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Involvement of the medial temporal lobe in priming for new associations

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Abstract

This study was addressed to the question of whether the medial temporal lobe (MTL) plays a critical role in implicit memory for new associations. Priming for new associations was examined in two different tasks in 18 patients with focal lesions all involving the MTL. In Experiment 1, following a study phase for pairs of unrelated words, subjects performed a perceptual identification task on old, recombined, and new pairs of words presented at brief exposure durations. In contrast to control subjects, and despite a normal level of item priming, the patients failed to show superior identification of the old pairs relative to the recombined pairs, the measure of associative priming. In Experiment 2, subjects engaged in speeded naming of the print color for previously studied words presented in the original color or in a different old color, and for unstudied words. Again, in contrast to control subjects and despite a normal level of item facilitation on color naming reaction time (RT), the patients failed to show priming for recently experienced new associations between words and colors. Explicit recognition memory by the patients was abnormal in both experiments. This study records an absence of priming for new associations, in two different tasks in which the nature of the stimuli was considerably different, in a large group of patients with lesions in the MTL. Although some previous research has reported significant associative priming in other tasks for patients with MTL lesions, the present results suggest that this region is critical for forming new associations of the types assessed here.

Keywords: Associative priming; Medial temporal lobe; Lesion; Implicit memory

1. Introduction

Priming is an important technique for assessing implicit memory that does not require conscious retrieval processes. There are two major types of priming effects: item priming, and priming for new associations, also called associative priming. Item priming is hypothesized to reflect the operation of perceptual representation systems that are described as functionally independent of the episodic or declarative memory system [36,41]. Associative priming should reflect the formation of a new association, which has no prior existence in the memory system and is encountered for the first time during a study episode [1,18,41]. To form new associations, subjects must integrate the individual items or components, by processing the co-occurrence and/or relation between them. In the test session, memory for one part of the new association can facilitate the retrieval of other parts of the association. For example, in the stem completion test, after learning some unrelated word pairs (e.g. *window–reason*, *apple–kite*), subjects are asked to complete the stem of the second word of old pairs (*window–rea_*), recombined pairs (*apple–rea_*) and new pairs (*bottle–pic_*) with the first words that come to mind. If the proportion of completions for the old pairs is higher than that for the recombined ones, this is regarded as an effect of priming for new associations. Superior performance for word completion within recombined pairs relative to new pairs is regarded as a single word, or item priming, effect. The commonly used paradigms for testing priming for new associations include stem completion (e.g. [18,23,24,32]), speeded naming (e.g. [25–29,31]), lexical decision (e.g. [15–17,23]) and perceptual identification (e.g. [12]).

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It has been suggested that item priming relies not on the medial temporal lobe (MTL)–diencephalic system, but rather on neocortical regions, such as occipital or frontal cortex [4,36,40,41]. The finding of a double dissociation between item repetition priming and recognition memory strongly supports this suggestion [10,11,21]. Research with positron emission tomography (PET) also seems to fit with this idea. For example, blood flow reduction in right posterior cortex during the stem completion task contrasts with increased regional cerebral blood flow in regions related to recognition, including right prefrontal cortex and the right hippocampal region [2,35,39]. Some recent functional magnetic resonance imaging (fMRI) studies have also revealed priming-related reduction of activity in occipital and infero-temporal cortex [3,4,20], for a review, see [5], although the results of Henson et al.'s study suggest that this effect may be modulated by stimulus familiarity [20].

The mnemonic processes and neuroanatomical basis of associative priming are less clear. One issue, on which the available data are mixed or even in conflict, is the status of priming for new associations in amnesic patients. For example, using word stem completion, Graf and Schacter [18,19] demonstrated that priming for new associations was seen only in mild to moderate amnesia, but not in dense amnesia, which suggested different neural bases for item priming and associative priming. Shimamura and Squire [37], and Mayes and Gooding [22] reported a significant correlation between associative priming and the General Memory Index of the Wechsler Memory Scale (WMS). Furthermore, Chun and Phelps [6] explored the neural correlates of priming for new associations with an implicit contextual learning paradigm. The experimental task was to locate a visual target stimulus (the rotated letter 'T') among a background of many rotated 'L' distractors. The amnesic patients were no faster to detect the old displays than the new ones, but their perceptual learning was intact [6]. This result suggests that the medial temporal lobe system is engaged in contextual learning, not because of its role in conscious retrieval processes, but because of its critical function in forming associations between items or stimuli [9]. In contrast, other studies have concluded that normal associative priming can be demonstrated in amnesia. For instance, Moscovitch et al. [25] reported that amnesic patients, as well as those with Alzheimer's disease, read old pairs of words faster than both recombined and new pairs. Similarly, Gabrieli et al. [12] demonstrated equivalent priming for new associations in amnesic cases and normal controls, although the patients' explicit memory was of course impaired. More recently, Goshen-Gottstein et al. [17] also showed that, when tested in an implicit lexical decision task and an explicit speeded-recognition task, amnesic patients responded more quickly and accurately to the old pairs than to the recombined ones, whereas their explicit performance was impaired.

In short, the status of associative priming in amnesia remains controversial. And this controversy about the behavioral data corresponds to a debate about whether associative priming is mediated by the medial temporal lobe–diencephalic system, because these are the principal brain regions impaired in, and generally accepted to be responsible for, the amnesic syndrome. Two theoretical viewpoints seem to exist. In both accounts, the patients' impaired explicit memory is attributed to medial temporal lobe–diencephalic damage. According to one hypothesis, which would be supported by normal associative priming in amnesia, item priming and associative priming arise from the same cortical processing mechanism(s) which must be intact in amnesic patients. According to the other hypothesis, which would fit with demonstrations of absent or severely reduced associative priming in amnesia, only item priming is supported by the intact cortical region(s). On this latter view, the formation of new associations between previously unrelated events or representations, even if assessed by implicit techniques, requires the medial temporal lobe–diencephalic system in the same way that explicit memory does.

Note that the neuroanatomical expression of these hypotheses could, and should, be made even more specific, as it seems unlikely that the MTL and the diencephalon perform identical functions or share equal responsibility for various aspects of memory. Unfortunately, because most of the studies germane to these questions have tested patients of mixed etiologies and without very precise lesion specification, it would be difficult to draw firm conclusions from existing data about the neuroanatomical underpinnings of associative priming even if the behavioral data were unambiguous.

There is a fair amount of evidence consistent with the hypothesis that MTL regions, including the hippocampus and adjacent cortical structures, are essential for the formation of associations or connections between previously unrelated stimuli or features [38,40,42]. In this study, therefore, instead of making amnesia the criterion for inclusion, we selected exclusively cases with focal MTL lesions as subjects, with the goal of directly investigating the role of the MTL in associative priming. To better characterize the relationship between associative priming and explicit memory, we measured the severity of each patient's memory deficits before the priming experiments, and the patients were divided into mild and severe memory deficit subgroups based on this measure. We employed word identification and speeded naming tasks to index associative priming, because it has been suggested (e.g. [17,25]) that associative effects in these tasks are less open to explicit contamination than in the stem completion task. To further reduce the potential of explicit contamination, we used an awareness questionnaire, similar to the one in McKone and Slee [23], to exclude control participants who consciously retrieved the stimuli in the test session. We also conducted two separate experiments, with different types of stimuli, because the MTL may be differentially important in associations between two separate items with an abstract relation between them versus associations between two features of a single stimulus, where the relationship between the features may be more perceptually based [6,33].

In Experiment 1, the test phase consisted of a perceptual identification task, in which subjects were asked to identify briefly presented and masked pairs of words. With reference to word pairs from the study phase, word pairs at test were old (original pairings), recombined (studied words but in different combinations), or new. In Experiment 2, the subjects studied a series of colored words, and then were asked to name the color in which test words appeared; test items could be old words in their original colors, old words in old but different colors, or new words in old colors. In both experiments, we also measured recognition memory for the same test stimuli so as to compare associative priming with explicit memory. The order of the two experiments was counterbalanced across subjects, but explicit memory tests always followed the corresponding implicit memory tests. The two experiments were performed on the same day, with an interval of about half an hour between them.

2. Subjects

Eighteen patients (12 male, 6 female) with lesions confined to the MTL were all recruited from neurosurgical or neurological departments of hospitals in Beijing, China. The mean age of the patients was 35.72 ± 13.74 years, and their mean level of education was 11.50 ± 2.75 years. None of the patients had aphasia, anomia, apraxia or agnosia, and none had difficulty in following task instructions. Patients with severe paralysis were also excluded. All cases had normal or corrected-to-normal vision, and none had achromatopsia. No patient had a relevant family history or a previous personal history of neurological illness. Based on pathological studies of the lesioned tissue, all patients except one were diagnosed as having brain tumors. Among these, six patients had astrocytic gliomas, four had meningiomas, four had malignant gliomas, two had metastatic tumor, and one had oligodendroglioma. The patients had various neurological signs and symptoms to varying degrees, such as headache (16 patients), dizziness (16), difficulty in recalling recent events (14), epileptic phenomena (12), vomiting (10), and olfactory hallucination (1).

All of the patients' lesions were localized to medial temporal lobe regions with CT and/or MRI scanning. The lesions, 12 on the left and 6 on the right, were mainly limited to the hippocampus (including the dentate gyrus and subiculum), amygdala and parahippocampal region (including entorhinal and perirhinal cortex) [38,42]; but some extended to adjacent neocortical regions such as lateral temporal cortex. We categorized the lesioned ranges into three degrees (small, medium and large), according to the lesion's size and whether it extended beyond the medial temporal lobe. Information on the location, extent and pathology of damage for each patient is listed in Table 1.

The mean memory quotient (MQ) of the patients was 77.28 ± 18.89, as measured by the Chinese version of the WMS [14]. For purposes of comparison with other related papers, we divided the patients into two sub-groups with MQ = 80 as cutoff criterion. The mean MQ's of the mildly impaired (8 subjects) and severely impaired (10 subjects) sub-groups were 94.00 ± 10.28 and 63.90 ± 12.01, respectively. Mean standard scores from individual subtests of the WMS for the patient and control groups are presented in Fig. 1.

Subjects in the control group were matched to the patients in terms of age, gender, education and profession. Initially, 25 control subjects participated in the experiments, but seven were discarded from the data analysis with reference to the criteria of McKone and Slee [23], because these

Table 1
Basic information for MTL lesioned patients

Patient	Gender	Age (years)	Education (years)	Pathology	Lesioned location	Extent of the lesions	MQ
2	Male	36	12	Astrocytic gliomas	Left H, fornix	Small	51
12	Female	24	16	Malignant gliomas	Left H, TL	Large	51
13	Male	50	9	Malignant gliomas	Left H, PH, TL	Large	51
14	Male	43	19	Malignant gliomas	Left PH, H, A, TL	Large	51
10	Male	39	9	Astrocytic gliomas	Right H, PH, TL	Large	65
3	Male	43	9	Meningiomas	Right H, PH	Medium	66
1	Female	47	9	Astrocytic gliomas	Left H, PH, A, TL	Medium	71
8	Male	59	16	Metastatic tumor	Left H	Medium	76
18	Female	43	12	Astrocytic gliomas	Right H, A, TL	Large	77
15	Male	21	12	Unknown	Left H	Small	80
7	Female	17	9	Oligodendroglioma	Left H, A, TL	Medium	84
11	Male	19	9	Meningiomas	Left H, A, TL	Medium	84
16	Male	58	9	Metastatic tumor	Right H, A, TL	Large	85
4	Male	21	12	Meningiomas	Left H, thalamus	Medium	90
9	Female	37	16	Astrocytic gliomas	Left H, A, TL	Large	95
5	Male	19	12	Meningiomas	Right PH, TL	Medium	97
17	Male	24	12	Astrocytic gliomas	Right PH, H, TL	Large	106
6	Female	43	12	Malignant gliomas	Left A, H	Small	111

Abbreviation: H, hippocampus; PH, parahippocampus; A, amygdala; TL, temporal lobe.

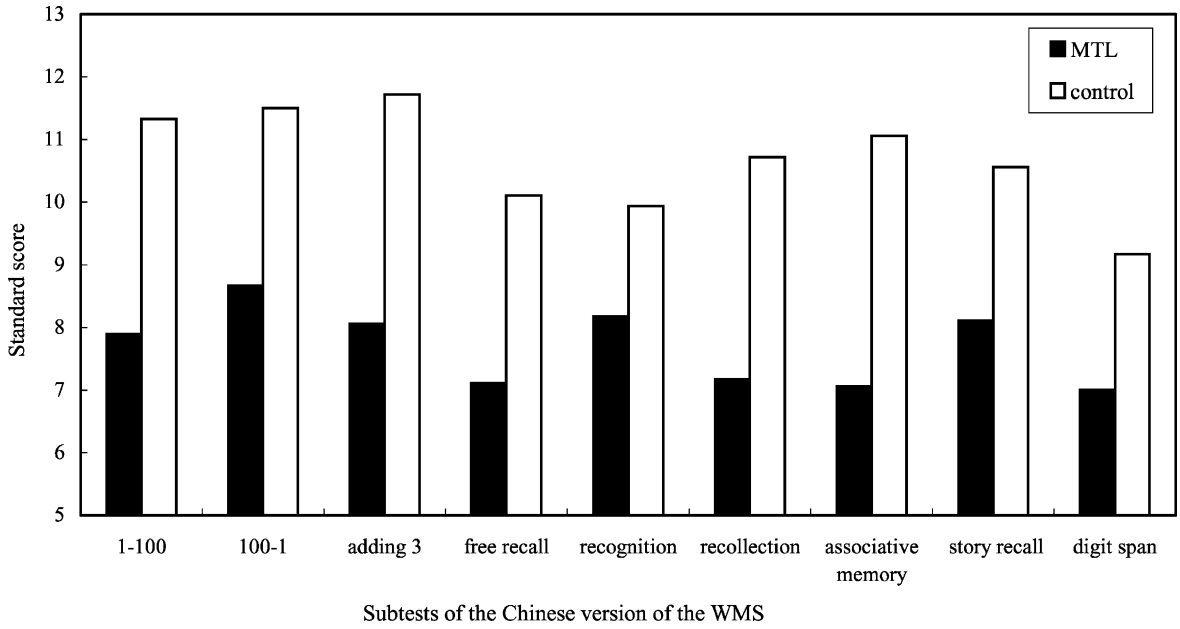

Fig. 1. Mean standard scores for each subtest of the Chinese version of the WMS. With the exception of scores on the recognition and digit span tests, all others yielded a significant difference between the MTL patients and control subjects, $P < 0.05$.

participants' responses on an awareness questionnaire suggested conscious retrieval of primed information in either experiment (see below). For the $N = 18$ control subjects included in the analysis, mean age was 34.89 ± 11.58 years, mean level of education was 11.72 ± 3.14 years, and mean MQ was 107.61 ± 11.22.

3. Experiment 1

3.1. Methods

3.1.1. Materials

A total of 210 two-character Chinese words were selected to form 105 unrelated word pairs, for example, 玫瑰 –磁铁 (rose–magnet) 钥匙 –核桃 (key–walnut), 直觉 –名誉 (intuition–honor). No obvious semantic, orthographic or phonological relationship existed between the two words in each pair. All the context and target words had medium frequencies of occurrence (372 ± 160 per million) and medium numbers of strokes (17.10 ± 3.24). Since all Chinese characters correspond to one spoken syllable, each word (two characters) had two syllables. No target word or its component characters occurred more than once in the study session.

Out of 105 word pairs, 65 word pairs, including five pairs for pretraining, were used to determine the exposure duration for each subject. Thirty word pairs were used as study and test material. These target pairs were divided into three sets of 10 each to be used as old, recombined and new pairs, respectively. Two sets were presented in the study session, while the third set was used as the baseline in the perceptual identification test. Of the remaining 10 pairs, 5 were used for practice and 5 as fillers. The arrangement of these materials was counterbalanced such that each set appeared equally often in the different experimental conditions.

A five-item awareness questionnaire, based on the questionnaire in McKone and Slee [23], was used in the control group to exclude those who consciously retrieved the word pairs in the perceptual identification test. Compared to Bowers and Schacter [1], the assessment prepared by McKone and Slee [23] has two additional questions designed to determine whether subjects had noted, during perceptual identification, the presence of some word pairs encountered during the study phase, and if so, whether their strategy had changed as a result. For any subject meeting criteria for conscious awareness plus strategy change on this questionnaire, the experimental data were excluded from the subsequent analysis.

3.1.2. Procedure

3.1.2.1. Determination of the exposure duration yielding 20–30% accuracy for each subject. Sixty pairs of words were divided into six groups, 10 pairs per group. The initial exposure duration was 200 ms for the patients and 100 ms for the control subjects. The instructions for the perceptual identification task were the following: "This task is to test your reaction time. You will see some word pairs on the screen which are presented very rapidly. Please say aloud what you saw as quickly as possible." Subjects were seated approximately 60 cm from the screen and looked directly at the center of the screen in preparation for the brief appearance of the pair. The characters of each word were arranged

horizontally like "玫瑰 –磁铁 " (rose–magnet). Preceding the presentation of each word pair, a fixation character "+" was displayed at the center of the screen, and an auditory signal was also presented to alert the subject to the imminent arrival of the stimulus pair. Following fixation, 500 ms later, a word pair was presented for the appropriate duration and then masked immediately by an irregular and meaningless drawing consisting of character-like strokes. Then subjects were asked to say aloud what they had seen as quickly as possible. The experimenter recorded the responses, which were considered correct if the subject reported both words in the correct order. Measurements began after the subject had seen the five practice pairs two times each. If the percentage of correct report was higher than 30%, the exposure duration of the next 10 pairs was reduced by 16.7 ms. On the other hand, if the percentage correct was lower than 20%, the duration of the next 10 pairs was increased by 16.7 ms. If subjects identified none or all of the 10 pairs, the duration was changed by 33.4 ms. Using this procedure over the six sets of word pairs, the exposure duration for each subject was gradually set to yield a percentage of correct identification of word pairs in the range of 20–30%.

3.1.2.2. Study session. Five minutes after the duration-setting phase, subjects were asked to generate a meaningful sentence for each of 20 word pairs and say the sentences aloud. Pairs were presented at the center of the screen. At the beginning of the session, subjects practiced with five word pairs to make sure that they understood the instructions and were familiar with the procedure. Each pair was presented for 5 s and then replaced with "+" on the screen until the subject produced a sentence and then pressed "ENTER" to continue.

3.1.2.3. Test session. After the study phase, subjects performed mental arithmetic (serial subtraction of 7 starting from 100) continuously for 3 min. Then subjects were asked to finish the perceptual identification task. Thirty test pairs, which included old, recombined and new pairs, were presented in random order with the predetermined exposure duration. Then subjects performed an explicit recognition test on word pairs, presented for 5 s each, in either the same or different combinations as those in the study session. Subjects were asked to respond "same" or "different" as quickly and accurately as possible. Note that both old and recombined pairs were identically constituted for the perceptual identification and recognition tests. At the end of the experiment, normal subjects were asked to fill in the awareness questionnaire.

3.1.3. Statistical analysis

The experimental manipulations included group as a between-subjects factor (MTL lesioned versus control group), and both type of word pair (old, recombined, new pairs) and task (perceptual identification versus recognition) as within-subject factors. In the perceptual identification task, the level of performance on old pairs relative to recombined ones was regarded as an index of associative priming, while performance on recombined pairs relative to new ones was treated as the measure of item repetition priming.

Table 2
Proportion correct in the perceptual identification test (mean ± S.D.) for each subject group in each experimental condition

Group	*N*	Old pairs	Recombined pairs	New pairs
Control	18	0.66 ± 0.12	0.48 ± 0.14	0.23 ± 0.11
MTL patients	18	0.49 ± 0.14	0.52 ± 0.16	0.23 ± 0.06
Mildly impaired MQ	8	0.59 ± 0.08	0.55 ± 0.14	0.24 ± 0.05
Severely impaired MQ	10	0.42 ± 0.13	0.49 ± 0.18	0.22 ± 0.06

3.2. Results

Table 2 presents the proportions of correct perceptual identification of word pairs by each subject group for each of the three pair types. Normal subjects identified more old pairs than recombined ones and more recombined pairs than new ones; but MTL patients, in both mild and severe memory deficit sub-groups, were only more successful on old and recombined pairs than new ones, with no advantage for old relative to recombined words. A two-way repeated measures analysis of variance (ANOVA) revealed a significant main effect of pair type, $F(2, 34) = 211.99$, $P < 0.01$, and a reliable interaction between group and pair type, $F(1, 34) = 11.41$, $P < 0.01$. The main effect of group failed to achieve significance, $F(1, 34) = 2.03$, $P = 0.16$. The difference between recombined and new pairs in both groups reached significance, $t(17) = 6.64$, $P < 0.001$ and $t(17) = 8.64$, $P < 0.001$, respectively, which indicated reliable item repetition priming in patients as well as controls. But the difference between old and recombined pairs was significant only in the control group, $t(17) = 5.17$, $P < 0.001$, indicating a failure of priming for new associations in MTL damaged subjects. Supporting this conclusion, there was a statistically significant difference between groups in the proportion of correctly identified old pairs, 0.66 for the controls versus 0.49 for the patients, $t(34) = 3.79$, $P < 0.001$. The subgroup of patients with the milder memory deficit identified numerically more old pairs than recombined ones (0.59 versus 0.55), but the difference was not statistically significant, indicating a lack of notable associative priming even in these milder memory deficit patients.

In a correlational analysis for patient data only, the correlation between associative priming and MQ was moderate and significant (Pearson's $r = 0.63$, $P < 0.05$, two-tailed). In the mild memory deficit subgroup, however, this correlation was not significant, $r = 0.25$, $P = 0.55$. Pearson's correlation between item priming and MQ was also not reliable, $r = 0.17$, $P = 0.31$, and there was no significant correlation between associative priming and the extent of brain lesion.

To assess explicit recognition memory, for each subject we calculated the proportion of old pairs correctly recognized

Table 3
Explicit recognition scores (mean ± S.D.) in Experiment 1: hit rate, false-alarm rate and d'

Group	Hit rate	False-alarm rate	d'
Control	0.87 ± 0.12	0.34 ± 0.18	2.88 ± 1.30
MTL patients	0.79 ± 0.15	0.46 ± 0.26	1.30 ± 1.32
Mildly impaired MQ	0.85 ± 0.13	0.34 ± 0.28	1.90 ± 1.51
Severely impaired MQ	0.74 ± 0.15	0.56 ± 0.21	0.81 ± 0.96

Note: d' scores are means of the individual-subject d' values, not d' scores based on the mean hit and false-alarm rates.

(hit rate), the proportion of recombined pairs incorrectly attributed to the study list (false-alarm rate), and d' (see Table 3). Discrimination between old and recombined pairs in the MTL lesioned group (mean $d' = 1.30$) was significantly lower than that of the normal group (mean $d' = 2.88$), $t(34) = 3.62$, $P < 0.01$, which confirms the patients' impaired explicit memory. No significant correlation was obtained between associative priming and d' either in MTL patients as a whole group ($r = 0.40$, $P = 0.08$) or in the milder memory deficit subgroup ($r = 0.42$, $P = 0.21$).

3.3. Discussion

This experiment revealed three noteworthy results regarding the patients with MTL lesions. (1) Item repetition priming was observed in both the patient and control groups, as measured by a significant advantage for perceptual identification of recombined word pairs relative to completely new pairs; this benefit was of virtually identical magnitude across normal and impaired subject groups. (2) Associative priming was observed for the control subjects but not the MTL patients; unlike controls, the patients showed no advantage in identifying briefly presented words in old pairs relative to recombined pairs. (3) The patient group as a whole, and especially the more severe subgroup, showed impaired explicit recognition memory as measured by discrimination between true old and recombined word pairs.

The results of this experiment are consistent with the hypothesis that the MTL mediates learning of and priming for new associations. Since all words in old and recombined pairs were seen in the study session, the only difference between them was the presence or absence of an experimental, episodic association between particular word combinations. The fact that the patients displayed not only abnormal recognition memory for, but also an absence of priming from, old pairs suggests that the MTL is vital in the formation of new associations, whether the task is explicit or implicit.

Data from control subjects whose answers on the awareness questionnaire suggested deliberate reference to explicit, episodic memory for studied pairs during performance of the perceptual identification test were excluded from the analysis. (Although we did not test the MTL patients with the awareness questionnaire, it seems unlikely that their performance was affected much if at all by explicit memory, because both their associative priming and recognition were significantly impaired.) Moreover, correlation measures between associative priming and explicit recognition memory were insignificant in both MTL patients as a whole and the milder memory deficit subgroup. For these reasons and others, we treat the significant advantage for identification of old > recombined pairs in the control group as an associative priming effect that does not depend crucially on explicit memory for studied pairs. We do, however, acknowledge the possibility of some contribution from episodic memory to the associative priming effect documented in the normal subjects, and we will return to this important issue in the general discussion.

Two kinds of relations can be the basis of associative priming: an association between two separate stimuli, or an association between two features of a single stimulus. Some previous results indicate that forming associations between unrelated word pairs depends on semantic encoding [18,19]. While the present results suggest that the MTL is required for forming this kind of association, it remains to be determined whether MTL lesioned patients would be more likely to display priming for an association between two features of a single stimulus, which might depend more on perceptual processing. We addressed this question in Experiment 2 by use of colored words as stimuli [28], in which the relationship that constitutes the basis for the new association is between two features or components of the same perceptual object.

4. Experiment 2

4.1. Methods

4.1.1. Materials

Forty-five Chinese two-character words were selected, such as "名誉" (honor). Each word was printed in blue, green, yellow or purple. The stimulus characteristics were the same as for the words in Experiment 1, except that all words in Experiment 2 had abstract meanings so as to avoid any relationship (congruent or incongruent) between the words and colors. Of 45 words, four were used as practice items and five as filler items. The remaining 36 words were used as formal study and test material, with nine words printed in each of the four colors. They were divided into three sets of 12 words each to be used as old, recombined and new words, respectively. Two sets were presented in the study session, the third only in the subsequent color naming test session. The new words appeared in the same four colors as the old and recombined words in the test session. The materials were counterbalanced so that each set would appear equally often in the three different experimental conditions.

4.1.2. Procedure

In the study session, we encouraged subjects to unitize the word and the color of the word together, by asking them

to attend to both features jointly. The subjects were asked say aloud the word's color, and then rate how much they liked the word in that color on a three-point scale. During the study session, each word was presented for 4 s and then disappeared, being replaced with "+" at the center of the screen. Two seconds later, another word appeared automatically. At the beginning of the study session, each subject practiced with four colored words to become familiar with the procedure. After naming the word colors and rating each of the 24 colored words, subjects subtracted 7 from 100 continuously for 3 min. Then subjects were asked to complete another color naming task. The instruction was the following: "This task is to test your reaction time. You will see some colored words on the screen. Please say aloud the name of the color in which each word appears as quickly as possible." All three sets of words (total $N = 36$) were presented; the computer recorded the reaction time (RT) from a voice key, and the experimenter recorded any errors in color naming. Afterward, subjects performed an explicit recognition memory test with the following instructions: "This task is a memory test. You will see some colored words on the screen. All of the words were seen in the study session. However, some of them are in the same color as in the study session (old words), some are in different colors (recombined words). Please press 'y' for the old words, and press 'n' for the recombined words as quickly as possible." Finally, normal subjects filled in the awareness questionnaire.

4.1.3. Statistics

The experimental manipulations included group as a between-subjects factor (MTL lesioned versus control group), and both word type (old, recombined, new words) and the type of task (color naming versus recognition) as within-subject factors. If subjects named the colors of words presented in their original (study session) colors significantly more quickly than the colors of the recombined words, this was treated as an index of positive associative priming. If subjects named the colors of the recombined words more rapidly than the colors of the new words, this was taken to reflect item repetition priming.

4.2. Results

Table 4 presents the mean reaction time for naming the colors of old, recombined and new colored words in the different subject groups. Normal subjects named the colors of words presented in their original colors more quickly than the recombined words, and those of recombined items more quickly than the colors of new words. By contrast, MTL patients as a whole group, and also in both mild and severe memory deficit subgroups, only named the colors of studied words (both old and recombined) more quickly than the colors of new words, with no advantage for original word–color pairings over recombinations. A two-way repeated measures ANOVA on color naming RTs revealed a main effect of word type, $F(1, 34) = 41.27$, $P < 0.01$, but neither a main effect of group (despite the fact that the patients had slower RTs overall than the control group) nor an interaction between group and word type (both $F < 1$). Both groups showed a significant RT advantage for naming the colors of recombined relative to new words, control: $t(17) = 5.83$, $P < 0.001$, and patients: $t(17) = 2.61$, $P < 0.05$, which indicated reliable item priming in both groups. There was also a significant difference between the recombined and old words in both groups, but in opposite directions: normal subjects named word color more quickly in old than in recombined words, as expected, $t(17) = 3.07$, $P < 0.001$; but the MTL patients showed the reverse pattern, $t(17) = 5.31$, $P < 0.001$. It should be noted that, in addition to the RT advantage for recombined relative to new words already reported, the MTL patients also named the colors of old words more quickly than the new words, $t(17) = 5.20$, $P < 0.0001$.

Table 4
Mean reaction time (ms) in color naming task (mean ± S.D.) for each subject group in each experimental condition

Group	*N*	Old words	Recombined words	New words
Control	18	807 ± 142	840 ± 147	862 ± 147
MTL patients	18	1068 ± 307	1034 ± 288	1116 ± 295
Mildly impaired MQ	8	897 ± 211	883 ± 199	959 ± 211
Severely impaired MQ	10	1204 ± 307	1155 ± 300	1242 ± 300

Mean accuracy for word color naming in the control group was about 0.95 in all three test conditions; in MTL patients, average accuracy was 0.93, 0.91 and 0.91 for old, recombined and new words, respectively. Although there was no significant difference in accuracy of word color naming for the different word types in either group as a whole, those patients whose mean RT to recombined words was less than that to old words did show higher accuracy for old than recombined words. The patients were divided into two subgroups according to whether the response times to recombined words were quicker or slower than those to old words. Percentages of correct responses for old and recombined words in each subgroup were tested, respectively. Subjects in the "negative" priming subgroup (i.e. where the mean RT to recombined words was less than that to old words) showed higher accuracy for old than recombined words that virtually reached conventional levels of significance (0.92 versus 0.87, $t(9) = 2.20$, $P = 0.055$). In the other subgroup, the mean accuracies for the old and recombined colored words were 0.95 and 0.94, respectively, $t(7) = 0.94$, $P = 0.38$. This result indicates that the apparent negative priming is related to the accuracy of the color naming task.

The correlation in the patient data between associative priming and MQ was moderate and significant (Pearson's $r = 0.58$, $P < 0.05$, two-tailed). In the mild memory deficit subgroup, however, this correlation was not significant, $r = 0.38$, $P = 0.33$. Pearson's correlation between item priming and MQ was also not reliable, $r = 0.34$, $P = 0.17$, and there

Table 5
Explicit recognition scores (mean ± S.D.) in Experiment 2: hit rate, false alarm rate and d'

Group	Hit rate	False alarm rate	d'
Control	0.73 ± 0.14	0.52 ± 0.19	0.83 ± 0.44
MTL patients	0.61 ± 0.14	0.58 ± 0.18	0.40 ± 0.45
Mildly impaired MQ	0.62 ± 0.14	0.54 ± 0.22	0.57 ± 0.60
Severely impaired MQ	0.60 ± 0.15	0.63 ± 0.15	0.27 ± 0.22

Note: d' scores are means of the individual-subject d' values, not d' scores based on the mean hit and false-alarm rates.

was no significant correlation between associative priming and the extent of damage.

As for explicit recognition of old pairings of words and colors, the patient group had a lower hit rate and a higher false-alarm rate than the controls, yielding a significant difference in d' (0.83 and 0.40, for control and MTL group, respectively), $t(34) = 2.88$, $P < 0.01$ (see Table 5). Note, however, that discrimination between original and recombined pairings of words and colors in this experiment, as measured by d', was very low in both groups. No significant correlation obtained between associative priming and d' in either MTL patients as whole ($r = 0.12$, $P = 0.9$) or the milder memory deficit subgroup ($r = 0.15$, $P = 0.72$).

4.3. Discussion

In Experiment 2, patients with MTL lesions failed to show any RT advantage in naming the colors of words presented in their originally studied colors, although item repetition priming (old or recombined versus new words) did have the expected significant benefit on speed of word color naming. Predictably, the patients' explicit memory for the word–color associations was also poorer than that of normal control subjects. This experiment not only corroborated and strengthened the results of Experiment 1, but also demonstrated that establishing a new implicit association depends on the MTL even when the items to be associated are two components or aspects of one stimulus rather than two separate stimuli.

In this experiment, the words were selected to have abstract meanings to ensure that there were no preexisting relations between the word and any color. Subjects were encouraged to attend to both the word and the color, and to store them together as a unit [28,29]. The only difference between the old and the recombined colored words was that the former stimuli were exactly what subjects had studied, whereas in the latter, the combination between color and word changed. A similar result was obtained in some previous studies of auditory priming, in which subjects were asked to identify low-pass filtered words when the speaker's voice was the same or different at study and test [7,34]. Unlike control subjects, the amnesic patients showed no word-identification advantage in the same-voice condition relative to the different-voice condition. Both their results and the results reported here suggest that priming for recently encountered new associations of two features of one stimulus depends on an intact MTL system.

Unexpectedly, the MTL patients named word color more slowly in old than in recombined words. This result could suggest a meaningful impact of associative priming in a negative direction, but we consider this unlikely. Note that, although it was a reliable difference, the RT advantage for color naming in recombined over old words was numerically smaller than the advantage for old words relative to new words in the MTL patients as a whole group and also in the mild subgroup. Furthermore, this apparent negative priming effect may be partly explained in terms of a small speed–accuracy trade-off, since accuracy of color naming was higher for old words than for recombined words. Although this effect was not significant when analyzed with the whole group, analysis with only those patients whose response times to recombined words were quicker than those to old words did show higher accuracy (with borderline significance) for old than recombined words. In other words, the apparent negative priming is related to accuracy of the naming task. We are reluctant to give too much weight or interpretation to this small effect, but suggest that it will be worthwhile to be vigilant for a similar phenomenon in future studies of this kind.

5. General discussion

The present study employed a task of perceptual identification of briefly presented word pairs in Experiment 1, and a task of speeded single word color naming in Experiment 2, to explore the role of the medial temporal lobe in the learning of new associations. Patients with MTL lesions, relative to matched controls, were characterized by (a) impaired explicit memory for, and (b) an absence of priming by, recently encountered new associations between the words of a pair in Experiment 1 and between words and the colors in which they were printed in Experiment 2. By contrast, the patients' performance was facilitated to a completely normal degree by item repetition priming in both experiments.

The functional architecture of human memory is revealed by dissociation among memory capacities in brain damaged patients, many from the study of amnesic patients. However, these findings do not necessarily elucidate the nature of the neural circuits on which various aspects of memory depend, unless the researchers are able to provide crucial information about lesion location. This was one of our aims in selecting exclusively cases with MTL lesions. Furthermore, terms like mild, moderate and severe amnesia are only rather imprecise descriptions of memory impairment and are likely to be used differently by various researchers [37]. In this study, we used the WMS to provide a systematic pre-experimental assessment of the patients' degree of memory deficit, which could then be related to various aspects of the experimental outcomes.

Studies of human amnesia plus animal models for this disorder have led to the view that the MTL is crucial in order to bind together previously unrelated events or representations [38,40,42]. Such binding is believed to be one of the mechanisms underlying explicit memory, and it is widely agreed that damage to the medial temporal lobe disrupts the creation of new explicit episodic memories that link such events or representations. Whether implicit memory for associated events also depends on this mechanism is debated; but the results in the present study offer a positive answer to this question. In our study, instead of using amnesia as the criterion for selecting subjects, we chose patients with focal MTL lesions. The outcome for the patients relative to matched controls was considerably reduced or even absent associative priming, even for the subgroup of patients with a mild memory deficit, in two different tasks with different types of stimuli. This outcome is most consistent with the hypothesis that any significant damage to the MTL compromises learning of new associations, whether the association concerns two separate items or two aspects of a single stimulus and whether the test is explicit or implicit.

The distinction between implicit and explicit memory has been intensively studied, with a combination of experimental psychology, neuropsychology, and recently of functional neuroimaging techniques. Converging evidence from all three approaches suggests that the source of implicit perceptual priming is activation of perceptual representations, but that explicit memory depends on episodic and/or semantic memory systems. Neuroanatomically speaking, implicit perceptual priming is thought to rely mainly on posterior neocortex, while explicit memory is mediated by the medial temporal lobe–diencephalic system. Most studies that support the dissociation of implicit memory and explicit memory, however, have used single items as experimental materials, with only a few extending the investigation to the relation between items. The distinction between implicit memory and explicit memory revealed by previous studies thus need not apply to all kinds of implicit memory tasks. If, as suggested by this and at least some other studies (e.g. [6,18,22,37]), amnesic patients can show normal item priming but reduced or absent associative priming, this would imply different brain mechanisms underlying these two kinds of priming effects. The present study further demonstrated an association between abnormal associative priming and impaired explicit memory in patients with MTL lesions. In general, our results support the hypothesis of Schacter et al. [34] that there are two forms of implicit memory. The form supported by the perceptual representation systems in posterior cortex is preserved in amnesic patients. The form resulting from an interaction between perceptual representations and episodic memory systems in the medial temporal lobe–diencephalic system is not preserved in amnesic patients, at least not those with focal MTL lesions.

It is important to deal with a potential problem in interpreting the absence of associative priming for the patients as a failure of implicit priming. The techniques employed here were *intended* to produce facilitation as a result of implicit, automatic priming; but of course normal participants also have recourse to explicit retrieval of episodic memories for previous stimulus presentations. Such explicit retrieval is presumably not available, or at least much less so, for the MTL patients. For control subjects, despite our use of tasks (masked perceptual identification and speeded naming) that are thought to be less prone to explicit 'contamination' [17,23,30]; and despite our exclusion of results from control subjects who admitted deliberate retrieval of studied information; we acknowledge that a contribution of episodic memory still cannot be completely ruled out.

Explicit contamination is a problem faced by all studies of this type, not just the present one. This problem was insightfully reviewed by Goshen-Gottstein et al. [17], who proposed three key criteria for a valid demonstration of intact implicit memory in amnesia. In one sense, because our experiments did not yield significant associative priming in the amnesic group, these criteria might seem irrelevant here; but we would like to argue that one of the criteria is germane to our claim that significant associative priming in the *control* group is not primarily attributable to explicit memory. According to Goshen-Gottstein et al., to interpret a priming effect in patients as deriving from implicit memory, "the same patients must show impaired performance on an explicit test, in which identical retrieval cues are provided to those presented in the implicit test" (p. 571). Both of our experiments did provide identical retrieval cues in the explicit and implicit tests; and we therefore consider it noteworthy that the control participants were substantially below ceiling in their explicit recognition of old as opposed to recombined word pairs in Experiment 1 (mean $d' = 2.88$), and even more noteworthy that they were frankly 'impaired' in their explicit recognition of original word–color pairs in Experiment 2 (mean $d' = 0.83$). Relatively poor performance in explicit memory by controls has also been reported in other studies. For example, in Chun and Phelps [6], the d' score of the control subjects was about 0.80, which is very similar to our results of experiment 2. Of course, this middling to poor explicit memory by control participants does not prove a complete absence of any contribution from explicit memory to their significant associative priming, but it does seem to reduce its likely importance.

There is another point. As stated above at the beginning of our discussion of this issue, the paradigms applied here were of course designed to permit implicit priming for the amnesic patients. It is essential to emphasize that they fully succeeded in this regard where *item* priming is concerned. In Experiment 1, the measure of item priming—benefit in perceptual identification of recombined pairs relative to new pairs—was of precisely the same magnitude for the control group and for the patients, even the severely impaired subgroup. And in Experiment 2, the RT benefit for naming the colors of recombined words relative to new words was actually larger for the patients (82 ms, or a 7.3% priming effect relative to the new word baseline) than for the controls

(a 22 ms advantage, which is a 2.5% priming effect). Given that the size of priming effects tends to rise with longer baseline RTs, we would not want to make too much of the fact that the item priming RT effect was larger in the patients who were also slower overall than controls; but it was certainly not smaller. In other words, single item priming effects were just as large for MTL patients as for controls in both experiments. Therefore, unless one were prepared to argue either (a) that the patients could use explicit retrieval for single words but not for pairs, or (b) that control subjects did use explicit retrieval for pairs but not for single words, the most plausible conclusion is that both normal and MTL subjects demonstrated implicit priming for items but only normal subjects showed implicit associative priming.

Additional evidence against a significant contribution of explicit memory to implicit memory comes from the absence of a significant correlation between recognition memory and associative priming in both experiments. Although this result still cannot conclusively eliminate the possibility of explicit contamination, it is more compatible with the hypothesis that the associative priming documented in the control subjects was not significantly affected by explicit retrieval.

Our results are of course consistent with previous research documenting reduced or absent associative priming in amnesia, either with a similar paradigm (e.g. [30]) or with different tasks (e.g. stem completion [18,22,37]; contextual learning [6]). But our results are also discrepant from reports of preserved priming for new associations between word pairs (e.g. [12,17,25]), and we need to try to understand these discrepant outcomes. One possible account is the methodological differences. For example, Gabrieli et al. [12], having observed intact associative priming in global amnesia, attributed its absence in the results from Paller and Mayes [30] to sequential presentation of the two words in each pair. They argued that new associations underlying visual priming "must be formed in a single percept of simultaneously presented words, and cannot be accessed across two sequential percepts" (p. 329). Goshen-Gottstein and Moscovitch [16] directly compared simultaneous and sequential presentation, and also highlighted the importance of simultaneous presentation for priming for new associations. The present study, however, makes it clear that simultaneous presentation of the items (or features) to be associated is not sufficient to guarantee positive associative priming. Two methodological differences between Gabrieli et al. and our Experiment 1 seem worth noting too, even though we are not confident that either or even both can account for the different outcomes. First, in the study session, target pairs were presented twice each by Gabrieli et al. but only once in our experiment. Second, the task performed at test was the same as that at study (reading word pairs aloud) in Gabrieli et al. but different in our experiment (sentence formation at study, perceptual identification at test). Goshen-Gottstein et al. [17] suggested that both of these characteristics might have contributed to an apparent associative priming effect in the study by Gabrieli et al. that was instead explicable in terms of a "gradual skill-learning mechanism."

The other possibility is that there may be two kinds of associative priming, one of which is dependent on MTL regions while the other is not. These two might be viewed as qualitatively different or (in our view, more likely) as forming a continuum. The type of associative priming encouraged in a particular experiment would depend on the stimuli and experimental procedures. We suggest that, if the association to be formed is more configurational, MTL structures are more likely to play a critical role and therefore amnesic patients with MTL lesions will be less likely to demonstrate significant associative priming. For example, Chun and Phelps [6] showed impaired implicit contextual learning in hippocampal patients in a spatial configuration task. They argued that this may "indicate that our patients were impaired at learning novel spatial configurations (which involves binding several relational associations between objects), rather than novel simple associations between global context and target locations." (p. 846). Goshen-Gottstein et al. [17] reported a positive associative priming effect in amnesic patients in a verbal association task. Thus, "whereas a word form system may be designed to form new entities by combining elements (as the case of Goshen-Gottstein et al.), other systems may require the hippocampal complex to do so. For example, systems implicated in representing spatial configurations may require the hippocampal complex for the formation of new associations ... (as the case of Chun and Phelps)" (Goshen-Gottstein et al. [17], p. 576). Our results were similar to Chun and Phelps [6] in that the explicit performance of our normal subjects was not very high (especially in Experiment 2), and our amnesic patients failed to show associative priming effects. Our results not only replicate but extend those of Chun and Phelps in that the lesions of our patients were all limited to unilateral MTL, and even the mild memory deficit patients had impaired associative priming.

There is another regard in which the outcome of our study may extend the conclusions of both Chun and Phelps [6] and Goshen-Gottstein et al. [17], in particular, and contribute to this issue in general: the demonstration of impaired associative priming in amnesic patients in verbal tasks involving the Chinese writing system. Chinese characters are morphographic linguistic elements, not pictures or ideograms; but they almost certainly invoke more spatial, configural processing than words written in alphabetic characters. For example, letters of an alphabetic word are always arranged in a strictly left-to-right (or, in Arabic and Hebrew, right-to-left) order, whereas the spatial organization of the semantic and phonetic radicals of Chinese characters can be left/right, top/bottom, or even outside/inside. Moreover, in contrast to the letters of the Roman alphabet, Chinese characters vary greatly in their number of strokes/visual complexity. Although this hypothesis is only tentative and needs experimental confirmation, these factors may mean that new associations involving written words are more likely to depend

on spatial processing (and hence the MTL system) in Chinese than in alphabetic writing.

The suggestion from the present study that the medial temporal lobe system is implicated in associative priming as well as explicit memory does not mean, of course, that there are no differences between these two phenomena, either functionally or neuroanatomically. Some researchers have recently attempted to differentiate the functions of the hippocampal and parahippocampal regions [8,13], suggesting that the parahippocampal region can bind different information into a semantic association, whereas the hippocampus can add contextually rich episodic or spatial information to the representation. Further study is needed to explore the cognitive functions of, and brain regions involved in, priming for new associations and the corresponding explicit memory.

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