The Hippocampus Generalizes across Memories that Share Item and Context Information

Laura A. Libby, Zachariah M. Reagh, Nichole R. Bouffard J. Daniel Ragland, and Charan Ranganath

Abstract

■ Episodic memory is known to rely on the hippocampus, but how the hippocampus organizes different episodes to permit their subsequent retrieval remains controversial. One major area of debate hinges on a discrepancy between two hypothesized roles of the hippocampus: differentiating between similar events to reduce interference and assigning similar representations to events that share overlapping items and contextual information. Here, we used multivariate analyses of activity patterns measured with fMRI to characterize how the hippocampus distinguishes between memories based on similarity at the level of items and/or context. Hippocampal activity patterns discriminated between events that shared either item or context information but generalized across events that shared similar item–context associations. The current findings provide evidence that, whereas the hippocampus can reduce mnemonic interference by separating events that generalize along a single attribute dimension, overlapping hippocampal codes may support memory for events with overlapping item–context relations. This lends new insights into the way the hippocampus may balance multiple mnemonic operations in adaptively guiding behavior. ■

INTRODUCTION

Memories for past events include information about who or what was encountered ("items"), as well as information about the place, time, and situation in which the event took place ("context"). For instance, seeing a friend's dog (an item) at the neighborhood park (a context) might remind you of the time you played with that dog in your friend's backyard (same item, different context), or you might remember that, the last time you visited the park, you ran into a coworker (different item, same context). This example illustrates how the human brain can both distinguish between specific events and generalize across events according to similarity in item and/or context information (Mitchell & Johnson, 2009; Johnson, Hashtroudi, & Lindsay, 1993). Memory for item–context associations is known to rely on the hippocampus (Brown & Aggleton, 2001; Cohen, Poldrack, & Eichenbaum, 1997; Vargha-Khadem et al., 1997; Scoville & Milner, 1957). However, it is unclear how the hippocampus organizes memories to facilitate item and context retrieval when content is highly overlapping, as in many of our real-world experiences.

One prominent model holds that the hippocampus has a computational specialization for mapping distinct events onto orthogonal neural codes, a process known as pattern separation (Yassa & Stark, 2011; Rolls & Kesner, 2006; Norman & O'Reilly, 2003; Marr, 1971). Pattern separation is thought to prevent catastrophic interference between representations with similar features; when hippocampal pattern separation fails, episodic memory is predicted to break down due to overgeneralization (Norman, 2010; Norman & O'Reilly, 2003). Results from single-unit recording studies in rats support this view, showing that spatial coding in the hippocampus dramatically "remaps" with slight changes in spatial context (Neunuebel & Knierim, 2014; Leutgeb, Leutgeb, Moser, & Moser, 2007; Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005; Guzowski, Knierim, & Moser, 2004; Lever, Wills, Cacucci, Burgess, & O'Keefe, 2002; Bostock, Muller, & Kubie, 1991). Studies in rodents have not yet characterized a role for the hippocampus in pattern separation of items independent of their spatial context. However, several human neuroimaging studies measuring the similarity of hippocampal voxel activity patterns across trials as an indirect measure of neuronal population coding (Kriegeskorte, Mur, & Bandettini, 2008; Kriegeskorte, Goebel, & Bandettini, 2006) have found that hippocampal activity patterns tend to differentiate between similar items to a greater extent than cortical regions (Berron et al., 2016; Huffman & Stark, 2014; Liang, Wagner, & Preston, 2013). Further evidence (LaRocque et al., 2013) suggests that greater hippocampal differentiation between similar items during learning predicts memory for these items after a delay.

University of California, Davis

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A second framework for understanding hippocampal function suggests that, whereas item and context information are respectively processed in distinct neocortical pathways through the perirhinal and parahippocampal cortex (Ritchey, Libby, & Ranganath, 2015; Ranganath & Ritchey, 2012), the hippocampus specifically represents item–context associations (Ranganath, 2010; Davachi, 2006; Knierim, Lee, & Hargreaves, 2006; Eacott & Gaffan, 2005). Consistent with this idea, single-unit recording studies in rats have shown that hippocampal neuronal ensemble coding for items encountered in a particular spatial context is highly reliable across repeated exposures (McKenzie et al., 2014; Manns & Eichenbaum, 2009). Complementary results in humans have shown that hippocampal voxel patterns are similar when the same item is presented repeatedly in the same position within a temporal context (Ritchey, Montchal, Yonelinas, & Ranganath, 2015; Hsieh, Gruber, Jenkins, & Ranganath, 2014; Libby, Hannula, & Ranganath, 2014). There is also evidence for similar item-level voxel patterns in the human hippocampus based on both spatial and temporal proximity in virtual environments (Deuker, Bellmund, Schröder, & Doeller, 2016). Finally, hippocampal activity patterns carry information about item–context bindings in the case of even imagined links between objects and spatial locations (Sheldon & Levine, 2015).

The "pattern separation" (Yassa & Stark, 2011; Rolls & Kesner, 2006; Norman & O'Reilly, 2003; Marr, 1971) and "items-in-context" (Ranganath, 2010; Davachi, 2006; Knierim et al., 2006; Eacott & Gaffan, 2005) views are largely complementary, in that the former addresses how the hippocampus organizes distinct events with respect to each other and the latter focuses on the relative importance of item–context associations in episodic memory. However, a fundamental and currently unresolved question is how these processes coexist and interact. A strong version of the view emphasizing pattern separation would suggest that the hippocampus sharply differentiates between events, even if they share information along one or more attribute dimensions (i.e., item and/or context information). That is, the tendency to orthogonalize similar inputs may override associative binding. A strong version of the items-in-context perspective, in turn, would suggest that the hippocampus assigns overlapping neural representations to events in which similar items were encountered in similar contexts. That is, context stability may override the demand to orthogonalize similar inputs. The stability and generalization of hippocampal codes may also map onto different regions along its longitudinal axis (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013), as the anterior hippocampus has been hypothesized to support coarse, generalized representations compared with more granular representations in the posterior extent (Brunec et al., 2018).

To address these outstanding questions, we used fMRI to examine hippocampal activity patterns during a memory test that required retrieval of both item and context information. Critically, we manipulated overlap of both item and/or context information: Different exemplars from the same item category were learned in each of four different context locations, resulting in sets of events with overlapping item attributes, context associations, or both (Figure 1A). Participants were then scanned during a recognition test that required recall of item–context relations (Figure 1B). We analyzed the similarity of voxel activity patterns evoked during successful retrieval of item–context relations to estimate the extent to which brain areas differentiated or generalized across memories with overlapping item, context, and item-in-context information (Figure 2A). In addition to whole-brain activity patterns, we focused specifically on the hippocampus (including head/body/tail subdivisions), as well as the perirhinal and parahippocampal cortex for comparison.

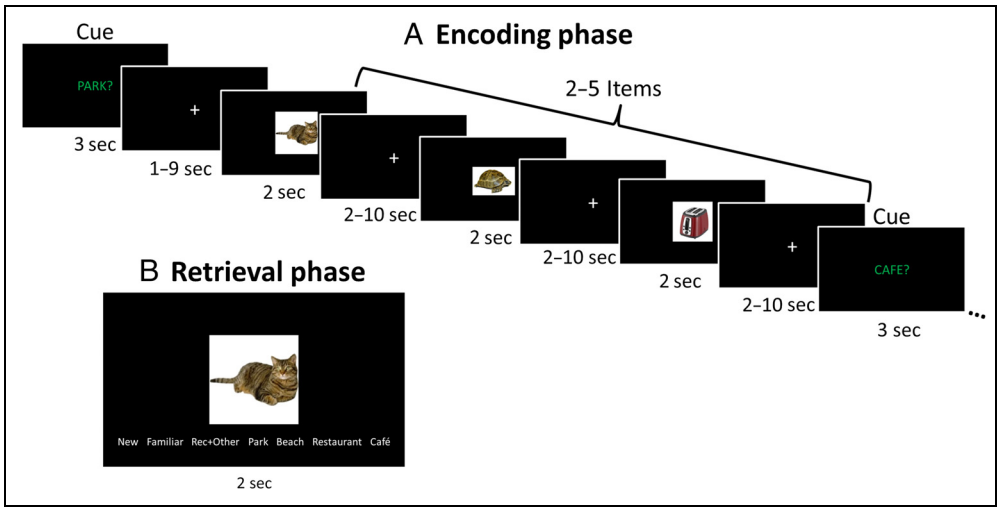

Figure 1. Task design. (A) During encoding, trial-unique exemplars from a set of categories were presented sequentially, broken down into miniblocks separated by a cue screen indicating the encoding context. Two exemplars from each category were encoded in each context. (B) At retrieval, all targets and a fully category-matched set of foils were presented in a combined recognition/cued recall test. Only trials given correct source memory judgments were included in voxel pattern similarity analyses.

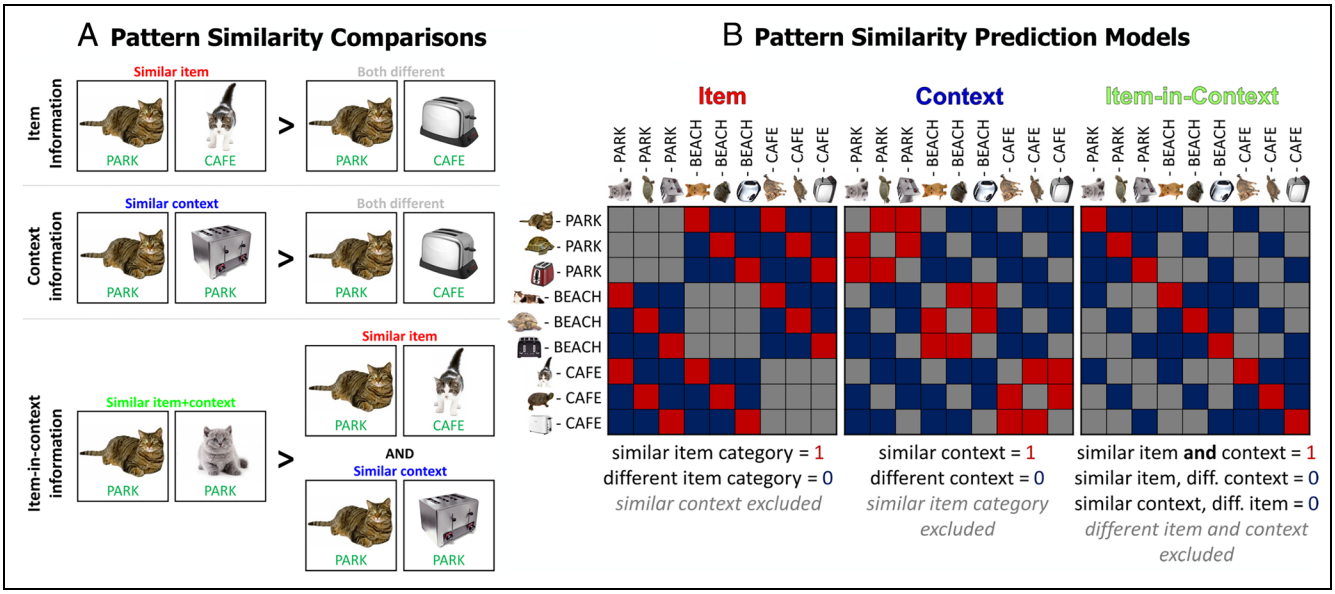

Figure 2. Trial pair similarity comparisons and models. (A) Example trial pair organization for pattern similarity analyses. Item information coding was estimated by contrasting pattern similarity estimates between "similar item" and "both different" trial pairs. Context coding was estimated by contrasting "similar context" and "both different" trial pairs. Item-in-context coding was calculated by contrasting "similar item + context" trial pairs against both "similar item" and "similar context" pairs. (B) Example trial-by-trial similarity model matrices. Item and context predicted similarity models were orthogonal to each other; the item-in-context predicted similarity model was hierarchical to the item and context models. Individual participant pattern similarity matrices were correlated (biserial) with model matrices to test for item, context, and item-in-context generalization.

METHODS

Participants

Twenty-five healthy participants (11 women; mean age = 24.4 years, *SD* = 4.6 years) underwent fMRI scanning during a long-term memory encoding and retrieval task. Participants with head motion greater than 3 mm from origin ($n = 2$) or chance-level context memory performance ($n = 3$) were excluded from analysis, resulting in a total of 20 included participants (eight women). All procedures were approved by the University of California, Davis, institutional review board.

Materials

Item stimuli consisted of 336 visual objects evenly distributed across 28 categories (e.g., toasters, dogs, jackets, muffins), with 12 unique exemplars per category. For each participant, within each category, eight objects were randomly assigned to the list of target stimuli and four objects were assigned to the list of foils, for a total of 224 targets (presented in the encoding and retrieval phases) and 112 foils (presented only in the retrieval phase). Target stimuli were then randomly assigned to one of four encoding context locations (either park, beach, restaurant, or café), for a total of 56 stimuli per context. Two exemplars from each category were presented in each context.

Procedure

Context Personalization and Task Practice Phase—Behavioral

During the encoding phase, participants were cued to visualize each item in one of four spatial contexts: a park, a beach, a restaurant, or a café; at test, participants were asked to retrieve the context originally associated with each item. To ensure that the locations evoked by context cues were visualizable and consistent over the course of the task, context cues were personalized for each participant before the start of the task. Participants were asked to select a specific park, beach, restaurant, and café from their past experience that they could picture vividly and were then instructed to bring only those venues to mind in response to the context cues. Participants then received task instructions and completed practice encoding and retrieval runs (using the same four context cues but an independent practice set of item stimuli) on a computer outside the scanner. Participants were permitted to repeat the practice runs as many times as was necessary to become comfortable with the task timing and response mappings.

Encoding Phase

Over four encoding runs (Figure 1A), target items were presented sequentially for 2 sec each. Item trials were broken down into miniblocks varying in size from two

to five items per block. At the beginning of each miniblock, one of four context cue screens was presented for 3 sec, either "PARK," "BEACH," "RESTAURANT," or "CAFÉ," cuing participants to visualize a specific context location for the duration of the miniblock. Then, for each item in the miniblock, participants visualized the item in that particular context location and made a yes/no response (via a button press) to the question, "In real life, would you be likely to see this item in this location?" Item category, context location, and item category–context pairings were counterbalanced across runs. Within run, item order was pseudorandomized for each participant, with the constraint that no adjacent item trials contained exemplars from the same category. Block order was also pseudorandomized for each participant such that no adjacent miniblocks contained the same context cue, and block length was counterbalanced across context question and across scanning run. Context cue and item trial screens were presented with a jittered ISI optimized for event-related fMRI (SOA 4–12 sec with a mean of 6 sec).

Retrieval Phase

Immediately following each encoding run, participants completed a mixed-item recognition/source memory test during fMRI scanning (Figure 1B). All target items from the most recent encoding run and a full set of category-matched foils were presented sequentially for 2 sec each. For each trial, participants indicated the quality and content of their memory for that item by selecting one of seven response button options: (1) the item was novel ("New"); (2) they were familiar with the item but could not recollect any contextual details associated with having seen it before ("Familiar"); (3) they recollected having seen the item before and could bring some contextual information to mind but *not* the specific location with which the item was originally associated ("Recollect"); (4–7) if they recollected the item and could remember which of the four encoding context locations was originally associated with that item, they pressed a button indicating that location ("Park," "Beach," "Restaurant," or "Café"). Retrieval trials were pseudorandomized such that no adjacent trials contained exemplars from the same category and jittered for event-related fMRI (SOA = 4–12 sec with a mean of 6 sec). In total, four encoding runs were interleaved with four retrieval runs.

Image Acquisition

MRI scanning was conducted at the University of California, Davis, Facility for Integrative Neuroscience on a 3T Siemens Skyra with a 32-channel phased-array head coil. High-resolution T1-weighted structural images were acquired using a MPRAGE pulse sequence (1 mm^3 voxels, matrix size = 256 × 256, 208 slices). Images sensitive to BOLD contrast were acquired using a whole-brain multiband gradient EPI sequence (3 mm^3 voxels; repetition time = 1220 msec, echo time = 24 msec, flip angle = 67°, multiband acceleration factor = 2, 38 interleaved slices, field of view = 192 mm, matrix size = 64 × 64) during task performance.

Behavioral Analysis

For the purposes of the fMRI-based multivoxel pattern similarity analysis, detailed below, it was important to establish (1) that correct context memory judgments were likely to be driven by real memory signal and (2) whether there were any systematic differences in item recognition or context memory across encoding contexts. Discriminability (via the d' sensitivity index) was calculated as the z-scored hit rate minus the z-scored false alarm rate. For item discriminability, hit rate was calculated as the percentage of target trials given any "old" item response ("Familiar," "Recollect," or any of the encoding context location judgments—even if the specific location was incorrect) for items encoded in each context location—and overall item false alarm rate was calculated as the proportion of "old" item responses given on foil trials. Differences in item d' across encoding contexts were tested via a one-way repeated-measures ANOVA (with a Huynh–Feldt correction for nonsphericity).

To estimate the meaningfulness of context memory judgments, context discriminability (d') was calculated separately for each encoding context as the difference between the probability of a correct context judgment (e.g., an item encoded in the café given a "Café" response at test) and the probability of a false alarm to that particular context location (e.g., an item encoded in the park or a foil item given a "Café" response at test). Participants with context d' at floor (i.e., not significantly above chance) for any encoding context were excluded from fMRI analysis (n = 3). Context discriminability estimates were entered into a one-way repeated-measures ANOVA to test for differences across encoding contexts (with a Huynh–Feldt correction for nonsphericity).

Multivoxel Pattern Similarity Analysis

Because we were interested in understanding how the medial-temporal lobe (MTL) organizes item and context information during successful reinstatement of item–context relations, multivoxel pattern similarity analysis focused on fMRI data from the retrieval phase. EPI time series underwent motion correction and high-pass filtering (0.01 Hz) in FMRIB's Software Library (FSL). In preparation for multivoxel pattern similarity analysis pro cedures, spatial smoothing was omitted. Event-related BOLD signal change was estimated separately for each item trial, controlling for signal change due to all other trials and motion artifact, using ordinary least squares regression, resulting to 336 single-trial beta images (Mumford, Turner, Ashby, & Poldrack, 2012; Xue et al., 2010). Single-trial beta images from Runs 2–4 were

coregistered with single-trial beta images from Run 1 using FSL's FLIRT linear registration software (6 degrees of freedom). Coregistered single-trial beta images with atypically high mean absolute z score (based on the distribution of beta estimates for each gray matter voxel across all trials) were excluded from further analysis (mean absolute z threshold = 1.5; between 0 and 10 trials excluded per participant, median = 4.5 trials). This objective noise trial exclusion procedure has been effective in previous pattern similarity studies (Libby et al., 2014), and in the current study, beta images were additionally visually inspected to verify that subjectively noisy trials were not overlooked. Critically, to pinpoint retrieval trials containing both (perceived) item and (reinstated) context information, the subsequent pattern similarity analysis was restricted to correct context memory judgment trials.

To determine the spatial distribution of information coding effects across the hippocampus and surrounding cortical areas, we employed multivoxel pattern similarity analysis (Kriegeskorte, 2011; Kriegeskorte et al., 2008) using a searchlight approach (Kriegeskorte et al., 2006). For every voxel in the brain, correlation coefficients (Pearson's r) were calculated for all pairs of trials based on the pattern of beta coefficients contained in a sphere with a 5-voxel diameter centered on that voxel, resulting in an observed pattern similarity (correlation) matrix. Searchlight spheres centered within a given ROI excluded voxels from other ROIs. To reduce the influence of temporal autocorrelation and within-run dependencies on pattern information coding effects (Mumford, Davis, & Poldrack, 2014), observed similarity estimates from trial pairs within the same fMRI run were discarded. Between-run observed pattern similarity estimates were entered into second-order similarity analyses. Here, we refer to "second-order similarity" as the z-transformed point-biserial correlation between observed pattern similarity estimates and an "ideal" binary model of predicted pattern similarity (Figure 2B), where trial pairs that were similar along a dimension of interest were coded as 1 and trial pairs that differed along that dimension were coded as 0. In this case, the point-biserial correlation is effectively identical to a two-sample t test and was selected because it is sensitive to within-subject variance, providing a somewhat conservative metric of multivoxel pattern similarity.

We examined pattern similarity effects based on shared item and context information in two separate analyses with orthogonal predicted pattern similarity models. To identify brain regions where voxel patterns carried information about the item category, a binary model was constructed labeling trial pairs according to whether they contained items from the same category (e.g., two dog trials—"similar item" pairs) or different categories (e.g., one dog trial and one toaster trial—"different item" pairs), excluding trial pairs with the same context location. To identify brain regions with voxel patterns carrying retrieved context information, a binary model was constructed labeling trial pairs according to whether the retrieved context was the same (e.g., two park trials—"similar context" pairs) or different (e.g., a park trial and a beach trial—"different context" pairs), excluding trial pairs with the same item category. The reason we here refer to shared contexts as "similar" is because, although the context is ostensibly the same, we cannot be sure that its mental construction is identical across experiences. Moreover, it is likely that different items have unique associations with the same context, leading to subtle differences in spite of overall stability.

To test for pattern similarity effects driven by shared item–context relations that were distinguishable from item or context effects alone, we constructed a binary model for item-in-context similarity that was superordinate to the item and context models. Trial pairs with both item category and context location in common (e.g., two dog-in-the-park trials—"similar item + context" pairs) were coded as 1 and trial pairs with overlapping item category or context location, but not both (i.e., similar item and similar context pairs), were coded as 0; trial pairs that were different on both item category and context location dimensions were excluded. This model as well as the similar item and similar context models are visualized in Figure 2B.

For each of the three predicted similarity models, the resulting second-order similarity estimate was assigned to the center voxel of each searchlight, resulting in three whole-brain pattern similarity images for each participant. Single-subject pattern similarity images were normalized to the MNI 152 template via the application of linear transformation matrices calculated in a two-step registration process: Using FLIRT, representative single-subject EPI images were coregistered with high-resolution anatomical MPRAGE images (6 degrees of freedom), MPRAGE images were normalized to the template image (12 degrees of freedom), and the two resulting transformation matrices were mathematically concatenated (multiplied). Brain regions that reliably carried each type of information across participants ($p_{FWE} < .05$) were identified nonparametrically based on the distribution of maximum cluster mass (after a voxelwise t threshold of 2.539) across 10,000 permutations of the data (sign-flipping approach) using the Randomise function in FSL (Nichols & Holmes, 2002). Because we had a priori interest in the hippocampus and surrounding cortex, group analyses were restricted to MTL voxels using a statistically conservative (anatomically liberal) MTL mask generated with the WFU Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) consisting of the parahippocampal gyrus, the hippocampus, the uncus, and the amygdala and dilated in three dimensions by 4 mm. The dilated anatomical MTL mask extended laterally and ventrally into the fusiform cortex, posteriorly to the level of the posterior horn of the lateral ventricles, and anteriorly into the medial temporopolar cortex. We additionally explored pattern

similarity effects outside the MTL using the same nonparametric permutation test procedure, but with whole-brain gray matter masks (p(gray matter) > .36, corresponding to a threshold of 90 out of 245 of the FSL MNI 152 segmentation gray matter priors) that excluded voxels contained in the MTL mask.

To allow for visualization and comparison of pattern similarity effects specifically in the hippocampus, for each participant, a second set of searchlight images was generated containing average pattern similarity estimates for each combination of item category and context location overlap. That is, one image contained average similarity estimates for similar item pairs, one image contained average similarity estimates for similar context pairs, one image contained the average across similar item + context pairs, and one image contained the average across trial pairs that were different on both item category and context location ("both different" pairs). From these images, mean pattern similarity estimates were extracted using individually defined ROIs corresponding to head, body, and tail divisions of the hippocampus. Because items-in-context and pattern separation accounts of MTL function both predict that adjacent MTL cortical areas tend to generalize across similar events, pattern similarity estimates were also extracted from anatomical ROIs in the perirhinal cortex and the parahippocampal cortex. All ROIs were defined separately for right and left hemispheres, and anatomical landmarks for ROI definition are thoroughly described by Moore et al. (2014).

Pattern similarity estimates were entered into a full factorial repeated-measures ANOVA with ROI and Information overlap as factors of interest (using a Huynh–Feldt correction for nonsphericity), controlling for hemisphere. Significant interactions were broken down separately by ROI. A priori contrasts testing for item generalization (similar item > both different), context generalization (similar context > both different), and item-in-context generalization (similar item + context > similar item + similar context) were defined for information overlap, in keeping with the prediction model hierarchy described above. When two or more a priori contrasts were significant within an ROI, we also applied post hoc contrasts (with Bonferroni correction for multiple comparisons) to determine which significant effect was strongest (e.g., similar item + context > similar item). Contrasts were additionally applied to pattern similarity estimates extracted from eroded hippocampal head ROIs that excluded edge voxels (binary erosion in three dimensions with 3 mm spherical kernel) to reduce any possible influence of signal from neighboring voxels.

RESULTS

Because we were interested in voxel patterns associated with memory for items in context, it was important to establish the presence of two behavioral effects: (1) that memory (particularly context memory) existed, that is, that any given correct context memory response could be attributed to real memory signal, and (2) that there were no systematic differences in memory performance across encoding contexts. One-way repeated-measures ANOVAs confirmed that both item discriminability, $F(1, 19) = 238.34$, $p < .0001$, and context discriminability, $F(1, 19) = 77.20$, $p < .0001$, were significantly different from zero across encoding contexts, but that neither metric differed significantly between encoding contexts (Fs < 1.39, ps > .25; Figure 3).

To examine the neural organization of memories for similar events, we performed a set of multivoxel pattern similarity searchlight analyses (Kriegeskorte et al., 2006, 2008). Analysis was restricted to retrieval phase trials characterized by accurate context recall based on an item cue. Local voxelwise patterns of evoked activity were correlated between all pairs of these trials, and trial pair correlations were contrasted according to the similarity of

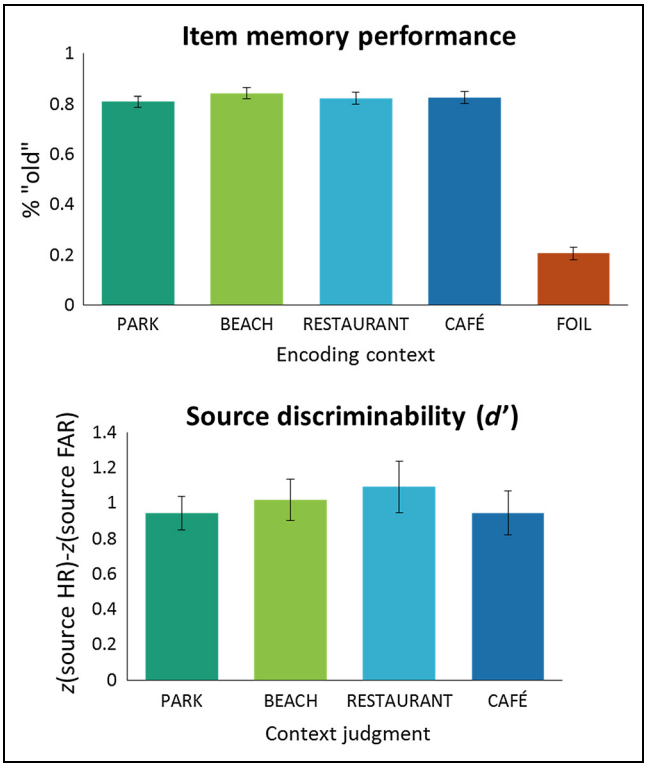

Figure 3. Behavioral expressions of item and context memory were equivalent across encoding context locations. Item memory performance (top) was calculated as the proportion of old items from each encoding context given any "old" response ("Familiar," "Recollect," or any source judgment); item false alarm rate was calculated as the proportion of foils given any "old" response. Source discriminability (bottom) was calculated as the difference between the inverse normal cumulative distributions of source hit rate (HR) and source false alarm rate (FAR). For each context judgment, source HR was calculated as the proportion of items correctly attributed to a particular encoding condition; source FAR was calculated as the proportion of items (targets or foils) incorrectly attributed to that encoding condition. Error bars indicate *SEM* across participants.

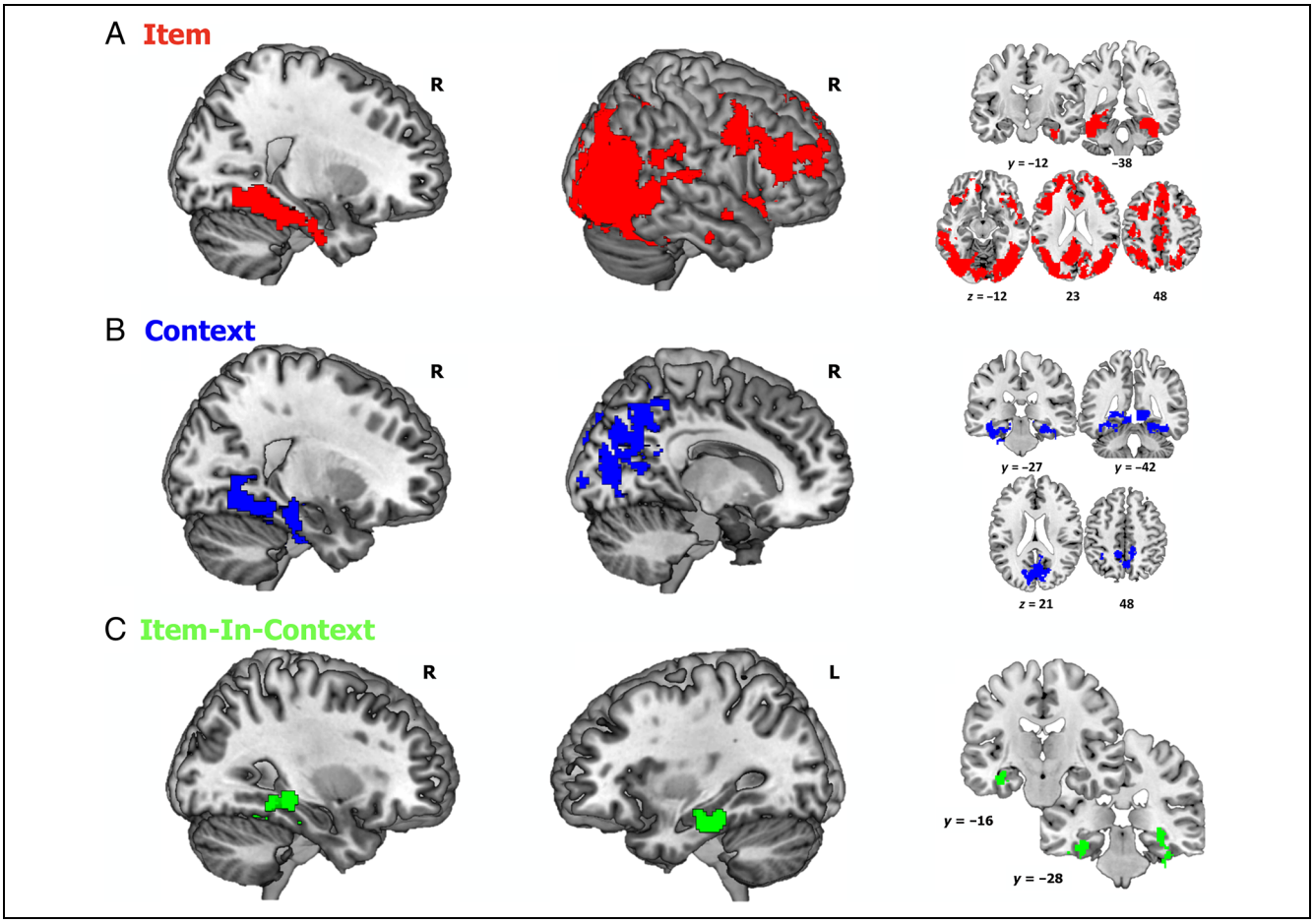

Figure 4. Voxel pattern similarity analysis results. (A) similar item > both different contrast. Using an MTL mask, significant clusters were identified in the ventral and medial temporal cortex, including the perirhinal cortex. Using a whole-brain gray matter mask (excluding MTL voxels; middle), extensive significant clusters were identified, with the global maximum in the posterior fusiform cortex (MNI 40, −56, −14; t = 10.22). (B) Association between similar context > both different pattern similarity and context memory performance. With an MTL mask, the global maximum in the parahippocampal cortex (MNI 28, −24, −20; t = 6.61) was significant at $p_{TFCE} < .05$, FWE-corrected (for display purposes, threshold is set to $p < .001$, uncorrected). With a whole-brain gray matter mask (excluding MTL voxels; middle), significant clusters were identified in posterior medial regions, with the global maximum in cuneus (MNI −10, −86, 16; t = 6.82). (C) Searchlight results for similar item + context > (similar item or similar context) contrast in sagittal and coronal views. Thresholds set to $p < .05$, FWE-corrected.

item and/or context information contained in each pair (Figure 2).

We first investigated whether local voxel patterns in the hippocampus generalized across different exemplars of the same item. Voxelwise pattern similarity was contrasted between trial pairs containing different item exemplars from the same category ("similar item" pairs) against pattern similarity between trial pairs that included exemplars from different item categories ("both different" pairs). To isolate item-level pattern information, this analysis excluded trial pairs that had been associated with the same encoding context. In the MTL, significant clusters extended throughout the ventral and medial-temporal neocortex, including perirhinal cortex, and the amygdala but no hippocampal voxels were identified as generalizing across events on the basis of item information alone (Figure 4A), consistent with previous studies of item pattern separation in the hippocampus and medial-temporal cortex (Huffman & Stark, 2014; LaRocque et al., 2013; Liang et al., 2013). Across the whole brain, item-level pattern information was identified extensively in the frontal, parietal, and occipital cortex, with the strongest effects in the right lateral occipital cortex and the posterior fusiform cortex (Figure 4A).

We next examined whether the hippocampus generalized across different items according to whether they had been studied with the same encoding context. We contrasted voxel pattern similarity between trial pairs with different item cues that shared a study context ("similar context" pairs) and both different pairs. No suprathreshold clusters in the hippocampus or neocortex were identified as generalizing across events on the basis of contextual information alone, either within the MTL or across the whole brain. Given that items in this study have concrete sensory attributes whereas contexts are imagined, subtler context-driven effects are perhaps not surprising. To enhance our sensitivity to detect effects of shared context, we examined whether the strength of

neural pattern similarity evidence for context reinstatement might be related to individual differences in behavioral evidence for context memory. In a voxelwise regression (with nonparametric inference testing, as above, but with full permutations), we identified regions where pattern similarity evidence related to context similarity were positively associated with individual behavioral context discriminability estimates (averaged across contexts). Family-wise error rate was determined on the basis of cluster mass using independent MTL and non-MTL gray matter masks. Because no clusters in the MTL surpassed the stringent cluster mass-based family-wise error rate correction applied in other analysis, we additionally applied threshold-free cluster enhancement (TFCE) to detect the presence of any relatively weaker but reliable voxelwise effects ($p < .05$, FWE-corrected; Smith & Nichols, 2009). Pattern similarity driven by retrieval of similar contexts was positively associated with context discriminability across participants in the parahippocampal cortex, the retrosplenial cortex, the lingual gyrus, and the precuneus (Figure 4B). However, again, no significant hippocampal voxels were identified.

Our third analysis tested the possibility that the hippocampus generalized across memories that included similar item and context information. If the hippocampus organizes memories on the basis of item–context associations, voxel pattern similarity should be substantially higher across events with similar items and similar contexts, compared with events that shared only a single attribute. Therefore, we contrasted voxel pattern similarity between trial pairs with that included similar items that had been associated with the same study context location ("similar item + context" pairs) against pattern similarity between trial pairs that overlapped on one, but not both, of these dimensions (i.e., similar item and similar context pairs). Searchlight analysis identified clusters showing this effect with centers of mass in the anterior and middle hippocampus bilaterally, extending partially into the ventral and medial-temporal neocortex (Figure 4C).

To further characterize item and context organization within the hippocampus and adjacent cortical regions, mean pattern similarity estimates (z scores) for both different, similar item, similar context, and similar item + context pairs were extracted from anatomically defined hippocampal and cortical ROIs. Because of previously reported functional differences along the anterior–posterior axes of the hippocampus (Poppenk et al., 2013), we evaluated hippocampal head, body, and tail separately using established anatomical landmarks (Moore et al., 2014). A full factorial repeated-measures ANOVA revealed a significant main effect of ROI, $F(4, 19) = 16.37$, corrected $p_{HF} < .0001$, $\varepsilon_{HF} = 0.54$, a significant main effect of Information overlap, $F(3, 19) = 4.45$, corrected $p_{HF} < .05$, $\varepsilon_{HF} = 0.41$, and, critically, a significant ROI × Information overlap interaction, $F(12, 19) = 4.25$, corrected $p_{HF} < .005$, $\varepsilon_{HF} = 0.36$; there was no significant main effect of Hemisphere or interaction between Hemisphere and either factor of interest (Fs < 1.58, ps > .18). Based on the significant interaction, we examined the effect of Information overlap within each ROI, controlling for hemisphere, using a set of a priori and follow-up post hoc contrasts to detect the presence of item, context, and item-in-context generalization separately for each ROI.

In addition to the hippocampus, we examined the extent to which MTL cortical ROIs generalized across items as points of comparison. Within the perirhinal cortex, there was a trend toward greater pattern similarity estimates for similar item compared with both different trial pairs, $F(1, 19) = 3.12$, $p = .08$), and similarity estimates were greater for similar item + context relative to similar item pairs, $F(1, 19) = 12.9$, $p < .005$, Bonferroni-corrected, suggesting that item generalization in the perirhinal cortex is strengthened by context similarity (Figure 5A). In the parahippocampal cortex, pattern similarity between similar item pairs was significantly greater than both different pairs, $F(1, 19) = 8.38$, $p < .01$, but were not significantly different from similar item + context pairs, $F(1, 19) = 12.9$, $p < .005$, Bonferroni-corrected, suggesting that item generalization in the parahippocampal cortex was insensitive to context similarity (Figure 5B).

In contrast to item generalization effects in the cortex, within hippocampal head, pattern similarity estimates were significantly and selectively greater for similar item + context pairs compared with similar item and similar context pairs, $F(1, 19) = 5.19$, $p < .05$, consistent with voxelwise results (Figure 5C). This pattern of results suggests that hippocampal head only generalized across trials that shared similar item-in-context information. Eroded hippocampal head ROIs excluding edge voxels demonstrated a highly similar pattern of results, although the selective similar item + context effect was attenuated somewhat, $F(1, 19) = 3.68$, $p = .06$. Moreover, we note the overlap between these ROI-based results and the whole-brain searchlight results from the prior section. This suggests that the generalization effect in the hippocampal head was not driven by edge voxels, which could potentially include signal outside the hippocampus. There were no significant pattern similarity differences in hippocampal body or tail ROIs (Fs < 1.72, ps > .19).

The above contrasts suggest that the hippocampal head may selectively generalize across items that share both similar item and context information. However, it is possible that generalization within the hippocampus was graded, such that item-in-context generalization actually reflected the additive coding of item and context information separately. To arbitrate between additive (graded) and conjunctive (thresholded) accounts, pattern similarity estimates from hippocampal head were fit to a set of linear models, controlling for hemisphere: an additive model (*both different* = 0, *similar item* = 1, *similar context* = 1, *similar item + context* = 2), a conjunctive model (*both different* = 0, *similar item* = 0,

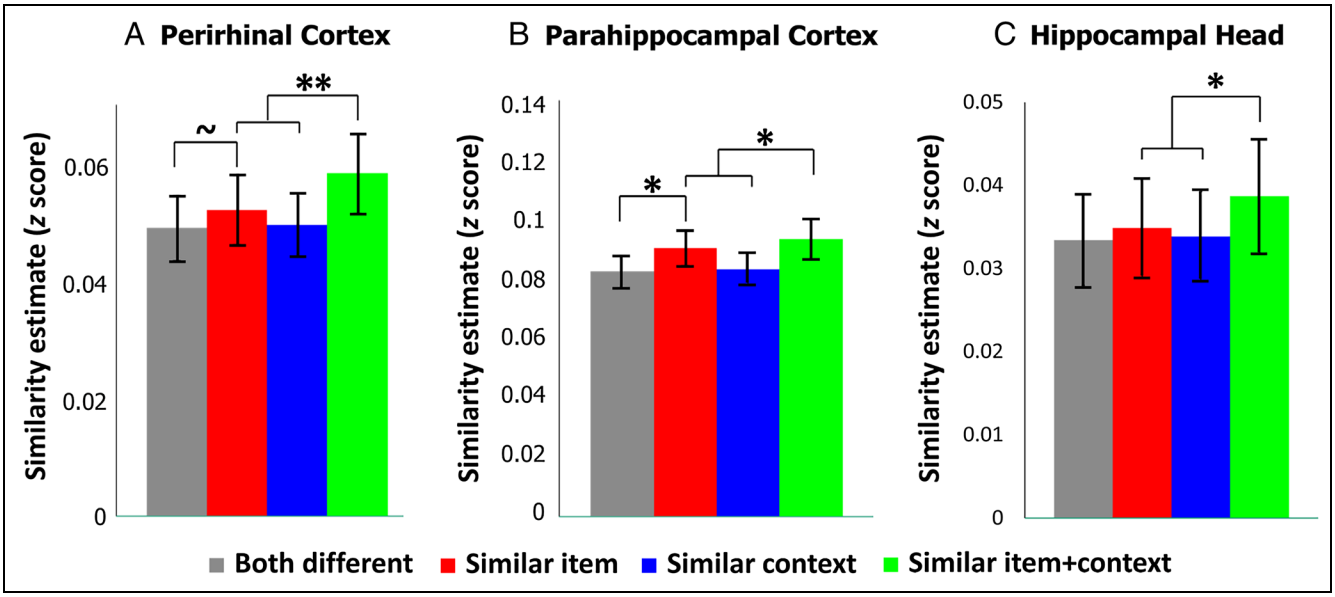

Figure 5. Pattern similarity results across MTL ROIs. Mean pattern similarity estimates for both different, similar item, similar context, and similar item + context trial pairs are plotted. (A) In the perirhinal cortex, there was evidence for both item and item-in-context generalization. (B) In the parahippocampal cortex, item-incontext generalization was redundant with item coding effects. (C) In the hippocampal head, there was evidence for generalization due to item-in-context associations, but not item or context similarity individually. ~ $p \approx .05$ (trend level), *$p < .05$ for a priori contrasts (indicated by brackets), **$p < .05$ for both a priori and post hoc (similar item + context > similar item) contrasts. Error bars refer to standard error across participants. Because there was no significant differences across hemisphere, results are collapsed across right and left ROIs.

similar context = 0, *similar item* + *context* = 1), and a combined model containing both additive and conjunctive terms. Model fit was quantified using Bayesian information criterion (BIC; lower BIC values indicate better model fit; Schwarz, 1978) and compared between the three models. BIC was slightly lower (indicating a better fit) for the conjunctive model (BIC = −952.36) than the additive model (BIC = −950.69). BIC was highest for the combined model (BIC = −942.63), suggesting that this model tended to overfit the data. These results suggest that the current pattern of hippocampal results is most consistent with conjunctive coding. Although additive coding cannot be conclusively ruled out on the basis of this analysis, there is no evidence for additive coding above what can be explained by conjunctive coding in our data.

Finally, we conducted a control analysis to determine whether pattern similarity in hippocampal head could be driven by the similarity of motor responses between trials, independent of memory for context information. Evoked patterns of activity across voxels in hippocampal head ROIs were correlated for each pair of trials given either a "Familiar" response (trials characterized by item familiarity without context recollection) or "New" response (forgotten trials). If pattern similarity was merely sensitive to motor response rather than episodic memory details, similarity estimates between trial pairs containing two "Familiar" or two "New" trials (i.e., within trials with the same motor response) would be expected to be higher than between trial pairs containing one "Familiar" and one "New" trial (i.e., between trials with different motor responses). However, a repeated-measures ANOVA on response similarity, controlling for hemisphere, revealed no significant effects (Fs < 1.89, ps > .18), suggesting that hippocampal pattern similarity was not driven by specific motor responses.

DISCUSSION

In the current study, we used multivoxel pattern similarity analysis to investigate event representation in the hippocampus and MTL cortical areas during episodic retrieval. Anterior hippocampal voxel activity patterns were similar for events that involved similar items that had been associated with the same study context, but not for events with similar item or context information in isolation. These findings provide novel insight into the neural basis of memory for episodic details, suggesting that, although neural coding in the hippocampus may differentiate between events with some overlapping attributes, it may generalize across events that share similar item–context relations.

Studies of BOLD signal magnitude (Lacy, Yassa, Stark, Muftuler, & Stark, 2011; Bakker, Kirwan, Miller, & Stark, 2008) and multivariate voxel patterns (Huffman & Stark, 2014; LaRocque et al., 2013; Liang et al., 2013) have shown that, compared with MTL cortical regions, the hippocampus (particularly a combined ROI consisting of the dentate gyrus, CA2, and CA3) sharply differentiates between similar items. In the current study, we also found that the hippocampus represented similar items distinctly, as long as they had different contextual associations.

However, when similar items shared contextual information, hippocampal activity patterns overlapped. This finding suggests an important and underexplored boundary condition on hippocampal pattern separation: The extent to which the hippocampus differentiates between similar items may depend on the context in which the items had been encountered.

This study used standard resolution fMRI, and it is possible that a richer pattern of results might have been revealed with high-resolution data. Most prior multivariate pattern similarity studies using high-resolution fMRI have not reported reliable subfield-level differences in item-level pattern separation (Huffman & Stark, 2014; LaRocque et al., 2013; Liang et al., 2013), but a recent study from our group found distinct representational profiles in CA1 versus a combined dentate gyrus/CA2/CA3 region during retrieval of item–context associations (Dimsdale-Zucker, Ritchey, Ekstrom, Yonelinas, & Ranganath, 2018). In that study, participants viewed sequences of visual objects presented in virtual reality videos, and they were scanned while performing a recognition test on the studied objects, in the absence of any contextual cues. Results showed that pattern similarity was higher in CA1 across pairs of different objects that were studied in the same context (i.e., the same video) than for pairs of objects that had been studied in different contexts, whereas the dentate gyrus/CA2/CA3 ROI showed the opposite pattern (i.e., strongly differentiating between objects studied in the same context. In this study, hippocampal activity patterns, aggregated across the subfields, were insensitive to context similarity if the items differed from one another. Based on the results of Dimsdale-Zucker et al. (2018), we can speculate that this null effect might have been the result of aggregating across CA1 (which might be expected to generalize across different items studied in the same context) and dentate gyrus/CA2/CA3 (which might be expected to differentiate between similar items studied in the same context). The present results, in turn, also suggest that both CA1 and dentate gyrus/CA2/CA3 might generalize across similar items that were studied in the same context. Future experiments can be designed to test this prediction at the subfield level.

The current results add importantly to previous work on hippocampal coding of item and context information. Previous studies have consistently suggested that hippocampal representations of items are context-dependent but have not manipulated the similarity of item and context information. Consistent with our results, neuronal ensemble recordings in rats (McKenzie et al., 2014; Manns & Eichenbaum, 2009) have shown that the stability of hippocampal coding for specific items across repeated exposures is dependent on spatial context. Also in line with present findings, a previous fMRI study found that voxel patterns in the anterior hippocampus were more consistent across pairs of trials characterized by successful reinstatement of bound item-in-context information, compared with trials without associative retrieval (Hannula, Libby, Yonelinas, & Ranganath, 2013). The current study focused only on trials characterized by associative retrieval, demonstrating that item-in-context coding in the hippocampus is not merely a function of memory quality and is sensitive to the content of individual episodic memories. In addition, our findings accord with recent fMRI studies in domains outside episodic memory that relate the fidelity of hippocampal voxel patterns to implicit memory for the temporal position of items in learned sequences (Hsieh et al., 2014) and to accurate working memory for spatial configurations of items (Libby et al., 2014). Together, these results suggest that a key function of the hippocampus is tracking conjunctions of items and their temporal or spatial contexts and that this phenomenon may override another key function—pattern separation—under certain conditions.

It is noteworthy that we observed similarity in hippocampal voxel patterns across similar item + context trial pairs, despite the fact that the corresponding study events were not exact duplicates. The events were similar at a schematic level but differed in their exact features. It could be argued that our results accord with the complementary learning systems (CLS; Norman, 2010; Norman & O'Reilly, 2003) computational model, which predicts that hippocampal pattern separation breaks down when the average overlap across events is high. According to this view, however, we would expect participants to exhibit poor discriminability between related events (Norman, 2010; Elfman, Parks, & Yonelinas, 2008; Norman & O'Reilly, 2003), whereas item and context discriminability were very high in the current study. High memory performance cannot be explained in terms of schema-based retrieval (e.g., "I remember that there was a dog in the park"), because similar exemplars from each category were encoded in each context, and these items had to be discriminated from similar unstudied exemplars. Accordingly, participants had to use detailed representations to overcome interference between related events. Moreover, we did not see evidence of graded similarity of hippocampal representations, as might be expected based on reported simulations with the CLS model (Norman, 2010; Norman & O'Reilly, 2003). For instance, we saw no evidence for higher hippocampal pattern similarity for similar item than for both different pairs, and model comparisons suggested that hippocampal coding was better characterized as the conjunction of item and context information than the additive combination of individual features. The present results therefore suggest that models like CLS may benefit from explicitly incorporating representations of item and context information. If the model were instantiated such that contextual features play a significant and explicit role in hippocampal representations, then we would expect that the CLS model would exhibit pattern completion during processing of similar items encountered in the similar context and pattern

separation during processing of similar items encountered in different contexts.

Several recent studies have reported a role for the hippocampus in the integration of separate events that share key conceptual information (Horner, Bisby, Bush, Lin, & Burgess, 2015; Milivojevic, Vicente-Grabovetsky, & Doeller, 2015; Schlichting, Mumford, & Preston, 2015; Chadwick, Hassabis, & Maguire, 2011). The present results suggest that the similarity of item–context relations across events may be an important underlying factor that determines hippocampal integration. For instance, Milivojevic et al. (2015) showed that hippocampal voxel patterns are more similar across seemingly unrelated narrative videos when an intervening video reveals a link between the people (items) and locations (contexts) in the videos. On the basis of the current results, we would predict that an intervening video that shared context or items with the surrounding episodes, but not both, would disrupt hippocampal integration, perhaps particularly in the anterior hippocampus. Indeed, in studies of complex pairwise item associations learned over the course of multiple trials, activity (Horner et al., 2015) and pattern similarity (Schlichting et al., 2015) in the anterior hippocampus were greatest when event elements were fully integrated into "holistic" representations after learning. Given that this study investigated single-shot episodic encoding and retrieval, our results suggest that the anterior hippocampus integration or generalization can occur rapidly when item–context relations are sufficiently conceptually overlapping.

Everyday experiences often involve many common elements, yet we are able to retrieve specific instances of item–context associations—to which rack you locked your bike this afternoon, or which dog you saw in the park over the weekend—with surprising accuracy (Mitchell & Johnson, 2009; Johnson et al., 1993). Results from the current study suggest that the hippocampus utilizes context as an organizing principle to reduce competition between memories that involve the same or similar items. These findings bridge two influential theoretical frameworks on hippocampal function (Ritchey, Libby, et al., 2015; Ranganath & Ritchey, 2012; Yassa & Stark, 2011; Norman, 2010; Ranganath, 2010; Davachi, 2006; Knierim et al., 2006; Rolls & Kesner, 2006; Eacott & Gaffan, 2005; Norman & O'Reilly, 2003; Marr, 1971) by suggesting a critical role for the binding of item and context information in hippocampal pattern separation and episodic memory.

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Reprint requests should be sent to Charan Ranganath, University of California, Davis, Center for Neuroscience, 1544 Newton Court, Davis, CA 95618, or via e-mail: cranganath@ucdavis.edu.

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