Recollection versus strength as the primary determinant of hippocampal engagement at retrieval

Melanie Cohn^{a,b,1}, Morris Moscovitch^{b,c}, Ayelet Lahat^b, and Mary Pat McAndrews^{a,b,1}

^aKrembil Neuroscience Centre, University Health Network, Fell Pavilion, 4-409, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8; ^bDepartment of Psychology, University of Toronto, 100 St. George Street, Toronto, Ontario, Canada M5S 3G3; and ^cRotman Research Institute and Department of Psychology, Baycrest Centre for Geriatric Care, 3560 Bathurst Street, Toronto, Ontario, Canada M6A 2E1

Edited by Mortimer Mishkin, National Institutes of Health, Bethesda, MD, and approved October 30, 2009 (received for review July 30, 2009)

We examined whether hippocampal activity in recognition relates to the strength of the memory or to recollective experience, a subject of considerable current debate. Participants studied word pairs and then made two successive recognition decisions on each item: first on the uncued target and then on the target presented with the studied cue word. We compared recollection and familiarity patterns of activation in fMRI for these decisions. Critically, our analyses attempted in two ways to equate perceived memory strength while varying the associative information available. First, activity for targets judged familiar before cueing was contrasted with activity for the same items in the second decision as a function of whether the targets converted to recollection or remained familiar when the context cues were provided. We found increased hippocampal activity following cueing only with recollective conversion. Second, we investigated whether hippocampal activity was modulated by the rated familiarity strength of cued items or whether it increased uniquely in recollection. Hippocampal activation was not modulated parametrically by familiarity strength and recollected items were associated with greater activity relative to highly familiar items. Together, our results support the notion that it is recollection of context, rather than memory strength, that underlies hippocampal engagement at retrieval.

fMRI | medial temporal lobe | recognition memory

The precise role of the hippocampus in recognition memory is contested. According to the dual-process view of recognition, the hippocampus is crucial to recollection, which is a process that supports retrieval of contextual information, but not to familiarity, which is a process that leads to a feeling that an item was previously encountered without retrieval of contextual details (1, 2). Unitary accounts of recognition propose that there is a single process and that hippocampal involvement is related to memory strength, irrespective of whether or not recognition is accompanied by retrieval of context (3). Although both views can account for the majority of functional neuroimaging results at encoding and retrieval (4), there are fundamental differences in their respective emphases on key memory concepts including stored memory representations, memory processes, and associated conscious experience. By the recollection view, the critical variable underlying hippocampal engagement is retrieval of contextual information. The strength view emphasizes memory representation, such that retrieval of strongly encoded memories is likely to engage the hippocampus, irrespective of recovery of context. It is difficult to adjudicate between these proposals, as recollection is typically associated with strong memories and strong memories often include contextual information.

Ideally, one would compare hippocampal activation related to subjective familiarity and recollection while minimizing differences in strength. We attempted to do this in two ways. First, we kept the target (and presumably the memory strength) constant and provided cues that could potentially transform the memory experience from familiarity-based to recollection-based recognition across two successive decisions. We modeled this after the everyday experience in which one sees a target individual in an

unfamiliar setting [e.g., the butcher on the bus (5)] and is unable to recollect anything about previous encounters despite a strong conviction that the person is highly familiar. With minimal appropriate cues (e.g., from conversation or context), one can now readily access a full-blown recollection of the individual. Although there have been numerous experiments attempting to elucidate the effects of various independent variables (such as experimental conditions, aging, or brain lesions) on familiarity and recollection (for reviews, see refs. 2, 6, and 7), none has directly examined the “conversion” of the memory experience with cueing and its possible hippocampal correlate.

Second, we compared hippocampal activation for items of the same perceived strength before cueing but different associative properties (i.e., cohorts of items judged highly familiar with and without recollection), a strategy used by others. As a more powerful statistical control, we also used masking to exclude brain regions that were modulated by degree of familiarity. This was an attempt to minimize, as much as possible in a study comparing different items, the influence of variations in strength as a contributing factor to increased hippocampal activation typically observed with the recollection of context. Any remaining activation in the hippocampus would therefore have to be attributed to the effect of recollection.

In the present experiment (see Fig. 1 for schematic), participants studied pairs of words (A–B) and were scanned while performing a recognition task for the first member of the pairs (A). There were two types of trials at test: (i) uncued trials that included studied (A) and new (C) words, and (ii) cued trials that included intact pairs (A–B) and new–old pairs (C–B). For each trial type (uncued and cued), participants made memory decisions for the target items using a variant of the Remember-Know procedure. This procedure was initially described by Tulving (8) and adapted by Gardiner (9) to capture the subjective experience of familiarity and recollection and has been used in many subsequent studies to show dissociations based on a variety of factors including hippocampal damage (for reviews, see refs. 6 and 7). The version used here, identical to one used by Yonelinas and colleagues (10), includes a subjective recollection response (R), as well as a four-point confidence rating scale for nonrecollected items (1 = sure new, 2 = unsure new, 3 = unsure familiar, 4 = sure familiar). It has been established that carefully instructing participants regarding the familiarity/recollection judgment is critical to ensure that the decision is not simply based on confidence; otherwise it is possible that they may simply treat R as “even more sure familiar” (11). Here, we stressed that

Author contributions: M.C., M.M., A.L., and M.P.M. designed research; M.C. performed research; M.C. and M.P.M. analyzed data; and M.C., M.M., and M.P.M. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

¹To whom correspondence may be addressed at: Krembil Neuroscience Centre, University Health Network, Fell Pavilion, 4-409, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8. E-mail: mary.mcandrews@uhn.on.ca or melcohn@gmail.com.

This article contains supporting information online at www.pnas.org/cgi/content/full/0908651106/DCSupplemental.

Table 3. Hippocampal activation as a function of contrasts (SVC, $P < 0.05$)

Analyses	Left or right hippocampus	MNI coordinates			Z-value
		x	y	z	
1. Same items (cueing effect)					
Remain familiar (cFF > uFF)	n.s.				
Conversion to recollection (cFR > uFR)	L	-32	-12	-12	2.01
Initial familiarity (uFR > uFF)	n.s.				
2. Same subjective confidence					
Familiarity strength (1→4)	n.s.				
Recollection excluding familiarity strength (cR > cF4 masked 1→4)	L	-20	-12	-16	3.63
	L	-32	-24	-16	2.53
	R	24	-8	-24	2.99

these components of recognition. We compared activation for the very same items, and thus the same representations, but before and after cueing, which could give rise to different experiential effects. As shown by the comparison between the initial activation of items that are later recollected or remain familiar, there is no demonstrable relation between the initial strength of the item, as determined by the participant's rating, and the changes effected by the cues. The effect is also not related to memory for the cues themselves or the cue-target pairings. This is supported by the fact that we found greater hippocampal activation with cueing only for the converted items despite the fact that all cues were previously studied.

Proponents of the strength view place their emphasis on the encoded trace, leaving the question of ecphoric strength (i.e., combination of retrieval cues and activated information) somewhat ambiguous in their accounts. For example, Wais (4) has written that hippocampal activation at retrieval may "contribute to strong memories that were associated with hippocampal activation at encoding," but the nature of that contribution is not specified. In a subsequent publication from the same group, presented as a critical test of the strength view, initial hippocampal activity at encoding was examined as a function of subsequent memory, the assumption being that the strength of initial encoding is a determinant of subsequent memory (12). Thus, it

appears that this view is more closely aligned with a "read out" of representational strength at encoding. Such a view would certainly have difficulty accounting for the set of findings we present in this study, which shows that hippocampal activation is determined by recollection at retrieval and not by item strength either before or after the presentation of retrieval cues.

Taken as a whole, the current data are some of the most compelling to be offered in this debate. They not only argue in favor of the recollection hypothesis of hippocampal function, but also emphasize that the neural basis of memory, and its experiential correlate, cannot be understood fully without considering the interaction between encoding and retrieval. These findings confirm an insight that Endel Tulving and others (19) reached decades before the advent of functional neuroimaging, and provide a neurobiological foundation for it.

Methods

Participants. Thirteen participants (six women) were recruited from the University of Toronto community and received \$60 compensation. Their mean age was 26.8 (range of 20–35). All were right-handed fluent English speakers, had normal or corrected vision, and had no history of neurological disease or any contraindications for MRI. This project was approved by the research ethics board of University Health Network.

Material and Procedure. We selected 444 words (252 seven-letter words and 192 six-letter words) from the MRC psycholinguistic database. We created 252

Fig. 2. Pattern of hippocampal activation. (A) Lack of hippocampal engagement for items that remain familiar after cueing or for initial presentation (uncued) of cohorts of familiar items based on recognition decision following cueing (R vs. F). (B) Left hippocampal activation for items that become recollected following cueing. (C) Percent signal change in the peak hippocampal voxel from the contrast described in B as a function of item types [i.e., items that remain familiar (uFF, cFF), convert to recollection (uFR, cFR) or are judged as novel on uncued and cued trials (uNN, cNN)]. (D) Absence of hippocampal activity modulation with familiarity ratings on cued trials. (E) Bilateral hippocampal activity for recollected versus highly familiar cued items with exclusive masking for regions showing linear familiarity function (i.e., ratings 1 to 4). (F) Percent signal change in the peak hippocampal voxel from the contrast described in E as a function of recognition responses.

word pairs by combining one seven-letter word to an unrelated six-letter word; 60 of these were alternate pairings (i.e., one word had two possible associates). These pairs were equated in terms of Kucera-Francis frequencies (first word: $M = 25.54$, $SD = 0.58$; second word: $M = 42.41$, $SD = 3.69$) and concreteness ratings (first word: $M = 467.48$, $SD = 7.15$; second word: $M = 482.58$, $SD = 21.20$).

The experiment was programmed using E-prime software (Psychology Software Tools Inc). Practice and study phases were conducted outside the scanner. The study phase consisted of two 11.2-min blocks, each containing 90 critical pairs (A–B) and six buffer pairs (three at the beginning and three at the end of each block to control for primacy and recency effects). Each pair was presented for 6 s and was followed by a 1 s fixation cross. Participants were instructed to generate a sentence mentally that incorporated both words and to indicate, for each pair, the difficulty level of this task on a 5-point scale ("1" – very easy, "5" – very difficult).

The test phase began approximately 30 min after the end of the study phase. Items were presented using MR-compatible goggles (Avotec Inc.) and recognition responses were made using two four-button handheld response pads (FORP).

Participants were scanned while performing a recognition task for the first member of the pairs (A). This task was divided into six 9.3-min runs. Participants were presented with an uncued test item, which was either a studied (A) or new word (C), and indicated whether the item was new (rated 1 = sure new or 2 = unsure new), familiar (rated 3 = unsure familiar or 4 = sure familiar), or recollected. Detailed instructions were provided to explain each response. Crucially, participants were instructed that they should not distinguish between "sure familiar" responses and "recollected" responses based on response confidence, as confidence should be equivalent for both types, but rather based on their ability to retrieve contextual information (i.e., subjective experience). A practice run in which participants justified their responses was conducted to ensure they understood and applied this distinction. A cued trial followed immediately each uncued trial, in which intact pairs (A–B) or new-old pairs (C–B) were presented; the recognition decision was again to be based only on the first item (A or C), which was the same item as the one presented in the previous uncued trial. The recognition task included 120 uncued target items (A), 120 cued lure items (A–B), 60 uncued lure items (C), and 60 cued new items (C–B). The test phase also included 30 uncued low level baseline items (+ + + + +) and 30 cued low level baseline items (+ + + + + + + + + + +) for which participants were instructed to give a "3" answer.

Each test item was presented for 5.5 s followed by a 500 ms fixation cross randomly jittered by 2 s (mean of 8 s per trial). Thus, each block contained 35 uncued and 35 cued items (20 uncued and 20 cued targets, 10 uncued and 10 cued lures, and five uncued and five cued low level baseline items). Item presentation was pseudorandomised with the restriction of a maximum of three subsequent items of the same type. New responses (1 and 2) were entered using the left hand, and familiar (3 and 4) and recollected answers were entered using the right hand.

Data Acquisition. Anatomical and functional data were acquired on a 3-T Signa MR System (GE Medical Systems). The anatomical scans were taken first (T1-weighted sequence, 120 slices, 220 mm FOV, 256×256 matrix, resulting

in a voxel size of $0.78125 \times 0.78125 \times 1.0$). Functional data were acquired in an interleaved order (TR = 2 s; 28 slices for six participants and 35 slices for seven participants, 440 mm FOV, 64×64 matrix, resulting in a voxel size of $3.75 \times 3.75 \times 5.0$). These were taken in an oblique orientation, with each slice being perpendicular to the long axis of the hippocampus. For each of the six runs, 285 frames were acquired. The first three of these were dropped for signal equilibrium.

Data Processing and Statistical Analyses. Functional and structural scans were coregistered using a Matlab script. Slice timing, realignment, normalization to the Montreal Neurological Institute EPI template, and smoothing (FWHM 8 mm) were performed using SPM5 (Statistical Parametric Mapping 5; Wellcome Department of Imaging Neuroscience). SPM5 was also used for contrast analyses. Each stimulus event was modeled by SPM5's canonical hrf (applied at item presentation onset). First level analyses of individual participants' data were conducted using a fixed-effects model. Second level analyses were conducted on the contrast images obtained in the previous step using a random-effect model.

Whole brain results are presented in the [SI Text](#) and [Tables S1, S2, and S3](#). All maxima reported were significant at a level of $P < 0.005$ (uncorrected) and survived an extent threshold of five contiguously activated voxels ($4 \times 4 \times 4$ mm³). For the familiarity exclusive mask, we used a conservative threshold of $P < 0.05$.

To investigate hippocampal activation, we used small volume correction with an ROI mask from MARINA (Bertram Walter Bender Institute of Neuroimaging, University of Giessen) with a threshold of $P < 0.05$ and five contiguous voxels ($4 \times 4 \times 4$ mm³). We reported only local maxima identified to fall within the hippocampus proper based on cytoarchitectonic probabilities using the SPM5 Anatomy Toolbox v.1.5 (Institute of Medicine, Research Center Jülich).

Using SPM5 Marsbar Toolbox ROI analyses were conducted on the peak hippocampal voxels (spherical ROIs radius = 3 mm) from the conversion (cFR > uFR) contrast and for the recollection contrast (cR > cF4 masked with familiarity). For the conversion/cueing analyses, percent signal change was extracted for six item types (uFF, cFF, uFR, cFR, uNN, cNN). For the confidence analyses, percent signal change was extracted for cued recollected (cR), sure familiar (cF4) and sure correct rejection (cN1) as well as for all cued items rated sure new (1), unsure new (2), unsure familiar (3), sure familiar (4), and recollected (R).

Partial datasets were acquired for two participants due to technical problems (three and four runs were collected). Furthermore, two runs were excluded for one participant due to excessive head motion. All participants were included in the conversion analyses and eleven participants were included in the recollection versus high familiarity analyses. Two participants (with incomplete datasets) were excluded because they had few sure familiar judgments to cued items (<10).

ACKNOWLEDGMENTS. We thank Marilyne Ziegler for her programming skills, Sybille Schulz and Megan Walberg for their help with the pilot phase, and Deborah Schwartz for her help with data analyses. We also thank Andrea Protzner for her comments. This work was supported by the Canadian Institutes of Health Research Grant MT6694 to M.M. and Gordon Winocur.

- Mayes A, Montaldi D, Migo E (2007) Associative memory and the medial temporal lobes. *Trends Cogn Sci* 11:126–135.
- Eichenbaum H, Yonelinas AP, Ranganath C (2007) The medial temporal lobe and recognition memory. *Annu Rev Neurosci* 30:123–152.
- Squire LR, Wixted JT, Clark RE (2007) Recognition memory and the medial temporal lobe: A new perspective. *Nat Rev Neurosci* 8:872–883.
- Wais PE (2008) fMRI signals associated with memory strength in the medial temporal lobes: A meta-analysis. *Neuropsychologia* 46:3185–3196.
- Mandler G (1980) Recognizing: The judgment of previous occurrence. *Psychol Rev* 87:252–271.
- Yonelinas AP (2002) The nature of recollection and familiarity: A review of 30 years of research. *J Mem Lang* 46:441–517.
- Skinner EI, Fernandes MA (2007) Neural correlates of recollection and familiarity: A review of neuroimaging and patient data. *Neuropsychologia* 45:2163–2179.
- Tulving E (1985) Memory and consciousness. *Canadian Psychology* 26:1–12.
- Gardiner JM (1988) Functional aspects of recollective experience. *Mem Cognit* 16:309–313.
- Yonelinas AP, Otten LJ, Shaw KN, Rugg MD (2005) Separating the brain regions involved in recollection and familiarity in recognition memory. *J Neurosci* 25:3002–3008.
- Geraci L, McCabe DP, Guillery JJ (2009) On interpreting the relationship between remember-know judgments and confidence: The role of instructions. *Conscious Cogn* 18:701–709.
- Kirwan CB, Wixted JT, Squire LR (2008) Activity in the medial temporal lobe predicts memory strength, whereas activity in the prefrontal cortex predicts recollection. *J Neurosci* 28:10541–10548.
- Daselaar SM, Fleck MS, Cabeza R (2006) Triple dissociation in the medial temporal lobes: Recollection, familiarity, and novelty. *J Neurophysiol* 96:1902–1911.
- Montaldi D, Spencer TJ, Roberts N, Mayes AR (2006) The neural system that mediates familiarity memory. *Hippocampus* 16:504–520.
- Humphreys MS (1976) Relational information and the context effect in recognition memory. *Mem Cognition* 4:221–232.
- Vilberg KL, Rugg MD (2007) Dissociation of the neural correlates of recognition memory according to familiarity, recollection, and amount of recollected information. *Neuropsychologia* 45:2216–2225.
- Vilberg KL, Rugg MD (2009) Left parietal cortex is modulated by amount of recollected verbal information. *Neuroreport* 20:1295–1299.
- Kumaran D, Maguire EA (2007) Match mismatch processes underlie human hippocampal responses to associative novelty. *J Neurosci* 27:8517–8524.
- Tulving E (1983) Ecphoric processes in episodic memory. *Phil Trans R Soc Lond B* 302:361–371.
- Addis DR, McAndrews MP (2006) Prefrontal and hippocampal contributions to the generation and binding of semantic associations during successful encoding. *NeuroImage* 33:1194–1206.
- Addis DR, Moscovitch M, Crawley AP, McAndrews MP (2004) Recollective qualities modulate hippocampal activation during autobiographical memory retrieval. *Hippocampus* 14:752–762.