

Research report

Functional asymmetry of human prefrontal cortex in verbal and non-verbal episodic memory as revealed by fMRI

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Abstract

Functional neuroimaging studies have demonstrated preferential involvement of bilateral prefrontal cortex during episodic memory encoding and retrieval. The aim of the present study is to address the question whether left prefrontal model for encoding holds when highly non-verbal material is used, and which region of the brain is critically related to successful retrieval. To do this, seven normal subjects were investigated using functional magnetic resonance imaging (fMRI) during encoding and retrieval of word and checkerboard pattern. Our results revealed that word encoding activated the left prefrontal cortices and right cerebellum, whereas pattern encoding activated the bilateral middle frontal gyrus, superior parietal lobule, premotor area, and occipital visual cortex. Word-specific activation was found in the ventral prefrontal cortices, and pattern-specific activation located in the right dorsal prefrontal cortex. Conjunction analysis during encoding of word and pattern showed that activity in the left dorsal prefrontal cortex and the right cerebellum might relate to common neural network for encoding regardless of the type of material. Finally, the present study demonstrates strong association between the left ventral prefrontal cortex and retrieval success for word. The evidence, that both encoding and retrieval of words activated the left ventral prefrontal cortex, indicates that this area is involved in active and strategic operation of the mnemonic representation. A lack of the right prefrontal activation during retrieval was interpreted as that activity in this region might relate to retrieval effort rather than success. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Word; Checkerboard pattern; Encoding; Retrieval; Conjunction analysis

1. Introduction

Episodic memory enables an individual to remember his or her own experienced past in subjective time. Neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are useful tools for investigation of this memory system in human subjects. The major impact of studies using PET or fMRI has been the evidence for consistent involvement of the prefrontal cortex in episodic memory. Several reviews for the functional neuroanatomy of episodic memory have emphasized activation in prefrontal cortex including Brodmann's area (BA) 9, 10, 45, and 46 during encoding and retrieval of verbal or non-verbal materials [9,10,13,16,32]. Furthermore, it has been reported that there exists functional asymmetry of activation

in the prefrontal cortex during episodic memory, specifically relative increases of regional cerebral blood flow (rCBF) in the left prefrontal area during encoding and in the right prefrontal area during retrieval [49]. However, the left prefrontal activation during encoding may not be surprising given the type of the material presented to subjects to learn. In most cases, subjects were instructed to remember verbal materials during scanning, and semantic processing involves the left hemisphere.

Several PET studies employing the encoding of non-verbal information such as object location, unfamiliar faces, and abstract pictures have shown inconsistent results regarding the functional asymmetry of prefrontal cortex during encoding. Owen et al. [33,34] reported that encoding of object location preferentially activated the left frontal lobe. Grady et al. [18] and Haxby et al. [21] found robust activation in the left prefrontal cortex during face encoding. By contrast, learning of colored geometric patterns activated the bilateral prefrontal cortex, with greater in-

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creases of rCBF in the right hemisphere than in the left hemisphere [40]. Klingberg and Roland [25] reported that the right prefrontal cortex was activated while subjects were learning paired associates of abstract pictures and sounds. In an fMRI study, Kelley et al. [24] demonstrated that lateralization of activation in the dorsolateral prefrontal cortex was material specific, that is left-lateralized during word encoding and right-lateralized during face encoding. Similarly, Wagner et al. [51] reported the right frontal activation during encoding of textures. In sum, there are still arguments with respect to the lateralization of prefrontal activation during encoding of non-verbal materials, and a study using fMRI may provide additional findings on this issue.

On the other hand, involvement of the right prefrontal cortex in episodic retrieval appears to be more consistently found regardless of the material presented during scanning. However, it is still debatable whether right prefrontal activation is associated with successful retrieval. Rugg et al. [41,42] found a positive correlation between rCBF in the right prefrontal area and the proportion of studied items, and significant activation during recognition test for the lists with high proportion of studied words, both indicating strong association with retrieval success. By contrast, Kapur et al. [22] and Nyberg et al. [31] showed, in their PET study using word recognition test, that activation of the right prefrontal cortex was not associated with retrieval success. Similarly, Schacter et al. [45] and Buckner et al. [8] failed to detect a significant difference in the prefrontal activation between hit and false alarm, and between hit and correct rejection, respectively. Finally, Wagner et al. [53] showed that subtraction of unstudied condition from studied condition during retrieval yielded no activation in the right prefrontal cortex. Recent studies show that the right dorsal prefrontal cortex is associated with monitoring processes [9] or retrieval attempt [53] rather than retrieval success. Thus, brain regions specifically activated while subject is making correct response to retrieval cue are still uncertain.

The purpose of our study was to assess whether verbal and non-verbal episodic memory involve differential neural system in human prefrontal cortex, and whether there are common or overlapping areas that are activated by both of them. Second, we aimed to elucidate the relationship between prefrontal activation and successful retrieval. To do this, we used visual presentation of words and checkerboard patterns as verbal and non-verbal materials, respectively. Random checkerboard patterns have been used as stimuli to test non-verbal or visual memory in experimental psychology [1,6]. In previous neuroimaging studies of non-verbal memory [25,40,51], colored stimuli were used, and confounding effects of color processing were expected. Therefore, simple black and white patterns employed in the present study were more suitable to investigate the neural substrate of non-verbal episodic memory when contrasted with verbal materials. The sub-

jects were instructed to encode and retrieve these items in an fMRI block design experiment. In the encoding phase, the subjects studied new items which were presented successively or single items which were presented repeatedly, while in the retrieval phase, the subjects performed yes/no recognition test for previously studied items or new items. We predicted that both verbal and non-verbal encoding processes would activate prefrontal cortex and that word encoding would be predominantly left-lateralized. However, we did not have an a priori hypothesis with regard to the lateralization of activation during encoding of the checkerboard patterns. We thought that our study may provide evidence that a differential neural network is involved in encoding of non-verbal material as compared to verbal material. Finally, we sought to identify brain regions predominantly associated with successful retrieval by subtracting scans for non-studied items from those for studied items.

2. Materials and methods

2.1. Subjects

Eight right-handed healthy volunteers participated in the study after giving written informed consent; however, one subject was excluded from the analysis due to a significant motion artifact. Therefore, we present the data for the remaining seven subjects (three male and four female, mean age 29.9 years, S.D. 5 years). Subjects were excluded if they had medical, neurological, or psychiatric illness or if they were taking medications. Prior to the fMRI experiment, they took part in a practice session of a short version of the task to be performed during the experiment. The study was approved by the ethics committee of the Fukui Medical University.

2.2. Task paradigm

The experiment consisted of verbal and non-verbal sessions, and these sessions were identical except for a type of the material to be memorized (Fig. 1). The verbal

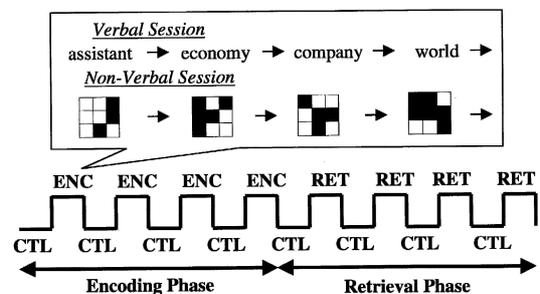


Fig. 1. A schematic illustration of stimuli and temporal organization of the task paradigm (for details, see Section 2). ENC: encoding task condition; RET: retrieval task condition; CTL: control condition. Samples of words presented in verbal session (translated to English words) and checkerboard patterns presented in non-verbal session are illustrated. Each block was 48-s long and comprised eight image acquisitions.

items were selected from a list of three- to five-letter plain Japanese words. Eight study lists, each containing eight different words, with mean frequency and length equalized, were constructed. The words were presented in syllabogram (kana words) because rCBF activation during kana word reading and English word reading is similar [44]. For the non-verbal session, we used 3×3 checkerboard patterns with black and white squares (three to six were filled with black); the location of white and black squares was randomly selected. Patterns that resembled alphabets or symbols were excluded. In behavioural study, the image of 3×3 pattern was processed in a single inspection or eye fixation, but the processing of complex pattern (4×4 or more) took longer and was accompanied by an increase in error [6]. Eight study lists, each containing eight different patterns, with mean number of black squares equalized, were constructed. These words and checkerboard patterns were projected by an LCD projector connected to a personal computer which generated visual stimuli onto a half-transparent screen hung approximately 2 m from the subject's eye. The subject saw the items on the screen through a tilted mirror mounted on the head coil of the scanner. The presentation rate was 6 s/item with 4.5 s duration and 1.5 s interval.

For the verbal and non-verbal sessions, there were 16 condition blocks. The first eight blocks alternated the control task and encoding, and the last eight blocks alternated the control task and retrieval (see Fig. 1). Four study lists were assigned to encoding task conditions, and the remaining four study lists were assigned to retrieval control conditions. Eight different items were successively presented one at a time during each encoding task condition (32 different items during four task conditions), whereas single items (not included in any other list) were repeatedly presented during the encoding control conditions. The instruction to the subjects for the task and control condition was to memorize the items for the subsequent retrieval phase. For the verbal session, subjects were told to memorize words by rehearsing them in their mind. For the non-verbal session, subjects were instructed to memorize the pattern of black squares in each checkerboard. After completion of the encoding phase, a brief instruction for the retrieval phase was visually presented to the subjects. During the retrieval task, items which were studied during the corresponding encoding task condition were randomly presented (items in the first encoding task condition were presented during the first retrieval task condition, and the items in the second encoding task condition were presented during the second retrieval condition, and so on). During the retrieval control condition, all new items were presented. The subjects were told to extend their thumb when they recognize the item as "old" (previously presented) and to extend their index finger when they recognize the item as "new" (not previously presented) by their right hand. The verbal and non-verbal sessions were conducted in two separate fMRI runs, and

the order of the session was alternated across subjects. The order of the lists was also counter-balanced across subjects. The proportion of hits and false alarms during retrieval for words and patterns was subject to ANOVA. In addition, ANOVA on the proportion of correct response in each of the four alternating task cycles during retrieval was computed.

2.3. Image acquisition

In each subject, functional (T_2^* weighted) images, followed by an anatomical (T_1 weighted) image, were acquired with a 1.5-T Horizon MRI scanner (General Electric, USA). Functional images consisted of echo-planar image volumes which were sensitive to BOLD contrast in axial orientation (TE = 40 ms, TR = 6000 ms). Prior to each run, four discarded volumes were acquired to allow stabilization of magnetization. The volume covered the whole brain with a 64×64 matrix and 24 slices (voxel size = $3.75 \text{ mm} \times 3.75 \text{ mm} \times 6 \text{ mm}$, slice thickness = 5 mm, gap = 1 mm). Two runs of 128 volumes of images with 32 volumes in each of four experimental conditions were acquired.

2.4. Data analysis

The 256 successive functional images for each subject were realigned to the final image, normalized to Talairach and Tournoux [48] standard space matched to the MNI template (Montreal Neurological Institute), and spatially smoothed with a 10-mm Gaussian kernel using SPM96 (Wellcome Department of Cognitive Neurology, London, UK). To test hypotheses regarding regional-condition-specific effects, the appropriate experimental design matrix was specified (see below). Condition and subject effects were estimated according to the general linear model at each voxel in brain space. Global changes of BOLD signal were removed using proportional scaling, and motion artifacts were also removed using a high pass filter of 200 s. Finally, the images were temporally smoothed using Gaussian kernel of 2.8 s.

Significant hemodynamic changes for each contrast were assessed using t -statistics on a voxel-by-voxel basis. The set of t -values obtained constituted a statistical parametric map (SPM) (t) transformed into an SPM (Z). Resulting areas of activation were characterized in terms of their peak heights and spatial extents. We analyzed the image data of the seven subjects as a group to obtain the statistical parametric map. For a group analysis, we reported activation above a threshold corresponding both to $p < 0.0001$ (corrected for multiple comparison, $Z > 4.5$) for height and to $p < 0.05$ for extent (uncorrected). Location of significant signal increase in a group analysis was listed in terms of region name, BA, coordinates according to Talairach and Tournoux [48], and Z -value.

We conducted four subtraction analyses to identify brain regions activated during each task. (1) Word encod-

Table 1

Location of significant increase of BOLD signal during encoding of word and pattern

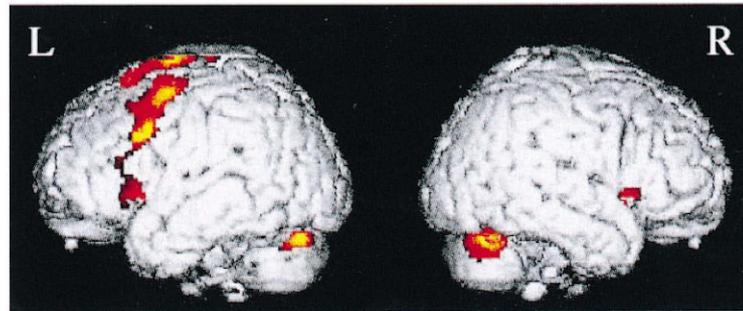
L: left; R: right; BA: Brodmann's area; SMA: supplementary motor area.

	Number		Region	BA	x	y	z	Z
<i>(a) Word encoding</i>								
Frontal	1	L	inferior frontal gyrus	45/47	-58	18	0	7.26
			middle frontal gyrus	9	-58	14	34	6.23
			premotor area	6	-42	0	56	7.65
	2	L	SMA	6	-6	6	70	6.13
			3	R	inferior frontal gyrus	47	56	16
Cerebellum	4	L	cerebellum		-28	-74	-26	5.91
	5	R	cerebellum		34	-64	-28	7.44
<i>(b) Pattern encoding</i>								
Frontal	1	L	middle frontal gyrus	9	-52	10	34	7.76
	2	L	superior frontal gyrus	10	-22	56	0	5.47
	3	L	premotor area	6	-30	2	64	7.7
	4	R	middle frontal gyrus	9	52	16	30	7.39
			R	inferior frontal gyrus	46	46	36	18
	5	R	premotor area	6	34	6	62	6.68
Temporal	6	L	fusiform gyrus	37	-52	-56	-18	8.13
Parietal	7	L	superior parietal lobule	7	-22	-62	50	7.83
	8	R	superior parietal lobule	7	30	-68	44	8.19
Occipital	9	L	inferior occipital gyrus	18	-40	-80	-4	7.13
	10	R	middle occipital gyrus	19	44	-68	-10	6.35

ing (word encoding minus control during word encoding) — this subtraction was expected to show the neural correlates of encoding novel verbal material. (2) Pattern encoding (pattern encoding minus control during pattern encod-

ing) — this subtraction was expected to show the neural correlates of encoding novel non-verbal material. (3) Word retrieval (word retrieval minus control during word retrieval) — as both word retrieval and its control condition

(a) Word encoding



(b) Pattern encoding

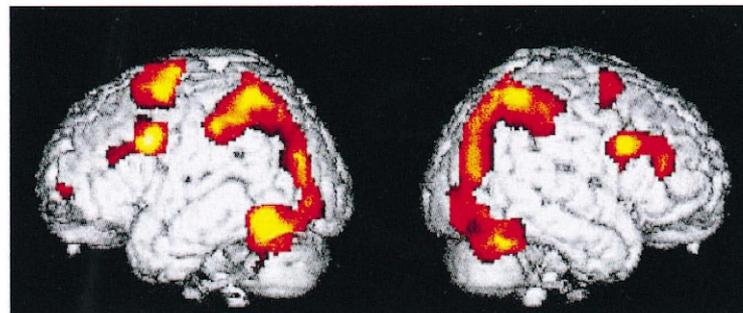


Fig. 2. Areas activated by (a) word encoding and (b) pattern encoding are rendered on a template (SPM96). For the locations of significant activations, see Table 1a and b, respectively.

Table 2
Location of significant difference in BOLD signal between word and pattern encoding

	Number	Region	BA	x	y	z	Z	
<i>(a) Word-specific activation during encoding</i>								
Frontal	1	L	inferior frontal gyrus	45/47	-58	18	0	5.3
	2	R	inferior frontal gyrus	45/47	56	14	-2	5.56
<i>(b) Pattern-specific activation during encoding</i>								
Frontal	1	R	middle frontal gyrus	46	50	40	20	6.43
	2	R	premotor	6	32	8	62	4.93
	3	L	inferior frontal gyrus	44	-48	4	30	5.01
Parietal/Temporal	4	R	superior parietal lobule	7	28	-68	44	7.87
	5	L	superior parietal lobule	7	-32	-50	56	6.76
	6	L	inferior temporal gyrus	37	-52	-54	-12	7.52
Occipital	7	R	middle occipital gyrus	19	42	-72	22	7.59
	8	L	middle occipital gyrus	19	-30	-74	20	7.21
Cerebellum	9	R	cerebellum		38	-48	-22	5.48

included retrieval processes, the difference was in the type of item for which the subject made a recognition judgement (i.e., studied word vs. non-studied word); this subtraction was expected to show the neural correlates of successful retrieval. (4) Pattern retrieval (pattern retrieval minus control during pattern retrieval) — this subtraction was made to identify regions associated with successful retrieval of non-verbal material.

In addition to these four main contrasts, we conducted four interaction analyses to depict brain regions selectively involved in each of four experimental conditions. (5) Word-specific activation during encoding — this interaction was computed by subtracting pattern encoding from word encoding. To avoid potential contribution from deactivation related to pattern encoding, we interrogated only those brain regions that were activated significantly by word encoding than by control (i.e., word encoding minus control ($p < 0.01$) contrast was used to mask the entire brain). This masking procedure was also used in the following three analyses. (6) Pattern-specific activation during encoding — subtraction of word encoding from pattern encoding. (7) Word-specific activation during retrieval — subtraction of pattern retrieval from word retrieval. (8) Pattern-specific activation during retrieval — subtraction of word retrieval from pattern retrieval. Finally, to identify common regions of activation for both word and pattern during encoding or retrieval, we performed conjunction analyses [39]. These were (9) common activation for word and pattern during encoding (masked by both word encoding and pattern encoding) and (10) common activation for word and pattern during retrieval (masked by both word retrieval and pattern retrieval).

2.5. Correlation analysis

The percent signal change in a given peak voxel was calculated for each subject and task condition using the average signal intensity during control condition for the same subject as a baseline. Because the fMRI response

typically lags 4–6 s behind the neural response, we omitted the first functional image in each block from the analysis [15]. Given that the purpose of the study was to investigate prefrontal involvement in episodic memory, we calculated correlation coefficient between memory performance (according to signal detection theory, hit rate and false alarm rate in each block during retrieval phase were transformed to d') and percent signal change in each peak voxel in prefrontal cortex.

3. Results

3.1. Behavioural data

For words, the proportion of “old” response during word retrieval (hit) and during its control condition (false

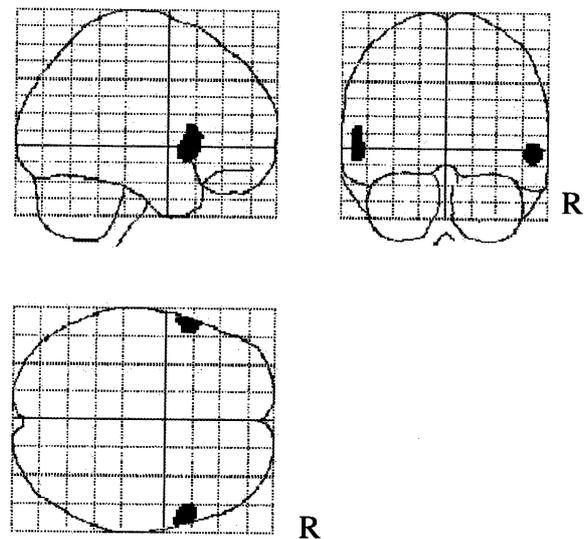


Fig. 3. Statistical parametric map for word-specific activation during encoding; pattern encoding was subtracted from word encoding (threshold at $p < 0.0001$) and masked by word encoding (threshold at $p < 0.01$). For localizations of activation, see Table 2a.

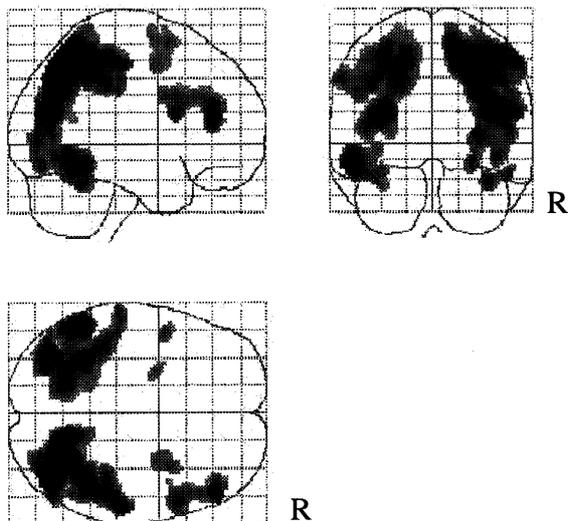


Fig. 4. Statistical parametric map for pattern-specific activation during encoding; word encoding was subtracted from pattern encoding (threshold at $p < 0.0001$) and masked by pattern encoding (threshold at $p < 0.01$). Localization of activation corresponds with Table 2b.

alarm) was 0.72 (S.D. 0.15) and 0.04 (S.D. 0.06), respectively. For checkerboard patterns, the proportion of “old” responses during pattern retrieval and during its control condition was 0.63 (S.D. 0.14) and 0.28 (S.D. 0.16), respectively. The proportion of “old” responses differed significantly between the words and checkerboard patterns ($p < 0.01$) for false alarms, but not for hits ($p > 0.3$). In a debriefing after the experiment, we questioned each subject about whether they noticed that the items during retrieval phase were presented in a specific manner. No subject reported noticing the alternating conditions of the

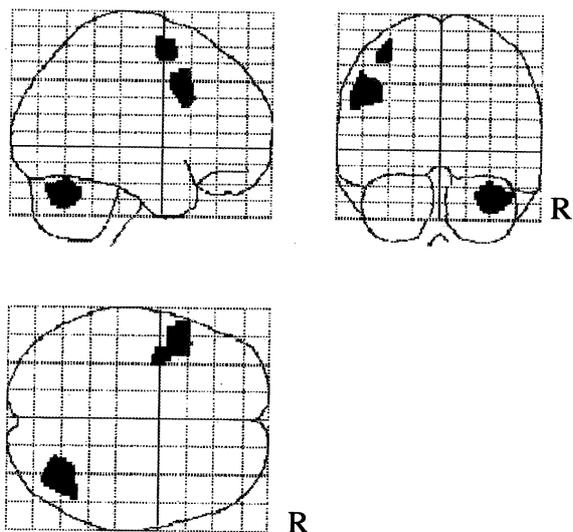


Fig. 5. Common activation for both word encoding and pattern encoding as revealed by conjunction analysis (threshold at $p < 0.0001$) masked by word encoding and pattern encoding (threshold at $p < 0.0001$). Three activated foci were found in the left middle frontal gyrus (BA 9; $x = -54$, $y = 14$, $z = 34$), left premotor (BA 6; $x = -40$, $y = 0$, $z = 58$), and right cerebellum ($x = 34$, $y = -62$, $z = -28$).

Table 3

Location of significant increase of BOLD signal during retrieval of word and pattern

Number	Region	BA	x	y	z	Z
<i>(a) Word retrieval</i>						
Frontal 1	L inferior frontal gyrus	47	-44	28	-8	4.66
<i>(b) Pattern retrieval</i>						
No significant increase						

block design experiment. There was no significant difference in the proportion of correct response among the four alternating task cycles (words: $F = 1.49$, $p = 0.24$; pattern: $F = 0.45$, $p = 0.71$).

3.2. fMRI data

3.2.1. Word encoding

Locations of significant increase in BOLD signal during word encoding are listed in Table 1a and rendered on a surface template (Fig. 2a). Activation was found predominantly in the dorsolateral part of the left frontal lobe, and in the right cerebellum. The ventrolateral part of the frontal lobe (BA 45/47) was also activated bilaterally. As shown in Table 2a and Fig. 3, word-specific activation was observed in the bilateral inferior frontal gyrus (BA 45/47).

3.2.2. Pattern encoding

Pattern encoding activated a widespread area in both hemispheres. Locations of these areas are listed in Table 1b and rendered in Fig. 2b. In the frontal lobe, clusters were symmetrically located in the bilateral middle frontal gyrus and premotor area. Large clusters in the bilateral parieto-occipital area included the superior and inferior parietal lobule, and extended to the inferior temporal and occipital visual area.

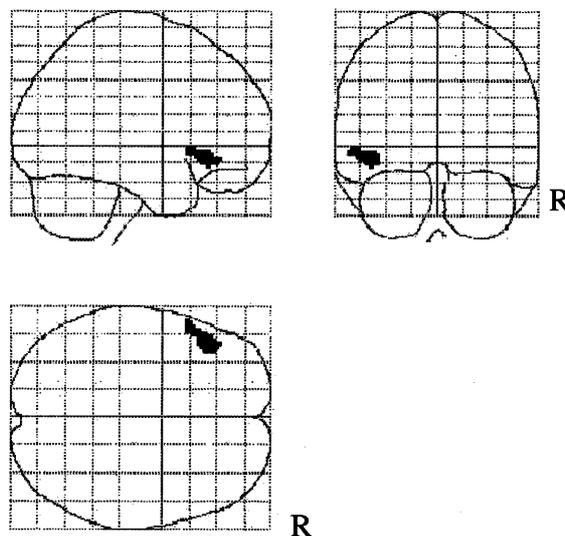


Fig. 6. Significant signal increase in the left inferior frontal gyrus (BA 47) during word retrieval. For localization of activation, see Table 3a.

Table 4
Location of significant correlation between performance and signal change

Number	Region	BA	<i>r</i>	<i>p</i>
<i>Word encoding</i>				
1	L inferior frontal gyrus	45/47	0.38	*
2	L middle frontal gyrus	9	0.47	*
<i>Word retrieval</i>				
3	L inferior frontal gyrus	47	0.48	**

* $p < 0.05$, ** $p < 0.01$.

The locations of pattern-specific activation are listed in Table 2b. Most of the activated regions were identical with those in the simple main subtraction analysis as listed in Table 1b except that there was little activation in the left prefrontal cortex. As shown in Fig. 4, pattern-specific activation was depicted in the bilateral parieto-occipital area and in the right prefrontal area.

3.2.3. Common activation for word and pattern during encoding

Conjunction analysis revealed that activations in the left prefrontal (BA 6 and 9) and in the right cerebellum were commonly involved in both word encoding and pattern encoding (Fig. 5).

3.2.4. Word retrieval and pattern retrieval

In word retrieval, a single cluster in the left inferior frontal gyrus survived our statistical threshold (Table 3a, Fig. 6). Although no region met our criteria in pattern retrieval, there was a single activation in the right prefrontal cortex ($x = 44$, $y = 46$, $z = 18$, BA 10/46) when a lenient threshold was used ($Z = 3.85$, $p < 0.001$, uncorrected). There was no significant result in the contrast for word- or pattern-specific activation during retrieval. Neither conjunction analysis revealed significant activation.

3.2.5. Correlation analysis

Table 4 shows that percent signal changes in the left prefrontal cortex during verbal memory task had significant positive correlation with memory performance. A robust finding was the strong correlation during word retrieval (Table 4, no. 3). There was no significant result for pattern encoding or retrieval.

4. Discussion

The present study provides evidence that the left prefrontal cortex was predominantly activated during word encoding, whereas a widely distributed neural network in both hemispheres was engaged during pattern encoding. Pattern encoding, but not word encoding, activated the right dorsal prefrontal cortex. However, encoding of both types of material involved left dorsal prefrontal cortex and the right cerebellum. In addition, the present study demonstrates a strong relationship between retrieval success for

words and activation in the left ventral prefrontal cortex. Thus, our findings replicate and add to previous reports on the functional asymmetry of prefrontal activation during episodic memory [9,10,13,16,32,49].

4.1. Activation during word encoding

Word encoding activated the left dorsolateral and ventral prefrontal cortex, and the supplementary motor area. In addition, activity in the two distinct areas in the left prefrontal cortex had significant positive correlation with memory performance (Table 4, nos. 1 and 2). This result is in keeping with a previous study by Kapur et al. [23] employing an intentional learning task of verbal materials. Kelley et al. [24] and Wagner et al. [52] also reported the left dorsal prefrontal activation during word encoding, location of which was close to our peak. The magnitude of activity in the left dorsal prefrontal cortex was critically related to subsequent memory performance [52]. Another finding in the present study is that the bilateral inferior frontal gyrus (BA 45/47) was specifically involved in word encoding. In an fMRI study, activity in the left ventral frontal cortex (BA 45/47) was word-specific [51], and was critically related to later memory performance [52]. This area has been implicated in semantic and naming processes of words as revealed by a PET study using word-naming task [7]. These results suggest that concurrent activity in the left dorsal and ventral prefrontal cortex facilitates effective learning of words, and that function of the ventral part is more specialized for verbal materials than that of the dorsal part.

4.2. Activation during pattern encoding

4.2.1. Prefrontal cortex

In contrast to word encoding, pattern encoding engaged larger cortical network, symmetrically and bilaterally distributed in the frontal, parieto-occipital, and temporal lobes. The subtraction of word encoding from pattern encoding revealed that pattern-specific encoding activation was situated in the right prefrontal cortex, but not in the left prefrontal cortex. The bilateral or right-dominant activation contrasts with the hypothesis that episodic encoding preferentially involves the left prefrontal cortex. However, several studies have demonstrated the right-dominant prefrontal activation during non-verbal encoding [5,24,25,51]. For example, Klingberg and Roland [25] found that rCBF in the right dorsolateral prefrontal cortex significantly increased during the learning task of abstract pictures and sounds. Kelley et al. [24] demonstrated the activity during face encoding located in posterior prefrontal cortex in the right hemisphere. In addition, Brewer et al. [5] reported that activity in the right dorsolateral prefrontal cortex during encoding of scenic pictures was significantly related to later memory performance. These authors attributed the lack of left prefrontal activation to difficulty in verbal encoding of non-verbal materials. The present results showing the bilateral dorsal prefrontal activation dur-

ing pattern encoding replicate a study by Roland and Gulyas [40] using a learning task of geometric patterns. In addition, location of pattern-specific activity in the right middle frontal gyrus is close to that of texture-specific activity reported by Wagner et al. [51]. Thus, our study provides evidences that episodic encoding of patterns involves the prefrontal cortex bilaterally, and that right frontal lobe is likely specialized for learning of non-verbal information.

However, it could be argued that the right prefrontal activation specific to pattern encoding merely reflected the differences in task difficulty because false alarm rate was significantly higher for pattern than for word. Grady et al. [19] examined the effect of task difficulty on the prefrontal activation during face matching task. The authors concluded that although the bilateral prefrontal cortex showed activation during the most difficult task, the right prefrontal area played a more critical role than the left because blood flow in this region positively correlated with performance measures. Their conclusion supports the present results that an involvement of the right prefrontal cortex is specific to non-verbal encoding.

Other PET studies observed left-lateralized prefrontal activation during encoding of non-verbal materials such as object location [33], and faces [18,20,21]. However, we speculate that activation of the left frontal lobe is attributed to the strategy adopted by subjects. The authors [20,33] also concluded that subjects might have used analytical or elaborative (i.e., verbal or semantic) strategy to encode the stimuli. Presentation rate of stimuli likely affected the laterality of prefrontal activation because relatively longer duration or subject pace was employed in these studies.

4.2.2. Parietal and premotor area

Pattern encoding activated bilateral cortical network in the temporo-parieto-occipital lobes, which appear to reflect processing of visually presented items. Activation in the bilateral posterior parietal cortex was found in studies using non-verbal encoding task [24,25,33], and spatial working memory task [4,12]. The arrangement of black and white squares in a checkerboard pattern likely recruited spatial analysis. Several authors [11,14,29] reported that the bilateral premotor area was associated with visual attention or working memory for spatial information. These results indicate that concurrent activity in the premotor and posterior parietal area in both hemispheres may subservise short-term maintenance of visuo-spatial information [26] through reciprocal neuronal connections [35].

4.3. Common neural network during encoding of word and pattern

A novel finding was that the location of common neural substrates for word and pattern encoding was spatially restricted in the left dorsal prefrontal cortex and the right cerebellum. There is considerable evidence that the cerebellum is involved in higher cognitive function [47]. An

anatomical study in monkey showed neural connections between cerebellum and prefrontal cortex [27]. It is highly likely that during word encoding, the lateral cerebellum and left premotor area play a role for verbal rehearsal [2]. Owen et al. [34] reported concurrent activation in the left dorsolateral prefrontal cortex and right cerebellum during encoding of location. Finally, an fMRI study of learning artificial grammar system showed that the left dorsal prefrontal cortex and right cerebellum were critical components for rule learning [17]. However, previous studies of non-verbal memory [25,40] did not demonstrate conjunctive activation in these structures. It may be possible to speculate that these two regions are implicated in essential features of encoding or learning regardless of the material. By contrast, within frontal lobe, processes specialized for verbal materials involve ventral regions such as BA 45/47 in both hemispheres and those specialized for non-verbal materials involve dorsal regions such as BA 46 in the right hemisphere.

4.4. Activation during word retrieval

The retrieval conditions were designed to identify the neural activity associated with retrieval success, as scans for non-studied items were subtracted from those for pre-studied items. This experimental design did not yield activation in the right prefrontal cortex; similar with a study by Wagner et al. [53] (Experiment 2). However, we found significant activation in the left inferior frontal gyrus (BA 47). This cluster is located in the same vicinity as activation specific to word encoding in the left hemisphere. An explanation for the discrepancy between the present study and that of Wagner et al. [53] is uncertain, but longer alternating task cycles might affect the results. A particularly interesting and novel finding was a significant positive correlation between memory performance and percent signal change in the left inferior frontal gyrus (Table 4, no. 3). This implies that subject or task block with better memory performance had greater degree of left prefrontal activation during word retrieval. Petrides et al. [37] reported activation in the left ventrolateral frontal cortex during retrieval when they subtracted scans for word repetition from those for word recall. CBF in the ventral prefrontal was greater during recognition condition than during observation of novel stimuli [38]. Wagner et al. [51] also found word-specific activation during retrieval mainly in the left frontal lobe, and the magnitude of activation was greatest in the left ventral prefrontal cortex. Nolde et al. [30] and Rugg et al. [43] showed left prefrontal activation by contrasting two different retrieval conditions. They attributed the left lateralization of activation to demanding cognitive processes during source recognition [30] or depth of processing effect during encoding [43]. It is highly likely that in the present study, “old” words during retrieval had been processed semantically during encoding, and that recognition of these words required re-activation of brain areas related to semantic operation of stimuli.

The present results, with a significant involvement of the ventral prefrontal cortex both during encoding and during retrieval, accord with the model proposed by Petrides [38]. The author suggests that this area is critical for the active and strategic encoding and retrieval of information, and for selecting, comparing, or deciding on information in short-term and long-term memory. In lesion studies in monkeys, ablation of the bilateral ventral frontal cortices yielded severe impairments in visual memory [3,28,36]. Anatomical connections between the inferior temporal area specialized for visual perception and the inferior convexity of the prefrontal cortex [50] may subserve the functional integration of information and successful retrieval from episodic memory.

With regard to the right prefrontal activation during retrieval found in the previous studies [9,10,13,16,32,49], we speculate that activity in this region is cancelled out by the subtraction as reported by several authors [22,31,53]. Similarly, fMRI studies have failed to detect a significant BOLD signal difference between correct response and false response [45], and between hits and correct rejections [8]. These results are inconsistent with those by Rugg et al. [41,42] showing evidence that the right prefrontal cortex is associated with retrieval success of words. A possible explanation for this discrepancy is that in the previous PET studies, the subjects may have noticed the difference in density of the “old” targets across lists and may have adjusted their retrieval strategy accordingly. By contrast, in our study, no subject noticed the difference in the proportion of old words presented. Supportive evidence is that the proportion of correct answer did not differ among the four alternating task cycles. In a practice session before the experiment, we used a random presentation of “old” items during recognition. We speculate that the subjects did not expect a block-design experiment, and failed to adjust their retrieval strategy.

4.5. Activation during pattern retrieval

It could be argued that pattern encoding and retrieval in our study failed to engage episodic memory, because memory performance was poor. However, Schacter et al. [46] observed modest but reliable activation of the hippocampus and prefrontal cortex during a picture recognition test for 3D objects. Their recognition performance (hit rate 62%, false alarm rate 42%) was comparable to the behavioural data in the present study. This result indicates that the hippocampus and prefrontal cortex, which are thought to be critical for episodic memory, are engaged even when performance on the task is relatively low. In fact, using a lenient threshold ($p < 0.001$, uncorrected), we found a single activation in the right middle frontal gyrus (BA 10/46) when the control condition was subtracted from pattern retrieval. This result agrees with the report of Wagner et al. [51] showing that texture retrieval activated the right dorsal prefrontal cortex.

4.6. Lack of hippocampal activation

The present study failed to demonstrate hippocampal activity during encoding and retrieval of visually presented materials. This may be attributed to technical issues concerning image acquisition and/or the task paradigm employed. A possible explanation is that, due to a magnetic susceptibility effect, the BOLD signal was not efficiently detected in the inferior part of the temporal lobe where paranasal sinuses are located adjacently. Second, the experimental design with both control condition and encoding or retrieval alternated might be insufficient to produce a signal increase because the hippocampus may have been activated comparably during all conditions.

5. Conclusion

The present study demonstrates dissociation between the involvement of prefrontal cortex during episodic encoding and retrieval using verbal and non-verbal materials. First, in keeping with the previous studies, we found that word encoding activation is predominantly left-dominant, whereas pattern encoding activation is mediated by the bilateral prefrontal cortex. This indicates that the laterality of prefrontal encoding activation depends on the type of material presented. In addition, conjunctive activation during word and pattern encoding in the left dorsal prefrontal cortex and right cerebellum implies that these regions are likely associated with a common encoding network. Further processes specialized for verbal and non-verbal materials appear to involve the ventral convexity and the right dorsal convexity of the frontal lobe, respectively. Pattern encoding activates a widespread neural network in the parieto-occipital and premotor area of both hemispheres. Finally, we demonstrated that successful retrieval is associated with activation in the left ventral prefrontal cortex. This result, together with significant correlation between memory performance and signal change, supports hypothesis that the ventral prefrontal cortex is preferentially engaged during active and strategic manipulation of mnemonic representation.

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