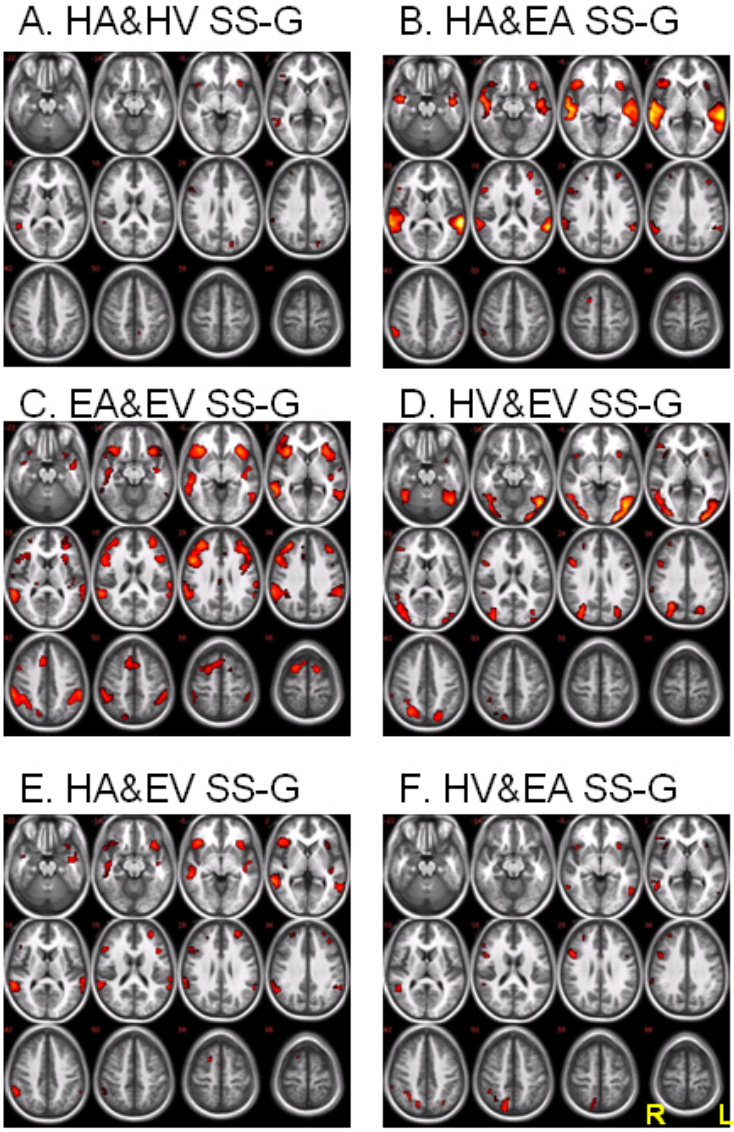
Block analysis: response control during blocks of each task (Study 1)



Contrast maps of response control during blocks of each task.
(A) Suprathreshold activations of response control during HA blocks.
(B) Suprathreshold activations of response control during HV blocks.
(C) Suprathreshold activations of response control during EA blocks.
(D) Suprathreshold activations of response control during EV blocks.
All $p<0.05$, FDR corrected. The first letter ("R" and "L") of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Appendix 5

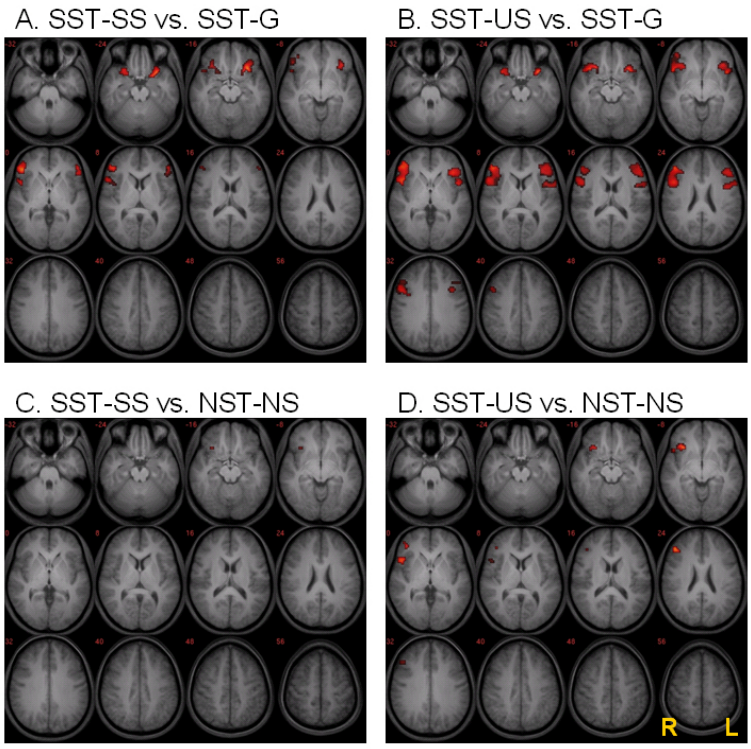
Conjunction event-related analysis: common activation during successful response inhibition (Study 1)



Common activation in successful response inhibition: (A) Hand successful response inhibition: suprathreshold activations in SS-G (successful stop vs. go) contrasts in both HA and HV tasks. (B) Auditorily guided successful response inhibition: suprathreshold activations in SS-G contrasts in both HA and EA tasks. (C) Eye successful response inhibition: suprathreshold activations SS-G contrasts in both EA and EV tasks. (D) Visually guided successful response inhibition: suprathreshold activations in SS-G contrasts in both HV and EV tasks. (E) Suprathreshold activations in SS-G contrasts in both HA and EV tasks. (F) Suprathreshold activations in SS-G contrasts in both HV and EA tasks. All $p<0.001$, uncorrected. The first letter (“R” and “L”) of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Appendix 6

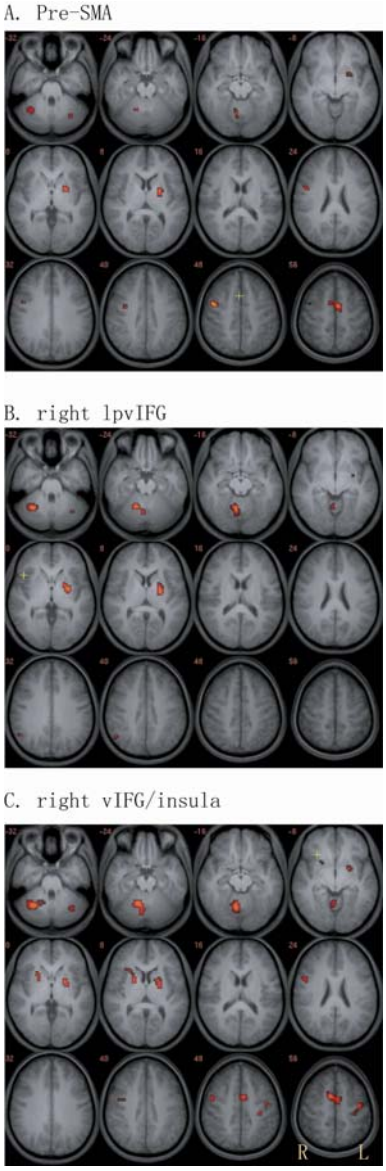
Event-related analysis (Study 2)



Event-related analysis: (A) Suprathreshold activation of SST-SS vs. SST-G (successful stop trials versus go trials in SST), $p<0.05$, FDR corrected. (B) Suprathreshold activation of SST-US vs. SST-G (unsuccessful stop trials versus go trials in SST), $p<0.05$, FDR corrected. (C) Suprathreshold activation of SST-SS vs. NST-NS (successful stop trials in SST versus not-stop trials in NST), $p<0.005$, uncorrected. (A) Suprathreshold activation of SST-US vs. NST-NS (unsuccessful stop trials in SST versus not-stop trials in NST), $p<0.05$, FDR corrected. The first letter (“R” and “L”) of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Appendix 7

Functional connectivity during response inhibition (Study 2)



Functional connectivity during response inhibition: (A) Increased functional connectivity with pre-SMA during the SST than during the NST. (B) Increased functional connectivity with right lateral posterior ventral IFG during the SST than during the NST. (C) Increased functional connectivity with right ventral IFG/insula. All $p<0.001$, uncorrected. The yellow cross represents the averaged MNI coordinates of pre-SMA (x=3, y=13, z=51), right lateral posterior ventral IFG (x=47, y=20, z=0), right ventral IFG/insula (x=31, y=26, z=-7). The first letter ("R" and "L") of the abbreviations for the anatomical structures indicated the side of the hemisphere (right and left, respectively).

Appendix 8

Individual center coordinates of VOIs used in PPI analysis (Study 1)

left IFG	x	y	z
Conjunction AS-G	-33	24	-9
Subjects			
1	-48	24	-3
2	-45	18	-6
3	-36	27	-3
4	-33	18	-3
5	-24	30	-3
6	-33	21	0
7	-33	27	-6
8	-30	24	3
9	-30	30	-6
10	-42	21	-12
11	-33	18	3
12	-54	24	0
13	-30	30	0
14	-33	24	0
15	-33	18	-12
16	-33	24	-3
17	-30	18	3
18	-48	24	6
19	-36	24	-9

right IFG	x	y	z
Conjunction AS-G	39	27	-9
Subjects			
1	48	24	-9
2	57	24	-6
3	48	24	3
4	42	24	-6
5	33	27	-9
6	36	24	-3
7	36	27	0
8	45	24	3
9	36	24	3
10	60	27	6
11	33	21	0
12	51	27	-3
13	42	33	-6
14	30	27	3
15	36	21	-9
16	42	30	-6
17	48	21	-6
18	36	18	6
19	39	18	-9

Appendix 9

Individual center coordinates of VOIs used in PPI analysis (Study 2)

right pdIFG	x	y	z
Group			
SST-NST	48	6	33
Subjects			
1	39	15	24
2	45	15	33
3	51	12	30
4	54	21	27
5	54	12	30
6	51	12	36
7	57	12	30
8	51	15	33
9	57	21	24
10	48	12	33
11	54	12	30
12	57	21	30
13	48	12	33
14	54	21	27
15	51	12	33
16	48	6	27
17	-	-	-
18	45	21	33
19	48	6	33
20	45	18	15
21	54	12	24
22	54	9	21
23	54	12	42

right lpvIFG	x	y	z
Group			
SST-NST	45	21	0
Subjects			
1	51	18	3
2	45	21	0
3	54	24	-6
4	45	21	0
5	51	21	0
6	48	18	-3
7	51	30	-6
8	45	18	3
9	45	21	0
10	48	24	-6
11	48	18	-3
12	51	21	6
13	51	15	-3
14	48	18	-3
15	42	27	6
16	45	21	6
17	45	18	3
18	48	18	-3
19	45	21	0
20	-	-	-
21	45	21	0
22	45	21	0
23	45	21	0

right vIFG/insula	x	y	z
Group SST-NST	33	24	-6
Subjects			
1	27	27	-12
2	33	27	-12
3	30	27	-9
4	30	27	-9
5	-	-	-
6	30	24	-9
7	33	24	-6
8	33	24	-6
9	33	30	3
10	30	27	-9
11	33	27	-9
12	36	27	-9
13	30	24	-12
14	30	24	-6
15	30	30	-9
16	33	27	-6
17	39	30	0
18	33	27	-9
19	30	27	-9
20	30	21	6
21	30	30	0
22	36	21	-9
23	30	27	-3

pre-SMA	x	y	z
Group SST-NST	6	15	48
Subjects			
1	3	15	48
2	3	21	45
3	3	15	54
4	12	15	60
5	21	18	51
6	9	18	57
7	6	30	48
8	3	24	51
9	0	18	45
10	15	9	54
11	3	18	45
12	-	-	-
13	-3	12	54
14	-6	6	48
15	0	9	48
16	-3	9	54
17	12	12	45
18	3	6	54
19	-3	12	51
20	0	6	51
21	-3	6	48
22	6	12	48
23	3	0	54

right FPC	x	y	z
Group SST-NST	33	57	15
Subjects			
1	24	54	18
2	39	54	18
3	33	63	9
4	39	60	9
5	39	48	12
6	30	63	15
7	36	60	9
8	36	51	3
9	36	51	3
10	27	54	27
11	36	57	15
12	36	63	12
13	24	66	15
14	36	54	21
15	36	60	9
16	27	48	12
17	24	48	42
18	36	54	18
19	33	63	15
20	-	-	-
21	39	45	27
22	36	54	18
23	30	63	15

left a IFG		x		y		z
Group						
SST-NST		-48		45		9
Subjects						
	1	-45		45		9
	2	-		-		-
	3	-		-		-
	4	-48		45		9
	5	-36		48		9
	6	-		-		-
	7	-39		45		12
	8	-48		42		9
	9	-48		36		0
	10	-45		45		12
	11	-39		42		12
	12	-48		45		3
	13	-33		48		9
	14	-33		51		9
	15	-48		45		12
	16	-48		51		3
	17	-27		57		12
	18	-		-		-
	19	-		-		-
	20	-45		48		0
	21	-39		36		-3
	22	-		-		-
	23	-42		48		9

right MFG/adIFG		x	y	z
Group SST-NST		42	36	27
Subjects				
	1	42	36	24
	2	45	30	30
	3	39	30	27
	4	48	30	30
	5	-	-	-
	6	42	36	27
	7	45	36	27
	8	45	36	27
	9	42	36	27
	10	51	36	24
	11	42	36	27
	12	39	33	24
	13	45	39	24
	14	42	36	27
	15	36	33	27
	16	36	33	27
	17	-	-	-
	18	36	33	21
	19	42	36	27
	20	45	33	33
	21	42	36	27
	22	42	30	27
	23	42	33	30