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Research Report

Neural correlates of associative memory: The effects of negative emotion

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### Abstract

We explored brain activation associated with negative emotionality, during an associative memory task that involved the encoding and retrieval of word pairs. Participants were instructed to memorize word pairs and subsequently retrieve them. The word pairs consisted of either emotional or neutral words. Significant hippocampal activation was observed during both encoding and retrieval of the neutral word pairs, and was correlated with correct response rates during retrieval. However, the negative word pairs activated the left middle temporal gyrus during both encoding and retrieval. These results suggest that hippocampal activation is involved in both the encoding and retrieval of word pairs. However, negative emotionality does not necessarily enhance hippocampal activity and memory performance.

Keywords: associative memory, hippocampus, left middle temporal gyrus, emotion, fMRI

## Introduction

Humans and animals experience various events, and acquire vast knowledge through such experience. The whole of such stored knowledge and information constitutes “memory”. Most or all human (and animal) activities are supported by memory. The relationship between memory and emotion is of paramount importance, given that people experience various affective states over the course of daily life. Memory cannot truly be understood unless the effects of emotion are taken into account. Emotion may enhance memory processes that occur at all stages, including encoding, storage, and retrieval (LaBar and Cabeza, 2006). The majority of studies that have examined the neural mechanisms thought to underlie emotional memory have focused on encoding and storage, with little information being available about how emotion affects retrieval. A better understanding of how emotionality affects retrieval from memory is sorely needed, as such an understanding has important implications for how we conceptualize the dysfunctional accessibility of traumatic memory traces in various affective disorders.

Forming associations between to-be-remembered items is an important strategy for the successful formation of long-term memories, and neuroimaging studies have provided crucial information about the neural correlates that underlie this process. A variety of associative encoding tasks result in robust hippocampal activation, including the encoding of word pairs (Henke et al., 1999; Jackson and Schacter, 2004; Meltzer and Constable, 2005; Prince et al., 2005) and triplets

(Lepage et al., 2000; Addis and McAndrews, 2006), object pairs (Kohler et al., 2005), and name-face pairs (Sperling et al., 2001; Sperling et al., 2003). In addition to hippocampal activation, there have been several reports that successfully remembering words is associated with activation in the medial temporal cortex (Schacter and Wagner, 1999), parietal cortex, prefrontal cortex, and occipital cortex (Otten and Rugg, 2001).

Studies to date have investigated the effects of learning strategy (Henke et al., 1999) and degree of semantic relationships among stimuli (Lepage et al., 2000) on the neural activity that is observed during associative memory tasks. However, possible effects of negative emotionality associated with paired items (negative emotional valence of the items) have not been reported, even though it is known that emotional events are often better remembered than neutral events (Reisberg and Hertel, 2005). In studies of memory for single items, the medial temporal lobe (including the hippocampus) showed greater activation for emotional items than for neutral items, during both encoding (Dolcos et al., 2004) and retrieval (Dolcos et al., 2005). Furthermore, enhanced hippocampal activity during encoding is correlated with enhanced emotional memory (Hamann et al., 1999).

The memory-enhancing effect of emotion likely reflects the influence of the amygdala on the medial temporal lobe memory system. Although much functional neuroimaging evidence links the memory-enhancing effect of emotion to amygdalic modulation during encoding (Cahill et al.,

1996; Hamann et al., 1999; Canli et al., 2002; Kilpatrick and Cahill, 2003; Dolcos et al., 2004; Phelps, 2004; Richardson et al., 2004), few such effects have been reported for retrieval. Dolcos et al. (2005) showed that emotion enhances successful retrieval, which (like emotional encoding) appears to be associated with amygdalic functioning. Emotion-related enhancements of memory occur for both negative and positive events (Hamann et al., 1999). However, the effects of negative emotionality could be more important, at least from the standpoint of the negative rumination that is a core feature of various affective disorders.

Single item memory studies predominate in the emotion and memory literature. It is not yet clear whether similar emotionality effects can be observed on memory for associated word pairs. Indeed, emotion does not necessarily enhance memory. When faced with negative events, people tend to pay attention to central features of such events while ignoring peripheral details (Christianson, 1992; Berntsen, 2002). As a result, memory of the negative event itself is enhanced, whereas memory for peripheral events is impaired, relative to non-emotional events (Safer et al., 1998). We hypothesized that memory for the associations between paired items may be impaired by negative emotionality of the items. In the current study, we used fMRI to investigate the effect of negative item valence on brain activation, and we explicitly examined the relationship between memory performance and hippocampal activation.

## Method

Participants were 25 right-handed adults (13 female, 12 male; mean age = 23.5 years,  $SD = 2.7$  years) with normal or corrected-to-normal vision. Participants were undergraduate or graduate students with no depressive symptoms (measured using Beck Depression Inventory). Mean duration of education was 15.3 ( $SD 1.4$ ) years. Informed written consent was obtained from each participant after the study's procedure was explained. The Ethics Committee of Hiroshima University approved this study.

Participants were explicitly instructed to encode and later recognize 24 word pairs. Each word consisted of two Chinese characters (*kanji*), and words were either negative or neutral nouns. Over 200 nouns were randomly selected from a Japanese dictionary (classification lexis table, National institute for Japanese language), and were rated on emotional valence and familiarity by a different group of participants ( $n = 20$ ) in a pilot study. The rating scales ranged from 1 (*negative or unfamiliar*) to 5 (*positive or familiar*). Negative words were subsequently defined as those with average scores of less than 2 points on the emotional valence scale. Neutral words were defined as those with valence scores between 2 and 4 points. We selected 24 negative words and 24 neutral words based on emotional valence and familiarity ratings. The valence ratings of these words averaged  $1.6 \pm 0.2$  and  $3.0 \pm 0.1$  for the negative and neutral words, respectively. Corresponding familiarity rating values were  $3.9 \pm 0.3$  and  $3.9 \pm 0.5$ . From these words, we created 12 negative

word pairs and 12 neutral word pairs, such that there were no obvious semantic associations between the two words that comprised each pair. Three researchers validated this absence of semantic associations. Days of the week that consisted of two Chinese characters were used as a control condition.

We used a block-designed associative memory task developed by Wagner et al. (Wagner et al., 2005), with some modifications. Figure 1 shows the sequenced of blocks used. During encoding, the participants were instructed to memorize the word pairs, which were viewed for 6 s each (plus 2 s of black screen in between stimuli). Four word pairs constituted an encoding block (32 s), and the encoding phase consisted of 6 blocks in total (negative blocks = 3, neutral blocks = 3). During the control condition, participants were presented with pairs of weekdays for 6 s (plus 2 s of black screen), and were instructed to indicate via a button press whether the stimuli were identical or not. Three weekday pairs constituted a control block (24 s). During each retrieval trial, the participants were presented with three words (both words from a pair and one word from a different pair) for 6 s (plus 2 s of black screen). As was the case during the encoding phase, four word sets constituted a retrieval block (32 s), and the retrieval phase consisted of 6 blocks in total (negative = 3, neutral = 3). During each trial, one word from the pair was positioned at the top of the screen, with the accompanying word from that pair and the distracter word positioned at the bottom. Participants pressed a button to indicate which of the two words at the bottom of the screen had been paired with

the word at the top during the encoding phase. The control condition during the retrieval phase followed the same procedure as during the encoding phase, according to Wagner et al. (Wagner et al., 2005). The negative and neutral conditions were alternated during the encoding and retrieval phases. The number of left and right button presses was balanced across the entire experiment, which lasted 672 s.

Figure 1 around here

fMRI was performed using a Magnex Eclipse 1.5 T Power Drive 250 (Shimazu Medical Systems, Kyoto, Japan). One scan consisted of 176 volumes (including 4 volumes of pre / post baseline) acquired with a T2\*-weighted, gradient echo, echo planar imaging (EPI) sequence. Each volume consisted of 40 slices, with a slice thickness of 3.5 mm and no gap, and covered the entire cerebral and cerebellar cortices. The interval between two successive acquisitions of the same image (TR) was 4000 ms, the echo time (TE) was 50 ms, and the flip angle was 90°. The field of view (FOV) was 256 mm, and the matrix size was 64 × 64, giving voxel dimensions of 4 × 4 × 3.5 mm. Scan acquisition was synchronized to the onset of each individual trial. Structural MR images were acquired using a T1-weighted gradient echo pulse sequence for anatomical registration of the fMRI data (TR = 12 ms; TE = 4.5 ms; flip angle = 90°; FOV = 256 mm; voxel dimensions of 1 × 1 × 3.5 mm).

Data were analyzed using the statistical parametric mapping software package SPM5



(Wellcome Department of Cognitive Neurology, London, UK), running in MATLAB 7.1 (The Mathworks, Inc.; Natick, MA). The first three volumes of the fMRI run were discarded to ensure a steady-state MR signal. Each set of functional volumes was realigned to the first volume, spatially normalized to a standard template based upon the Montreal Neurological Institute (MNI) reference brain, and spatially smoothed using an 8-mm FWHM Gaussian kernel.

We modeled four contrasts for each individual, using a general linear model that included each condition (neutral encoding, negative encoding, neutral retrieval, and negative retrieval) compared to the relevant control conditions. Second level analyses were performed according to a random effect model. First, one-sample  $t$ -tests were performed for each contrast, with the significance threshold set at  $p < 0.05$ , corrected for whole-brain familywise error (FWE). Furthermore, small volume corrections (SVC) for the hippocampus and amygdala were applied to the activation map from these contrasts (thresholded at FWE corrected  $p < 0.05$ ). The hippocampal and amygdalic region of interest mask was created in Montreal Neurological Institute (MNI) space using the WFU Pick Atlas (Maldjian et al., 2003). Second, paired  $t$ -tests comparing the emotional and neutral conditions were performed during encoding and retrieval. The statistical threshold for these comparisons was set at an uncorrected  $p < 0.001$ , with cluster level set at an uncorrected  $p < 0.05$ . SVC for the hippocampus and amygdala was applied to the activation map generated from the paired  $t$ -tests (thresholded at an uncorrected  $p < 0.001$ , and cluster level set at an uncorrected  $p <$

0.05). Third, a simple regression analysis was performed to search for image voxels within the area of hippocampal activation during encoding and retrieval, and these were then correlated with correct response rate. The resulting correlation maps were thresholded at FWE corrected  $p < 0.05$ .

## Results

The mean correct response rates during retrieval were  $82.3 \pm 14.3\%$  for negative word pairs and  $94.0 \pm 9.8\%$  for neutral word pairs. Accuracy rates across the two emotional conditions differed significantly,  $t(24) = 5.17, p < 0.001$ .

We performed one sample  $t$ -tests on the four contrasts, subtracting the control condition from each experimental condition (see Table 1). The left lateral prefrontal cortex and bilateral visual cortex were activated during both the neutral and emotional conditions of the encoding phase. In addition, the medial prefrontal cortex and bilateral parietal lobe were activated during the retrieval phase. The left anterior hippocampus showed significant activation during the neutral encoding condition, and the left posterior hippocampus showed significant activation during the neutral retrieval condition (Figure 2). The left middle temporal gyrus (MTG) showed significant activation during the emotional encoding and retrieval conditions. Significant hippocampal activation was not observed in the negative encoding or retrieval conditions. Significant activation of the amygdala was not observed in any condition.

Table 1 and Figure 2 around here

Next, paired t-tests were performed to examine the effects of negative emotion on encoding and retrieval. During encoding, the left temporal pole, MTG, and posterior cingulate showed more activation for the emotional than for the neutral condition. No region was more activated in the neutral than in the emotional condition during encoding. During retrieval, activations of the MPFC, right MTG, precuneus, and hippocampus were greater for the neutral than for the emotional condition. Inversely, activations of the left MTG and bilateral visual cortex were greater for the emotional condition than for the neutral condition (Table 2 & Figure 3).

Table 2 and Figure 3 around here

To examine whether hippocampal activation was correlated with memory performance, correct response rates were regressed against the degree of hippocampal activation for each of the contrasts, during both encoding and retrieval (see Figure 3). This analysis revealed that activation of the anterior hippocampus during retrieval was positively correlated with correct response rate (all:  $r = 0.58$ ,  $p < 0.0001$ , neutral:  $r = 0.65$ ,  $p < 0.001$ , negative:  $r = 0.41$ ,  $p < 0.05$  in  $[-26 -6 -22]$ ), but activation during encoding was not significantly correlated with correct response rates for any part of the hippocampus. Activation in other regions identified in earlier analyses was not significantly correlated with memory performance.

Figure 4 around here

## Discussion

To our knowledge, the present study was the first to examine the effects of emotion on memory for paired items. In this experiment, the hippocampus showed robust activation during the encoding and retrieval of neutral word pairs. In contrast, left middle temporal activation was observed during the encoding and retrieval of negative word pairs. The activation pattern for neutral word pairs was consistent with that seen in previous studies (Henke et al., 1999; Jackson and Schacter, 2004; Meltzer and Constable, 2005; Prince et al., 2005), but the activation pattern produced by the negative word pairs was quite different.

The finding of robust hippocampal activation during both encoding and retrieval of neutral word pairs further reinforces the notion that the hippocampus plays an important role in these processes. The peak voxel activation of the hippocampus was observed in the anterior section during encoding, but in the posterior section during retrieval. This rostrocaudal division of memory functions along the hippocampus has been discussed. A review of PET imaging studies of medial temporal lobe functioning suggested that anterior hippocampal functioning is associated with encoding, whereas posterior hippocampal functioning is associated with retrieval (Lepage et al., 1998). However, a meta-analysis of fMRI studies revealed that such a rostrocaudal gradient has not been clearly established, at least for the medial temporal lobe (Schacter and Wagner, 1999). Such a functional division of the anterior and posterior hippocampus remains to be investigated in depth.

In contrast, the hippocampus was not significantly activated during the encoding and retrieval of negative word pairs. Previous research on memory and emotion has generally demonstrated that emotional events are often better remembered than neutral events. For example, Dolcos and his colleagues have reported that emotion enhances both encoding (Dolcos et al., 2004) and retrieval (Dolcos et al., 2005) related activity in the hippocampus. Furthermore, Hamann et al. (1999) reported that hippocampal activity during encoding was positively correlated with memory for emotional stimuli. In the present study, hippocampal activity was actually *lower* (and memory performance was *poorer*) for emotional word pairs, as compared to neutral pairs. Procedural differences between previous studies (Hamann et al., 1999; Dolcos et al., 2004; Dolcos et al., 2005) and the present one may have contributed to this discrepancy. First, previous studies presented pictures as the stimuli to be encoded, whereas we presented words. Second, the encoding of an association between items may have played a role, as compared to encoding single items. Third, we employed an intentional memory task, whereas other researchers have used incidental memory tasks in which participants were not told about a subsequent memory test before or during encoding. Any or all of these factors, along with the enhanced semantic processing described in the introduction, may have influenced the encoding and retrieval of the emotional word pairs.

Some studies of emotional autobiographical memory have found that event memory for emotion-related details appears to be facilitated, whereas memory for more peripheral details seems

to be diminished (Christianson, 1992; Berntsen, 2002). This phenomenon has also been observed in other experimental studies, where it has been called “tunnel memory” (Safer et al., 1998). This notion refers to a narrowing of attention and memory such that the most emotionally central parts of an event are better remembered relative to a neutral situation, whereas the peripheral details are actually remembered more poorly. Studies of attention have indicated that negative features generally appear more salient than neutral ones (Tylor, 1991). In our experiment, however, participants had to remember the relationships between words, rather than the words themselves. It is possible that the word meanings themselves constitute emotional details, while the relationships between the words constitute more peripheral, less salient aspects of the encoding task. If participant attention was turned toward the relationships between the words, memory for the negative words themselves would be expected to suffer, and hence recognition performance in the negative emotion condition was worse than in the neutral condition.

Perhaps strangely, significant activation of the amygdala was not observed for the negative word pairs in the present study. Just viewing negative words typically causes amygdalic activity (Kensinger and Schacter, 2006; Lewis et al., 2007), as do memory tasks that employ negative word stimuli (Hamann et al., 1999; Dolcos et al.,

2004; Dolcos et al., 2005). The reason for this absence in the present experiment is not clear. However, it may be that the absence of amygdalic activation was not irrelevant to the reduced hippocampal activity that was observed during retrieval of the negative word pairs.

In contrast to the above, significant activations during both the encoding and retrieval of negative word pairs were present in the MTG. Previous functional neuroimaging studies have implicated the posterior temporal regions in the storage of information (Demonet et al., 1992; Martin et al., 1995; Wiggs et al., 1999). Since these regions are also consistently activated during semantic retrieval tasks, it is possible that these regions underlie semantic rather than linguistic operations (Cabeza and Nyberg, 2000). In addition, posterior temporal regions have been shown to be more active during semantic processing than during episodic memory operations (Wiggs et al., 1999). Mechelli et al. (2007) reported that semantic relationships between word pairs modulate neuronal responses in a left-lateralized network that includes the MTG. Furthermore, semantic maintenance has been shown to elicit greater activity in the left MTG (Shivde and Thompson-Schill, 2004). These results demonstrate that the left MTG is involved in stimulus-driven semantic processes, as well as the maintenance of the semantic meaning of words. Given our finding of left MTG activation in the negative but not the neutral word condition, semantic processes may have been enhanced for the negative word pairs relative to the neutral pairs.

A secondary finding of note was that the hippocampal activation observed during retrieval was positively correlated with memory performance. This finding is consistent with a previous study that reported a significant correlation between retrieval-related hippocampal activity and memory performance (Bosshardt et al., 2005). Furthermore, the current study indicates that an integrated hippocampal system is involved in the retrieval of associative memories, in agreement with the findings of Meltzer and Constable (2005). The posterior hippocampus appears to be activated during retrieval; however, in the present study correct response rates were correlated with activity in the anterior but not posterior portion of the hippocampal formation. The reason for this discrepancy is not apparent, although anatomical input from the neocortex to the medial temporal lobe (including the hippocampus) is topographically arranged such that anterior neocortical regions connect to the anterior medial temporal lobe, while posterior neocortical regions connect to the posterior medial temporal lobe (Insausti et al., 1987; Suzuki and Amaral, 1994). It may be that this anatomical topography effects hippocampal activation.

Our study has some limitations. First, why the amygdala was not active during memory operations on the negative word pairs remains unclear. In the preliminary data, unpleasantness ratings were much greater for the negative than the neutral words ( $p < 10^{-20}$ ). However, the participants in the fMRI study did not evaluate word unpleasantness. We therefore cannot exclude the possibility that the negative words used in this study were not sufficiently unpleasant for the



fMRI participants. Second, it is not clear why regions such as the left prefrontal cortex were not more active, if indeed semantic processing of the negative words was enhanced. Further studies are needed to clarify this issue. Third, the anterior portion of the hippocampus was not significantly activated during retrieval, compared to the control condition. This absence of significant activity might be due to this region also being activated in the control condition.

In conclusion, robust activation of the hippocampus was observed during both encoding and retrieval of neutral word pairs. In contrast, negative word pairs did not produce significant hippocampal activation, but did produce activation of the left MTG during both encoding and retrieval. These findings suggest that negative emotion does not necessarily promote good memory performance and associated hippocampal activation.

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## Figure legends

Figure 1. Illustration of the experimental design. Participants were scanned while encoding and subsequently retrieving word pairs. During encoding, participants were alternately presented with neutral word pairs, control word pairs (days of the week), and negative word pairs. In the subsequent retrieval task, participants were presented with a word at the top of the screen, and they were to pick the word that it had been paired with during encoding. One of the choices was correct, and the second choice consisted of a word that had been part of a different pair. The actual background screen was black; however, it is shown here as a different color for the sake of comprehensible presentation.

Figure 2. Statistical maps of hippocampal activation during the neutral condition: Encoding (A) and retrieval (B). The thresholds were set FWE corrected  $p < 0.05$  in small volume correction.

Figure 3. Statistical maps of whole brain contrasts between conditions: Encoding (A) and retrieval (B). The thresholds were set noncorrected  $p < 0.0001$  at voxel level and  $p < 0.05$  at cluster level. MTG: middle temporal gyrus.

Figure 4. Activation of anterior hippocampus ([-26 -6 -22]) during retrieval correlated with correct response rates. The circles and crosses show individual data points for the neutral and negative word pairs, respectively. The thin and dotted lines show regression lines for the neutral and negative word pairs, respectively, and the thick line shows the regression line for all data points. Activation map shows region identified in the regression analyses for correct responses during retrieval.

Table 1. Results of one sample t-tests.

Region	Encoding				Retrieval			
	Neutral		Negative		Neutral		Negative	
L lateral PFC	[-42 10 28]	1776	[-54 30 14]	1730	[-40 10 26]	1407	[-48 18 28]	2183
Medial PFC	[-6 20 60]	175			[2 30 42]	153	[2 30 42]	320
L MTG			[-48 -44 0]	441			[-50 -44 -2]	36
L Parietal lobe	[-26 66 44]	185			[-28 -64 44]	3431	[-26 -62 44]	10526
R Parietal lobe					[32 -58 42]	3431	[36 -62 44]	396
L visual cortex	[-38 -86 -10]	555	[-22 -98 -10]	798	[-12 -94 -4]	6339	[-20 -64 -10]	10526
R visual cortex	[24 -96 -4]	444	[24 -98 0]	817	[22 -96 -2]	6339	[22 -94 -2]	10526
L Hippocampus	[-22 -12 -12]	75			[-22 -30 -4]	42		

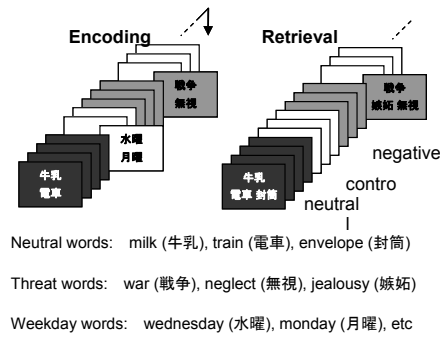
FWE corrected  $p < 0.05$  small volume correction in hippocampus. PFC: prefrontal cortex, MTG: middle temporal gyrus  
 Values of each region show xyz MNI coordinate and activation voxels.

Table 2. Results of paired t-tests

Region	Encoding		Retrieval	
	Negative > Neutral		Negative > Neutral	Neutral > Negative
Medial prefrontal cortex				[-4 54 2] 203
L temporal pole	[-48 12 -38]	216		
L middle temporal gyrus	[-52 -42 4]	156	[-52 -42 -4]	70
R middle temporal gyrus				[54 0 -26] 76
Posterior cingulate cortex	[-4 -42 28]	265		
Precuneus				[-8 -64 22] 259
L visual cortex			[-24 -100 0]	151
R visual cortex			[20 -100 10]	277
L Hippocampus				[-22 -16 -20] 77

Voxel level uncorrected  $p < 0.001$  and cluster level uncorrected  $p < 0.05$

Values of each region show xyz MNI coordinate and activation voxels



**Figure 1.**

**Onoda et al. Neural correlates of associative memory: The effects of negative emotion.**

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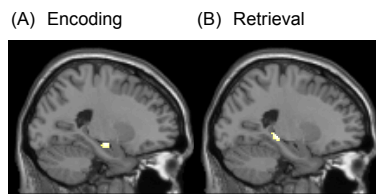


Figure 2.

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of associative memory: The  
effects of negative emotion.**

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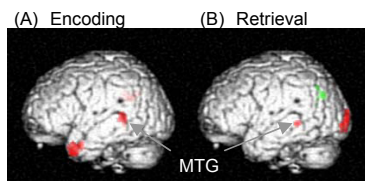


Figure 3.

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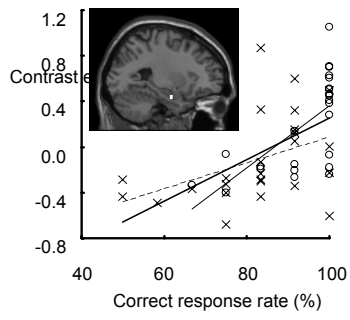


Figure 4.

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