

Contribution of Working Memory to Transient Activation in Human Inferior Prefrontal Cortex during Performance of the Wisconsin Card Sorting Test

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The Wisconsin Card Sorting Test (WCST) is the standard task paradigm to detect human frontal lobe dysfunction. In this test, subjects sort card stimuli with respect to one of three possible dimensions (color, form and number). These dimensions are changed intermittently, whereupon subjects are required to identify by trial and error a new correct dimension and flexibly shift cognitive set. We decomposed the cognitive requirements at the time of the dimensional changes of the WCST, using functional magnetic resonance imaging (fMRI). By explicitly informing subjects of a new correct dimension, the working memory load for the trial-and-error identification of the new dimension was removed. Event-related fMRI still revealed transient activation time-locked to the dimensional changes in areas in the posterior part of the inferior frontal sulci. However, the activation was significantly smaller than in the original WCST in which subjects had to use working memory to identify the new dimension by trial and error. Furthermore, these areas were found to spatially overlap the areas activated by a working memory task. These results suggest that working memory and set-shifting act cooperatively in the same areas of prefrontal cortex to adapt us to changing environments.

Introduction

The Wisconsin Card Sorting Test (WCST) (Grant and Berg, 1948; Milner, 1963; Drewe, 1974; Nelson, 1976; Robinson *et al.*, 1980; Owen *et al.*, 1993) is the most popular task paradigm to detect human frontal lobe dysfunction. In this study we attempt to decompose the cognitive requirements of the test. In this test, subjects choose one of four reference card stimuli that had the same attribute as that of a target card stimulus with respect to one of three possible categories, or so-called 'dimensions' (color, form and number) (Fig. 1A). The dimension is intermittently changed without warning, and the subjects have both to identify a new dimension by trial and error and flexibly shift attention (cognitive set) to the new dimension (Fig. 1A). Performance of this task is impaired by damages to the dorsolateral prefrontal cortex in both humans (Milner, 1963) and monkeys (Passingham, 1972; Dias *et al.*, 1996). Previous positron emission tomography (PET) studies also reported that dorsolateral prefrontal cortex was more active during the performance of the WCST than during the performance of control tasks which do not contain dimensional changes (Berman *et al.*, 1995; Nagahama *et al.*, 1996).

In our previous event-related functional magnetic resonance imaging (fMRI) study (Konishi *et al.*, 1998b), we isolated transient activity time-locked to the dimensional changes and specified the prefrontal activation foci in the posterior part of the bilateral inferior frontal sulci. This transient activity was separate from sustained activity derived from the working memory component related to maintenance of current dimension or sorting of card stimuli (Fig. 1B), because such sustained component was subtracted out using event-related fMRI method (Blamire *et al.*, 1992; Friston *et al.*, 1994; Buckner *et al.*, 1996b;

Konishi *et al.*, 1996; Kim *et al.*, 1997; Zarahn *et al.*, 1997; Rosen *et al.*, 1998). However, it is possible that the transient activity contains multiple cognitive components. As the dimensions change, subjects are required to shift cognitive set, which is regarded as a critical component of the WCST (Milner, 1963; Passingham, 1972; Dias *et al.*, 1996). At the same time, the inferior prefrontal activation in the context of the WCST may also include a working memory component (Goldman-Rakic, 1987), because the WCST requires subjects to identify a new dimension by trial and error.

In the present study, we first aimed to isolate the contribution of working memory to the transient inferior prefrontal activation time-locked to the dimensional changes of the WCST. By explicitly informing subjects of the new dimension, they were deprived of the working memory load for the trial-and-error identification ('instruction condition'), thereby replacing the trial and error in the original condition with this instruction. In this sense, the instruction condition is similar to other set-shifting tasks in which only two dimensions were used and alternated. We tested whether transient activation could be detected even in the instruction condition, and then compared the brain activity in the two conditions (the original versus instruction conditions). Second, we directly tested whether the dimensional changes of the WCST activate the same areas as those activated by a working memory task in which the WCST stimuli were used (Fig. 2). This control experiment was conducted in order to see whether the results of previous working memory studies can be used to characterize the inferior prefrontal areas in this study.

Materials and Methods

Cognitive Tasks

The WCST (Original Condition)

The WCST we used was designed to closely resemble the original (Grant and Berg, 1948; Nelson, 1976; Konishi *et al.*, 1998b). A five-card stimulus (Fig. 1A) was displayed on a screen for each trial. The stimulus contained four reference cards (one red triangle, two green stars, three yellow crosses and four blue circles) depicted at the corners and one target card depicted in the center. The subjects were instructed to choose the reference card that had the same attribute, with respect to one of three possible 'dimensions' (color, form and number), as that of the target card, without being informed of the correct dimension. Hence, if the dimension was color and the target card was green, the green reference card (the upper left card in Fig. 1A) had to be chosen. After they pushed a particular response button with their right thumb, subjects were informed whether the response was correct or incorrect by visual presentation of a feedback stimulus (correct: O, incorrect: X), and then had to identify the dimension using the feedback stimulus. Following many consecutive correct trials, the dimension was changed to one of the other two dimensions in a random order without warning, and again

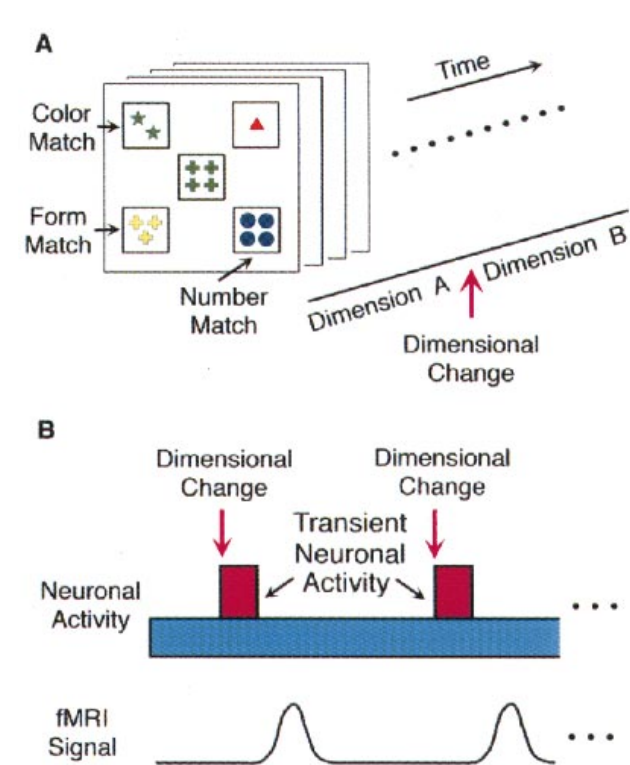


Figure 1. The computerized WCST and the data-processing strategy. (A) A five-card (one target card and four reference cards) stimulus was presented once in a trial. Subjects were required to match the target card to one of the four reference cards based on one of three possible dimensions (color, form and number) by pushing a particular response button. The dimension was changed after at least 10 consecutive correct trials. (B) The brain activity observed during performance of the WCST consists of the sustained activity related to sorting and the transient activity elicited by the dimensional changes. By comparing the signal obtained after dimensional changes with that before the changes, the transient signals time-locked to the dimensional changes were extracted (event-related fMRI).

subjects had to identify the new dimension and flexibly adapt themselves to it. The target card stimuli were randomly selected from a pool of two sets of 64-card decks.

To perform event-related fMRI analysis, image scan was partly time-locked to the dimensional changes and partly to subjects' self-paced performance using the following time parameters. The five-card stimulus shown in Figure 1A was presented until the next image scan, which came within 0.5 s after the subjects responded. Therefore, the length of the stimulus presentation depended on the subjects' reaction time, and varied by 0.5 s in a stepwise fashion paced by the image scan. After a 0.1 s delay from the image scan, a feedback stimulus (correct: O, incorrect: X) was presented for 0.5 s. And 0.1 s after the end of the feedback stimulus, the five-card stimulus of the next trial was presented. Since it took at least 0.5 s for the subjects to respond, one trial lasted for at least 1.5 s.

Modification of the WCST (Instruction Condition)

Two conditions of the WCST were designed, an 'original condition' (described above) and an 'instruction condition'. We devised the instruction condition by introducing an instruction cue that explicitly informed subjects of a new dimension by visual presentation of the word 'color', 'form' or 'number'. After the end of the 'incorrect' feedback stimulus given for 0.1 s after dimensional changes, this instruction cue was presented for 0.5 s. This modification was made to deprive the subjects of the load of working memory used when the subjects identified a new dimension by trial and error. Dimensional changes in the original and instruction conditions were intermixed in each run, with a ratio of two dimensional changes in the original condition to one dimensional change in the instruction condition. The total number of

N-Back Task

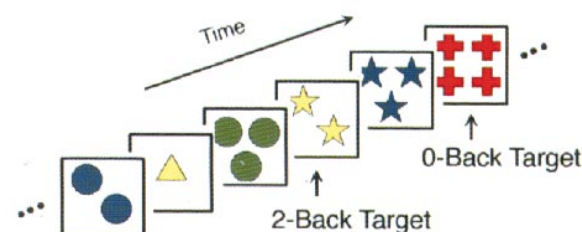


Figure 2. The working memory task (the n -back task). A pseudorandom sequence of the WCST card stimuli was presented. The trials in which subjects must attend to the 'color' of the WCST card stimuli are shown above. In the control trials (the 0-back condition) subjects detected pre-specified targets ('red' card stimuli), and in the test trials (the 2-back condition) the target was any color identical to the one presented two trials back. These conditions were given in a block and were switched within a run. Similarly, the other dimensions (form and number) were also tested in separate runs.

dimensional changes analyzed in each slice was 48 to 46 and 24 to 23 for the original and instruction conditions, respectively.

Working Memory Task (N-back Task with Card Stimuli)

We chose the n -back task as a standard working memory task (Fig. 2). The working memory task consisted of three periods given for each run, one control period (0-back condition), one test period (2-back condition) and another control period (0-back condition). A sequence of the card stimuli used in the WCST experiments was visually presented to the subjects (stimulus duration 1.5 s; interstimulus interval 1.5 s), and subjects responded to each of the stimulus with their right hands, pressing one button for targets (33% of trials) and another for nontargets. In the 2-back condition, the subjects were required to attend to one pre-specified dimension and to press a button when any card stimulus with the attribute of the attended dimension matched the one presented two trials back, and to press another button when the card stimulus did not. In the 0-back condition the subjects were required to press a button when a 'red' 'triangle' or 'one' card (for the dimension of color, form or number respectively) was presented, and to press another button when other stimuli were presented. The subjects were informed of the dimension that should be attended to prior to each run. Switch of the 2-back and 0-back conditions was signaled by presenting a word stimulus '2-back' or '0-back'. Fifteen runs (five runs for each dimension) were collected for each subject.

Subjects and fMRI

Seven healthy subjects (six males and one female, all right-handed, aged 24–40) participated in both the WCST and the working memory experiments. We used 1.5 T gradient-echo echo-planar imaging system ($T_R = 2$ s, flip angle = 90°) (Sakai *et al.*, 1995a,b; Konishi *et al.*, 1998b). The range of $z = 12$ –36 mm at $y = 0$ mm (oblique by 10°) of Talairach's coordinates was covered by four contiguous transverse slices (slice thickness = 6 mm, in-plane resolution = 3×3 mm²). We took T_1 -weighted spin-echo images of the corresponding slices every six runs to estimate head movement and rejected runs in which head movement greater than 1.5 mm in any direction had occurred.

Data Analysis

The data processing strategy and statistical procedures used in the original and instruction conditions of the WCST experiment (Fig. 1B) are essentially the same as those used in our previous event-related fMRI study of the WCST (Konishi *et al.*, 1998b). The time zero was defined as the time at onset of the presentation of the 'incorrect' feedback stimulus given immediately after the dimensional change, and all the image data of each slice were classified into data for -5, -3, -1, 1, 3, 5, 7, 9, 11 or 13 s. We then calculated the across-change mean and variance of the difference between the images taken at each time point after time zero and the averaged images obtained from three time points before time zero. We set a time window of 5–9 s after the onset of the 'incorrect' feedback stimulus to detect transient activation at the time of the dimensional

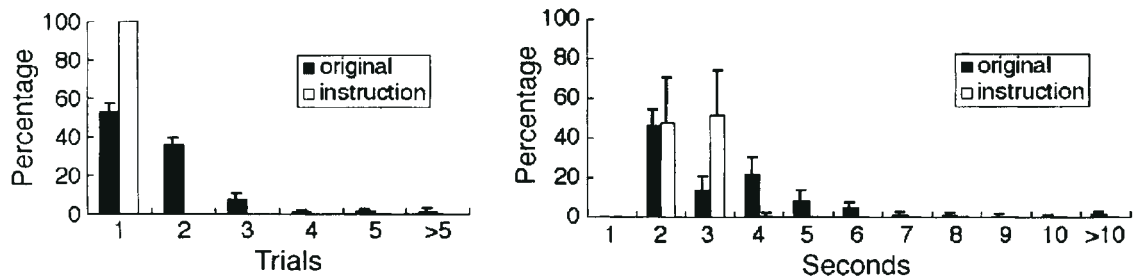


Figure 3. Normalized distribution of the number of trials and the time to complete set shifting in the original and instruction conditions. Completion of set shifting was defined as three or more consecutive correct responses. The time taken was defined as the interval between the onset of the 'incorrect' feedback stimulus of the first incorrect trial after the dimensional change, and the onset of the 'correct' feedback stimulus of the first correct trial in a sequence of three or more correct trials. Error bars indicate the SD of the seven subjects.

changes, because it is within this time window that we can effectively detect the transient hemodynamic signals elicited by the short neuronal activity which begins at time zero (Friston *et al.*, 1994; Buckner *et al.*, 1996b; Konishi *et al.*, 1996; Kim *et al.*, 1997; Zarahn *et al.*, 1997).

In the WCST experiment, a replication approach (Buckner *et al.*, 1996a) was used to identify activated regions, because one of the main goals of this study was to compare the magnitude of the transient activation of the original and instruction condition in the regions activated during set-shifting in the original WCST. Data sets of the original condition were divided into two separate sets by alternately classifying the data from each dimensional change as the hypothesis-generating (first) data set and the hypothesis-testing (second) data set. The first data set was used to delineate regions of interest (ROIs) with four or more contiguous pixels above the significance level of $P < 0.005$ (paired *t*-test, uncorrected) within the time window. The second data set was then used to test whether the ROIs replicated with the significance level of $P < 0.005$ (paired *t*-test) within the time window of 5, 7 and 9 s (3-fold Bonferroni corrected). Similar procedures were used to obtain the time course of signals of the original and instruction conditions. First, a ROI was delineated by the first data set of the original condition. Then the time course of the ROI was calculated from the second data set of the original condition and the whole data of the instruction condition. The difference of the time courses in the two conditions was tested by averaging the data of 5–9 s after the dimensional changes. This time window of 5–9 s is consistent with previous studies of transient hemodynamic response as stated above.

In the working memory experiment, conventional analysis for blocked-trial design was used to determine activated regions, because the main goal of this experiment was to effectively detect areas activated by the working memory task and to compare them with the inferior prefrontal areas. Both the test and control periods consisted of 15 images per slice. The first five images of each period were not used for analysis in order to exclude the transient shift-related signals elicited at the time of switch of the control and test periods. The average of 20 images in the two control periods and the average of the 10 images in the test period were compared by a paired *t*-test. To compare the areas activated by the working memory task and the WCST in each subject, data of the two experiments from each subject were aligned using AIR (Woods *et al.*, 1992). Regions with eight or more contiguous pixels above $P = 0.005$ (paired *t*-test, uncorrected) were defined as activated areas.

Results

The WCST With and Without Instruction

Behavioral Results

We designed for the computer the original WCST ('original condition') and further devised the 'instruction condition' by introducing an instruction cue that explicitly informed subjects of a new dimension by visual presentation of the word 'color', 'form' or 'number'. Dimensional changes in the original and

instruction conditions were intermixed in each run, with a ratio of two dimensional changes in the original condition to one dimensional change in the instruction condition.

We estimated, from performance data, the duration of the transient neuronal activity elicited by the dimensional changes. Figure 3 shows the normalized distribution of the trial (left) and time (right) to completion of set-shifting in the original and instruction conditions. Completion was defined as three or more consecutive correct responses. The time taken was defined as the interval between the onset of the 'incorrect' feedback stimulus of the first incorrect trial after the dimensional change, and the onset of the 'correct' feedback stimulus of the first correct trial in a sequence of three or more correct trials. The durations were 3.1 ± 0.3 s, 1.7 ± 0.1 trials (mean \pm SD) in the original condition and 2.3 ± 0.1 s, 1.0 ± 0.0 trial in the instruction condition, and the difference between the durations of these conditions was significant (paired *t*-test, $P < 0.001$). Although this procedure only provides the upper limit of the shift time in the instruction condition, it ensures that the number of trials to complete shifting in these conditions is almost equated when the shift time is within 3 s. The short duration (3.1 or 2.3 s) of neuronal activity validates the time window of 5–9 s to detect the transient signals elicited by the short neuronal activity (Friston *et al.*, 1994; Buckner *et al.*, 1996b; Konishi *et al.*, 1996; Kim *et al.*, 1997; Zarahn *et al.*, 1997).

fMRI Results

Transient activation in the original condition was reproducibly detected in the posterior part of the bilateral inferior frontal sulci in all seven subjects. These activated regions were located within the range of $x = 40 \pm 6$ mm, $y = 15 \pm 7$ mm, $z = 24 \pm 6$ mm (right) and $x = -38 \pm 2$ mm, $y = 15 \pm 6$ mm, $z = 25 \pm 7$ mm (left) of Talairach's coordinates (Talairach and Tournoux, 1988). A typical example in one subject is shown in Figure 4A. The activated pixels at 1–13 s after the dimensional changes are enlarged and shown sequentially in panels. In these regions, the transient signals peaked 7 s after the dimensional changes, consistent with the durations of the transient neuronal activity estimated above. We compared the transient signals of these regions of this subject in the original and instruction conditions using the replication approach, as shown in Figure 4B. The ROIs were delineated by the hypothesis-generating (first) data set of the original condition, and the time courses were calculated from the hypothesis-testing (second) data set of the original condition (red line) and from all of the data of the instruction condition (green line). Both of these regions showed significant activation in the original condition ($P < 0.001$, right and left) and

in the instruction condition ($P < 0.001$, right and left). The activation in the original condition was greater than in the instruction condition (right: $P < 0.005$; left: $P < 0.05$), reflecting the difference of cognitive requirement between the two conditions.

Figure 4C shows time courses averaged from all seven subjects. The time course of the original condition was similar to Figure 4B, and the activation was significant (right: $P < 0.005$; left: $P < 0.001$). In the instruction condition, the activation was also significant (right: $P < 0.01$; left: $P < 0.005$), and the percentage signal change in the original condition was significantly larger than in the instruction conditions (right: $P < 0.005$; left: $P < 0.001$). One of possible explanations of this larger activity in the original condition would be that it took longer to complete set-shifting in the original condition than in the instruction (Fig. 3). To exclude this possibility, we excluded data of trials in which set-shifting lasted for a long time (>3.0 s) to match the duration of neuronal activity at the time of the dimensional changes in the two conditions. Then the time courses of signal change of the two conditions were recalculated. The resulting time courses are shown in Figure 4D. The estimated duration of neuronal activity is now 2.0 ± 0.1 s for the hypothesis-testing data set of the original condition, and 2.3 ± 0.1 s for all of the data of the instruction condition (mean \pm SD). The signal change of the original condition was still significantly larger than that in the instruction condition (right: $P < 0.05$; left: $P < 0.01$).

Comparison with a Working Memory Task

Behavioral Results

The transient signals in the original condition of the WCST were larger than in the instruction condition. The difference between the signals could be due to the working memory requirement in the original condition. To test this hypothesis, a working memory experiment (2-back versus 0-back condition) was conducted and compared with the WCST. The subjects' correct performance in the working memory experiment was $98.8 \pm 1.6\%$ (mean \pm SD) in the 2-back condition and $99.9 \pm 0.3\%$ in the 0-back condition.

fMRI Results

The inferior prefrontal areas were successfully activated in all the subjects, as reported by previous studies of working memory tasks. We directly compared the spatial extent of these inferior prefrontal areas with those activated at the dimensional changes in the WCST. A typical example of this comparison is shown in Figure 5A. The activation maps of the working memory task and the WCST are shown in the top half of the figure. In the bottom half, the activated areas in the working memory task are enclosed in black, and overlaid on the expanded activation maps of the WCST. To indicate correspondence, the expanded maps are enclosed in the same color as that in the original activation maps. The areas detected in the working memory task were

largely included by those detected at the time of the dimensional changes of the WCST. This was reproducible in all other six subjects as shown in Figure 5B. To evaluate the degree of the contribution of working memory to the WCST, we quantified the overlap of the inferior prefrontal activation. Figure 6 shows the percentage of activated pixels of the working memory task that are also activated in the WCST. Three different significance levels ($P < 0.0005$, 0.005 and 0.05) were used for the WCST activation, and two strict thresholds ($P < 0.0005$ and 1 ± 10^{-5} for the open and filled columns respectively) were used for the ROI delineation in the working memory activation. The overlap ratio was highly significant ($P < 0.002$, 6-fold Bonferroni corrected) in the right and left inferior prefrontal areas of all the subjects, as determined by a Poisson distribution.

Discussion

The comparison of the original and instruction conditions of the WCST decomposed the transient inferior prefrontal signals elicited at the time of dimensional changes into (i) a working memory component for the trial-and-error identification and (ii) a set-shifting component. This method is distinct from our previous work in which we subtracted the transient component statistically *post hoc*. In the current study we employed a novel method of fractionating the task such that we can subtract this component *a priori*. In addition, the significant overlap of the areas activated by the working memory task and the dimensional changes of the WCST ensures that the results of previous working memory studies can be used to characterize the inferior prefrontal areas in this study, as discussed below.

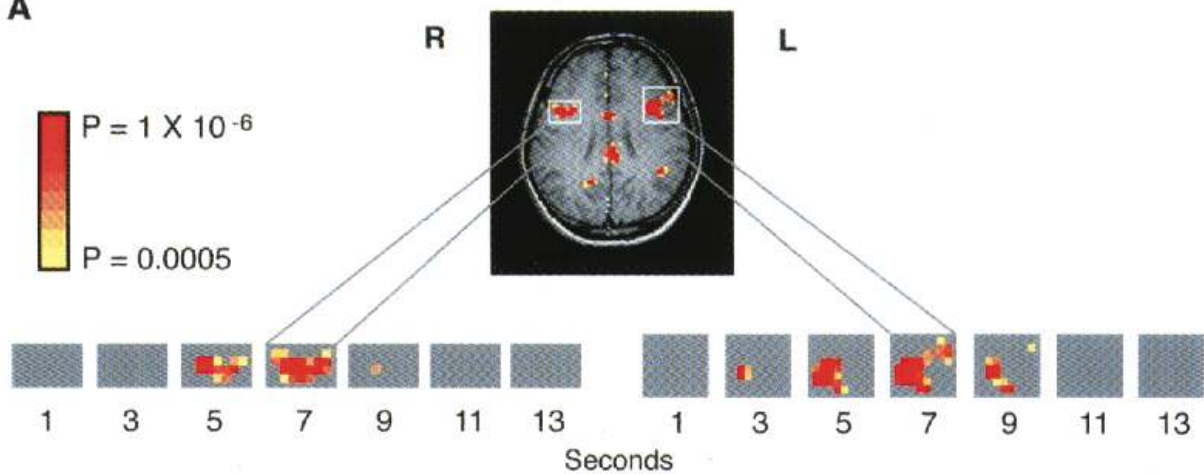
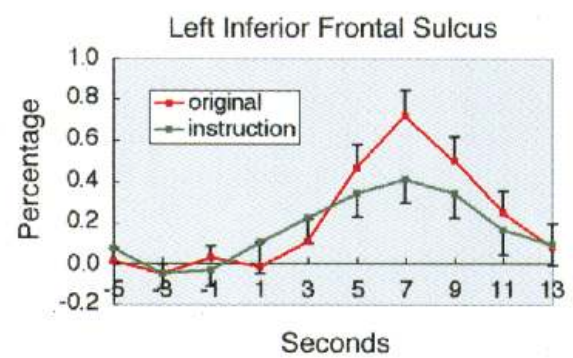
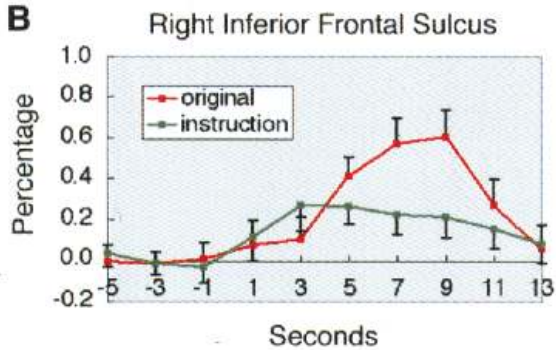
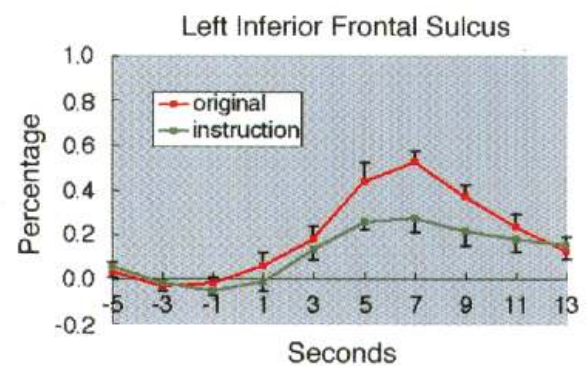
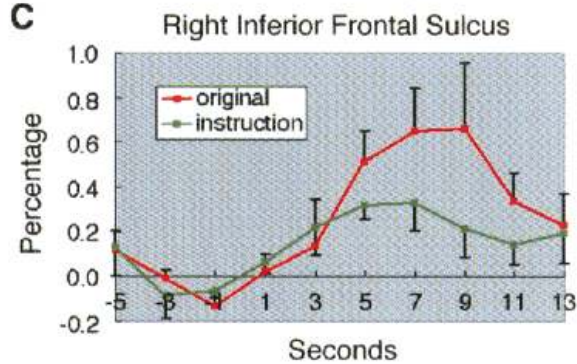
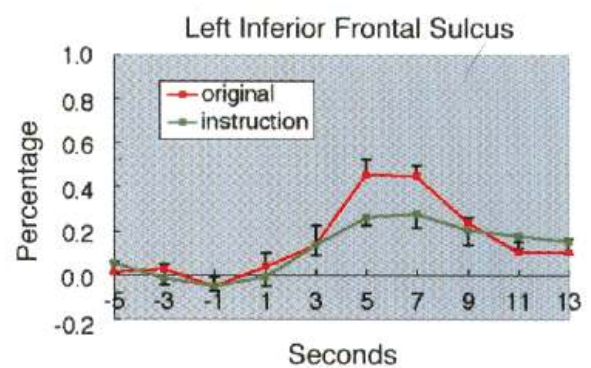
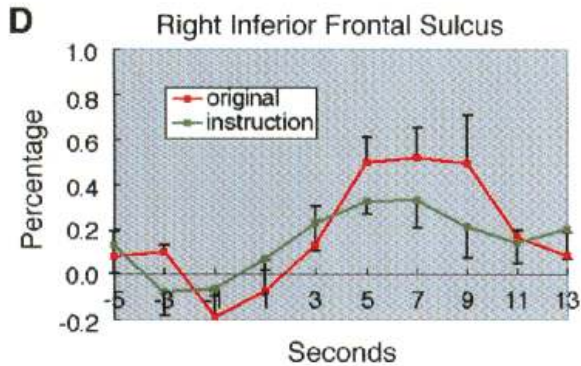
Event-related fMRI and the Transient Activity in the WCST

We isolated the transient signals at the time of dimensional changes of the WCST using event-related fMRI, in which the signals obtained 5–9 s after the dimensional changes was compared with the signals obtained before the changes. This event-related fMRI procedure is based on the consideration that signals observed during performance of the WCST contained transient and sustained signals; transient signals were elicited by the dimensional changes, and sustained signals were elicited by maintenance of cognitive set or sorting of target card stimuli (Fig. 1B). The signals obtained after the dimensional changes were compared with the signals obtained before the changes, subtracting out the baseline activation level that is derived from maintenance of current dimensions or sorting of card stimuli. The event-related fMRI procedures also allowed us to intermix two different conditions (the original and instruction conditions) during the performance of the WCST, enabling us to minimize the difference between the mental state and task strategy of the subjects in the two conditions and to compare the data of these two conditions.

Transient Activity With and Without Instruction

Obviously, many processes are associated with the transient

Figure 4. Transient shift-related activity in inferior frontal sulci. (A) Bilateral activity in the inferior frontal sulci time-locked to the dimensional changes in the original condition in one subject. The pixel-wise statistical significance level of 7 s after the changes in the original condition is color-coded and mapped on the corresponding T_1 -weighted image. The activated regions in the right and left inferior frontal sulci are enlarged, and the activated pixels at 1–13 s after the dimensional changes are shown sequentially in panels. The color scale at top left represents the P -value calculated from all the data in the original condition using paired t -test. (B) The time courses of percentage increase of the transient signals in the right and left inferior frontal sulci (shown in the left and right figures respectively) of the same subject as in (A). First, a region of interest (ROI) was delineated by the hypothesis-generating data set of the original condition (see Materials and Methods). Then the time course of the ROI was calculated from the hypothesis-testing data set of the original condition and all of the data from the instruction conditions. (C) Similar to (B) but for the average from all seven subjects. (D) The time courses recalculated so as to match the duration of the transient neuronal activity of the original and instruction conditions elicited by the dimensional changes. The ROI remained the same, but the trials in which set-shifting lasted >3 s were excluded from the hypothesis-testing data set of the original condition, and from all of the data from the instruction conditions.

A**B****C****D**

A

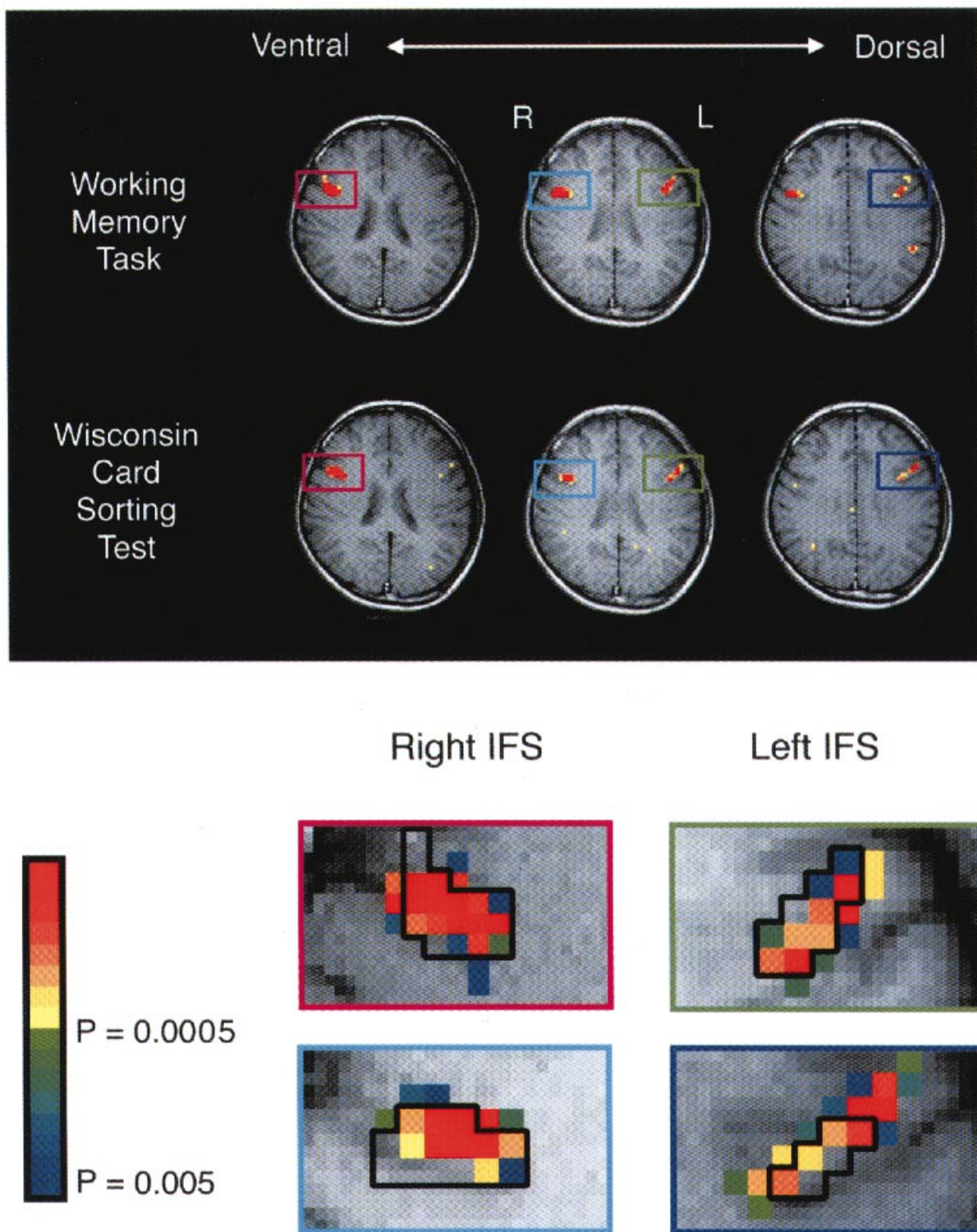


Figure 5. Spatial overlap of the inferior prefrontal areas activated in the working memory task and the WCST. (A) (Top) The pixel-wise statistical significance level of the activation in the working memory task and the original condition of the WCST (7 s after the dimensional changes) from one subject is color-coded and mapped on the corresponding three contiguous T_1 -weighted images (right = dorsal; left = ventral). (Bottom) The activated areas in the working memory task are enclosed in black and overlaid on the expanded activation maps of the WCST. The expanded activation maps are enclosed in the same color as that in the original activation maps. (B) The expanded activation maps in the right and left inferior prefrontal areas of other six subjects are shown.

B

Right IFS

Left IFS

Subject 2

3

4

5

6

7

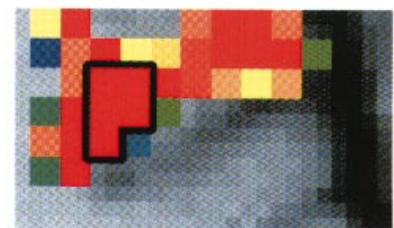
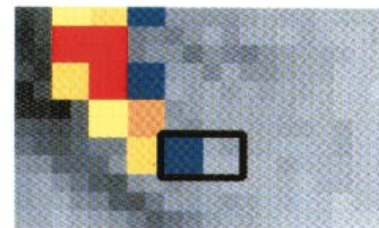
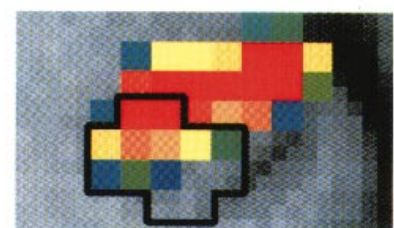
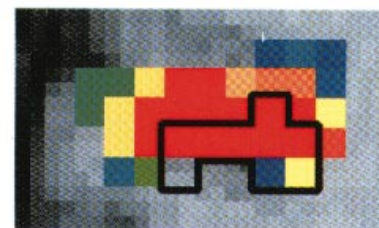
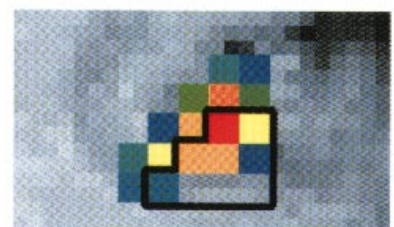
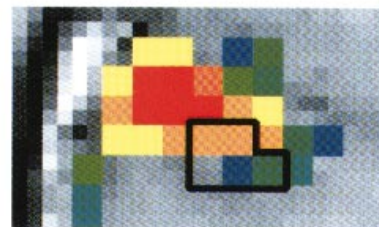
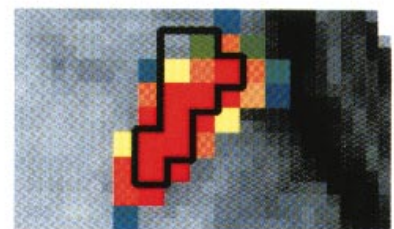
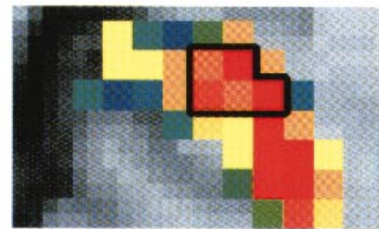
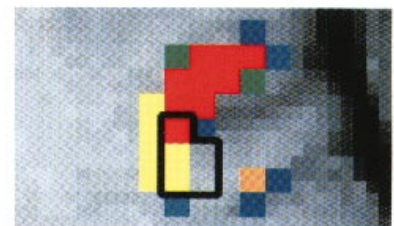
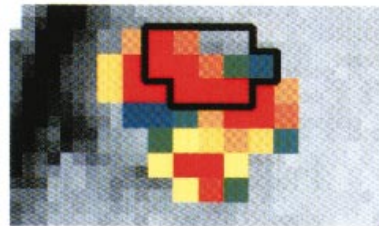
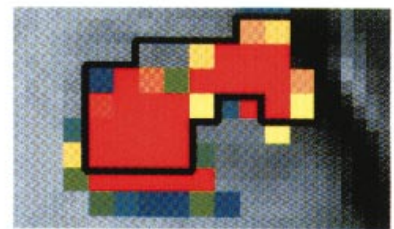
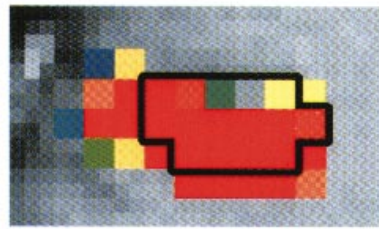


Figure 5B

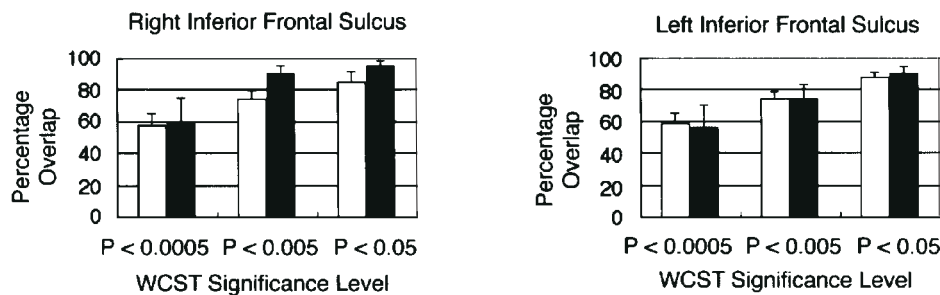


Figure 6. Overlap ratio of working memory activation with the WCST activation in the right and left inferior prefrontal areas. Open and filled columns indicate percentage overlap of working memory areas determined by the thresholds of $P < 0.0005$ and 1×10^{-5} respectively. The WCST activation was estimated by three different significance levels ($P < 0.0005$, 0.005 and 0.05). Error bars indicate the standard error of means of the seven subjects.

signal at the time of dimensional changes in the context of the WCST (the original condition), including the discovery that one set is no longer adaptive and the search for a more adaptive set. These may all be seen as components of a general shift process. To distinguish these components, we first confined them to those used in the instruction condition in which the subjects are still required to shift the cognitive set. This modification is consistent with the traditional interpretation of set-shifting: shifting the subjects' set away from the previously relevant dimension and refocusing their set on the previously irrelevant dimension (Milner, 1963; Dias *et al.*, 1997).

The transient inferior prefrontal activation was reproducibly observed even when the subjects shifted the cognitive set without trial and error in the instruction condition. This activation was not contaminated by residual working memory components related to maintenance of current dimension or sorting of card stimuli, because event-related fMRI subtracted out such activity. Therefore, this observation suggests that the inferior prefrontal area comprises critical foci for the set-shifting ability, consistent with neuropsychological studies of cognitive set-shifting in humans (Milner, 1963) and monkeys (Passingham, 1972; Dias *et al.*, 1996, 1997). The involvement of these areas in prefrontal inhibitory functions has also been suggested by human functional neuroimaging studies (Paus *et al.*, 1993; Taylor *et al.*, 1997; Konishi *et al.*, 1998a) and lesion studies in monkey (Butter, 1969; Iversen and Mishkin, 1970; Rushworth *et al.*, 1997). Therefore, the activity in the instruction condition can be interpreted as reflecting cognitive processes underlying set-shifting, as contrasted with working memory. On the other hand, the transient activity in the instruction condition can also reflect updating of the contents of working memory (Funahashi and Kubota, 1994). Although the present study does not provide sufficient information to distinguish whether the inferior prefrontal activity reflects set-shifting or updating of working memory content, it seems natural to think that updating of working memory content and shifting of cognitive set have similar cognitive aspects in common. Thus we suggest that these areas update temporarily maintained internal states such as working memory content and cognitive set (Konishi *et al.*, 1999).

We observed additional activation when the subjects shifted cognitive set by trial and error in the original condition, as compared to set-shifting without trial and error in the instruction condition (Fig. 4C). To exclude the possibility that the additional activity is derived from the longer duration of neural activity underlying set-shifting, the time to completion of set-shifting was adjusted between the original and instruction conditions, and the difference was still significant (Fig. 4D). Thus, it follows

that the transient activity was enhanced by the working memory load. This working memory component would be equivalent to 'second-order' working memory (Goldman-Rakic, 1987) that provides correct response. This working memory may also contribute to the selection of currently relevant information (Rushworth and Owen, 1998); in this case, a new appropriate dimension.

Spatial Overlap of the Areas Activated in the WCST and the Working Memory Task

We successfully replicated the inferior prefrontal activation reported by previous PET and fMRI studies of working memory (Fig. 5) (Jonides *et al.*, 1993; Petrides *et al.*, 1993; McCarthy *et al.*, 1994; D'Esposito *et al.*, 1995; Baker *et al.*, 1996; Courtney *et al.*, 1996, 1997; Dehaene *et al.*, 1996; Fiez *et al.*, 1996; Cohen *et al.*, 1997; Klingberg *et al.*, 1997; Prabhakaran *et al.*, 1997). We further demonstrated the spatial overlap between the inferior prefrontal areas activated at the time of dimensional changes of the WCST and those activated by the working memory task (Fig. 5). This result ensures that the research results regarding the inferior prefrontal areas in the previous studies of working memory tasks can be used to characterize the inferior prefrontal areas of the WCST in this study. In particular, the event-related fMRI studies of working memory tasks by Cohen *et al.* (Cohen *et al.*, 1997) and Courtney *et al.* (Courtney *et al.*, 1997) reported a composite pattern of sustained and transient activation in the inferior prefrontal areas. This suggests that the activation reflects both working memory and some other cognitive functions, consistent with our results of the concurrent involvement of these areas in working memory for the trial-and-error and set-shifting function. Taken together, these results suggest that the same areas in the inferior prefrontal cortex implement both cognitive set-shifting and working memory to support flexible adaptation to changing environments.

Notes

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