Neuron
Report

A Hippocampal Marker of Recollection Memory Ability among Healthy Young Adults: Contributions of Posterior and Anterior Segments

Jordan Poppenk[1,2,3,*] and Morris Moscovitch[1,2]
[1]Department of Psychology, University of Toronto, 100 St. George Street, Toronto, ON M5S 3G3, Canada
[2]Rotman Research Institute, Baycrest, 3560 Bathurst Street, Toronto, ON M6A 2E1, Canada
[3]Princeton Neuroscience Institute, Princeton University, Green Hall, Princeton, NJ 08540, USA
*Correspondence: jpoppenk@princeton.edu
DOI 10.1016/j.neuron.2011.10.014

SUMMARY

The hippocampus is known to support recollection memory, but the relation between its structure and recollection in healthy adults has not been established. Here we show that the hippocampus (including subiculum, DG, and CA1–CA4), when separated into posterior and anterior segments, can reliably predict recollection in healthy young adults. Better memory was associated with larger posterior and smaller anterior segments, as evaluated relative to the uncal apex. Overall hippocampal volume, however, did not predict memory. This pattern was confirmed in four separate data sets from different studies and laboratories. The relationship between the posterior hippocampus and memory was mediated by the structure's functional connectivity with a neocortical network identified during a postencoding resting-state scan. The relationship was also weakest in an experiment involving no appreciable study-test interval. These findings suggest that enhanced posterior-hippocampal postencoding processes may account for the memory benefit associated with larger posterior hippocampi.

INTRODUCTION

Efforts to explain individual differences in human memory using brain anatomy have centered on the hippocampus (defined here as the subiculum, dentate gyrus, and cornu ammonis regions, including fields CA1–CA4). This structure has known functional importance for the encoding, storage, and, many argue, retrieval of recollection memory (RM), a form of memory involving a detailed reexperiencing of individual episodes that is characterized by retrieval of an item and its context (Moscovitch et al., 2005; Eichenbaum et al., 2007). Indeed, among dementia and amnesic patients, smaller hippocampi predict worse memory (Van Petten, 2004), just as hippocampal volume and memory decline together with age in older adults (Raz, 2000). However, among healthy young adults, published correlations between hippocampal volume and memory approach a normal distribution of about zero (Van Petten, 2004). Nonetheless, Maguire et al. (2000) have shown that extensive spatial memory acquisition leads to enlargement of the posterior hippocampus at the expense of anterior hippocampal volume (pHPC and aHPC; dorsal ventral in nonprimate mammals). This suggests that the crucial predictor of individual differences in recollection may not be overall hippocampal volume (HPC) but the separate contributions of pHPC and aHPC segments, a hypothesis we test in this paper.

This hypothesis is supported by neuroanatomical and functional evidence that pHPC and aHPC have dissociable properties. For instance, in primates, the segments connect with different bands of the entorhinal cortex, a key link between the hippocampus and cerebral cortex (Fanselow and Dong, 2010). Also, hippocampal connections with the retrosplenial cortex and the mammillary bodies arise primarily from pHPC in primates (Aggleton et al., 2005; Kobayashi and Amaral, 2003), and the link between these structures and the hippocampus has been shown to be important specifically for RM (Vann et al., 2009). This anatomical link is suggestive of favorable conditions for recollection in pHPC, and consistent with this notion, damage to the dorsal, but not ventral, portion of the rodent hippocampus impairs Morris water maze performance (Moser and Moser, 1998). In humans, Scoville and Milner (1957) and Penfield and Milner (1958) noted that global amnesia in patients with medial temporal lobe resection was evident only when pHPC was affected bilaterally, and Smith and Milner (1981) observed a similar drop in performance on tests of object-location memory following right pHPC lesions in patients with unilateral temporal lobectomy, although all of these patient observations were confounded with the amount of resected tissue. More recently, high-resolution neuroimaging and single-unit recordings have hinted at greater pHPC involvement in spatial and verbal memory (Maguire et al., 2000; Ludowig et al., 2008). Finally, pHPC in particular has been found to be sensitive to spatial information, which is thought to play a role in RM (Ryan et al., 2010).

To the extent that pHPC is more closely associated with RM and that pHPC and aHPC volumes trade off against one another, relatively large pHPC volumes—and conversely, small aHPC volumes—might be expected to predict enhanced RM, even in the absence of any effect of HPC. To test this hypothesis, we collected anatomical magnetic resonance imaging (MRI) and functional MRI (fMRI) scans from healthy young adults, derived various measures of hippocampal volume and connectivity (see Table S1 available online), and examined their correlations

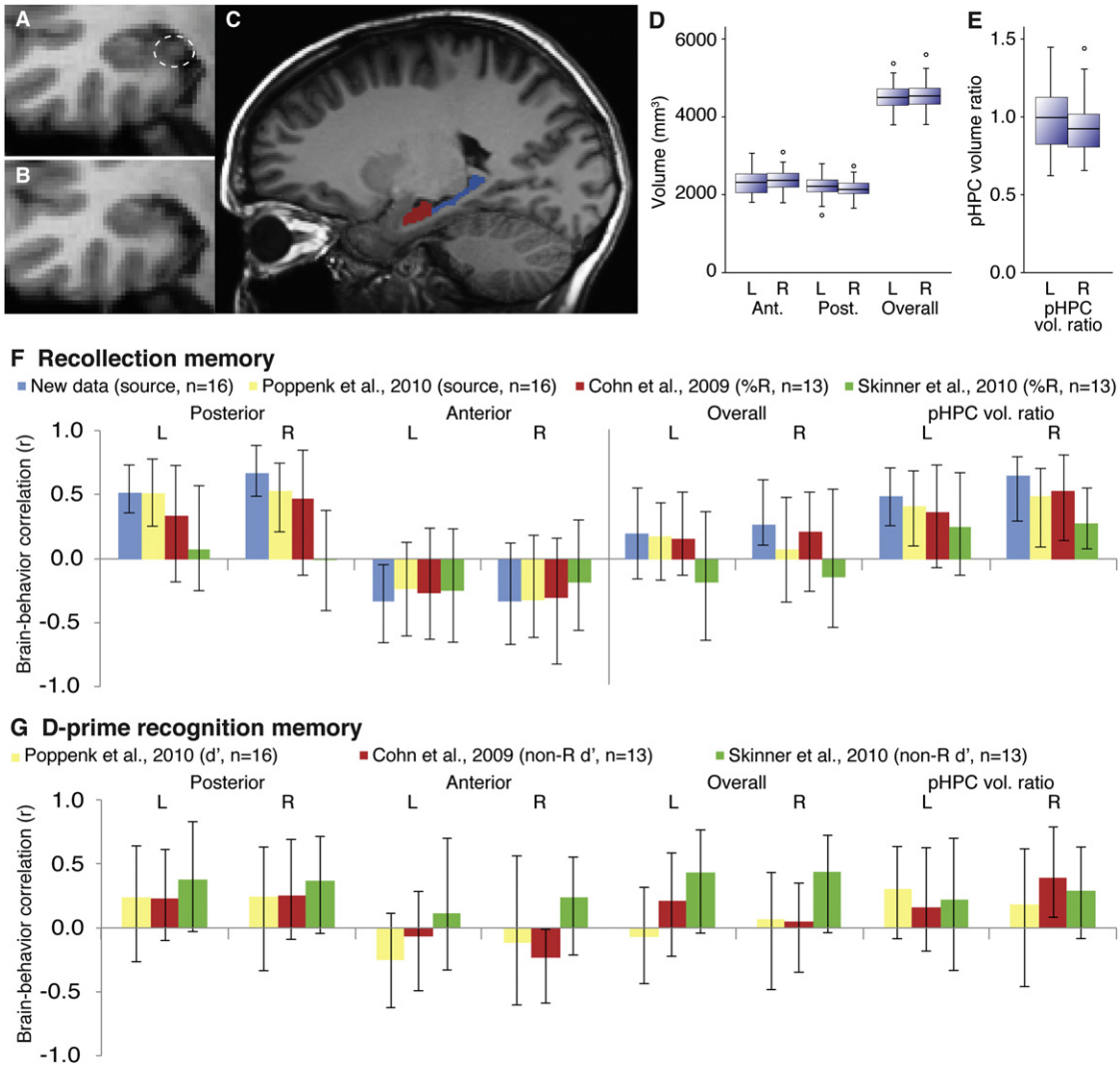

Figure 1. Hippocampus-Memory Correlations in Four Data Sets

The posterior boundary of the aHPC was the most posterior coronal slice in which the uncal apex was visible (indicated in A; absent in B; Weiss et al., 2005). Example aHPC (red) and pHPC parcellations (blue) from one participant's T1 scan are overlaid on a sagittal anatomical image (C). Boxplots illustrate hippocampus metric distributions (D and E). Correlations between hippocampus metrics and RM (F) and recognition memory (G) are plotted for four data sets. Coefficients are bounded by bootstrapped 95% confidence intervals (those excluding zero indicate reliable linear fits at $\alpha = 0.05$). pHPC-based measures correlated most reliably with RM (less so with *d'*). See also Figure S1 for entorhinal cortex correlations.

with source memory. Because source memory directly measures retention of contextual information, it is well matched to the construct of RM, which entails retrieval of contextual information (Tulving, 1985). Also, under conditions in which familiarity cannot contribute to source judgments, source memory closely resembles modeled RM parameters in recognition memory (Yonelinas, 1999). To test the generality of our findings, we submitted three other RM studies with different materials and protocols to the same analysis.

RESULTS AND DISCUSSION

Source memory correlated positively with pHPC volume in both hemispheres and negatively with aHPC volume in the left hemisphere (Figure 1). To distinguish between absolute hippocampus volume and the relative size of pHPC, we calculated HPC (pHPC + aHPC) and pHPC (pHPC/aHPC) volume ratio in both hemispheres. Source memory correlated positively with pHPC volume ratios in both hemispheres, but not with HPC (Figure 1).

To validate this result and probe for possible dissociations between recollection and nonrecollection forms of memory, we obtained three published data sets with RM measures and anatomical brain images. The behavioral measures (see Table S2 for descriptive information) were source and recognition memory for scenes (Poppenk et al., 2010b), remember/know recognition for pairs of words (Cohn et al., 2009), and remember/know recognition for picture-word pairs

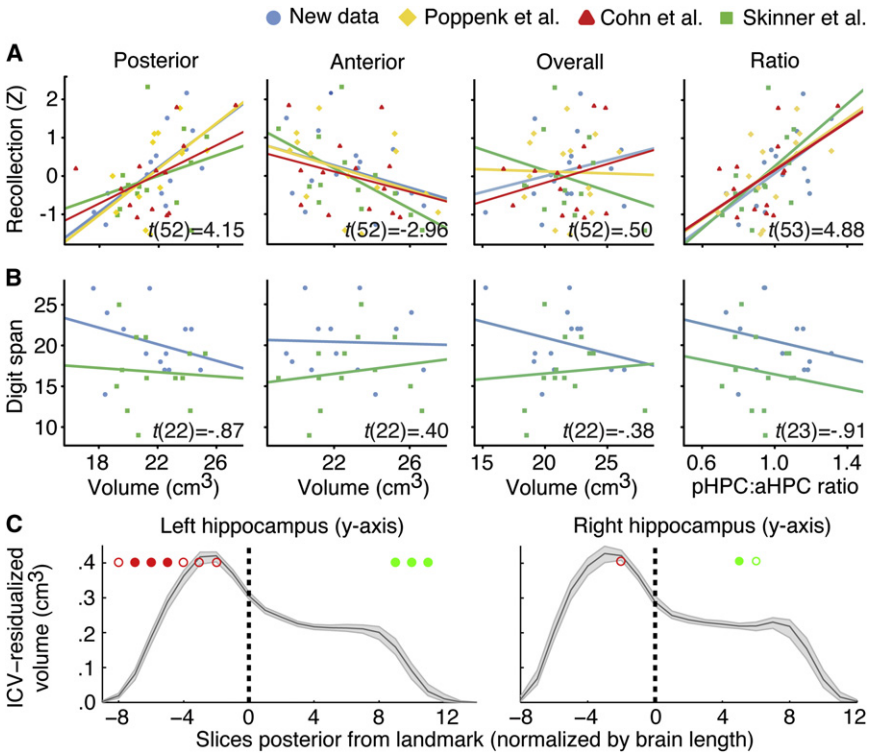

Figure 2. Brain-Behavior Correlations in Aggregate Data Set

Larger pHPC volumes and volume ratios and smaller aHPC volumes predicted better RM (A, averaged across hemispheres, mean-centered within experiment). No positive relations were observed for digit span (B). Mean left and right hippocampus volume is plotted along the structure's long axis with a shaded 95% confidence interval (C, aligned to uncal apex at dashed line). Filled green and red full circles depict coordinates at which volume positively and negatively correlated with RM, respectively (thresholded at $p < 0.05$). Empty circles depict near-significant trends, $p < 0.1$. See also Figure S2 for hemisphere-specific plots.

(Skinner et al., 2010). We derived RM (*R*) and familiarity (*d'*) estimates for each study: right pHPC volume ratios, but not HPC, predicted *R* in all three data sets (Figure 1F). Effects of *d'* resembled weaker and less reliable *R* effects among hippocampal measures (Figure 1G; cf. entorhinal cortex in Figure S1).

Correlations between aHPC and RM were consistently negative, but not reliable, within single data sets. For a more sensitive test, we conducted a multilevel analysis that combined data points from all four studies (Supplemental Experimental Procedures). We found that the negative correlation was reliable in both hemispheres (Figures 2A and S2A). Greater pHPC volumes and volume ratios predicted better RM, whereas HPC did not. Also, two of the data sets included a WAIS-III digit span test. In line with the view that the hippocampus is less pivotal for working memory than RM, no correlations with digit span were observed (Figures 2B and S2B). These results confirmed our hypothesis that pHPC volume, but not HPC, would predict RM and suggested that this prediction was selective to long-term memory.

Because several of our hippocampal measures predicted RM, we explored whether their predictive power could be combined to form a stronger model. However, a forward stepwise version of our multistudy analysis (Supplemental Experimental Procedures) included only the right pHPC volume ratio in the final model, suggesting that our metrics shared most of their predictive power.

In light of this shared variance, it is interesting to consider that the correlation we observed between pHPC volume ratios and RM may have been driven by the relative position of the uncal apex along the longitudinal hippocampal axis because longer segments of the hippocampus could be expected to include greater proportions of hippocampal volume. Indeed, pHPC length ratios were reliable predictors of pHPC volume ratios (left $t(53) = 7.80$, $p < 0.001$; right $t(53) = 7.51$, $p < 0.001$). In addition, coordinate-based analysis of hippocampal volume and RM appeared to capture a memory benefit associated with a longer pHPC and shorter aHPC (Figure 2C), especially in the left hemisphere (peak left pHPC $t(52) = 3.87$, $p < 0.001$; left aHPC $t(52) = -2.42$, $p < 0.05$; right pHPC $t(52) = 2.27$, $p < 0.05$; right aHPC $t(52) = -1.84$, $p = 0.071$). However, pHPC volume ratios were predictive of RM even after separating variance associated with pHPC length ratios (left $t(52) = 2.01$, $p < 0.05$; right $t(52) = 3.48$, $p < 0.001$), whereas the opposite pattern did not hold (left $t(52) = 1.02$, $p > 0.3$; right $t(52) = -0.49$, $p > 0.6$). That is, hippocampal volumetric information contributed the same information provided by apex position, plus additional information.

Just as concurrent increases in pHPC volume and decreases in aHPC volume have been observed following massive accumulation of spatial memories by London taxi drivers (Maguire et al., 2000), a negative relationship was observed between left pHPC and aHPC volumes in our combined analysis ($t(52) = -3.36$, $p < 0.005$) confirming that a tradeoff effect was present (although this effect did not reach significance in the right hemisphere, $t(52) = -1.22$, $p > 0.2$). That pHPC and aHPC also made opposite, but overlapping, predictions about RM further suggests a tradeoff effect. Along these lines, although variance in pHPC was predicted by HPC (left $t(52) = 4.12$, $p < 0.001$; right $t(52) = 5.63$, $p < 0.001$), it was the non-HPC portion of pHPC variance that predicted RM in both hemispheres. pHPC was in fact a slightly better predictor in the left hemisphere after controlling HPC ($t(51) = 4.48$, $p < 0.001$; without control $t(52) = 4.02$, $p < 0.001$) and in the right hemisphere after controlling HPC ($t(51) = 3.91$, $p < 0.001$; without control $t(52) = 3.38$, $p < 0.005$). This pattern may explain why HPC has failed to predict RM in past studies involving healthy adults, even though pHPC volume ratio was a reliable predictor in all of the studies we analyzed.

In part because there is both little direct communication between pHPC and aHPC (Moser and Moser, 1998; Fanselow

and Dong, 2010) and in part because different large-scale connectivity (i.e., neural context; McIntosh, 2000) has been associated with each region (Moser and Moser, 1998; Kahn et al., 2008; Fanselow and Dong, 2010; Poppenk et al., 2010b), the notion of functional specialization along the long hippocampal axis has gained favor (Moser and Moser, 1998; Fanselow and Dong, 2010). Drawing upon this idea, we tested the hypothesis that pHPC neural context differs from that of aHPC and is supportive of RM. We began by searching for patterns in the ambient functional networks associated with left pHPC, left aHPC, right pHPC, and right aHPC in our resting-state fMRI data. To this end, we entered correlation maps associated with these hippocampal seed regions into multivariate analysis (PLSGUI; McIntosh and Lobaugh, 2004). The only significant latent variable to emerge corresponded to a contrast of pHPC and aHPC bilaterally, with this divergence especially apparent in the right hemisphere ($n = 13$; singular value = 8.9, $p < 0.05$) (Figure 3A). A nonrotated version of this analysis confirmed that a contrast of pHPC and aHPC connectivity was significant at the whole-brain level. The underlying spatial pattern involved preferential correlation between pHPC and bilateral dorsolateral prefrontal cortex, left anterior cingulate cortex, bilateral posterior cingulate cortex and retrosplenial cortex, left precuneus, bilateral thalamus (including anterior and dorsomedial nuclei), bilateral inferior parietal lobe, and bilateral occipital gyrus regions (Figures 3B–3E; Table S3). aHPC correlated preferentially with the lateral temporal cortex in both hemispheres, extending to the temporal poles bilaterally (Figures 3B–3E). Similar findings have been reported elsewhere (Kahn et al., 2008), but the current results extend prior evidence by formally demonstrating the stability of the overall pattern.

Interestingly, the above pHPC- and aHPC-correlated regions are, respectively, the cortical connections of the polysynaptic intrahippocampal pathway (which connects with frontal and parietal cortices via the fornix) and the direct intrahippocampal pathway (which projects to the anterior temporal lobe via the uncinate fasciculus; Duvernoy, 2005; Figure 3F). Connections of the polysynaptic pathway are believed to support RM by mediating perceptual (precuneus), attentional (inferior parietal), and strategic (lateral frontal) contributions to it (Spaniol et al., 2009). Integrity of the fornix, which connects the polysynaptic pathway to cortex, is also important for RM (Tsivilis et al., 2008; Gilboa et al., 2006). In contrast, anterior temporal connections of the direct pathway are associated with the processing of semantic information and social and emotional cues (Rogers et al., 2006; Olson et al., 2007). Because pHPC linked preferentially with polysynaptic pathway connections, a neural context interpretation is consistent with our finding that larger pHPC volume ratios predict better RM.

Hippocampal covariance effects during postencoding rest that are linked to memory success have been interpreted as evidence of hippocampal consolidation (Tambini et al., 2010; Ben-Yakov and Dudai, 2011). Along these lines, and because pHPC is linked preferentially to regions associated with RM, we explored whether greater pHPC covariance with its functionally connected network during postencoding rest could explain the relationship between pHPC volume ratios and RM. A mediation analysis based on individual differences in pHPC ratios,

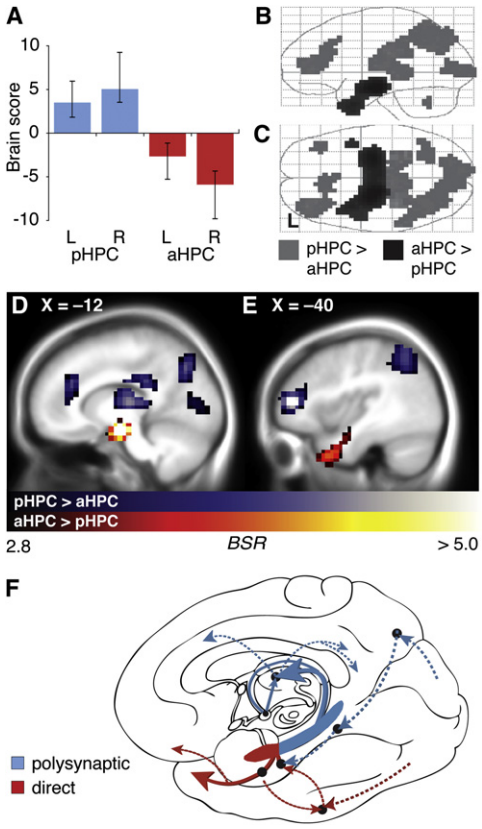

Figure 3. Long Axis Functional Connectivity Effects

Rotated partial least squares revealed a significant large-scale network dissociating pHPC and aHPC covariance (A). Mean brain score is bounded by a 95% confidence interval. Reliable differences are depicted on a glass brain in a sagittal and transverse view (B and C) and on a template brain based on 200 young adults scanned at the Rotman Research Institute (D and E). Differences corresponded to the cortical connections of the two hippocampal pathways (F). (F) was modified from Duvernoy (2005) with kind permission of Springer Science+Business Media. See also Table S3 for a list of regions and Figure S3 for a mediation model of volume, recollection, and connectivity.

source memory, and pHPC covariance with the region's cortical connections revealed that conditions required for mediation were satisfied, with mediation explaining 55% of the volumetric effect (Figure S3).

Mediation analysis cannot rule out the possibility that an unknown factor is the true mediator (Judd and Kenny, 1981) or that pHPC covariance and RM capture the same underlying quantity. That is, mediation analysis cannot confirm that the relationship between pHPC covariance and RM was causal. However, pHPC covariance in a prestudy proverb interpretation task (measured in the same manner as poststudy rest pHPC connectivity) was unrelated to RM ($r(12) = -0.15$, $p > 0.4$). Although the presence of a prestudy task precludes a direct comparison of pre- and poststudy connectivity, this result does help rule out an explanation of our result based on person-general, noncognitive factors, such as less noisy pHPC signal in large-pHPC individuals. Further support for a consolidation-based account arises from the post hoc

observation that the Skinner et al. (2010) data set featured a study-test interval of only 30 s, whereas all other studies had an interval of approximately 20–30 min. Interestingly, the Skinner et al. (2010) study featured much weaker relations between pHPC measures and RM than the other studies. This observation, together with our mediation results, newly establishes increased hippocampal consolidation as a possible mechanism for the relationship between pHPC volume ratios and memory.

In conclusion, our results show that pHPC volume, especially expressed as a ratio to aHPC volume, reliably predicts RM ability in healthy adults. Although correlates of retrieval have been observed along the entire hippocampal axis using functional neuroimaging (Schacter and Wagner, 1999), the current evidence, combined with anatomical and lesion evidence, indicates that the contribution of pHPC is particularly crucial (see also Fanselow and Dong, 2010; Maguire et al., 2000; Moser and Moser, 1998; Smith and Milner, 1981), confirming the observation of Scoville and Milner (1957) and Penfield and Milner (1958). That pHPC was related to RM in four different studies involving various materials and procedures further indicates that this pHPC contribution is not limited to forms of RM involving spatial memory. We propose that the longstanding failure to observe reliable HPC correlations with memory in past studies (Van Petten, 2004), also observed here, may be attributable to an inverse relationship with RM in aHPC and a tradeoff between pHPC and aHPC volume. Finally, a mediation model was supported by pHPC connectivity as measured between study and test, by the absence of a comparable relationship during a task before study, and by the observation that volumetric effects were strongest in experiments with longer study-test intervals. Together, this evidence suggests the above volumetric effects may have been underpinned by enhanced hippocampally based postencoding processes, possibly related to consolidation, in individuals with larger pHPC volume ratios.

EXPERIMENTAL PROCEDURES

We scanned 18 participants, collecting MRI, resting-state fMRI, and memory data (experiment 1). We also obtained permission to reanalyze three independent fMRI data sets conducted with healthy young participants, an RM measure such as source memory or subjective recollection, and high-resolution T1 anatomical images (experiments 2–4; Poppenk et al., 2010b; Skinner et al., 2010; Cohn et al., 2009). fMRI data in these data sets were collected for other primary uses and are not reported here. No additional data sets were assessed.

Experiment 1

Overview

Experiment 1 contained a scanned study phase and poststudy resting phase, followed by a source memory test outside of the scanner (Table S1). In addition, a prestudy repetition phase served to make some materials familiar (Table S1), and study and test phases incorporated some blocks of these familiarized materials to support investigation of stimulus novelty (to be described elsewhere). Study-test stimuli consisted of novel proverbs (Asian origin), repeated proverbs (Asian origin), and proverbs known in advance (English origin), which allowed us to manipulate familiarity based on repetition and prior cultural knowledge. To facilitate comparison with other studies, including the three we obtained, we analyzed only novel items here. However, between-subjects performance for novel items was highly correlated with overall performance ($r(15) = 0.83$, $p < 0.001$).

Participants

Eighteen right-handed young adults, all fluent in English, participated in the experiment (11 female; aged 21 to 34 years, mean age 26.1). Participants were screened for the absence of neurological and psychiatric conditions and received financial remuneration for their participation. All procedures were approved by research ethics boards at the University of Toronto and Baycrest Centre for Geriatric Care. One participant was excluded for outlier behavioral performance (more than four quartiles from the median), and one was excluded due to outlier hippocampus volume. Due to technical issues, we acquired resting-state data for only 15 participants. Scans for two participants were discarded due to excess motion artifact. In total, 16 participants were entered into structure-function correlations and 13 into resting-state analyses.

Stimuli

Two lists of proverbs were prepared, one containing 80 common English proverbs (e.g., "Too many cooks spoil the broth") and the other 160 Asian proverbs (e.g., "A single hair can hide mountains"; for a complete list, see Poppenk et al., 2010a). The Asian list was randomly split into "repetition" and "novelty" sets of 80 Asian proverbs for each participant.

Procedure

Three phases were of greatest importance to our analyses (Table S1): (1) a study phase (participants were scanned with fMRI) in which proverbs were novel or familiar (only novel items were considered in the current investigation); (2) an eyes-closed resting phase between study and test (participants were scanned with fMRI); and (3) a source memory test for all of the proverbs encountered in the study phase. During the study phase (Table S1), half of each proverb list was presented in a target age task: using a button-press, participants rated whether each proverb would be more suitable for an adolescent or an adult. The other half of each list was presented in a quality-rating task: using a button press, participants decided whether each proverb was of good or poor quality. In the source memory test (Table S1), participants later indicated whether each proverb was in the target age or quality task. Repetition of proverbs from the repeated list (items we excluded) took place prior to study (Table S1), and a WAIS-III digit span test was administered in a follow-up session. Scanning was performed using a 3 Tesla whole-body MRI system (Siemens, Erlangen, Germany) installed at Baycrest Hospital in Toronto, Canada (Supplemental Experimental Procedures).

Analysis of MRI Data

We derived left and right aHPC, pHPC, HPC, and entorhinal volumes from our anatomical MRI scans using a semiautomated procedure based on FreeSurfer (http://surfer.nmr.mgh.harvard.edu; see Supplemental Experimental Procedures for details and validation). To determine whether the various measures predicted any of our behavioral measures, we evaluated Pearson correlations between each anatomical and behavioral measure. To evaluate the reliability of each correlation, we employed bootstrap resampling with 100 samples to establish 95% confidence intervals around the relationship between each pair of variables. Correlations were considered reliable at $p < 0.05$ when intervals did not encompass zero. Where data from multiple studies were combined, multilevel modeling analysis was employed to remove between-study sources of variance (Supplemental Experimental Procedures). To evaluate the extent to which different variables predicted unique variance, we conducted a stepwise linear regression with RM as a dependent variable (Supplemental Experimental Procedures). Finally, we examined relationships between RM and volume of individual y axis slices of the hippocampus. Hippocampi were aligned at the uncal apex, downsampled, and entered into analysis as above (Supplemental Experimental Procedures).

Analysis of fMRI Data

Preprocessing of the T2-weighted functional images was performed using FSL (Oxford Centre for Functional MRI of the Brain Software Library; Smith et al., 2004) and included a standard denoising and spatial normalization pipeline (Supplemental Experimental Procedures). To conduct functional connectivity analyses using the pHPC and aHPC as seeds, we required a time series of the mean signal from each of the two regions in each hemisphere. We first projected each participant's pHPC and aHPC segmentations into functional image space. For each mask, we then created a corresponding seed vector by recording the mean intensity of masked voxels at each time point. Next, images were smoothed using a three-dimensional Gaussian kernel (full-width half-maximum = 6 mm). For each participant, we separately assessed the

within-subject correlation between each voxel in the smoothed image time series and each seed vector. This yielded a separate functional connectivity image for each of four seeds: left pHPC, left aHPC, right pHPC, and right aHPC.

We entered these images into multivariate analysis using PLSGUI (McIntosh and Lobaugh, 2004). Briefly, we concatenated correlation images of all seeds and participants into a large matrix, applied singular value decomposition to identify any latent variables (LVs), and evaluated the reliability of these LVs and their singular images using resampling (Supplemental Experimental Procedures). Because the only significant LV corresponded to a contrast of pHPC and aHPC, we also evaluated a nonrotated version of this analysis in which we tested this contrast explicitly. We inspected the associated bootstrap ratio maps to determine where in the brain pHPC and aHPC connectivity differed (Supplemental Experimental Procedures).

To explore the possibility that pHPC volume ratios expressed their effects on RM via postencoding pHPC connectivity, we tested a mediation model. We first obtained a connectivity summary for each participant (i.e., brain score) by taking the product of a salience vector containing voxels that correlated preferentially with pHPC and the matrix of participant pHPC covariance images (obtained from the nonrotated analysis above). The resulting brain score reflected the extent to which pHPC expressed a correlation with its neural context in each participant. Next, we specified a causal model constrained by the flow of time. We reasoned that postencoding brain scores could not have influenced pHPC volume ratios, whereas pHPC volume ratios could have influenced brain scores (Figure S3), and that RM sampled after rest could not have influenced brain scores, whereas resting brain activity could have influenced RM (Figure S3). Applying the steps in establishing mediation discussed by Baron and Kenny (1986), we performed three necessary tests to show that (1) pHPC volume ratios are correlated with brain scores (*a*), (2) the pHPC volume ratios are correlated with RM (*c*), and (3) brain scores are correlated with RM (*b*), even while controlling for pHPC volume ratios (*b'*). We evaluated degree of mediation as $1 - ab/c$ (Kenny et al., 1998).

Experiments 2–4: Obtained Data Sets. Although behavioral protocols for the obtained data sets are published elsewhere, for convenience, brief summaries are provided (Supplemental Experimental Procedures). In all data sets, anatomical images were originally acquired to support spatial normalization of fMRI data and were not themselves analyzed. We applied the same MRI preprocessing and analysis procedures described in experiment 1 and included all individuals meeting the demographic criteria used for our own data set (i.e., healthy right-handed young adults aged 18–34 who are native speakers of English; only two individuals did not qualify).

Group Pooling and Outlier Handling. We searched for outliers by aggregating all unique individuals and identifying values falling more than four quartiles from the median. We did this for both behavior and anatomical variables (Figures 1D and 1E). This led to the removal of two individuals in the data set we gathered (n = 16 instead of n = 18), zero individuals in Poppenk et al. (2010b) (n = 16), one individual in the data set collected by Skinner et al. (2010) (n = 13 instead of n = 14), and zero individuals in the data set collected by Cohn et al. (2009) (n = 13).

For the RM aggregate analysis, we combined our measure from the current study (source memory accuracy) with that from Poppenk et al. (2010b) (source memory accuracy), Skinner et al. (2010) (proportion of hits subjectively recollected), and Cohn et al. (2009) (proportion of hits subjectively recollected). Measures were *Z* scored within-study to help control for between-study effects. One individual participated in three of these studies and was sampled only once; all other participants participated in only one of the studies. In total, 56 individuals were included in the aggregate RM analysis.

For the digit span aggregate analysis, we combined our WAIS-III digit span measurements with those of Skinner et al. (2010). One individual participated in both studies and was sampled only once, and digit span data were not available from two individuals in our data set. In total, 26 individuals were included in the aggregate digit span analysis.

SUPPLEMENTAL INFORMATION

Supplemental Information includes three figures, Supplemental Experimental Procedures, and three tables and can be found with this article online at doi:10.1016/j.neuron.2011.10.014.

ACKNOWLEDGMENTS

We thank M. Cohn, E. Skinner, and M. Fernandes for contributing data sets, N. Bakker, S. Freel, and P. Lin for manual segmentations, M. Ziegler for stimulus programming, F. Tam for imaging sequences, W. Cunningham and A. Yonelinas for statistical advice, and H. Chapman for helpful comments. Supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) postgraduate scholarship (J.P.), NSERC postdoctoral scholarship (J.P.), NSERC A8347 (M.M.), Canadian Institutes of Health Research MOP49566 (M.M), and J.S. McDonnell Foundation 22002082 (A.R. McIntosh).

Accepted: October 13, 2011
Published: December 21, 2011

REFERENCES

Aggleton, J.P., Vann, S.D., and Saunders, R.C. (2005). Projections from the hippocampal region to the mammillary bodies in macaque monkeys. Eur. J. Neurosci. *22*, 2519–2530.

Baron, R.M., and Kenny, D.A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J. Pers. Soc. Psychol. *51*, 1173–1182.

Ben-Yakov, A., and Dudai, Y. (2011). Constructing realistic engrams: poststimulus activity of hippocampus and dorsal striatum predicts subsequent episodic memory. J. Neurosci. *31*, 9032–9042.

Cohn, M., Moscovitch, M., Lahat, A., and McAndrews, M.P. (2009). Recollection versus strength as the primary determinant of hippocampal engagement at retrieval. Proc. Natl. Acad. Sci. USA *106*, 22451–22455.

Duvernoy, H.M. (2005). The Human Hippocampus: Functional Anatomy, Vascularization, and Serial Sections with MRI (New York: Springer).

Eichenbaum, H., Yonelinas, A.P., and Ranganath, C. (2007). The medial temporal lobe and recognition memory. Annu. Rev. Neurosci. *30*, 123–152.

Fanselow, M.S., and Dong, H.W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? Neuron *65*, 7–19.

Gilboa, A., Winocur, G., Rosenbaum, R.S., Poreh, A., Gao, F., Black, S.E., Westmacott, R., and Moscovitch, M. (2006). Hippocampal contributions to recollection in retrograde and anterograde amnesia. Hippocampus *16*, 966–980.

Judd, C.M., and Kenny, D.A. (1981). Process analysis: Estimating mediation in treatment evaluations. Eval. Rev. *5*, 602–619.

Kahn, I., Andrews-Hanna, J.R., Vincent, J.L., Snyder, A.Z., and 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.

Kenny, D.A., Kashy, D.A., and Bolger, N. (1998). Data analysis in social psychology. In The Handbook of Social Psychology, Fourth Edition, D. Gilbert, S. Fiske, and G. Lindzey, eds. (Boston: McGraw-Hill), pp. 233–265.

Kobayashi, Y., and Amaral, D.G. (2003). Macaque monkey retrosplenial cortex: II. Cortical afferents. J. Comp. Neurol. *466*, 48–79.

Ludowig, E., Trautner, P., Kurthen, M., Schaller, C., Bien, C.G., Elger, C.E., and Rosburg, T. (2008). Intracranially recorded memory-related potentials reveal higher posterior than anterior hippocampal involvement in verbal encoding and retrieval. J. Cogn. Neurosci. *20*, 841–851.

Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., and Frith, C.D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. Proc. Natl. Acad. Sci. USA *97*, 4398–4403.

McIntosh, A.R. (2000). Towards a network theory of cognition. Neural Netw. *13*, 861–870.

McIntosh, A.R., and Lobaugh, N.J. (2004). Partial least squares analysis of neuroimaging data: applications and advances. Neuroimage *23* (*Suppl 1*), S250–S263.

Moscovitch, M., Rosenbaum, R.S., Gilboa, A., Addis, D.R., Westmacott, R., Grady, C., McAndrews, M.P., Levine, B., Black, S., Winocur, G., and Nadel, L. (2005). Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J. Anat. *207*, 35–66.

Moser, M.B., and Moser, E.I. (1998). Functional differentiation in the hippocampus. Hippocampus *8*, 608–619.

Olson, I.R., Plotzker, A., and Ezzyat, Y. (2007). The Enigmatic temporal pole: a review of findings on social and emotional processing. Brain *130*, 1718–1731.

Penfield, W., and Milner, B. (1958). Memory deficit produced by bilateral lesions in the hippocampal zone. AMA Arch. Neurol. Psychiatry *79*, 475–497.

Poppenk, J., Köhler, S., and Moscovitch, M. (2010a). Revisiting the novelty effect: when familiarity, not novelty, enhances memory. J. Exp. Psychol. Learn. Mem. Cogn. *36*, 1321–1330.

Poppenk, J., McIntosh, A.R., Craik, F.I.M., and Moscovitch, M. (2010b). Past experience modulates the neural mechanisms of episodic memory formation. J. Neurosci. *30*, 4707–4716.

Raz, N. (2000). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In The Handbook of Aging and Cognition, F.I.M. Craik and T.A. Salthouse, eds. (Mahwah, NJ: Erlbaum), pp. 1–90.

Rogers, T.T., Hocking, J., Noppeney, U., Mechelli, A., Gorno-Tempini, M.L., Patterson, K., and Price, C.J. (2006). Anterior temporal cortex and semantic memory: reconciling findings from neuropsychology and functional imaging. Cogn. Affect. Behav. Neurosci. *6*, 201–213.

Ryan, L., Lin, C.Y., Ketcham, K., and Nadel, L. (2010). The role of medial temporal lobe in retrieving spatial and nonspatial relations from episodic and semantic memory. Hippocampus *20*, 11–18.

Schacter, D.L., and Wagner, A.D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus *9*, 7–24.

Scoville, W.B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatry *20*, 11–21.

Skinner, E.I., Grady, C.L., and Fernandes, M.A. (2010). Reactivation of context-specific brain regions during retrieval. Neuropsychologia *48*, 156–164.

Smith, M.L., and Milner, B. (1981). The role of the right hippocampus in the recall of spatial location. Neuropsychologia *19*, 781–793.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage *23* (*Suppl 1*), S208–S219.

Spaniol, J., Davidson, P.S., Kim, A.S., Han, H., Moscovitch, M., and Grady, C.L. (2009). Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. Neuropsychologia *47*, 1765–1779.

Tambini, A., Ketz, N., and Davachi, L. (2010). Enhanced brain correlations during rest are related to memory for recent experiences. Neuron *65*, 280–290.

Tsivilis, D., Vann, S.D., Denby, C., Roberts, N., Mayes, A.R., Montaldi, D., and Aggleton, J.P. (2008). A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. Nat. Neurosci. *11*, 834–842.

Tulving, E. (1985). Memory and consciousness. Can. Psychol. *26*, 1–12.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia *42*, 1394–1413.

Vann, S.D., Tsivilis, D., Denby, C.E., Quamme, J.R., Yonelinas, A.P., Aggleton, J.P., Montaldi, D., and Mayes, A.R. (2009). Impaired recollection but spared familiarity in patients with extended hippocampal system damage revealed by 3 convergent methods. Proc. Natl. Acad. Sci. USA *106*, 5442–5447.

Weiss, A.P., Dewitt, I., Goff, D., Ditman, T., and Heckers, S. (2005). Anterior and posterior hippocampal volumes in schizophrenia. Schizophr. Res. *73*, 103–112.

Yonelinas, A.P. (1999). The contribution of recollection and familiarity to recognition and source-memory judgments: a formal dual-process model and an analysis of receiver operating characteristics. J. Exp. Psychol. Learn. Mem. Cogn. *25*, 1415–1434.