Role for Presupplementary Motor Area in Inhibition of Cognitive Set Interference

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Abstract

■ Proactive interference (PI), which is formed through repetition of certain behavior and lasts for a while, needs to be inhibited in order for subsequent behavior to prevail over the antecedent one. Although the inhibitory mechanisms in the pFC have been reported that are recruited long after one behavior is updated to another, very little is known about the inhibitory mechanisms that are recruited immediately after the update. The WCST was modified in the present fMRI study such that inhibition of PI could be examined both immediately after and long after update of behavior. Use of "dual-match" stimuli allowed us to compare two types of trials where inhibition of PI was and was not required (control and release trials, respectively). Significant activation was observed in the left pre-SMA during control versus release trials. The pre-SMA activation was selective to PI inhibition required immediately after update of behavior, which exhibited marked contrast to the left anterior prefrontal activation selective to PI inhibition required long after the update. These results reveal dissociable inhibitory mechanisms in these two regions that are recruited in the different temporal contexts of the inhibitory demands imposed during performance of the task. ■

INTRODUCTION

Proactive interference (PI) from past behavior prolongs for a while even after one behavior is updated to another, and the interference needs to be inhibited for flexible behavior (Meiran, Chorev, & Sapir, 2000; Allport, Styles, & Hsieh, 1994). The inhibitory function has often been tested using the WCST, where the frontal patients characteristically adhered to previously appropriate responses on the basis of one of the three stimulus features (i.e., color, form, and number) or "dimensions" (Grant & Berg, 1948). It has been demonstrated that performance of the WCST is impaired following lesion to the pFC (Aron, Monsell, Sahakian, & Robbins, 2004; Stuss et al., 2000; Dias, Robbins, & Roberts, 1996, 1997; Owen et al., 1993; Janowski, Shimamura, Kritchevski, & Squire, 1989; Nelson, 1976; Drewe, 1974; Passingham, 1972; Milner, 1963). Consistent with the neuropsychological studies, prominent activation as measured with neuroimaging has been detected in the pFC during performance of the WCST (Nyhus & Barcelo, 2009; Specht, Lie, Shah, & Fink, 2009; Konishi et al., 1998, 2002, 2008; Hampshire & Owen, 2006; Lie, Specht, Marshall, & Fink, 2006; Monchi et al., 2004; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000; Nagahama et al., 1999) and the task switching paradigms (Wylie, Murray, Javitt, & Foxe, 2009; Crone, Donohue, Honomichl, Wendelken, & Bunge, 2006; Brass & von Cramon, 2004; Cools, Clark, & Robbins, 2004; Braver, Reynolds, & Donaldson, 2003; Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2002; Rushworth, Passingham, & Nobre, 2002; Pollmann, Weidner, Muller, & von Cramon, 2000; Sohn, Ursu, Anderson, Stenger, & Carter, 2000). It is to be noted, however, that the brain activity measured at the time of the dimension/task changes may reflect both inhibition of PI and reconfiguration of a task new set (Monsell, 2003), and thus it is not clear whether the detected prefrontal activation at the time of the dimension/task changes is specific to inhibition of PI.

The "dual-match" stimulus (Figure 1) is a useful tool to detect brain activity related to inhibition without contamination of the component related to reconfiguration (Konishi, Chikazoe, Jimura, Asari, & Miyashita, 2005; Konishi, Jimura, Asari, & Miyashita, 2003). In the case of the Figure 1, for example, when the dimension to be attended shifted from color to form, the dual-match stimulus presented in control trials requires subjects to select the form match by inhibiting PI of selecting the color match. By contrast, the dual-match stimulus presented in release trials does not require inhibition of PI because selection of the form match coincides with selection of the color match. By comparing the brain activity in control trials with that in release trials, the cognitive component associated with inhibition of PI is expected to be isolated. In our previous study, we presented, immediately after the dimension changes of the modified WCST, two or four consecutive release trials where inhibition was not required and then a single-match trial

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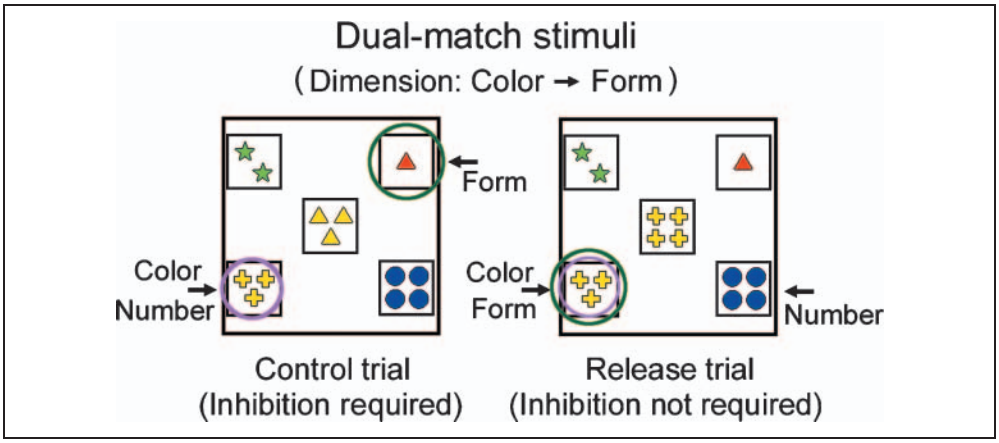

Figure 1. The dual-match stimuli used in the control and the release trials. In this particular case, the dimension is shifted from "color" to "form." In control trials, PI of selecting the color match (purple circle) has to be inhibited to select the form match (green circle). In release trials, by contrast, PI of selecting the color match does not have to be inhibited because the color match is also the form match.

where inhibition was required for the first time in the dimension block and reported the superior prefrontal activation associated with inhibition at the third or fifth trials required for the first time long after the dimension changes (Konishi et al., 2003). We also presented the control and the release trials at the third trials after the dimension changes of the modified WCST and reported the anterior prefrontal activation associated with inhibition of prolonged PI from a previous set, as assessed by the contrast of control minus release trials (Konishi et al., 2005). In these studies, however, inhibitory processes were investigated that were recruited long after the dimension changes, and it remains to be explored whether and where the inhibitory mechanism exists that is recruited immediately after the dimension changes, despite its importance in task switching (Monsell, 2003; Meiran et al., 2000; Allport et al., 1994). To explore the neural correlates of the inhibitory mechanism, in the present fMRI study, we used the control and the release trials presented immediately after the dimension changes of the modified WCST.

METHODS

Subjects and fMRI Procedures

Informed consent was obtained from 78 healthy right-handed subjects (35 men and 43 women, age = 20–28 years). They were scanned by fMRI using experimental procedures approved by the institutional review board of the University of Tokyo School of Medicine. Scanning was conducted using a 1.5-T fMRI system. Scout images were first collected to align the field of view centered on the subject's brain. Then T2-weighted spin-echo images were obtained for anatomical reference (repetition time = 5.5 sec, echo time = 30 msec, 75 slices, slice thickness = 2 mm, in-plane resolution = 2 × 2 mm). For functional imaging, gradient echo echo-planar sequences were used (repetition time = 3 sec, echo time = 50 msec, flip angle = 90°, cubic voxel of 4 mm, 21 slices). Twelve runs were collected, and each run contained 34 volume images. The first four images in each run were excluded from the analysis to take into account the equilibrium of longitudinal magnetization.

Behavioral Procedures

The task used in this study was derived from the WCST (Milner, 1963; Grant & Berg, 1948). In each WCST trial, a five-card display was presented until subjects responded to one of four reference card stimuli at the corner of the screen by matching the attribute of a central card on the basis of the dimension of color, form, or number (Konishi et al., 1998, 2002). A four-channel button was pressed using the right thumb for the choice of one of the four reference card stimuli. A feedback stimulus (correct = O, incorrect = X) was then presented.

Each eight-trial dimension block contained two types of trials of interest where the dual-match stimuli were presented: (1) control trials that required selection of a correct answer based on the current dimension by inhibiting PI from the last dimension and (2) release trials that did not require inhibition because the selection of correct answer based on the current dimension matches the one based on the last dimension (Figure 1). In one half of the blocks, the control trials were presented in the first and fifth trials, and the release trials were presented in the third and seventh trials, whereas in the other half of the blocks, the control trials were presented in the third and seventh trials and the release trials were presented in the first and fifth trials. These two types of blocks were alternated within runs. Ordinary single-match stimuli were presented in the other trials of no interest.

After eight successive correct trials, the currently relevant dimension was changed to one of the others, and subjects were instructed of the subsequent dimension by visual presentation of the word color, form, or number. The order of the dimensions and the pseudorandom sequences of correct buttons were counterbalanced across runs. The task used a self-paced design, and the feedback and instruction stimuli were presented for 0.5 sec, with

each stimulus separated by a blank image for 0.5 sec (therefore, the time between response and presentation of the next trial is 1.5 sec: 0.5 sec blank + 0.5 sec instruction/feedback + 0.5 sec blank). One block contained eight trials, and one run contained four to five blocks that were followed by dimension changes. The number of blocks per run depended on the RT of the subjects because of the self-paced design. The first four blocks were common to all the subjects and were analyzed, but the last fifth blocks were not always available and were discarded.

Data Analysis

Data were analyzed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). Functional images were realigned, slice timing corrected, normalized to the default template with interpolation to a 2 × 2 × 2-mm space, and spatially smoothed (FWHM = 6 mm). When head movement occurred by more than 2 mm in any direction, the entire run was excluded (three runs from two subjects). Event timing was coded into a general linear model (GLM) (Worsley & Friston, 1995). The control and the release trials of central interest presented in the first, third, fifth, and seventh trials after the dimension changes, together with others of no interest such as dimension changes (instruction cue) and run-specific effects, were coded into a GLM using the canonical hemodynamic response function, time locked to the onset of stimulus presentation. Feedback was not modeled in the GLM because feedback was always followed by card-stimulus presentation of the next trial that was constantly separated by only 1 sec. However, the contrast of interest (control minus release trials) subtracted the feedback component. Images of parameter estimates for signal response magnitudes in these events were then analyzed for group analysis using a random effect model.

Peak coordinate locations in activation maps were generated using a threshold of 19 or more contiguous significant voxels above $p < .001$ ($z > 3.3$) (each voxel = 2 × 2 × 2 mm^3) (Konishi, Donaldson, & Buckner, 2001; Buckner et al., 1998) and the peaks that also survived the threshold of $p < .05$ determined by false discovery rate (FDR) (Genovese, Lazar, & Nichols, 2002) were reported. For the activation related to inhibition in the third + fifth trials, all the peaks above the threshold of 19 or more contiguous significant voxels above $p < .001$ were above the FDR threshold of $p < .05$. However, no peaks related to inhibition in the first trials survived the FDR threshold. To verify activation related to inhibition in the first trials, we reanalyzed a separate data set from our previous study (N = 36) (Konishi et al., 2003) where similar control and release trials were presented in the first trials after the dimension changes. In that study, the control and the release trials were included in the first trials after the dimension changes, but were not analyzed to extract inhibitory components in the first trials. We reanalyzed the previously published data set in a way control and release trials were contrasted, similarly to the present study, and the results were used to validate activation of this study related to inhibition in the first trials (see Results).

RESULTS

Behavioral Results

The performance on this task was high: Subjects made a correct answer in 99.4 ± 0.5% (mean ± *SD*) of total trials. The RTs in the control and the release trials are presented in Figure 2. The RT difference (mean ± *SEM*) between the control and the release trials was 70.0 ± 8.0, 49.7 ± 6.3, 79.8 ± 6.6, and 4.6 ± 4.3 msec in the first, third, fifth, and seventh trials, respectively, and was significant in the first, $t(77) = 8.7$, $p < .001$, third, $t(77) = 7.9$, $p < .001$, and fifth, $t(77) = 12.2$, $p < .001$, trials but not in the seventh trials ($p > .05$). The behavioral results indicate that the inhibitory mechanisms were recruited in the first, third, and fifth trials but not in the seventh trials after the dimension changes.

Neuroimaging Results

The inhibitory mechanism recruited long after the dimension changes was examined by the contrast of control minus release trials in the third and fifth trials after the dimension changes (approximately five or more seconds after the dimension changes). The seventh trials were excluded on the basis of the behavioral data that failed to show RT difference between the control and the release trials. Figure 3 shows prominent activation related to inhibition in the third and fifth trials observed in multiple brain regions including the left anterior pFC, as previously reported (Konishi et al., 2005). All the activations related to inhibition in the third + fifth trials were significant ($p < .05$) after whole-brain multiple comparisons using FDR. A full list of activations is presented in Table 1.

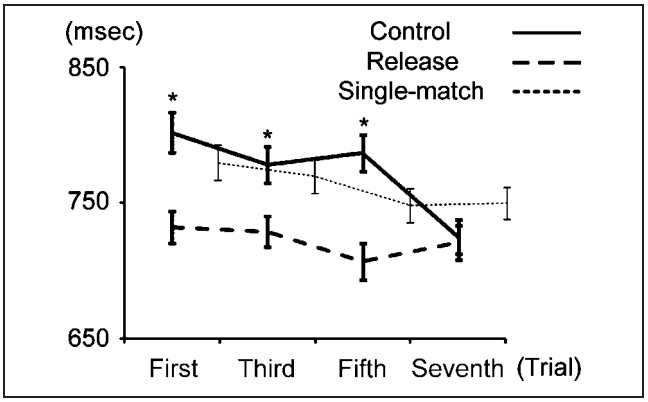

Figure 2. The time course of RT in the control and the release trials at the first, third, fifth, and seventh trials after the dimension changes. The RT in the single-match trials at the second, fourth, sixth, and eighth trials was also shown in a thinner line; *$p < .001$.

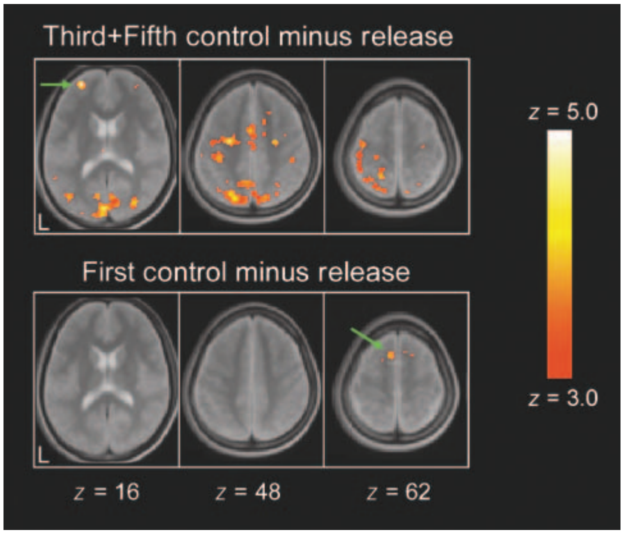

Figure 3. Statistical activation maps for the contrast "control minus release" at the third + fifth (top) and first (bottom) trials after the dimension changes. Activation maps are displayed as transverse sections and are overlaid on top of the anatomic image averaged across subjects. Statistical significance is indicated using the color scale to the right (display threshold: $z = 3.0$), and the transverse section level is indicated by the z coordinates of Talairach space at the bottom (Talairach & Tournoux, 1988).

The inhibitory mechanism recruited immediately after the dimension changes of central interest of the present study was examined by the contrast of control minus release trials in the first trials after the dimension changes (1 sec after the dimension changes). Activation in the left pre-SMA was above the threshold of 19 or more contiguous significant voxels above $p < .001$ ($z > 3.3$) (Figure 3), and no other activation was detected. However, the pre-SMA activation failed to survive the whole-brain multiple comparison using FDR. Therefore, the pre-SMA activation did not fulfill the two criteria and was not significant using this data set only. To validate the pre-SMA activation, we used a separate data set ($n = 36$) from our previous study (Konishi et al., 2003), where similar control and release trials in the first trials were included but were not contrasted against each other. The reanalysis of the already-published data in a way similar to the present study revealed the pre-SMA activation at (−8, 6, 62) ($t = 5.0$). Although no significant activation was detected in the second data set only, including the pre-SMA activation, the pre-SMA activation was used for a replication test (see Methods). The pre-SMA activation was located away from the activation in the present study only by approximately 6 mm. The spatial extent of the pre-SMA activation is presented in Figure 4. The left panel shows the results from the present data set, and the right panel shows the results from the previous data set. The lower panel shows the partially overlapping activations in the left pre-SMA across the two data sets. The spherical region with a radius of 6 mm centered from the activation peak in the present study cleared $p < .05$ in the previous data set, $t(35) = 2.2$. The replication results assure that the pre-SMA activation is significant at $p < .05$ after correction for whole-brain multiple comparisons using the two independent data sets.

Figure 5 shows a significant correlation between the magnitude of the pre-SMA activation (control minus release trials) and the difference in RT between control and release at the first trials ($r = .25, p < .05$). The correlation at the third + fifth trials was not significant in the anterior prefrontal region ($r = .13, p > .05$). No correlation

Table 1. Brain Regions Showing Signal Increase (Control vs. release Trials)

Coordinates				
x	*y*	*z*	*t*	*BA/Area*
First				
−6	12	62	4.9	6
Third + Fifth				
Frontal cortex				
−28	54	16	5.9	10
−26	−10	48	5.2	6
26	−12	46	4.9	6
−40	−6	54	4.7	6
−4	2	46	4.7	6/32
Parietal cortex				
−44	−26	54	5.6	40/2
26	−72	54	5.5	7
10	−78	54	4.8	7
−8	−56	44	4.7	7
−58	−24	42	4.6	40/2
26	−82	44	4.5	7
Occipital cortex				
26	−80	20	5.6	19/18
4	−72	0	5.5	18
10	−82	12	5.3	18/17
−26	−66	−10	5.2	19/18
−42	−72	18	4.8	19/18
28	−56	−2	4.6	19/18
−14	−88	−18	4.4	18
−16	−68	4	4.2	18/17
Others				
18	−66	−16	6.6	Cerebellum
−36	−58	−20	4.4	Cerebellum

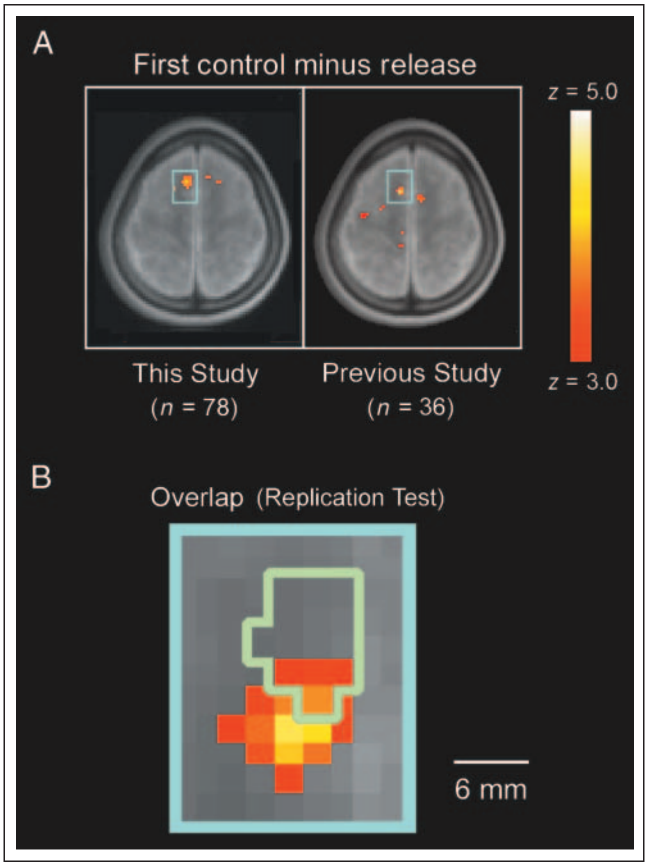

Figure 4. (A) Statistical activation maps of the present study (left panel, $n = 78$) and of our previous study (right panel, $n = 36$) for the contrast "control minus release" at the first trials. Statistical significance is indicated using the color scale to the right (display threshold: $z = 3.0$). (B) A replication test using two independent data sets. The activation map of our previous study is enlarged below, and the boundary of the pre-SMA activation of this study is overlaid. The threshold for the display is lowered for the activation in our previous study (display threshold: $z = 2.0$) for comparison.

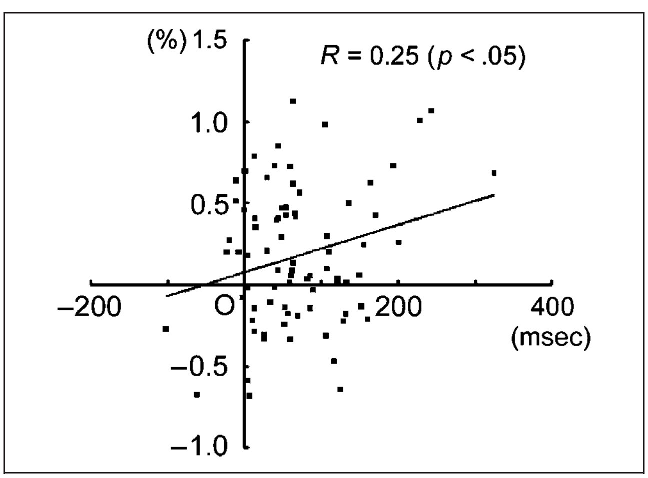

Figure 5. Correlation between the magnitude of the pre-SMA activation (control minus release trials) and the RT difference between the control and the release trials at the first trials. Each plot indicates data from one subject.

was observed between the signal magnitudes of the pre-SMA region at the first trials and the signal magnitudes of anterior prefrontal region at the third + fifth trials ($r = .02$, $p < .05$).

To assess the double dissociation between the pre-SMA and the anterior prefrontal activations, an ROI analysis was performed, using coordinates from separate data sets for unbiased comparison. For the pre-SMA activation, the center of the region was (−8, 6, 62) taken from the previous data set reanalyzed above (Konishi et al., 2003), and for the anterior prefrontal activation, the center was (−30, 50, 18) taken from our previous study reporting the anterior prefrontal region (Konishi et al., 2005). The double dissociation is presented in Figure 6. Significant interaction, $F(1, 68) = 13.3$, $p < .001$, was observed in the two-way ANOVA with regions (pre-SMA/anterior prefrontal) and contrasts (first / third + fifth) as main effects, indicating that these two regions are functionally dissociable in terms

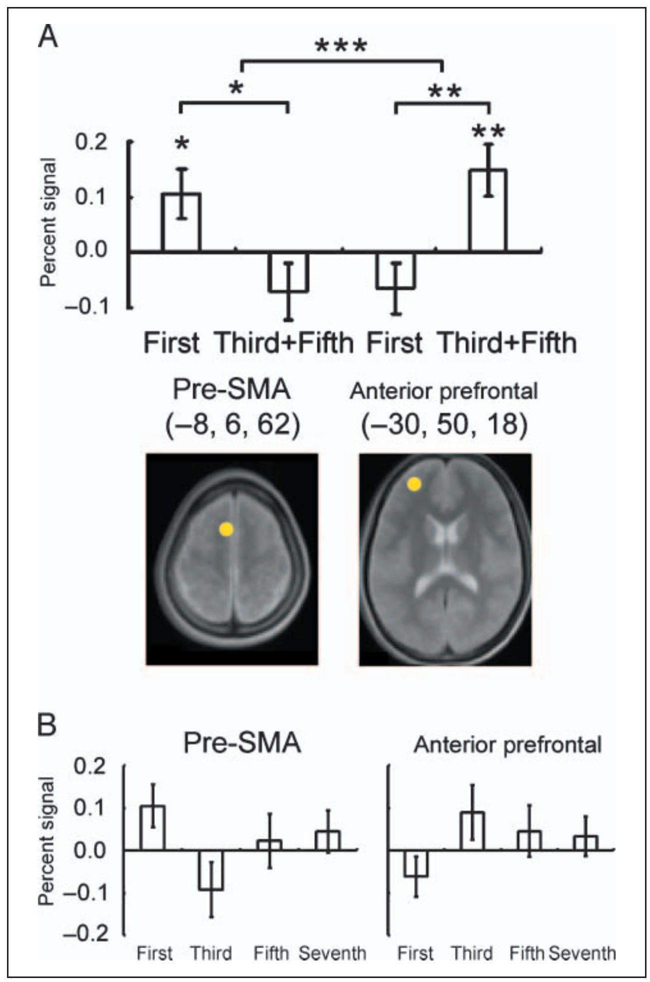

Figure 6. (A) Double dissociation of the brain activity in the pre-SMA and anterior prefrontal regions during PI inhibition immediately (first) and long (third + fifth) after the dimension changes. ***$p < .001$, **$p < .01$, and *$p < .05$. (B) The brain activity in the same coordinates for the control minus release trials at the first, third, fifth, and seventh trials.

of temporal contexts where the inhibitory mechanisms were recruited.

Finally, a correlation analysis was performed in the second level between the signal estimates for the contrast of control minus release and the RT difference between control minus release trials at the first, third, fifth, and seventh trials. This analysis is expected to reveal the brain regions that are systematically responsive to the degree of inhibition over time as assessed by the RT difference since the dimension changes. To ensure the positive brain activity in the control minus release at the first, third, and fifth trials, the analysis was masked by the *t* maps ($p < .05$, uncorrected) for control minus release at the first and the third + fifth trials. No significant regions were detected, suggesting that the inhibitory mechanisms depend on the temporal context of inhibition.

DISCUSSION

The present fMRI study used the dual-match stimuli that permit extraction of brain activity associated with inhibition of PI by comparing the brain activity in control trials where inhibition was required with that in release trials where inhibition was not required. Significant activation was observed in the left pre-SMA when inhibition was required in the first trial after the dimension changes, whereas the inhibitory mechanism in the left anterior pFC was recruited in the third and fifth trials after the dimension changes. The double dissociation of brain activity in these two regions suggests dissociable inhibitory mechanisms recruited, depending on the temporal contexts of the inhibitory demands imposed during performance of the task.

The pre-SMA activation yielded by the contrast of control minus release trials is expected to reflect inhibition of PI, but other alternative interpretations are possible. For example, the pre-SMA activation may reflect response conflict monitoring (Nachev, Kennard, & Husain, 2008), in the sense that control trials may be more effortful to the subjects and required more demands of monitoring. It seems unlikely that the pre-SMA activation reflects reconfiguration because both the control and the release trials required reconfiguration at the first trials to answer correctly on the basis of the new dimension.

The medial part of the frontal cortex has been implicated in shifting during performance of the WCST (Stuss et al., 2000; Drewe, 1974), inhibitory control (Sumner et al., 2007; Floden & Stuss, 2006), and updating motor plans (Shima, Mushiake, Saito, & Tanji, 1996). Of close relevance is the pre-SMA activation reported in the previous study that was activated relative to card-sorting baseline (Nagahama et al., 1999). The average *y* coordinate reported in Nagahama et al. (1999) was 13.1, which is close to that in the present study ($y = 12$), suggesting that the main component of the pre-SMA activation reported in Nagahama et al. was related to inhibition of PI from the last dimension. It is rather surprising that only the left pre-SMA region was activated during inhibition of PI in the first trials in the present study. Previous neuroimaging studies have examined set shifting/task switching by contrasting dimension change minus dimension repeat/task switch minus task repeat (Nyhus & Barcelo, 2009; Specht et al., 2009; Wylie et al., 2009; Crone et al., 2006; Hampshire & Owen, 2006; Lie et al., 2006; Konishi et al., 2002, 2005; Brass & von Cramon, 2004; Cools et al., 2004; Monchi et al., 2001, 2004; Braver et al., 2003; Dove et al., 2002; Rushworth et al., 2002; Pollmann et al., 2000; Rogers et al., 2000; Sohn et al., 2000; Nagahama et al., 1999). Assuming that set shifting/task switching consists of inhibition of PI from a previous set and reconfiguration of a new set, the weak activation associated with inhibition, as opposed to reconfiguration, reported in the present study suggests that the major component of the lateral prefrontal activation during set shifting/task switching reported previously, including the inferior prefrontal activation, might be related to reconfiguration of a new task set.

We previously reported the activation in the superior prefrontal region during set shifting in naive subjects using the contrast of the first round shifts minus the second round shifts (Konishi et al., 2008). As suggested previously (Konishi et al., 2003), the superior prefrontal activation may be involved in inhibitory processes. Anatomically, the pre-SMA is located in the medial wall, whereas the superior prefrontal region is located in the dorsolateral surface of the pFC. One critical functional difference between the pre-SMA and the superior prefrontal regions is that the pre-SMA region is involved repeatedly in the first trials after the dimension changes, whereas the superior prefrontal region is involved under novel situations, only in the first round shifts but not the second, during which subjects were naive to shifting to the other dimensions. Although the two activations are commonly observed early in one dimension block, the related inhibitory mechanisms have distinct features.

The contrast of "control minus release trials" has previously revealed the inhibitory mechanisms in the anterior pFC recruited in the later phase of dimension blocks of the modified WCST (Konishi et al., 2005). The pre-SMA activation significantly correlated with the RT data of individual subjects, whereas the anterior prefrontal activation did not. Although the present study is not designed to test the prefrontal hierarchical control system (Badre & D'Esposito, 2009; Koechlin & Summerfield, 2007), the correlation results were supportive in the sense that the pre-SMA was more directly associated with behavioral output: If the activity per unit time is constant, the activation should be positively correlated with RT. On the other hand, the anterior prefrontal region, situated to be in the highest level in the hierarchical control system (Badre & D'Esposito, 2009; Koechlin & Summerfield, 2007), appears to be irrelevant to direct behavioral output and to be involved in PI inhibition in a more indirect manner, exerting its role possibly through more posterior regions such as premotor and parietal regions listed in Table 1.

The inhibitory mechanism is most often associated with the inferior frontal gyrus, as has been demonstrated by

neuropsychological studies (Hodgson et al., 2007; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Rushworth, Nixon, Eacott, & Passingham, 1997; Butters, Butter, Rosen, & Stein, 1973; Iversen & Mishkin, 1970; Butter, 1969). The inhibitory mechanism in the inferior frontal gyrus has generally been supported by neuroimaging studies of response inhibition (Chikazoe et al., 2009; Duann, Ide, Luo, & Li, 2009; Velanova, Wheeler, & Luna, 2009; Nakata et al., 2008; Zheng, Oka, Bokura, & Yamaguchi, 2008; Aron, Behrens, Smith, Frank, & Poldrack, 2007; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Leung & Cai, 2007; Li, Huang, Constable, & Sinha, 2006; Wager et al., 2005; Hester et al., 2004; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002a; Durston, Thomas, Worden, Yang, & Casey, 2002; Rubia et al., 2001; Garavan, Ross, & Stein, 1999; Konishi et al., 1999), interference suppression (Morimoto et al., 2008; Hazeltine, Bunge, Scanlon, & Gabrieli, 2003; Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002b; Milham et al., 2002; Ullsperger & von Cramon, 2001), and inhibition during memory (Jimura et al., 2009; Caplan, McIntosh, & de Rosa, 2007; Feredoes, Tononi, & Postle, 2006; Badre & Wagner, 2005; D'Esposito, Postle, Jonides, & Smith, 1999; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorentz, 1998; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). However, the present study failed to reveal the inhibitory mechanism in the inferior pFC. Given the abundant evidence for the inhibitory mechanism in the inferior frontal gyrus, the negative results of this study suggest that the inhibitory mechanism in the inferior pFC that is recruited by the various inhibitory demands was not recruited in this task under this experimental condition, presumably because the present task did not require trial and error to identify the next dimension (Hampshire & Owen, 2006). Another possibility would be that the IFG, as part of the ventral attention system (Corbetta & Shulman, 2002), was equally activated due to target detection demands during control and release trials presented immediately after the dimension changes (Duann et al., 2009; Li et al., 2006, 2007). Although more investigation would be required to determine the precise role of the IFG, the present results indicate that the inhibitory mechanism recruited in the first trials after the dimension changes is located in the pre-SMA.

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