

## Functional Dissociation in Right Inferior Frontal Cortex during Performance of Go/No-Go Task

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**The contribution of the right inferior frontal cortex to response inhibition has been demonstrated by previous studies of neuropsychology, electrophysiology, and neuroimaging. The inferior frontal cortex is also known to be activated during processing of infrequent stimuli such as stimulus-driven attention. Response inhibition has most often been investigated using the go/no-go task, and the no-go trials are usually given infrequently to enhance prepotent response tendency. Thus, it has not been clarified whether the inferior frontal activation during the go/no-go task is associated with response inhibition or processing of infrequent stimuli. In the present functional magnetic resonance imaging study, we employed not only frequent-go trials but also infrequent-go trials that were presented as infrequently as the no-go trials. The imaging results demonstrated that the posterior inferior frontal gyrus (pIFG) was activated during response inhibition as revealed by the no-go vs. infrequent-go trials, whereas the inferior frontal junction (IFJ) region was activated primarily during processing of infrequent stimuli as revealed by the infrequent-go versus frequent-go trials. These results indicate that the pIFG and IFJ within the inferior frontal cortex are spatially close but are associated with different cognitive control processes in the go/no-go paradigm.**

**Keywords:** human, fMRI, prefrontal cortex, response inhibition

### Introduction

The contribution of the frontal cortex, especially the inferior frontal cortex, to response inhibition has been demonstrated by previous studies of neuropsychology (Iversen and Mishkin 1970; Butters et al. 1973; Aron et al. 2003; Chambers et al. 2006; Hodgson et al. 2007), electrophysiology (Pfefferbaum et al. 1985; Kok 1986; Sasaki et al. 1989; Funahashi et al. 1993; Bokura et al. 2001; Sakagami et al. 2001; Nakata et al. 2005), and neuroimaging (Kawashima et al. 1996; Garavan et al. 1999; Konishi et al. 1999; de Zubicaray et al. 2000; Liddle et al. 2001; Rubia et al. 2001; Menon et al. 2001; Bunge et al. 2002; Durston et al. 2002; Hester et al. 2004; Kelly et al. 2004; Matsubara et al. 2004; Aron and Poldrack 2006; Li et al. 2006; Feredoes et al. 2006; Leung and Cai 2007). The inferior frontal cortex has been also reported to be activated during processing of infrequent stimuli (McCarthy et al. 1997; Downar et al. 2000; Bledowski et al. 2004; Huettel and McCarthy 2004; Stevens et al. 2005).

The go/no-go and stop tasks are most often used to investigate response inhibition. These paradigms require subjects to inhibit prepotent responses in the no-go and stop trials in the go/no-go and stop tasks, respectively, against the go trials that require subjects to respond to presented stimuli. However, to enhance prepotent response tendency at the time

of the no-go/stop trials, these trials are usually given infrequently relative to the go trials, because simply presenting the go and no-go/stop trials in equal proportions may weaken response inhibition in the no-go/stop trials. Therefore, processing of infrequent stimuli such as stimulus-driven attention, which should be separated from inhibitory processes, is contained in these paradigms in the no-go/stop trials. Thus, it is not clear whether the right inferior frontal activation during the go/no-go and stop tasks is associated with response inhibition or processing of infrequent stimuli, both of which are known to activate the inferior frontal cortex. Moreover, previous neuroimaging results associated with the go/no-go and stop tasks have reported prominent activation in the inferior frontal regions such as the posterior part of the inferior frontal gyrus (pIFG) and the inferior frontal junction (IFJ) (see Brass et al. 2005 for anatomical details) that are located very close to each other, separated by only approximately 2 cm (Konishi et al. 2001). Thus, spatially extensive activation in the inferior frontal cortex may stem from the fact that the go/no-go task includes processing of infrequent stimuli, besides response inhibition.

In the present functional magnetic resonance imaging (fMRI) study, we employed a modified go/no-go task that contained not only frequent-go trials but also infrequent-go trials which were presented as infrequently as the no-go trials. Brain regions associated with response inhibition were revealed by comparing the no-go trials with the infrequent-go trials, whereas brain regions associated with processing of infrequent stimuli were revealed by comparing the infrequent-go trials with the frequent-go trials. By using these contrasts, the inferior frontal cortical activation that was related to each of these component processes was dissociated.

### Methods

#### *Subjects and Imaging Procedures*

Written informed consent was obtained from 25 healthy right-handed subjects (10 males, 15 females; age 20–27). They were scanned using experimental procedures approved by the institutional review board of the University of Tokyo School of Medicine. The experiments were conducted using a 1.5-T fMRI system. Scout images were first collected to align the field of view centered on each subject's brain.  $T_2$ -weighted spin-echo images were obtained for anatomical reference (repetition time [TR] = 6660 ms; echo time [TE] = 30 ms; 90 slices, slice thickness = 2.0 mm; in-plane resolution =  $2 \times 2$  mm). For functional imaging, a gradient echo echo-planar sequence was used (TR = 4000 ms; TE = 50 ms; flip angle =  $90^\circ$ ). Each functional run consists of 37 whole brain acquisitions ( $28 \times 4$  mm slices; in-plane resolution of 4 mm). The first four functional images for each run were excluded from analysis to account for the equilibrium of longitudinal magnetization.

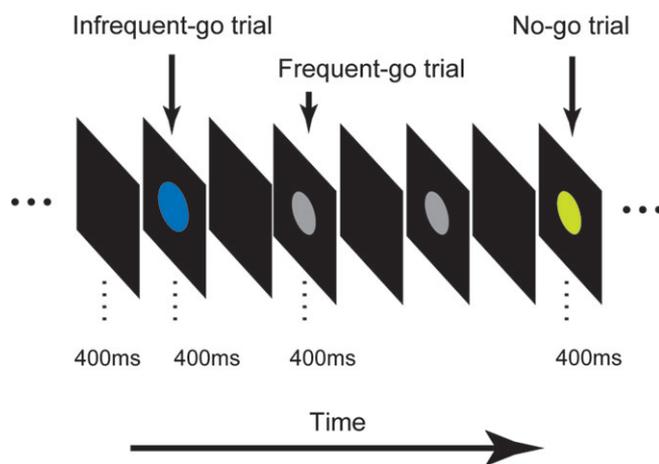
### Behavioral Procedures

Visual stimuli were presented to the subjects by projecting stimuli onto a screen. The subjects viewed the screen through prism glasses. A magnet-compatible button was pressed using the right thumb in response to the presented stimuli. The go/no-go task employed in the present study consisted of three types of trial: frequent-go, infrequent-go and no-go trials (Fig. 1). In the frequent-go and infrequent-go trials, the subjects were required to press a button as quickly as possible, and in the no-go trial, the subjects were required not to press the button, withholding the prepotent response tendency. For each trial, a colored circle ( $2.4^\circ \times 2.4^\circ$  in size) was presented for 400 ms, which was followed by a 400-ms intertrial interval. The color of the circle indicated the type of trial: gray indicated the frequent-go trial, whereas yellow or blue indicated the infrequent-go or no-go trial. The relationship between color (yellow/blue) and trial type (infrequent-go/no-go) was counterbalanced across subjects.

The go/no-go task in the present study was modified in order to dissociate the activation associated with response inhibition and that associated with processing of infrequently presented stimuli. The infrequent-go trials were presented as infrequently as the no-go trials, equating the demands for processing of infrequent stimuli, but the infrequent-go trials did not require response inhibition. Thus, the contrast of “no-go trials versus infrequent-go trials” was expected to reveal brain regions associated with response inhibition, whereas the contrast of “infrequent-go trials versus frequent-go trials” was expected to reveal brain regions associated with processing of infrequently presented stimuli. Twelve runs were administered to each subject. In total, 1440 (75.4%) frequent-go, 234 (12.3%) infrequent-go, and 234 (12.3%) no-go trials were intermixed in pseudorandom order. Filler frequent-go trials were presented at the beginning of each run (10 trials at the beginning). The subjects practiced 1 or 2 runs prior to scanning.

### Data Analysis

Data were analyzed using SPM2 software (<http://www.fil.ion.ucl.ac.uk/spm/>). Functional images were realigned, slice timing was corrected, normalized to the Montreal Neurological Institute template with interpolation to a  $2 \times 2 \times 2$  mm space, and spatially smoothed (full width, half maximum = 8 mm). Then event timing was coded into a general linear model (Worsley and Friston 1995). Transient events at the time of the correct no-go and the correct infrequent-go trials, and other events of no interest including error trials in the three types of trial were modeled as events using the canonical function in SPM2. The



**Figure 1.** The go/no-go task devised in the present study. Three types of trial (frequent-go, infrequent-go, and no-go) are intermixed in pseudorandom order. In the frequent-go and infrequent-go trials, the subjects were required to press a button as quickly as possible, and in the no-go trial, the subjects were required not to press a button, inhibiting prepotent response tendency. The no-go trials were presented infrequently to enhance prepotent response tendency, and the infrequent-go trials were presented as infrequently as the no-go trials. The relationship between color (blue/yellow) and trial type (no-go/infrequent-go) was counterbalanced across subjects.

correct frequent-go trials were used as a baseline, and were not coded as events. Group analyses were conducted using a random effects model. Significant activations were detected using two thresholds: 1) a threshold of 19 or more contiguous significant voxels (1 voxel:  $2 \times 2 \times 2$  mm) above  $P < 0.001$  ( $z > 3.3$ ) (Buckner et al. 1998; Konishi et al. 2001) and 2)  $P < 0.05$  corrected by false discovery rate (Genovese et al. 2002). The reported activation in the three contrasts cleared both the thresholds.

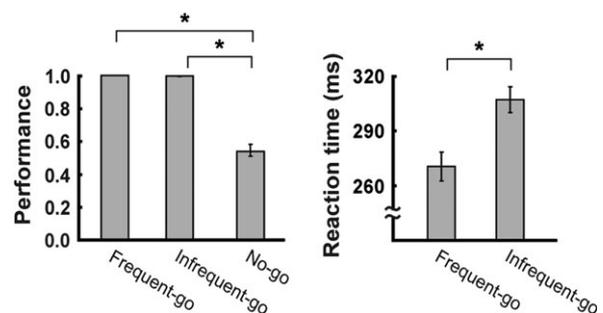
## Results

### Behavioral Results

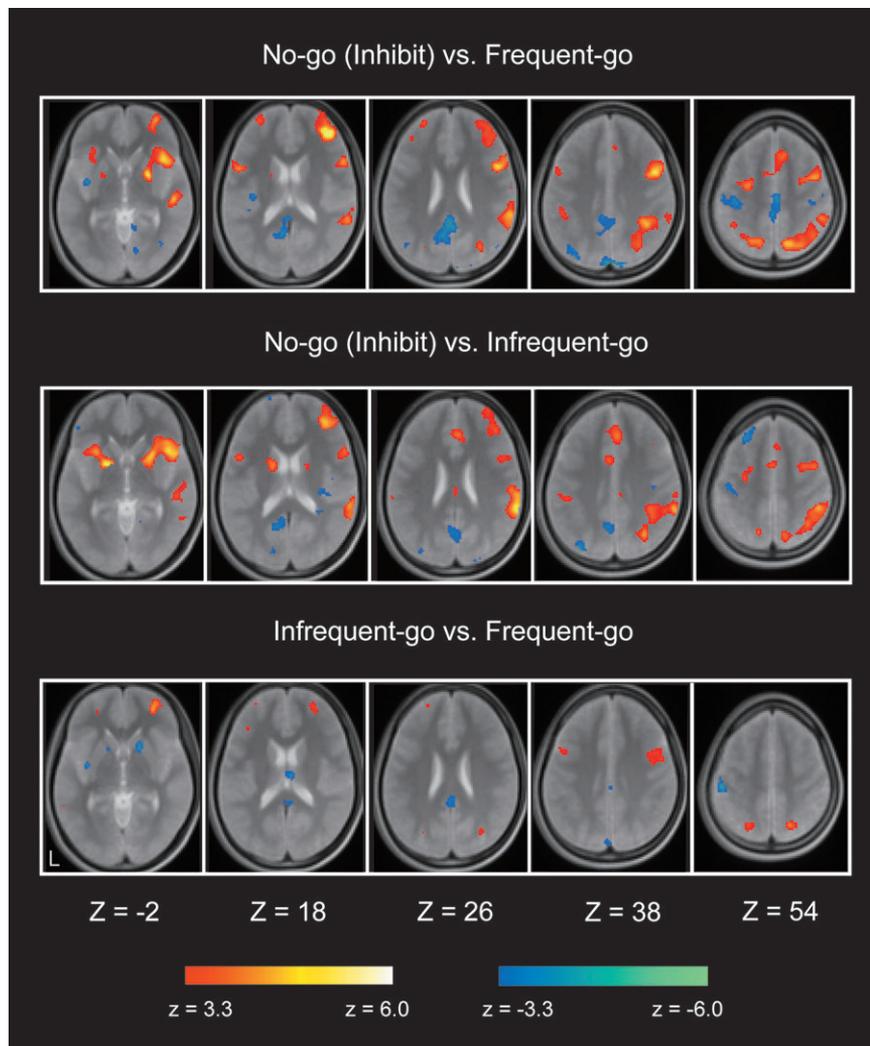
Mean correct performances (mean  $\pm$  SEM) were  $99.6 \pm 0.1\%$ ,  $99.7 \pm 0.1\%$ , and  $55.0 \pm 3.4\%$  in the frequent-go, infrequent-go and no-go trials, respectively (Fig. 2). The difference between the infrequent-go and no-go trials was significant ( $44.6 \pm 3.4\%$ ,  $t_{(24)} = 13.1$ ,  $P < 0.001$ ). Mean reaction times (mean  $\pm$  SEM) were  $270.5 \pm 8.0$  ms and  $306.9 \pm 6.9$  ms in the frequent-go and infrequent-go trials, respectively (Fig. 2). The difference between the infrequent-go and frequent-go trials was significant ( $36.4 \pm 4.6$ ,  $t_{(24)} = 8.0$ ,  $P < 0.001$ ). The correct performance difference between the infrequent-go and no-go trials suggests that the no-go trials in the present study contained sufficient amount of processes associated with response inhibition. Moreover, the reaction time difference between the infrequent-go and frequent-go trials indicates that the infrequent-go trials contained sufficient amount of processes associated with processing of infrequent stimuli.

### fMRI Results

The functional image data set from 25 subjects was analyzed using a general linear model implemented in SPM2, and was group-analyzed using a random effect model. As shown in Figure 3 and Table 1, the contrast of “no-go trials versus frequent-go trials” elicited prominent activations in multiple regions, including the pIFG, IFJ, dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), presupplementary motor area (pre-SMA), insula/IFG, rostromedial prefrontal cortex, precuneus and intraparietal sulcus (IPS), consistent with previous results of the go/no-go and stop tasks (Kawashima et al. 1996; Garavan et al. 1999; Konishi et al. 1999; de Zubicaray et al. 2000; Liddle et al. 2001; Menon et al. 2001; Rubia et al. 2001; Bunge et al. 2002; Durston et al. 2002; Hester et al. 2004; Kelly et al. 2004; Aron and Poldrack 2006; Leung and Cai 2007; Sumner et al. 2007).



**Figure 2.** Behavioral data during performance of the go/no-go task. Correct performance in the frequent-go, infrequent-go, and no-go trials and reaction time in the frequent-go and infrequent-go trials are displayed on the left and right, respectively.  $*P < 0.001$ , based on a paired  $t$ -test.



**Figure 3.** Statistical activation maps for signal increase and decrease in the contrasts of “no-go versus frequent-go trials” (top), “no-go versus infrequent-go trials” (middle), “infrequent-go versus frequent-go trials” (bottom). Activation maps are displayed as transverse sections and overlaid on top of the anatomic image averaged across subjects. Statistical significance is indicated using the color scale at the bottom, and the transverse section level is indicated by the Z coordinates of Talairach space (Talairach and Tournoux 1988). The color scale at the bottom is given in z-value.

To extract response inhibition more precisely in a way that processing of infrequent stimuli was excluded, “no-go trials versus infrequent-go trials” was calculated (Fig. 3 and Table 2). The contrast revealed that most of the above-mentioned regions including the pIFG, DLPFC, ACC, pre-SMA, insula/IFG, and IPS were significantly activated. To investigate processing of infrequent stimuli, “infrequent-go trials versus frequent-go trials” were calculated. The contrast revealed that the IFJ, the anterior prefrontal cortex, and the posterior part of the IPS were significantly activated (Fig. 3 and Table 3).

Most interestingly, the pIFG and IFJ were very close (approximately only 2 cm apart) but showed different activation patterns (Fig. 4a). In the contrast of “no-go trials versus frequent-go trials”, the activation of the pIFG and IFJ formed a large cluster that showed no clear dissociation in spatial extent. Figure 4b shows the signal magnitude for the contrast of “no-go trials versus infrequent-go trials” and the contrast of “infrequent-go trials and frequent-go trials” in the pIFG and IFJ, based on the regions of interest determined by the contrast “no-go trials versus frequent-go trials.” The

introduction of the infrequent-go trials clearly demonstrated that the pIFG was predominantly associated with response inhibition, whereas the IFJ was associated with both response inhibition and processing of infrequent stimuli. The signal difference between the contrasts in the pIFG was significant [ $t_{(24)} = 2.8, P < 0.05$ ]. Furthermore, the functional dissociation of the pIFG and IFJ was also significant, as revealed by the region-by-contrast interaction in repeated measure two-way ANOVA ( $F_{1,24} = 7.4, P < 0.05$ ). Incorrect no-go trials were also analyzed for the pIFG region (Fig. 4c). Signal difference was observed between the correct no-go and correct infrequent-go trials [ $t_{(24)} = 5.5, P < 0.001$ ] and between the incorrect no-go and correct infrequent-go trials [ $t_{(24)} = 2.2, P < 0.05$ ]. The difference between these two contrasts was also significant [ $t_{(24)} = 3.1, P < 0.01$ ], suggesting that the pIFG activation may not be purely related to response inhibition, but that the activation still included the components related to response inhibition. In contrast, no significant difference was observed between the incorrect no-go and correct infrequent-go trials (Fig. 4c), consistent with the interpretation that the IFJ activity

**Table 1**

Brain regions showing signal increase in the contrasts of "no-go versus frequent-go"

	x	y	z	t Value	Brodman Area (BA)
Lateral frontal cortex	26	-4	62	12.1	6
	42	42	18	8.6	10/46
	48	4	38	7.4	6/9/44
	40	18	-2	7.1	47/12
	50	10	26	7.1	6/44
	-52	8	20	6.5	6/44
	42	-2	56	6.5	6
	32	46	0	6.2	10
	40	56	6	6.2	10
	56	16	16	6.1	44/45
	-22	-4	58	6.0	6
	32	58	-2	5.9	10
	-30	58	14	5.7	10
	-26	56	24	5.3	10
	44	32	32	5.1	9/46
	30	22	-6	5.0	47/12
	-36	-6	58	4.9	6
	-40	38	22	4.8	9/46
	-52	6	38	4.4	6/9/44
	Medial frontal cortex	32	18	12	4.4
-8		2	58	7.0	6
-2		-4	64	6.7	6
6		10	60	6.3	6
10		20	56	5.9	6
Parietal cortex	8	0	60	4.6	6
	6	30	36	4.1	32
	36	-44	42	7.7	7/40
	24	-68	48	7.6	7
	66	-14	32	6.8	1/2/3
	64	-38	28	6.7	40
	14	-68	54	6.6	7
	-24	-66	48	6.5	7
	-20	-62	60	6.4	7
	56	-42	48	6.0	40
	16	-68	64	5.7	7
	40	-62	56	5.3	40/7
	-48	-36	40	5.3	40
	-42	-48	52	4.7	40/7
	Occipital cortex	30	-68	30	5.2
30		-68	30	5.2	19/39
Temporal cortex	52	-22	-2	6.6	21/22
	66	-32	20	5.2	22/42
	52	-46	14	5.0	21/37
Others	-30	-58	-30	5.8	Cerebellum
	-32	-62	-16	4.7	Cerebellum
	-36	-50	-34	4.7	Cerebellum
	-14	-64	-32	4.3	Cerebellum
	24	4	0	8.3	Putamen
	-30	16	8	6.8	Insula
	-18	12	10	6.4	Caudate
	18	10	6	5.8	Putamen
	-26	2	4	4.5	Putamen
	-32	26	-2	4.4	Putamen

primarily reflects processing of infrequent stimuli. Figure 4*d* shows the time courses of the signals in each contrast in the pIFG and IFJ. Figure 4*e* demonstrates activation related to no-go and infrequent-go trials relative to a common baseline (frequent-go trials).

## Discussion

The present study using the go/no-go task introduced the infrequent-go trials, besides the frequent-go trials, and revealed the dissociation between the brain activation associated with response inhibition and that associated with processing of infrequent stimuli. In particular, within the posterior part of the right inferior frontal cortex, differential activation patterns were found between the pIFG and IFJ. These results suggest that there are at least two subregions in the inferior frontal cortex, which are anatomically very close to each other, but are functionally different.

**Table 2**

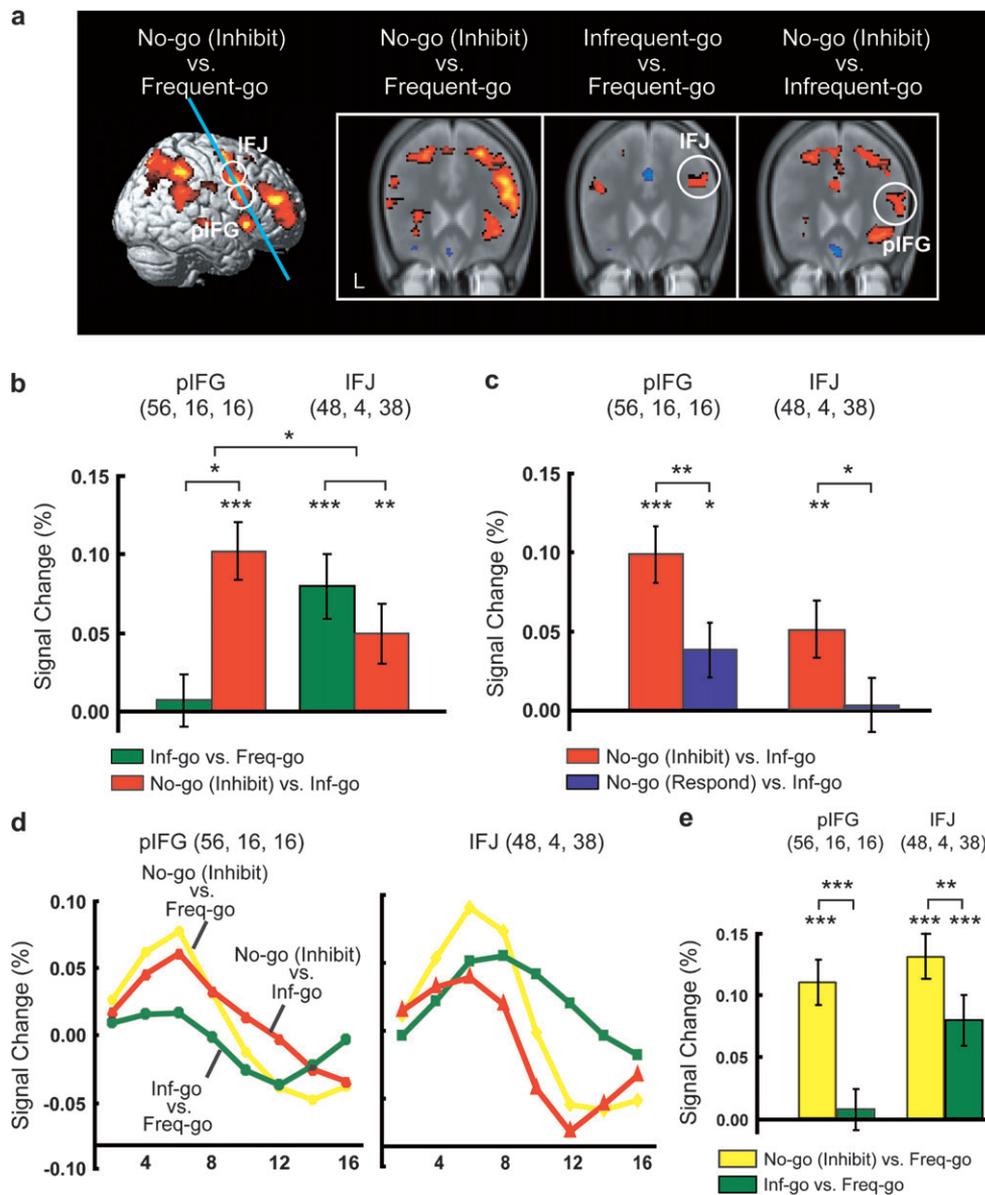
Brain regions showing signal increase in the contrasts of "no-go versus infrequent-go" (response inhibition)

	x	y	z	t Value	BA	
Lateral frontal cortex	42	16	-2	7.2	47/12	
	36	40	20	6.7	10/46	
	24	-4	62	6.5	6	
	-24	-4	58	5.9	6	
	30	24	-6	5.9	47/12	
	58	14	16	5.6	44/45	
	44	0	56	5.3	6	
	-50	10	18	5.0	6/44	
	38	56	10	4.8	10	
	-50	6	4	4.6	6/44	
	48	10	26	4.5	6/44	
	60	10	28	4.1	6/44	
	-58	12	10	4.1	6/44	
	44	2	44	3.9	6/9/44	
	-46	14	-8	4.4	47/12	
	Medial frontal cortex	6	-12	32	6.3	24/23
		2	2	50	6.0	6
		2	30	36	5.6	32
		4	34	26	5.3	32
		4	-28	32	5.4	23/31
12		-32	44	5.2	7/24	
-4		6	36	5.2	24	
2		0	62	5.1	6	
-6		-6	64	5.0	6	
0		12	44	4.9	32/6	
Parietal cortex	10	16	60	4.3	6	
	54	-42	48	7.6	40	
	44	-46	46	7.4	7/40	
	38	-56	48	6.8	40/7	
	62	-44	36	6.6	40	
	64	-28	28	6.5	40	
	12	-70	52	5.6	7	
	32	-64	50	5.3	7	
	-14	-66	54	5.2	7	
	-22	-60	64	4.8	7	
Occipital cortex	-48	-32	40	4.7	40	
	30	-68	38	6.0	19/39	
	62	-40	24	7.6	22/42	
Temporal cortex	52	-26	0	4.8	21/22	
	-60	-34	22	4.5	22/42	
	58	-50	-2	4.2	21/37	
	60	-18	-2	4.2	21/22	
	28	-54	-32	5.7	Cerebellum	
	-30	-62	-28	3.6	Cerebellum	
	-20	2	-4	8.2	Putamen	
Others	22	6	-6	7.7	Putamen	
	-14	4	12	6.9	Caudate	
	32	12	-10	6.8	Putamen	
	-24	10	4	6.6	Insula	
	26	0	4	6.0	Putamen	
	16	4	12	6.0	Caudate	
	-30	16	-4	6.0	Putamen	

**Table 3**

Brain regions showing signal increase in the contrasts of "infrequent-go versus frequent-go" (processing of infrequent stimuli)

	x	y	z	t Value	BA
Lateral frontal cortex	32	52	-2	5.9	10
	30	52	14	5.2	10
	26	-4	64	5.0	6
	-50	10	34	4.9	6/9/44
	42	-4	40	4.8	6/9/44
	52	0	40	4.6	6/9/44
	-50	6	46	4.4	6/9/44
Medial frontal cortex	-4	12	60	4.4	6
Parietal cortex	-24	-68	46	6.6	7
	22	-64	46	6.3	7
	28	-74	22	4.7	19/39
Others	-32	-64	-14	4.3	Cerebellum
	-36	-54	-22	4.2	Cerebellum



**Figure 4.** Different activation patterns observed in the pIFG and IFJ in the inferior frontal cortex. (a) The contrast of “no-go versus infrequent-go” predominantly activated the pIFG, whereas the contrast of “infrequent-go versus frequent-go” primarily activated the IFJ. (b) Region of interest (ROI) analyses. The panel shows the signal magnitude for the contrast of “no-go trials versus infrequent-go trials” and the contrast of “infrequent-go trials versus frequent-go trials” in the pIFG and IFJ, based on the regions of interest determined based on the contrast “no-go trials versus frequent-go trials,” as listed in Table 1. \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . (c) The panel shows the signal magnitude for the contrast of “correct no-go trials versus correct infrequent-go trials” and the contrast of “incorrect no-go trials versus correct infrequent-go trials” in the pIFG and IFJ. (d) Signal time courses in the pIFG and IFJ. The ROIs were determined similarly to Figure 4b. Red, yellow and green lines indicate the signal magnitude of the “no-go versus frequent-go,” “no-go versus infrequent-go,” and “infrequent-go versus frequent-go” trials, respectively. (e) The panel shows the signal magnitude for the contrast of “no-go trials versus frequent-go trials” and the contrast of “infrequent-go trials versus frequent-go trials” in the pIFG and IFJ.

The pIFG was specifically activated during response inhibition, but not during processing of infrequent stimuli. The pIFG activation in the present study was consistent with the activation results of previous studies of response inhibition (Konishi et al. 1999; Bunge et al. 2002; Durston et al. 2002; Maguire et al. 2003; Horn et al. 2003; Kelly et al. 2004; Rubia et al. 2005; Aron and Poldrack 2006; Li et al. 2006; Chikazoe et al. 2007; Leung and Cai 2007), and also with those of other types of inhibitory control (Thompson-Schill et al. 1997, 1998; Monchi et al. 2001; Braver et al. 2003; Hazeltine et al. 2003; Konishi et al. 2003, 2005; Brass and von Cramon 2004; Cools et al. 2004; Crone et al. 2006; Parris et al. 2007). On the other

hand, the IFJ was activated in the present study during both response inhibition and processing of infrequent stimuli, consistent with previous studies of response inhibition and processing of infrequent stimuli (Downar et al. 2001; Kiehl et al. 2001). The present study successfully demonstrated the functional dissociation between the adjacent pIFG and IFJ regions in the same task paradigm, that is, the pIFG being activated during response inhibition and the IFJ being activated primarily during processing of infrequent stimuli.

The present study revealed the pIFG activation associated with response inhibition. The contribution of the pIFG to response inhibition has been established by previous studies on

the brain-function causality using neuropsychology (Aron et al. 2003; Hodgson et al. 2007) and transcranial magnetic stimulation (Chambers et al. 2006). The IFJ activation in the present study, on the other hand, showed a composite activation pattern consisting of both response inhibition and processing of infrequent stimuli. It is noteworthy that a neuropsychological study posited a negative view on the role of the IFJ in response inhibition (Aron et al. 2006), which suggests that the IFJ is involved in cognitive processes other than response inhibition. Indeed, the saliency of the stimulus indicating the no-go trials should be greater than that of the stimulus indicating the infrequent-go trials, because the no-go trials required more infrequent response outcome (i.e., no-go), instead of more frequent-go response required in the infrequent-go and frequent-go trials (Downar et al. 2001; Laurens et al. 2005). Therefore it is possible that the no-go stimulus with the greater saliency may recruit cognitive control processes other than response inhibition in the no-go trials. One prominent view provided to date on the role of the IFJ is that it contributes to the maintenance of task-relevant information, which is used to bias posterior brain systems that may represent the individual S-R mapping necessary to perform a task (Derrfuss et al. 2004).

One caveat regarding the pIFG activation was that the present task design does not include frequent no-go trials that would have completed the factorial design of response inhibition and cue frequency. Therefore, the design leaves open the possibility that the pIFG activation in the present study may be related to the interaction between these effects. However, the factorial design is not feasible in this particular case, because it is clear that response inhibition is greater when a cue is presented more infrequently. It is also possible to administer two types of no-go trials where one type was substantially more frequent. At the same time, it is still likely that response inhibition is greater when a cue is presented more infrequently, which makes it difficult to match requirement for response inhibition even within trial type. Although more precise accounts of the role of the pIFG and IFJ need further exploration, the present study suggests that the IFC is heterogeneous and consists of at least two subregions that contribute to the successful performance of the go/no-go task in different manners.

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## Notes

*Conflict of Interest:* None declared.

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