

Published in final edited form as:

J Cogn Neurosci. 2015 February ; 27(2): 234–245. doi:10.1162/jocn_a_00717.

Relating Hippocampus to Relational Memory Processing across Domains and Delays

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Abstract

The hippocampus has been implicated in a diverse set of cognitive domains and paradigms, including cognitive mapping, long-term memory, and relational memory, at long or short study–test intervals. Despite the diversity of these areas, their association with the hippocampus may rely on an underlying commonality of relational memory processing shared among them. Most studies assess hippocampal memory within just one of these domains, making it difficult to know whether these paradigms all assess a similar underlying cognitive construct tied to the hippocampus. Here we directly tested the commonality among disparate tasks linked to the hippocampus by using PCA on performance from a battery of 12 cognitive tasks that included two traditional, long-delay neuropsychological tests of memory and two laboratory tests of relational memory (one of spatial and one of visual object associations) that imposed only short delays between study and test. Also included were different tests of memory, executive function, and processing speed. Structural MRI scans from a subset of participants were used to quantify the volume of the hippocampus and other subcortical regions. Results revealed that the 12 tasks clustered into four components; critically, the two neuropsychological tasks of long-term verbal memory and the two laboratory tests of relational memory loaded onto one component. Moreover, bilateral hippocampal volume was strongly tied to performance on this component. Taken together, these data emphasize the important contribution the hippocampus makes to relational memory processing across a broad range of tasks that span multiple domains.

INTRODUCTION

In studying the functional role of the hippocampus and related medial-temporal lobe structures, the fields of psychology and neuroscience are not wanting for paradigms or methods, as an impressive diversity of tests is apparent across the respective literatures. For example, countless investigations of hippocampal function in rodent models use one or another sensitive test of spatial memory, inspired largely by the ideas of cognitive mapping theory (O’Keefe & Nadel, 1978). By contrast, clinical investigation of hippocampal damage in humans historically involves testing memory at long delays, often for verbal materials.

For example, disproportionate impairments on the delayed test condition of the California Verbal Learning Test (CVLT) are often indicative of early clinical Alzheimer's disease and also correlate with residual hippocampal tissue in amnesic patients who are severely impaired on this task (Weintraub, Wicklund, & Salmon, 2012; Allen, Tranel, Bruss, & Damasio, 2006). The relationship between performance on tests like the CVLT or delayed recall of stories in the Logical Memory (LM) subtest of the Wechsler Memory Scale and the integrity of the hippocampus is consistent with findings as far back as those with patient HM, who had grossly impaired memory at long delays but seemingly intact memory when delays were very short (Milner, Corkin, & Teuber, 1968; Sidman, Stoddard, & Mohr, 1968; Wickelgren, 1968).

Recently though, emerging findings in cognitive neuroscience indicate a critical role for the hippocampus in memory across even short delays. Hippocampal amnesic participants are impaired when they must process and remember the relationships between elements such as a face with a scene or an object–location binding, thereby requiring relational memory, even when the delay between study and test is only several seconds (Yee, Hannula, Tranel, & Cohen, 2014; Pertzov et al., 2013; Watson, Voss, Warren, Tranel, & Cohen, 2013; Hannula, Tranel, & Cohen, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006). Furthermore, studies using a variety of stimuli indicate hippocampal/medial-temporal lobe-damaged patients perform more poorly on certain visual search tasks even with no experimenter-imposed delay; that is, patients are impaired even when all of the information necessary to correctly answer a trial remains present on the display for the participant, and the only delays are those occurring across successive saccades (Warren, Duff, Jensen, Tranel, & Cohen, 2012; Warren, Duff, Tranel, & Cohen, 2011; Lee et al., 2005). Finally, neuroimaging studies report hippocampal activity during encoding and maintenance at short delays for novel stimuli or for relations among items (Olsen et al., 2009; Hannula & Ranganath, 2008; Axmacher et al., 2007; Ranganath, Cohen, & Brozinsky, 2005; Ranganath & D' Esposito, 2001).

Viewing across the different literatures exploring hippocampal function, one gains an appreciation for the breadth of cognitive tasks that involve the hippocampus. But, how is the hippocampus involved in all of these disparate tasks? It is possible that the hippocampus makes a range of contributions to cognition by carrying out qualitatively different computations when supporting memory for a word list after a long delay compared with when aiding in remembering a face–scene pair at a short delay or when creating and maintaining representations that can distinguish among multiple similar stimuli. The possibility of multiple functional roles for the hippocampus would seem to be encouraged by recent findings critically implicating the hippocampus in functions even less obviously related to those tapped by classical memory tasks (reviewed in Wang, Cohen, & Voss, 2014; Shohamy & Turk-Browne, 2013), such as future imagining (Schacter et al., 2012), and aspects of language (Duff & Brown-Schmidt, 2012), decision-making (Coronel et al., 2012; Gupta et al., 2009), and high-level perception (Lee, Yeung, & Barense, 2012).

An alternative possibility is that the hippocampus supports core memory computations and processes that are invoked by multiple cognitive systems in service of a range of task performances. The idea that the hippocampus performs a common computation across these

domains is in line with classifying memory systems and the task performances they support, less by parameters such as conscious versus nonconscious, short versus long delay, or spatial versus non-spatial, and instead focusing on the type of representations and information processing accomplished by a system (Olsen, Moses, Riggs, & Ryan, 2012; Yassa & Stark, 2011; Henke, 2010; Eichenbaum, Otto, & Cohen, 1994; Cohen & Eichenbaum, 1993). Empirical data testing the possible commonality of the hippocampal contribution across different memory tasks are scant, however, because most studies of hippocampal memory only include tasks from one tradition (e.g., in humans, long-delay verbal recall, recollection responses in a recognition task, or nonverbal relational memory binding at short delays).

In the work reported here, we used multivariate analyses on data from a battery of cognitive tasks to investigate whether hippocampal involvement in a range of disparate paradigms reflects a common cognitive construct. More specifically, this work is based on the hypothesis that a critical commonality of hippocampal functioning is the use of relational memory representations and processing in supporting task performance. This hypothesis is based on relational memory theory (Eichenbaum & Cohen, 2001; Cohen & Eichenbaum, 1993) and the suggestion that the hippocampus is critical for relational memory binding, creating memory representations of all manner of relations among the constituent elements of scenes or events, irrespective of temporal delay or stimulus modality. These representations are said to be flexible/compositional in that the relations among elements are linked rather than fused, allowing for flexible expression and recombination of such representations in service of various cognitive demands and performance challenges.

The test battery used here included 12 tasks. Four in particular were deemed critical for our examination of hippocampal function. There were two delayed verbal recall tasks, the CVLT and the LM from the Wechsler Memory Scale. These are classic neuropsychological tests, with study–test intervals of 20–30 min, widely shown to be sensitive to memory impairment because of hippocampal dysfunction (Weintraub et al., 2012; Allen et al., 2006; Milner et al., 1968). These tasks also depend upon relational memory for binding of the various commonly heard words to the specific temporal-spatial context of the experimental setting in the CVLT and for binding together of the various pieces of the story, including actors, temporal sequence of events, and geographic setting in the LM. The test battery also included two relational memory tasks currently used regularly in our laboratory. One was a recognition memory test for face–scene pairings, with a delay between encoding and recognition of any given pair less than 5 min and as short as 30 sec, based on a variant (Monti et al., 2013) of a task shown to be highly dependent on relational memory and hippocampal integrity (Hannula, Ryan, Tranel, & Cohen, 2007). The second was a spatial reconstruction (SR) task in which on each trial participants studied the spatial arrangement of a set of five novel stimuli and then had to reconstruct the array (objects in their locations) after just a 4-sec delay, based on Watson et al. (2013; see Methods for further details on all tasks).

In addition to these tasks, we added memory tests that do not depend critically on the formation and use of new relational representations to be performed successfully, including tasks measuring remote semantic memory, a verbal *n*-back task, and a spatial working memory task. Finally, to ensure we tested a wide range of cognitive abilities, we included

tasks of executive function and processing speed. To the extent that there is a commonality of hippocampal functioning based on the use of relational memory representations and processing in supporting task performance, we expected that performance on the two traditional, longer-delay tests of verbal recall (CVLT and LM) and the two short-delay laboratory tasks (face–scene recognition paradigm and SR task) would load on one component in the PCA, despite involving different stimulus types, delay intervals, and response requirements. Although such a finding would not directly rule out the possibility that the hippocampus does perform qualitatively different computations, the predicted finding here would support the notion that relational memory processing is a core function of the hippocampus used in support of various task performances. Finally, we expected performance on this component to be strongly tied to hippocampal volume.

METHODS

Participants

One hundred thirty-five healthy, cognitively normal individuals participated as part of a multisession study examining the effects of aging on brain and cognition across the lifespan. Data from participants aged 60 and older came from the pretesting sessions of a cognitive training intervention, and the data from individuals below the age of 60 were collected for the purposes of obtaining a cross-sectional sample to study cognitive aging. All participants were screened for a history of neurological disorders, traumatic brain injury, and current use of psychotropic medications and excluded if they indicated a positive response.

Furthermore, participants were right-handed and did not indicate any contraindication to MRI. All adults over the age of 60 were screened with the Mini-Mental Status Examination, and only those with a score of 27 or greater were included in the study.

Of the original 135 participants, data from 14 individuals were discarded due to chance performance on one of the tasks. Furthermore, an additional 12 participants' MRI data were not usable due to participant movement that rendered the images not suitable for subcortical segmentation. Thus, the final sample for the behavioral data contained 109 participants (63 women), with an age range of 18–83 years ($M = 51.18$, $SD = 20.83$) and a mean education of 16.9 years ($SD = 2.89$). Only a subsample of this larger group was used in relating behavioral measures to subcortical volumes (see below). The University of Illinois institutional review board approved all procedures, and participants signed an informed consent document. All individuals were compensated monetarily for their time.

Cognitive Tasks

A battery of 12 tasks assessing a variety of cognitive functions was used in this study, consisting of a mix of standard neuropsychological tasks and laboratory tasks. Participants completed the Trail Making Tests A and B (Armitage, 1946) and the Digit Symbol Substitution Task (DSST) from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981). An abbreviated version of the CVLT II (Delis, Kramer, Kaplan, & Ober, 2000) was given, which included the initial five learning trials (with a free recall after each reading of the word list) and then a delayed free recall, which took place approximately 20 min later. Participants also completed LM Story B from the Wechsler Memory Scale (Wechsler &

Stone, 1973) by listening to a reading of the story and immediately recalling all they can remember and then participating in a delayed free recall approximately 30 min later. Two measures of category fluency were administered by having participants name as many fruits and vegetables as they could in 1 min and then naming as many animals in 1 min.

A computerized *n*-back task consisting of lower-case letters as stimuli and trials that included 1- and 2-back blocks was also given. Following 13 practice trials for the 1-back condition, participants completed 100 trials broken into five blocks of 20 trials; the identical procedure, with practice, was repeated for the 2-back blocks. There was also a task-switching paradigm where participants were required to respond to whether a presented number was odd or even, if presented on a pink background, or if it was above or below the value 5, if presented on a blue background (Baniqued et al., 2013; Verstynen et al., 2012). This task was administered in three blocks, and each block had a practice session. First, participants completed back-to-back practice blocks of 24 trials each. In the first practice block, participants only responded to stimuli on blue backgrounds using a high/low judgment, and in the second block, participants responded to stimuli on pink backgrounds using an odd/even judgment; participants were given feedback about their accuracy during these practice blocks. Participants then completed two identical blocks for data collection, with the only difference being there was no feedback given. The final block was a mixed condition where trials contained numbers on pink or blue backgrounds within a block in a randomly ordered fashion, and participants needed to make the appropriate judgment based on the color of the background. There was one 32-trial practice block with feedback, followed by a 120-trial block with no feedback used for data collection.

Participants also completed a version of a spatial working memory paradigm previously used in our lab (Baniqued et al., 2013; Erickson et al., 2009, 2011). In this task, individuals were required to remember the location of dots on a computer screen. In the encoding phase of a trial, individuals studied the locations of two, three, or four dots for 500 msec. This was followed by a 3000-msec delay period where the screen was blank, after which one probe dot appeared on the screen and participants were instructed to indicate yes/no as to whether the probe dot occupied the same space as one of the dots in the encoding phase; participants were given 2000 msec to respond, and trials were separated with a 1000-msec intertrial interval (ITI). Following 24 practice trials, participants completed the actual experiment that contained 40 trials for each set size, presented in an intermixed fashion.

Finally, two relational memory tasks developed in our lab were used in this study. The first was a task where individuals had to remember pairs of faces and scenes (the Monti et al., 2013, variant of Hannula et al., 2007; also see Walker, Low, Cohen, Fabiani, & Gratton, 2014; Hannula, Federmeier, & Cohen, 2006). This task was conducted during an fMRI session; data relating to brain activity were not considered in this report and will be reported elsewhere. The task was divided into three separate runs, with 24 encoding and 24 recognition trials in each run; the encoding and recognition phases were separated by a 20-sec rest period. Encoding and recognition trials consisted of the presentation of a scene for 2000 msec followed by a face overlaid on the scene for an additional 2000 msec. A fixation cross was displayed during the ITI, which was jittered and ranged from 2000 to 12000 msec (Figure 1). Participants completed a practice session outside the scanner before proceeding.

On each encoding trial, participants made a yes/no judgment indicating whether the individual depicted “fit” with the scene; this was an arbitrary decision to elicit deep encoding. At recognition two trial types were presented, “intact” face–scene pairs, which were the identical face–scene combinations presented during encoding, and “re-pair” trials, created by recombining a previously displayed face and scene that were not shown together at encoding. Hence, all stimuli were equally familiar at recognition, and the task had to be completed via relational memory. Participants made a yes/no judgment as to whether the pair displayed was an exact match of a pair shown at encoding, with 12 trials from each trial type composing the recognition phase of a run.

The second task was a computerized version of an SR task reported in Watson et al. (2013). On each trial, participants studied the arrangement of five novel line drawings (Figure 2). Study time was self-paced, and participants were instructed to use the mouse to click on each image during study. Following the study phase, a 4000-msec delay occurred where participants saw a blank screen; after this period, a self-paced test phase began. In the test phase, stimuli appeared aligned at the top of the screen, and participants used the mouse to click and drag them into where they thought they were positioned in the study phase; trials were separated with a 2000-msec ITI. Participants completed three practice trials and 15 trials for data collection.

Behavioral Measures

One measure for each task was selected for the PCA. For Trail Making Tests A and B, the dependent variable used was time to accurately complete each task. For the DSST, the dependent measure was number of correct symbols completed in 2 min. The numbers of animals, and fruits and vegetables named, excluding repetitions, were entered to assess performance on these two tasks. Overall accuracy on the spatial working memory task was used as the measure for this task. Cost measures for the *n*-back and task-switching tasks were selected for these paradigms. In the *n*-back task, accuracy on the 1-back condition was subtracted from accuracy on the 2-back condition to create a cost measure of accuracy. A global switch cost for accuracy was calculated to evaluate performance on the task-switching paradigm; we derived this by subtracting accuracy from the first two blocks (non-switch) from accuracy of the third (switch block), with more negative values indicating more difficulty with task switching.¹

Delayed recall from both the CVLT and LM tasks was selected as the variable of interest for the analysis of these tasks. The selection of delayed recall from both of these tasks was due to the long-standing finding that delayed recall from these types of measures is severely impaired in hippocampal amnesic patients and related to hippocampal volume (Allen et al., 2006) and, thus, provides a benchmark with which to compare the laboratory-based relational memory tasks.

In the face–scene task, a d' value was collected for each individual by using the overall hit rate and false alarm rate; in the event a participant had a hit rate of one or an false alarm rate

¹Choosing overall 2-back accuracy as the measure from the *n*-back task or local switch cost for the task-switching task yielded the same qualitative results in the PCA reported in the Results.

of zero, these values were calculated by using $1 - (1/2N)$ and $1/2N$ respectively, with N equaling the number of trials going into the analysis, to calculate d' . For the SR task, the dependent variable was the proportion of pairwise object–location bindings that the participant erroneously “swapped” during the reconstruction phase (see Figure 2; Watson et al., 2013). Conceptually, a swap occurs when a participant places two objects in spatial locations that were previously occupied in the study phase, but not by the specific objects placed by the individual. Operationally, a swap is calculated as occurring when the sign of the x and y components of the vector representing the spatial relationship between two objects switch from the study to test phase. A swap error is recorded as a binary event, and the final metric is the number of swap errors divided by the number of possible pairwise relations in a trial (which was held constant in this experiment). The rationale for choosing the swap measure as the main metric for analysis stems from previous work indicating swap errors disproportionately occur in hippocampal amnesic patients because of the high relational demand entailed in remembering two or more object–location bindings (Pertzov et al., 2013; Watson et al., 2013).

Behavioral Data Analysis

To understand which tasks rely on similar cognitive constructs, PCA was utilized for dimension reduction. Before conducting the PCA, any task where a high value represented poorer performance was reverse-scored to simplify interpretation. These 12 measures were entered into a PCA using a varimax rotation, and components with initial eigenvalues larger than 1.0 were extracted (Kaiser, 1958). All reported eigenvalues and loadings are after varimax rotation. Measures loading on a component with a value greater than 0.5 were deemed to significantly contribute to that component. A metric for each component was created by averaging the standardized scores of the tasks that significantly contributed to that component; these values, as well as the scores on the individual subtasks, were used in correlational and regression analyses comparing cognition to brain structure.

Structural MRI Acquisition

Structural images were acquired with a T1-weighted 3-D magnetization prepared rapid gradient-echo imaging protocol of 192 contiguous sagittal slices (repetition time = 1900 msec; echo time = 2.26 msec; flip angle = 9°; field of view = 256 × 256 mm; voxel size = 1 × 1 × 1 mm).

Subcortical Volume Measures

Automated segmentation of the hippocampus, striatum (caudate and putamen), and amygdala was performed using Freesurfer (v 5.3; <http://surfer.nmr.mgh.harvard.edu>); details of the subcortical segmentation process utilized by Freesurfer are available in Fischl et al. (2002). We chose the striatum and amygdala as additional regions to compare with task performance, because both are subcortical structures implicated in learning and memory. An automated measure of intracranial volume (ICV), which is comparable to manual tracing, was obtained for each participant via Freesurfer using the methods described in Buckner et al. (2004). This measure of estimated ICV was used to correct subcortical volume for head size by regressing each ROI volume onto ICV to obtain a slope (b) for the relationship

between an ROI and ICV. The resulting slope was then used to normalize each ROI for head size via the following formula: normalized volume = raw volume – b (ICV – mean ICV); this correction has been used in multiple studies reporting subcortical volume measures (Erickson et al., 2009; Head, Rodrigue, Kennedy, & Raz, 2008; Raz et al., 2005).

Only MR data from middle-aged and older adults were included in the subcortical volume analyses. We chose to only include this age range due to the somewhat bimodal distribution of age in our sample. The age range of young adults ($n = 29$) in our sample was 18–29, and all other participants ($n = 80$) were in the 40–83 age range. Moreover, the distribution of young adults was mostly college-aged students $M = 21.3$, $SD = 2.8$, whereas those in the middle-aged and older group represented a more continuous sample ($M = 62.0$, $SD = 12.0$; 49 women, mean education = 17.4 years, $SD = 2.87$). The rationale for excluding the young adults in the MR analyses relates to the idea that the size of brain structures in our healthy, homogenous young adult sample is likely stable, and any variation in the size of a structure may be less meaningful; thus, including these values would introduce noise in the data.² Indeed, correlations among brain regions and components for just the younger adults were all nonsignificant ($p > .05$). However, because of aging, the size of the subcortical regions begins to shrink by the fifth decade of life (Fjell et al., 2013), making the variation in size of a structure and its relationship to cognitive function much more meaningful. Finally, a family-wise Bonferroni correction for multiple comparisons for correlations between the variables of interest was used.

RESULTS

PCA

The PCA revealed four components with eigenvalues greater than one, and these components explained 63.39% of the variance. As can be seen in Table 1, each of the 12 measures loaded onto only one component. Critically, both of the two measures from the laboratory-based relational memory tasks (SR and face–scene memory) loaded along with the two canonical neuropsychological measures of hippocampal memory (CVLT and LM delayed free recall) onto one component, PC-2 ($\lambda_2 = 1.95$), suggesting performance on these four tasks relies on a common cognitive construct. The largest amount of variance among the full set of 12 tasks was explained by a component containing Trail Making Tests A and B as well as DSST (PC-1; $\lambda_1 = 2.34$). A third factor included the number of animals named and the number of fruits and vegetables named (PC-3; $\lambda_3 = 1.74$). Finally, the fourth factor included the measures from the n -back, spatial working memory, and task-switching tasks (PC-4; $\lambda_4 = 1.58$). Table 2 provides a correlation matrix containing all 12 tasks. Although the observation-to-variable ratio was reduced, the PCA using just the middle-aged and older adults yielded nearly identical results, with the only qualitative difference being the spatial working memory task loading shifting from 0.64 to 0.46 on PC-4, and its loading on PC-1 moving from 0.35 to 0.5, placing it technically more with PC-1 rather than PC-4.

²Regional brain volume in young adults is not inherently uninteresting, but to see meaningful individual differences related to volume, one may need to intervene on the young adult brain (e.g., with an exercise intervention); under these circumstances, it is worthwhile to consider regional brain volume.

Subcortical Volumes: Correlation Analyses

Using a Bonferonni-corrected p value of .004, hippocampal volume was significantly correlated with PC-1, $r(78) = .46, p < .001$, and PC-2, $r(78) = .41, p < .001$, and had a modest correlation with PC-3 that was nonsignificant after multiple comparison correction, $r(78) = .23, p = .03$. The amygdala significantly correlated with performance on PC-1, $r(78) = .37, p = .001$, and was moderately related to PC-2, $r(78) = .24, p = .03$. After multiple comparison correction, striatal volume was not significantly related to any components; however, it did display a relationship with PC-2, $r(78) = .31, p = .005$, and a modest link with PC-3, $r(78) = .27, p = .02$. Correlation values for all principal components and the three brain regions are reported in Table 3, and Figure 3 displays a scatterplot of PC-2 performance and hippocampal volume. To ascertain how performance on the four tasks putatively most reliant on the hippocampus related to the volume of that structure, correlations between the CVLT, LM, SR, and face–scene tasks were conducted. Before multiple comparison correction, only hippocampal volume significantly correlated with performance on all four of the subtasks comprising PC-2; both the amygdala and striatum were positively related to the LM tasks, with striatal volume also correlating with the SR task (Table 4). However, after the conservative correction, only the SR task and hippocampal volume were significantly correlated.

Subcortical Volumes: Regression Analyses on PC-2

Given the focus on the relationship between the hippocampus and the four memory tasks that loaded on PC-2, we wished to assess the specificity with which performance on this component was related to hippocampus. Although the striatum and amygdala were not significantly correlated with PC-2 after the Bonferonni correction, the r values indicate a potential relationship. Thus, we completed stepwise hierarchical linear regression models to understand the unique contribution of the three brain regions to performance on these memory tasks and to evaluate if, among these subcortical brain regions implicated in memory processes, hippocampal volume displays the strongest relationship with PC-2, as predicted. In the first model, we entered striatal and amygdala volume in Steps 1 and 2, respectively, to see if adding hippocampal volume contributed in explaining a significant amount of the residual variance. The full results are presented in Table 5. In Step 1, striatal volume significantly explained 9.8% of the variance in PC-2 performance, $F(1, 78) = 8.49, p = .005$; including amygdala volume in Step 2 did not significantly improve the model, $R^2 = 1.8\%$, $F(1, 77) = 1.6, p = .21$. In the last step, the addition of hippocampal volume explained 10.3% of the residual variance from the tasks comprising PC-2; this increase in explained variance was significant, $F(1, 76) = 10.0, p = .002$. In the second model, we entered hippocampal volume first to test the idea that the inclusion of striatal or amygdala volume would not significantly contribute to the model. Entering hippocampal volume first to predict the PC-2 variable explained 17.2% of the variance, a highly significant amount, $F(1, 78) = 16.15, p < .001$. The inclusion of striatal volume in Step 2 produced only a modest increase in R^2 , 3.4%, which was marginally significant, $F(1, 77) = 3.29, p = .07$; including the amygdala in Step 3 did not improve the model, $R^2 = 1.3, F(1, 76) = 1.32, p = .25$.

Relationship between Age, Principal Components, and Subcortical Volume

In an effort to understand the effect of age on the cognitive and volumetric data, we correlated age among the middle-aged and older adults with each principal component and subcortical volume of the structures of interest, using a Bonferroni corrected p value of .007. As indicated in Table 6, age was negatively correlated with brain volume in all of the structures, as well as PC-1, PC-2, and PC-4, with the relationship between age and PC-3 becoming nonsignificant after multiple comparison correction. To ascertain if the significant brain-behavior relationships observed here were independent of age effects, we conducted partial correlations controlling for age on PC-1 with amygdala and hippocampus and PC-2 with hippocampus, using a Bonferroni corrected p value of .0167. When controlling for age, the relationship between PC-1 performance and the hippocampus or amygdala was markedly reduced: PC-1 and hippocampus, $r(77) = .16$, $p = .17$; PC-1 and amygdala, $r(77) = .08$, $p = .5$. When investigating the effect of age on the critical brain-behavior relationship here, PC-2 with the hippocampus, the partial correlation revealed that the association between hippocampal volume and PC-2 was attenuated, but to a lesser degree, $r(77) = .25$, $p = .02$, narrowly missing significance after correcting for multiple comparisons.

DISCUSSION

Confirming our prediction, the PCA revealed a clear component indicating common variance in performance among delayed recall for the CVLT and LM tests and performance on the two laboratory-based relational memory tasks, involving recognition of face-scene pairs and reconstruction of the object-location relations among novel stimuli. Critically, the common variance in performance occurred despite the tasks being different in multiple ways: in the delay imposed between study and test (from 4 sec to 30 min), the materials and domains tested (verbal, visual, spatial), and the response demands (verbal responses, button presses, SR with a computer mouse). We also confirmed our second prediction that these tasks would correlate significantly with hippocampal volume. Taken together, the finding of common variance in performance occurring in the face of such disparities in the nature of the testing, in combination with their common association with hippocampal volume, suggests that these tasks may rely upon a common feature of hippocampal processing.

Consideration of the similarities and differences in the details of these multiple memory tasks permits some speculation about what the common denominator is that ties them to hippocampal processing. A critical factor in common among them is the demand placed on memory for the relations among elements (words with context, faces with scenes, objects with locations). Emphasizing this commonality conforms with the view that the hippocampus is central to relational memory binding for all manner of relations among the constituent elements of experience (Konkel, Warren, Duff, Tranel, & Cohen, 2008; Eichenbaum, 2004; Eichenbaum & Cohen, 2001; Cohen & Eichenbaum, 1993). Although these results support the relational memory theory, it should be noted that the alternate possibility of the hippocampus performing qualitatively different computations to successfully complete the tasks in the second principal component is not completely incompatible with these findings. It may be the case that these different computations are similar enough to be grouped into one principal component. Future work that examines

hippocampal subfields or hippocampal shape with regard to performance on different tasks associated with the hippocampus may be informative to this question.

It is interesting to note that the length of study–test delay had little effect on which memory tasks clustered together. With respect to PC-2, hippocampal volume was related to memory performance for the tasks used here regardless of temporal delay. Such findings add support to recent claims that the traditional memory taxonomy centered on temporal distinctions may not be useful (Watson et al., 2013; Hannula, Tranel, et al., 2006; Ranganath & Blumenfeld, 2005) based on the numerous findings from imaging and patient studies, cited earlier, suggesting hippocampal involvement in tasks that tap memory on the timescale usually associated with working memory. These findings, taken together, may have clinical implications in that neuropsychologists need not impose long delays in testing to assess hippocampal function for disorders such as Alzheimer’s disease (also see Monti, Balota, Warren, & Cohen, 2014). Rather, valid and reliable tests with high demands on relational processing can be incorporated into neuropsychological batteries, potentially providing more data on hippocampal function in a shorter period of time.

The current findings also speak to the issue of whether the hippocampus primarily performs spatial memory computations (O’Keefe & Nadel, 1978). If memory involving spatial information relied on a common cognitive ability, one would expect the spatial working memory and SR tasks to load on the same component. However, the swap error rate from the SR task clustered with three other tasks that have no obvious spatial demands, whereas the spatial working memory task clustered with two nonspatial tasks that have more heavily tax attentional and executive control processes. Thus, it seems that space is but one of many domains for which the hippocampus makes its contributions to memory. This conclusion is consistent with many other converging lines of evidence (see Eichenbaum & Cohen, 2001, 2014), including findings in rodents of hippocampal “time cells,” which are presumed to be able to support the contribution of the hippocampus to temporal memory processing in much the same way as “place cells” can support the spatial memory processing contribution of the hippocampus (MacDonald, Lepage, Eden, & Eichenbaum, 2011), and findings that human amnesic patients with hippocampal damage are impaired not just in memory for spatial relations but also temporal relations and associative relations among the same stimuli (Konkel et al., 2008).

Although the spatial working memory task used here has shown to be related to hippocampus (Erickson et al., 2009, 2011), performance on this measure did not load with the tasks in PC-2. Although relational memory representations can certainly contribute to a successful outcome on this task, successful performance can also be supported by simply holding a single perceptual image of the study trial in mind during the delay phase and then, upon appearance of the test probe, computing a match/mismatch with the stored perceptual image. This simpler strategy greatly reduces the relational load required to accurately answer a trial, thereby making it reasonable that this task could cluster more with a nonhippocampal working memory task like the *n*-back than with the tasks that have larger relational memory processing loads.

The other eight tasks in the analysis cleanly loaded onto three additional factors. PC-1 contained Trail Making Tests A and B as well as the DSST. On the basis of the tasks comprising this component, it is possible that the common cognitive construct linking these tasks is processing speed, although Trail Making Test B also contains elements of executive function (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Previous multivariate analyses, however, have found Trail Making Test B to cluster with the DSST, Trail Making Test A, and other processing speed tasks (Salthouse, Fristoe, & Rhee, 1996), providing a clear precedent for this interpretation. Bilateral hippocampal volume had the highest numerical correlation with this component, and amygdala volume was also significantly correlated with performance on PC-1. One explanation for the hippocampal and amygdala relationships with PC-1 centers on the notion that both processing speed and brain volume decrease with age (Fjell et al., 2013; Salthouse, 1996). Indeed, when conducting partial correlations between PC-1 and the brain structures controlling for age, these relationships disappeared, indicating the volumetric correlations with PC-1 are largely due to sharing a relationship with the third variable of age. Notably, the relationship between PC-2 and the hippocampus was less impacted by age, suggesting a more direct structure–cognition relationship with the tasks in PC-2 and hippocampal volume.

A complimentary explanation as to the PC-1 and brain volume correlations has to do with the distributed nature of processing speed in the brain (Borghesani et al., 2013) coupled with the notion that speed of processing undergirds numerous cognitive operations. From this perspective, one may expect the integrity of numerous brain regions to correlate with processing speed abilities. It is interesting that striatum volume was not strongly correlated with PC-1 given the motor processing element of the tasks composing that component. Nonetheless, further analyses of the relation between various clusters of cognitive processing performances and the components of large-scale brain networks are clearly warranted. This idea is supported from the hierarchical regression analysis of regional brain volume and PC-2 performance. It was clear that hippocampus carried the most unique variance pertaining to performance on PC-2 tasks, with striatal contributions being attenuated after controlling for hippocampal volume. Still, there was a marginally significant relationship between striatal volume and PC-2 performance, even with hippocampal volume entered in the model. This is somewhat unsurprising given the linkage of the striatum to hippocampal memory (Scimeca & Badre, 2012), but it serves to underscore the larger point that performance on all of these cognitive tasks rely on a network of interacting brain regions.

The two tasks clustering with PC-3 (“fruits and vegetables” and “animals”) likely grouped together based on their common reliance on aspects of remote semantic knowledge, a cognitive ability usually associated with temporal cortical regions rather than the subcortical structures investigated here. The tasks associated with PC-4, containing the *n*-back, task-switching, and spatial working memory tasks, may cluster together because of their reliance on executive functioning and/or the type of working or STM computations aided by pFC. The presumed dependence on pFC explains why this component was not related to any of our subcortical structures.

Returning at the end to the major finding of this work, we report here that performance on four memory tasks differing substantially in the type of stimuli used, the delay imposed, and/or the modality of required response nonetheless clustered on a single component in PCA and, moreover, was positively associated with bilateral hippocampal volume. In common among the tasks was a demand for relational memory processing, supporting the idea that relational memory is a core component of hippocampal processing that cuts across time delays, stimulus modalities, and cognitive domains.

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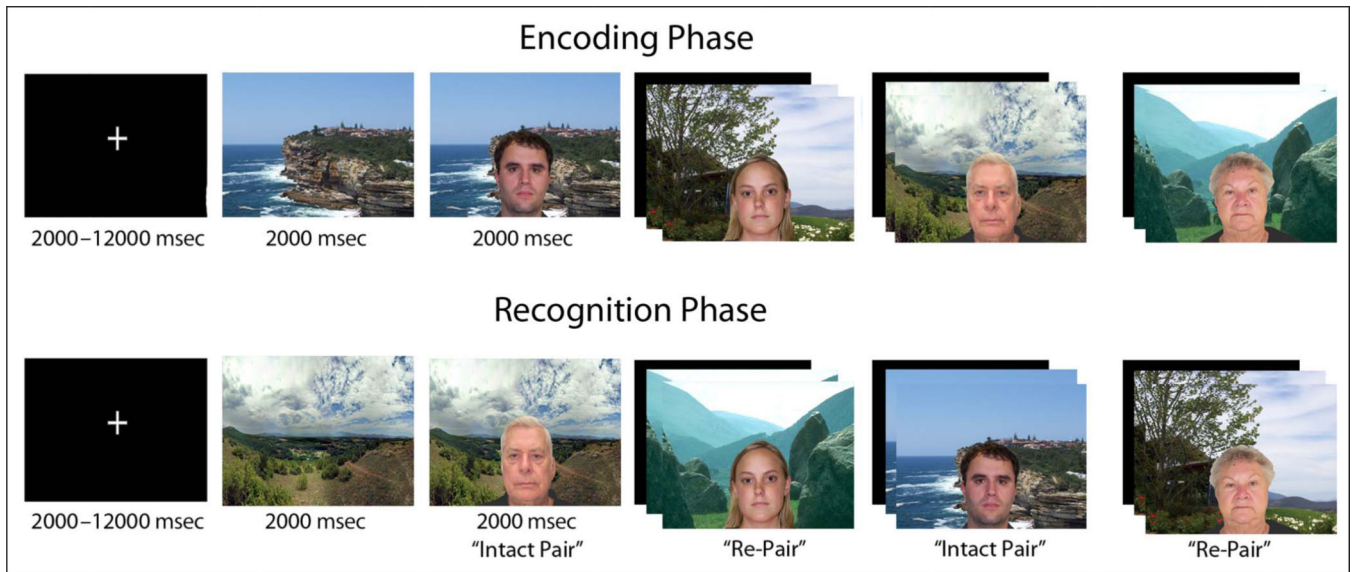


Figure 1. Example trials from encoding and recognition phase of face–scene task. The two phases were separated by a 20-sec break.

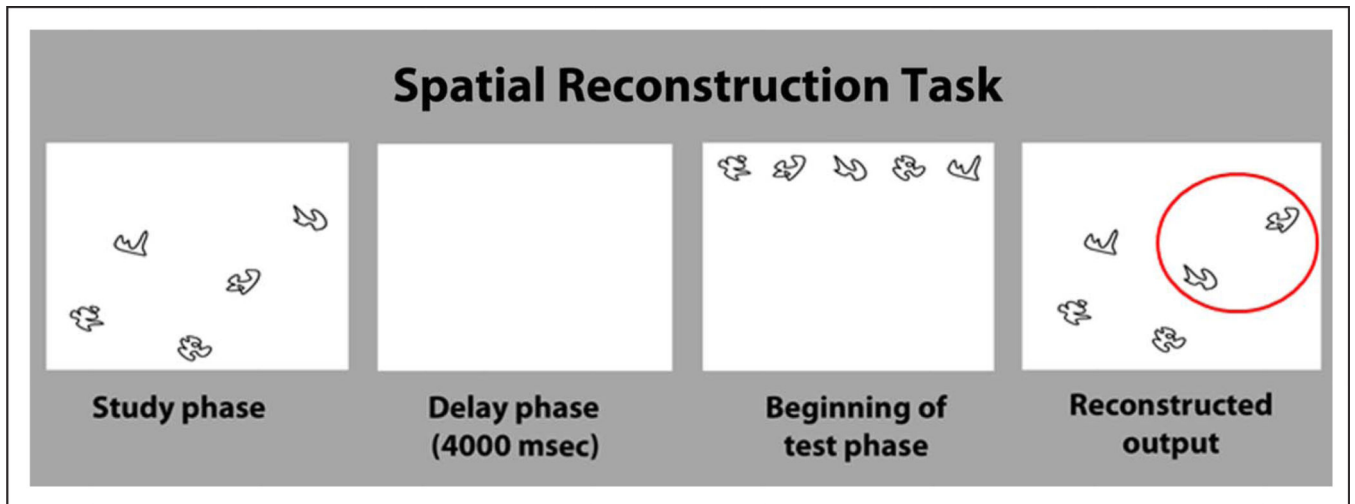


Figure 2.

Example trial from SR task. Left: an example of study phase. Right: an example of a participant's reconstruction. Note the swap error, indicated by the circle.

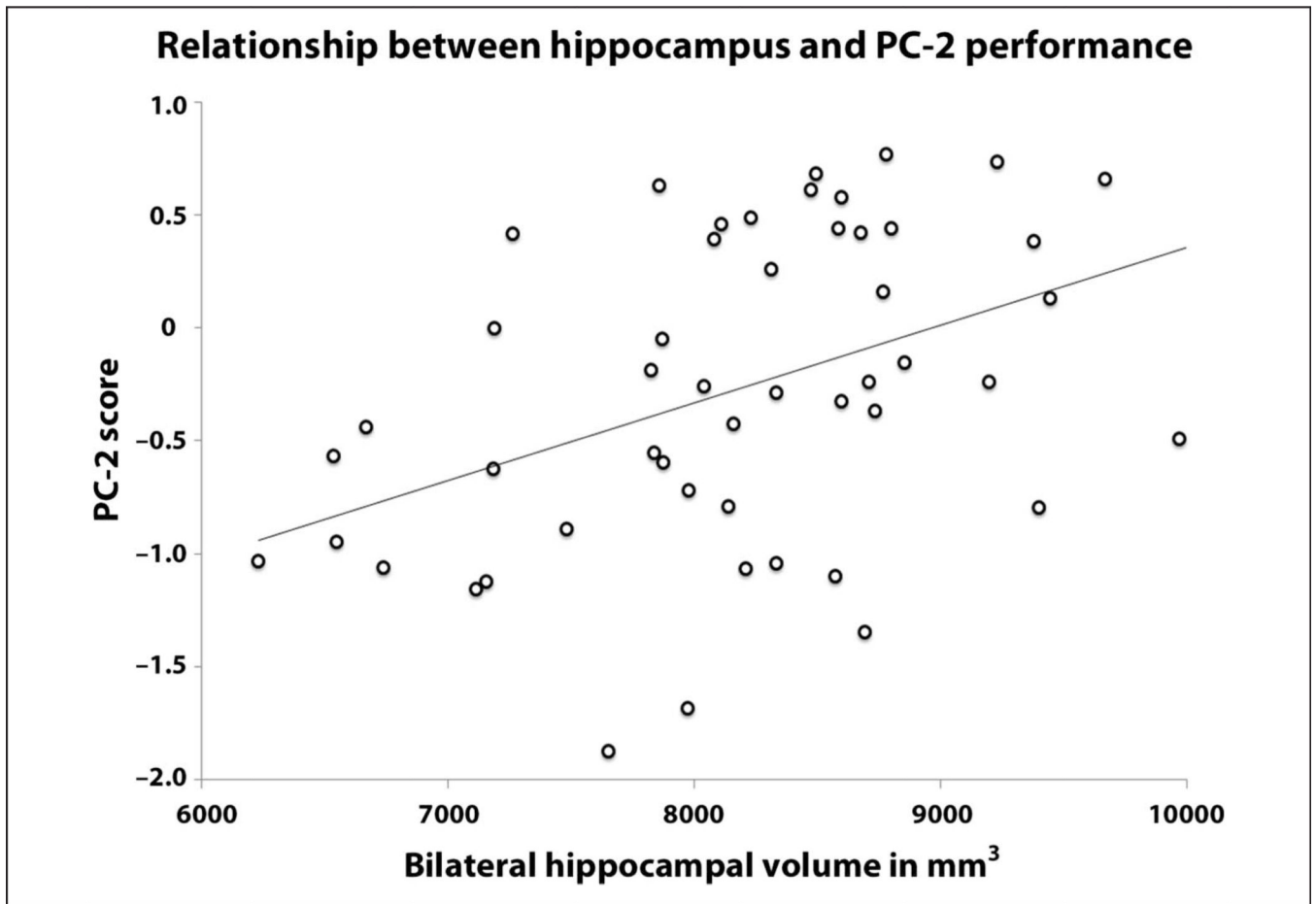


Figure 3.
Relationship of hippocampal volume in middle-aged and older adults and performance on tasks composing PC-2, $r(78) = .41, p < .001$.

Table 1

Results from PCA

Task	Components			
	PC-1	PC-2	PC-3	PC-4
Trails A	.85	.04	.04	.14
Trails B	.82	.25	.05	.20
DSST	.79	.26	.17	.12
CVLT	-.01	.68	.20	.13
LM	.13	.64	.06	-.06
Face-scene	.13	.63	-.09	.21
SR	.34	.68	.07	.02
Animals	.17	.11	.87	.12
Fruits & Veg	.03	.07	.92	-.02
SPWM	.35	.17	.01	.64
Task Switch	.14	-.06	-.08	.75
<i>n</i> -back	.02	.16	.21	.68
% Variance	19.49%	16.22%	14.5%	13.13%

PC = principal component; Fruits & Veg = fruits and vegetables; SPWM = spatial working memory task.

Bolded values indicate tasks that were deemed to significantly contribute to a principal component.

Table 2

Correlation Matrix

	Trails A	Trails B	DSST	CVLT	LM	Face-scene	SR	Animals	Fruits & Veg	SPWM	Task-switch	n-back
Trails A	–	.65***	.58***	.17	.17	.13	.27**	.18	.06	.29**	.26**	.16
Trails B		–	.65***	.22*	.28**	.28**	.41***	.20	.12	.45***	.25**	.20*
DSST			–	.18	.23*	.31**	.43***	.33**	.16	.38***	.13	.24*
CVLT				–	.28**	.24*	.39***	.18	.23*	.19*	.10	.13
LM					–	.24*	.29**	.13	.11	.05	.05	.14
Face-scene						–	.34***	.15	-.01	.28**	.11	.12
SR							–	.19*	.12	.26**	.02	.19
Animals								–	.68***	.16	.05	.22*
Fruits & Veg									–	.04	-.03	.11
SPWM										–	.31**	.31**
Task-switch											–	.23*
n-back												–

Fruits & Veg = fruits and vegetables; SPWM = spatial working memory task.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 3

Correlations between Subcortical Volume and Components

	PC-1	PC-2	PC-3	PC-4
Hippocampus	.46 ***	.41 ***	.25*	.20
Amygdala	.37 ***	.24*	.21	.12
Striatum	.17	.31**	.27*	.10

PC = principal component. Interpretations of PCs: PC-1 = processing speed; PC-2 = relational memory; PC-3 = semantic memory; PC-4 = executive function/working memory.

Bolded numbers indicate significance after Bonferonni correction ($p < .004$).

*
 $p < .05$.

**
 $p < .01$.

 $p < .001$.

Table 4

Correlations between Hippocampal Volume and RM Subtasks

	CVLT	LM	Face-scene	SR
Hippocampus	.25*	.27*	.26*	.39***
Amygdala	.07	.27*	.20	.15
Striatum	.18	.27*	.17	.26*

Bolded numbers indicate significance after Bonferonni correction ($p < .004$).

* $p < .05$.

*** $p < .001$.

Table 5

Results from Hierarchical Linear Regression Analyses

<i>Step</i>	<i>Brain Structure</i>	<i>R</i> ²	<i>F</i>	<i>p</i>
<i>Model 1</i>				
1	Striatum	9.8	8.47 (1, 78)	.005
2	Amygdala	1.8	1.60 (1, 77)	.21
3	Hippocampus	10.3	10.0 (1, 76)	.002
<i>Model 2</i>				
1	Hippocampus	17.2	16.15 (1, 78)	<.001
2	Striatum	3.4	3.29 (1, 77)	.07
3	Amygdala	1.4	1.32 (1, 76)	.25
<i>Brain Structure</i>	<i>Standardized Beta</i>	<i>t</i>	<i>p</i>	
<i>Beta Coefficients (Both Models)</i>				
Hippocampus	.46	3.16	.002	
Striatum	.22	2.0	.05	
Amygdala	-.17	1.15	.25	

Table 6

Correlation of Age with Principal Components and Subcortical Volume

	r	p
PC-1	-.64	<.001
PC-2	-.39	<.001
PC-3	-.29	.01
PC-4	-.30	.006
Hippocampus	-.58	<.001
Amygdala	-.49	<.001
Striatum	-.33	.003

PC = principal component. Interpretations of PCs: PC-1 = processing speed; PC-2 = relational memory; PC-3 = semantic memory; PC-4 = executive function/working memory.

Bolded numbers indicate significance after Bonferonni correction ($p < .007$).