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Cerebral activation during performance of a card sorting test

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Summary

The Wisconsin Card Sorting Test (WCST) is used clinically for evaluating frontal lobe function, but there is some controversy as to its specificity for detecting frontal lobe damage. To investigate the cerebral regions essential to the performance of the Card Sorting Test, we measured the regional cerebral blood flow (rCBF) in 18 normal subjects by PET under the three conditions: (i) during the Modified Card Sorting Test (MCST); (ii) during a matching-to-sample (MTS) task, based on the MCST, but with selective attention to one of three stimulus categories (colour, number or shape) as a control to cancel the effects of maintenance of sets in the MCST; (iii) under resting conditions as overall control. When rCBF during the MCST was compared with that during each MTS task separately, significant activations were observed during the MCST in the left or bilateral dorsolateral prefrontal cortex (DLPFC), bilateral inferior parietal lobes, left superior occipital gyrus and left cerebellum. Compared with all the MTS tasks inclusively, significant increase in rCBF was detected during the MCST in the bilateral DLPFC, inferior parietal lobes, striate cortex, cerebellum and left occipital cortex. These results suggest the involvement of the DLPFC and other related areas such as the inferior parietal cortex in the execution of the MCST, and may help explain why a variety of brain lesions can result in impaired performance on the Card Sorting Test.

Keywords: Card Sorting Test; prefrontal; maintenance of sets; attention; PET

Abbreviations: DLPFC = dorsolateral prefrontal cortex; MCST = Modified Card Sorting Test; MTS = matching-to-sample; rCBF = regional cerebral blood flow; WCST = Wisconsin Card Sorting Test

Introduction

Since the original report by Grant and Berg (1948), the WCST and its modified simple version, the MCST (Nelson, 1976) have been used as a means of assessing abstract reasoning, particularly the ability to conceptualize abstract categories and to shift cognitive sets according to changing contingencies. Neuropsychological studies suggested that patients with frontal lobe lesions, especially lesions in the DLPFC, show greater impairment on the WCST than do patients with lesions in other areas (Milner, 1963; Drewe, 1974; Robinson *et al.*, 1980; Arnett *et al.*, 1994). Accordingly, the WCST has been applied as a test of frontal lobe function in a variety of patient populations. However, the specificity of the test for prefrontal cortex function has recently been questioned in some reports (Wallesch *et al.*, 1983; Grafman *et al.*, 1990; Anderson *et al.*, 1991; van den Broek *et al.*, 1993).

Several neuroimaging techniques, though principally ^{133}Xe inhalation and single photon emission tomography, have been used to investigate cerebral activation during performance of the WCST in normal subjects and in neuropsychiatric patients, particularly those with schizophrenia. It has been noted that in normal subjects the DLPFC is activated more during the performance of the WCST than during the resting state or during simple sensorimotor control task such as the number-matching task (Weinberger *et al.*, 1986; Berman and Weinberger, 1990; Rezai *et al.*, 1993; Parellada *et al.*, 1994; Rubin *et al.*, 1994; Berman *et al.*, 1995). However, when the objective is to explore the brain regions participating specifically in the performance of the WCST, it is doubtful whether the resting state serves as an appropriate control condition, because the WCST involves complex cognitive and sensorimotor processes.

In their recent neuropsychological studies, Owen and

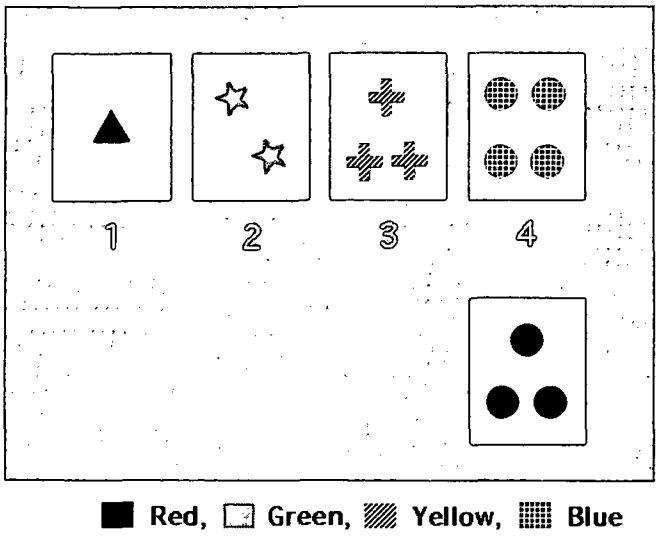

Fig. 1 The scheme of the MCST presented on the monitor. The upper row shows the 'reference' cards which include the three categories, number, colour and shape; below is the 'target' card. The subjects have to match 'target' card to 'reference' cards on the basis of one of the three possible categories.

colleagues (Owen *et al.*, 1991, 1993) observed that patients with frontal lobe lesions showed selective impairment in their ability to shift the response set to a previously irrelevant dimension (extradimensional set shift) but not in their ability to shift attention to new exemplars of a previously relevant dimension (intradimensional set shift). Extradimensional set shift is analogous to shifting of sets involved in WCST, and is, in fact, a core component of the WCST. Likewise, intradimensional set shift is analogous to maintenance of sets. To investigate the essential brain regions for performance of the WCST in normal subjects, we measured the rCBF during the Card Sorting Test and the control tasks using PET. We designed our studies within several specific constraints. First, to reduce the ambiguity of the task and the anxiety and confusion of the subjects, we used the card sets of the MCST (Nelson, 1976). Secondly, during the MCST, the subjects had to maintain sets according to one of the three categories consisting of number, colour and shape and shift the dimensional set according to the feedback responses. Therefore, to cancel the effect of maintenance of sets, we used the MTS tasks with selective attention to a single category as control tasks for comparison with the MCST. Finally, as it is thought that the focusing of attention on different categories would activate different brain areas, we divided the subjects into three subgroups according to the category chosen for the control task, and compared the results among these subgroups. Thereafter, to confirm the cerebral regions mainly responsible for performance of the MCST, we compared the rCBF on the composite for all the MTS tasks with that during the MCST.

Subjects and methods

Subjects

Eighteen right-handed male subjects (mean age 24.7 years, range 21–35 years) took part in the study. All subjects were fully informed as to the nature of the study, and written consent was obtained from each volunteer under the guidance of the Ethics Committee of Kyoto University Faculty of Medicine. All subjects had the education level of 16 years or more of formal education. Subjects were screened for a past as well as present history of neurological, psychiatric or other medical problems.

Activation tasks

For this study we used a computerized version of the MCST, which was written in BASIC for a PC9801 computer (Nihon Electric Co., Tokyo, Japan) (Fig. 1). The subjects were instructed to match 'target' card to 'reference' stimuli on the basis of one of the three possible categories; number, colour or shape. The correct sorting principle changed in a prescribed way of which the subject was not informed. The subjects had to determine which one was correct based just on the feedback, which was displayed on the monitor, and indicated whether each response was right or wrong. When the subject maintained a correct progression through six trials, the principle was changed without warning, and the subject had to search for the new correct category.

The MTS task with selective attention was designed to be similar to MCST in visual stimulation, by employing the same set of cards as used in the MCST, with the same motor response, but not requiring the attentional set shift or rule learning. Subjects simply matched the target card to one of the four reference stimuli by maintaining attention to one of the three categories. The category to which the subject had to attend was indicated just before the scan. The subjects were divided into three subgroups according to the category on which they were asked to focus (colour, number or shape group; each consisting of six subjects). There were no significant differences in age (mean±SD) among the subgroups (number, 22.2±1.2 years; colour, 26.5±2.9 years; shape, 25.5±5.7 years) as revealed by ANOVA.

Stimuli were presented on a monitor placed 60 cm in front of the subject. The subjects responded to each trial by pushing one of four buttons fixed on a plate which was held in the right hand. The buttons were arranged in an array corresponding to the layout of visual stimuli on the monitor. Prior to the PET scan, the subjects were trained in this mode of response until they could press appropriate buttons without difficulty. The tasks were started 30 s prior to the start of scanning and continued until 72 cards had been sorted. The subjects were encouraged to work as efficiently and rapidly as possible, but otherwise were allowed to proceed at their own pace. The MCST performance was scored using Heaton's criteria (Grant and Berg, 1981) except that 'failure to maintain set' was calculated as the number of times in the test that

the subject made at least three correct responses successively, but failed to get the six that are required to complete the category. Resting condition was also scanned by having the subject simply look at the same visual stimuli as those used in the MCST on the monitor with no response.

PET scanning

Six sets of rCBF images were obtained for each subject under three conditions: (i) at rest (A); (ii) during one of the MTS tasks (B); (iii) during the MCST (C). The sequence ABCCBA or ACBBCA was used in a counterbalanced way across the subjects to avoid order and habituation effects. The PCT-3600W system (Hitachi Medical Co., Tokyo, Japan) was used for acquisition of PET scans (Sadato *et al.*, 1993). This system simultaneously acquired 15 slices with a centre-to-centre distance of 7 mm. All scans were obtained at a resolution of 7.5 mm full width half-maximum in the transaxial direction and 6.5 mm in the axial direction. Subjects were positioned with the orbitomeatal line parallel to the detector rings, and headholders were used to limit head movement. A venous line was inserted into the antecubital vein of the left arm for tracer injection. After a transmission scan was obtained, the subject received a bolus injection of 925–1110 MBq (25–30 mCi) of $H_2{}^{15}O$ for each scanning. Scan data were acquired for 120 s after the injection, and the transaxial images, which represented the distribution of rCBF, were reconstructed with corrections for attenuation.

Data analysis

The data were analysed with Statistical Parametric Mapping (from the Wellcome Department of Cognitive Neurology, Hammersmith Hospital, London, UK) implemented in Matlab (Mathworks Inc., Natick, Mass., USA) (Friston *et al.*, 1991, 1994; Worsley *et al.*, 1992) on the workstation (Sun SPARC station 5, Sun Microsystems Co., Mountain View, Calif., USA).

The original 15-slice scans were interpolated to 43 planes with approximately cubic (2.0×2.0×2.33 mm) voxels. The scans from each subject were realigned using the first image as a reference. Following realignment, all images were transformed into a stereotactic standard space by Talairach and Tournoux (Talairach and Tournoux, 1988), and the images were smoothed using an isotropic Gaussian filter. The stereotactically normalized rCBF images were then adjusted for individual differences in global blood flow using an analysis of covariance (Friston *et al.*, 1995). Finally, within-group between-task comparisons were performed on a pixel-by-pixel basis for all voxels common to all subjects. The threshold was set at $P < 0.001$ or $Z > 3.09$ without correction for multiple comparisons.

To examine the activated areas common to all subgroups during the MTS task and MCST, we also compared the rCBF during all the MTS tasks inclusively with that during the resting condition and that during the MCST. This approach is similar to the one employed in a previous study by Dolan *et al.* (1993), who examined the cerebral areas commonly disturbed in two different diseases. In this analysis, all subjects were regarded as a group irrespective of dimensions, and the scans in each subject were divided into three conditions: (i) MCST; (ii) the MTS task with maintenance of set; (iii) rest. Then, MCST was contrasted with the MTS task, and the MTS task with rest.

Table 1 *The MCST performance in three subgroups divided according to the categories that were attended to in the MTS tasks*

Group	Colour	Number	Shape
Total errors	19.9 (11.1)	17.0 (4.1)	19.2 (6.9)
Total correct	52.1 (11.1)	55.0 (4.1)	52.8 (6.9)
Categories	7.8 (2.4)	7.9 (1.2)	7.8 (1.7)
Perseverative errors	4.1 (6.3)	2.6 (2.4)	3.9 (4.6)
Nonperseverative errors	14.3 (3.1)	13.4 (1.9)	14.8 (2.3)
% Perseverative errors	0.06 (0.09)	0.04 (0.03)	0.05 (0.06)
Trial to first category	7.0 (1.1)	7.8 (2.6)	9.9 (9.8)
% Conceptual responses	0.69 (0.20)	0.73 (0.07)	0.71 (0.11)
Failure to maintain set	0.30 (0.67)	0.92 (0.99)	0.83 (0.72)
Unique responses	1.5 (2.7)	1.0 (2.1)	0.5 (0.9)
Learning to learn	−0.18 (0.25)	−0.15 (0.19)	−0.12 (0.24)

Values = means (SD) of the scores.

Results

Cognitive performance

The subjects generally performed well on the MCST (Table 1). The subgroups showed similar performance levels on the MCST [$F(2,31) = 0.335$, $P = 0.71$, by repeated ANOVA].

CBF increase on the MTS tasks

Each MTS task versus rest (Table 2)

During the number matching task, rCBF was significantly increased in the left primary motor and premotor cortex, right premotor cortex, left inferior parietal lobule, right precuneus and right cerebellum. These areas were also activated in the colour- and shape-matching tasks. In addition, during the colour-matching task, there was significant rCBF increase in the right fusiform gyrus and collateral sulcus, left lingual gyrus, and left superior and right inferior occipital gyri. During the shape-matching task, there were significant activations in the right middle occipital gyrus and collateral sulcus, right inferior and middle temporal gyri, right primary visual cortex, bilateral superior occipital gyri and left cerebellum. In addition, slight activation was seen in the right occipitoparietal junction and the left frontal pole. In the colour- and shape-matching tasks, rCBF was also increased in the cingulate gyrus and the medial frontal gyrus.

Table 2 *Activated cerebral areas during the MTS task with selective attention to each category*

Number						Colour						Shape					
Area	(BA)	*x*	*y*	*z*	*Z*	Area	(BA)	*x*	*y*	*z*	*Z*	Area	(BA)	*x*	*y*	*z*	*Z*
L sulcus centralis	(4)	−40	−18	48	4.97	L gyrus precentralis	(4)	−26	−12	44	4.40	L gyrus precentralis	(4)	−32	−22	52	4.45
L gyrus precentralis	(6)	−52	−2	28	3.61		(6)	−38	−6	44	5.09			−30	−16	44	3.19
R gyrus precentralis	(6)	24	−12	48	3.98	L gyrus frontalis medialis	(6)	−12	−2	48	4.59	L gyrus frontalis medius	(6)	−22	−8	56	4.40
						R gyrus frontalis medius	(6)	32	−6	48	4.07			−22	−4	44	3.89
												L gyrus frontalis medialis	(6)	−4	−4	52	3.42
												R gyrus precentralis	(6)	26	−12	40	3.93
														34	−14	48	3.53
														26	−14	52	3.43
L lobulus parietalis inferior	(40)	−50	−32	44	3.65	L gyrus supramarginalis	(40)	−42	−48	36	3.72	L lobulus parietalis inferior	(40)	−36	−34	44	4.71
		−36	−48	44	3.32	L lobulus parietalis inferior	(40)	−40	−40	40	3.29	L gyrus supramarginalis	(39)	42	−54	36	3.58
		−36	−38	48	3.57	R precuneus	(31)	24	−54	36	3.41	R precuneus		16	−68	32	3.63
Precuneus	(7)	0	−56	36	3.90												
R precuneus	(31)	14	−64	36	4.35												
		12	−58	24	3.33												
R cerebellum		18	−50	−28	3.63	R cerebellum		26	−60	−24	5.15	L cerebellum		−30	−62	−24	4.20
		28	−58	−28	3.36			36	−68	−16	4.93			−24	−70	−28	4.27
		48	−70	−28	3.51			34	−60	−20	4.87	R cerebellum		20	−74	−24	4.40
		10	−56	−24	3.41									24	−56	−16	4.30
														10	−70	−20	4.07
												cerebellar vermis		0	−70	−24	4.80
						R gyrus cinguli	(24)	34	16	4	3.25	L gyrus cinguli	(23)	−20	−26	32	5.22
													(31)	−22	−18	40	4.70
													(24)	−12	2	36	3.40
R gyrus occipitalis superior	(19)	28	−64	32	3.19	L gyrus occipitalis superior	(19)	−26	−64	36	4.52	R sulcus collateralis		18	−68	−12	5.32
						L gyrus occipitalis inferior	(18)	−28	−84	−4	3.53	R gyrus temporalis medius	(37)	34	−60	4	4.24
						L gyrus lingualis	(18)	−8	−72	−12	3.27	R gyrus temporalis inferior	(37)	42	−60	−8	3.57
						R sulcus collateralis		14	−80	−12	3.99	R gyrus occipitalis medius	(19)	38	−72	−8	3.27
						R gyrus fusiformis	(18)	8	−74	−12	3.79	R gyrus occipitalis superior	(19)	30	−70	36	3.25
								30	−82	−12	3.60	L gyrus occipitalis superior	(19)	−24	−76	36	3.34
						R nucleus subthalamicus		10	−12	−4	3.48	L gyrus temporalis superior		−28	−50	20	4.65
						L gyrus postcentralis		−26	−28	44	3.24	R primary visual cortex	(17)	14	−80	12	3.64
												R parietooccipital junction	(19)	36	−64	40	3.61
												L gyrus frontalis superior	(10)	−24	60	−4	3.89

BA = Brodmann area; R = right, L = left; *x*, *y*, *z* = coordinates as in Talairach's atlas; *Z* = *Z* score that shows significance of cerebral blood flow change; threshold: $P < 0.001$ or $Z > 3.09$

The composite of all the MTS tasks versus rest (Table 3)

When the composite rCBF for all the MTS tasks was compared with that in the resting condition, significant activation was revealed during the MTS tasks in the left primary motor and premotor cortex, right premotor cortex, left supplementary motor area, bilateral inferior parietal lobule, right precuneus, bilateral cerebellum, cingulate gyrus and right occipital cortex.

CBF increase during the MCST (Fig. 2, Table 4)

The MCST versus the number-matching task

Compared with the rCBF during the number-matching task, the rCBF during the MCST was significantly increased in part of the left DLPFC (middle and inferior frontal gyri, Brodmann areas 9 and 45), the more rostral part of bilateral middle frontal gyrus (area 10), left inferior parietal lobule, right intraparietal sulcus and angular gyrus, bilateral ventral occipital cortices, left lateral occipital cortex, left parieto-occipital sulcus, right parahippocampal gyrus, and the left cerebellum.

The MCST versus the colour-matching task

Compared with that during the colour-matching task, the rCBF during the MCST was significantly increased in part of the left DLPFC (middle frontal gyrus, area 9), the more rostral part of left superior frontal gyrus (area 11), left intraparietal sulcus, right inferior parietal lobule, left middle temporal gyrus, right premotor cortex, left superior occipital gyrus and the left cerebellum.

The MCST versus the shape-matching task

When the rCBF during the MCST was compared with that during the shape-matching task, there was significant activation during the MCST in part of the bilateral DLPFC (middle frontal gyri, areas 9 and 46), the more rostral part of left middle frontal gyrus (area 10), left inferior parietal lobule, right supramarginal gyrus, bilateral superior occipital gyri, left visual cortex, right inferior temporal cortex, parieto-

Table 3 *Activated cerebral areas in the composite for all the MTS tasks compared with those in the resting condition*

Area	(Brodmann area)	*Z* score	*x*, *y*, *z* coordinates in Talairach atlas		
L. sulcus centralis	(4)	6.52	−28	−20	44
L. gyrus precentralis	(6)	4.96	−30	−8	44
R. gyrus precentralis	(6)	5.33	26	−10	48
L. gyrus frontalis medialis	(6)	5.91	−14	−2	48
L. gyrus angularis	(39)	4.88	−26	−58	32
L. gyrus supramarginalis	(40)	5.61	−40	−48	36
L. lobulus parietalis inferior	(40)	5.93	−40	−44	40
L. sulcus postcentralis		6.91	−40	−30	44
R. lobulus parietalis inferior	(40)	3.15	42	−48	32
R. precuneus	(31)	5.42	22	−66	36
R. cerebellum		7.41	22	−52	−28
		6.88	32	−60	−16
		6.20	4	−70	−20
L. cerebellum		4.34	−44	−60	−28
		3.54	−32	−54	−28
L. gyrus cinguli	(32)	3.42	−12	20	32
R. gyrus cinguli	(23)	3.62	4	−26	24
R. gyrus fusiformis	(19)	5.90	16	−74	−12
R. gyrus occipitalis medius	(19)	4.04	26	−86	8

R = right, L = left; *x*, *y*, *z* = coordinates as in Talairach's atlas; threshold: $P < 0.001$ or $Z > 3.09$.

occipital sulcus and bilateral precuneus, and in the left cerebellum.

The MCST versus the composite of all matching-to-sample tasks (Fig. 2D, Table 5)

In this comparison, the rCBF during the MCST was significantly increased in the bilateral DLPFC (areas 9 and 46), the more rostral part of bilateral superior and middle frontal gyri (areas 10 and 11), bilateral inferior parietal lobules, parieto-occipital sulcus, left medial frontal gyrus, left dorsolateral and ventrolateral occipital cortex, bilateral primary visual cortices, and the cerebellum.

Discussion

In all three categories of the MTS tasks employed in the present study, there were significant rCBF increases seen in the motor cortices including the primary motor, lateral premotor and supplementary motor areas, in the inferior parietal lobe, precuneus and the cerebellum. Contribution of these areas to the MTS tasks was confirmed by the result in the comparison of the composite for the MTS tasks with the resting condition. These areas may subserve the motor responses in connection with visuospatial cues (Colebatch *et al.*, 1991; Deiber *et al.*, 1991; Grafton *et al.*, 1992). As was revealed in the previous PET studies (Corbetta *et al.*, 1991; Gulyas and Roland, 1994), our results also showed that attention to colour was correlated with activation in the ventro-occipital and left superior occipital cortex, and attention to shape with activation in the inferior occipitotemporal cortex. The anterior cingulate gyrus is also an important part of the attention system (Pardo *et al.*, 1990; Posner and Petersen, 1990; Heinze *et al.*, 1994), and it was activated in the colour- and shape-matching tasks. These results suggest that, in spite of overlap in the major activated areas, selective attention to different categories may activate different cerebral areas. Therefore, when we attempt to use the MTS tasks as a control condition against the Card Sorting Test, it may be appropriate to take the influence of these differences produced by attention into account.

When the rCBF during the MCST was compared with that during each MTS task separately, we found some different patterns of rCBF activation. Despite this variety, the MCST usually activated part of left or bilateral DLPFC (especially area 9 in the middle frontal gyri), the more rostral part of the prefrontal cortex (areas 10 and 11), bilateral inferior parietal lobes, left superior occipital gyrus and the left cerebellum. Although the observed activation in the DLPFC during the MCST is consistent with the results of previous neuroimaging studies (Weinberger *et al.*, 1986; Rezai *et al.*, 1993; Parellada *et al.*, 1994; Rubin *et al.*, 1994; Berman *et al.*, 1995), the present results suggest that not only the DLPFC, but also some other areas, such as the inferior parietal lobes, are involved in the essential cognitive processing during the MCST. Electrophysiological studies have revealed that right parietotemporal and prefrontal activity varies when the sort criterion is changed during the performance of the WCST (Silberstein *et al.*, 1995). The present results, while confirming the importance of the DLPFC in performing the MCST, may offer an explanation for the finding that brain lesions in a variety of loci other than the DLPFC can also result in impaired performance on the Card Sorting Test (Grafman *et al.*, 1990; Anderson *et al.*, 1991; van den Broek *et al.*, 1993; Upton and Corcoran, 1995).

Recently, Berman *et al.* (1995), using PET, studied

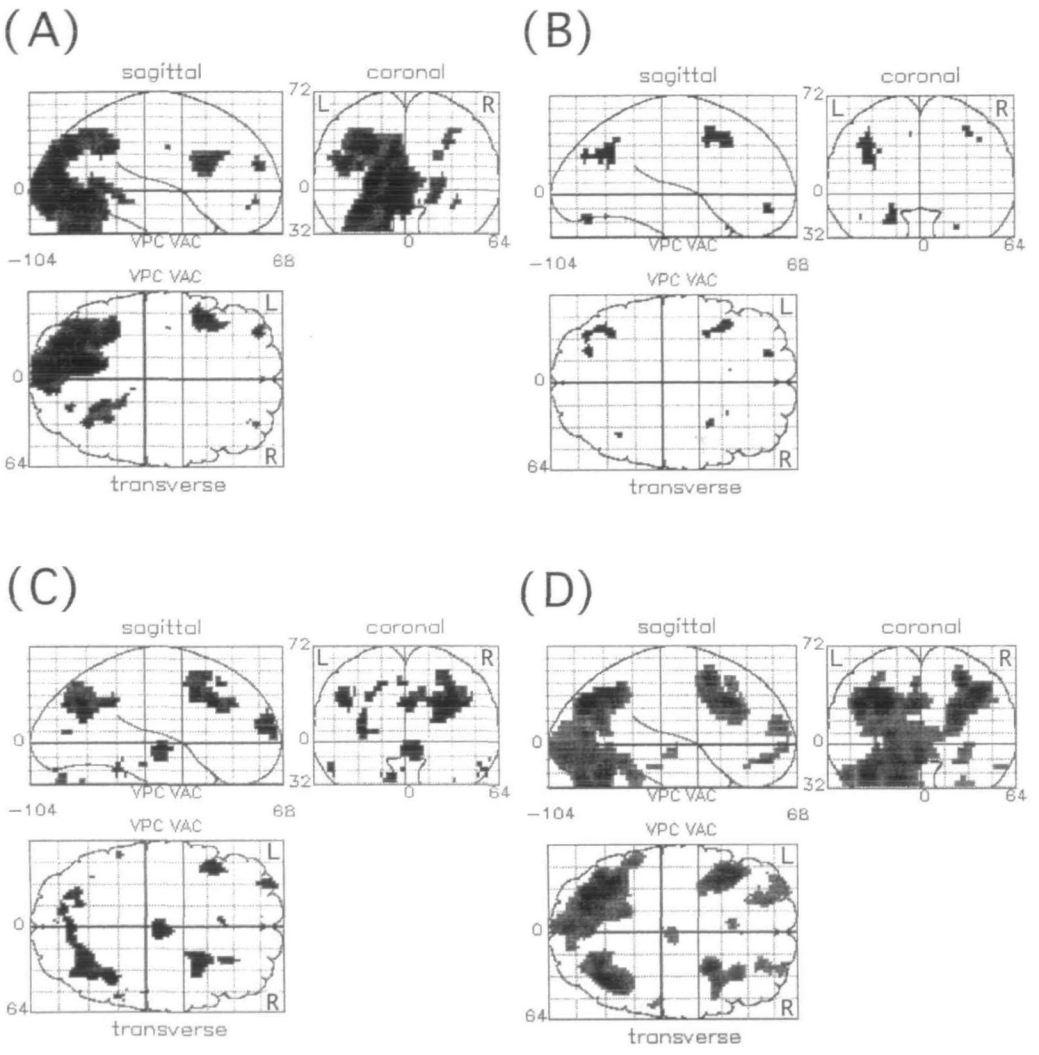

Fig. 2 The statistical parametric mapping projections of comparison of the MCST with the MTS tasks (significance level is $P < 0.001$). (**A**) MCST versus number-matching task ($n = 6$); (**B**) MCST versus colour-matching task ($n = 6$); (**C**) MCST versus shape-matching task ($n = 6$). (**D**) Comparison of the MCST with the composite for all the matching-to-sample tasks ($n = 18$). *See* Tables 4 and 5 for measured values of coordinates.

cerebral activations during performance of the WCST, and reported activations in the prefrontal, parietal and occipitotemporal cortices. They used the simple card matching task as their control task against WCST, and found considerable activations in the orbitofrontal cortex as well as in the DLPFC. In contrast, we found little activation in the orbitofrontal cortex during the MCST when we evaluated separately against the subgroups for each MTS task, as shown in Fig. 2. Even when we treated all the subgroups as a whole, we found only slight activations in the orbitofrontal cortex as contrasted with relatively large activations in the DLPFC. This difference may result from the utilization of a portion of the cognitive process for maintaining sets. During the MTS tasks in the present study, the subjects had to maintain attention on one relevant category throughout the test, and inhibit attention shift to irrelevant categories. This process was scarcely involved in the control task used by Berman *et al.* (1995). On the other hand, the subjects in the present study needed the ability to shift attention between sets, as well as to maintain attention on a particular set, during the performance of the MCST. Therefore, the reduction of activations in the orbitofrontal cortex noted in our study suggests that the orbitofrontal cortex may play a role in the process of maintenance of sets during the MCST. At the probability level of $P < 0.05$, we found activations in the orbitofrontal regions during the MTS tasks: in the left orbitofrontal cortex during the shape-matching task ($x = -20$, $y = 34$, $z = -16$, in Talairach's coordinates) and in the frontopolar cortex during the number-matching task ($x = 10$, $y = 64$, $z = -4$). A study of patients with orbitofrontal lesions also supports this assumption that the orbitofrontal region may play a role in

Table 4 *Activated cerebral areas during the MCST) compared with each MTS task*

MCST versus number-matching task						MCST versus colour-matching task						MCST versus shape-matching task					
Area	(BA)	*x*	*y*	*z*	*Z*	Area	(BA)	*x*	*y*	*z*	*Z*	Area	(BA)	*x*	*y*	*z*	*Z*
L gyrus frontalis medius	(9)	−38	28	28	3.52	L gyrus frontalis medius	(9)	−38	16	40	3.58	L gyrus frontalis medius	(9)	−44	18	32	4.82
	(10)	−34	50	20	3.90			−34	4	36	3.14		(10)	−32	60	12	3.87
L gyrus frontalis inferior	(45)	−44	14	20	4.61	L gyrus frontalis superior	(11)	−20	48	−12	3.28	L gyrus frontalis medialis	(6)	−4	26	44	3.56
R gyrus frontalis medius	(44)	30	44	−12	3.28	R gyrus frontalis medius	(6)	30	4	48	3.28	R gyrus frontalis medius	(9)	30	8	36	4.64
	(10)	32	48	−8	3.26								(9/46)	26	30	28	3.83
													(6/8)	24	8	52	3.73
L lobulus parietalis inferior	(40)	−36	−50	32	4.87	L intraparietal sulcus		−36	−64	36	3.47	L precuneus	(7)	−16	−74	44	3.53
		−34	−58	44	3.74	R lobulus parietalis inferior	(40)	40	−58	40	3.11	L lobulus parietalis inferior	(40)	−36	−62	40	3.15
L intraparietal sulcus	(19/40)	−26	−62	40	4.05							R gyrus supramarginalis	(39)	40	−48	28	3.72
L sulcus parieto–occipitalis		−8	−86	28	4.44							R precuneus	(31)	24	−68	24	4.50
		−8	−76	36	4.08								(7)	10	−78	40	3.33
R sulcus intraparietalis	(40/7)	32	−64	44	3.51												
R gyrus angularis	(39)	30	−52	36	3.76												
L gyrus occipitalis superior	(19)	−26	−78	32	4.84	L gyrus occipitalis superior	(19)	−34	−80	28	3.29	L gyrus occipitalis superior	(19)	−24	−74	36	3.40
L gyrus occipitalis medius	(19)	−26	−84	4	4.69							L primary visual cortex	(17)	−22	−78	8	3.57
	(18)	−18	−84	20	4.47							R gyrus occipitalis superior	(19)	26	−70	32	4.39
L cerebellum		−14	−66	−24	4.31	L cerebellum		−22	−78	−20	3.80	L cerebellum		−10	−80	−28	3.38
		−36	−72	−24	4.05									−18	−84	−24	3.14
		−20	−72	−28	3.84												
L cuneus	(18)	−6	−102	4	5.41	L gyrus temporalis medius	(39)	−34	−62	24	3.43	sulcus parieto–occipitalis	(18)	0	−78	28	3.76
R cuneus	(18)	20	−80	24	3.27			−38	−68	28	3.39	R gyrus temporalis inferior	(20)	50	−28	−16	3.29
L gyrus lingualis	(18)	−8	−68	−4	5.06									54	−48	−20	3.21
		−4	−92	−8	4.88							R gyrus temporalis medius	(21)	56	−42	−12	3.16
L gyrus fusiformis	(19)	−28	−76	−8	4.34							L gyrus temporalis inferior	(20)	−52	−44	−20	3.22
		−32	−66	−12	4.45							R nucleus ruber		4	−18	−8	4.52
R gyrus lingualis	(18)	18	−56	4	4.12												
R gyrus parahippocampi		18	−42	−4	3.86												
L gyrus precentralis	(6)	−36	−10	32	3.30												

BA = Brodmann area; R = right, L = left; *x*, *y*, *z* = coordinates as in Talairach's atlas; *Z* = *Z* score that shows significance of cerebral blood flow change; threshold: $P < 0.001$ or $Z > 3.09$.

the maintenance of sets during WCST (Stuss *et al.*, 1983). Therefore, the relatively large activations in the DLPFC during the MCST in the present study may also suggest that the DLPFC may be more important in other cognitive processes, such as shifting of sets or rule learning during the MCST, than in the maintenance of sets.

Some previous neuropsychological and neuroimaging studies have disclosed a tendency for left DLPFC dominance, as opposed to the right DLPFC, on WCST performance (Milner, 1963; Drewe, 1974; Berman and Weinberger, 1990; Grafman *et al.*, 1990). However, there are also several reports from behavioural studies that there is no right–left difference on WCST performance (Robinson *et al.*, 1980; Anderson *et al.*, 1991). We found left dominant activation in the DLPFC when we used the number- or colour-matching task as the control for the MCST. On the other hand, when we compared the MCST with the shape-matching task, we found little evidence of lateralized activation in DLPFC. Therefore, these differences seem to be due to differences in the nature of each control task employed. These three MTS tasks are different only in terms of the categories to be attended to, but this difference influences the results for lateralization of the physiological activation during the MCST. However, these different results concerning lateralization may be due, in part, to the relatively small number of the samples in each subgroup. The fact that apparent bilateral DLPFC activity was observed during the MCST in the analysis of the composite for three subgroups suggests that CBF was increased in the bilateral DLPFC during the performance of the MCST compared with that during the MTS tasks, perhaps, even in the number and colour subgroup. Therefore, the present findings suggest that the results of these activation studies have to be carefully interpreted if the identification of functional lateralization location is to be based on a brain area identified by the subtractive approach.

The present study showed that during the MCST, the prefrontal cortex, parietal association cortex and the cerebellum are frequently activated in comparison with the various control conditions, and confirmed the importance of the DLPFC and involvement of other related regions during the performance of the MCST. These data may provide basic information useful in interpreting the results of behavioural studies of patients with frontal or nonfrontal lesions. It can be postulated that, by the comparison of the MCST with the MTS tasks adopted in the present study, the effects of maintenance of sets may be cancelled out, and thus the main factors contributing to the resultant activations are shifting of sets and rule learning. However, the temporal resolution of the PET technique did not allow us to further isolate the cognitive processes involved in the MCST. Therefore, it will be necessary to perform investigations using additional approaches, such as electrophysiological studies and correlation analysis of rCBF

Table 5 *Activated cerebral areas during the MCST compared with those during the composite for all the matching-to-sample tasks*

Area	(Brodmann area)	*Z* score	*x*, *y*, *z* coordinates in Talairach atlas		
Frontal cortices					
L gyrus frontalis medius	(9)	5.09	−42	22	32
		4.58	−36	12	32
		3.88	−36	2	40
	(11)	3.34	−26	34	−16
	(10)	3.58	−26	54	−8
		3.78	−32	54	12
L gyrus frontalis superior	(11)	3.99	−22	48	−12
L gyrus frontalis medialis	(6)	3.78	−6	20	44
R gyrus frontalis medius	(9)	4.02	36	12	32
	(9/46)	3.96	30	24	28
	(10)	3.48	28	50	−8
R gyrus frontalis inferior	(9/44)	3.45	48	10	32
R gyrus frontalis superior	(8)	4.96	26	6	48
	(11)	3.66	24	42	−12
Parietal cortices					
L lobulus parietalis inferior	(40)	3.74	−40	−54	40
L intraparietal sulcus		5.74	−34	−62	36
R lobulus parietalis inferior	(40)	5.29	36	−64	40
R sulcus parieto-occipitalis		4.73	22	−70	24
Cerebellum					
L cerebellum		5.12	−18	−78	−28
		4.84	−38	−68	−20
R cerebellum		3.59	26	−80	−28
		3.24	32	−72	−28
Occipital cortices					
L gyrus occipitalis superior	(19)	6.33	−26	−78	32
L sulcus parieto-occipitalis	(19)	4.46	−4	−78	32
L gyrus occipitalis medius		4.54	−22	−78	8
L gyrus lingualis	(18)	4.62	−4	−90	−8
L gyrus fusiformis	(19)	4.55	−20	−74	−8
L primary visual cortex	(17)	3.70	−8	−90	8
R primary visual cortex	(17)	3.56	10	−88	8
R nucleus ruber		3.56	4	−18	−4

R = right, L = left; *x*, *y*, *z*, = coordinates as in Talairach's atlas; threshold: $P < 0.001$ or $Z > 3.09$.

activations with behavioural parameters, in order to further clarify the cognitive components active during performance of the MCST.

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