Hippocampal subfields integrate information about past temporal and cognitive contexts

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Abstract. The hippocampus plays a critical role in supporting episodic memory. Although we know that temporal context is a defining feature of episodic memory, we understand relatively little about how this information may be represented by the hippocampus. Research in rodents has suggested that the hippocampus represents temporal information on an absolute scale or in terms of relative temporal intervals, but cognitive models of memory have argued that temporal context in episodic memory is a consequence of changes in cognitive states and experiences. Here, we combined high-resolution fMRI imaging with voxel pattern similarity analyses to answer the question of how human hippocampal subfields represent retrieved information about cognitive states and the time at which a past event took place. As participants recollected previously presented items, activity patterns in the CA23DG subregion carried information about prior cognitive states, along with coarse-grained information about when the item was previously encountered. These findings are consistent with the idea that CA23DG supports temporal context in episodic memory by encoding an integrated representation of discrete and gradually-changing cognitive states.

Introduction. Converging evidence suggests that the hippocampus plays a critical role in memory for events and their episodic details (Eichenbaum et al., 2007; Scoville & Milner, 1957; Vargha-Khadem et al., 1997). For a memory to be considered episodic, it must be associated with a particular moment in time, or temporal context (Reiff & Scheerer, 1959; Tulving, 1983). Consistent with its integral role in episodic memory,

studies in rodents (Allen et al., 2016; Cai et al., 2016; Kraus et al., 2013, 2015; Salz et al., 2016), non-human primates (Naya et al., 2017), and humans (Dimsdale-Zucker et al., 2018; Hsieh et al., 2014; Jenkins & Ranganath, 2010, 2016; Thavabalasingam et al., 2018; Tubridy & Davachi, 2011) have shown that the hippocampus represents information about time.

At present, there are at least two major accounts of how this might happen. One possibility is that the hippocampus maintains a continuously varying representation of temporal context, possibly via internally generated cell assembly sequences (Buzsáki & Llinás, 2017; Levy, 1996; Rodriguez & Levy, 2001; Wallenstein et al., 1998). Consistent with this idea, results from single-unit recording studies in rodents have suggested that cell populations in the hippocampus can faithfully represent temporal relationships across both short (Kraus et al., 2013, 2015; MacDonald et al., 2011; Salz et al., 2016) and longer (Cai et al., 2016; Mankin et al., 2012, 2015; Ziv et al., 2013) intervals. Another possibly complementary account comes from cognitive theories of episodic memory that operationalize temporal context in terms of changes in cognitive *states* or experiences (Estes, 1955; Howard & Kahana, 2002). Although temporal context models generally assume that representations of temporal context change gradually, these models also predict that context can abruptly change to reflect one's current cognitive state (Lohnas et al., 2015; Polyn et al., 2009). The current study was designed to adjudicate between the possibility that neural representations are sensitive to the actual passage of time or that they are sensitive to the concomitant fluctuations in mental state that lead to the perception of time. A third possibility, uniquely observable by using representational similarity analysis, is that neural representations actually track the

conjunction of slowly drifting temporal features along with continuously varying cognitive states.

Much of the existing human work into temporal coding has considered the hippocampus as a single functional unit (DuBrow & Davachi, 2016; Ezzyat & Davachi, 2014; Hsieh et al., 2014; Thavabalasingam et al., 2018; Tubridy & Davachi, 2011). However, there is reason to think that different hippocampal subfields might make distinct contributions (Dimsdale-Zucker et al., 2018) in representing cognitive states and temporal contexts. For instance, some models emphasize the role of area CA1 in encoding of temporal context (e.g., (Kesner & Rolls, 2015) others emphasize the importance of the dentate gyrus and CA3 (Levy, 1996; Lisman, 1999; Wallenstein et al., 1998), and some recent evidence has suggested that area CA2 may be disproportionately important (Mankin et al., 2015). For the purposes of the current study, we were interested in characterizing whether the hippocampus represented temporal contexts as absolute temporal signals or in relation to variations in cognitive states. Given the extant evidence that multiple subfields can represent temporal contexts, this leaves open the question of whether different subfields represent temporal information in different ways.

Here, we used high-resolution functional magnetic resonance imaging (fMRI) to clarify whether or how the hippocampus encodes temporal and cognitive contexts during episodic memory retrieval. We also examined contributions of medial temporal cortical regions, as, for instance, parahippocampal cortex is known to be important for representing contextual information (Davachi, 2006; Diana et al., 2007). We scanned participants while they recollected objects that were studied in sequentially-organized

lists, and used voxel pattern similarity (PS) analyses (Dimsdale-Zucker & Ranganath, 2018; Kriegeskorte et al., 2008) to examine whether patterns of activity in hippocampal subfields at the time of retrieval carried information about temporal and cognitive contexts instantiated at encoding. In order to adjudicate between context models that propose slowly drifting signal versus those that predict the possibility of rapid changes concurrent with modulation of cognitive state, we embedded both 'drifting' and 'shifting' (DuBrow et al., 2017) manipulations of context in the current paradigm.

Method.

Participants. 32 participants were recruited from the community and were compensated $50 for their time. This study was approved by the Institutional Review Board at the University of California, Davis. Four participants were excluded due to missing behavioral data, two participants were excluded for excessive motion that prevented tracing of hippocampal subfields, one participant was excluded due to an experimenter error at data collection that resulted in the incorrect stimuli being seen, and one participant was excluded because they only had one run of usable data after discarding motion-contaminated and data-collection contaminated runs. The results below reflect data from 24 remaining participants (Mage = 22.85 years, SD = 3.06 years, Nfemale = 13). One of these 24 participants was excluded from behavioral cognitive and temporal context analyses due to partially missing data; since the brain imaging data for this participant were complete and did not depend on this behavior being recorded, they were included in all other analyses.

Encoding. Participants viewed eight 36-item lists of still pictures of everyday objects (e.g., contact lens case, french fries; http://cvcl.mit.edu/mm/uniqueObjects.html;

see Figure 1). Object assignment to list and presentation order of objects within a list were uniquely randomized for each participant via the Matlab randperm function. To encourage participants to learn temporal relationships amongst items in a list (Palombo et al., 2019), each list was presented three times in a mini-block before subjects saw items from the next list (e.g., 1, 1, 1, 2, 2, 2...8, 8, 8). A label with a list number (e.g., “List 1”) appeared at the beginning of each list prior to seeing any objects. Mini-blocks were separated with a self-paced break. Presentation order of objects within a list was identical for all three list presentations.

Objects remained on the screen for 2.5 seconds (timing and presentation parameters were controlled via Presentation [Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com]) while the participant made a yes/no button response to an orienting question (cognitive context). To manipulate cognitive context, each object was associated with one of four questions: Would this item fit in a refrigerator?, Would this item fit in a bathtub?, Would you find this item in a convenience store?, Would you find this item in a supermarket?. Each of the four questions was presented equally often in each block, and question/object pairs remained the same across all three list presentations. Participants were instructed that this was a decision-making task and that there would be some repetition but to concentrate on doing the task. Participants were not aware that memory for these questions would be tested later, thus the learning of question and temporal context information was incidental. Grouping items into lists was meant to capture slowly drifting cognitive state signals. We reasoned that items studied near in time would be related by slow, ongoing fluctuations that co-varied across presentation of the items. A similar temporal grouping strategy has been used

120 previously to encourage connections between items in this fashion (Palombo et al.,
121 2019). In addition, to target continuously varying representations, we affiliated each item
122 with a question. Previous work has shown that interspersing questions throughout the
123 encoding phase can result in fast, shifting variations in context that are aligned to
124 changes in cognitive state (Polyn et al., 2009).

125 **Scanned object recognition.** While in the MRI scanner, participants saw each
126 of the 288 old objects from encoding as well as 72 new objects presented one at a time
127 for 2.5 seconds with a jittered ITI ranging from 2-15 seconds (mean ITI jitter = 6
128 seconds). Objects were divided into 6 runs (60 trials per run). Object order within a run
129 was pseudo-randomized such that objects with the same encoding question always had
130 at least one intervening object (e.g., fridge, convenience store, bathtub, fridge,
131 supermarket, fridge, etc.) to help minimize encoding context reinstatement biases on PS
132 results (see Multivariate Results below). Proximity of objects from encoding mini-blocks
133 (1-8) was not considered in the pseudo-randomization.

134 While in the scanner, participants were instructed to indicate via button press
135 whether or not they remembered the object on a 4-point scale: 1=new, 2=familiar (old
136 but no remembered details), 3=remembered non-temporal details (e.g., the encoding
137 question, something about the object itself, or an association they made with the
138 object), 4=remembered temporal detail (e.g., in what list or when they had seen the
139 object during encoding). Responses for remembered judgments were collapsed into a
140 single response bin for behavioral and fMRI analyses.

141 **Source memory: Cognitive context.** After completing MRI scanning,
142 participants returned to the lab where they completed a cognitive context source

memory task. In this phase, participants saw all 288 studied objects from encoding and were asked to indicate which encoding question (fridge/bathtub/convenience store/grocery store) had been associated with the object. Objects were presented across four blocks of 72 trials each. Within each block, there were an equal number of objects from each encoding mini-block (1-8). Presentation order of objects was uniquely randomized by participant within each source memory block. Objects appeared on the screen until the participant had made their source memory judgment. There was no opportunity to guess or skip objects.

Source memory: Temporal context. After completing the cognitive context source memory test, participants again saw the 288 old objects from encoding and this time were asked to indicate in which mini-block (1-8) the object had appeared. Objects were presented centrally on the screen and a number line displaying the numeric options 1-8 appeared below. Participants were told to use the numbers at the top of the keypad to make their response. Objects were again divided across four blocks of 72 trials with a different randomization order than was used in the task context source memory test. Objects remained on the screen until the participant had made their response. There was no opportunity to guess or skip temporal context judgments.

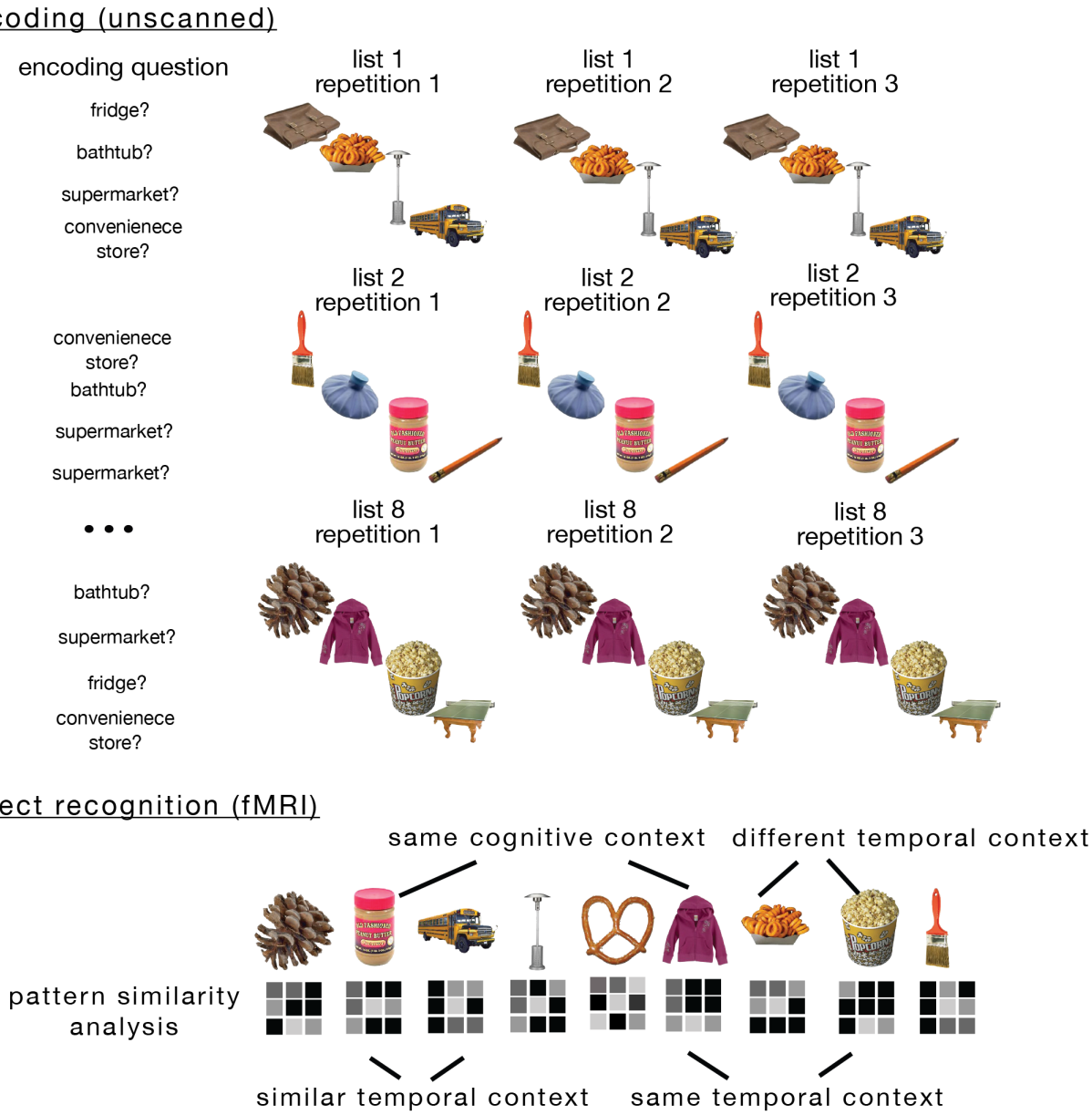

Figure 1. Task structure. During the encoding phase, each participant studied lists of 36 objects that were each randomly paired with one of four encoding questions ("Would this item fit in a fridge?", "Would this item fit in a bathtub?", "Would you find this item in a supermarket?", "Would you find this item in a convenience store?"). Each list was repeated three times in a row to promote learning of the temporal relationships amongst the items. Objects appeared in the same order and with the same question (cognitive context) across all repetitions. High-resolution functional magnetic resonance brain imaging (fMRI) was used to examine hippocampal activity patterns during a recognition memory test for these objects, allowing us to examine activity pattern similarity as a function of whether pairs of items were encoded within the same or similar temporal contexts (i.e., studied in the same list or temporally proximal lists), and/or the same cognitive context (i.e., associated encoding question).

174 **fMRI acquisition and pre-processing.** Scans were acquired on a Siemens
175 Skyra 3T scanner with a 32 channel head coil. Two sets of structural images were
176 acquired to enable subfield segmentation: A T1-weighted magnetization prepared rapid
177 acquisition gradient echo (MP-RAGE) pulse sequence image (1 mm isotropic voxels),
178 and a high-resolution T2-weighted image (TR = 4200 ms; TE= 93 ms; field of view =
179 200 mm^2; flip angle = 139°; bandwidth = 199 Hz/pixel; voxel size = 0.4 x 0.4 x 1.9 mm;
180 58 coronal slices acquired perpendicular to the long-axis of the hippocampus). High-
181 resolution functional (T2*) images were acquired using a multiband gradient echo planar
182 (EPI) imaging sequence (TR = 2010 ms; TE = 25 ms; field of view = 216 mm; image
183 matrix = 144 x 152; flip angle = 79°; bandwidth = 1240 Hx/pixel; partial phase Fourier =
184 6/8; parallel imaging = GRAPPA acceleration factor 2 with 72 reference lines; multiband
185 factor = 2; 52 oblique axial slices acquired parallel to the long-axis of the hippocampus
186 slices; voxel size = 1.5 mm isotropic).
187 SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) was used for image pre-processing.
188 Functional EPI images were realigned to the first image and resliced. No slice timing
189 correction was performed due to the acquisition of multiple simultaneous slices with the
190 multiband sequence (capabilities to handle multiband timing do not exist in SPM8). Co-
191 registration between the native-space ROIs defined in T2 space and the functional
192 images was done with SPM's Coregister: Estimate and Reslice procedure. This
193 procedure uses a linear normalized mutual information cost-function between a
194 reference (mean functional) image and source (T2) image to compute and apply a
195 voxel-by-voxel affine transformation matrix. This transformation matrix was then applied
196 to the subfield ROIs that had been defined in T2 space (see *ROI segmentation*) to bring

them into register with the functional images. The T1 image was co-registered to the mean EPI. Then, nonlinear spatial normalization parameters were derived by segmenting the coregistered T1 image. Quality assurance included identifying suspect timepoints via custom code (https://github.com/memobc/memolab-fmri-qa) defined as time-points in excess of 0.5 mm frame displacement (based on (Power et al., 2012) or 1.5% global mean signal change (based on ARTRepair recommendations, (Mazaika et al., 2005)). Runs were excluded if the frame displacement exceeded the voxel size. As reported earlier, three participants were excluded for motion in excess of these thresholds; of the 24 subjects included in the analyses, 9 had runs excluded based on these thresholds (mean number of removed runs = 0.92, SD = 1.38; ranging from 0-4 runs).

Pattern similarity analyses. PS analyses were conducted on beta maps generated from unsmoothed data in native subject space. Following the least squares separate procedure described by Mumford (2012), single trial models were generated to estimate the unique beta map for every trial in a run (N=60). Within each single trial model, the first regressor modeled the trial of interest with a stick function, the second regressor modeled all other trials in that run, six regressors were used to capture motion, and any additional spike regressors as identified by our QA scripts were used to capture additional residual variance. Voxel-wise patterns of hemodynamic activity were separately extracted for each ROI from the single trial beta images. To ensure robust ability to detect differences in PS, we required temporal signal-to-noise ratios (TSNR) in a region to be above 20 (approximately 2 standard deviations below the mean global TSNR of 50.4). This required the removal of entorhinal cortex and its subregions (mean

TSNR ranged between 10-20), despite its compelling role in the representation of temporal context (Bellmund et al., 2019; Montchal et al., 2019)

Within each ROI, correlations (Pearson's r) were computed between these trial-wise betas to yield a trial-by-trial correlation matrix that related each voxel's signal on a trial to all other trials across all runs. We restricted comparisons to those trials for which participants made a correct "remember" response (during MRI scanning). Trials were sorted on the basis of encoding context (cognitive, temporal), however source memory for these contexts was not taken into consideration. Correlation values were z-transformed prior to statistical analysis. Statistical analyses tested for differences in correlations between trial pairs on the basis of encoding context (cognitive context: same vs. different encoding question; temporal context: same vs. different encoding list, or similar vs. different list half). To more accurately characterize both within- and across-subject error variance (Baayen et al., 2008; Clark, 1973; Dixon, 2008; Jaeger, 2008; Mumford & Poldrack, 2007; Singmann & Kellen, in press), we implemented a mixed-modelling approach to evaluate statistical significance with the *lme4* packing in R (Bates et al., 2014); for a similar approach, see (Dimsdale-Zucker et al., 2018). We used an alpha of $p < 0.05$ and performed permutation testing for all of the pattern similarity results reported in the manuscript. Only between-run correlations were used to maximize the number of possible trial pairs without mixing within- and between-run correlations. Trial pairs of interest were extracted from these trial-by-trial correlation matrices.

All relevant code (https://github.com/hallez/tempcon_pub), a reproducible compute environment (https://doi.org/10.24433/CO.0129473.v1), and relevant data (https://osf.io/qfcjg/) are available online.

ROI definition. Hippocampal subfields were defined following the procedure reported in (Dimsdale-Zucker et al., 2018; see Figure 2). In short, the ASHS automated segmentation procedure was used to delineate subfields in subject-native space (Yushkevich et al., 2010). We restricted our analyses to hippocampal body where discriminating subfields is most agreed upon. Medial temporal lobe cortical regions were manually-traced (see the Libby and Ranganath protocol in (Yushkevich et al., 2015)). In accordance with prior findings suggesting functional distinctions between anterior and posterior parahippocampal gyrus (Aminoff et al., 2007; Baldassano et al., 2013, 2016), we subdivided parahippocampal cortex one slice posterior to the wing of the ambient cistern (Frankó et al., 2014).

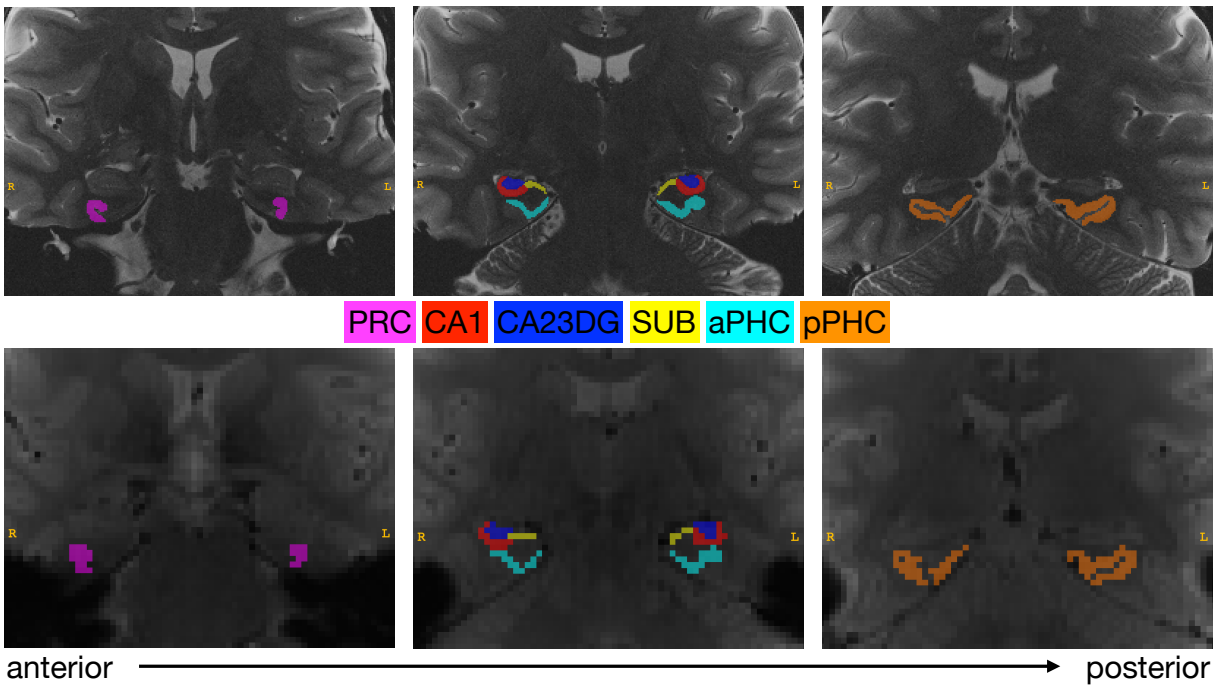

Figure 2. Top: Segmentations of hippocampal subfields (Cornu Ammonis [CA] 1, a combined CA2/3 and dentate gyrus [CA23DG] region, and subiculum [SUB]) as well as cortical medial temporal lobe regions (perirhinal cortex [PRC], anterior parahippocampal cortex [aPHC], and posterior parahippocampal cortex [pPHC]). Segmentations are depicted for a representative subject in the coronal plane of a T2 image. Slices move from anterior to posterior from left-to-right. Bottom: Segmentations following reslicing to functional (EPI) space displayed on a mean functional image from the same subject.

Results.

Behavioral results. During MRI scanning participants performed a recognition memory test requiring judgments as to whether each item was recognized on the basis of recollection of specific item and source information from the study phase (see *Method*). Pattern similarity analyses were restricted to correctly remembered items. On average, this yielded 200 trials (SD = 51.9; minimum trials = 71; maximum trials = 282) from which we constructed all possible trial pairs and then compared activity patterns (see fMRI Results).

Correct remember judgments were the most common response (mean hit rate = 0.69, SD = 0.19), and, for these items, participants showed high accuracy at remembering the associated encoding task context (mean hit rate = 0.71, SD = 0.12). Memory for the exact ("same") temporal context (list 1-8) was poor (mean hit rate = 0.18, SD = 0.03), but, we reasoned that, even if participants were unable to recall the exact list identity, they might have memory for the "similar" temporal context associated with each item. We therefore re-scored each trial according to whether the participant could accurately determine whether it was presented in the "similar" (first half (lists 1-4) or the second half (lists 5-8)) versus "different" (across halves, i.e., list 1/list5, list 1/list 6, etc.) temporal context of the encoding phase. On this metric, memory for similar temporal context (mean hit rate for list half = 0.59, SD = 0.04) was reliably greater than

chance of 0.5, $t(22) = 8.74$, $p < 0.001$. Thus, although participants did not have access to the precise list in which an item had been studied, they were able to retrieve information about the item's temporal context at a coarse level.

fMRI results: Hippocampal Subfields We next tested whether activity patterns in the hippocampal subfields (CA1, CA23DG, subiculum) during memory retrieval carried information about the context in which the item was previously encountered. Specifically, we examined voxel PS during retrieval as a function of whether pairs of trials shared a temporal (defined either as same list vs. different list [*same* temporal context] or as same half of the experiment vs. different halves of the experiment [*similar* temporal context]) and/or cognitive (i.e., same encoding task vs. different encoding task) context when the items were originally learned.

We first considered when items came from the "same" temporal encoding context (same vs. different list). No hippocampal subfield varied its PS at retrieval with respect to the same temporal context (all $X^2 < 0.5$, all *p*s > 0.40). In CA23DG, we found that PS was higher during retrieval of items associated with the same cognitive context compared to items associated with different cognitive contexts ($X^2(1) = 4.63$, $p^{perm1000} = 0.031$). No other subfield varied its PS at retrieval with respect to cognitive context alone (all $X^2 < 0.3$, all *p*s > 0.55) nor the combination of temporal and cognitive context (all $X^2 < 0.80$, all *p*s > 0.30).

We next considered whether PS might depend on whether items shared a "similar" temporal context at encoding (same vs. different half of the encoding phase). This was intended to give us a coarser measure of temporal context. The choice of list half was informed by the fact that participants were behaviorally able to discriminate

coarse temporal context reliably greater than chance. PS levels did not vary by similar temporal context alone ($X^2(1) = 0.08$, $p^{perm1000} = 0.815$). Thus, PS levels were not modulated by same or similar temporal context alone. In CA23DG, we found that PS was higher during retrieval of items that were associated with the same cognitive context than for items that were associated with different cognitive contexts ($X^2(1) = 4.68$, $p^{perm1000} = 0.037$; see Figure 3). Thus, irrespective of how we defined temporal context (same, similar), PS in CA23DG was higher for items that were associated with the same cognitive context. This effect was qualified by a significant similar temporal by cognitive context interaction ($X^2(1) = 8.11$, $p^{perm1000} = 0.008$), such that the effect of cognitive context was larger for items that were in similar temporal contexts (same half) than for items that were in different temporal contexts (different half) particularly when these items shared the same cognitive context.

In CA1, PS levels did not vary by similar temporal context ($X^2(1) = 2.42$, $p^{perm1000} = 0.122$), cognitive context ($X^2(1) = 0.08$, $p^{perm1000} = 0.757$), nor when we considered both temporal and cognitive context ($X^2(1) = 0.84$, $p^{perm1000} = 0.329$). In subiculum, PS levels did not vary by similar temporal context ($X^2(1) = 0.11$, $p^{perm1000} = 0.751$) or cognitive context ($X^2(1) = 0.27$, $p^{perm1000} = 0.622$), however, we found that PS was marginally higher for items that were studied relative to the same question but studied in different list halves as compared to all other conditions ($X^2(1) = 2.91$, $p^{perm1000} = 0.082$).

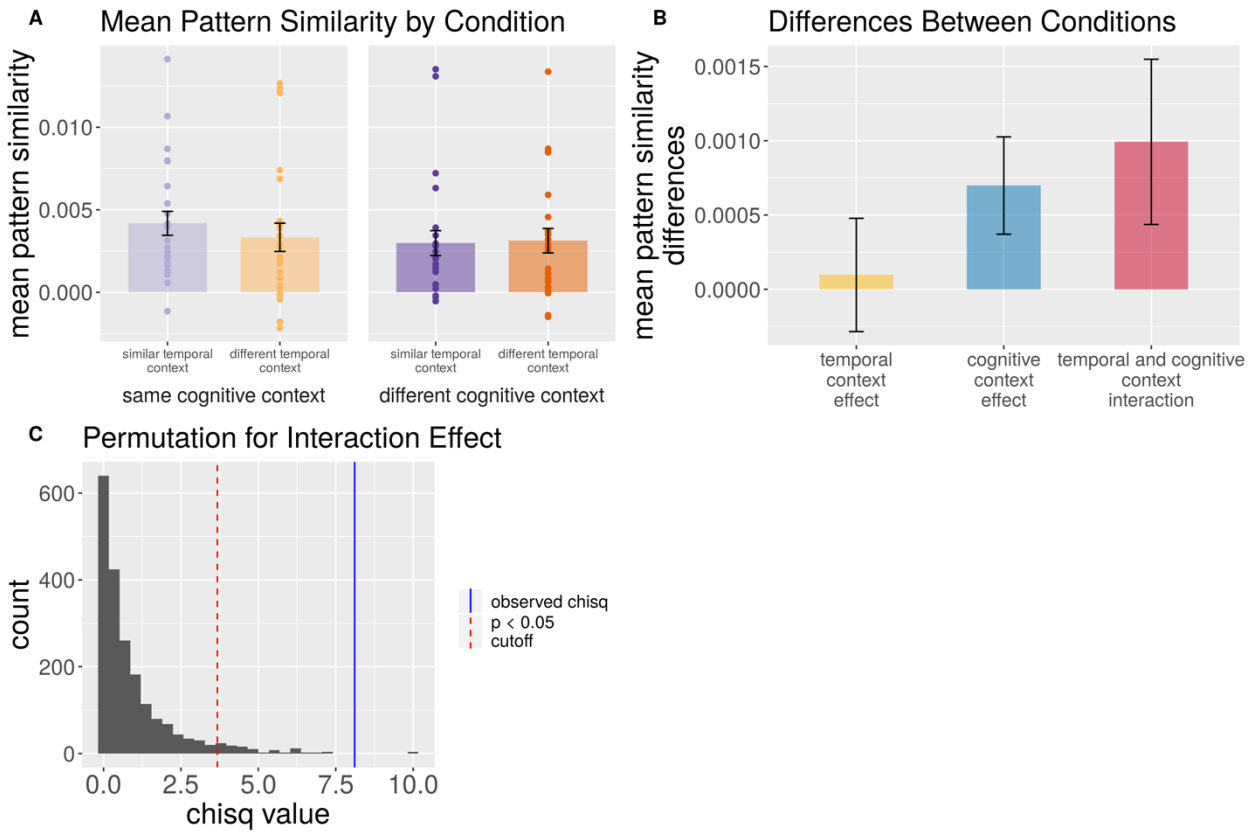

Figure 3. Pattern similarity values in CA23DG during memory retrieval carry information about temporal and cognitive encoding contexts. A. Mean pattern similarity scores, with scatter of individual subject observations for the combination of different encoding contexts. B. Differences between same/different list half ("similar" temporal context), same/different question (cognitive context), and the interaction of temporal and cognitive context ([same question, same list half – different question, same list half] – [same question, different list half – different question, different list half). C. Permuted chi-square values to determine significance of cognitive-by-temporal interaction.

fMRI Results: Medial Temporal Lobe (MTL) Neocortical Areas

Our next analyses investigated activity in MTL regions outside of the hippocampus. Previous work has suggested that regions in parahippocampal cortex (PHC) should process information about cognitive context (Diana et al., 2012, 2013; F. Wang & Diana, 2017). We first considered items from the same temporal encoding context (same versus different list). In aPHC, we found that PS with higher during retrieval of items associated with the same temporal encoding context (same list) as compared to items associated with different temporal contexts ($X^2(1) = 4.79$, $p^{perm1000}$ =

342 0.024, Supplemental Figure 1). No other neocortical regions varied their PS with respect
343 to the same temporal context (all $X^2 < 2.90$, all ps > 0.06). In aPHC, we also found that
344 PS was higher during retrieval of items associated with the same cognitive context
345 compared to items associated with different cognitive contexts ($X^2(1) = 5.92$, $p^{perm1000} =$
346 0.012, Supplemental Figure 2). There was a trend in the same direction (greater PS for
347 same versus different cognitive context) in PRC ($X^2(1) = 3.53$, $p^{perm1000} = 0.054$). PS in
348 pPHC did not vary with respect to cognitive context alone ($X^2(1) = 0.64$, $p^{perm1000} =$
349 0.44). In pPHC there was an interaction such that PS was greater for items that shared
350 a temporal context as well as a cognitive context but was lower when these items did
351 not share a cognitive context ($X^2(1) = 9.44$, $p^{perm1000} = 0.004$, Figure 4). No other regions
352 modulated their PS based on the combination of same temporal and cognitive contexts
353 (all $X^2 < 1$, all ps > 0.3).
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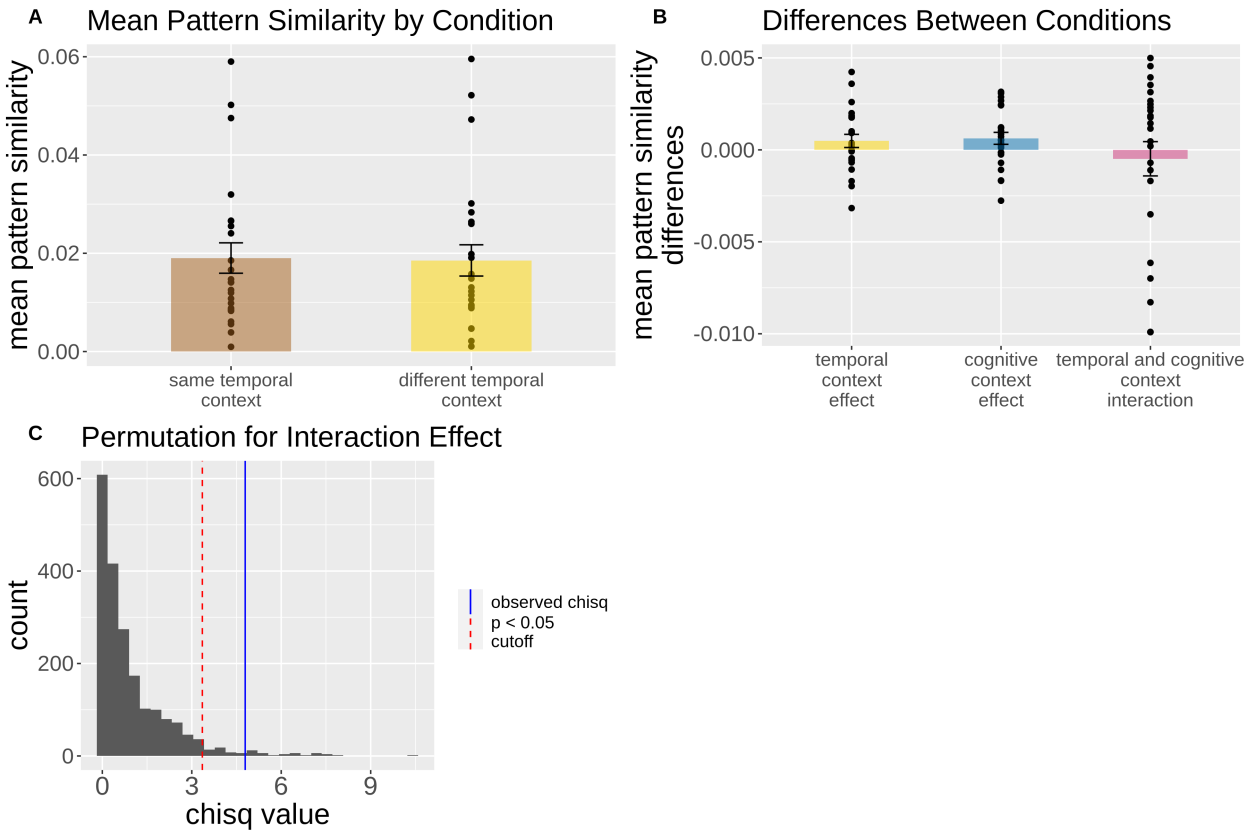
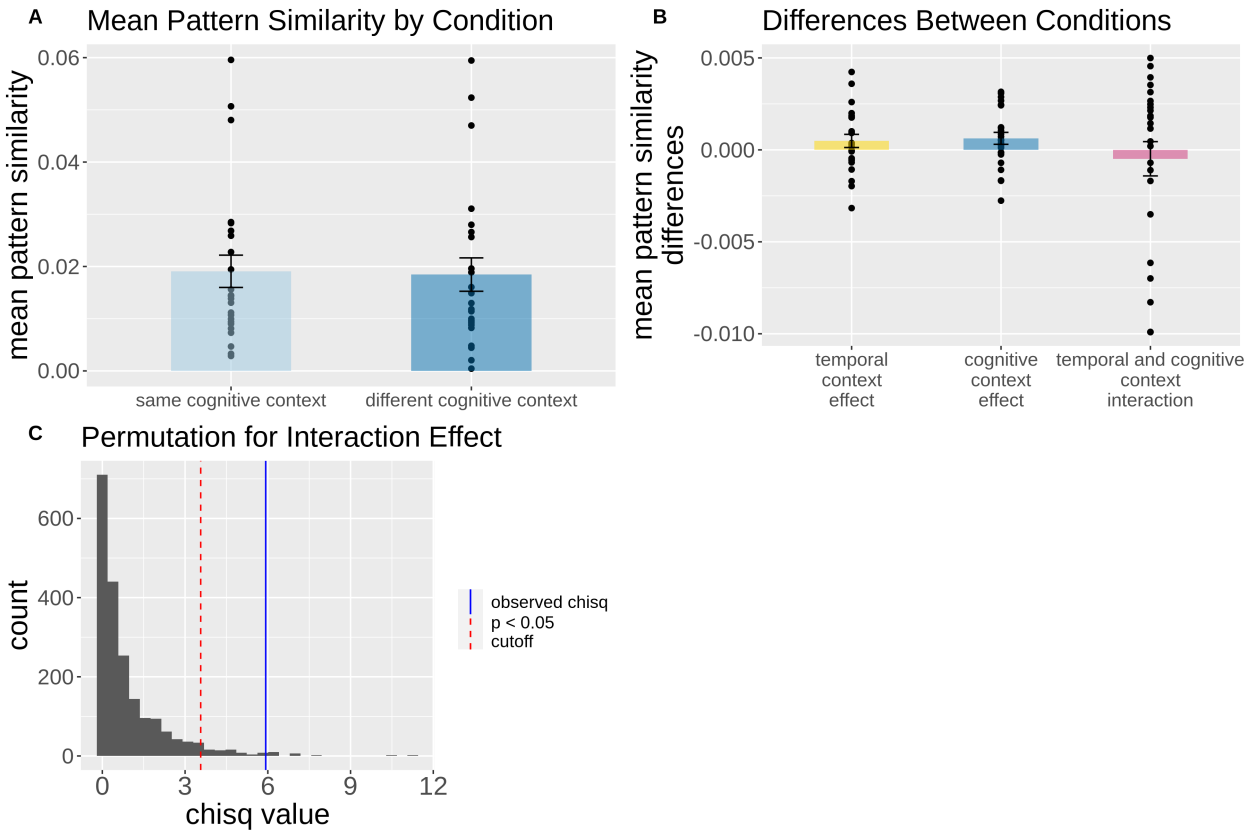


Supplemental Figure 1. Pattern similarity values in aPHC during memory retrieval carry information about the same temporal encoding context. A. Mean pattern similarity scores, with scatter of individual subject observations for same/different encoding context (list). B. Differences between same/different list (temporal context), same/different question (cognitive context), and the interaction of temporal and cognitive context ([same question, same list – different question, same list] – [same question, different list – different question, different list]). C. Permuted chi-square values to determine significance of same temporal context.



Supplemental Figure 2. Pattern similarity values in aPHC during memory retrieval carry information about the cognitive encoding context. A. Mean pattern similarity scores, with scatter of individual subject observations for same/different encoding question (cognitive context). B. Differences between same/different list (temporal context), same/different question (cognitive context), and the interaction of temporal and cognitive context ([same question, same list – different question, same list] – [same question, different list – different question, different list]). C. Permuted chi-square values to determine significance of cognitive context.

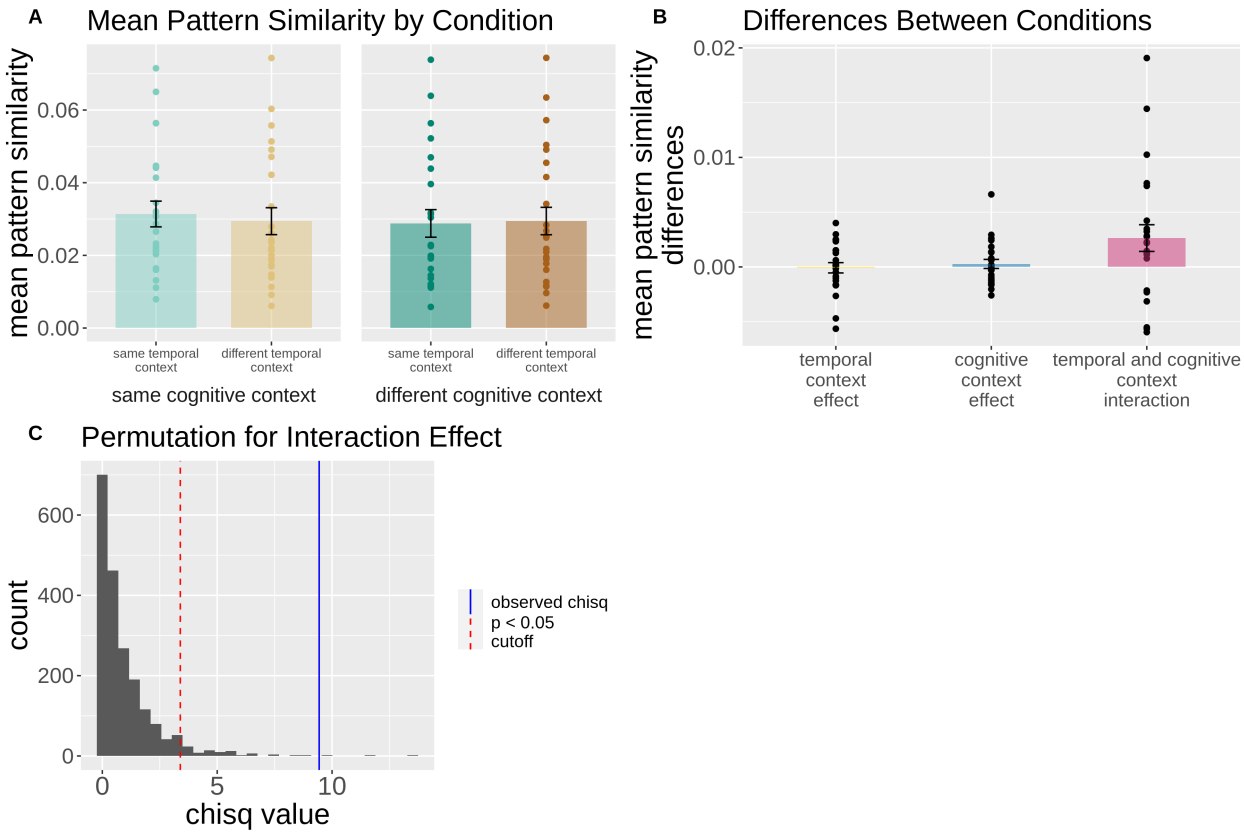
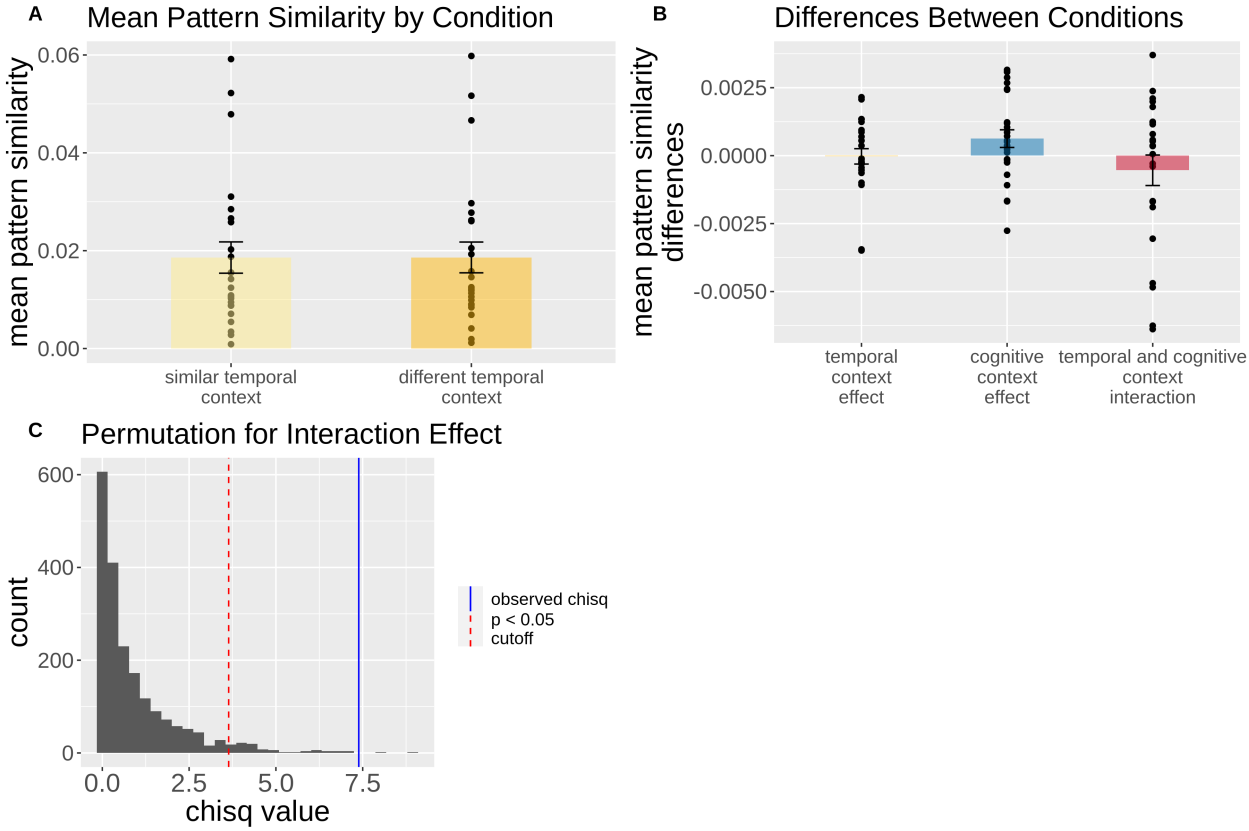


Figure 4. Pattern similarity values in pPHC during memory retrieval carry information about temporal and cognitive encoding contexts. A. Mean pattern similarities scores, with scatter of individual subject observations for the combination of different encoding contexts. B. Differences between same/different list (temporal context), same/different question (cognitive context), and the interaction of temporal and cognitive context ([same question, same list – different question, same list] – [same question, different list – different question, different list]). C. Permuted chi-square values to determine significance of cognitive-by-temporal interaction.

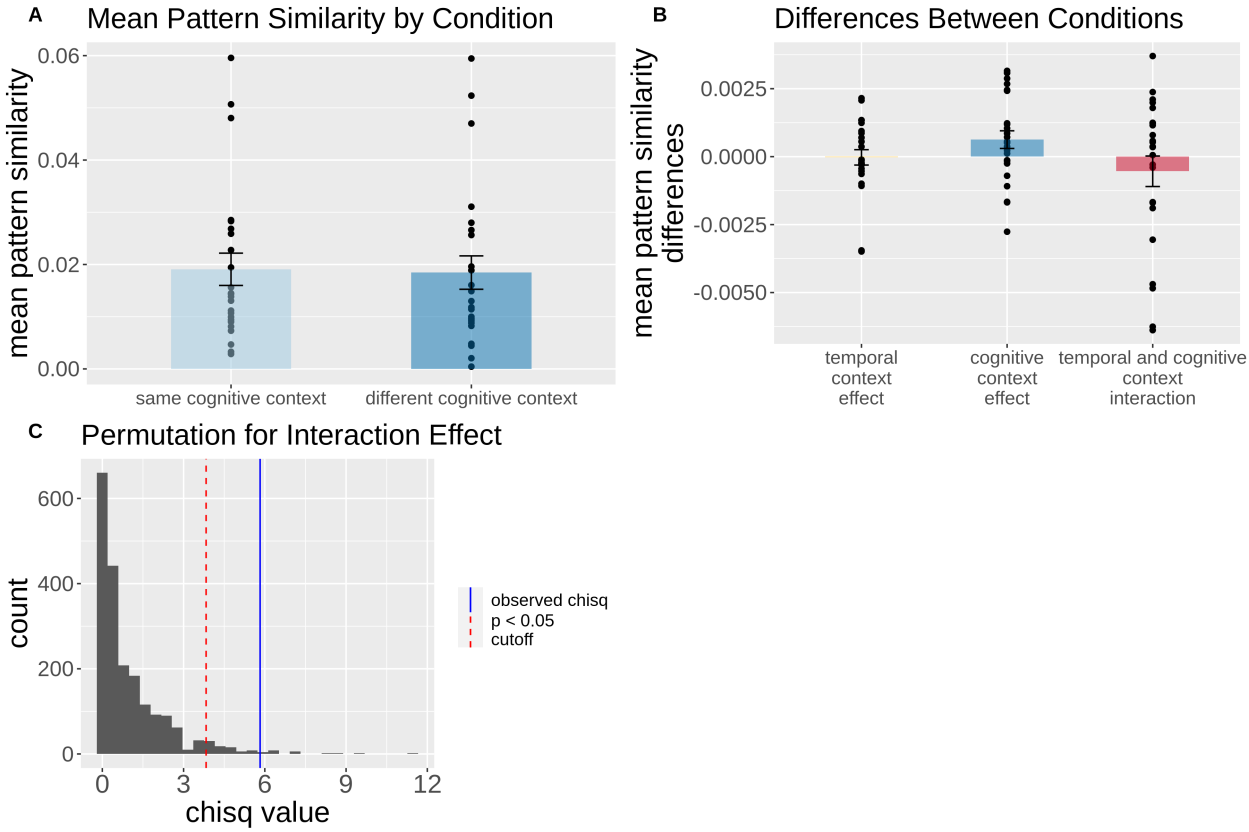
We next considered whether PS in MTL neocortical areas might depend on whether items shared a similar temporal context at encoding. In aPHC, we found that PS was higher during retrieval of items associated with a different temporal context as compared to items with similar temporal encoding contexts ($X^2(1) = 7.39$, $p^{perm1000} = 0.003$, Supplemental Figure 3). No other neocortical regions varied their PS with respect to similar temporal context (all $X^2 < 2.2$, all ps > 0.13). In aPHC, we also found that PS was higher during retrieval of items associated with the same cognitive context compared to items associated with different cognitive contexts ($X^2(1) = 5.83$, $p^{perm1000} =$

0.013, Supplemental Figure 4). There was a trend in the same direction (greater PS for same versus different cognitive context) in PRC ($X^2(1) = 3.55$, $p^{perm1000} = 0.051$). PS in pPHC did not vary with respect to cognitive context alone ($X^2(1) = 0.68$, $p^{perm1000} = 0.41$). In pPHC there was an interaction such that the effect of cognitive context was larger for items that were in similar temporal contexts (same half) than for items that were in different temporal contexts (different half) particularly when these items shared the same cognitive context ($X^2(1) = 4.67$, $p^{perm1000} = 0.029$, Figure 5). No other regions modulated their PS based on the combination of similar temporal and cognitive contexts (all $X^2 < 1.5$, all ps > 0.20).



Supplemental Figure 3. Pattern similarity values in aPHC during memory retrieval carry information about the similar temporal encoding context. A. Mean pattern similarity scores, with scatter of individual subject observations for similar temporal contexts (list half). Although pattern similarity values were very close in magnitude, there was a small

but reliable effect such that pattern similarity values for items studied in different list halves were greater than for items in the same half of lists. B. Differences between same/different list half (temporal context), same/different question (cognitive context), and the interaction of temporal and cognitive context ([same question, same list half – different question, same list half] – [same question, different list half – different question, different list half]). C. Permuted chi-square values to determine significance of similar temporal context.



Supplemental Figure 4. Pattern similarity values in aPHC during memory retrieval carry information about the cognitive encoding context. A. Mean pattern similarity scores, with scatter of individual subject observations for same/different encoding question (cognitive context). B. Differences between same/different list half (temporal context), same/different question (cognitive context), and the interaction of temporal and cognitive context ([same question, same list half – different question, same list half] – [same question, different list half – different question, different list half]). C. Permuted chi-square values to determine significance of cognitive context.

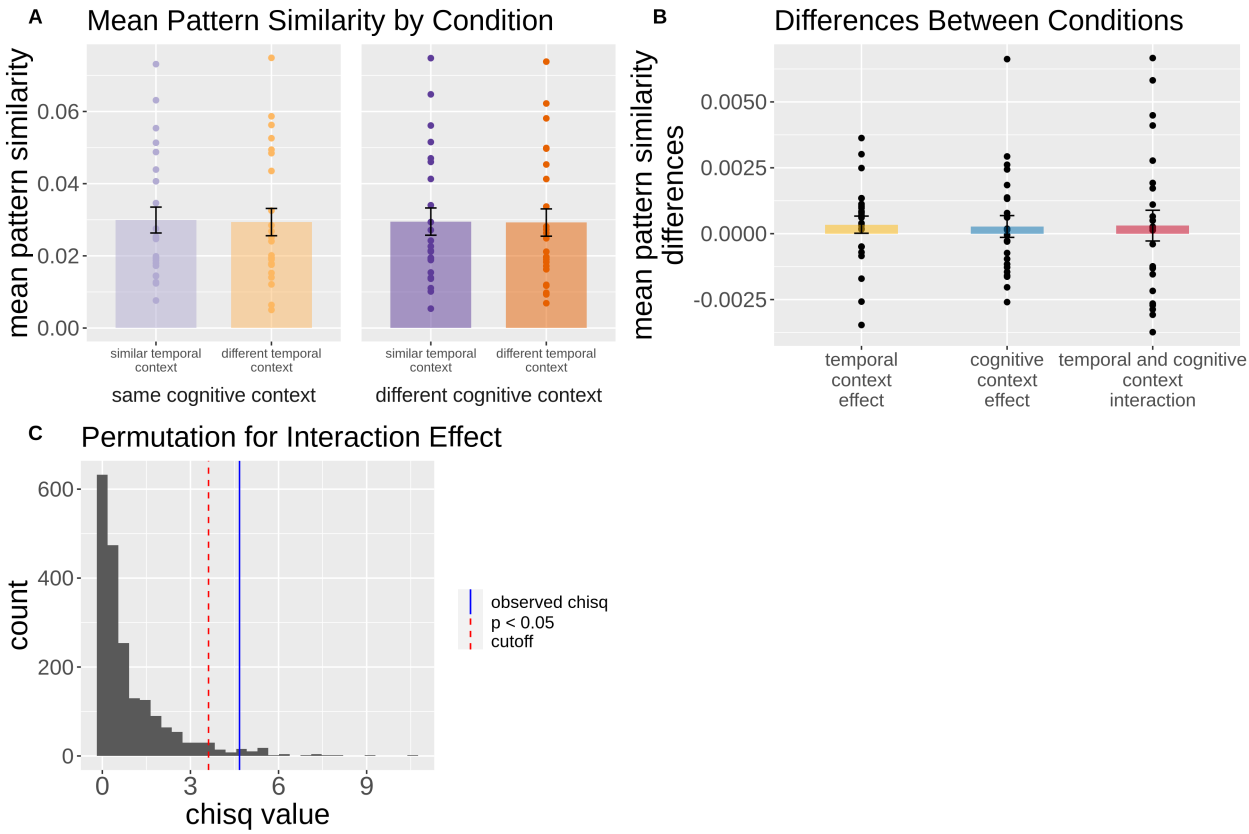


Figure 5. Pattern similarity values in pPHC during memory retrieval carry information about similar temporal and cognitive encoding contexts. A. Mean pattern similarities scores, with scatter of individual subject observations for the combination of different encoding contexts. B. Differences between same/different list half (temporal context), same/different question (cognitive context), and the interaction of temporal and cognitive context ([same question, same list half – different question, same list half] – [same question, different list half – different question, different list half]). C. Permuted chi-square values to determine significance of cognitive-by-similar temporal interaction.

Discussion.

The goal of the present study was to test the extent to which the hippocampus represents absolute temporal information and information about particular cognitive states during recollection of past events. Although cognitive states typically fluctuate over time in a continuous manner, the design of our experiment allowed us to examine the influence of these two aspects of context separately. We found that, during recollection of a study item, CA23DG activity patterns carried information about the cognitive context associated with that item during the study phase. Additionally,

cognitive context information evident in CA23DG activity patterns varied over a coarse timescale, such that pattern similarity was highest for pairs of items that were associated with similar temporal and cognitive contexts. Collectively, these findings demonstrate that the hippocampus represents information about past events in a manner that is consistent with temporal context models (Howard et al., 2014; Howard & Kahana, 2002; Manning, 2019; Norman et al., 2008; Polyn et al., 2009; Ranganath, 2019; Sederberg et al., 2008; Shankar & Howard, 2010, 2012).

We have long understood that context is central for recall (Clewett & Davachi, 2017; Davachi & DuBrow, 2015; Zacks & Swallow, 2007) and recollection-based recognition (Eichenbaum et al., 2007), but we do not yet understand how *temporal* context may be encoded in the brain. These representations of temporal and cognitive state contexts seem to rely on the hippocampus (Eichenbaum, 2017; Ranganath, 2019). In the hippocampus, one candidate mechanism is the coordinated firing of self-organized cell assemblies, or time cells (Lisman & Jensen, 2013; Y. Wang et al., 2015). These cells can track how long an animal has been running on a treadmill where distance, speed, and duration of run time can be decorrelated (Kraus et al., 2013, 2015; Salz et al., 2016), code for meaningful gaps or pauses (MacDonald et al., 2011), and represent ordered sequences and experiences even during rest periods (Pastalkova et al., 2008). Hippocampal ensembles also drift in their representations of space when recorded across days, thus it seems that they can encode both fine and coarse temporal information (Mankin et al., 2012, 2015; Rubin et al., 2015; Ziv et al., 2013). These findings provide evidence for the idea that hippocampal neurons may encode information about temporal intervals or the passage of time. That said, available

evidence indicates that hippocampal time cells are highly sensitive to changes in task context. In one such demonstration, immobilized rats learned to maintain information about specific odors across a delay period (MacDonald et al., 2013). Results showed that different cell assemblies encoded temporal intervals across the delay period depending on the odor that was to be maintained. In other words, changes in the task context led to substantial changes in the neural ensembles that encoded temporal information during the task.

In the present study, we found evidence for the idea that information about cognitive states (i.e., specific task contexts) was carried in hippocampal activity patterns during recollection, and that these patterns also carried relatively coarse-grained information about the temporal context in which the recollected item was initially encountered (see also (DuBrow et al., 2017) for evidence that contexts can drift slowly). This is consistent with the scale of temporal information participants had access to behaviorally; they were poor at retrieving the exact list an item had been in but had access to information about in which half of the study lists it had occurred. These findings are generally in line with what would be predicted by cognitive models of the representation of temporal context in episodic memory. Initial theories operationalized temporal context as random fluctuations in cognitive states over time (Estes, 1955), and subsequent theories have incorporated the assumption that temporal context also reflects a time-weighted average of recently processed items and experiences (Howard & Kahana, 2002; Norman et al., 2008; Sederberg et al., 2008). These models would predict that activity patterns during memory retrieval should reflect information about the temporal context associated with each study item (e.g., Manning et al., 2011; Deuker et

490 al., 2016; Nielson et al., 2015). The Context Maintenance and Retrieval (CMR) model
491 goes farther by incorporating information about the current task or cognitive state into
492 the temporal context representation. CMR predicts that if there are abrupt changes in
493 one's cognitive state (e.g., a change in the task that one is performing), items that are
494 temporally proximal can actually have distinct contextual associations (Polyn et al.,
495 2009). Thus, the CMR model predicts that, during memory retrieval, reinstatement of
496 temporal context should reflect a conjunction of task-related information and information
497 that reflects elapsed time, similar to what was observed in CA23DG and pPHC. Though
498 CMR most explicitly incorporates semantic relationships into the temporal context
499 model, we suggest that contextual associations associated with task or cognitive states
500 likely tap into a similar mechanism. Moreover, the model suggests that changing tasks
501 during encoding would break up the temporal context representation during encoding of
502 each list. This prediction is consistent with the fact that we did not see evidence of high
503 pattern similarity across items within the same list, and instead only saw representation
504 of temporal information across coarser timescales.

505 At a broader level, our findings converge with results from a number of recent
506 studies showing that hippocampal activity patterns carry information that generalizes
507 across events that share common elements (Horner et al., 2015; Schlichting & Preston,
508 2015). Here, we found that activity patterns in the CA23DG subregion generalize across
509 items that shared both temporal and task context. Other findings, however, suggest that
510 hippocampal representations can amplify differences between overlapping experiences
511 (Chanales et al., 2017; Libby et al., 2018; Ritvo et al., 2019; Yassa & Stark, 2011). One
512 potential cause of the divergence of results in CA23DG across studies is that human

513 functional imaging aggregates patterns across CA3 and DG due to current limitations of
514 fMRI (Chen et al., 2011; Copara et al., 2014; Dimsdale-Zucker et al., 2018; Ekstrom et
515 al., 2009; LaRocque et al., 2013; Stokes et al., 2015) CA3 and DG have separately
516 been tied to pattern completion (Guzowski et al., 2004; Kesner & Rolls, 2015; Treves &
517 Rolls, 1994; Vazdarjanova & Guzowski, 2004; Yassa & Stark, 2011) and separation
518 (Hasselmo & Wyble, 1997; Kesner & Rolls, 2015; Redish, 1999; Yassa & Stark, 2011).
519 Thus, it may be the case that by averaging their activity patterns together, we are
520 blurring the true underlying signal. Though this methodological caveat could explain
521 some patterns of results, we suggest that differences in the cognitive demands of the
522 tasks used may also be relevant to consider. A further complication is that there may be
523 divergence in function along the proximal/distal axis of CA3 itself suggesting that even
524 CA3 alone has the computational circuitry to perform both pattern separation and
525 completion operations (Lee et al., 2020).

526 In one recent study, for instance, we found that CA23DG activity patterns during
527 memory retrieval were more different for across pairs of items that were associated with
528 the same episodic context (i.e., objects seen within the same movie) than across pairs
529 of items that were associated with different contexts. In addition, a recent report using
530 ultra-high resolution fMRI that could isolate CA3 from DG found evidence for greater
531 reinstatement of encoding activity patterns in CA3 when retrieving items associated with
532 coherent, as compared to partially-overlapping, events (Grande et al., 2019). The
533 findings of Dimsdale-Zucker et al. (2018), considered alongside the present results,
534 raise an important question: When does CA23DG assign similar or distinct
535 representations to overlapping events?

To answer this question, it may be informative to consider the conflicting role of shared context in facilitating inter-item relationships (Sederberg et al., 2010) while diminishing item distinctiveness (El-Kalliny et al., 2019). During recognition memory tests, people are generally more likely to recollect events that were distinctive than events that were overwhelmingly similar to one another (Hunt, 1995). If CA23DG represents information about one's cognitive state during an event, then we would expect that this area would be most likely to support successful recollection when those representations are distinctive. In the present study, changes in the encoding task encouraged participants to shift cognitive states abruptly across items within a list. By attending to the task context, a participant could form distinctive memories for the different items that were in the same list. In our previous study (Dimsdale-Zucker et al., 2018), however, participants studied lists of items presented in virtual reality videos that depicted navigation through two homes. Thus, the environmental context was overwhelmingly similar across items in the same list, and the cognitive context was not explicitly controlled (i.e., cognitive context likely tracked with environments and the passage of time). To successfully encode items from the study phase, participants needed to form representations that highlighted the distinctive aspects of each item in the list in order to overcome contextual interference at the time of retrieval (Park, Arndt, & Reder, 2006). We therefore propose that, by binding information about items with information about cognitive contexts, CA23DG can support successful retrieval of overlapping memories that would otherwise be difficult to disambiguate (Yassa & Reagh, 2013).

Our findings also highlight the relative paucity of direct access to memory for temporal context at retrieval. Behavioral measures of memory for temporal context show clustered recall; that is, items studied nearer in time to one another are more likely to be recalled close together (Kahana, 1996). These findings suggest that, during episodic memory retrieval, people may be mentally transported back to a past cognitive state (Manning et al., 2011; Tulving, 1983). Yet, when people are explicitly asked about temporal order information, they often cannot produce reliable estimates (Jenkins & Ranganath, 2010). In the present study, we also found that participants had little explicit access to an item's temporal encoding context. When asked to choose in which of eight lists an item had been studied, participants were essentially at chance. This is not surprising because temporal context models only suggest that memories for temporally proximal events should be associated with similar context representations, but retrieval of context information would not automatically enable a person to determine the exact time at which a previous item was encountered. There is considerable evidence to suggest that people rely on heuristics strategies in order to roughly reconstruct the time at which an event took place (Friedman, 1993). In our study, this might have been more challenging because, as we have stated above, changes in cognitive context within a list most likely disrupted the continuity of temporal context representations (for a related finding, see (Polyn et al., 2009)).

In addition to the hippocampus, medial temporal lobe cortical regions have also been implicated in representing context. A substantial body of work has suggested a particular role for parahippocampal cortex in supporting representations of context (Davachi, 2006; Diana et al., 2007, 2013; Hsieh et al., 2014; Tubridy & Davachi, 2011;

F. Wang & Diana, 2017). In line with these findings, we also saw that parahippocampal cortex carried information about cognitive and temporal contexts as well as their conjunction both for same and similar temporal contexts. Recent work has also suggested a role for lateral entorhinal cortex in absolute representations of time (Bellmund et al., 2019; Montchal et al., 2019; Sugar & Moser, 2019). Unfortunately, we could not assess whether lateral entorhinal cortex represented elapsed time because our scanning protocol was not optimized for entorhinal cortex coverage, and the temporal signal-to-noise ratio was therefore insufficient. Thus, it is possible that in this task where participants had access to both a sense of ongoing time and fluctuating cognitive states, hippocampus and entorhinal cortex could play complementary roles.

Taken together, we have shown that activity patterns in the CA23DG region of the human hippocampus reflected an integrated representation of cognitive and coarse temporal contexts. This finding can help explain how we represent continuously unfolding episodes in a changing world. Outside of the laboratory, we are constantly multitasking between competing goals and responsibilities. The hippocampus, and, specifically CA23DG, may allow us to differentiate between experiences that are associated with different tasks while preserving the temporal flow between experiences.

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