Activation of Right Inferior Frontal Gyrus during Response Inhibition across Response Modalities

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Abstract

■ The go/no-go task, which effectively taps the ability to inhibit prepotent response tendency, has consistently activated the lateral prefrontal cortex, particularly the right inferior frontal gyrus (rIFG). On the other hand, rIFG activation has rarely been reported in the antisaccade task, seemingly an oculomotor version of the manual go/no-go task. One possible explanation for the variable IFG activation is the modality difference of the two tasks: The go/no-go task is performed manually, whereas the antisaccade task is performed in the oculomotor modality. Another explanation is that these two tasks have different task structures that require different cognitive processes: The traditional antisaccade task requires (i) configuration of a preparatory set prior to antisaccade execution and (ii) response inhibition at the time of antisaccade execution, whereas the go/no-go task requires heightened response inhibition under a minimal preparatory set. To test these possibilities, the traditional antisaccade task was modified in the present functional magnetic resonance imaging study such that it required heightened response inhibition at the time of antisaccade execution under a minimal preparatory set. Prominent activation related to response inhibition was observed in multiple frontoparietal regions, including the rIFG. Moreover, meta-analyses revealed that the rIFG activation in the present study was observed in the go/no-go tasks but not in the traditional antisaccade task, indicating that the rIFG activation was sensitive to the task structure difference, but not to the response modality difference. These results suggest that the rIFG is part of a network active during response inhibition across different response modalities. ■

INTRODUCTION

The prefrontal cortex allows efficient adaptation to the environment by inhibiting prepotent response tendency. The go/no-go task, which involves withholding manual responses against a prepotent response tendency, is most often used to investigate response inhibition. The contribution of the prefrontal cortex to response inhibition, particularly that of the inferior frontal gyrus (IFG) in the right hemisphere, has been demonstrated by previous studies of neuropsychology (Aron, Bullmore, Sahakian, & Robbins, 2003; Butters, Butter, Rosen, & Stein, 1973; Iversen & Mishkin, 1970), electrophysiology (Nakata, Inui, Wakasa, Akatsuka, & Kakigi, 2005; Bokura, Yamaguchi, & Kobayashi, 2001; Sakagami et al., 2001; Funahashi, Chafee, & Goldman-Rakic, 1993; Sasaki, Gemba, & Tsujimoto, 1989; Kok, 1986; Pfefferbaum, Ford, Weller, & Kopell, 1985), and neuroimaging (Aron & Poldrack, 2006; Buchsbaum, Greer, Chang, & Berman, 2005; Rubia et al., 2005; Matsubara, Yamaguchi, Xu, & Kobayashi, 2004; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Durston, Thomas, Worden, Yang, & Casey, 2002; Braver, Barch, Gray, Molfese, & Snyder, 2001; Liddle, Kiehl, & Smith, 2001; Menon, Adleman, White, Glover, & Reiss, 2001; Rubia et al., 2001; de Zubicaray, Andrew, Zelaya, Williams, & Dumanoir, 2000; Garavan, Ross, & Stein, 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Kawashima et al., 1996).

Despite the abundant knowledge on the IFG regarding the manual go/no-go task, little is known about its contribution to response inhibition in the oculomotor modality. Antisaccade, making saccades away from a peripherally presented stimulus (Hallett, 1978), recruits inhibitory control for successful performance and provides a unique opportunity of investigating inhibitory control of the oculomotor system (Husain, Parton, Hodgson, Mort, & Rees, 2003; Guitton, Buchtel, & Douglas, 1985). Traditional antisaccade paradigms most often present antisaccade trials successively in a block (Gaymard, Francois, Ploner, Condy, & Rivaud-Pechoux, 2003; Pierrot-Deseilligny et al., 2003; Walker, Husain, Hodgson, Harrison, & Kennard, 1998; Paus, Petrides, Evans, & Meyer, 1993; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991) or introduce a preparatory period prior to antisaccade execution (Ford, Goltz, Brown, & Everling, 2005; Munoz & Everling, 2004; Curtis & D'Esposito, 2003; DeSouza, Menon, & Everling, 2003). Thus, the traditional paradigms require configuration of

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a preparatory set for subsequent antisaccades and inhibition of prepotent responses at the time of antisaccade execution, both of which contribute to successful inhibitory control of prepotent saccades in a complementary manner. Previous neuroimaging studies showed prominent activity during antisaccade task primarily in the frontal eye field (FEF), supplementary eye field (SEF), dorsolateral prefrontal cortex (DLPFC), presupplementary motor area (pre-SMA), intraparietal sulcus (IPS), and precuneus (Ford et al., 2005; Matsuda et al., 2004; Munoz & Everling, 2004; Curtis & D'Esposito, 2003; DeSouza et al., 2003; Connolly, Goodale, Menon, & Munoz, 2002; Raemaekers et al., 2002; Kimmig et al., 2001; Merriam et al., 2001; Connolly, Goodale, DeSouza, Menon, & Vilis, 2000; Doricchi et al., 1997; Sweeney et al., 1996; O'Driscoll et al., 1995; Paus et al., 1993). However, prominent brain activation in the IFG has rarely been demonstrated in the antisaccade task.

The variability of the IFG activation across the go/no-go and antisaccade tasks may stem from the fact that the go/no-go task is performed in the manual response modality, whereas the antisaccade task is performed in the ocular response modality (modality difference account). Another possible account is that these two tasks have different task structures that require different cognitive processes (structure difference account): The go/no-go task requires inhibition of prepotent responses under a minimal preparatory set, whereas the traditional antisaccade task requires active configuration of a preparatory set prior to antisaccade execution and less response inhibition at the time of antisaccade execution. The traditional antisaccade paradigm has the merit of enabling the investigation of configuration of a preparatory set for goal-directed saccades and of avoiding confounding factors of motor response per se. On the other hand, the antisaccade task was modified in the present functional magnetic resonance imaging (fMRI) study such that the cognitive components required during the modified antisaccade task include response inhibition components to a degree similar to those required during the manual go/no-go task. The modified antisaccade task was made to require heightened response inhibition under a minimal preparatory set by removing the traditional preparatory period provided prior to withholding the prepotent responses and by presenting an instruction cue of antisaccade simultaneously with peripheral stimulus presentation (Figure 1). Moreover, to further enhance the prepotent response tendency, antisaccade trials were given infrequently among more frequent prepotent saccades. Control saccade trials were presented as infrequently as the antisaccade trials to control for cognitive components of no interest, such as the sensory oddball effects of presentation of the antisaccade trials. Baseline saccade trials were presented much more frequently than the antisaccade and control saccade trials in order to form a baseline for the fMRI analysis. The neural correlates of response inhibition in the oculomotor modality were explored using event-related fMRI.

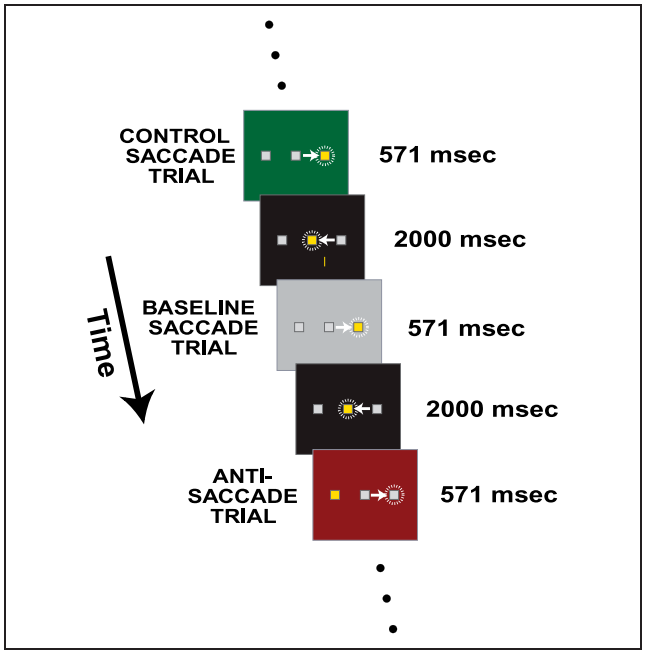

Figure 1. Antisaccade task devised in the present study. The three types of saccade trials (baseline, control, and antisaccade) are intermixed in a pseudorandom order. In the baseline and control saccade trials, the subjects were required to make a saccade to a peripherally presented stimulus, and in the antisaccade trial, the subjects were required to make a saccade away from the stimulus. The antisaccade trials were presented infrequently to enhance prepotent response tendency. The control saccade trials were presented as infrequently as the antisaccade trials to control for cognitive components of no interest such as the sensory oddball effect. The baseline saccade trials were presented much more frequently than the antisaccade and the control saccade trials, and were used as a baseline of fMRI analysis. The relationship between color (red/green) and trial type (antisaccade/control saccade) was counterbalanced across subjects.

Furthermore, it was tested whether the difference in the IFG activation was derived from the difference in the response modality or from the difference in the task structure: The activation during the modified antisaccade task was compared with that from a meta-analysis of manual go/no-go tasks (i.e., matched structures in different modalities) in order to test the modality difference account. The activation during the modified antisaccade task was also compared with that from a meta-analysis of the traditional antisaccade task (i.e., different structure in matched modalities) in order to test the structure difference account. The meta-analysis was used to ensure the typicality of the go/no-go task and the traditional antisaccade task. The activation foci determined in the modified antisaccade task of the present study were tested as to whether they were significantly likely to be reported previously in the go/no-go task and the traditional antisaccade task as estimated by the activation likelihood estimation (ALE) method.

METHODS

Subjects and Imaging Procedures

Written informed consent was obtained from 24 healthy, right-handed subjects (12 men, 12 women; age, 20–29 years). They were scanned by experimental procedures approved by the institutional review board of the University of Tokyo School of Medicine. The experiments were conducted using a 1.5T fMRI system. Scout images were first collected to align the field of view centered on the subject's brain. T2-weighted spin-echo images were obtained for anatomical reference (repetition time [TR] = 6660 msec; echo time [TE] = 30 msec; 90 slices, slice thickness = 2.0 mm; in-plane resolution = 2 × 2 mm]. For functional imaging, a gradient-echo echo-planar sequence was used (TR = 3000 msec; TE = 50 msec; flip angle = 90°). Each functional run consists of 46 whole-brain acquisitions (21 × 4-mm slices; in-plane resolution, 4 mm). The first four functional images for each run were excluded from analysis to take into account the equilibrium of longitudinal magnetization.

Eye Monitoring

The subjects' eyes were illuminated with infrared rays through an MRI-compatible optic fiber, and eye images were reflected on a front surface mirror (Asari, Konishi, Jimura, & Miyashita, 2005). The eye images were acquired at a sampling rate of 60 Hz by using a charge-coupled device camera sensitive to infrared rays through a telephoto lens fixed at 200 cm from the subjects' eyes, and were transmitted to the ISCAN system (ISCAN, Burlington, MA). The ISCAN system estimated the contour of the pupil and then its center, and calculated the point of regard (POR) on the basis of the pupil center with reference to the corneal reflex point that corrects for head movements, which achieved a spatial resolution of approximately 0.5°. Stored POR data were subjected to off-line analysis conducted after fMRI scans to evaluate oculomotor behavior. Saccadic reaction time was estimated by using semiautomatic routines that relied on the velocity of the eye movement. When a saccade was once executed to an incorrect direction after a target presentation, it was taken as an error.

Behavioral Procedures

Visual stimuli were presented to the subjects by projecting the stimuli onto a screen. The subjects viewed the screen through the front surface mirror. Eye movements were monitored and recorded throughout the task performance. The antisaccade task used in the present study consisted of three types of trial: baseline saccade trials, control saccade trials, and antisaccade trials (Figure 1). In the baseline and control saccade trials, the subjects were required to make a saccade to a peripherally presented stimulus, and in the antisaccade trial, the subjects were required to make a saccade away from the stimulus. In the MRI scanner, subjects viewed a horizontal array of three boxes (1° × 1° in size) that were positioned 7° apart (Figure 1). The central box was brightly illuminated with a black background for 2000 msec and the subjects were fixated on this box. The illumination of the central box was then turned off, and one of the two peripheral boxes was brightly illuminated instead. At the same instant, the color of the background changed, indicating the trial type. A change to gray indicated the baseline saccade trial, whereas a change to red or green indicated the control saccade or the antisaccade trial. The relationship between color (green/red) and trial type (control saccade/antisaccade) was counterbalanced across subjects. Subjects then made a saccade toward or away from the peripheral box based on the background color. After a short duration of 571 msec, the central box was again illuminated against the black background and subjects then returned to the central box and fixated on it.

In the present study, the antisaccade task was modified in several ways to increase the prepotent response tendency at the time of antisaccade execution. First, as has been used in the go/no-go task, the antisaccade trials, which require response inhibition, were given infrequently among more frequent reflexive saccades. One of the possible confounding factors concerning the infrequency in the antisaccade trials would be the involvement of cognitive processes of no interest including those associated with the ''sensory'' oddball effect. The sensory oddball effect is different from spatial attention or working memory that is enhanced in infrequent trials. Such sensory oddball components were designed to be matched by introducing the control saccade trials using another background color (i.e., green or red) that were presented as infrequently as the antisaccade trials. Second, to minimize preparatory set configuration, the traditional preparatory period was removed. Instead, to inform subjects of the trial type of subsequent trials, an indication of a trial type was presented simultaneously with a peripheral target. Removing the preparatory set period does not mean that the preparatory set activity was completely removed, but the shorter interval with which subjects configure preparatory set should decrease the preparatory set activity compared to the traditional antisaccade tasks. This view is supported by the lower performance of the present study compared with previous studies using the traditional antisaccade tasks after removing the preparatory period (see Results). Third, to allow the subjects to judge the trial type simultaneously with prepotent saccades, a whole-screen presentation was used to indicate the trial-type color. Fourth, to keep a natural pace of successive saccade trials, the duration of peripheral stimulus presentation and the intertrial interval were shortened (571 and 2000 msec, respectively) relatively to those used in most of previous event-related fMRI

studies. Thus, an outgoing saccade and a return saccade were not dissociated and were dealt with as a single event in the present study.

Twelve runs were administered to each subject. Four hundred fifty-six (73%) baseline saccade, 84 (13.5%) control saccade, and 84 (13.5%) antisaccade trials were intermixed in a pseudorandom order. In each run, the same numbers of rightward and leftward saccades were required. Moreover, saccade directions in each of the three trial types were counterbalanced across subjects by presenting in a directionally reversed sequence.

Data Analysis

Data were analyzed using SPM2 software (www.fil.ion.ucl.ac.uk/spm/). Functional images were realigned, and slice timing was corrected, normalized to the baseline template with interpolation to a 2 × 2 × 2-mm space, and spatially smoothed (full width half maximum = 8 mm). Then event timing was coded into a general linear model (Worsley & Friston, 1995). Transient events at the time of correct antisaccade and correct control trials, and other events of no interest including error trials in the baseline saccade, the control saccade, and the antisaccade trials, were modeled as events using the canonical function in SPM2. The baseline saccade trials were used as a baseline for the antisaccade and control saccade trials. Group analyses were conducted using a random effects model. Significant activations were detected using a threshold of 19 or more contiguous significant voxels (1 voxel: 2 × 2 × 2 mm) above $p < .001$ ($z > 3.3$) (Konishi, Donaldson, & Buckner, 2001; Buckner et al., 1998). Note that this threshold cleared $p < .05$ corrected by false discovery rate (FDR) (Genovese, Lazar, & Nichols, 2002) in the present data set.

Functional hemispheric asymmetry was tested for the contrast of the antisaccade versus control saccade trials using regions of interest (ROIs) determined without statistical bias between the left and right hemispheres. Briefly, the beta images of the anti versus control contrast that contained signal percentage values were flipped along the midline, and the ''flipped'' and ''non-flipped'' images were averaged for each subject (therefore, the result is independent of the threshold) (Konishi et al., 2002). The averaged images entered into a second-level analysis using a one-sample t test. Bilateral pairs of ROIs were generated from the frontal and parietal areas, based on the peak coordinates that cleared the threshold of 19 or more contiguous voxels above $p < .001$, and were used for testing the hemispheric asymmetry.

Meta-analysis Procedures

Meta-analysis was conducted by using a search and view software (www.brainmap.org/) based on ALE. ALE is a method of coordinate-based voxelwise meta-analysis (Laird et al., 2005; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Briefly, a localization probability distribution was modeled for each activation focus and the union of these probabilities was calculated to give the ALE value to each voxel. This value represents the probability that at least one of the activation foci lies within a given voxel. Significance was assessed via permutation analysis of randomly generated sets of foci. All the BrainMap databases of previous studies of the go/no-go and the antisaccade tasks tested for young healthy subjects available for the ALE were used in this study to ensure the typicality of the tasks and to keep the meta-analysis unbiased. The resultant number of the included studies was 17 for the go/no-go task and 10 for the antisaccade task, respectively. To test the ''modality difference account,'' the ALE analysis of go/no-go tasks was performed based on a previous meta-analysis study (Buchsbaum et al., 2005) using previous studies of the go/no-go task (Asahi et al., 2004; Bellgrove, Hester, & Garavan, 2004; Fassbender et al., 2004; Hester et al., 2004; Kelly et al., 2004; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Maguire et al., 2003; Mostofsky et al., 2003; Garavan, Ross, Murphy, Roche, & Stein, 2002; Watanabe et al., 2002; Braver et al., 2001; Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001; de Zubicaray et al., 2000; Garavan et al., 1999; Konishi et al., 1998). The resultant ALE map was compared with the activation during the modified antisaccade task in the present study. Next, to test the ''structure difference account,'' the ALE analysis of the traditional antisaccade tasks was also performed using previous studies of the antisaccade task (Ford et al., 2005; Matsuda et al., 2004; DeSouza et al., 2003; Kimmig et al., 2001; Merriam et al., 2001; Connoly et al., 2000; Doricchi et al., 1997; Sweeney et al., 1996; O'Driscoll et al., 1995; Paus et al., 1993). The ALE map was compared with the activation during the modified antisaccade task.

RESULTS

Behavioral Results

Eye movements were recorded throughout fMRI runs in all the subjects, and their traces were reconstructed from the time-series data of POR coordinates. Typical eye traces in one run from one subject are shown in Figure 2A. Performance and reaction time were calculated from the stored POR data by off-line analysis for all the subjects. Mean correct performances (mean ± *SEM*) were 95.9 ± 0.7%, 92.2 ± 1.3% and 59.8 ± 2.7% in the baseline, control, and antisaccade trials, respectively (Figure 2B). The difference between the baseline and control saccade trials was significant, 3.8 ± 1.1%, paired t test; $t(23) = 3.3$, $p < .01$, and the difference between the control and antisaccade trials was also significant, 32.4 ± 2.7%, $t(23) = 12.1$, $p < .001$. Mean reaction times

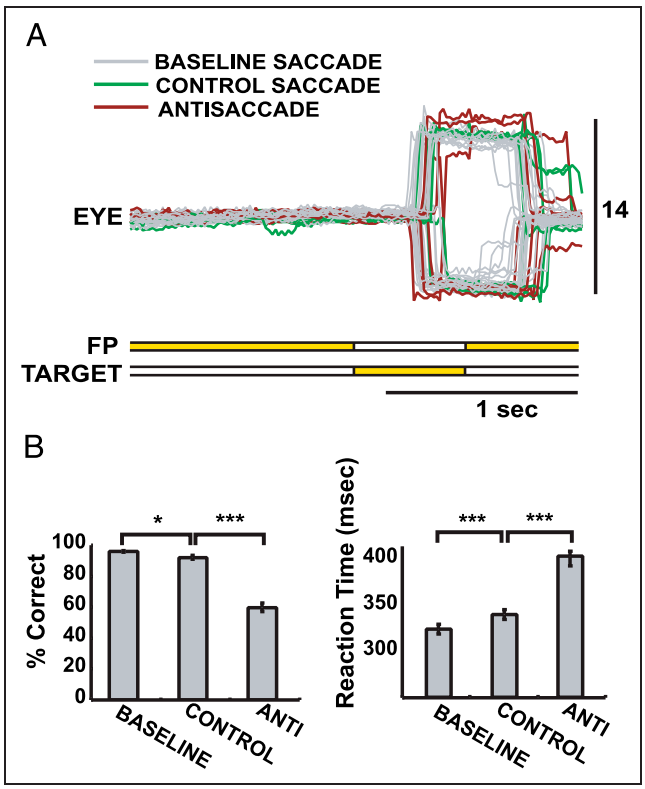

Figure 2. Behavioral data. (A) Typical eye traces in one run in the baseline saccade, control saccade, and antisaccade trials are displayed in gray, green, and red, respectively. Error antisaccade trials are included in the display. (B) Correct performance and reaction time are displayed on the left and right, respectively. *$p < .05$, ***$p < .001$, based on a paired t test.

(mean ± *SEM*) were 325.8 ± 22.8, 341.4 ± 26.4, and 403.1 ± 39.2 msec in the baseline, control, and antisaccade trials, respectively (Figure 2B). The difference between the baseline and control saccade trials was significant, 15.6 ± 3.1, $t(23) = 5.0$, $p < .001$, and the difference between the control and antisaccade trials was also significant, 61.7 ± 6.9, $t(23) = 8.9$, $p < .001$. The behavioral difference between the antisaccade and control saccade trials suggests that the antisaccade trials in the present study contained a sufficient amount of processes associated with response inhibition. Moreover, the difference between the control saccade and baseline saccade trials indicates that the use of the control trials as a control for the antisaccade trials was more appropriate than simply using baseline saccade trials as a control, although the control and baseline conditions are behaviorally similar except for the sensory oddball.

Behavioral results in previous studies used in the meta-analysis of the traditional antisaccade tasks were also analyzed in order to confirm that the inhibitory demand in our modified antisaccade task was enhanced compared with the traditional antisaccade task. It was found that the performance correct in the traditional antisaccade tasks was significantly higher than in our modified antisaccade task: The performance difference in the antisaccade versus control saccade trials in our study was 32%, whereas the difference in previous studies of the traditional antisaccade tasks whose behavioral data were available for this analysis ($n = 8$) was 11 ± 2.5%, and the difference between the traditional and modified antisaccade tasks was significant at $p < .001$, $t(7) = 8.6$. The difference was also significant when a nonparametric test was used (Wilcoxon test, $p < .005$). This result is consistent with the task modification, which caused less sufficient preparatory set configuration and required enhanced inhibitory demand at the time of saccade execution in our paradigm. The enhanced response inhibition demand was further confirmed by the greater activation in the right IFG (rIFG) of the present study that has been well established to reflect response inhibition demand shown in previous studies of response inhibition (e.g., Aron & Poldrack, 2006; Rubia et al., 2005; Bunge et al., 2002; Konishi et al., 1998).

fMRI Results

The functional image data set from a pool of 24 subjects was analyzed using a general linear model implemented by SPM2 and was applied to a random effect model. As shown in Figure 3A and Table 1, the contrast of central interest, ''the antisaccade trials versus the control saccade trials'' elicited prominent activations in multiple frontoparietal regions, including the FEF, DLPFC, anterior cingulate cortex (ACC), pre-SMA, insula/IFG, precuneus, and IPS, consistent with previous results of the antisaccade tasks (Curtis & D'Esposito, 2003; DeSouza et al., 2003; Connoly et al., 2002; Cornelissen et al., 2002; Kimmig et al., 2001; Doricchi et al., 1997; O'Driscoll et al., 1995; Paus et al., 1993). Interestingly, the posterior part of the IFG (near Brodmann's area [BA] 45/44) was prominently activated, which was previously little known to be activated during the antisaccade tasks. The time courses of the MRI signals were examined for the antisaccade and control saccade trials in eight ROIs selected from the peak coordinates (the antisaccade trials vs. the control saccade trials) listed in Table 1 (Figure 3B). A robust signal increase was observed in the antisaccade trials, but the control saccade trials elicited only modest signal changes.

To test functional hemispheric asymmetry with regard to the antisaccade versus control saccade contrast, bilateral pairs of ROIs were generated from a group analysis of images averaged from flipped and nonflipped magnitude images in each subject (see Methods). For the frontal areas, eight pairs of bilateral ROIs were generated (Table 2). Results revealed that the activation of the posterior part of the IFG was significantly right-hemisphere dominant, $t(23) = 4.4$, $p < .005$ after Bonferroni correction of 8 (Figure 4A). Furthermore, the average of the eight pairs of frontal areas showed

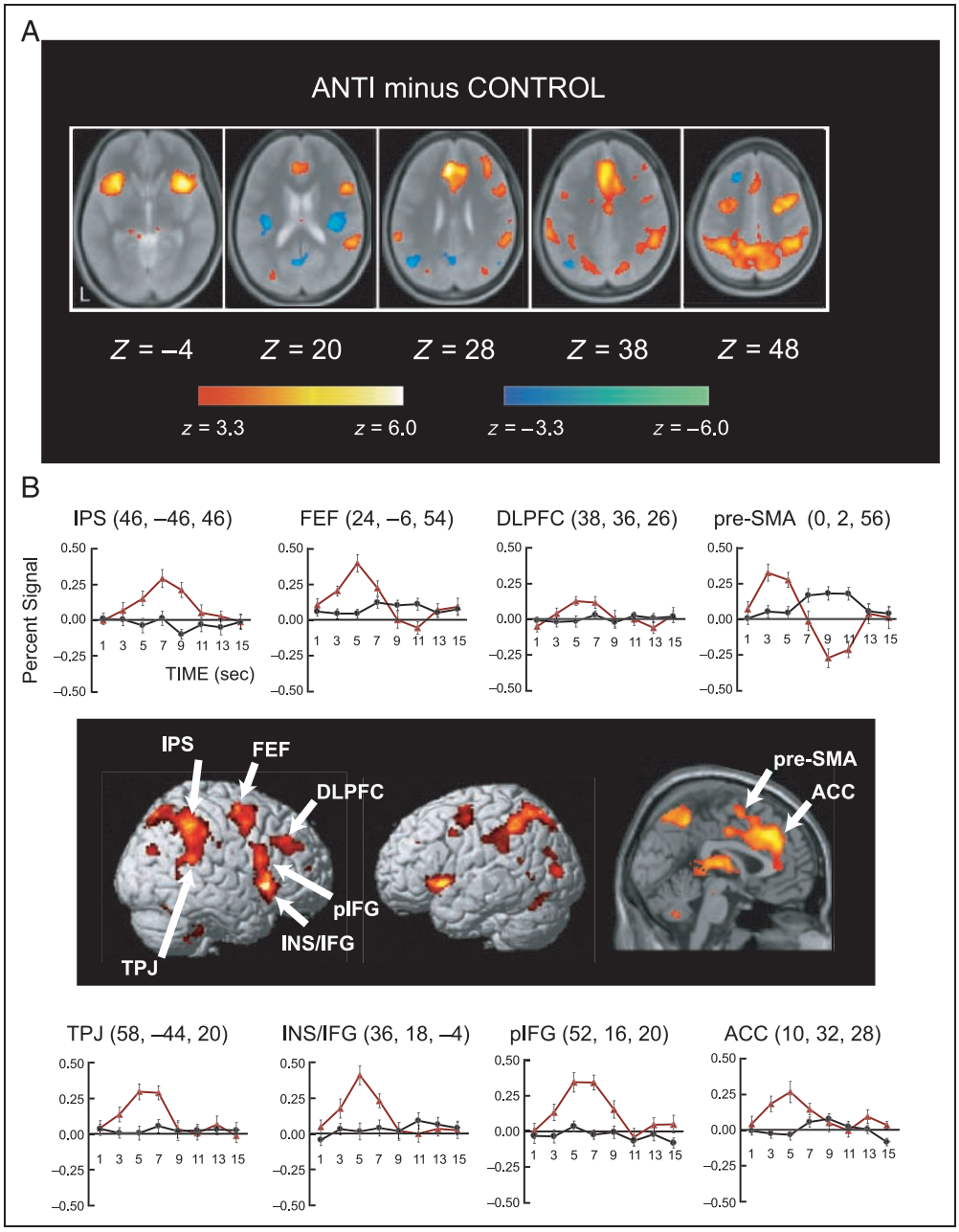

Figure 3. (A) Statistical activation maps for signal increase and decrease in the contrast of ''antisaccade versus control saccade trials.'' Activation maps are displayed as transverse sections and are overlaid on top of the anatomic image averaged across subjects. Statistical significance is indicated using the color scale at the bottom, and the transverse section level is indicated by the *z* coordinates of Talairach space (Talairach & Tournoux, 1988). (B) Signal time courses in the antisaccade and control saccade trials. ROIs were determined based on the contrast of antisaccade versus control saccade trials as listed in Table 1. Red and black lines indicate the antisaccade and control saccade trials, respectively. pIFG = posterior inferior frontal gyrus; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye field; INS/IFG = insula/IFG; pre-SMA = presupplementary motor area; IPS = intraparietal sulcus; TPJ = temporoparietal junction; ACC = anterior cingulate cortex.

significant right-hemisphere dominance, $t(23) = 4.4$, $p < .001$. For the parietal areas, seven pairs of bilateral ROIs were generated (Table 2). The activation of the temporoparietal junction (TPJ) was significantly right-hemisphere dominant, $t(23) = 3.2$, $p < .05$ after Bonferroni correction of 7 (Figure 4). The average of the seven pairs of parietal areas revealed significant right-hemisphere dominance, $t(23) = 2.5$, $p < .05$ (Figure 4A). To test the effect of the saccade direction on the lateralization pattern of the IFG activation (antisaccade vs. control saccade trials), the leftward and rightward saccades in the antisaccade and control trials were analyzed separately, and the signal magnitude was shown against the baseline (Figure 4B). Significant right-dominant activation was observed both in the rightward, $t(23) = 2.6$, $p < .05$, and leftward saccades, $t(23) = 3.7$, $p < .005$.

Meta-analysis

ALE meta-analysis was conducted and the significant voxels in the ALE map are shown in red (Figure 5). As has been reported in previous studies, the significant voxels associated with go/no-go tasks were observed in multiple frontoparietal regions primarily in the right hemisphere, including the posterior part of the IFG, DLPFC, insula/IFG, ACC, pre-SMA, TPJ, and IPS (Figure 5A). On the other hand, the significant voxels associated with

Table 1. Brain Regions Showing Signal Increase in "Antisaccade Minus Control Saccade"

Area	Coordinates			t	BA
	x	y	z		
Lateral frontal cortex	24	−6	54	9.6	6
	36	18	−4	9.5	47/12
	−34	18	−4	8.4	47/12
	36	−2	50	7.5	6
	52	16	20	6.5	45/44
	−34	−6	50	6.3	6
	−26	−6	60	6.3	6
	38	36	26	5.9	9/46
	−22	−2	46	5.6	6
	−46	6	40	5.3	6/44
	42	56	10	4.4	10/46
	32	22	36	4.2	9
Medial frontal cortex	−4	36	28	10.2	32
	−4	24	36	8.1	32
	10	32	28	6.9	32
	12	18	36	6.3	32
	2	−10	40	5.7	24
	0	2	56	5.2	6
	14	36	4	4.7	24/32
	8	20	60	4.1	6
Parietal cortex	8	−68	56	8.5	7
	−28	−58	54	8.0	7/40
	46	−46	46	7.5	7/40
	−6	−56	50	7.0	7
	−16	−46	50	6.6	7
	−18	−68	52	6.5	7
	54	−42	34	6.2	40
	−54	−46	44	6.1	40
	−62	−36	38	5.8	40
	−4	−62	62	5.6	7
	58	−30	52	5.5	40
	20	−70	40	5.2	7
	20	−52	50	5.2	7
	−62	−24	36	4.9	40
	−10	−78	40	4.8	7
	44	−32	40	4.3	40
	64	−22	32	4.1	40
Temporal cortex	−10	−34	0	6.6	27/30
	58	−44	20	6.3	22/39
	46	−54	16	4.4	22/39
	56	−54	4	3.9	21/37
Occipital cortex	−40	−80	8	5.9	18/19
	36	−76	26	4.9	19/39
	−30	−76	24	4.5	19/39
Others	−2	−20	10	6.9	Thalamus
	26	−36	−42	5.9	Cerebellum
	−6	−2	0	5.8	Globus pallidus
	4	−34	2	5.7	Midbrain
	28	−60	−24	5.4	Cerebellum
	−6	−22	−18	5.3	Midbrain
	10	0	−2	5.0	Globus pallidus
	32	−50	−46	5.0	Cerebellum
	14	−26	−10	4.9	Midbrain
	−36	−66	−20	4.5	Cerebellum

the traditional antisaccade tasks were observed in multiple regions in the DLPFC, FEF, ACC, pre-SMA, and IPS (Figure 5B).

To test the modality difference account of the rIFG activation, the peak coordinates of the present study, shown in yellow, were superimposed onto the ALE map of go/no-go tasks. This analysis revealed that most of the peak coordinates of the modified antisaccade task in the present study were common to the significant voxels in the go/no-go task (Figure 5A), including the rIFG ($p < .001$). Therefore, the modality difference account was rejected for the rIFG activation. Next, to test the structure difference account, the result of the present study was compared to the meta-analysis of the traditional antisaccade tasks. The analysis revealed that the rIFG was not common to the traditional antisaccade task ($p > .05$) (Figure 5B). Therefore, the structure difference account was supported for the rIFG activation.

DISCUSSION

The present study modified the traditional antisaccade task such that response inhibition demand at the time of antisaccade execution was enhanced. Prominent activation associated with antisaccade versus control saccade trials was observed in multiple frontoparietal regions including the FEF, DLPFC, pre-SMA, ACC, IPS, and

Table 2. Bilateral Brain Regions Showing Signal Increase in Average of Flipped and Nonflipped Images of "Antisaccade Minus Control Saccade"

	Coordinates					
Area	*x*	*y*	*z*	*t*	*BA*	*t (R > L)*
Frontal cortex	±36	18	−6	11.0	47/12	1.1
	±6	34	28	9.1	32	1.0
	±34	−8	52	8.3	6	0.6
	±52	16	18	5.3	45/44	4.4
	±40	32	32	5.1	9/46	1.3
	±46	4	42	5.0	6/44	1.5
	±40	54	10	4.8	10/46	1.5
	±28	48	30	4.1	9/46	0.9
	All voxels					4.4
Parietal cortex	±38	−48	48	7.3	7/40	−0.5
	±16	−68	54	7.2	7	1.2
	±6	−52	50	7.2	7	−0.9
	±62	−38	28	6.3	40	1.9
	±54	−42	38	5.9	40	1.6
	±58	−44	18	5.7	22/39	3.2
	±20	−70	40	5.1	7	−0.7
	All voxels					2.5

ROI-based right–left difference is shown in the rightmost column.

precuneus, consistent with previous results using the antisaccade task. Moreover, the posterior IFG region in the right hemisphere was also prominently activated, the region previously little known to be activated in the antisaccade task. Furthermore, comparison of the present results with meta-analysis data of the go/no-go task and the traditional antisaccade task revealed that the activation in the rIFG was not sensitive to the response modality difference but was sensitive to the task structure difference. These results suggest the rIFG is part of a network active during response inhibition in both the oculomotor and manual response modalities.

The frontal and parietal activation during the performance of the present modified antisaccade task, particularly the rIFG activation, agrees well with previous studies using the manual go/no-go task (Buchsbaum et al., 2005; Nakata et al., 2005; Rubia et al., 2005; Matsubara et al., 2004; Aron et al., 2003; Bunge et al., 2002; Durston et al., 2002; Braver et al., 2001; Liddle et al., 2001; Menon et al., 2001; Rubia et al., 2001; Sakagami et al., 2001; de Zubicaray et al., 2000; Garavan et al., 1999; Konishi et al. 1998; Kawashima et al., 1996; Funahashi et al., 1993; Sasaki et al., 1989; Kok, 1986; Pfefferbaum et al., 1985; Butters, Butter, Rosen, & Stein, 1973; Iversen & Mishkin, 1970). The frontoparietal activation is also consistent with previous studies using the antisaccade task (Ford et al., 2005; Matsuda et al., 2004; Munoz & Everling, 2004; Curtis & D'Esposito, 2003; DeSouza et al., 2003; Connolly et al., 2002; Raemaekers et al., 2002; Kimmig et al., 2001; Merriam et al., 2001; Connolly et al., 2000; Doricchi et al., 1997; Sweeney et al., 1996; O'Driscoll et al., 1995; Paus et al., 1993), although little has been reported regarding the posterior IFG activation. The meta-analysis using ALE method revealed that the IFG activation observed in the present study was derived from the task structure of the modified antisaccade task: The preparatory period in the traditional antisaccade task was removed and the antisaccade trials were presented infrequently among other prepotent saccade trials such that response inhibition at the time of antisaccade execution was required to a greater degree. Thus, the prominent IFG activation in the present study can be understood in the context of the heightened response inhibition demands. The right-dominant activation, on the other hand, contrasts with frontoparietal activation in the left hemisphere implementing other cognitive processes such as cognitive set shifting (Asari et al., 2005; Barber & Carter, 2005; Derrfuss et al., 2005; Konishi et al., 2005; Brass & von Cramon, 2004; Cools et al., 2004; Braver et al., 2003; Konishi et al., 2003; Konishi et al., 2002; Weidner, Pollman, Muller, & von Cramon, 2002; Monchi, Petrides, Petre, Worsley, & Dagher, 2001) and controlled retrieval tasks (Sohn, Goode, Stenger, Carter, & Anderson, 2003; Wheeler & Buckner, 2003; Gold & Buckner, 2002; Thompson-Schill et al., 1998; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997).

The present results included a novel pattern of activation in the rIFG, and this finding was not reported in previous studies of the traditional antisaccade tasks. The negative results were further confirmed by our meta-analysis of the traditional antisaccade tasks that revealed no IFG activation (Figure 5B). It is unlikely that the rIFG activation during performance of the modified antisaccade task observed in the present study reflects preparatory set because previous studies using the traditional antisaccade tasks, which required active preparatory set configuration in the preparatory periods, did not report the rIFG activation. Moreover, the control saccade trials should control for the cognitive processes of the preparatory set at the antisaccade trials: Previous studies using the traditional antisaccade task use preparatory periods that ranged from 500 msec to several seconds, which indicates that the preparatory set configuration takes a considerable amount of time. On the other hand, the reaction time difference between the antisaccade trials and the control trials in our modified saccade task was only 62 msec, which indicates that 62 msec, at longest, is permitted for the preparatory set configuration at the antisaccade trials of the present study. The preparatory set configuration is an active conscious process, and it is

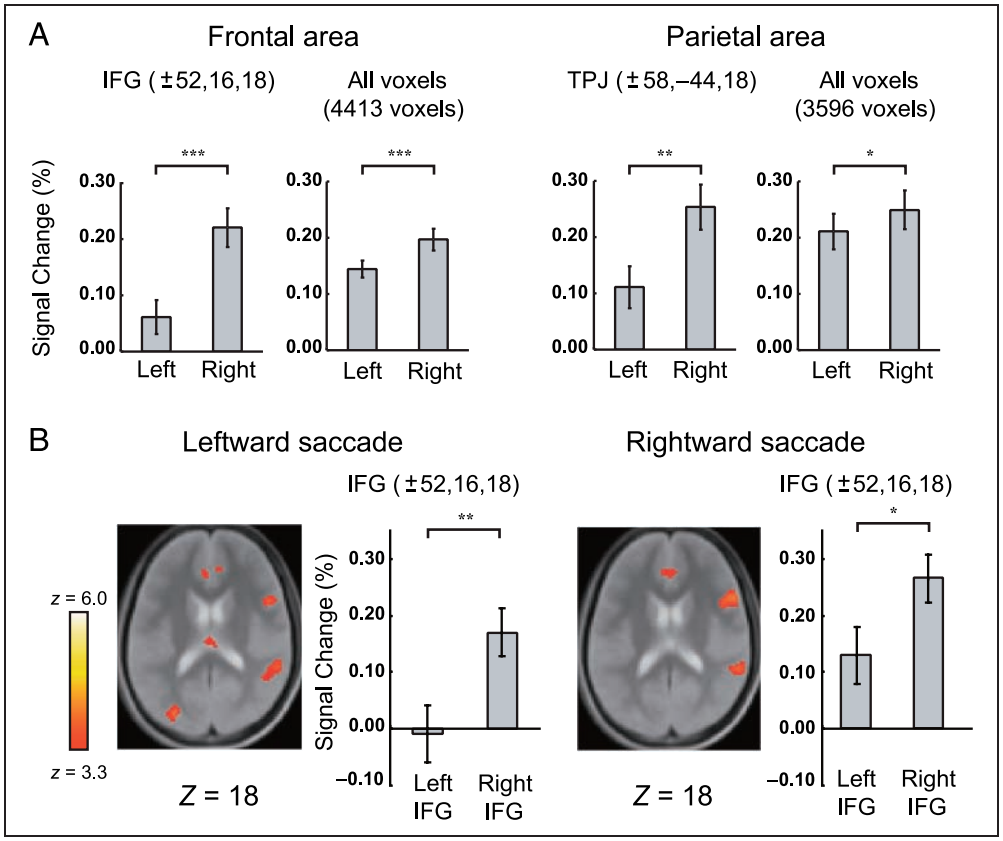

Figure 4. (A) Functional hemispheric asymmetry (antisaccade vs. control saccade trials) in the frontal cortex. ROIs were selected based on the average of flipped and nonflipped magnitude images as listed in Table 2. The result for the sum of these voxels in all the ROIs is also shown. *$p < .05$, **$p < .01$, ***$p < .001$, based on a paired t test. (B) Effect of saccade directions on the lateralized pattern of the rIFG activation (antisaccade vs. control saccade trials). The activation map and signal magnitude in the leftward and rightward saccades are shown in the left and right, respectively. *$p < .05$, **$p < .01$, based on a paired t test. Format of the activation maps is similar to that of Figure 2.

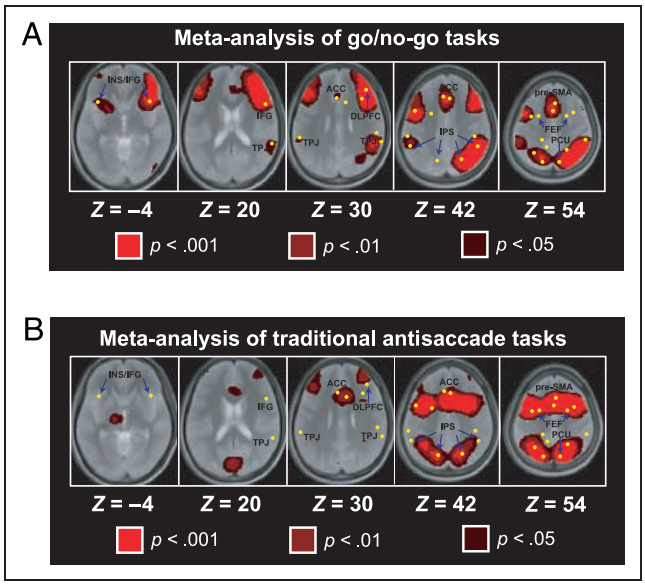

Figure 5. Comparison between the results of the present study and the results of the meta-analysis of the go/no-go task (A) and the traditional antisaccade task (B). Significant voxels based on ALE method are shown in red. The peak coordinates of the activation related to the modified antisaccade task in the present study (Table 1) are shown in yellow. The figure format is similar to that of Figure 3.

evident that 62 msec is not sufficient for it. Therefore, the level of preparatory set can be considered minimal in the antisaccade trials, and well matched between the antisaccade and control trials.

The antisaccade trials were presented infrequently in the modified antisaccade task. The frequent trial may place a lower cognitive load on spatial attention (Corbetta et al., 2000; Hopfinger, Buonocore, & Mangun, 2000) or working memory, but the lower cognitive load is a result of an enhanced response tendency of the frequent trial. The inhibition demand includes cognitive processes that are required in order to overcome such tendency, so the higher cognitive load on spatial attention or working memory in the infrequent task, if any, can be regarded as a part of processes related to response inhibition. Moreover, it is unlikely that the IFG activation is accounted for by the difference of the antisaccade task versus oculomotor go/no-go task: Comparing the traditional antisaccade task with the modified antisaccade task, the cognitive components derived from the anti versus no-go difference is absent, but the activation of the IFG was changed. Comparing the modified antisaccade task with the manual go/no-go task, the cognitive components derived from the anti versus no-go difference is present, but the activation

of the IFG was not changed. Furthermore, it is unlikely that the rIFG activation is due to the performance difference in the oculomotor modality only: Our previous studies using the go/no-go task where performance correct in the go and no-go trials matched (Konishi et al., 1999), revealed the rIFG activation during the no-go versus go trials.

The right frontoparietal network revealed in the present study consisted of multiple prominently activated regions including the FEF, DLPFC, pre-SMA, and IPS. The FEF has been investigated most intensively in previous electrophysiological and neuroimaging studies. As shown in the meta-analysis of the traditional antisaccade task where response inhibition was not maximally required but preparatory set configuration was characteristically required, the activation in the FEF has repeatedly been reported, and the FEF has been implicated in configuration of a preparatory set (Ford et al., 2005; DeSouza et al., 2003; Connolly et al., 2002; Everling & Munoz, 2000). At the same time, the role of the FEF in response inhibition has also been pointed out (Curtis & D'Esposito, 2003), consistent with the present study. Preparatory set configuration has also been implicated in the DLPFC (Ford et al., 2005; DeSouza et al., 2003), pre-SMA (Ford et al., 2005; Curtis & D'Esposito, 2003), and IPS (Ford et al., 2005; DeSouza et al., 2003; Gottlieb & Goldberg, 1999). Moreover, preparatory activity that leads to later successful antisaccades has also been reported in the DLPFC (Ford et al., 2005) and pre-SMA (Ford et al., 2005; Curtis & D'Esposito, 2003). Although a more precise characterization of activation and recruited cognitive processes involved in the performance of the antisaccade task needs further exploration, the present study suggests that the rIFG is a part of the frontoparietal network active during response inhibition in both the manual and oculomotor response modalities under heightened prepotent response tendency.

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