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Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI

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Summary

Inhibition of an ongoing reaction tendency for adaptation to changing environments is a major function of the human prefrontal cortex. This function has been investigated frequently using the go/no-go task and set-shifting tasks such as the Wisconsin Card Sorting Test (WCST). Studies in humans and monkeys suggest the involvement of the dorsolateral prefrontal cortex in the two task paradigms. However, it remains unknown where in the dorsolateral prefrontal cortex this function is localized, whether a common inhibitory mechanism is used in these task paradigms and how this inhibitory function acts on two different targets, i.e. the go response in the go/no-go task and the cognitive set in the WCST. In the go/no-go task of this study, subjects were instructed to either respond (go trial) or not respond (no-go trial), depending on the cue stimulus presented. The signals of functional MRI (fMRI) related to the inhibitory function should be transient by nature. Thus, we used the temporal resolution of fMRI (event-related fMRI) by which transient signals in go and no-go trials can be analysed separately and compared with each other. We found a focus that showed transient no-go dominant activity in the posterior part of the inferior frontal sulcus in the right hemisphere. This was true irrespective of whether the subjects used their right or left hands. These results suggest that the transient activation in the right inferior prefrontal area is related to the neural mechanism underlying the response inhibition function. Furthermore, this area was found to be overlapped spatially with the area that was activated transiently during cognitive set shifting in the WCST. The transient signals in the go/no-go task peaked 5 s after the transient expression of the inhibitory function, and the transient signals in the WCST peaked 7 s after the transient expression, reflecting different durations of neuronal activity in the two inhibitory task paradigms. These results imply that the right inferior prefrontal area is commonly involved in the inhibition of different targets, i.e. the go response during performance of the go/no-go task and the cognitive set during performance of the WCST.

Keywords: response inhibition; set shifting; event-related fMRI; prefrontal cortex; human

Abbreviations: BA = Brodmann area; fMRI = functional MRI; MEG = magnetoencephalogram; WCST = Wisconsin Card Sorting Test

Introduction

The prefrontal cortex enables us to make appropriate choices under changing situations (Milner, 1964; Mishkin, 1964; Goldman-Rakic, 1987; Petrides, 1991; Passingham, 1993; Damasio, 1995; Frith and Dolan, 1996; Robbins, 1996; Fuster, 1997), especially by inhibiting inherent response tendency. This inhibitory function has been investigated frequently using the go/no-go task. In monkey studies using the go/no-go task, damage to the dorsolateral prefrontal cortex (Iversen and Mishkin, 1970; Butters *et al.*, 1973; Sasaki *et al.*, 1989) has been shown to impair the response inhibition function. In humans, PET and functional (fMRI) studies (Kawashima *et al.*, 1996; Casey *et al.*, 1997) have reported dorsolateral prefrontal activation during mixed go/no-go trial blocks compared with during go trial blocks. EEG and magnetoencephalogram (MEG) recordings have revealed frontal-maximal differential potential between no-go and go trials, or the so-called 'no-go potential' (Pfefferbaum *et al.*, 1985; Kok, 1986; Gemba and Sasaki, 1989; Sasaki *et al.*,

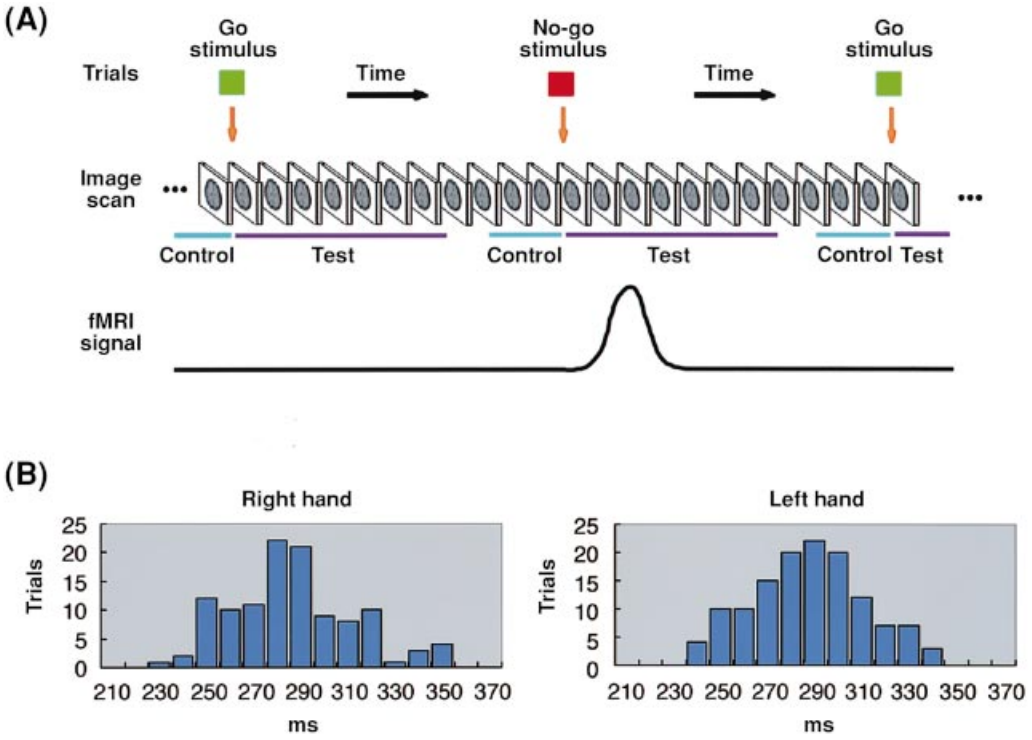

Fig. 1 (**A**) Event-related fMRI applied to the go/no-go task. (**B**) Distribution of the reaction time in correct go trials when subjects used their right thumbs (left) and left thumbs (right).

1996; Thorpe *et al.*, 1996). However, the precise functional localization in the dorsolateral prefrontal cortex remains unknown. In addition, the go/no-go task often has been thought to have aspects similar to set-shifting tasks such as the Wisconsin Card Sorting Test (WCST), which have also been found to be implemented in dorsolateral prefrontal cortex in both humans (Milner, 1963) and monkeys (Passingham, 1972; Dias *et al.*, 1996, 1997). The neural mechanism for the inhibitory function required in these tasks is intriguing because they require the inhibitory function, but of different targets, i.e. the go response in the go/no-go task and the cognitive set in the WCST.

In the present study, in order to specify the locus of activation elicited by the inhibitory function, we utilized event-related fMRI (Blamire *et al.*, 1992; Friston *et al.*, 1994; Buckner *et al.*, 1996; Konishi *et al.*, 1996; Kim *et al.*, 1997; Zarahn *et al.*, 1997; Rosen *et al.*, 1998). In the go/no-go task, subjects either responded (go trials) or withdrew a response (no-go trials), and these events were intermixed with each other, making them unpredictable. The activation of interest is the transient activation elicited by the inhibition of the go response in the no-go trials, which should be separated from and contrasted with the activation in the go trials. Event-related fMRI is suitable for analysis of the go/no-go task because it enables us to move away from the conventional blocked paradigm design (mixed go/no-go trial blocks) to a trial-by-trial analysis design (separated go or no-go trials). Using event-related fMRI (Fig. 1A), we analysed the fMRI data for the go and no-go trials separately, and attempted to identify the prefrontal areas in which brain activity in the no-go trials was dominant over that in go trials.

Furthermore, we directly compared the spatial extent of the areas activated by the go/no-go task with the areas activated by the set shifting in the WCST (Konishi *et al.*, 1998*b*). These two tasks may be related to each other in that they both should require the inhibitory function. However, they require the inhibition of different targets, i.e. the go response in the go/no-go task and the cognitive set in the WCST. We therefore tested whether these areas coincide or not. If the areas coincide, the area of coincidence may implement a common central mechanism for inhibition. If not, these areas may implement separate inhibitory mechanisms for each target. A preliminary report of this study has been published elsewhere (Konishi *et al.*, 1998*a*).

Material and methods

Behavioural paradigm

Computer graphics-based visual stimuli were projected onto a screen and the subjects in a supine position viewed the stimulus through prism glasses. In the go/no-go task, the subjects were instructed to fixate on a small cross located centrally on the screen, and a green or a red square (equally probable) was presented for 0.5 s over the cross once in a trial. In go trials, the go stimulus (green square) was presented

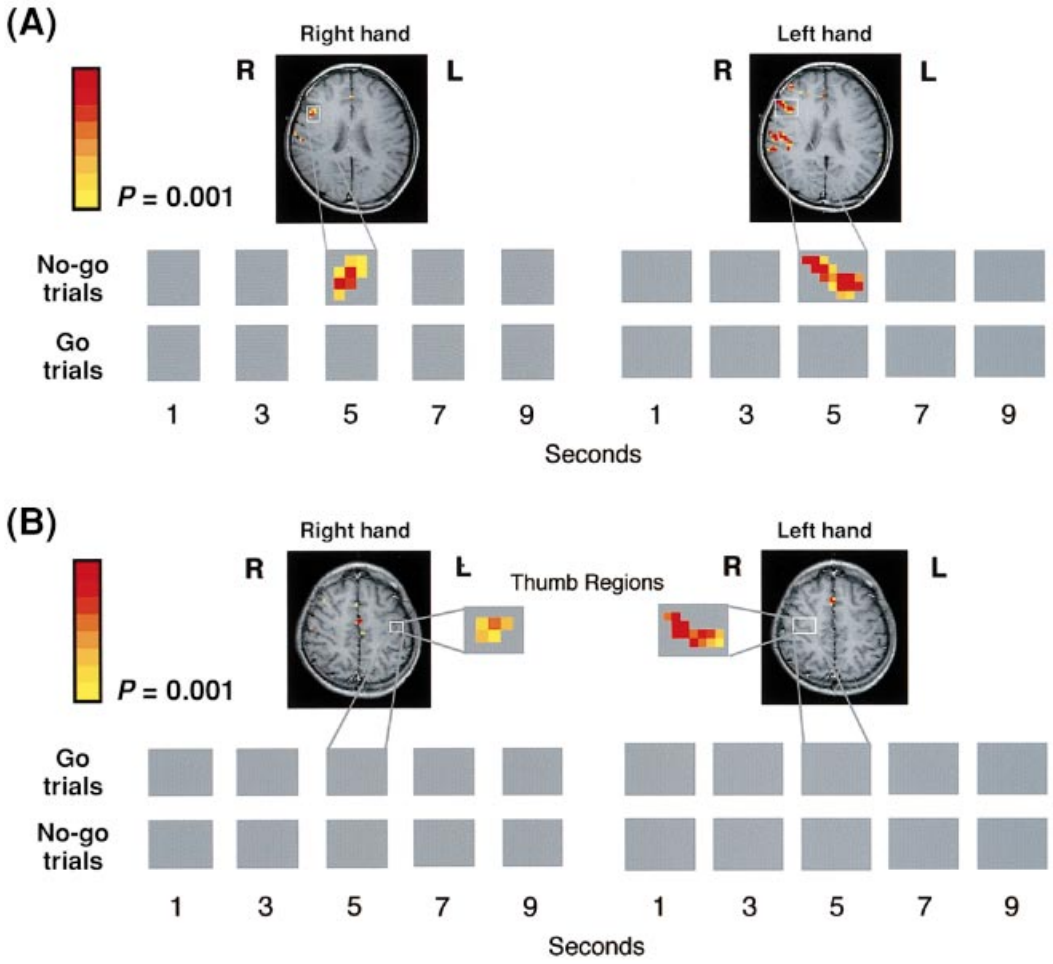

Fig. 2 (**A**) No-go dominant activity in the posterior part of the right inferior frontal sulcus in one subject. The pixel-wise statistical significance level (5 s after a no-go stimulus) is colour coded and mapped on the corresponding structural images. The results when the right thumb was used are shown on the left and the results when the left thumb was used are shown on the right. The inferior prefrontal areas are enlarged, and the activity at several time points after stimulus onset is shown in the upper panels for no-go trials and the lower panels for go trials. (**B**) Activity in the primary motor cortex of the same subject. The areas activated by sustained thumb movement (repeated button press at 4 Hz for 10 s) are enlarged and shown in the panels labelled 'Thumb Regions'. Similar to **A**, except that the upper panels represent go trials and the lower no-go trials.

and the subjects were instructed to respond by promptly pushing a button using their right or left thumbs, but in no-go trials, the no-go stimulus (red square) was presented and the subjects were instructed not to respond. A warning stimulus (brightening of the fixation cross for 2 s) appeared 6, 8 or 10 s (randomly) prior to the presentation of the go or no-go stimulus. In order to induce the response, i.e. the inhibition function, speed of decision was stressed and subjects were trained so that they achieved a reaction time of 350 ms and an 80% correct performance level. This training enhances the subjects' tendency to respond to the no-go stimulus, and promotes the reproducible expression of response inhibition in no-go trials. When the subjects responded in no-go trials or responded slowly in go trials, the trials were rejected. The percentage of correct trials was ~80–95%.

Subjects and fMRI

Six healthy volunteers (five males and one female, age 20–31 years) performed the go/no-go task. They were all right-handed as assessed by the Edinburgh Inventory (Oldfield, 1971). The experiments were undertaken with the understanding and written consent of each subject according to the declaration of Helsinki, and were approved by the institutional review board of the University of Tokyo School of Medicine.

A gradient echo echo-planar imaging sequence (repetition time = 2 s, flip angle = 90°) (Sakai *et al.*, 1995*a*, *b*; Konishi *et al.*, 1998*a*, *b*) at 1.5 T was used in this study. The range of z = 10–40 mm at y = 0 mm of Talairach's coordinates (Talairach and Tournoux, 1988) was covered by four contiguous transverse slices (slice thickness = 7.5 mm, in-plane resolution = 3 × 3 mm^2, oblique by 10°). The range

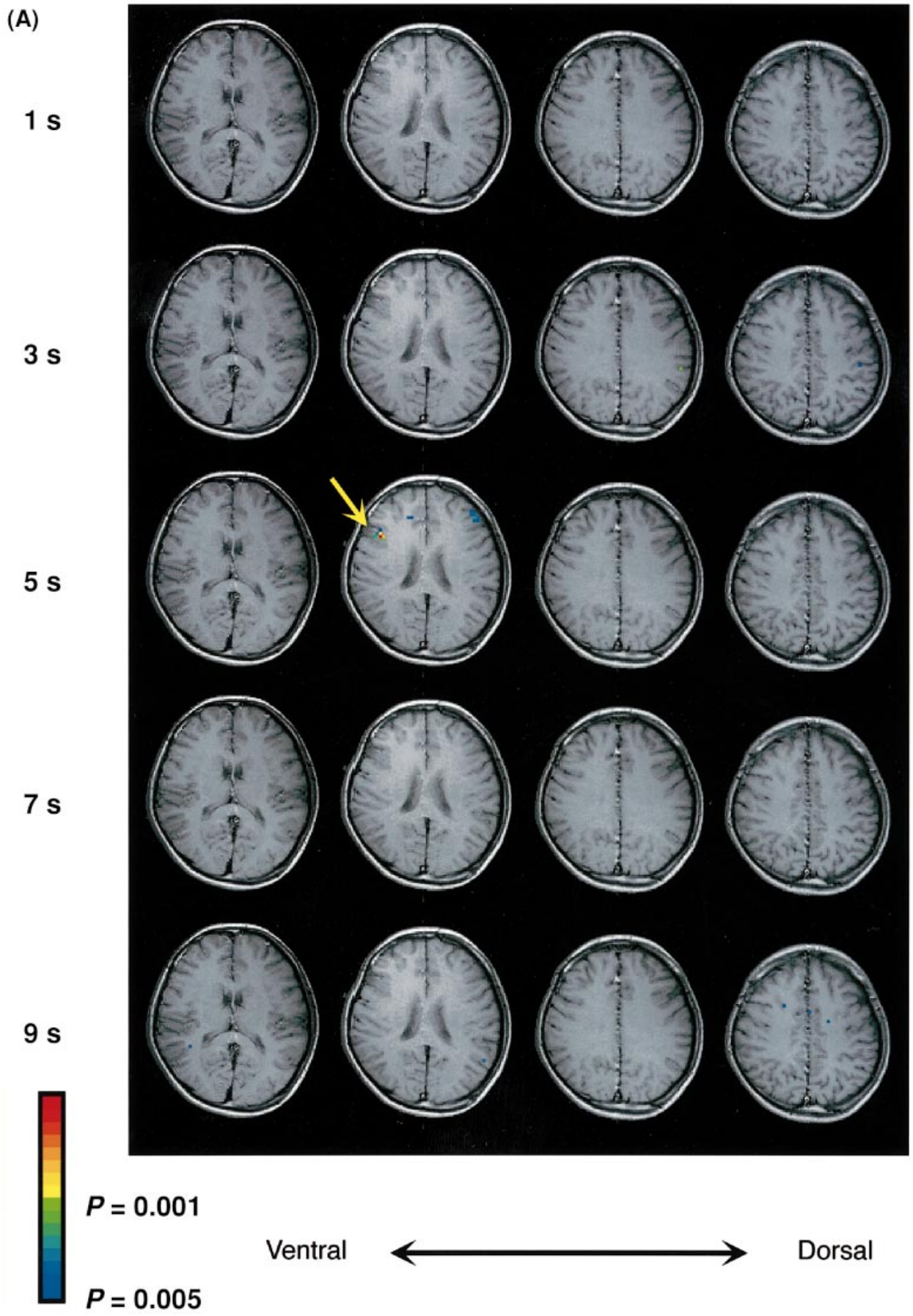

Fig. 3 (**A**).

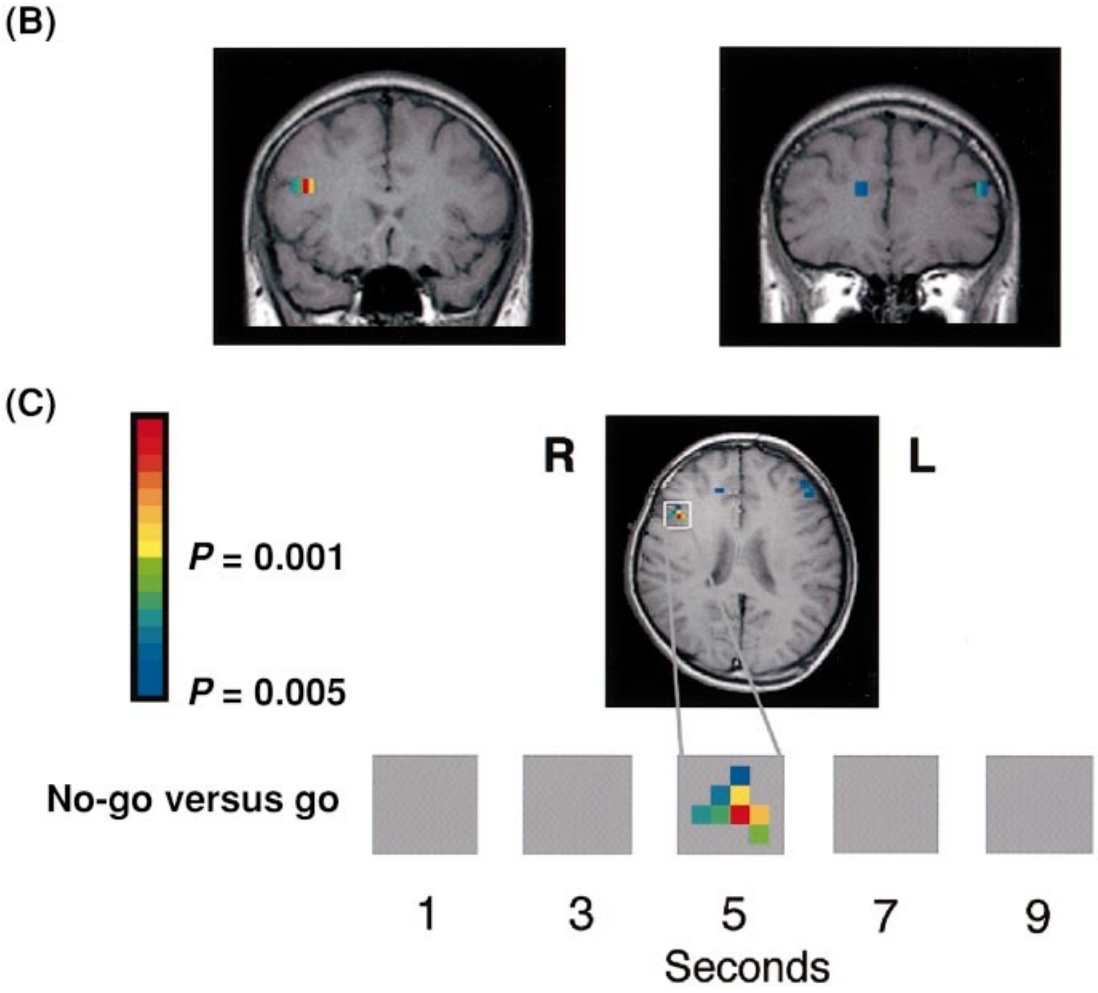

Fig. 3 (**A**) No-go dominant activity revealed by group analysis. The pixel-wise statistical significance was determined by the effect of trial type (go versus no-go) of the two-way ANOVA (trial type by hand laterality). The significance is colour coded and shown at each time point after the no-go or go stimulus. (**B**) No-go dominant activity (5 s) shown in coronal slices. (**C**) The time course of the no-go dominant activity in the right inferior frontal sulcus. Significant pixels are shown sequentially in the panels.

of $z = 40$–55 mm at $y = 0$ mm of Talairach's coordinates additionally was scanned in three subjects to cover the primary motor cortex. We could not scan the whole brain due to artefacts from nasal sinuses unsuitable for trial-based analysis in the present study. Thus, the activity in the orbitofrontal cortex, an area often associated with go/no-go tasks, would not have been seen. T_1-weighted spin-echo images of the corresponding slices were taken every four runs to estimate head movement, and runs in which substantial head movement (>1.5 mm in any direction) had occurred were rejected. In a full experiment, we performed 12–16 runs, each of which consisted of three trials, and the total number of trials in a full experiment was ~40, ~20 each for go and no-go trials.

Data analysis

Image data for go and no-go trials were analysed separately using an event-related fMRI method (Blamire *et al.*, 1992; Friston *et al.*, 1994; Buckner *et al.*, 1996; Konishi *et al.*, 1996; Kim *et al.*, 1997; Zarahn *et al.*, 1997; Rosen *et al.*, 1998). The time zero was defined as the time at the onset of the presentation of the go or no-go stimulus in each trial. To account for the different sampling times of different slices, pixel values were interpolated linearly. Then we calculated for each pixel the across-trial mean and variance of the difference between the images taken at each time point after time zero and the averaged images obtained from five time points before time zero, and applied the calculated pixel values to the paired *t*-test. Regions of four or more contiguous pixels above $P < 0.005$ (uncorrected) detected within the time window of 5–9 s after the go or no-go stimulus were regarded as activated areas.

Group analysis was conducted further to detect no-go dominant areas. Image data of each subject were aligned with a common standard atlas in two dimensions using AIR (automated image registration) (Woods *et al.*, 1992). To evaluate go or no-go dominance of each pixel, the two-way ANOVA (analysis of variance) (trial type of go versus no-go × hand laterality of right versus left) was applied to the

image data of each time point following subtraction of pixel values of image data obtained before time zero. Activation of four or more contiguous pixels above $P < 0.005$ (uncorrected) in the main effect of trial type (go versus no-go) was regarded as go or no-go dominant activity. The effects of hand laterality and the interaction were also tested.

The areas of interest in the go/no-go task were compared with the shift-related areas in the WCST, similarly to the strategy of cognitive conjunction (Price and Friston, 1997). The data of the WCST were provided from the 3D condition (7 s after dimensional changes) of our previous study of the WCST (Konishi *et al.*, 1998*b*). Image data of these tasks were aligned in three dimensions commonly with the standard atlas used in the group analysis of the go/no-go task. To quantify the spatial overlap with several shift-related areas, the regions of interest were determined by the data of the WCST, and the significance level of go or no-go dominance was calculated using the two-way ANOVA. The coordinates of the regions of interest were calculated by linearly transforming the standard atlas into the atlas of Talairach and Tournoux (1988).

Results

Behavioural data

The subjects were trained so that they could respond easily in ~300 ms after the stimulus onset. The correct performance was 86.7% (83.4 and 90.0% in go and no-go trials, respectively) when they used their right hands, and 90.0% (88.0 and 92.1% in go and no-go trials, respectively) when they used their left hands. Analysis of the performance data by the two-way ANOVA revealed no significant effect in either trial type (go or no-go trials) [F (1,20) = 2.62, $P > 0.1$] or hand laterality (right and left hand) [F (1,20) = 1.01, $P > 0.2$). The reaction time in correct go trials was 289 ± 20 ms when they used their right hands, and 287 ± 7 ms when they used their left hands. The distribution of the reaction time is shown in Fig. 1B. The mean reaction time was not significantly different when they used their right or left hands (paired t-test, $P > 0.5$).

fMRI data

No-go dominant activity was detected reproducibly in the posterior part of the right inferior frontal sulcus. A typical example in one subject is shown in Fig. 2A. In this region, when the subject used the right thumb (Fig. 2A, left), significant brain activity was detected 5 s after the onset of the no-go stimulus but not for the go stimulus. This 5 s lag is consistent with the haemodynamic delay of fMRI signals elicited by short neuronal activity (Blamire *et al.*, 1992; Friston *et al.*, 1994; Buckner *et al.*, 1996; Konishi *et al.*, 1996; Kim *et al.*, 1997; Zarahn *et al.*, 1997). Similar results were obtained when the same subject used the left thumb (Fig. 2A, right). We did not detect reproducible go dominant brain activity in either the right or left hand condition. In particular, the primary motor area contralateral to the hand is expected to elicit go dominant activity. We determined the regions of interest of the thumb representation of the primary motor area in the central sulcus by mixing runs in which sustained thumb movement (repeated button pressing at 4 Hz for 10 s) was performed. As shown in Fig. 2B, no significant brain activity in go or no-go trials was observed in the regions of interest when the subjects used their right or left hands.

Group analysis of all six subjects using the two-way ANOVA was conducted to identify go or no-go dominant areas, as shown in Fig. 3. No-go dominant activity was detected in the posterior part of the right inferior frontal sulcus (Fig. 3A and B). In this area, the difference in activation peaked 5 s after the onset of the no-go stimulus (Fig. 3C). The Talairach coordinates of the no-go dominant area were located at $x = 41$ mm, $y = 16$ mm, $z = 19$ mm (BA 45/44) [F (1,20) = 20.1]. No-go dominant activity was also found in the left inferior prefrontal area, although less significant than in the right. No other significant effect in the two-way ANOVA was detected in the effect of trial type, hand laterality or the interaction.

Comparison with the results of the WCST

The posterior part of the inferior frontal sulcus is also activated transiently during set shifting in the WCST (Konishi *et al.*, 1998*b*). Therefore, we examined the spatial relationship between the transient activation elicited by the two task paradigms. Image data of these tasks were aligned commonly with the standard atlas used in Fig. 3. A typical example in one subject is shown in Fig. 4. In the go/no-go task, the no-go dominant activity peaked 5 s after the onset of the no-go stimulus, whereas in the WCST the shift-related activity peaked 7 s after the onset of set shifting. In the right frontal sulcus, the activated areas of the peak time points in the two task paradigms overlapped well with each other. These results were also true for the results of group analysis as shown in Fig. 5. In fact, the peak pixel of the no-go dominant area (5 s) coincided exactly with the peak pixel of the shift-related area (7 s) ($x = 41$ mm, $y = 16$ mm, $z = 19$ mm). In the left hemisphere, the peak did not coincide. To quantify the overlap, we used the two-way ANOVA and calculated the no-go dominance in the regions of interest determined by the data of the WCST. The results of these areas are listed in Table 1. As expected from the exact coincidence of the peaks, the right inferior prefrontal area was highly no-go dominant [trial type: $F(1,20) = 17.31$, $P < 0.001$; hand laterality: $F(1,20) = 0.53$, $P > 0.4$; interaction: $F(1,20) = 0.03$, $P > 0.5$]. In addition, the left inferior prefrontal area was also significantly no-go dominant [trial type: $F(1,20) = 7.49$, $P < 0.05$; hand laterality: $F(1,20) = 0.01$, $P > 0.5$; interaction: $F(1,20) = 0.14$, $P > 0.5$], though the no-go dominance does not hold after fivefold Bonferoni correction.

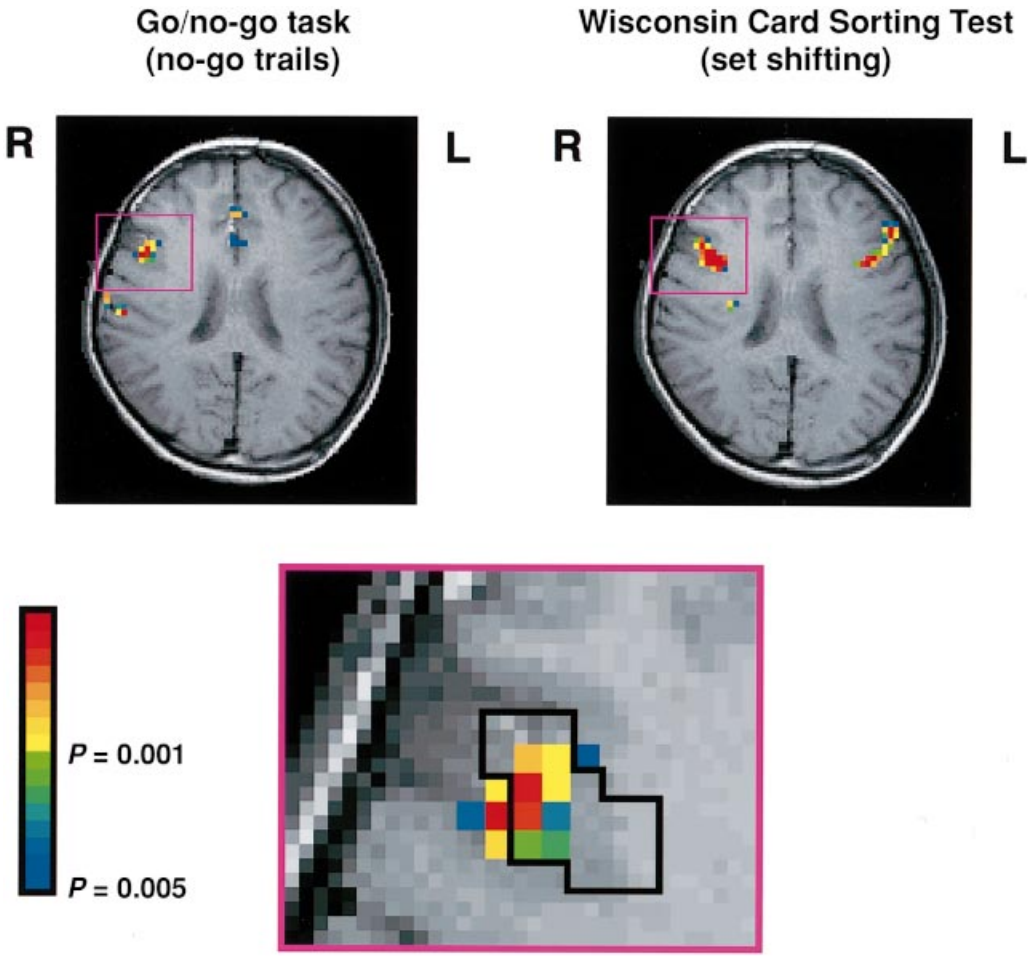

Fig. 4 Spatial overlap of the activation related to response inhibition with that related to set shifting in one subject. The activation observed 5 s after the no-go trials and 7 s after dimensional changes in the WCST is shown on the left and right, respectively. The area of no-go activity in the right inferior frontal sulcus is enlarged and superimposed on a black frame that encloses the shift-related area.

In contrast, the areas in posterior cortices were not no-go dominant.

Discussion

The use of event-related fMRI isolated transient activation related to inhibition of the go response and determined the functional localization in the posterior part of the right inferior frontal sulcus. This inferior prefrontal area was also activated transiently during set shifting in the WCST, suggesting that the inferior prefrontal area implements inhibition of both the go response and the cognitive set.

Application of event-related fMRI

The event-related fMRI fits well for the go/no-go task because this task requires transient expression of inhibitory function. The transient inhibitory function cannot be invoked simply by repetition of the same kind of trials but can be invoked by intermixing different kinds of trials that should be separated and contrasted with each other. The same is true of the WCST, in which the shift-related signal is transient by nature and cannot be sustained. The transient signals in the go/no-go task and the WCST peaked at different time points, i.e. 5 s after the onset of the no-go stimulus in the go/no-go task and 7 s after the onset of set shifting in the WCST. A likely explanation would be that the different time courses were derived from different durations of neuronal activity in these tasks. In the go/no-go task, the inhibitory function should act very briefly. In fact, according to EEG and MEG studies (Pfefferbaum *et al.*, 1985; Kok, 1986; Gemba and Sasaki, 1989; Sasaki *et al.*, 1996; Thorpe *et al.*, 1996), the neuronal activity lasts only ~100 ms. On the other hand, set shifting in the WCST was estimated to continue for ~3 s (Konishi *et al.*, 1998*b*). It is known that the time course of haemodynamic responses can be obtained by convolving the neural activity with the haemodynamic impulse response function (Friston *et al.*, 1994; Boynton *et al.*, 1996). Therefore, the longer delay of the peak in the WCST would be derived from the longer neuronal activity related to the set shifting. This explanation is consistent with our previous study of different time courses of haemodynamic responses elicited by two durations (0.2 versus 2.0 s) of visual stimulation (Konishi *et al.*, 1996).

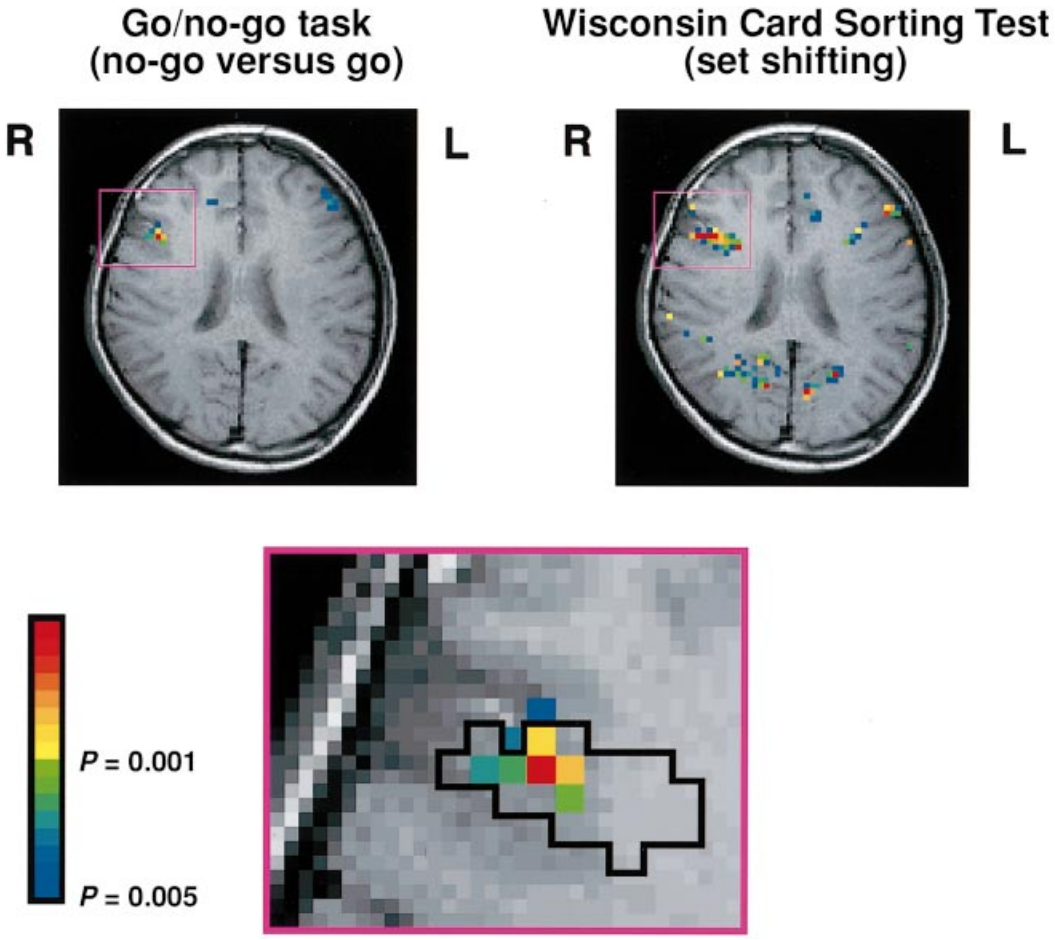

Fig. 5 Spatial overlap of the no-go dominant area with the shift-related area revealed by group analysis. The activity observed 5 s after the no-go trials and 7 s after dimensional changes in the WCST is shown on the left and right, respectively. The no-go dominant area in the right inferior frontal sulcus is enlarged and superimposed on a black frame that encloses the shift-related area.

Table 1 *Go or no-go dominance in the areas activated during set shifting*

Area (BA)	*x*	*y*	*z*	*F*(1,20)
Frontal				
R inferior frontal sulcus (BA 44/45)	41	16	19	17.3*** (no-go)
L inferior frontal sulcus (BA 44/45)	–46	29	17	7.5* (no-go)
Anterior cingulate cortex (BA 32)	–5	29	32	0.3
Parietal				
R supramarginal gyrus (BA 40)	46	–42	35	0.8
L supramarginal gyrus (BA 40)	–41	–32	41	8.7** (go)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Functional lateralization of no-go dominant activity

The no-go dominant activity was found in the posterior part of the inferior frontal sulcus of the right hemisphere and, less reliably, of the left hemisphere. The bilateral observation of the no-go dominant activity in this study is consistent with the bilateral observation of the 'no-go potential' in EEG and MEG studies (Pfefferbaum *et al.*, 1985; Kok, 1986; Gemba and Sasaki, 1989; Sasaki *et al.*, 1996; Thorpe *et al.*, 1996). Therefore, our results suggest that the posterior part of the inferior frontal sulci is the electrical source of the no-go potential. However, the right hemisphere dominance of the no-go dominant activity was clear. This is consistent with the observation of a previous PET study reporting that the right dorsolateral prefrontal cortex had many more activation foci than the left (Kawashima *et al.*, 1996).

Theoretical interpretation of no-go dominant activity

The go/no-go task involves basic inhibitory mechanisms in the simplest context (Iversen and Mishkin, 1970; Butters *et al.*, 1973; Sasaki *et al.*, 1989). In the go/no-go task of this study, the go and no-go trials were given randomly with equal probability, and no feedback was provided in go or no-go trials. Importantly, the subjects were instructed to respond promptly in go trials, maintaining the set of the go

response in both the go and no-go trials. This instruction requires subjects to overcome this motor set of the go response in the no-go trials. Therefore, in the go/no-go task of this study, motor set shifting, in addition to response inhibition, may contribute to the no-go dominant activity. This view is supported by the spatial overlap of the no-go dominant focus with the areas activated by the WCST in which cognitive set shifting is required (see Figs 4 and 5).

This task may also have another aspect. Since no feedback was provided in go or no-go trials, the go/no-go task in this study would correspond to a symmetrically reinforced variant of the task. Therefore, the go/no-go task in this study would have an aspect of conditional motor discrimination often investigated in monkey lesion studies (Passingham, 1993). However, it is unlikely that the conditional aspect of this task essentially contributed to the no-go dominant activity in the inferior prefrontal area of the present study. In fact, the superior branch of the arcuate sulcus (areas 6 and 8) of macaque monkeys is regarded as the critical focus of the conditional tasks (Goldman and Rosvold, 1970; Halsband and Passingham, 1985; Petrides, 1986), and the monkey arcuate cortex would not correspond to the human inferior prefrontal area of this study (Petrides and Pandya, 1994; Rajkowska and Goldman-Rakic, 1995). There was no no-go dominant activity in the human Brodmann area (BA) 6/8 (Talairach and Tournoux, 1988) detected in this study. This is consistent with the facts that the effects of arcuate lesion have been observed mainly during learning to achieve criteria (Goldman and Rosvold, 1970; Halsband and Passingham, 1985; Petrides, 1986) and that the difference in performance between go and no-go trials was reported for lesions to the inferior convexity (Iversen and Mishkin, 1970).

Inhibitory function in human inferior prefrontal cortex

The go/no-go task and the WCST are the major task paradigms used to investigate the inhibitory function of the human prefrontal cortex. Subjects were required to inhibit the go response in the go/no-go task and the cognitive set in the WCST. Comparison of the spatial extent of the no-go dominant areas with the shift-related areas revealed a substantial overlap in the posterior part of the right inferior frontal sulcus. These results suggest that the inhibition of the go response and of the cognitive set share a common neural mechanism implemented in this area.

Recent event-related fMRI studies of working memory (Cohen *et al.*, 1997; Courtney *et al.*, 1997) have reported activation of virtually the same area as the no-go dominant area of the present study in the posterior part of the right inferior frontal sulcus. This area showed sustained activity during the memory delay interval of the working memory tasks. However, the memory delay component of fMRI signals in this area was smaller than that in other prefrontal areas located more anteriorly (BA 9, 46 and 47) (Cohen *et al.*, 1997; Courtney *et al.*, 1997). This observation suggests that although the inferior prefrontal area may implement retention of working memory, the area also has some functions other than retention of working memory. A likely possibility would be that the area implements updating, instead of retention, of the contents of working memory (Goldman-Rakic, 1987; Funahashi and Kubota, 1994). This view is consistent with a recent lesion study (Rushworth *et al.*, 1997) showing that the posterior part of the inferior convexity (area 45) of macaque monkeys is not essential for the retention of working memory, assuming that BA 45/44 of human brain corresponds functionally to area 45 of the monkey brain (Petrides and Pandya, 1994; Rajkowska and Goldman-Rakic, 1995). Taken together, we suggest that the inferior prefrontal area implements updating of temporarily maintained internal states such as working memory contents, cognitive set and motor set.

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