Medial Temporal Lobe Activation During Context-Dependent Relational Processes in Episodic Retrieval: An fMRI Study

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Abstract: Previous studies have reported that the medial temporal lobe (MTL) structures contribute to the processing of relations among multiple stimuli in episodic encoding. There have been few studies, however, on the episodic retrieval requiring processing of relations among multiple components that was involved in our events. We used functional magnetic resonance imaging (fMRI) to investigate neural activities during the retrieval of relations within an organized episode and the recognition of an episodic component. Healthy, normal participants memorized 50 four-scene comic strips before fMRI scanning. In the retrieval phase with fMRI scanning, participants were engaged in three tasks: a visual identification (VI) task, a story recall (SR) task, and a picture recognition (PRe) task. In the VI task, participants were asked to judge whether they could identify at least one female character in the two scenes presented vertically. In the SR task, participants were shown the first and last scenes from strips memorized previously and asked to judge whether or not the two scenes were from the same strip. In the PRe task, participants were shown two scenes and asked to judge whether they both belonged to the memorized scenes. The two contrasts of SR with VI and PRe with VI demonstrated some commonly activated areas, such as the bilateral middle frontal gyrus and cerebellum. More importantly, the SR task differentially activated the bilateral parahippocampal gyrus, whereas the PRe task differentially activated right prefrontal areas, including the inferior frontal and precentral gyri. The results suggest that the activity of the MTL structures may be strongly associated with episodic memory retrieval requiring context-dependent relational processing. *Hum. Brain Mapping* 17:203–213, 2002. © 2002 Wiley-Liss, Inc.

Key words: medial temporal lobe; fMRI; episodic memory; recall; recognition; relational processing; context

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INTRODUCTION

Episodic memory refers to a type of memory that is stored with temporal and spatial information attached [Tulving, 1972]. There have long been consistent reports of the importance of the medial temporal lobe (MTL) structures (including the hippocampal formation, entorhinal, perirhinal and parahippocampal cortices) in episodic memory. Since the momentous finding of the case of H.M. [Scoville and Milner, 1957], many neuropsychological studies have reported that damage to the MTL structures causes an episodic memory disturbance, i.e., the amnesic syndrome [Fujii et al., 2000]. Furthermore, recent developments of functional neuroimaging techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) have contributed to our understanding of the relationship between the MTL structures and episodic memory encoding or retrieval, or both [Lepage et al., 1998; Schacter and Wagner, 1999].

With regard to the functional role of the MTL structures in memory, several researchers have proposed that this may be related to learning and consolidation of declarative memory [Squire and Alvarez, 1995; Squire and Zola-Morgan, 1991], novelty assessment and encoding [Tulving et al., 1996], formation and storage of multiple traces binding separate components together [Fujii et al., 2000; Nadel and Moscovitch, 1997], retrieval of deeply encoded items [Rugg et al., 1997], spatial learning [Henke et al., 1999a; Maguire et al., 1997, 1998], etc. In line with some of these proposals, some studies involving experimental animals or functional neuroimaging have indicated that the MTL structures may play an important role in establishing associations among the components of an episodic memory [Eichenbaum, 1997; Eichenbaum et al., 1996; Henke et al., 1997, 1999b]. The MTL activations reported in these earlier neuroimaging studies were found during the processing of relations among multiple stimuli in encoding. Relational processing in retrieval, as well as in encoding, must be an important requirement for daily life. For example, when we remember an episode that occurred at dinnertime in a restaurant, we can simultaneously recall visual images, the tastes or smells of foods, and the verbal content of conversations with friends. These components belonging to different modalities are recollected as having been experienced in the same context and are organized into a specific event. There have been few functional neuroimaging studies, however, on episodic retrieval that have specifically required the pro-

cessing of relations among the multiple components involved in our events.

This relational retrieval process must be more complicated than simple recognition such as old/new judgment. Reed and Squire [1997] claimed that impaired recognition memory is a robust feature of human amnesia after damage to the MTL structures. In addition, many neuroimaging studies have shown that the MTL structures are activated during the process of recognition of previously-learned components [for reviews, see Lepage et al., 1998; Schacter and Wagner, 1999]. Although both the relational retrieval process and the simple recognition process can be thought of as retrieval in the context of memory processes, it is possible that there may be some differences between these two retrieval processes.

Psychological studies have suggested that there are two different bases for these two retrieval processes of context-dependent retrieval and simple recognition [Jacoby and Dallas, 1981; Mandler, 1980]. Also, several neuroscientists have proposed neuroanatomical theories to explain these possible mechanistic differences between relational retrieval and simple recognition. For example, an fMRI study by Yonelinas et al. [2001] indicated that the occipital-temporal regions are involved in both types of retrieval processes; however, the hippocampal and parahippocampal regions were related to the recollection of associative information but not to old-item recognition. Another review study proposed that the perirhinal system contributes to simple recognition processes, whereas the hippocampal system is involved in associative retrieval processes [Brown and Aggleton, 2001]. It is not yet fully understood, however, which structures in the MTL or in other cortical areas are most involved in the two different retrieval processes.

We investigated neural activities during relational retrieval of an organized episode and recognition of an episodic component. To explore neural activities in the two retrieval conditions, we employed an fMRI blocked design procedure sensitive to a task-dependent hemodynamic response. Using this approach, we demonstrated that the processing of relations among multiple episodic components strongly activated specific regions of the MTL structures.

SUBJECTS AND METHODS

Subjects

Sixteen healthy, normal volunteers (4 women, 12 men) participated in the study. All subjects were right-handed and had scores above 90 on the Edinburgh

Figure 1.

Examples of encoding stimuli. The title of this four-scene comic is *Aimu-Yacchi* (*My name is Yacchi*). © Aska Gotho, reproduced with permission.

Handedness Inventory [Oldfield, 1971]. Head movements were recorded and checked before all procedures for data analyses, and the data sets from subjects with head motions exceeding 30% of the voxel size in any of three axes (x , y , z) were discarded. The data sets acquired from 13 subjects (2 women, 11 men; mean age 21.8 years) were used for analyses. Informed consent was obtained from all participants based on the Declaration of Helsinki [1975]. All procedures for this study received prior approval from the Institutional Human Research Review Committee of our institute.

Experimental tasks

In the encoding phase before MRI scanning, 50 comic strips from a comic book were prepared as encoding materials (Fig. 1). In this comic book, a story

is made up of four scenes, which are arranged vertically. All subjects were required to participate in two-step encoding procedures. First, the subjects were requested to concentrate on a story by reading the narrative portion of the strip and to memorize the story at their own pace. Subsequently, an experimenter asked the subjects to pay particular attention to the story's pictorial content. This session was started 1 hr before scanning, and was continued for about 30 min. Thus, the subjects had to retain these stimuli for approximately 30 min.

After the encoding phase, subjects were engaged in the retrieval phase with MRI scanning (Fig. 2). In this phase, each of the stimuli consisted of a pair of scenes chosen from the same comic book and arranged vertically. Each stimulus was presented for 4 sec. The stimuli were presented through a projector and back-projected to a screen placed beyond the subject's feet. The subjects were able to see the screen through a mirror fixed in a head cage.

The first task was a visual identification (VI) task, in which the subjects were required to judge whether they could identify at least one female character in the two scenes. This task did not involve retrieval demands on episodic memory, because all stimuli were novel. In the second task, the subjects were shown the first and last scenes from the strips that had been memorized before the scan. Subjects were asked to judge whether or not these two scenes were from the same strip. To succeed in this task, subjects had to retrieve the relation between two stimuli and the whole story of a strip. We called this a story recall (SR) task. In the third task, the subjects were shown two scenes and were asked to judge whether they both belonged to the memorized strips. We called this a picture recognition (PRe) task.

A sequential blocked design was employed, in which the three experimental tasks were alternated with box-car function. The subjects participated in two runs, which were designed with the same experimental procedures. One run consisted of six blocks and each block included 10 targets and 10 distracters. All stimuli employed in the SR task were scenes presented previously. In the PRe task, one of the stimuli presented as a distracter pair was a new scene that had not been learned previously. Thus, 30 old and 10 new stimuli were involved in one block of the PRe task. In the 10 distracter trials, the old and new items were counterbalanced across the top and bottom positions. The subjects were asked to push Button 1 with the index finger when a target appeared on the screen, and to push Button 2 with the middle finger when a distracter appeared. In both runs, the order of each

Figure 2.

Examples of stimuli presented in the retrieval phase with fMRI scanning. Examples of (A) the SR task, (B) the PRe task, and (C) the VI task.

block task was VI, SR, PRe, VI, SR, and PRe. Thus, subjects participated in four sessions of each task condition.

Scanning methods and data analyses

All magnetic resonance imaging (MRI) data were acquired with 3 T GE Signa LX (General Electric,

Milwaukee, WI). The subjects were positioned in the scanner, with their heads immobilized by support cushions. A gradient echo EPI sequence modified by EPIBOLD sequence was used for functional imaging with the following parameters: TR = 4,000 msec, TE = 32.3 msec, FOV = $20 \times 20 \text{ cm}^2$, matrix sizes = 64×64 , flip angle = 90 degrees, slice thickness/gap = 8/2 mm. Twenty coronal slices were obtained, and 120 sequential images of each slice were collected in each session.

Analyses of the fMRI data were performed using the software Statistical Parametric Mapping 99 (SPM99; Wellcome Department of Cognitive Neurology, London, UK) implemented with Matlab 5.3 (MathWorks, Natick, MA). First, to correct head movements and detrend due to scanner drift, 120 sequential images acquired from each subject were realigned to the first image with the sinc interpolated method. Second, the realigned images from each subject were transformed and normalized into standard space [Talairach and Tournoux, 1988] using EPI template and smoothed with Gaussian kernel of FWHM of 10 mm. Third, the effects of tasks on signal intensity at each voxel were estimated with a two-step random field theory [Price and Friston, 1997; Woods, 1996]. At the first step, specific effects were tested by applying appropriate contrasts to the parameter estimates for each task, resulting in a t statistic for every voxel. In this way, SPMs (statistical parametric maps) [Friston et al., 1995] were determined for each individual subject. In the second step, we carried out a one-sample t test on the resulting contrast images. The procedures were employed to entail weighting the size of the average effect with our estimation of the population error that we obtained from our samples. Activation was considered significant if it had a cluster of voxels above $t > 6.10$ ($P < 0.05$, corrected for multiple comparisons, $k > 1$) with maximum t -value.

RESULTS

Behavioral data

The number of hit and false-alarm responses was calculated in each task for each subject and compared by a two-way analysis of variance (ANOVA) with task conditions (SR, Pre, and VI) and task sessions (first–fourth sessions) as factors. For hit responses, the main effect of task conditions was significant ($F[2,36] = 72.6$, $P < 0.001$). The post-hoc analyses with LSD procedures showed significant differences among the three task conditions at $P < 0.01$ (SR: $M = 9.12$, $SD = 1.00$; Pre: $M = 7.79$, $SD = 1.30$; VI: $M = 9.87$, $SD = 0.53$). No

Figure 3.

The behavioral data of the three task conditions. The means of (A) hit responses, and (B) false-alarm responses. C: Reaction time data. Triangles, VI; diamonds, SR; squares, PRe.

significant main effect of task sessions and interactions between the two factors was observed ($F[3,108] = 0.63$, $P = 0.596$ for a main effect of task sessions and $F[6,108] = 0.58$, $P = 0.747$ for an interaction between the two factors). The mean scores are shown in Figure 3A. In the analysis of false-alarm responses, the ANOVA indicated a significant main effect of task conditions ($F[2,36] = 20.9$, $P < 0.001$), but not of task sessions ($F[3,108] = 1.13$, $P = 0.339$) and their interaction ($F[6,108] = 0.87$, $P = 0.520$). The post-hoc test with LSD procedures for task conditions showed significant differences between SR ($M = 1.50$, $SD = 1.09$) and VI

($M = 0.21$, $SD = 0.57$), and between PRe ($M = 1.65$, $SD = 1.34$) and VI ($P < 0.01$, respectively), but not between SR and PRe. The detailed data are shown in Figure 3B.

The reaction time data were also calculated and compared by a two-way ANOVA with task conditions (SR, Pre, and VI) and task sessions (first to fourth sessions). The significant main effect of task conditions was identified ($F_{[2,36]} = 223.519$, $P < 0.0001$). Neither the main effect of task sessions ($F_{[3,108]} = 0.36$, $P = 0.780$) nor their interaction ($F_{[6,108]} = 0.82$, $P = 0.554$) was significant. The post-hoc analyses with LSD procedures for the task condition showed significant differences between SR [$M = 2,743$ (msec), $SD = 507.17$] and VI [$M = 1,566$ (msec), $SD = 505.94$], PRe [$M = 3,376$ (msec), $SD = 253.69$] and VI, and SR and PRe ($P < 0.0001$, respectively). The reaction time data are illustrated in Figure 3C.

In addition, we compared reaction time data among three types of stimulus presentation pattern in the PRe task, in which the top and bottom panels were presented as old/old (target), old/new (Type 1 distracters) and new/old (Type 2 distracters). The one-way ANOVA showed no significant effect of stimulus presentation patterns [target; 3,391.2 msec ($SD = 652.4$), Type 1 distracters; 3,387.0 msec ($SD = 717.1$), Type 2 distracters; 3,368.5 msec ($SD = 664.1$); $F(2,1037) = 0.10$, $P = 0.903$].

Functional MRI data

First, the neural activities detected by MRI scanning during SR or PRe were compared to those during VI. The contrast of SR and VI showed significantly activated areas in the bilateral parahippocampal gyrus (BA 35), middle frontal gyrus (BA 9 and 6) and cerebellar hemisphere. In comparison of PRe with VI, we observed activations of the bilateral middle frontal (BA 9/46, 6/8 and 6) and cerebellar hemisphere, and the right inferior frontal gyri (BA 45/46).

Second, we directly compared fMRI data during two experimental tasks. In the comparison of SR with PRe, we identified activations in the parahippocampal gyrus (BA 28) and lingual gyrus (BA 18) in the left hemisphere. The opposite contrast of PRe with SR showed activations in the right inferior frontal gyrus (BA 47), right angular gyrus (BA 39) and left middle temporal gyrus (BA 21).

Finally, to clarify further the differential activations in each experimental task, the contrasts of SR and PRe with VI were inclusively masked with each contrast of SR minus PRe or PRe minus SR. The contrast of SR minus VI inclusively masked with SR minus PRe re-

Lt. parahippocampal gyrus **Rt. parahippocampal gyrus** **Figure 4.**

An activated image and the percent signal changes of voxels of interest (VOIs) in the bilateral parahippocampal gyrus. The left side of this figure is the actual left side of brain. To provide a means of descriptively rendering the magnitudes of activations in those

areas, two VOIs of 4-mm radius were conducted in the bilateral parahippocampal gyri with the activated peak voxels centered. The mean percent signal changes of these VOIs were statistically compared among three tasks of SR, Pre, and VI (* $P < 0.05$; ** $P < 0.01$).

vealed activations of the bilateral parahippocampal gyrus (BA 35) (Fig. 4). The analysis of PRe minus VI inclusively masked with PRe minus SR showed acti-

vations of the right inferior frontal (BA 44/45 and 45/46) and precentral gyri (BA 6) (Fig. 5). These activation sites are summarized in Table I.

Rt. inferior frontal gyrus (BA 44) **Rt. inferior frontal gyrus (BA 45/ 46)** **Figure 5.**

Activated images and percent signal changes of VOIs in the right inferior frontal gyri. The bottom of this figure is the actual right side of brain. Two VOIs of 4-mm radius were conducted in the right prefrontal areas with the activated peak voxels centered. The mean percent signal changes of these VOIs were statistically compared among three tasks of SR, Pre, and VI (* $P < 0.05$; ** $P < 0.01$).

TABLE I. Activation foci identified in each of the contrasts

Side Regions	BA	Talairach Coordinations			<i>t</i>
		<i>x</i>	<i>y</i>	<i>z</i>	
SR minus VI					
Right					
Middle frontal gyrus	9	56	24	28	7.10
	6	41	0	56	7.12
Parahippocampal gyrus	35	19	− 24	− 16	6.62
Cerebellar hemisphere		44	− 64	− 31	8.60
		34	− 88	− 22	6.26
Left					
Middle frontal gyrus	9/44	− 41	16	28	6.43
	6	− 41	8	53	8.64
Parahippocampal gyrus	35	− 19	− 24	− 16	9.02
Cerebellar hemisphere		− 47	− 56	− 28	6.37
		− 31	− 32	− 28	6.13
PRe minus VI					
Right					
Middle frontal gyrus	44/46	56	24	25	8.03
	6	41	0	50	7.42
	6	47	16	47	6.12
Inferior frontal gyrus	45/46	56	32	9	6.68
Cerebellar hemisphere		44	− 64	− 31	8.60
Left					
Middle frontal gyrus	6	− 41	8	53	8.19
	9	− 41	8	41	6.46
Cerebellar hemisphere		− 47	− 56	− 28	6.70
		− 31	− 32	− 28	6.36
SR minus PRe					
Left					
Parahippocampal gyrus	28	− 19	− 24	− 19	5.60
Lingual gyrus	18	− 9	− 56	6	3.61
PRe minus SR					
Right					
Inferior frontal gyrus	47	47	48	− 9	4.07
Angular gyrus	39	56	− 64	34	3.49
Left					
Middle temporal gyrus	21	− 47	− 24	− 9	3.70
SR minus VI masked inclusively by SR minus PRe at <i>P</i> < 0.05					
Right					
Parahippocampal gyrus	35	19	− 24	− 16	6.62
Left					
Parahippocampal gyrus	35	− 19	− 24	− 16	9.02
PRe minus VI masked inclusively by PRe minus SR at <i>P</i> < 0.05					
Right					
Inferior frontal gyrus	44	56	24	22	6.89
	45/46	56	32	9	6.68
Precentral gyrus	6	31	8	59	6.19

DISCUSSION

We examined brain activation patterns during two different conditions of retrieval of episodic compo-

nents: one requiring processing of the relation among stimuli and the other not. Our results showed subtle, but important, differences in the activation patterns during the two kinds of episodic memory retrieval.

Two basic contrasts of SR with VI and PRe with VI demonstrated some commonly activated areas, such as the bilateral middle frontal gyrus and cerebellum, which are probably involved in the network associated with the two different conditions of episodic memory retrieval in this study. The common process required during both SR and PRe, regardless of the task instructions, may be the recognition of stimuli presented, because almost all of the stimuli presented in both tasks were old, whereas all of the stimuli presented in VI were new. More importantly, SR differentially activated the bilateral parahippocampal gyrus, whereas PRe differentially activated the right prefrontal areas involving the inferior frontal and precentral gyri. These task-specific activations in the bilateral parahippocampal gyrus and the right inferior frontal gyrus were confirmed by the analyses using inclusive masking shown in Table I.

Before discussing the functional role of the activated areas, the possible artifacts should be considered. In this experiment, the condition order during scanning was fixed such that the conditions were always VI, SR, PRe, VI, SR, Pre. Thus, SR always occurred after VI, and PRe always occurred after SR. This raises the possibility that the differences between task conditions may reflect the effects of fatigue (or some other attentional shift) or the effects of proactive interference. The behavioral data, however, showed no significant changes of hit and false-alarm rates or of reaction time across all sessions. Therefore, it is unlikely that the present activation data reflect artifacts from the effects of fatigue or proactive interference.

MTL activation during episodic memory retrieval with relational processing

In the SR task of the present study, subjects were required to judge whether or not the two scenes presented were from the same story. For a correct judgment, subjects had not only to recognize two scenes (although they were not required to recognize them explicitly in this condition), but also to find a relationship between the two scenes in terms of a thematic context of a story memorized previously. In contrast, the PRe task in the present study required subjects to recognize the scenes presented but not to search for a relation between two scenes. Thus, the activity of the MTL structures may reflect episodic memory retrieval requiring relational processing of multiple components belonging to the same thematic framework of the episode, and may be associated with processes of recollecting a specific episodic memory.

The MTL activations in the present study are consistent with those found in a previous study, which reported that the activity in the MTL regions increased only when retrieval was accompanied by remembering but not knowing processes of the learning episodes [Eldridge et al., 2000]. The finding that the MTL structures were strongly activated during the processing of relations between stimuli is also consistent with the findings of some previous neurophysiological studies, suggesting that the MTL structures store the temporal patterns of neural coactivations during encoding [e.g., Eichenbaum, 1997; Eichenbaum et al., 1996; Mishkin et al., 1997; Squire and Alvarez, 1995; Squire and Zola-Morgan, 1991]. The experience of an episode typically involves the simultaneous processing of diverse sensory inputs, bodily sensations, thoughts, and emotions in the cortex. When reproducing these components during later retrieval as a specific episode, synchronous neural activations in diverse brain regions may be evoked by the activity of the MTL structures in which the temporal patterns of neural coactivations during encoding were stored.

There have been several neuroimaging studies on relational retrieval between contextual information and episodic content. These studies have reported that context-dependent relational retrieval of episodic memory may be mainly mediated not by the MTL structures but by the prefrontal areas [Cabeza et al., 1997; Eyler Zorrilla et al., 1996; Fujii et al., 2002; Henson et al., 1999; Nyberg et al., 1996a; Rugg et al., 1999]. Only one study [Burgess et al., 2001] reported posterior parahippocampal activation associated with location judgment. In this study, 'context' has a somewhat different meaning from the term used in the aforementioned studies. There may be two different kinds of context associated with episodic memory: temporal and spatial contexts in which the episodic contents were acquired and a thematic context that integrates several episodic components. The former have been found to be associated mainly with prefrontal activations. The present study suggests that the latter is associated with bilateral MTL activations.

As for the subregions in the MTL structures, our data showed that the parahippocampal gyrus was activated during relational retrieval processes. An fMRI study by Yonelinas et al. [2001] reported that the associative recognition compared to old-item recognition activated the bilateral hippocampal and parahippocampal regions as well as the left middle occipital gyrus. In addition, comparing new-item recognition to old-item recognition, the activated sites were restricted to the bilateral hippocampal regions and acti-

vation did not occur in the parahippocampal regions. The authors claimed that the parahippocampal regions might be related to relation processing in explicit remembering of episodes learned previously, but not to novelty detection related to the activity of the hippocampus. Thus, the results of Yonelinas et al. [2001] and our own suggest that the parahippocampal structures may differentially contribute to relational processing in episodic retrieval.

Finally, we consider an alternative explanation for the activation patterns of the MTL structures that were found in our study in the SR task. Nyberg et al. [1996b] proposed that medial temporal activity is related to retrieval success rather than to retrieval attempt. In the present study, all 40 of the probes were old in the SR task but 10 of the 40 probes were new in the PRe task. Thus, subjects might recognize presented stimuli at the higher frequency during the SR task (100%) than during the PRe task (75%). We should also consider another aspect that might increase this difference. In the present study, because the decision in the PRe task was whether both items presented were old, there was a possibility that subjects would essentially be able to stop their retrieval attempts as soon as they encountered a new item. This means that on the five trials in which the top panel was new, participants did not need to proceed to attempt to recognize the bottom panel (which was old). To assess this possibility, we conducted an ANOVA for reaction time data across three types of stimulus presentation (old/old, old/new, and new/old) during the PRe task. If participants stopped their retrieval attempts as soon as they encountered a new item, the reaction time for new/old would be shorter than for the other stimuli, for which participants have to check both panels for successful performance. The actual reaction time data for new/old were not different from those for old/old or old/new, suggesting that subjects scrutinized both panels during all three types of stimulus presentation. Thus, the difference between the SR and PRe conditions with respect to the likely engagement in item retrieval was 25% (100% vs. 75%) at most. Although we assume that the difference between 100% and 75% old is not substantial and that the observed activation difference during the SR vs. PRe conditions reflects relational retrieval processes, the present experimental design leaves room for the possibility that the activation of the MTL structures reflects the different frequency of the recognition process of the individual items. Further investigations are required to clarify this issue.

Right prefrontal activation during item recognition without relational processing

The PRe task in the present study differentially activated the right prefrontal areas, especially the lateral ventral prefrontal regions. Henson et al. [1999] argued that the dorsal lateral region of the right prefrontal cortex is associated with contextual monitoring demanding concentration, whereas a more ventral region of the right prefrontal cortex is associated with retrieval-related processes that are independent of such task demand. In line with their findings and suggestions, our finding of right ventral prefrontal activation may be related to simple recognition processes of stimuli studied previously in the absence of more complicated retrieval demands.

In the PRe task of this study, subjects were required to judge whether or not the two scenes presented were both learned previously. For correct responses, the subjects had to focus on the details of each scene without paying much attention to their contextual relationship or to the cartoon story. Thus, the right inferior frontal gyrus may play an important role in recognizing the details of an individual component involved in an event experienced previously. This cognitive demand requiring subjects to scrutinize stimuli in detail may explain the somewhat surprising finding that performance in the PRe condition was inferior to that in the SR condition.

Other researchers have speculated that these right prefrontal activations during episodic retrieval are related to the mode of retrieval [Lepage et al., 2000; Nyberg et al., 1995], degree of retrieval effort [Schacter et al., 1996] or post-retrieval processing [Rugg et al., 1996]. In our study, new stimuli were used in the PRe task but not in the SR task, and the result of behavioral performance showed that the PRe task was more difficult than the SR task. These facts suggest that the degree of retrieval effort may be higher in the PRe task than in the SR task. Thus, a possibility remains that the right prefrontal activations were related to retrieval effort, although there was not a large (25%) difference in the frequency of old stimuli between the SR and PRe tasks.

We used nonverbal figural stimuli as probes in this study. Several previous studies have reported that the right inferior frontal gyrus is activated during the processing of nonverbal materials, irrespective of encoding or retrieval processes [McDermott et al., 1999; Wagner et al., 1998]. In an fMRI study by McDermott et al. [1999], the inferior frontal gyrus showed left-lateralized activations during the processing of words, but right-lateralized activations during the processing

of unfamiliar faces. Because the stimuli used during all of the conditions in the present study were figures, the right inferior frontal activation during PRe is probably related to the differences of retrieval processes, rather than to the stimulus types.

Activation of bilateral middle frontal areas common to both retrieval tasks

Based on the meta-analysis of earlier PET studies, Tulving et al. [1994] proposed the hemispheric encoding/retrieval asymmetry (HERA) hypothesis, which emphasized the importance of the right prefrontal cortex for episodic memory retrieval and of the left prefrontal cortex for episodic memory encoding and semantic memory retrieval. Since its proposal, many reports have appeared that demonstrate right prefrontal activation in various episodic memory retrieval tasks [Buckner and Koutstaal, 1998; Cabeza and Nyberg, 2000; Desgranges et al., 1998; Fletcher et al., 1997; Nyberg, 1998]. In contrast, another meta-analysis of functional neuroimaging studies proposed that, in episodic memory retrieval, relatively simple processes are subserved by the right prefrontal cortex and the more reflectively demanding and systematic processes are subserved by the left prefrontal cortex. This is known as the theory of cortical asymmetry of reflective activity (CARA) [Nolde et al., 1998a]. In line with this account, several recent functional neuroimaging studies have presented evidence that the left prefrontal cortex is more important for episodic retrieval with memory sources [Nolde et al., 1998b; Rugg et al., 1999]. As for the lateralization of activity associated with episodic memory retrieval, the present finding that the bilateral middle frontal activation was commonly identified during two experimental tasks is consistent with the CARA theory, because even the PRe task in the present study may be regarded as more complex than the recognition tasks employed in previous studies.

CONCLUSION

We used fMRI to investigate neural activities during the retrieval of relation within an organized episode and recognition of an episodic component. Both retrieval conditions were associated with the activity of some common regions. The MTL structures, especially the parahippocampal areas, differentially contributed to the relational processing across components in episodic memory retrieval, whereas the right inferior

frontal and precentral gyri contributed to item recognition without relational processing. The present findings suggest that the MTL structures may be needed to retrieve and integrate several episodic components stored in diverse brain regions when context-dependent relational retrieval is required.

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REFERENCES

- Brown MW, Aggleton JP (2001): Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat Rev Neurosci* 2:51–61.
- Buckner RL, Koutstaal W (1998): Functional neuroimaging studies of encoding, priming, and explicit memory retrieval. *Proc Natl Acad Sci U S A* 95:891–898.
- Burgess N, Maguire EA, Spiers HJ, O'Keefe J (2001): A temporoparietal and prefrontal network for retrieving the spatial context of lifelike events. *Neuroimage* 14:439–453.
- Cabeza R, Mangels J, Nyberg L, Habib R, Houle S, McIntosh AR, Tulving E (1997): Brain regions differentially involved in remembering what and when: a PET study. *Neuron* 19:863–870.
- Cabeza R, Nyberg L (2000): Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 12:1–47.
- Desgranges B, Baron JC, Eustache F (1998): The functional neuroanatomy of episodic memory: the role of the frontal lobes, the hippocampal formation, and other areas. *Neuroimage* 8:198–213.
- Eichenbaum H, Schoenbaum G, Young B, Bunsey M (1996): Functional organization of the hippocampal memory system. *Proc Natl Acad Sci U S A* 93:13500–13507.
- Eichenbaum H (1997): Declarative memory: insights from cognitive neurobiology. *Annu Rev Psychol* 48:547–572.
- Eldridge LL, Knowlton BJ, Furmanski CS, Bookheimer SY, Engel SA (2000): Remembering episodes: a selective role for the hippocampus during retrieval. *Nat Neurosci* 3:1149–1152.
- Eyler Zorrilla LT, Aguirre GK, Zarahn E, Cannon TD, D'Esposito M (1996): Activation of the prefrontal cortex during judgments of recency: a functional MRI study. *Neuroreport* 7:2803–2806.
- Fletcher PC, Frith CD, Rugg MD (1997): The functional neuroanatomy of episodic memory. *Trends Neurosci* 20:213–218.

- Friston KJ, Frith CD, Frackowiak RS, Turner R (1995): Characterizing dynamic brain responses with fMRI: a multivariate approach. *Neuroimage* 2:166–172.
- Fujii T, Moscovitch M, Nadal L (2000): Memory consolidation, retrograde amnesia, and the temporal lobe. In: Cermak LS, editor. *Handbook of neuropsychology*. 2nd ed. Amsterdam: Elsevier. p 23–250.
- Fujii T, Okuda J, Tsukiura T, Ohtake H, Miura R, Fukatsu R, Suzuki K, Kawashima R, Itoh M, Fukuda H, Yamadori A (2002): The role of the basal forebrain in episodic memory retrieval: a positron emission tomography study. *Neuroimage* 15:501–508.
- Henke K, Buck A, Weber B, Wieser HG (1997): Human hippocampus establishes associations in memory. *Hippocampus* 7:249–256.
- Henke K, Kroll NE, Behnia H, Amaral DG, Miller MB, Rafal R, Gazzaniga MS. 1999a. Memory lost and regained following bilateral hippocampal damage. *J Cogn Neurosci* 11:682–697.
- Henke K, Weber B, Kneifel S, Wieser HG, Buck A. 1999b. Human hippocampus associates information in memory. *Proc Natl Acad Sci U S A* 96:5884–5889.
- Henson RN, Shallice T, Dolan RJ (1999): Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis. *Brain* 122:1367–1381.
- Jacoby LL, Dallas M (1981): On the relationship between autobiographical memory and perceptual learning. *J Exp Psychol Gen* 110:306–340.
- Lepage M, Habib R, Tulving E (1998): Hippocampal PET activations of memory encoding and retrieval: the HIPER model. *Hippocampus* 8:313–322.
- Lepage M, Ghaffar O, Nyberg L, Tulving E (2000): Prefrontal cortex and episodic memory retrieval mode. *Proc Natl Acad Sci U S A* 97:506–511.
- Maguire EA, Frackowiak RS, Frith CD (1997): Recalling routes around London: activation of the right hippocampus in taxi drivers. *J Neurosci* 17:7103–7110.
- Maguire EA, Burgess N, Donnett JG, Frackowiak RS, Frith CD, O'Keefe J (1998): Knowing where and getting there: a human navigation network. *Science* 280:921–924.
- Mandler G (1980): Recognizing: the judgment of previous occurrence. *Psychol Rev* 87:252–271.
- McDermott KB, Buckner RL, Petersen SE, Kelley WM, Sanders AL (1999): Set- and code-specific activation in frontal cortex: an fMRI study of encoding and retrieval of faces and words. *J Cogn Neurosci* 11:631–640.
- Mishkin M, Suzuki WA, Gadian DG, Vargha-Khadem F (1997): Hierarchical organization of cognitive memory. *Philos Trans R Soc Lond B Biol Sci* 352:1461–1467.
- Nadel L, Moscovitch M (1997): Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr Opin Neurobiol* 7:217–227.
- Nolde SF, Johnson MK, Raye CL. 1998a. The role of prefrontal cortex during tests of episodic memory. *Trends Cogn Sci* 2:399–406.
- Nolde SF, Johnson MK, D'Esposito M. 1998b. Left prefrontal activation during episodic remembering: an event-related fMRI study. *Neuroreport* 9:3509–3514.
- Nyberg L, Tulving E, Habib R, Nilsson LG, Kapur S, Houle S, Cabeza R, McIntosh AR (1995): Functional brain maps of retrieval mode and recovery of episodic information. *Neuroreport* 7:249–252.
- Nyberg L, McIntosh AR, Cabeza R, Habib R, Houle S, Tulving E. 1996a. General and specific brain regions involved in encoding and retrieval of events: what, where, and when. *Proc Natl Acad Sci U S A* 93:11280–11285.
- Nyberg L, McIntosh AR, Houle S, Nilsson LG, Tulving E. 1996b. Activation of medial temporal structures during episodic memory retrieval. *Nature* 380:715–717.
- Nyberg L (1998): Mapping episodic memory. *Behav Brain Res* 90:107–114.
- Oldfield RC (1971): The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97–113.
- Price CJ, Friston KJ (1997): Cognitive conjunction: a new approach to brain activation experiments. *Neuroimage* 5:261–270.
- Reed JM, Squire LR (1997): Impaired recognition memory in patients with lesions limited to the hippocampal formation. *Behav Neurosci* 111:667–675.
- Rugg MD, Fletcher PC, Frith CD, Frackowiak RS, Dolan RJ (1996): Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. *Brain* 119:2073–2083.
- Rugg MD, Fletcher PC, Frith CD, Frackowiak RS, Dolan RJ (1997): Brain regions supporting intentional and incidental memory: a PET study. *Neuroreport* 8:1283–1287.
- Rugg MD, Fletcher PC, Chua PM, Dolan RJ (1999): The role of the prefrontal cortex in recognition memory and memory for source: an fMRI study. *Neuroimage* 10:520–529.
- Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS (1996): Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. *Proc Natl Acad Sci U S A* 93:321–325.
- Schacter DL, Wagner AD (1999): Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus* 9:7–24.
- Scoville WB, Milner B (1957): Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* 20:11–21.
- Squire LR, Zola-Morgan S (1991): The medial temporal lobe memory system. *Science* 253:1380–1386.
- Squire LR, Alvarez P (1995): Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr Opin Neurobiol* 5:169–177.
- Talairach J, Tournoux P (1988): Co-planar stereotactic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. Stuttgart: Georg Thieme.
- Tulving E (1972): Episodic and semantic memory. In: Tulving E, Donaldson W, editors. *Organization of memory*. New York: Academic Press. p 381–403.
- Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S (1994): Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad Sci U S A* 91:2016–2020.
- Tulving E, Markowitsch HJ, Craik FE, Habib R, Houle S (1996): Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cereb Cortex* 6:71–79.
- Wagner AD, Poldrack RA, Eldridge LL, Desmond JE, Glover GH, Gabrieli JD (1998): Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *Neuroreport* 9:3711–3717.
- Woods RP (1996): Modeling for intergroup comparisons of imaging data. *Neuroimage* 4:S84–94.
- Yonelinas AP, Hopfinger JB, Buonocore MH, Kroll NE, Baynes K (2001): Hippocampal, parahippocampal and occipital-temporal contributions to associative and item recognition memory: an fMRI study. *Neuroreport* 12:359–363.