Role of Medial Temporal Lobe in Extensive Retrieval of Task-Related Knowledge

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ABSTRACT: The role of medial temporal lobe (MTL) in deep semantic processing was examined in a triple semantic judgment task in which subjects were asked to decide which one of the two bottom words was more semantically fit to the top word. By changing the number of bottom words that are semantically related to the top word, we can disassociate effects of reactivating the "old" semantic associations and effects of establishing "new" semantic associations on the MTL. The results of event-related fMRI analysis indicated that MTL was more activated in the retrieval of old semantic associations than in the establishment of new semantic associations. The function of MTL in this semantic judgment task was explained as subserving the process of extensive retrieval of task-related knowledge. *Hippocampus 2002;12:487–494.*

KEY WORDS: semantic processing; retrieval of old semantic associations; establishment of new semantic associations; medial temporal lobe (MTL); event-related fMRI

INTRODUCTION

Previous neuroimaging research has proved the involvement of medial temporal lobes (MTL) in deep semantic processing (Kapur et al., 1996; Mottaghy et al., 1999; Wagner, 1998; Lepage et al, 2000). However, the precise role of MTL in deep semantic processing remains unknown. Recently, Henke et al. (1999) showed that there were more MTL activations in the condition in which subjects were required to decide whether the two presented words (e.g., "level" and "need") fit together in meaning than to decide whether each of the two presented words was pleasant or unpleasant. Based on this work, Henke et al. suggested that it was the formation of the new semantic associations between two unrelated words, rather than deep semantic processing of each single word, that led to activation of MTL. This hypothesis is extremely important in that MTL, especially the hippocampal formation, has generally been supposed to subserve the formation of associations (Moscovitch, 1995; Squire and Zola-Morgan, 1991; Squire, 1992; Eichenbaum et al., 1994).

However, the hypothesis put forward by Henke et al. (1999), i.e., that MTL participated in establishing new semantic associations, is not consistent with the observation that semantic memory can be acquired without hippocampal formation (Vargha-Khadem et al., 1997). We argue that it is the reactivation of previously formed ("old") semantic knowledge, rather than the formation of new semantic associations, that leads to MTL activation. In particular, the judgment of whether the two presented words fit together in meaning led to deeper and wider retrieval of the old semantic meanings of these two words than the simple judgment of pleasantness of each word did.

In the present research, a triple semantic judgment task, in which subjects were asked to decide which one of the two bottom words was more semantically fit to the top word, was adopted to test this possibility. By manipulating the number of bottom words that has previously established ("old") semantic associations with the top target word, as either no, one, or two semantic associations (condition unrelated, one-sided, and two-sided, respectively), we can examine the involvement of MTL in the retrieval of old semantic associations, and in the establishment of new semantic associations. In this task situation, the more bottom words are semantically related to the top word, the more "old" semantic association are retrieved; on the contrary, the fewer bottom words are semantically related to the top word, the more components of forming new semantic associations are involved. If MTL is more challenged by the process of forming "new" semantic associations, then it should be more activated in the unrelated condition than in one-sided and two-sided condition. By contrast, if MTL is more challenged by the retrieval of "old" associations, the reverse tendency should hold. This triple semantic judgment

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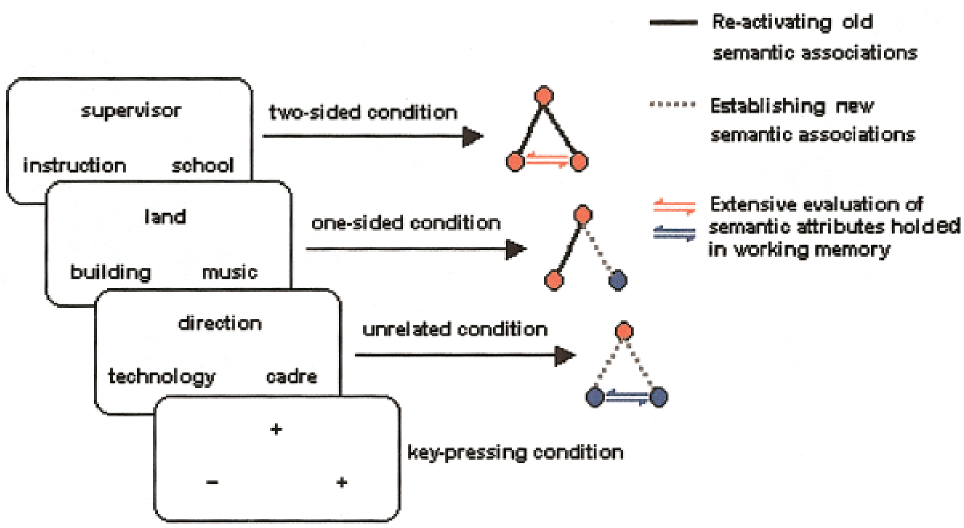

FIGURE 1. Experimental design. In the right hand of each semantic judgement condition, triangles constructed by red or blue dots demonstrated the components of re-activating old semantic associations and the components of establishing new semantic associations involved in each condition. Two-sided condition involved two-sided activation of old semantic associations (e.g., supervisor and instruction, supervisor and school) and competitions between the bottom items; one-sided condition involved one-sided activation of old semantic assocations (e.g., land and building) and one-sided establishment of new semantic associations (e.g., land and music); unrelated condition involved two-sided establishment of new semantic associations (e.g., direction and technology, direction and cadre) and competitions between the two bottom words.

task can also be used to examine the role of prefrontal cortex (PFC) in contradiction reconciliation. That is, when both or none of the two bottom words are semantically related to the top one (two-sided condition and unrelated condition), subjects must inhibit contradictions and competitions between two bottom words to achieve a decision. When only one word is semantically related to the top one (one-sided condition), such competition reconciliation process is unnecessary.

In a recent positron emission tomography (PET) research conducted by Lepage et al. (2000), a name of category was presented on the top, whereas two words for which both, one, or none belong to that category were presented on the bottom; in this study, subjects were asked to judge how many of the bottom words belonged to the top category. The results showed that activity in right parahippocampus increased with the number of words (0, 1, or 2) that belonged to the category (top word). This observation can be re-

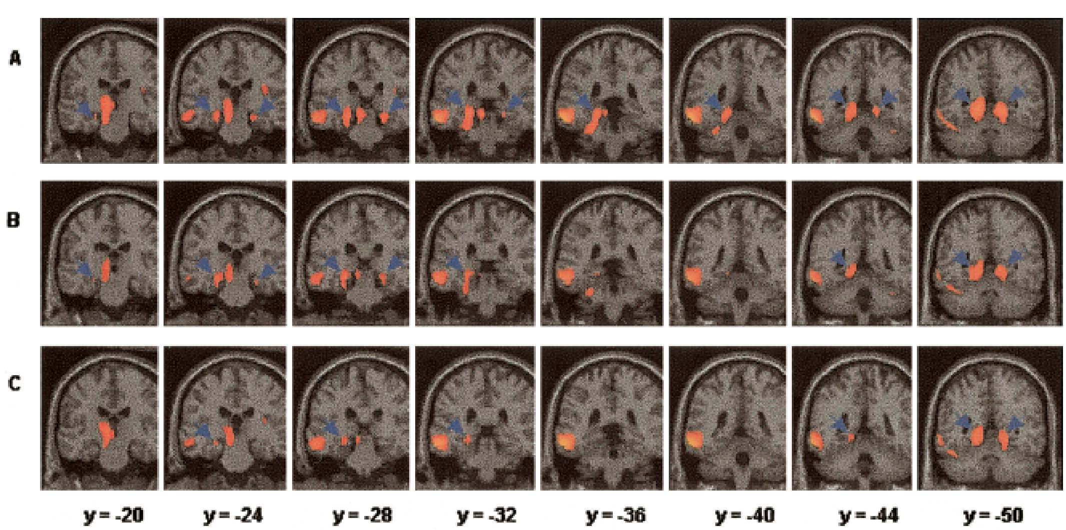

FIGURE 2. Coronal sections from $y = -20$ to $y = -50$ of Talairach space showing the high contrasted territories of activities when the three semantic judgement conditions were contrasted with the Key-pressing baseline respectively: A, Two-sided minus Key-pressing; B, One-sided minus Key-pressing; C, Unrelated minus Key-pressing. The activated MTL areas were marked by the blue arrows. These were the results of 12 subjects normalized into Talairach space and imposed on a universal brain. Contrasts were thresholded at T score $\geq$ 4.49 ($p < 0.05$, corrected).

TABLE 1.

Reaction Time of Three Semantic Judgement Conditions in the Practice Session (ms)

	Two-sided	One-sided	Unrelated
Minimum	1777	1447	2064
Maximum	2919	2497	3566
Mean	2401	1878	2978
SD	400	326	524

garded as evidence that the MTL participated in the reactivation of old semantic associations, rather than the formation of new semantic associations. However, the cognitive task in the research carried out by Lepage and colleagues was different from the fit-in-meaning judgment in the research performed by Henke et al.

Our present research employed the same fit-in-meaning judgment task as that reported by Henke et al. (1999), as well as an event-related method that could avoid the formation of specific mental "set" or strategy induced in a block design in which the same type of items were presented continuously.

MATERIALS AND METHODS

Subjects

Twelve healthy, right-handed volunteers (six females and six males) ages 20–26, with a mean age of 21.6 years, recruited from the undergraduates/graduates of University of Tsukuba, participated in this experiment. Subjects were excluded if they had any medical, neurological, or psychiatric illness, or, if they did not feel well in the magnetic resonance imaging (MRI) machine. All subjects were interviewed several days before they attended the functional fMRI experiment and gave informed consent that followed the MRI ethics committee in the Electrotechnical Laboratory (now the Neuroscience Research Institute, AIST).

Cognitive Tasks

In the key-pressing baseline condition, subjects were presented with three marks, either "−" or "+" arranged in a triple form, in which one mark was on the top of screen, while the other two were on the bottom (Fig. 1). The subject's task was to judge which of the bottom marks, the bottom left or right, was the same as the top one, and to press the corresponding left or right key. Only one of the two bottom marks was the same as the top mark.

In the three semantic judgment conditions, subjects were presented with triples of words (two-character Kanji words) with one on the top and the other two on the bottom. They were asked to make a subjective judgment as to which of the bottom words (the bottom left or the bottom right) was more semantically fit to the top word, and to press the corresponding left or right key to indicate their selection. In the two-sided condition, both bottom words were semantically related to the top target; in the one-sided condition, only one bottom word was semantically related to the top word; and in the unrelated condition, neither bottom word was semantically related to the top word (Fig. 1). All the words or ± marks in each triple were presented simultaneously for 4.5 s and followed by a 2.2-s unfilled delay; 72 triples generated from 216 popular Japanese two-character words were used in the formal experiment (there are 24 triples in each conditions). These triples were designed by the experimenter and evaluated by co-researchers.

The entire formal experimental session consisted of four blocks. There were 21 items in each block, 18 of them belonged to the three semantic judgment conditions with six items for each, three of the items belonged to the key-pressing baseline. (In addition, there was an arithmetic condition unrelated to the major topic of this article, which is therefore not reported here.) Within each block, various kinds of items were presented in a randomized order.

Before scanning, subjects received practice on the key-pressing condition and three semantic judgment conditions with another set of similar materials, in the same way as in the formal experiments.

fMRI Scanning

All scanning was performed on a 3.0-T MRI scanner (GE 3T Signa) equipped with EPI capability; 18 axial slices (5.5 mm thick, interleaved) were prescribed to cover the whole brain. A T2*-weighted gradient echo EPI was employed. The imaging parameters were TR = 2 s, TE = 32 ms, FA = 70 degrees, and FOV = 20 × 20 cm (64 × 64 mesh). To avoid head movement, subjects were asked not to talk during scanning, and to wear a neck brace.

Image Analysis

Images were preprocessed (time slice adjusted, realigned, normalized, and smoothed) by SPM99. The image data of 12 subjects were then estimated to establish a fixed-effect model, using the event-related analysis module of SPM99. Five types of events, including the key-pressing condition, the three semantic judgment conditions, and an arithmetic condition (not reported here) were defined. The threshold was set at $P < 0.05$, corrected for multiple comparisons (T = 4.49). The SPM coordinates for standard brain from Montreal Neurological Institute (MNI) were converted to Talairach coordinates by a non-linear transform method (Image Homepage, //www.mrc-cbu.cam.uk/Imaging/mnispace.html).

RESULTS AND DISSCUSSION

Behavioral Results

Reaction time (RT) was not recorded in the formal experimental session with fMRI scanning. RT in the practice session showed a significant difference among the three semantic judgment conditions, $F_{2,22} = 59.359$, $P = 0.000$; further analysis showed that the

TABLE 2.

Activations in the Six Sets of Contrasts Among the Three Semantic Judgment Conditions of the Experiments

Contrasts	Region	Coordinate (x,y,z)			T value
Two-sided minus one-sided					
	B. GFi45	−48	18	10	7.63
		54	14	10	5.53
	B. GFm46	−42	26	21	6.43
		54	27	25	6.16
	B. GFm9	−46	25	36	6.2
		42	19	27	4.64
	B. GFm6	−28	22	54	6.12
		38	11	55	5.31
		−40	1	53	4.65
	L. GFs8	−4	22	47	7.01
		−18	33	44	6.08
	R. GFm8	34	22	52	6.36
	L. GOs19	−34	−76	37	6.37
	L. Ga39	−46	−68	29	6.22
	L. LPi39	−57	−57	25	4.64
	L. Th	−6	−14	1	5.15
	L. Gh35	−20	−35	−8	4.73
	L. GC30	−8	−52	6	4.54
	R. LPi7	34	−66	37	5.57
One-sided minus two-sided					
	L. GFm9	−32	46	33	7.03
	L. GTs22	−61	−4	8	6.08
		−63	−17	6	5.58
	L. LPs7	−18	−61	60	4.56
	L. Cu19	−6	−88	32	4.5
	R. GpoC3	46	−17	56	4.88
Two-sided minus unrelated					
	B. GOs19	−36	−78	32	6.33
		−38	−74	39	5.82
		38	−74	31	4.98
	B. GC30	−6	−52	8	5.65
		6	−52	8	5.06
	B. Gh35	−20	−32	−12	5.51
		20	−30	−10	5.4
	L. GFi44	−50	10	7	4.9
	L. GFm8	−30	30	48	5.22
	L. LPi39	−48	−69	20	6.03
Unrelated minus two-sided					
	L. GFm10	−34	57	12	4.86
	R. GFm46	34	46	27	5.03
	R. Cu18	9.9	−88	17	4.66
One-sided minus unrelated					
	L. GTs22	−59	−8	4	6.06
	R. GFm10	46	44	−11	4.61
	R. Gh28	26	−24	−16	4.92
	R. Gh28/34	22	−16	−14	4.59

TABLE 2. (Continued)

Contrasts	Region	Coordinate (x,y,z)			T value
Unrelated minus one-sided					
	B. GFi47	−32	31	−8	5.38
		40	21	−4	5.22
	L. GFi45	−46	20	12	7.14
	L. GFm6	−46	6	44	6.93
		−40	2	50	6.32
	L. GFs8	−4	16	47	8.39
	R. GC32	10	23	32	5.82
	L. GTm21	−48	6	−32	4.71
	R. GOm18	28	−85	15	4.86
		28	−93	10	4.84

The coordinates (x, y, z) are the locations that contain the peak voxel within the area of activation in a given contrast. The anatomical regions (the abbreviation names and the Brodmann areas) were the approximate Talairach locations according to their coordinates (x, y, z). Contrasts were thresholded to $p < 0.05$, corrected for multiple comparisons, T score of each activation was shown in the right column. B., bilateral; L., left; R., right; GFi, inferior frontal gyrus; GFm, middle frontal gyrus; GFs, superior frontal gyrus; GOs, superior occipital gyrus; Ga, angular gyrus; LPi, inferior parietal lobule; Th, thalamus; Gh, parahippocampal gyrus; GC, cingulate gyrus; GTs, superior temporal gyrus; LPs, superior parietal lobule; Cu, cuneus; GPoC, postcentral gyrus; GOm, middle occipital gyrus.

RT in the unrelated condition was significantly longer than that of two-sided and one-sided condition, and the RT of the two-sided condition was also significantly longer than that of the one-sided condition (Table 1).

Image Results

When contrasted with the key-pressing baseline, all three semantic judgment conditions showed MTL activation, although the contrast of "unrelated minus key-pressing" involved less activation than the contrast of the "two-sided minus key-pressing" or "one-sided minus key-pressing" did (Fig. 2). The critical contrasts were conducted within the three semantic judgment conditions. Table 2 lists the activations exhibited in all possible contrasts. In particular, activations located in the MTL and those located in prefrontal areas were considered.

In summary, three contrasts revealed significant MTL activation. In the contrasts of "two-sided minus unrelated," there were bilateral parahippocampal activations; in the contrasts of "Two-sided minus one-sided," there were right parahippocampal activations; and in the contrasts of "one-sided minus unrelated," there were left parahippocampal activations. Moreover, in all of the highlighted parahippocampal locations, the event-related plots exhibited positive signal changes in the voxels that have the maximal value in the contrasts (Fig. 3). However, no MTL activation was exhibited in the contrasts of "unrelated minus two-sided," "unrelated minus one-sided" and "one-sided minus two-sided."

As for the prefrontal cortex, two contrasts exhibited dominant and strong activation: the "two-sided minus one-sided" contrast and the "unrelated minus one-sided" contrast. In these contrasts, activations were located in the bilateral ventral PFC (Brodmann area 45 and 47), bilateral dorsolateral PFC (Brodmann area 46 and 9), bilateral motor cortex (Brodmann area 6), and left superior frontal gyrus (Brodmann area 8). Although there were also PFC activations in other contrasts, such as "two-sided minus unrelated," "one-sided minus two-sided," "one-sided minus unrelated," and "unrelated minus two-sided" (Table 2), these activations were relatively weak and the event-related plots of the averaged signal change (%) of the best fitting canonical hrf from the voxels that have the maximal value in the contrasts exhibited negative changes, except for the one located in inferior frontal gyrus (Brodmann area 45) in the "two-sided minus unrelated" contrast, where the signal change was positive.

DISCUSSION

When contrasted with the key-pressing baseline, all of the three semantic judgment conditions exhibited significant MTL activation. However, these activations cannot be attributed to the formation of new semantic associations, because the contrasts of "unrelated minus two-sided," "unrelated minus one-sided," and "one-sided minus two-sided" failed to exhibit MTL activation. Rather, these activations can be attributed to the reactivating of old semantic associations, because there were significant MTL activations in the contrasts of "two-sided minus unrelated," "two-sided minus one-sided," and "one-sided minus unrelated."

It may not be the amount of retrieved semantic information, but rather the amount of available task-related knowledge, that makes the difference. The task-related knowledge is the semantic knowledge that is specifically useful and closely related to the task at hand. There were no more semantic memories retrieved in the two-sided and one-sided conditions than in the unrelated condition, considering the response time in unrelated condition was longer than in two-sided and one-sided conditions. At least subjects retrieved more semantic information to achieve a judgment in

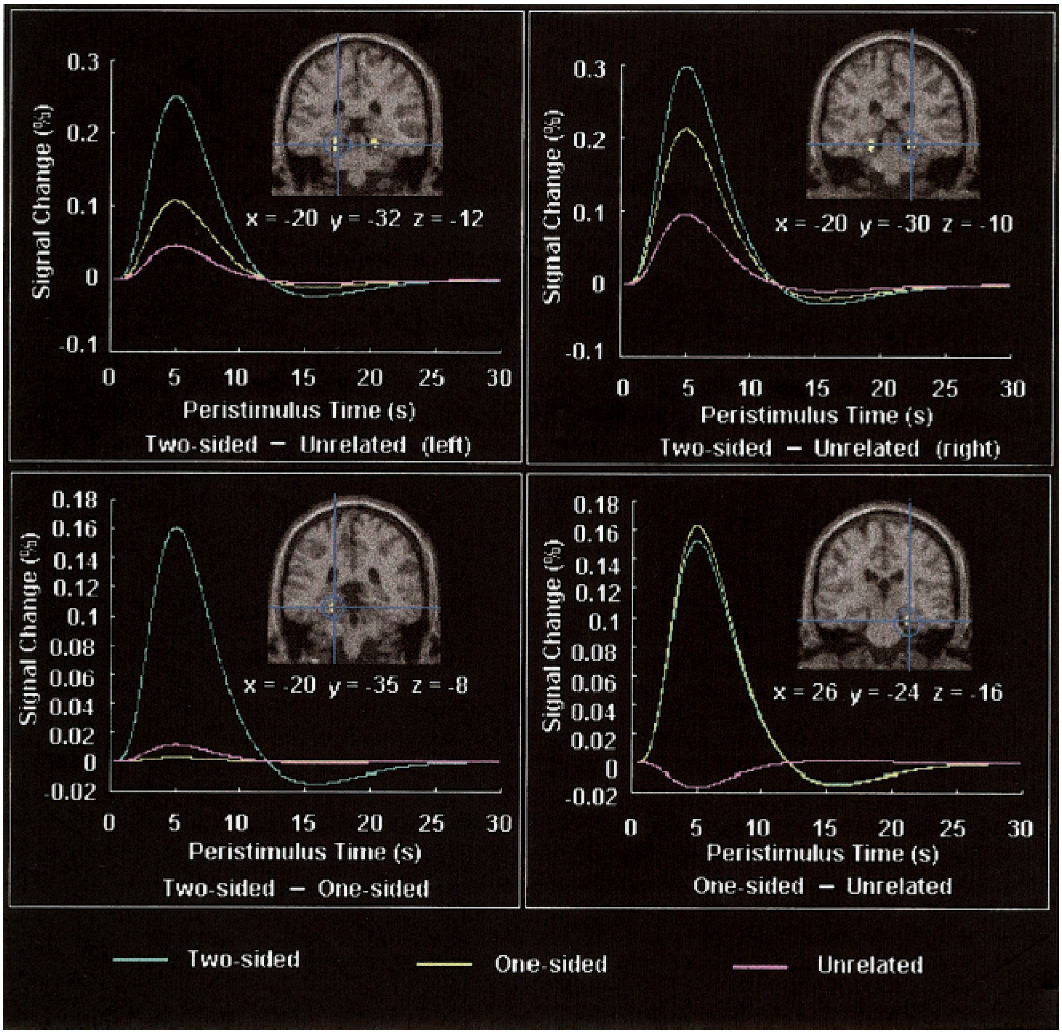

FIGURE 3. Parahippocampal activations that were revealed in the contrasts of "Two-sided minus Unrelated" (top two panels), "Two-sided minus One-sided" (bottom left panel), and "One-sided minus Unrelated" (bottom right panel). The coronal sections and event-related plots were shown in each panel, thresholded at T score $\geq$ 4.49 ($p < 0.05$, corrected). The coronal sections are the results of 12 subjects normalized into Talairach space and imposed on a universal brain. The event-related plots are averaged signal change (%) of the best-fitting canonical hemodynamic response function (HRF) of 12 subjects from the voxels (as marked by the blue circle and cross in the coronal sections and as located by the value of x, y, and z of Talairach space under the map) that have the maximal value in each contrast.

the unrelated condition than in the one-sided condition. However, the availability of related semantic information that was specifically useful to the task at hand must be different. In the two-sided and one-sided conditions, subjects received more "useful" semantic information related to their judgment than they did in the unrelated condition.

This hypothesis gives sense to the fact that the experiment carried out by Henke et al. (1999) failed to demonstrate significant MTL activation when the deep single word encoding condition was contrasted with the shallow single word encoding condition, but in a similar experiment by Wegner et al. (1998), the MTL was highlighted. In experiments conducted by Henke et al. (1999), the semantic task is pleasant/unpleasant judgment, and the materials were emotional neutral abstract words. Subjects could subjectively consider one abstract word as "pleasant" or "unpleasant," but they could not receive much task-related semantic information in such a condition. In contrast, in the experiments carried out by Wegner et al. (1998), the deep semantic judgment is a concrete/abstract judgment, in which one-half of the items were concrete and one-half were abstract. For this reason, the availability of task-related knowledge was greater in the task reported by Wegner et al. (1998) than in the task reported by Henke et al. (1999). Similarly, in the experiment conducted by Lepage et al.(2000), the greater the number of bottom words that belonged to the top category, the more task-related knowledge available, and MTL activation can also be attributed to the availability of task-related knowledge. In a research by Dolan and Fletcher (1997), the role of hippocampal formation was supposed to subserve the encoding of novel category-exemplar pairs while the left PFC subserves the changing of situational old category-exemplar pairs. However, it is also possible to attribute the hippocampal activations observed in their experiments to the process of extensive task-related knowledge, if we deeply consider their experimental situation. In their experiment, half of items (i.e., category-exemplar pairs) were changed subtly (e.g., the exemplar of "boxer" was paired with the category "dog" first, and then paired with another category "sportsman" in later trials). Subjects were asked to keep the pairs they saw in mind for a later memory test (an intentional encoding instruction). It is reasonable to suppose that subjects might involve subtle semantic retrieval (to predict a situation in which different categories paired with the exemplars, or different exemplars paired with the category) when they encoded the new category-new exemplar pairs, because they anticipated certain combination changes in the later trials. Also, it was the retrieval of task-related knowledge that occurred this process that really challenged the MTL.

However, the availability of task-related semantic information itself may be not enough to challenge the MTL, considering the fact that most semantic tasks failed to reveal hippocampal activations (reviewed in Cabeza and Nyberg, 2000). One possibility is the typical semantic cognitive task does not involve extensive and subtle semantic retrieval as our triple semantic judgment task does.

It is also worth noting that MacKay et al. (1998) found that the famous amnesia, H.M., also exhibited a deficit in the semantic tasks that required subtle utilities of semantic information (to discover the ambiguities in sentences). This implied that the MTL was involved in the deep semantic processing task (but see Schmolck et al., 2000, for a different point of view). More interestingly, H.M. did not exhibit the "aha" or insight-like reactions usually displayed by normal subjects when they resolve the problems successfully. This insight-like reaction can be considered a sudden retrieval or realizing of task-related knowledge. Because of the damage on MTL, H.M. lacked such kind of insight-like reactions.

Although it was well known that MTL is essential for declarative memory, it was also known that deep encoding (usually semantic processing task) could significantly promote episodic memory performance. In the SPI model (Tulving, 1995), encoding of episodic memory must go through the semantic memory system, and it is reasonable to suppose that, with more extensive involvement of the semantic process, the better the episodic encoding. Our present research implied that the MTL could (through subserving the extensive retrieval of task-related knowledge) contribute to efficient episodic encoding, just as the deep level-of-processing (LOP) did.

Memory is an adaptive mechanism of the organism. The purpose of memory is not for memory itself; memory is for survival. Throughout the long history of evolution, memory enables the organism to keep the information that owns great survival values in mind for future usage. And, in some sense, we can regard the extensive retrieval of task-related knowledge as a kind of mental events that owns great survival values. Treating the MTL as the cognitive mechanism that is sensitive to the extensive retrieval of task-related knowledge and as the cognitive mechanism that is responsible for keeping the mental events that own great survival values in mind for future usage may improve our understanding on the function of MTL in long-term memory. This is our future research target (see also Niki and Luo, 2002, for the time-limited role of MTL in long-term memory).

Prefrontal activation was frequently reported in semantic tasks; it has been hypothesized that the left PFC subserves semantic retrieval (Buckner et al., 1995; Demb et al., 1995; Demonet et al., 1992; Kapur et al., 1994). However, later research showed that it was semantic selections, rather than semantic retrieval, that led to left PFC activations (Thompson-Schill et al., 1997). Our results supported this hypothesis, in that there were strong left PFC activation in the contrasts of "two-sided minus one-sided" and "unrelated minus one-sided." The one-sided condition involved less competition and inhibition components than the two-sided and unrelated conditions did, and therefore called for fewer selecting activities (see also D'Esposito et al., 1999; Jonides et al., 2000, for a more general concept of inhibition functionally located in left PFC). Our results also highlighted right PFC in the above-mentioned contrasts, meaning that when the task was complicated and difficult, right PFC could also participate in reconciling the competitions (Garavan et al., 1999).

In sum, our research implied that if there was much task-related semantic knowledge available, the MTL would be involved in processing, and, if there were contradictions among the retrieved semantic information, the PFC would be involved in processing.

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