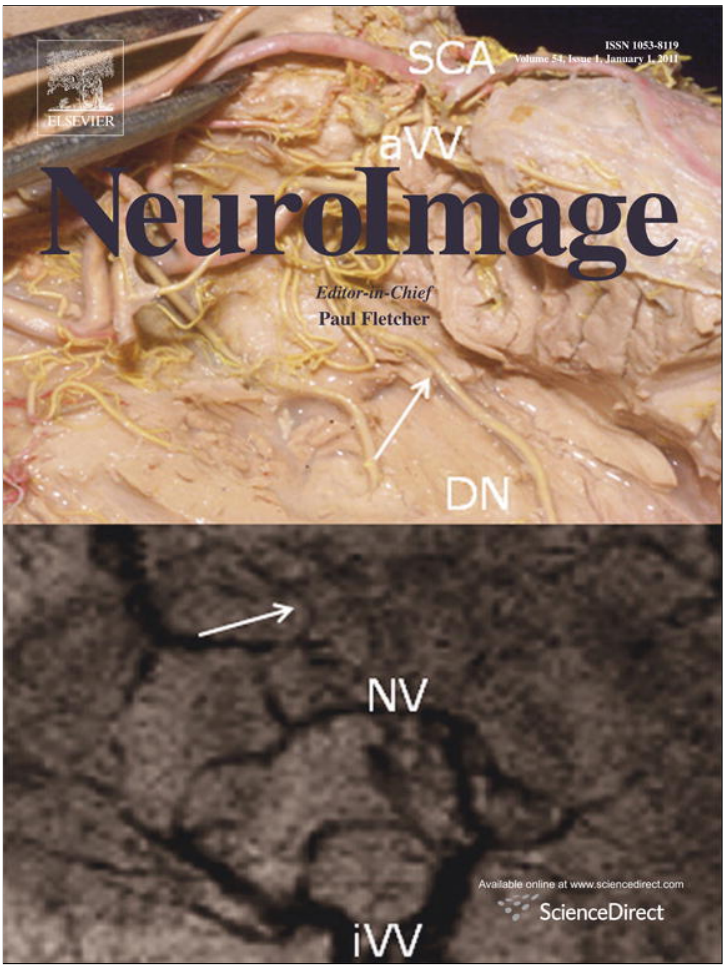

(This is a sample cover image for this issue. The actual cover is not yet available at this time.)

NeuroImage 60 (2012) 808–817

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Putting Humpty together and pulling him apart: Accessing and unbinding the hippocampal item-context engram

Talya Sadeh [a], Anat Maril [b], Tali Bitan [c], Yonatan Goshen-Gottstein [a,*]

[a] Department of Psychology, Tel Aviv University, Ramat Aviv, Israel
[b] Departments of Cognitive Sciences and Psychology, The Hebrew University of Jerusalem, Israel
[c] Department of Communication Sciences and Disorders, University of Haifa, Israel

ARTICLE INFO

Article history:
Received 30 August 2011
Revised 1 December 2011
Accepted 2 December 2011
Available online 20 December 2011

Keywords:
Binding
Dynamic causal modeling (DCM)
Hippocampus
Parahippocampal cortex (PHc)
Perirhinal cortex (PRc)
Context
Recall
Recognition
Medial temporal lobe (MTL)
Memory

ABSTRACT

A remarkable act of memory entails binding different forms of information. We focus on the timeless question of how the bound engram is accessed such that its component features—item and context—are extracted. To shed light on this question, we investigate the dynamics between brain structures that together mediate the binding and extraction of item and context. Converging evidence has implicated the Parahippocampal cortex (PHc) in contextual processing, the Perirhinal cortex (PRc) in item processing, and the hippocampus in item-context binding. Effective connectivity analysis was conducted on fMRI data gathered during retrieval on tests that differ with regard to the to-be-extracted information. Results revealed that recall is initiated by context-related PHc activity, followed by hippocampal item-context engram activation, and completed with retrieval of the study-item by the PRc. The reverse path was found for recognition. We thus provide novel evidence for dissociative patterns of item-context unbinding during retrieval.

Introduction

Systematic investigations of human memory have converged on the notion that one of the most remarkable acts of memory is its ability to bind and unbind component mnemonic features—typically item and contextual information (Hommel, 2004; Nadel, 1994). A timeless question in the study of memory is how, at retrieval, an item-context memory engram is accessed such that its individual components can be extracted—namely, how given contextual information, item information can be extracted from the item-context engram, and, likewise, how given item information, contextual information can be extracted from the item-context engram. This study aims to shed light on this important question by investigating the functional interaction between medial temporal lobe (MTL) structures which together mediate the binding and subsequent extraction of item and context.

The crucial role of the MTL to binding features into a memory engram and subsequently extracting them has long been established (Aggleton and Brown, 1999; Davachi, 2006; Eldridge et al., 2000; Nadel, 1994). Recent years have seen a surge of interest in subdivisions within the MTL, with data implicating the Parahippocampal cortex (PHc) in contextual processing, the Perirhinal cortex (PRc) in item processing, and the hippocampus in item-context binding (Davachi, 2006; Diana et al., 2007; Ranganath, 2010; but see Epstein and Ward, 2010). Current neural models (Diana et al., 2007; Eichenbaum et al., 2007) predict that differential patterns of functional interactions between these structures may be observed during memory retrieval, depending on the information which is to be unbound — item or context. Specifically, when the retrieval task involves presentation of the study context and demands retrieval of the item, PHc activity would first be elicited, followed by activation of the item-context engram in the hippocampus, and completed by PRc activity, associated with retrieval of the study item. In contrast, when the retrieval task involves presentation of the study item and demands retrieval of the context, PRc activity would first be elicited, followed by activation of the item-context engram in the hippocampus, and completed by PHc activity, associated with retrieval of the study context. Critically, the functional interactions between the three MTL structures which are described by these models have yet to be put to an empirical test.

To investigate the interactions between these structures, we used two memory tests—recall and recognition—which differ with regard to the information which is to be extracted as well as the information which triggers the retrieval process (Dennis and Humphreys, 2001). We contend that in our adaptation of these tests, item information must be extracted in recall—with context triggering the retrieval

* Corresponding author at: Department of Psychology, Tel-Aviv University, Ramat Aviv, 69978, Israel.
E-mail address: goshen@post.tau.ac.il (Y. Goshen-Gottstein).

1053-8119/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2011.12.004

process, whereas context information must be extracted in recognition—with item information triggering the retrieval process.

In both tests, cue-target word pairs were presented at study. In the cued–recall test, the cue word alone was presented, and participants had to recall the target word which had been studied together with the cue (for a detailed description, see Materials and Behavioral procedure). Because successful performance on the task required an answer to the question: 'what word was presented alongside the cue word during encoding?' the task demand was to retrieve the target item while the information used to initiate the retrieval process was the available contextual information. Thus, in recall, the target item was not physically reinstated at test and participants' successful performance mandated its retrieval.

The recognition test was a multiple choice test in which the cue was presented alongside the target and three intra-list foils and participants were asked to select the target. Because successful performance required an answer to the question: 'which pair of items appeared in the specific encoding environment of the present experiment?', the task demand was to retrieve information regarding the context in which the pair of items had been presented while the information used to initiate the retrieval process was the available item information. Thus, because the target item was physically reinstated at test, successful performance was not dependent on its retrieval from memory. Rather, successful performance was dependent on the ability to retrieve the encoding context in which the word pair had been encoded.

Importantly, for both of our tests, the context of a target item may have included other words in the study list, which were presented in adjacent positions to the target (as well as the feelings and associations aroused by these words; Polyn and Kahana, 2008; Sederberg et al., 2008).[1] Therefore, at retrieval, a certain word could serve as both the context which cued retrieval of other words, and when retrieved itself, as the to-be-retrieved item. What defined a nominal stimulus as 'item' or as 'context' was a function of the demands imposed by the retrieval task. Thus, in our cued–recall test, the task demand was to retrieve the target item, and the cue word was most likely part of the contextual information used to promote retrieval. In contrast, in our recognition test, participants needed to answer the question: 'which pair of items was presented in the study context?'. Therefore, both cue and target words most likely comprised the item information, and the task demand was to retrieve the contextual information in which they had been presented.

Based on this analysis, we hypothesized that the processes which support successful retrieval in the cued–recall and recognition tests we chose should differ with regard to the interactions between the PHc, the PRc and the hippocampus. We predicted that in cued–recall, contextual information will feed from the PHc into the hippocampus. In addition, successful retrieval would result in activation of the item-context engram in the hippocampus that would activate the PRc, leading to retrieval of the item. Thus, presentation of contextual information would probe the item-context engram, which would subsequently lead to extraction of item information. In contrast, in recognition, the opposite process would occur, such that information between the MTL structures would flow in the reverse route.

Note that the neural (Diana et al., 2007; Eichenbaum et al., 2007) and cognitive models (Dennis and Humphreys, 2001) on which we relied do not predict that the output from the hippocampus would be *exclusively* to the PRc in cued–recall and to the PHc in recognition. Thus, in cued–recall the hippocampus could potentially send output also to the PHc, thereby updating the relevant contextual information. Likewise, in recognition, the hippocampus could potentially send output also to the PRc, thereby updating the relevant item information. Still, we predicted that for cued–recall, the output pathway would necessarily be to the PRc (and possibly also to the PHc), with only the absence of output to the PRc disproving our hypothesis. Likewise for recognition, the output pathway would of necessity be to the PHc (and possibly also to the PRc), with only the absence of output to the PHc disproving our hypothesis. Thus, our predictions regarding the hippocampal output differed for cued–recall and recognition.

Importantly, our study was set to examine only the recollective processes underlying cued–recall and recognition, with the exclusion of any contribution of familiarity. Recollection entails a search for the memory engram as a function of interactions between item and context, whereas familiarity pertains to the fluency with which an item is processed and involves no active search for the memory engram (Whittlesea and Leboe, 2000; Yonelinas, 2002). Our wish to focus only on recollective processes excluded the use of single-item tests in which participants judge items as "old" or "new". In single-item tests, possible recollective processes that uncover the studied items are invariably tainted by the fact that old items appear more familiar than new ones. This familiarity has been shown to mediate judgment of the item as "old", independent of its successful reinstatement (Yonelinas, 2002). We therefore used associative (cue-target) tests—namely, tests which examine memory for word pairs—in which the foils were all intra-list items. In such tests, the target and the foils are equally familiar and therefore familiarity cannot be used to discriminate between them (Yonelinas, 1997). To reiterate, unlike item-specific recognition tests, which may involve both recollection and familiarity, recognition of cue-target associations with intra-list foils relies only on recollection (Diana et al., 2006; Yonelinas, 2002). The need to rely on recollective processes alone dictated, therefore, the use of associative (cue-target) memory tests.

To test our predictions, we measured participants' neural activity using fMRI during retrieval in the associative cued–recall and recognition tasks described above and examined the effective connectivity between the MTL regions of interest. Because we had a-priori predictions regarding the interactions between these regions, we used Dynamic Causal Modeling (DCM), which is a hypothesis-driven method (van Schouwenburg et al., 2010; see also Friston, 2009; Stephan et al., 2010) that examines causal interactions between specific brain regions.

Materials and methods

Participants

Participants were 22 native Hebrew speakers (12 women), who reported themselves to be neurologically-intact, right-handed and with normal or corrected-to-normal vision. To minimize exclusion of subjects due to excessive motion, participants were screened for attention and hyperactivity disorders. Indeed, data from only 3 participants were excluded due to excessive motion (over 3 mm). Data from an additional participant were excluded due to poor task compliance (less than 10 remembered items in the recall test). All reported analyses thus include data of 18 participants (10 women; ages 20–31 years, mean 24.3). Participants gave their informed consent prior to the experiment and were compensated for their time monetarily or with course credit. All experimental procedures were approved by the Tel-Aviv Medical Center's Clinical Investigation committee.

Materials

The stimuli consisted of 200 Hebrew noun–noun pairs. A pilot study was conducted to ensure that the first noun of each pair—the cue—was semantically unrelated to the second noun of the pair—the target. All nouns were 2-syllables long. Of the 200 pairs, 120 were used for the cued–recall test and 80 for the multiple-choice

[1] The contextual information may have also included other information such as the room in which the target word was studied. See also Discussion for further discussion of the possible nature of the contextual representation.

recognition test.[2] Thus, each pair of words presented at study was submitted either to a recognition test or to a recall test, but never to both tests. Materials were rotated across memory tests (recall, recognition) such that, across participants, each pair appeared for 60% of the participants in the recall test and for 40% of the participants in the recognition test. For the multiple-choice recognition test, each target was matched with three intra-list foils. Intra-list foils were used so that both targets and foils would be equally familiar (see Introduction). In addition, the foils were of the same semantic category as the target.[3] To this end, the 200 noun pairs were divided into 50 sets of four pairs such that the four targets in each set were of the same semantic category. Thus, during the multiple-choice test, each target was presented with its three semantically-matched targets four times (each time in a different, random order)—once alongside its corresponding cue and three times alongside each of the three cues corresponding to the other targets in the set (thus serving as a foil).[4]

Critically, the visual display was equated across the two memory tests (Fig. 1). For both tests, participants were presented with the cue (e.g., DOG). In the multiple-choice recognition task, along with the cue, four words were presented—the target word (e.g., ONION) and the three foils. In recall too, four words were presented alongside the cue. Here, however, the words were not targets and foils, but rather the spelled-out numbers ONE, TWO, THREE and FOUR, presented in a different random order on each trial (see Cabeza et al., 1997 for a similar design in this aspect).

Behavioral procedure

Prior to entering the scanner, participants were given detailed instructions and extensive practice of the encoding phase, which included overt pronunciation of the encoded words. A primary goal of this extensive practice session was to ensure that participants verbalized the words clearly, but at the same time softly enough so as to avoid head motion. In addition, cushions were arranged around participants' heads to increase their comfort and further minimize head motion.

The experiment consisted of the following phases: (1) encoding, (2) recall test, (3) recognition test. The order of the recall and recognition tests was counterbalanced across participants—such that for half of the participants recall was followed by recognition, and for the other half recognition was followed by recall. This counterbalancing was applied to cancel out possible order effects caused by interference of materials of one test with performance on the other test. All three phases followed a short practice session. Like retrieval, the encoding phase was also performed in the scanner, for goals extraneous to those of the present endeavor.

At encoding, each trial lasted 5 s during which a word pair was presented for 4000 ms, followed by a blank screen for 250 ms and concluded by a fixation cross which appeared in the center of the screen for the remaining 750 ms. Participants were required to mouth the words overtly as well as to form a detailed, bizarre mental image of the two, unrelated words together. These three manipulations—i.e., overt pronunciation, mental imagery and bizarreness—have been shown to enhance memory performance (Hourihan and MacLeod, 2008; McDaniel et al., 1995). To track task compliance, participants were asked to indicate, by button press, whether they successfully created a mental image of the words, or to press a second button if they didn't. We used an incidental encoding task to control for possible differences in encoding strategies between subjects that might emerge if participants were simply told to "try remember items" and not given uniform encoding instructions. Incidental encoding also ensured that participants did not rehearse studied items during baseline trials. During study, word-pairs subsequently submitted to the recall test and word-pairs subsequently submitted to the recognition test were presented in a random order with the constraint that no more than three word-pairs of each condition were presented successively.

For both recall and recognition tests each trial lasted 5 s. Participants were instructed to overtly tell which word had been presented alongside the cue during encoding or to say "don't remember" if they did not remember the word. Overt responses were recorded during the fMRI scanning sessions, using adaptive noise canceling microphone and headphones (FOMRI-III; Optoacoustics, Israel). The microphone virtually eliminated the scanner noise appendaged to the verbal responses recorded for transcription. The headphones virtually eliminated the scanner noise that participants would have otherwise heard throughout the experiment. Thus, the audio equipment enabled us to obtain high-quality audible recordings of the verbal responses, while allowing participants to speak quietly enough so as to prevent speech-related movements. The verbal responses were transcribed for subsequent data analysis.

As an incentive to enhance performance, participants were told that they would be awarded monetary prizes (comparable to $200) if they reached the best scores in the experiment.

Baseline trials were interleaved among both study and test trials using a rapid event-related design (Dale, 1999). The duration of the baseline trials varied randomly between 2.5 and 10 s, with the total duration of these trials equaling one third of the total duration of each phase. We used an active baseline task, as more traditional passive baseline tasks (like fixating on a crosshair) have been show to possibly involve mnemonic processing and thus mask out the effects of interest (Stark and Squire, 2001). During baseline trials, participants were required to press one of two keys according to the direction of arrows, randomly pointing left or right (Staresina and Davachi, 2006; Stark and Squire, 2001). The order and timing of experimental and baseline trials was determined using Optseq (http://surfer.nmr.mgh.harvard.edu/optseq).

Imaging procedure and data analysis

Participants were scanned on a GE 3 T Signa Horizon LX 9.1 echo speed scanner (Milwaukee, WI). The retrieval phase included one scanning session in which the recognition test was conducted and two scanning sessions in which the recall test was conducted, thus allowing participants a brief rest between recall sessions. During these sessions, whole-brain T2*-weighted EPI functional images were acquired (TR = 2500 ms, 20 cm FOV, 64×64 matrix, Flip Angle = 85, TE = 35, 44 coronal slices perpendicular to hippocampal axis, 3 mm thickness with 0.7 gap, sequential acquisition). The use of a relatively long TR was enabled due to the extension of DCM

[2] More items were presented in recall than in recognition to obtain a minimal number of correct responses (i.e., remembered items) in each of the two tests. This manipulation followed results of an initial pilot which indicated that the number of correct responses in recall was otherwise insufficient.

[3] Because our pilot data indicated that at recall many intrusions were of semantically-similar words, the intra-list foils at recognition were also semantically-similar to the targets (namely, from the same general semantic category as the target, e.g., types of vegetables), but never synonyms or high associates.

[4] Because each word served once as a target and three times as a foil, we were initially concerned that participants would develop an exclusion strategy towards the end of the recognition session, when the foils had already been presented several times. To test for this possibility, we ran a pilot study prior to the fMRI experiment with the exact same associative tests, and conducted a post-experiment questionnaire in which we asked participants whether (and to what extent) such a strategy was applied. Results of the pilot showed that such a strategy was applied very seldom. Most importantly, even among the very few participants and trials for which such a strategy was applied, it was only used to exclude part of the foils, because—as participants admitted—the trial wasn't long enough so as to exclude all three foils. Thus, successful retrieval relied primarily on retrieving the correct target (presumably, by reinstating its context), with exclusion serving, if at all, only as an augmenting strategy. Results of the same questionnaire which was given to each participant following the fMRI study indicated no need to exclude any participant due to the use of such a strategy.

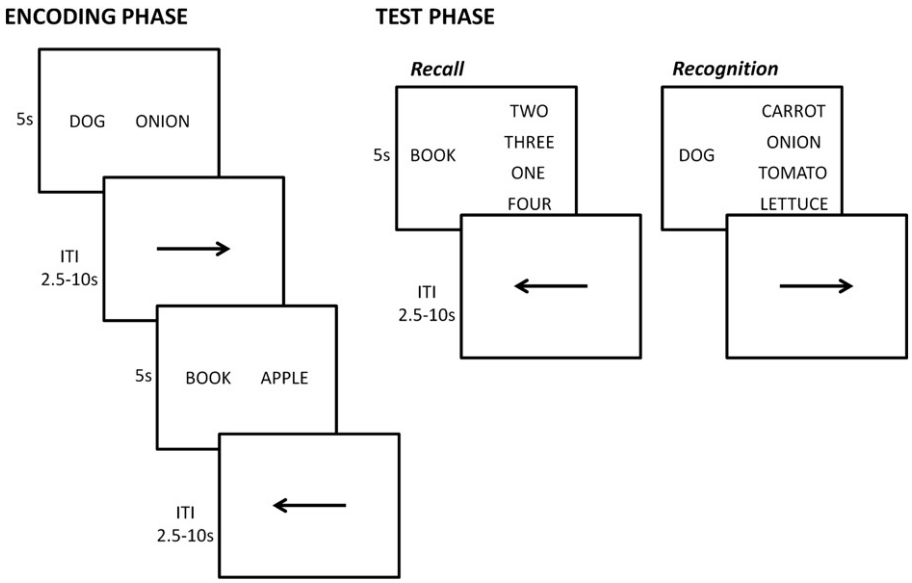

Fig. 1. *Stimuli and timing of events*. During the encoding phase, participants incidentally studied cue-target word pairs by overtly pronouncing them while also creating a detailed, bizarre mental image of the two words. The purpose of the words "ONE", "TWO", "THREE", "FOUR" in the recall test, presented in a different random order in each trial, was to equate the visual display with that of the recognition test and to signal to participants to recall the target word. Foils in the recognition test were semantically-similar to the target. During baseline trials (ITIs), participants were required to press one of two keys according to the direction of arrows, randomly pointing left or right.

with a model of slice-specific sampling times which adjusts the predicted hemodynamic output according to the times at which regional samples were sampled (Kiebel et al., 2007; for examples of studies using a similar or longer TR, see Fairhall and Ishai, 2007; Kumar et al., 2007; Kveraga et al., 2007; Leff et al., 2008; Siman-Tov et al., 2007). For the recall scans, 150 volumes were acquired in each of the two sessions. For the recognition scan, 200 volumes were acquired. Four additional volumes were acquired at the beginning of each session to allow for T1 equilibration (and were excluded from the analysis).

Conventional imaging analysis

Imaging data were preprocessed and analyzed using SPM5 (Wellcome Department of Cognitive Neurology, London). A slice-timing correction to the first slice was performed followed by realignment of the images to correct for subject movement. Next, data was spatially normalized to an EPI template based upon the MNI305 stereotactic space (Cocosco et al., 1997). The images were then resampled into 2 mm cubic voxels and spatially smoothed with a 6 mm FWHM isotropic Gaussian kernel.

Trials were classified into four categories, according to participants' responses in the memory tests: (1) trials in which the correct target was retrieved ("Remembered"); (2) trials in which participants indicated they could not retrieve the target ("Forgotten"); (3) trials in which participants retrieved an incorrect word (an irrelevant word in the recall test or a foil in the recognition test; "Wrong"); and (4) the remaining trials, including failures to respond and responses made outside the time window ("Other"). Because the length of each 5-second trial was equal to two 2.5-second TRs, each trial was treated as an event whose duration is two timepoints (i.e. TRs). Data were modeled using a canonical hemodynamic response. For each subject, a first level analysis was conducted whereby two fixed-effect models were implemented—one for the recall test and another for the recognition test. Session-specific effects and low-frequency signal components were treated as confounds. Group results were obtained using random effects analyses by combining subject-specific summary statistics across the group as implemented in SPM5 (Penny et al., 2004). Active regions, in the contrasts of 'Remembered > Baseline' ($p<0.001$, extent threshold 5 voxels), served to confirm activity at the group level in the Volumes Of Interest (VOIs; see next section for details on selection of VOIs).

Effective connectivity analysis

Four VOIs were chosen for the effective connectivity analysis: the hippocampus, the PHc, the PRc, and the primary visual cortex (V1). Regional responses were summarized as the principal eigenvariates of responses within a 5 mm radius sphere. To avoid spatial overlap between the VOIs due to the proximity of the MTL regions, the VOIs were extracted from unsmoothed data. All VOI coordinates were fixed across individuals due to the small size of the anatomical regions and their proximity. Note that there are no existing masks which can be used to discriminate between activations in the PHc and the PRc (Diana et al., 2007). More importantly, we wished to choose the same VOIs for recall and recognition. However, though all three regions were activated in both recall and recognition (see Fig. 2), the anatomic location of the peak of activations did not precisely overlap between the two tasks. Therefore, the centers of the three MTL VOIs used for the DCM analysis were chosen on the basis of the peak activation levels obtained in a previous study of episodic memory, which found activations in all three regions (Davachi et al., 2003)—regions which have been found to be associated with both recognition (e.g., Davachi et al., 2003) and recall (e.g., Habib and Nyberg, 2008). MTL regions included the hippocampus (−32 −20 −20), the PHc (−32 −40 −18) and the PRc (−36 −12 −32). Critically, to ensure that our DCM analysis includes only regions that are activated by the experimental manipulation (Leff et al., 2008), we confirmed that all three MTL VOIs showed above threshold activation within the VOIs' spheres in the 'Remembered > Baseline' contrast for both recall and recognition (Fig. 2).[5] For both the conventional and the DCM analyses, MTL VOIs were restricted by anatomical masks of the regions' surroundings defined based on WFUPickAtlas in SPM5 (Maldjian et al., 2003). For the PHc and the PRc VOIs, the mask

[5] Note that given the small size of MTL sub-regions, the mask applied on the PRc may not have excluded the Entorhinal cortex, which receives its projections from the PHc, as well as from the PRc. However, this fact should have no bearing on our results, because the portion of the Entorhinal cortex which was possibly included in the PRc VOI is the lateral Entorhinal area which receives its projections primarily from the PRc (Kahn et al., 2008).

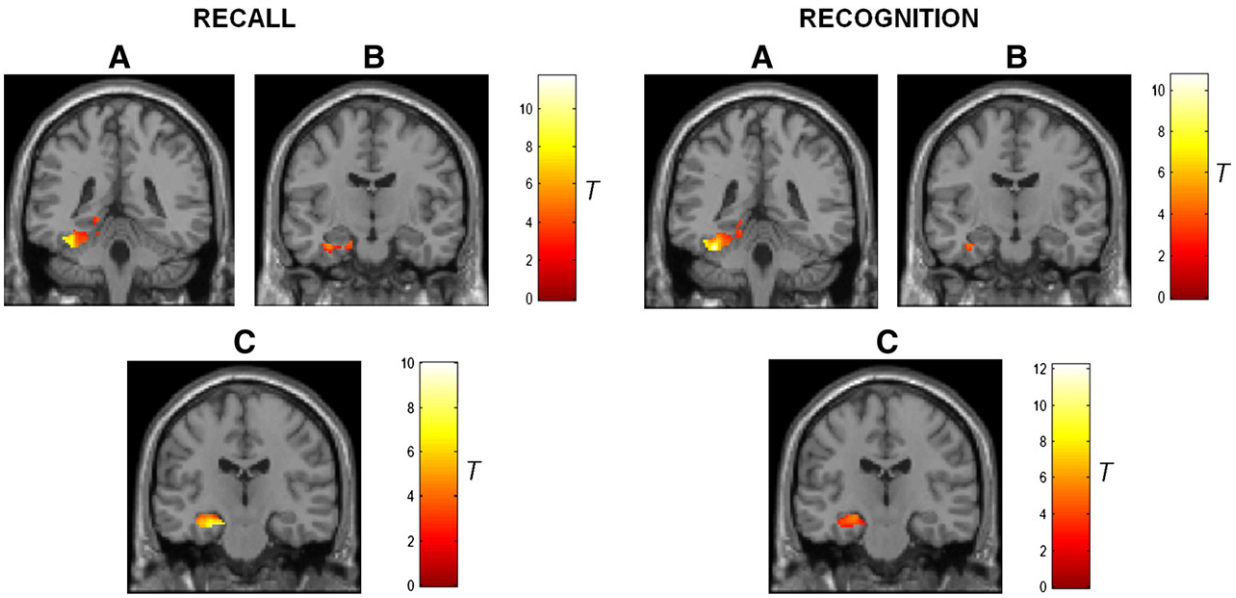

Fig. 2. *Group-level activations in MTL VOIs*. MTL regions observed in the 'Remembered > Baseline' contrasts for Recall (left panel) and Recognition (right panel; $p<0.005$ for illustration purposes, extent threshold 5 voxels). Statistical parametric maps confirm activations within the VOIs' spheres. (A) PHc ($y=-40$) (b) PRc ($y=-12$) (c) Hippocampus ($y=-20$). Activations rendered on an average MNI template brain. All activations are masked anatomically to include only the regions' surroundings (see Effective connectivity analysis for details on anatomical masks).

included the left parahippocampal gyrus, left middle temporal pole and left fusiform gyrus. Note that this mask includes both PHc and PRc, and therefore could not be used to discriminate between them, but only to crudely define their surroundings (Lee et al., 2006). For the hippocampus, the mask included the left hippocampus. In line with previous studies that used verbal materials (e.g., Davachi et al., 2003; Henson, 2005; Kelley et al., 1998), we too found that MTL activity was predominantly left-lateralized and therefore focused our analysis on the left MTL.

Because the cue word for retrieval was presented visually both for recall and for recognition, the primary visual cortex (V1) was chosen as an input region. Note that V1 is the primary structure along the visual stream, and would seem, therefore, to be the least biased in its functional projections towards any of the MTL structures we investigated. To obtain the maximal input activation into the critical MTL regions, and because the precise visual areas were of no inherent interest in the study, we chose the V1 VOIs in which we obtained the peak activations on the group level. Thus, the center of the VOIs was defined based on the voxel with strongest signal in the group's activation map in the contrast of 'All trials > Baseline' at a threshold of $p<0.001$, uncorrected ($-20\ -98\ -2$ for recall; $-18\ -94\ 4$ for recognition). Note that the distance between the peak voxels chosen for the recall and recognition VOIs was only 6 mm, and therefore these VOIs are mostly overlapping, given that their radii are 5 mm each.

Effective connectivity analysis was examined using the DCM tool (Penny et al., 2004) in SPM8, in which models are fitted to data of individual participants. DCM is a nonlinear system identification procedure that uses Bayesian estimation to make inferences about effective connectivity between neural systems and how it is affected by experimental conditions. In DCM, three sets of parameters are estimated: the direct influence of stimuli on regional activity; the intrinsic or latent connections between regions in the absence of modulating experimental effects; and the changes in the intrinsic connectivity between regions induced by the experimental design (i.e., bilinear or modulatory effects; Mechelli et al., 2003).

Data from each task—recall and recognition—were modeled in a separate analysis. Our analysis adopted a two-stage procedure. The first stage was a comparison among alternative DCM models that differ in terms of their connectivity between MTL regions using a random-effects Bayesian Model Selection analysis (BMS; Stephan et al., 2009). The second stage consisted of statistical comparisons of parameter estimates, using a frequentist (i.e., standard, non-Bayesian) approach to determine differences between directions of influence at the group level. Importantly, given that the BMS analysis often produces only minor differences between models, with no obvious best-fitting model (Stephan et al., 2010), we wished to avoid restriction of our inferences to a particular model chosen in this BMS analysis. Therefore, for each of the parameter estimates, we computed the weighted average—across the entire model space ("Average Model" parameter estimates; weighting given by the posterior probability of each model; Stephan et al., 2010). The Average Model parameter estimates were computed using the Bayesian Model Averaging (BMA) tool in SPM8 (Penny et al., 2010; Stephan et al., 2010). For each subject, a BMA analysis across all models was conducted, treating models as fixed effects.

Model space

To reiterate, the set of models on which Bayesian Model Selection (BMS) was conducted was the same for recall and recognition. All models shared the same intrinsic connections (Table 1), which were based on extant literature regarding anatomical projections within MTL regions and between MTL and other brain regions (Aggleton et al., 2000; Diana et al., 2007; Fernandez and Tendolkar, 2006; Kahn et al., 2008; Squire and Zola, 1997; Suzuki, 1996; Suzuki and Amaral, 2004). The intrinsic connections included reciprocal projections between each region and the three other regions, with three exceptions. First, there were no direct projections between V1 and the hippocampus because anatomical data have shown that all cortical input to the hippocampus and output from it are funneled through the PHc and/or the PRc (e.g., Squire and Zola, 1997; Suzuki, 1996). Second, there was no direct connection from the PRc to the PHc

Table 1
Intrinsic connections for all sixteen models submitted to BMS analysis. "+" indicates a connection between the two regions.

To/from	Hippocampus	PHc	PRc	V1
Hippocampus		+	+	
PHc	+			+
PRc	+	+		+
V1				

because the anatomical connection between these regions is considered relatively weak (Diana et al., 2007; Suzuki and Amaral, 2004). Third, there were no projections from MTL regions to V1 because such projections have not been found (Suzuki and Amaral, 2004).

The model space included 16 alternative models (Fig. 3). This set of models includes all models which are cognitively-defensible and pertain to the investigation of how the hippocampal item-context engram can be accessed such that its individual components can be extracted. Specifically, the model space comprised the exhaustive set of models that describe how contextual information can trigger activation of the item-context engram in the hippocampus leading to retrieval of item information and how item information can trigger activation of the item-context engram in the hippocampus leading to retrieval of contextual information. As described above, in all models, V1 served as the region receiving direct input (a regressor of all retrieval trials regardless of memory condition). The alternative models differed in terms of modulation of the "remembered" condition on connections within the MTL regions. The model space was defined such that it included all possible combinations of modulations on the intrinsic connections between the VOIs (see Table 1 for description of the intrinsic connections), with the following exceptions: (1) Because the focus of the present research was on understanding how the hippocampal item-context engram can be accessed such that its individual components can be extracted, models that did not include projections to the hippocampus were not included in the model space; (2) for this same reason, models that included the modulation on the connection from the PHc to the PRc were not included in the model space; (3) finally, models in which regions that received input from V1 but did not project this information to the hippocampus, were not included. This is because we had no theoretical interest in the V1 −> PHc/PRc projections per se, but only in the interactions between the PHc/PRc and the hippocampus.

Statistical analysis of model parameters

Second level, group analysis regarding the modulatory effects was conducted on the Average Model parameter estimates, using a random effects frequentist approach (ANOVA and t-tests). We tested the following directional hypotheses:

(1) To directly test our hypothesis that recall and recognition differ with regard to the input to the hippocampus, we explored the interaction between memory test (recall, recognition) and input to the hippocampus (PHc, PRc) in a 2×2 within-subject Analysis of Variance (ANOVA). We hypothesized that an interaction would be found, whereby in recall, the PHc −> hippocampus connection would be stronger than the PRc −> hippocampus connection, and in recognition the reverse pattern would be shown.
To further confirm our prediction that in recall the PHc constitutes the primary projection to the hippocampus, whereas in recognition the PRc constitutes the primary projection to the hippocampus, we tested the following hypothesis:

(2) The PHc−>hippocampus connection is significantly larger than zero for recall but not for recognition, and the PRc −>hippocampus connection is significantly larger than zero for recognition but not for recall.
Finally, we tested our prediction that in recall the hippocampus triggers item-related activity in the PRc, and in recognition, the hippocampus triggers context-related activity in the PHc. Thus, we hypothesized that:

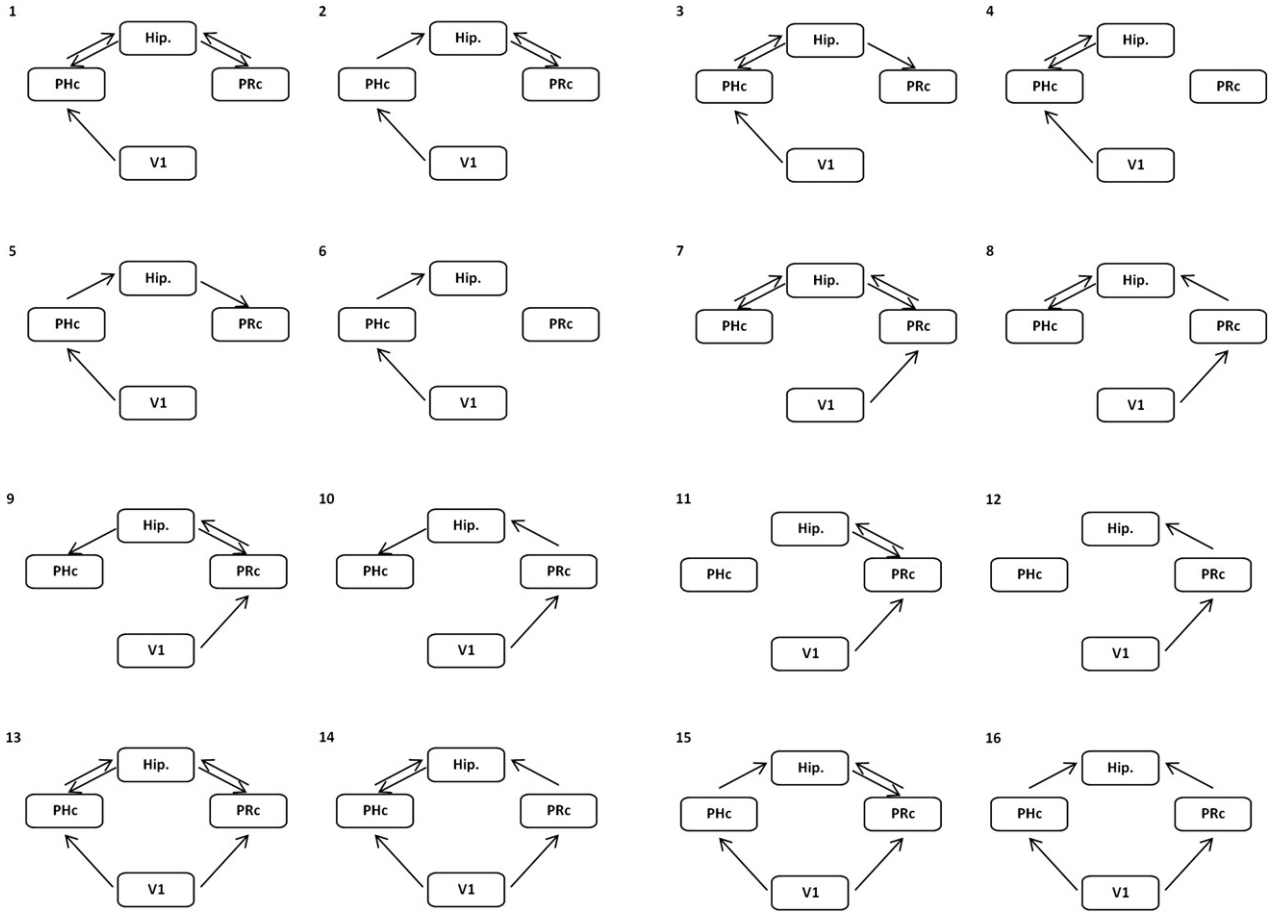

Fig. 3. *Model space*. Modulatory effects in the alternative DCM models submitted to the BMS analysis (Hip. = Hippocampus).

(3) For recall, the hippocampus−>PRc connection would be significantly larger than zero, and for recognition, the hippocampus−>PHc connection would be significantly larger than zero.

As stated in the Introduction, we had no a-priori prediction regarding the hippocampus−>PHc connection in recall and the hippocampus−>PRc connection in recognition.

Results

Behavioral results

In the recall test, a mean of 24.7 (20%; SE = 3.2) targets was Remembered, a mean of 80 (67%; SE = 3.6) was Forgotten and a mean of 11.7 (9.7%; SE = 1.3) was Wrong. In the multiple choice recognition test, a mean of 45.2 (56.6%; SE = 3.9) targets was Remembered, a mean of 23.2 (29%; SE = 3.7) was Forgotten and a mean of 10.4 (13%; SE = 1.4) was Wrong. Thus, for both recall and recognition we obtained a sufficient number of remembered trials to allow a meaningful fMRI analysis. In addition, we confirmed that both recall and recognition scores were significantly above chance by comparing the number of Remembered items to estimates of the number guesses. For recall, the estimate of guesses was the number of Wrong items, which indeed was significantly lower than the number of Remembered items ($t_{17} = 3.76$; $p = 0.002$). For recognition, our multiple-choice recognition test included four possible answers per trial (the target and three lures), setting the chance of guessing correctly at 25%. Like recall, recognition performance was well-above chance level—proportion of Remembered items (56.6%) was significantly larger than 25% ($t_{17} = 6.4$; $p < 0.001$).

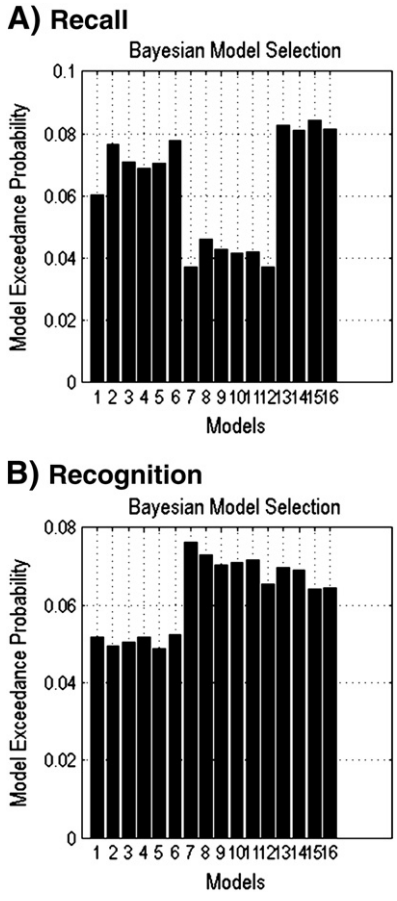

Fig. 4. *Results of BMS analysis.* Exceedence probabilities of the sixteen alternative models submitted to the BMS analysis for (A) Recall and (B) Recognition.

Model comparisons

Fig. 4 presents the exceedence probability for each of the models—namely, the evidence that "a certain model is more likely than any other model, given the group data", with the cumulative probability across all the models equaling one (Stephan et al., 2010). Examination of Fig. 4 revealed that the differences between models were of very small magnitude, with no significant best-fitting model (Kass and Raftery, 1995; Penny et al., 2007). Still, for recall, Fig. 4A shows that the model comparison yielded evidence in favor of the models in which PHc receives modulated input from V1 and projects to the hippocampus (models 1–6 and 13–16). Among these, the models with somewhat higher evidence were those in which both PHc and PRc receive modulated input from V1 and project to the hippocampus (models 13–16). For recognition, Fig. 4B shows that the model comparison yielded evidence in favor of the models in which the PRc receives input from V1 (models 7–16), regardless of whether PHc also gets input or not.

Statistical analysis of model parameters

As is often reported, the Bayesian Model Comparison revealed relatively minor differences between the 16 alternative models (for both recall and recognition). Therefore, examination of our a-priori hypotheses was based primarily on a statistical analysis of the model parameters. This analysis was conducted for the parameter estimates of the Average Model, computed using the Bayesian Model Averaging procedure (Penny et al., 2010; Stephan et al., 2010). The analysis was set to examine the hypotheses stated above (see Statistical analysis of model parameters) using a random effects frequentist approach (i.e., ANOVA and t-tests).

(1) At a descriptive level, the pattern of interaction between memory test (recall, recognition) and input to the hippocampus (PHc, PRc) was in the direction of our hypothesis. For recall, the PHc−>hippocampus connection was stronger than the PRc−>hippocampus connection, and the reverse pattern was found for recognition. We submitted the data to a 2×2 ANOVA with memory test (recall, recognition) and input to the hippocampus (PHc, PRc) as within-subject factors. This analysis revealed a significant interaction ($F_{(1,17)} = 3.67$, MSE = 0.0008, $p = 0.02$), establishing that recall and recognition differ with regard to which structure provides input to the hippocampus. In addition, the result of a t-test directly examining whether the PHc−>hippocampus connection was larger for recall than for recognition approached significance ($p = 0.06$).

Below we present a detailed description of the results of Hypotheses 2 and 3 for each of the memory tests. All reported p-values were corrected for multiple comparisons (Holm, 1979; see also Howell, 2009).

Recall results

(2) As predicted, the modulation on the PHc−>hippocampus connection was significantly larger than zero ($p = 0.02$), while the modulation on the PRc−>hippocampus connection was not ($p > 0.3$).
(3) As predicted, the hippocampus−>PRc connection was significantly larger than zero ($p = 0.046$). In addition, the hippocampus–PHc connection was significantly larger than zero ($p = 0.03$).

Recognition results

(2) As predicted, the modulation on the PRc−>hippocampus connection was larger than zero ($p = 0.03$), while the modulation on the PHc−>hippocampus connection was not ($p > 0.3$).
(3) Here too results confirmed our predictions. The hippocampus−>PHc connection was significantly larger than zero ($p = 0.002$). The hippocampus−>PRc connection was not significantly larger than zero ($p > 0.3$).

Discussion

Our study examines the paths in which hippocampal item-context engrams are accessed and the eventual unbinding of these engrams. We provide novel evidence for dissociative, task-dependent patterns of accessing the hippocampal item-context engram such that its individual components can be extracted from it during memory tests that differ with regard to the to-be-extracted information. To obtain such evidence, we investigated the functional interaction between core MTL structures that mediate the binding and extraction of mnemonic features by comparing the neural dynamics between these structures during recall and recognition. This comparison was based on a mapping of predictions made by current neural models regarding the causal interactions between the MTL structures onto the cognitive processes underlying recall and recognition. By using Dynamic Causal Modeling (DCM), which is a hypothesis-driven method (van Schouwenburg et al., 2010; see also Friston, 2009; Stephan et al., 2010), we were able to confirm these a-priori predictions (see Fig. 5 for a summary of the results).

Specifically, the comparison of models using the BMS procedure suggested that the two memory tests—recall and recognition—differ with regard to the source of input to the hippocampus. A detailed analysis of modulatory connections of interest revealed that the PHc −>hippocampus connection was significant for recall but not for recognition, while the PRc−>hippocampus connection was significant for recognition but not for recall. Moreover, the significant interaction found between memory test and input to the hippocampus provides the most direct evidence that the two memory tests differ with regard to the structure which projects to the hippocampus. Thus, in recall the PHc triggers activation of the item-context engram in the hippocampus, whereas in recognition it is the PRc which triggers activation of the item-context engram in the hippocampus.

Critically, results confirmed our predictions regarding the output from the hippocampus. In recall, activation of the item-context engram in the hippocampus with contextual information resulted in PRc activity, presumably associated with extraction of item information. In recognition, activation of the item-context engram in the hippocampus with item information resulted in PHc activity, presumably associated with extraction of contextual details.

With regard to the BMS analysis, we note that although the differences between the exceedence probabilities of the models submitted to this analysis were small and insignificant, the models in which input to the hippocampus comes from both the PHc (associated with contextual information) and the PRc (associated with item information) showed relatively high exceedence probabilities. Thus, it is possible that in our cued–recall task, not only the PHc, but also the PRc projects information to the hippocampus. If so, the cue word that is presented at retrieval might constitute partial item information which provides secondary input—used in synthesis with the available contextual information—to prompt the retrieval process. Likewise, in recognition, the PHc may project partial contextual information to the hippocampus, which provides secondary input—used in synthesis with the more abundant item information—to prompt the retrieval process.

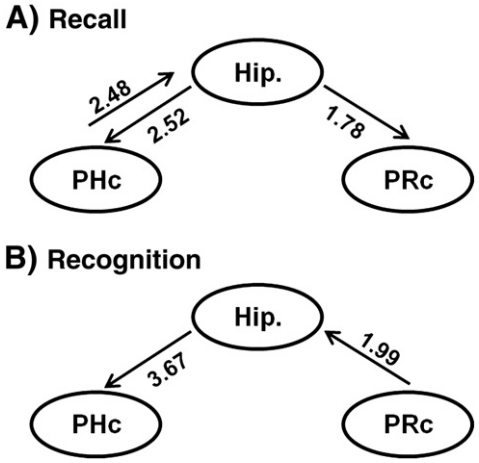

Fig. 5. *The significant modulatory projections between the three key MTL regions.* BMA parameter estimates as a function of their variability (t values), for (A) Recall and (B) Recognition (Hip. = Hippocampus).

We stress, however, that—for both recall and recognition—the possibility that both PHc and PRc project to the hippocampus is implicated only by the exceedence probabilities of the models, computed by the BMS analysis. An analysis of the ratios between the exceedence probabilities of the alternative models—in analogy to Bayes factors (Kass and Raftery, 1995; Penny et al., 2007)—reveals insignificant evidence in favor of any of the models, even for the ratios between the best and worst models (see also Fig. 4). Therefore, the primary examination of our hypotheses was not based on the BMS analysis, but rather on an analysis of the parameter estimates computed using Bayesian Model Averaging (BMA).[6] Results of the BMA analysis revealed more valid information regarding the differential modulations of the PHc and the PRc on the hippocampus than did results of the BMS analysis.

Note that the discrepancies between the results of the BMS analysis and the BMA analysis are not surprising given the different statistical methods and outcomes of each analysis, with the former making inferences on model structure, and the latter making inferences on particular model parameters (Stephan et al., 2010). The BMA analysis revealed that the only modulations on the hippocampus are of the PHc in recall and of the PRc in recognition. Thus, the existence of a hippocampalPRc input in recall and of a hippocampal–PHc input in recognition are not strongly supported by the data. Furthermore, even if such inputs exist, they are most probably secondary inputs, with the PHc providing the primary hippocampal input in recall and the PRc providing the primary hippocampal input in recognition.

Although in both recall and recognition we obtained a sufficient number of trials for meaningful DCM analysis, our results revealed a smaller number of retrieved items in recall than in recognition. This finding is in line with the pattern of results generally reported in studies of recall and recognition, a pattern which is believed to reflect the fact that recall tests are typically more difficult than recognition tests (e.g., Craik and McDowd, 1987; Haist et al., 1992). Note that the differences in difficulty between the tasks cannot account for the differential patterns of interactions between the MTL regions that we found. Stated simply, we report a PHc − > Hippocampus − > PRc route in recall and a PRc − > Hippocampus − > PHc route in recognition—namely, different routes between the exact same set of structures. Had the routes in one task been a subset of the routes in the second task, this could have perhaps entailed that the latter task is more difficult and therefore recruits more interactive processes between brain regions. However, given that the routes in one task were not a subset of the routes in the other task, but rather entirely different routes, the differences we report between recall and recognition cannot be explained in terms of task difficulty.

Comparisons of the neural underpinnings of recall and recognition at retrieval, such as that undertaken in the current study, have been scarcely made in studies using fMRI. In fact, even recall alone has rarely been examined using fMRI because of the challenge in

[6] We note that the number of models in which the hippocampus receives input from both PHc and PRc was smaller than the number of models in each of the other two groups of models: that in which the hippocampus receives input only from the PHc and that in which the hippocampus receives input only from the PRc. Importantly, however, the unequal size of the three groups of models does not bias the results of the BMA analysis because BMA is not a simple average, but a weighted average. The weighting is given by each model's posterior probability, with the sum of posterior probabilities across all models equaling 1 (Penny et al., 2007; Stephan et al., 2010).

gathering overt-speech responses within the fMRI scanner due to head motion artifacts. We addressed this challenge by using special audio equipment which enabled us to record overt responses within the fMRI scanner while minimizing such artifacts (see Behavioral procedure).

Because the focus of the current study was on how the item-context engram is unbound, we wished to tap only recollective processes comprising item-context interactions, while controlling for familiarity. As explained in the Introduction and Materials, we controlled for familiarity by giving all test-words (i.e., both target and foils) an equal exposure during the study phase, thus rendering all test-words equally familiar. Still, a possible interpretation of our results is that though participants could not have relied on familiarity for the words themselves, they may have nevertheless relied on familiarity for the word pairs. This notion is based on recent studies which have shown that under certain conditions recognition of item pairs may be governed by familiarity (Diana et al., 2008; Giovanello et al., 2006; Haskins et al., 2008; Opitz and Cornell, 2006; Quamme et al., 2007; Rhodes and Donaldson, 2007). Furthermore, on the neural level, familiarity-based recognition has been associated with activation of the PRc (Daselaar et al., 2006; Gonsalves et al., 2005; Haskins et al., 2008)—activation which was detected also in the current study. Thus, it may be that—at least in some of the trials—word-pairs were unitized during encoding and the PRc activity we detected reflects differential assessment of familiarity of unitized versus non-unitized pairs during retrieval.

This familiarity interpretation, however, is difficult to reconcile with the finding that during recognition the PRc interacted with the hippocampus, which subsequently projected to the PHc—the hippocampus and the PHc being regions which have long been associated with recollection (Diana et al., 2007). Moreover, the previous studies which reported familiarity for word pairs differed fundamentally from our study in their methodology. In these previous studies, words composing a pair were either associations of each other (Opitz and Cornell, 2006), or created a compound word (Giovanello et al., 2006; Haskins et al., 2008; Quamme et al., 2007; Rhodes and Donaldson, 2007). In contrast, in our study, words composing a pair were neither semantically related, nor were participants encouraged to create a compound word from them. Therefore, even if familiarity played a role in our recognition task, recollection was still the predominant process.

We now address the nature of the PHc-associated contextual representations which underlay the recollective processes we investigated. Given that our encoding task required participants to create a bizarre, detailed mental image of each word pair, it is possible that the contextual representation we tapped was predominantly visuo-spatial (see also Epstein and Ward, 2010 for the role of the PHc in processing spatial layouts). However, this idea should be regarded as speculative, considering that participants were not instructed or encouraged to retrieve visual images. In any case, our finding of increased connectivity from the PHc to the hippocampus at recall but not at recognition is in line with the notion that context triggers recall more so than recognition (e.g., Davelaar et al., 2005; Dennis and Humphreys, 2001; Sederberg et al., 2008; Yonelinas, 2002), regardless of the exact nature of the contextual representation.

While our focus in the current study was on the interactions between MTL regions, an interesting question for future research regards the functional, causal interactions of these MTL regions—and specifically, of the PHc and the PRc—with other cortical regions. This question stems from ample anatomical research which indicates that the PHc and the PRc receive distinct cortical inputs. Thus, the PHc receives most of its input from various multimodal regions in the parietal and temporal lobes, and particularly from the dorsal visual stream (Cavada and Goldman-Rakic, 1989; Kahn et al., 2008; Suzuki, 1996; Witter et al., 1989), and also receives input from the dorsolateral prefrontal cortex (Suzuki, 1996). In contrast, the PRc receives most of its input from the ventral visual stream (Cavada and Goldman-Rakic, 1989; Suzuki, 1996). It would therefore be interesting to investigate whether the PHc and PRc show different functional, causal connectivity patterns with other cortical regions, and how these patterns are influenced by the cognitive tasks applied.

Our hypotheses regarding dissociative patterns of item-context interactions during our cued–recall and associative recognition tests—inspired by a prominent model of human memory (Dennis and Humphreys, 2001)—relied on the task demands of these two tests. While we used associative memory tests, the cognitive model we relied on suggests that similar item-context interactions should underlie other types of memory tests, such as tests for single-items. Further research is therefore needed to determine whether—despite their inability to control for familiarity during recognition—single-item tests produce a pattern of functional interaction between MTL regions which is similar to the pattern detected in the current study.

Finally, this study has identified the neuronal pathway in which either context or item information probes the hippocampal engram and has shown that this pathway only terminates with the extraction of the to-be-unbound information in the PRc or the PHc, respectively. Possible alternatives have been described for how an unbinding mechanism may be computationally instantiated (e.g., Davelaar et al., 2005; Murdock, 1982; Sederberg et al., 2008; Shiffrin and Steyvers, 1997). Future studies may examine which, if any, of these models can be realized biologically. That is, having established the unique routes by which information flows to achieve task-dependent mnemonic goals, it remains to be seen how each of the three MTL structures performs its appropriate computations at either the molecular, neuronal or perhaps even-higher level of analysis.

Acknowledgments

Portions of this article are part of a doctoral dissertation submitted at Tel-Aviv University. We thank O. Linkovski and A. Spiegel and for assisting in data collection. We also thank an anonymous reviewer in the finer articulation of our ideas. This research was supported by The Israel Foundations Trustees (in part; Doctoral Grant No. 29 to T.S.); the Adams Super Center for Brain Studies in Tel-Aviv University (in part, to Y.G.G.); The Israel Science Foundation (in part; grant No. 1418/06 to A.M.); the European Community under the Marie Curie International Reintegration Grant (in part; MIRG-CT-2007-046457 to A.M.); The National Institute for Psychobiology in Israel — Founded by The Charles E. Smith Family (in part, to A.M); T.S. was supported in part by The Levy Edersheim Gitter Institute for Neuroimaging.

References

Aggleton, J.P., Brown, M.W., 1999. Episodic memory, amnesia, and the hippocampal–anterior thalamic axis. Behav. Brain Sci. 22, 425–444.
Aggleton, J.P., Vann, S.D., Oswald, C.J.P., Good, M., 2000. Identifying cortical inputs to the rat hippocampus that subserve allocentric spatial processes: a simple problem with a complex answer. Hippocampus 10, 466–474.
Cabeza, R., Kapur, S., Craik, F.I.M., McIntosh, A.R., Houle, S., Tulving, E., 1997. Functional neuroanatomy of recall and recognition: a PET Study of Episodic Memory. J. Cogn. Neurosci. 9, 254–265.
Cavada, C., Goldman-Rakic, P.S., 1989. Posterior parietal cortex in rhesus monkey: I Parcellation of areas based on distinctive limbic and sensory corticocortical connections. J. Comp. Neurol. 287, 393–421.
Cocosco, C.A., Kollokian, V., Kwan, R.K.-S., Evans, A.C., 1997. BrainWeb: online interface to a 3DMRI simulated. Neuroimage 5, S425.
Craik, F.I., McDowd, J.M., 1987. Age differences in recall and recognition. J. Exp. Psychol. Learn. Mem. Cogn. 13, 474–479.
Dale, A.M., 1999. Optimal experimental design for event-related fMRI. Hum. Brain Mapp. 8, 109–114.
Daselaar, S.M., Fleck, M.S., Cabeza, R., 2006. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. J. Neurophysiol. 96, 1902–1911.
Davachi, L., 2006. Item, context and relational episodic encoding in humans. Curr. Opin. Neurobiol. 16, 693.
Davachi, L., Mitchell, J.P., Wagner, A.D., 2003. Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. Proc. Natl. Acad. Sci. U.S.A. 100, 2157–2162.
Davelaar, E.J., Goshen-Gottstein, Y., Ashkenazi, A., Haarmann, H.J., Usher, M., 2005. The demise of short-term memory revisited: empirical and computational investigations of recency effects. Psychol. Rev. 112, 3–42.

Dennis, S., Humphreys, M., 2001. A context noise model of episodic word recognition. Psychol. Rev. 108, 452–478.
Diana, R., Reder, L., Arndt, J., Park, H., 2006. Models of recognition: a review of arguments in favor of a dual-process account. Psychon. Bull. Rev. 13, 1–21.
Diana, R.A., Yonelinas, A.P., Ranganath, C., 2007. Imaging recollection and familiarity in the medial temporal lobe: a three-component model. Trends Cogn. Sci. 11, 379–386.
Diana, R.A., Yonelinas, A.P., Ranganath, C., 2008. The effects of unitization on familiarity-based source memory: testing a behavioral prediction derived from neuroimaging data. J. Exp. Psychol. Learn. Mem. Cogn. 34, 730.
Eichenbaum, H., Yonelinas, A.P., Ranganath, C., 2007. The medial temporal lobe and recognition memory. Annu. Rev. Neurosci. 30, 123–152.
Eldridge, L.L., Knowlton, B.J., Furmanski, C.S., Bookheimer, S.Y., Engel, S.A., 2000. Remembering episodes: a selective role for the hippocampus during retrieval. Nat. Neurosci. 3, 1149–1152.
Epstein, R.A., Ward, E.J., 2010. How reliable are visual context effects in the parahippocampal place area? Cereb. Cortex 20, 294–303.
Fairhall, S.L., Ishai, A., 2007. Effective connectivity within the distributed cortical network for face perception. Cereb. Cortex 17, 2400–2406.
Fernandez, G., Tendolkar, I., 2006. The rhinal cortex: 'gatekeeper' of the declarative memory system. Trends Cogn. Sci. 10, 358–362.
Friston, K., 2009. Causal modelling and brain connectivity in functional magnetic resonance imaging. PLoS Biol. 7, e1000033.
Giovanello, K.S., Keane, M.M., Verfaellie, M., 2006. The contribution of familiarity to associative memory in amnesia. Neuropsychologia 44, 1859–1865.
Gonsalves, B.D., Kahn, I., Curran, T., Norman, K.A., Wagner, A.D., 2005. Memory strength and repetition suppression: multimodal imaging of medial temporal cortical contributions to recognition. Neuron 47, 751–761.
Habib, R., Nyberg, L., 2008. Neural correlates of availability and accessibility in memory. Cereb. Cortex 18, 1720–1726.
Haist, F., Shimamura, A.P., Squire, L.R., 1992. On the relationship between recall and recognition. J. Exp. Psychol. Learn. Mem. Cogn. 18, 691–702.
Haskins, A.L., Yonelinas, A.P., Quamme, J.R., Ranganath, C., 2008. Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. Neuron 59, 554–560.
Henson, R., 2005. A mini-review of fMRI studies of human medial temporal lobe activity associated with recognition memory. Q. J. Exp. Psychol. 58, 340–360.
Holm, S., 1979. A simple sequentially rejective multiple test procedure. Scand. J. Stat. 6, 65–70.
Hommel, B., 2004. Event files: feature binding in and across perception and action. Trends Cogn. Sci. 8, 494–500.
Hourihan, K.L., MacLeod, C.M., 2008. Directed forgetting meets the production effect: distinctive processing is resistant to intentional forgetting. Can. J. Exp. Psychol./Revue canadienne de psychologie exp ©rimentale 62, 242.
Howell, D.C., 2009. Multiple Comparisons Among Treatment Means. Statistical Methods for Psychology. Wadsworth, Cengage Learning, Australia.
Kahn, I., Andrews-Hanna, J.R., Vincent, J.L., Snyder, A.Z., Buckner, R.L., 2008. Distinct cortical anatomy linked to subregions of the medial temporal lobe revealed by intrinsic functional connectivity. J. Neurophysiol. 100, 129–139.
Kass, R.E., Raftery, A.E., 1995. Bayes factors. J. Am. Stat. Assoc. 90, 773.
Kelley, W.M., Miezin, F.M., McDermott, K.B., Buckner, R.L., Raichle, M.E., Cohen, N.J., Ollinger, J.M., Akbudak, E., Conturo, T.E., Snyder, A.Z., Petersen, S.E., 1998. Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. Neuron 20, 927–936.
Kiebel, S.J., Klöppel, S., Weiskopf, N., Friston, K.J., 2007. Dynamic causal modeling: a generative model of slice timing in fMRI. Neuroimage 34, 1487–1496.
Kumar, S., Stephan, K.E., Warren, J.D., Friston, K.J., Griffiths, T.D., 2007. Hierarchical processing of auditory objects in humans. PLoS Comput. Biol. 3, e100.
Kveraga, K., Boshyan, J., Bar, M., 2007. Magnocellular projections as the trigger of top-down facilitation in recognition. J. Neurosci. 27, 13232–13240.
Lee, A.C.H., Bandelow, S., Schwarzbauer, C., Henson, R.N.A., Graham, K.S., 2006. Perirhinal cortex activity during visual object discrimination: an event-related fMRI study. Neuroimage 33, 362–373.
Leff, A.P., Schofield, T.M., Stephan, K.E., Crinion, J.T., Friston, K.J., Price, C.J., 2008. The cortical dynamics of intelligible speech. J. Neurosci. 28, 13209–13215.
Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19, 1233–1239.
McDaniel, M.A., Einstein, G.O., DeLosh, E.L., May, C.P., Brady, P., 1995. The bizarreness effect: It's not surprising, it's complex. J. Exp. Psychol. Learn. Mem. Cogn. 21, 422–435.
Mechelli, A., Price, C.J., Noppeney, U., Friston, K.J., 2003. A dynamic causal modeling study on category effects: bottom up or top down mediation? J. Cogn. Neurosci. 15, 925–934.
Murdock, B.B., 1982. A theory for the storage and retrieval of item and associative information. Psychol. Rev. 89, 609–626.
Nadel, L., 1994. Multiple memory: what and why, an update. In: Tulving, D.L.S.E. (Ed.), Memory Systems 1994 MIT Press. Bradford Books, Cambridge, MA, pp. 39–63.
Opitz, B., Cornell, S., 2006. Contribution of familiarity and recollection to associative recognition memory: insights from event-related potentials. J. Cogn. Neurosci. 18, 1595–1605.
Penny, W., Mattout, J., Trujillo-Barreto, N., 2007. Bayesian model selection and averaging. In: Friston, K., Ashburner, J., Kiebel, S., Nichols, T., Penny, W. (Eds.), Statistical Parametric Mapping: The Analysis of Functional Brain Images. Elsevier, Amsterdam, pp. 454–467.
Penny, W.D., Stephan, K.E., Daunizeau, J., Rosa, M.J., Friston, K.J., Schofield, T.M., Leff, A.P., 2010. Comparing families of dynamic causal models. PLoS Comput. Biol. 6, e1000709.
Penny, W.D., Stephan, K.E., Mechelli, A., Friston, K.J., 2004. Comparing dynamic causal models. Neuroimage 22, 1157–1172.
Polyn, S.M., Kahana, M.J., 2008. Memory search and the neural representation of context. Trends Cogn. Sci. 12, 24.
Quamme, J.R., Yonelinas, A.P., Norman, K.A., 2007. Effect of unitization on associative recognition in amnesia. Hippocampus 17, 192–200.
Ranganath, C., 2010. Binding items and contexts. Curr. Dir. Psychol. Sci. 19, 131–137.
Rhodes, S.M., Donaldson, D.I., 2007. Electrophysiological evidence for the influence of unitization on the processes engaged during episodic retrieval: enhancing familiarity based remembering. Neuropsychologia 45, 412.
Sederberg, P.B., Howard, M.W., Kahana, M.J., 2008. A context-based theory of recency and contiguity in free recall. Psychol. Rev. 115, 893.
Shiffrin, R., Steyvers, M., 1997. A model for recognition memory: REM-retrieving effectively from memory. Psychon. Bull. Rev. 4, 145–166.
Siman-Tov, T., Mendelsohn, A., Schonberg, T., Avidan, G., Podlipsky, I., Pessoa, L., Gadoth, N., Ungerleider, L.G., Hendler, T., 2007. Bihemispheric leftward bias in a visuospatial attention-related network. J. Neurosci. 27, 11271–11278.
Squire, L., Zola, S., 1997. Amnesia, memory and brain systems. Philos. Trans. R. Soc. B Biol. Sci. 352, 1663–1673.
Staresina, B.P., Davachi, L., 2006. Differential encoding mechanisms for subsequent associative recognition and free recall. J. Neurosci. 26, 9162–9172.
Stark, C.E.L., Squire, L.R., 2001. When zero is not zero: the problem of ambiguous baseline conditions in fMRI. Proc. Natl. Acad. Sci. 98, 12760–12766.
Stephan, K.E., Penny, W.D., Daunizeau, J., Moran, R.J., Friston, K.J., 2009. Bayesian model selection for group studies. Neuroimage 46, 1004.
Stephan, K.E., Penny, W.D., Moran, R.J., den Ouden, H.E.M., Daunizeau, J., Friston, K.J., 2010. Ten simple rules for dynamic causal modeling. Neuroimage 49, 3099–3109.
Suzuki, W.A., 1996. Neuroanatomy of the monkey entorhinal, perirhinal and parahippocampal cortices: organization of cortical inputs and interconnections with amygdala and striatum. Semin. Neurosci. 8, 3–12.
Suzuki, W.A., Amaral, D.G., 2004. Functional neuroanatomy of the medial temporal lobe memory system. Cortex 40, 220–222.
van Schouwenburg, M.R., den Ouden, H.E.M., Cools, R., 2010. The human basal ganglia modulate frontal-posterior connectivity during attention shifting. J. Neurosci. 30, 9910–9918.
Whittlesea, B.W.A., Leboe, J.P., 2000. The heuristic basis of remembering and classification: fluency, generation, and resemblance. J. Exp. Psychol. Gen. 129, 84.
Witter, M.P., Groenewegen, H.J., Lopes da Silva, F.H., Lohman, A.H.M., 1989. Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. Prog. Neurobiol. 33, 161–253.
Yonelinas, A., 1997. Recognition memory ROCs for item and associative information: the contribution of recollection and familiarity. Mem. Cognit. 25, 747–763.
Yonelinas, A.P., 2002. The nature of recollection and familiarity: a review of 30 years of research. Journal of Memory and Language 46, 441–517.