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Temporo-prefrontal coordination increases when semantic associations are strongly encoded

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Abstract

Relational association of disparate semantic concepts can strengthen encoding of episodes. Previous research has shown that the left medial temporal lobe (MTL) and the left prefrontal cortex (PFC) are the primary brain regions activated during both verbal encoding and the association of disparate semantic concepts. In the current functional magnetic resonance imaging (fMRI) study, our goal was to compare the coordinated response of the left MTL and left PFC when disparate semantic associations are strongly encoded compared to when they are weakly encoded. To achieve this goal, subjects were scanned while creating sentences based on a presented pair of words, and were asked to free-recall these sentences at a later time. Half the word pairs were semantically unrelated, and half were semantically related. Analysis of relatedness activations (unrelated–related contrast) suggested that the PFC was active whether or not the items were free-recalled, and increased activation of the MTL was required to promote encoding. Analyses of coordination of relatedness activations comparing free-recalled items to not free-recalled items showed an increase in left MTL–left PFC coordination for relatedness activations on free-recalled items. These results suggest that formation of relational semantic associations that lead to strongly encoded episodes requires increased coordination of the left MTL–left PFC neural pathway.

Keywords: Medial temporal lobe; Hippocampus; Inferior frontal gyrus; Middle frontal gyrus; Ventrolateral prefrontal cortex; Dorsolateral prefrontal cortex; Semantic association; Memory encoding; Free-recall; Memory; Connectivity; Functional magnetic resonance imaging

Episodic encoding refers to cognitive processes that transform incoming information into an enduring memory representation that supports later remembering (Tulving, 1983). Since the ancient philosophers it has been recognized that formation of relational associations between verbal semantic concepts can enhance episodic encoding, and later remembering of episodes (Eichenbaum, 1992, 1999). Thus, the neural basis of relational association of verbal semantic concepts can be informative for understanding the neural basis of verbal episodic encoding. In the current functional magnetic resonance imaging (fMRI) study, our goal was to compare the coordinated response of brain regions activated for subsequently free-recalled items to that activated for subsequently not free-recalled items. Our expectation was that consolidation strong enough to promote free-recall would correspond with increased coordination of neural responses when associating disparate verbal semantic concepts.

The brain regions that support both relational association between verbal semantic concepts and episodic encoding are quite well established. It has long been known that encoding verbal memories involves the left medial temporal lobe (MTL; particularly the hippocampal formation) (Davachi & Wagner, 2002; Gabrieli, Brewer, Desmond, & Glover, 1997; Lepage, Habib, & Tulving, 1998; Scoville & Milner, 1957). The left MTL is also involved in relational association of verbal semantic concepts (Davachi & Wagner, 2002; Degonda et al., 2005; Giovanello, Schnyer, & Verfaellie, 2004; Henke, Weber, Kneifel, Wieser, & Buck, 1999; Mayes et al., 1998; Sperling et al., 2003). The role of the MTL in relational association of verbal semantic concepts is thought to be the storage of a “neocortical index” (Moscovitch & Winocur, 2002) that codes the brain regions

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mutually activated when relational associations are made, and is thus particularly active for novel relational associations.

Strategic or volitional cognitive operations may also be required, involving the frontal cortices (Moscovitch & Winocur, 2002). The involvement of prefrontal cortical regions in episodic memory is well established, and has been widely demonstrated in the neuroimaging literature (Buckner, Kelley, & Petersen, 1999; Buckner, Logan, Donaldson, & Wheeler, 2000; Fernandez & Tendolkar, 2001; Fletcher & Henson, 2001; McDermott, Buckner, Petersen, Kelley, & Sanders, 1999; Nyberg et al., 1996; Wagner, Koutstaal, & Schacter, 1999). Converging support is available from lesion research (Moscovitch, 1992; Moscovitch & Winocur, 2002; Shimamura, Janowsky, & Squire, 1991; Wheeler, Stuss, & Tulving, 1995). Recent work suggests that inferior regions of the prefrontal cortex are involved in episodic memory encoding (viz., overlapping regions of Brodmann areas 44, 45 and 47), referred to here is the inferior frontal gyrus (IFG; Braver et al., 2001; Buckner et al., 1999, 2000; Fernandez & Tendolkar, 2001; Fletcher & Henson, 2001; Gabrieli, Poldrack, & Desmond, 1998; Kapur et al., 1996; Petrides, 1994; Wagner et al., 1999). The IFG is also involved in relational association of verbal semantic concepts (Henke et al., 1999, 2003; Mayes et al., 1998). The role of the left IFG in the relational association of verbal semantic concepts is thought to be selection of the most effective semantic linkages from candidates maintained in working memory (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997).

A second region of the prefrontal cortex involved in verbal episodic encoding is the left middle frontal gyrus (MFG; Buckner & Koutstaal, 1998; Dolan & Fletcher, 1997; Fletcher & Henson, 2001; Fletcher, Shallice, & Dolan, 1998; Golby et al., 2001; Grady, McIntosh, & Craik, 2003; Kelley et al., 1998; Rossi et al., 2001; Sandrini, Cappa, Rossi, Rossini, & Miniussi, 2003). The left MFG plays a role in manipulation of information being actively maintained in working memory, as required for high-level planning (Cairo, Liddle, Woodward, & Ngan, 2004; Moscovitch & Winocur, 2002; Petrides, 1994; Woodward et al., 2006). For episodic encoding, the MFG would support intentional, volitional strategies invoked to promote effective selection of candidate semantic relations, such as generating scenarios that lead to increased candidate semantic linkages in working memory, thereby promoting relational association of disparate semantic concepts (Mayes & Montaldi, 1999; Montaldi et al., 2002; Petrides, 1994).

The left MTL, left IFG and left MFG are often studied as components of an integrated episodic memory system, and some theorizing focuses on their functional and anatomical interconnectivity (Fernandez & Tendolkar, 2001). Empirical evidence for functional connectivity (Friston et al., 1997) is occasionally reported for memory encoding. For example, correlations have been reported between the hippocampus and IFG, extrastriate regions, and occipital regions (Grady, McIntosh, Beig, et al., 2003; Lepage, Habib, Cormier, Houle, & McIntosh, 2000). However, to our knowledge, connectivity and/or coordination between the MTL and PFC has not yet been investigated for formation of relational semantic associations that lead to encoded episodes.

To investigate this issue, we used a sentence creation task and event-related fMRI. On each trial participants were presented with a word pair and were asked to use these words to create a sentence. Half of the word pairs were related (e.g., river–stream) and half of the word pairs were not (e.g., peanut–comet). In order to observe connectivity for sentence creations that led to strong encoding, we back-sorted the sentence creation scanning trials by word pairs that were free-recalled in a session taking place outside the scanner (observation of the "subsequent memory effect", Henson, 2005). The interaction between this recalled/not recalled factor and the related–unrelated word-pair factor were used to create regions of interest (ROIs) for connectivity analyses. Changes in connectivity for PFC and MTL regions were then assessed when comparing relatedness activations for free-recalled trials to that for not free-recalled trials. We expected to observe increased connectivity of the left MTL and left PFC when the relational associations were later free-recalled.

1. Method

1.1. Participants

Twelve right handed, healthy, native English speakers (five women, mean age = 24.92 years, standard deviation age = 6.65) were recruited by advertisement and word of mouth from the community of Vancouver, British Columbia. All subjects had 20/20 or corrected to 20/20 vision. Participants underwent screening for MRI compatibility and gave their written consent. The procedures administered complied with ethical approval at the University of British Columbia.

1.2. Materials

Two sets of word pairs were prepared. Half of them were required to be related, the other half were required to be unrelated. Initially, 720 concrete nouns, consisting of 4–9 letters, were selected from the MRC psycholinguistic database (Coltheart, 1981). These words were composed in pairs: 180 word pairs that were related and 180 word pairs that were unrelated. The resulting 360 word pairs were used in a pilot study in which 48 University of British Columbia undergraduate students were instructed to rate each word pair on the degree of association between the word meanings. They were given three options for their answers: strongly related, slightly related or not related. The results were used to compose the material for the present fMRI study: we selected the 40 word pairs that had the highest concordance as being strongly related and the 40 word pairs that had the highest concordance as being not related. For the related pairs, between 65% and 90% of the subjects rated them as strongly related. For the not related pairs, between 81% and 94% of the subjects rated them as not related. An additional set of 10 word pairs (five related and five unrelated) were used for practice trials.

2. Procedure

2.1. Practice

Before entering the scanner, subjects were given the instructions for the sentence creation task and a practice trial. They were told that they would see pairs of words on the screen, and that their task would be to create a sentence that connects the two words. They then practiced the sentence creation task on 10 word pairs, five of which were related word pairs, and five of which were unrelated, presented in random order.

2.2. Scanning

For scanning trials, in a darkened room, stimuli were presented on a rear projection screen mounted at the entrance to the magnet bore. Participants viewed the screen by means of a mirror system attached to the head coil. For all scanning runs, RELAX trials were displayed for 77 s, followed by a blank screen for 2 s, and a fixation cross for 1 s. For trials which required a response, the fixation point was presented for 900 ms, immediately followed by the word pair for 1900 ms, and then by a blank screen for 100 ms. Stimuli were presented using Presentation v. 0.50 (Neurobehavioral Systems, 2001).

Prior to presentation of the stimuli, the following instructions were read: "Now you will see pairs of words on the screen, just as you did in the practice session. As in practice, for each pair, create a sentence that connects the two words. To remind you of the procedure, you will see the word "relax" on the screen. After a while the screen is cleared and a fixation cross is presented. Then two words are presented and stay on the screen for 3 s. Create a sentence with the two words in your mind. There are no restrictions on the length of the sentence you create; however, a short moment after the words disappear, the next fixation cross is presented which indicates that you should prepare for the next word pair. After a series of trials, there will be a break during which you can relax again. Then the whole procedure repeats."

The experimental run lasted 723 s. At the beginning of the experiment, a 12 s blank screen, followed by a RELAX trial was presented. Following this, a total of 80 trials were presented, 40 in the unrelated condition, and 40 in the related condition. Following the 20th, 40th, 60th and 80th trial, RELAX trials were presented.

2.3. Free-recall

After scanning, subjects were asked to free-recall as many of the sentences that they could remember. They were provided three sheets of lined paper, and were instructed to write down the sentences that they created while being scanned. A sentence was scored as correctly recalled if it contained both words from a presented pair. Free-recall was favoured over cued recall or recognition because we expected substantially increased connectivity for strong memory traces only, and free-recall can be considered an effective method of separating strong memory traces from weak ones.

2.4. Processing and analysis

2.4.1. Image processing

Imaging was performed with a clinical GE 1.5 T whole body MRI system fitted with a Horizon echo speed upgrade. The participant's head was firmly secured using a custom head holder. Conventional spin echo T1 weighted sagittal localizers confirmed positioning. Functional image volumes were collected with a gradient echo sequence (TR/TE 3000/40 ms, flip angle 90°, FOV 24 cm × 24 cm, 64 × 64 matrix, 62.5 kHz bandwidth, 3.75 mm × 3.75 mm in plane resolution, 5 mm slice thickness, 29 slices) effectively covering the whole brain (145 mm axial extent). A total of 241 images of the entire brain were collected in a period of 723 s. The 12 s rest condition which preceded the first RELAX trial allowed T1-effects to stabilize. The four brain volumes collected during this period were not included in any subsequent analyses.

Functional images were reconstructed offline, and the scan series was realigned and motion corrected to the 120th scan using the method implemented in SPM2. Translation and rotation corrections did not exceed 3 mm or 3° for any of the participants. Parameters for spatial normalization into the modified Talairach space used in SPM2 were determined using mean functional images constructed from the realigned images of each participant and scan series. The normalized functional images were smoothed with an 8 mm full width at half maximum Gaussian filter. Low frequency noise was removed using a 0.1 Hz high pass filter. Note that all coordinates given in this article are given in MNI coordinates as provided by SPM2. Voxels were normalized to 2 mm × 2 mm × 2 mm.

2.4.2. Determination of regions of interest

Statistical parametric mapping was used only to determine the ROIs. The event-related responses to all events were modeled using a synthetic hemodynamic response function composed of two gamma functions (Josephs, Turner, & Friston, 1997). For each of the scan series, the model of the composite hemodynamic response for the entire run comprised a sequence of appropriately placed synthetic responses to four different event types: (1) related word pairs that were later free-recalled, (2) unrelated word pairs that were later free-recalled, (3) related word pairs that were not later free-recalled, and (4) unrelated word pairs that were not later free-recalled. The general linear model approach implemented in SPM2 allowed us to estimate parameters for the influence of contrasts of these event conditions on the hemodynamic response in each voxel under consideration.

The contrast used to determine the ROIs was the interaction between the relatedness contrast and the free-recall contrast: (unrelated–related, free-recalled items)–(unrelated–related, not free-recalled items). This provided regions where the contrast of unrelated word pairs-related word pairs was greater for recalled versus not recalled word pairs; that is to say, where relatedness activations were moderated by recall. ROIs for the connectivity analyses were computed based on the interaction between the relatedness and recall factors because we were specifically interested in how relatedness connectivity relates to recall; that is to say, the ROIs should take into account how relatedness activations depend on whether or not the items were free-recalled.

Free-recall may be the most effective method for isolating items with strongly encoded memory traces because only the most strongly encoded items are free-recalled; however, this method results in few events being classified as recalled. Due to the associated decrease in power, for the purpose of determining ROIs, a liberal *p*-value was used ($p < .01$ uncorrected). This analysis resulted in one ROI in the left MTL, and two in the left PFC (Fig. 1). The left MTL ROI consisted of a 16 voxel cluster that included six voxels located in the hippocampus proper. One PFC ROI was 145 voxels, and extended into the IFG and MFG, and included voxels in BA 45, 46 and 9. Thus, it was shared

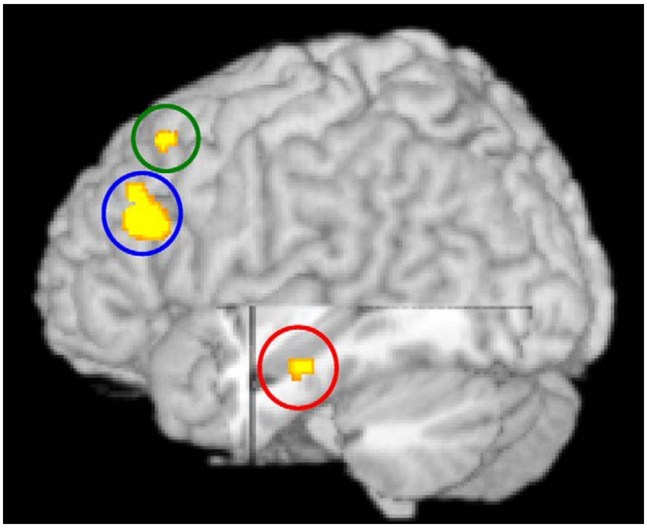

Fig. 1. Rendered regions of interest (ROIs) derived from relatedness/recall interaction. The colored circles are drawn to aid interpretation of Fig. 2. The left hemisphere is displayed, with the cortex cut out to expose the medial temporal lobe (MTL) and hippocampus ROI (labelled Hipp in Fig. 2, circled in red in Figs. 1 and 2). Displayed on the left cortical surface are BA 8: middle frontal gyrus (MFG, circled in green in Figs. 1 and 2), and BA 45/46/9: interior/middle frontal gyrus (IFG/MFG, circled in blue in Figs. 1 and 2).

equally between the dorsal left IFG and the ventral left MFG. A second left prefrontal ROI was 18 voxels, and was located entirely in the MFG, in BA 8. This neural region (caudal dorsolateral prefrontal cortex) is thought to be involved in switching attention between visual stimuli in accordance with conditional rules (Petrides, 2005). This may relate to attempts to combine the visually presented words, maximizing the relatedness activation when the created sentences were strongly encoding. The peak activation in each ROI were, in x, y, z MNI coordinates: MTL: −32, −22, −20, $Z = 2.59$; BA 45/46/9: −54, 24, 26, $Z = 4.13$; BA 8: −44, 20, 52, $Z = 2.90$. The median activation voxels in each ROI were, in x, y, z MNI coordinates: MTL: −34, −24, −20, $Z = 2.43$; BA 45/46/9: −54, 18, 24, $Z = 2.91$; BA 8: −40, 18, 52, $Z = 2.51$.

2.4.3. Index of coordinated responses (IOC)

We computed an index of coordinated responses (IOC) to quantify coordination of neural responses when forming new semantic associations to encode memories. Semantic association IOCs for recalled items can be compared to those computed on not recalled items to test the hypothesis that coordination of semantic association activity increases when items are strongly encoded. IOCs are statistically compared between free-recalled and not free-recalled conditions using straightforward and well-established methods of comparing correlation coefficients (Raghunathan, Rosenthal, & Rubin, 1996). IOCs are based on correspondences between individual differences. A strong IOC implies: (1) if region A responds strongly to creation of semantic associations for individual A, region B must as well, and (2) if region A responds weakly to creation of semantic associations for individual B, region B must respond weakly as well for this subject. If region A and region B respond independently to creation of semantic associations for a substantial proportion of subjects, the IOC would be low.

This method involves performing computations on the contrast images that result from the unrelated–related contrast analyses carried out by SPM2. The basic SPM2 general linear model method involves creating synthetic hemodynamic response functions for the events of interest, and regressing the measured fMRI activation on these synthetic hemodynamic responses for each voxel. This provides parameter estimates (betas) for the correspondence of each event condition to the hemodynamic response, in each voxel under consideration. The unrelated–related contrast image contains the simple subtraction of the beta for the related condition from that for the unrelated condition, for each voxel under consideration.

Using these unrelated–related contrast images as the data on which the computations are based, the IOCs can be derived through the following steps:

1. For each subject, and for each median ROI voxel listed above, extract the beta associated from the unrelated–related contrast image for the recalled and not recalled conditions separately. Median ROI voxels were used instead of the peaks to avoid influence of extreme values on the correlations.
2. Compute Pearson's product moment correlations (over subjects) between ROIs for the values derived in step 1 (these are the IOCs). This is done separately for free-recalled and not free-recalled items;
3. Statistically test for differences between IOCs for free-recalled and not free-recalled items using significance tests for correlated but nonoverlapping correlation coefficients (Raghunathan et al., 1996).

The hypothesized recall-associated increase in connectivity between the PFC and MTL was tested by way of z-tests at $p = .05$. We also compared median activation levels for relatedness at each ROI for free-recalled and not free-recalled items using paired-sample t-tests at $p = .05$.

3. Results

Subject-specific contrast values at the three ROI peaks are presented as a function of free-recall in Table 1. For not recalled items, only the BA 45/46/9 ROI activation was significantly greater than zero ($p < .03$). In contrast, for recalled items, activation in all three ROIs was significantly greater than

Table 1
Mean (S.E.) relatedness contrast values for each ROI peak listed as a function of free-recall

Region of interest (ROI)	Not free-recalled	Free-recalled	t	p
BA 8	−0.42 (0.33)	1.35 (0.58)	−3.11	.01
BA 45/46/9	1.12 (0.45)	2.36 (1.08)	−1.16	.27
Hippocampus	0.15 (0.33)	2.07 (0.69)	−2.98	.01

Paired-sample t-tests were used to test for significant change between recalled and not-recalled items in response to relatedness.

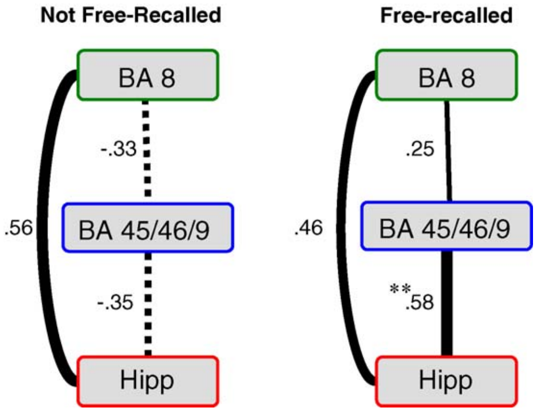

Fig. 2. IOC diagram for the relatedness contrast (unrelated–related) for not free-recalled items and free-recalled items. The colored boxes refer to the colors drawn onto Fig. 1. Line thickness corresponds to magnitude of the IOC coefficient, and negative relationships are represented by dotted lines. BA 8: middle frontal gyrus (MFG); BA 45/46/9: interior/middle frontal gyrus (IFG/MFG); Hipp: medial temporal lobe (MTL), hippocampus. ** Increase in connectivity for free-recalled compared to not free-recalled items significant at $p = .01$.

zero ($p \leq .05$ for all). Paired-sample t-tests assessing relatedness activation changes over recall conditions (see Table 1 for significance tests) revealed that BA 8 and MTL ROIs significantly increased for free-recalled compared to not free-recalled items, but that the BA 45/46/9 ROI did not. Significantly more associated items ($M = 10.0$, S.D. = 3.9) were free-recalled than non-associated items ($M = 3.67$, S.D. = 2.02), $t(11) = 6.68$, $p < .001$.

Although the pattern of results derived from of the paired-sample t-tests presented in Table 1 imply increased MTL–PFC coordination for strong consolidation, assessing means necessarily involves averaging over individual differences, and it is correspondences in these individual differences that are of primary interest for our coordination hypotheses (Cronbach, 1957). A more direct test of increased MTL–PFC coordination is presented in Fig. 2. The hypothesized increase in connectivity for the BA 45/46/9—MTL connection was significant, $Z = 2.29$, $p = .01$. No other connections changed significantly over free-recall conditions.

4. Discussion

In this study, we investigated the neural basis of relational association of verbal semantic concepts, and how this association leads to episodic encoding. Our main findings were as follows: (1) PFC activation was observed when forming verbal relational associations, regardless of whether or not they were free-recalled. (2) Left MTL activation increased when verbal relational associations were free-recalled. (3) Left MTL–left PFC coordination increased when verbal relational associations were free-recalled.

The PFC ROI for the connectivity analysis included aspects of both the IFG and MFG. The MFG is thought to be involved in strategic planning operations, such as strategies that generate a number of candidate semantic relations, and various ways of relating generated concepts. The IFG is thought to be involved in selection of specific semantic concepts from short- and long-term storage (Petrides, 1994). Thus the PFC for the connectivity analysis indexes both strategic generation of, and selection of, verbal relations. When the connectivity results are considered alongside the ROI activation results, PFC regions were active during sentence creation for unrelated words, whether or not items were strongly encoded, but that strong encoding occurred only when the MTL was also activated and coordinated with the PFC.

A paradoxical aspect of this study was that although our main interest was in activation associated with creating sentences with unrelated word pairs while controlling for sentence creation using related word pairs, in fact more related items were free-recalled than unrelated items. We assume that sentences formed from disparate semantic associations were more determined by relational/associative operations than those formed from related words. Recall for related words is presumably largely attributable to the support that familiarity provides for those items, and in that sense may overlap with “know” memory experiences at recall (Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Knowlton, 1998; Yonelinas et al., 2002). In contrast, recall for unrelated items is presumably more determined by memory for the MTL–PFC based volitional association carried out when forming sentences from unrelated word pairs, producing detailed experiences at recall typically referred to as “remember” experiences (Holdstock et al., 2005; Knowlton, 1998; Yonelinas et al., 2002).

This study was subject to a number of limitations. First, although free-recall can be considered the most effective method for isolating items with strongly encoded memory traces, use of this methodology leads to a limited number of recalled items. Ideally a larger set of items would be used, increasing the probability that more free-recalled items would be produced at test, and decreasing the standard errors associated with activation estimates. Second, the analysis of coordination was based on a small sample, increasing the risk of spurious correlations. Thus, the results presented here must be considered preliminary.

To our knowledge, this is the first empirical evidence that increased connectivity of the left MTL and left PFC occurs when formation of verbal relational associations leads to strong encoding. Based on the literature reviewed above (e.g., Moscovitch et al., 2005; Petrides, 1994), the current functional interpretation of this increased connectivity is: (1) the MFG supports strategic *generation* of candidate verbal relational associations maintained in working memory; (2) the left IFG supports *selection* of candidate verbal relational associations maintained in working memory; (3) the left MTL supports the storage of a “neocortical index” that coding these relational associations; therefore, (4) although selection and strategic generation of verbal relational associations may be carried out by the PFC, strong encoding appears to require coordinated activation of the MTL. This empirical evidence supports previous theoretical suggestions of the importance of PFC–MTL connectivity for the translation of verbal relational associations into episodic memories (Fernandez & Tendolkar, 2001; Moscovitch & Winocur, 2002).

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