



Research report

Roles of human hippocampal subfields in retrieval of spatial and temporal context



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HIGHLIGHTS

- We probe spatial and temporal order memory retrieval within the human hippocampus.
- We employ high-resolution imaging to visualize subfields of the hippocampus.
- Multiple hippocampal subfields involved in retrieving spatial and temporal context.
- Hippocampal similarity shows unique patterns for spatial and temporal distance.

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ABSTRACT

While numerous studies indicate the involvement of the hippocampus in encoding and retrieval of spatial and temporal context, the neural basis of spatial and temporal processing within the hippocampal circuit remains unclear. We employed a novel paradigm in which participants encoded stores within a spatial layout by visiting them in a specific temporal order. Participants then underwent high-resolution functional magnetic resonance imaging (fMRI) targeting the hippocampus while retrieving details of the spatial or temporal context in alternating blocks. During retrieval, participants made judgments about either near or far intervals within the spatial layout or temporal sequence. Across both near and far intervals, we found that retrieving spatial layout and temporal order information resulted in comparable levels of activation in the hippocampus that was not preferentially localized to a specific subfield. Furthermore, using a multivariate approach called multivariate pattern similarity analysis (MPSA), we found that correct near judgments vs. correct far judgments differed in their patterns of activity for spatial vs. temporal order judgments. Despite these differences in MPSA patterns, we did not find any specific subfields differentially recruited for spatial vs. temporal order retrieval. We discuss our results in terms of their relation to computational models of hippocampal subfield function and suggest mechanisms by which the hippocampus could process space and temporal order without the need for specific contributions from hippocampal subfields.

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1. Introduction

Details regarding where and when an event occurred form critical parts of our episodic memory [1–4]. For example, where we were or what time we met a friend that day often serve as potent cues for remembering what we had for dinner last night. As part of its role in storage and retrieval of episodic memories [3,5–8], recent

evidence strongly implicates the hippocampus and surrounding cortices in processing spatial and temporal context. Lesion evidence suggests the human medial temporal lobes support aspects of processing both spatial and temporal details of recently learned information [9,10]. fMRI evidence demonstrates hippocampal and parahippocampal involvement, as indexed by increases in the BOLD signal, during encoding and retrieval of spatial [11–15] and temporal [16,17] context. Paradigms involving retrieval of both spatial and temporal context similarly demonstrate hippocampal involvement [18–22]. Finally, recent evidence suggests that the hippocampus contains not only ‘place cells,’ but also ‘time cells,’ [4,23–26]. Yet while there is fairly broad consensus that the hippocampus is

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important for storing and retrieving spatial and temporal context as part of episodic memory, the exact manner in which it processes spatial and temporal context remains unknown.

The hippocampus is comprised of cytoarchitecturally distinct subfields, the dentate gyrus, CA3, CA1, and the subiculum. While several past studies have suggested the importance of hippocampal subfields to human episodic memory, particularly CA3 and CA1 [27–29], pinpointing their contributions to spatial and temporal episodic memory remains an important challenge. Gilbert et al. [30], for example, found a double dissociation in deficits for spatial distance discriminations (distinguishing two object-location pairs on a grid from the previous sample phase) and spatial temporal order discriminations (distinguishing two maze arms based on their presentation order from the previous sample phase) following DG and CA1 lesions. The authors concluded differential subregion involvement for spatial and (spatial) temporal processing [30]. An equivalent subfield distinction for spatial vs. temporal processing, however, has yet to be reported in the human fMRI literature [21,22]. Azab et al. found that judgments about spatial arrays and temporal order of presentation resulted in comparable levels of adaptation across hippocampal subfields. Similarly, Copara et al. found that activation patterns for spatial and temporal order judgments spanned multiple subfields but did not find differences between spatial and temporal retrieval, suggesting that spatial and temporal order judgments were not restricted to specific subfields.

One possibility, however, is that these two studies did not see differences in subfield involvement in spatial vs. temporal processing due to features of their task design. Specifically, one important factor not controlled for in the two studies is that of interval distance. For instance, the deficits present in Gilbert et al. vary according to distance in both the spatial and temporal tasks. Nearby trials in the [30] experiment were more difficult for rats to discriminate than more distant trials, which in turn showed greater deficits following CA3 and CA1 lesions, respectively. Additionally, several studies have shown that deficits and general performance depend on spatial and temporal distance [31–34], showing that discrimination is more difficult as distance decreases for both spatial and temporal judgments. Thus, it is unclear whether the distance discrimination in Copara et al. elicited similar task demands to that of Gilbert et al. For example, in the Copara et al. study, participants were asked which of two items was closer to a reference item. It is possible that the participants in the Copara et al. study consistently relied on the farther of the two distances in order to correctly respond. Similarly, Azab et al. did not explicitly manipulate spatial or temporal distance when participants viewed arrays that varied their spatial or temporal information during encoding. Thus, it could be that a task that better controls distance may show the distinction that Azab et al. and Copara et al. did not. By better controlling near vs. far intervals between spatial and temporal judgments, based on past animals studies [30], it would be reasonable to expect greater CA3/DG activation during spatial trials and greater CA1 activation for temporal trials. We might also expect differences as a function of near vs. far intervals.

To better understand how spatial and temporal context might be coded within the hippocampal circuitry, we employed high-resolution fMRI coupled with both a univariate and multivariate approach to our fMRI data. Univariate approaches are generally recognized to provide insight into the degree to which a brain area is recruited during a task (e.g., [35]). Multivariate pattern similarity [36,37], in contrast, is a technique involving comparison of patterns of activity in a collection of voxels between different trials. This necessitates correlating the pattern of voxel activity during different trials, which we did by comparing patterns of voxels during judgments involving multiple cued elements that were either nearby or faraway with regard to space or time. The pattern of

voxels recruited may in turn provide insight into the nature of representations used to solve the task [37]. We employed high-resolution imaging to better localize signals within the medial temporal lobe to subareas such as PHC, CA1, and CA2/CA3/DG (CA2/CA3/DG cannot be segmented at the acquired resolution), using the same imaging sequence as our previous study [22]. By asking participants to judge whether the two probe stores were the same or different interval distance from the reference, we could inquire about the degree of activation as well as the patterns of activity evoked within the hippocampus for successful retrieval of spatial vs. temporal context during both near (contiguous) and far (non-contiguous) judgments. Judgments during which participants successfully determined that two probe stores were the same distance from the reference store better control for spatial or temporal distance than trials that involved different intervals, as used in our past study [22], and thus same interval trials were the primary focus of our analysis. This in turn allowed us to investigate (1) whether the degree of activation differed as a function of subfield during spatial vs. temporal order retrieval; (2) whether the degree of activation differed as a function of subfield during near vs. far judgments; (3) whether the (multivariate) patterns of activation differed during spatial vs. temporal order retrieval; (4) whether the (multivariate) patterns of activation differed during near vs. far judgments.

2. Materials and methods

2.1. Participants

We tested a total of 18 participants (10 female; ages 18–30) from the University of California-Davis and the surrounding communities; two participants were excluded due to below chance performance on all four conditions leaving a total of 16 participants. All were right-handed and screened for neurological disorders, and were paid for their participation. All procedures were in accordance with our Internal Review Board (IRB) Guidelines for experimental testing.

2.2. Behavioral design: encoding

Participants navigated a virtual city designed using the Landmarks 1.0 package for the Unity game development platform (Unity Technologies, San Francisco, CA). The city contained six stores unevenly spaced in a rectangular environment, such that each store was equidistant from at least one pair of stores, and of unequal distance from at least one pair of stores. This ensured that later retrieval of relative distances would be unbiased by the relative probability of an equidistant or unequally distant comparison. Field-of-view, depth-of-view, and the dimensions of the layout were designed such that active navigation of the whole environment was required to encode the relative locations of the stores and the geometry of the environment.

Participants were instructed to deliver to each store in a specified order, moving directly from one store to the next. This delivery order was designed to be uncorrelated with the spatial arrangement of the stores. We further designed the delivery order to avoid any spatial pattern to the temporal sequence (i.e., the order of deliveries defining a star shape), discouraging the use of spatial strategy in encoding the delivery order. Following one round of practice encoding and retrieval (consisting of colored, unlabeled block-shaped stores in a smaller city to avoid similarity to the testing environment), participants encoded the experimental city as part of the main experiment over six blocks (see Fig. 1A and B). These six blocks were broken into three consecutive encoding blocks during which participants were instructed to attend space

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