CA1 and CA3 differentially support spontaneous retrieval of episodic contexts within human hippocampal subfields

Halle R. Dimsdale-Zucker, Maureen Ritchey, Arne D. Ekstrom, Andrew P. Yonelinas, Charan Ranganath

Abstract

The hippocampus plays a critical role in supporting spatial and episodic memory. Mechanistic models predict that the hippocampal subfields have computational specializations that support memory in different ways. However, there is little empirical evidence to suggest substantial differences between the subfields, particularly in humans. To clarify how hippocampal subfields support human spatial and episodic memory, we used multivariate analyses of high-resolution functional magnetic resonance imaging (fMRI) data from a novel virtual reality paradigm. Multi-voxel pattern similarity analyses revealed that CA1 represented items that shared an episodic context as more similar than those from different episodic contexts. CA23DG showed the opposite pattern, leading to a subfield-by-condition interaction. The complementary characteristics of these subfields explain how we can parse our experiences into cohesive episodes while retaining the specific details that support vivid recollection.

Main text

Considerable evidence suggests that the hippocampus is essential for episodic memory and plays a particular role in binding information about items and the context in which they were encountered (Davachi, 2006; Eichenbaum, Yonelinas, & Ranganath, 2007; Knierim, Lee, & Hargreaves, 2006). Most mechanistic models suggest that the hippocampal subfields play complementary roles in the representation of episodic context (Kesner & Rolls, 2015). Although these models would lead to the expectation of large differences between coding in CA1 and CA3, between-subfield differences at the level of single-units in rodents and in overall activity in human fMRI studies have been relatively modest. Indeed, both CA1 and CA3 have been implicated in representations of temporal (Kraus, Robinson, White, Eichenbaum, & Hasselmo, 2013; Salz et al., 2016) and spatial (Kyle, Smuda, Hassan, & Ekstrom, 2015; Lee, Jerman, & Kesner, 2005) contextual information. Leutgeb and Leutgeb (2007) argued that the different computations supported by CA3 and CA1 should be most apparent when one analyzes the population-level activity patterns elicited by different contexts—whereas CA3 should differentiate between specific experiences in the same context, CA1 should globally differentiate between different contexts.

Here, we used high-resolution fMRI and multivariate analysis methods to test how different hippocampal subfields contribute to representations of spatial and episodic context. We designed a virtual reality environment consisting of two houses (spatial contexts; Figure 1). After becoming familiarized with the spatial layouts of each house, participants viewed a series of 20 videos (episodic contexts) depicting first-person navigation through each house while they encountered a series of objects. Each object was studied only once; it was uniquely placed in a single house that was shown in a single video. We scanned participants while they performed an item recognition test that required them to differentiate between studied and novel objects. Although the items were displayed without any contextual information, based on cognitive models of recognition memory and models of human hippocampal function, we predicted that recollection-based item recognition should trigger reactivation of information about the context in which that item was encountered (Davachi, 2006; Eichenbaum et al., 2007).

Accordingly, we tested whether multi-voxel patterns elicited during item recognition carried information about the associated spatial (house) or episodic (same house and video) context.

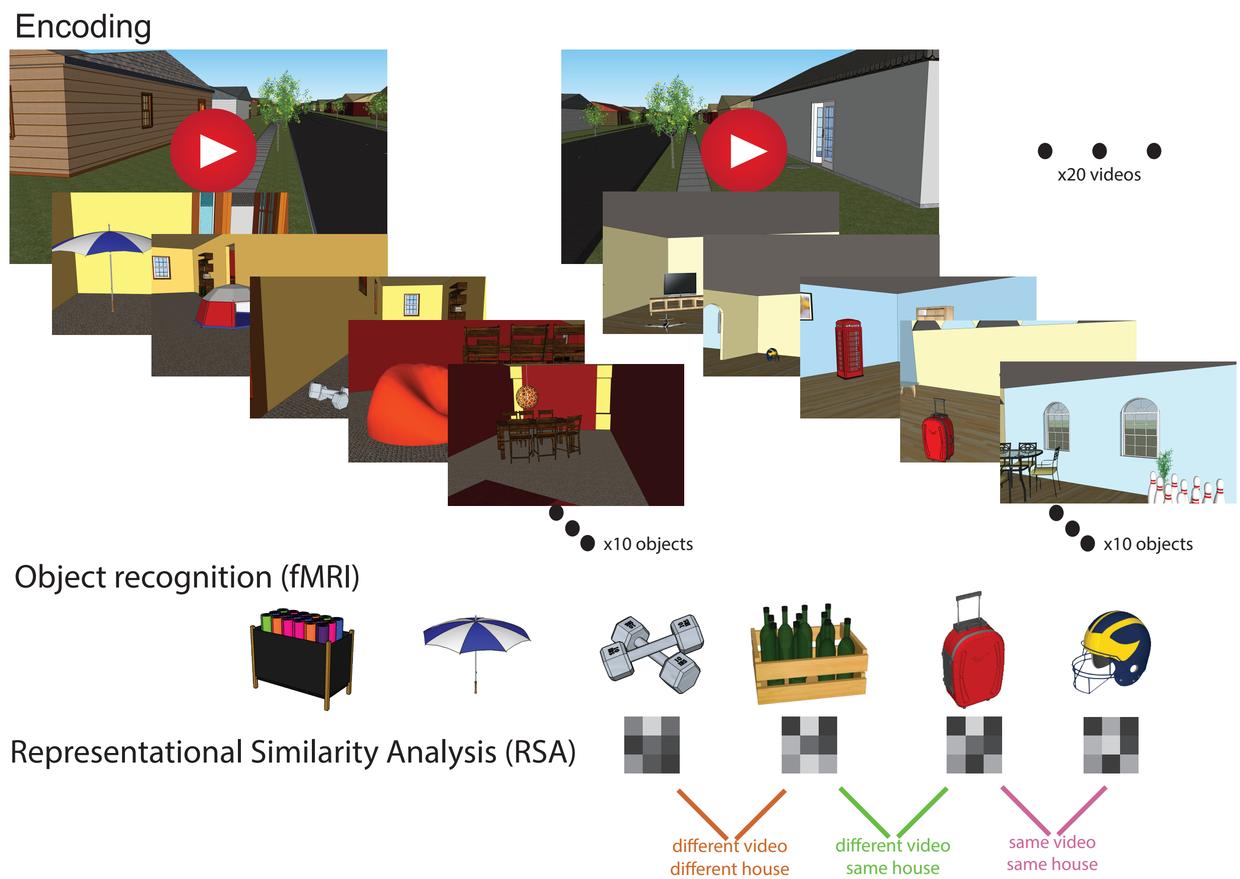

Figure 1. Experimental Approach. During encoding, participants studied objects uniquely located within one of two spatial locations (Spatial Contexts) across a series of 20 videos (Episodic Contexts). At object recognition (scanned), participants made a memory judgment (remember/familiar/new) to old and new objects presented without any contextual information. We used representational similarity analyses to compare the voxel patterns for each object to other objects that had been studied in the same (or different) house or video.

Recognition data collected in the scanner indicated high rates of recollection for studied items (mean “Remember” hit rate = 0.68 [SD = 0.17]; Supplemental Table 1). These subjective ratings were corroborated by high hit rates on the post-scan context memory test (mean context memory hit rate = 0.71 [SD = 0.11]; Supplemental Results). Consistent with previous studies, univariate fMRI analyses revealed that hippocampus was more active for correctly recollected items than familiar or missed items (Supplemental Figure 2A). Having established hippocampal recruitment for item recollection, we proceeded to investigate whether hippocampal activity patterns carried information related to spontaneous retrieval of spatial and episodic contexts for these recollected trials.

As shown in Figure 1, we estimated single-trial multi-voxel patterns within regions of interest (ROIs) corresponding to CA1 and a combined CA2/CA3/dentate gyrus (CA23DG) subregion within the body of hippocampus. Specifically, we computed voxel pattern similarity (PS) between trial pairs for recollected items that shared the *same episodic context* (i.e., same-video/same-house), shared the *same spatial context* but different episodic contexts (different-video/same-house), or were associated with *different episodic and spatial contexts* (different-video/different-house). To maximize the likelihood of identifying trials that were associated with successful context retrieval, we restricted analyses to trials that were associated with correct recollection-based item recognition *and* correct identification of spatial context (house) in the post-scan context memory test.

To test whether regions carried information about an item's encoding context, we fitted a mixed model with a random effect of subject (Gordon, Rissman, Kiani, & Wagner, 2014) testing for effects of ROI (CA1, CA23DG), Context Similarity (same episodic, same spatial, different context), and Hemisphere (left, right), as well as their interactions on PS values. There was a significant ROI x Context Similarity x Hemisphere interaction

($\chi^2(2) = 13.30$, $p = 0.001$). Follow up analyses revealed that this was driven by a reliable interaction between ROI and Context Similarity in left ($\chi^2(2) = 15.64$, $p < .001$) but not right ($\chi^2(2) = 1.65$, $p = 0.44$) hemisphere. This finding indicates that left CA1 and CA23DG were differentially sensitive to Context Similarity. To further break down this interaction, we conducted separate analyses restricted to left hemisphere in our ROIs to assess representation of Context Similarity.

To investigate whether regions carried information about an item's spatial encoding context, we compared PS values for items that had been studied in the same house or different house. In the same house condition, we eliminated trial pairs that had been studied within the same video to ensure that any observed effects could uniquely be attributed to Spatial Context Similarity and not Episodic Context Similarity. Based on traditional models (Kesner & Rolls, 2015; Marr, 1971), we expected to see greater PS for same-house as compared to different-house pairs in CA23DG but not in CA1. As can be seen in Figure 2, neither CA23DG ($\chi^2(1) = 0.08$, $p = 0.78$) nor CA1 ($\chi^2(1) = 0.03$, $p = 0.86$) systematically differed in their representation based on an item's spatial context. These results indicate that neither CA1 nor CA23DG were differentially sensitive to Spatial Context Similarity alone.

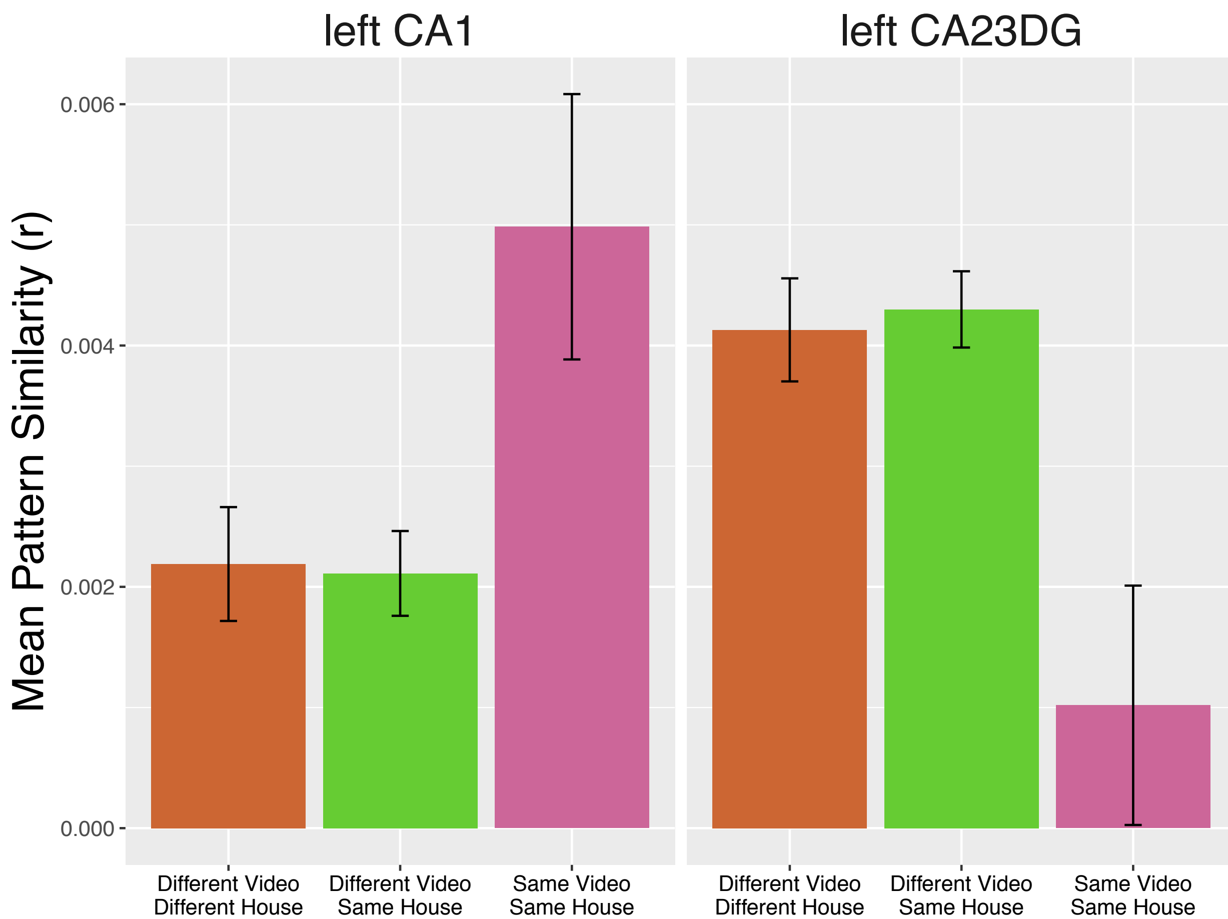

Figure 2. Neural pattern similarity for spatial and episodic contexts. Pattern similarity was higher in left CA1 for items studied in the same episode (Same Video Same House) than for items in different episodes (Different Video Same House). Left CA23DG showed a reversal of this pattern such that pattern similarity was higher for items studied between episodes versus within the same episode. Neither CA1 nor CA23DG patterns were sensitive to spatial context similarity.

To investigate whether activity patterns in hippocampal subfields carried information about episodic context, we compared PS values for items that were studied in the same video (which necessarily meant that that the items had also been studied in the same spatial context) against items that were studied in different videos that depicted the same spatial context. Some models (Kesner & Rolls, 2015; Leutgeb & Leutgeb, 2007) predict that CA1 should treat items from the same episodic context as more similar to one another than CA23DG. Indeed, in CA1, activity patterns were more similar across pairs of items from the same episodic context than across pairs from different episodes ($\chi^2(1) = 6.50$, $p = 0.01$). Intriguingly, CA23DG showed the reverse pattern; that is, PS was significantly *lower* for items in the same episode than for items in different episodes ($\chi^2(1) = 10$, $p = 0.002$). We observed a significant interaction, ($\chi^2(1) = 15.45$, $p < .001$; Figure 2), indicating that the PS profiles of CA1 and CA23DG were qualitatively different for Episodic Context Similarity. Control analyses that matched the number of trials across conditions revealed consistent results, ruling out the possibility that this effect can be explained by differing numbers of trial pairs in each condition.

Our results reveal striking differences in retrieval of contextual information across the hippocampal subfields and provide a rare statistical dissociation between CA1 and CA23DG. In CA1, PS was *higher* when recollecting items encountered in the same episodic context (same video) than for items associated with different episodic contexts (different videos); in CA23DG, PS was *lower* when recollecting items encountered in the same episodic context than when recollecting items from different episodic contexts. These results are consistent with the idea that CA1 represents global contextual regularities across items ("pattern completion"), whereas CA23DG exaggerates differences between items that have competing associations within the same episodic context ("pattern separation"). Together, CA1 and CA23DG can play complementary roles in supporting episodic memory by allowing one to remember specific items, as well as their relationships, within a shared context.

Differences between the subfields are a prominent component of models of subfield function (Kesner & Rolls, 2015; Leutgeb & Leutgeb, 2007), which, in turn, are based on anatomical differences in the inputs, connections, and firing properties of the subfields. Studies in rodents have reported different effects of lesions (Farovik, Dupont, & Eichenbaum, 2010; Ji & Maren, 2008) and in population-level coding (Gusev, Cui, Alkon, & Gubin, 2005; Lee, Rao, & Knierim, 2004; Leutgeb & Leutgeb, 2007) between CA3 and CA1 for representations of both spatial and non-spatial contextual information. However, we are not aware of any prior findings in humans that have reported dissociations between the roles of CA1 and CA23DG during spontaneous retrieval of contextual information.

One previous human fMRI study reported a statistical dissociation between CA1 and CA23DG as participants monitored the spatial layouts of cities that varied in similarity (Stokes, Kyle, & Ekstrom, 2015). Stokes et al. found that CA23DG represented cities with the same layout as more similar than cities with different layouts whereas CA1 was not sensitive to the change in layouts (Stokes et al., 2015). One critical difference between their study and ours is that Stokes et al. (2015) directly assessed memory for spatial layouts whereas we assessed incidental retrieval of contextual information during item recognition. Our results challenge traditional notions that CA3 is particularly sensitive to changes in spatial contexts (Leutgeb & Leutgeb, 2007; Stokes et al., 2015) in that we did not see a difference in pattern similarity for items that were studied within the same spatial context or between spatial contexts.

The present results converge with other findings (Kyle, Smuda, et al., 2015) in showing that, when spatial information alone is insufficient to resolve context, spatial information does not drive representations within CA3. Our findings also accord with

Leutgeb and Leutgeb's (2007) proposal that, through rate remapping, CA3 can differentiate between different sensory cues that are encountered in the same place.

Our findings dovetail with extant evidence that CA1 plays a critical role in representing time (Kraus et al., 2013), in representing sequences of ordered information (Allen, Salz, McKenzie, & Fortin, 2016; Farovik et al., 2010), and in using this temporal information to define episodes (Wang & Diana, 2016) under demands that mimic a realistic, real-world episodic context. Additionally, our findings support the idea that CA1 is critical for distinguishing similar temporal contexts (Kesner & Rolls, 2015), given that we saw greater pattern similarity in CA1 for items within the same episode as compared with those that occurred between episodes.

The fact that CA23DG showed lower neural similarity for items encountered during the same episode as compared to items encountered during different episodes seems at odds with theories proposing a critical role for CA3 in episodic memory retrieval (Kesner & Rolls, 2015). Examined more closely, however, the results align with recent findings indicating that the hippocampus differentiates between related information in an episode (Chanales, Oza, Favila, & Kuhl, 2017; Favila, Chanales, & Kuhl, 2016; LaRocque et al., 2013; Schlichting, Mumford, & Preston, 2015). For instance, building on the theory of Marr (1971), it has been argued that dentate gyrus and CA3 work together to distinguish related information (i.e., "pattern separation"). Our finding that CA23DG is more likely to individuate items within an episode—resulting in lower neural similarity—is consistent with the idea that CA3 pushes apart representations of similar items that were encountered in the same episode (see also

(Kim, Norman, & Turk-Browne, 2017; Kyle, Stokes, Lieberman, Hassan, & Ekstrom, 2015; Schapiro, Kustner, & Turk-Browne, 2012) for related findings).

Another possibility is that the coding scheme of CA3 may be flexible based on the elements that have priority in the task (Guzowski, Knierim, & Moser, 2004). Successful performance on our task requires one to differentiate between representations of items encountered in the same video. However, if we could construct a task in which there were lower demands to orthogonalize item-specific features, we might expect CA3 to show a representational scheme more consistent with pattern completion. That is, we would expect CA3 to show increased similarity for items in the same context relative to items encountered in different contexts. Emerging evidence suggests that CA3 can represent commonalities between mental states (Aly & Turk-Browne, 2016), but it remains to be seen whether, under task conditions emphasizing similarities among items, what coding scheme CA3 would adopt.

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