

What Versus Where: Non-spatial Aspects of Memory Representation by the Hippocampus

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Abstract Since the discovery of place cells and other findings indicating strong involvement of the hippocampus in spatial information processing, there has been continued controversy about the extent to which the hippocampus also processes non-spatial aspects of experience. In recent years, many experiments studying the effects of hippocampal damage and characterizing hippocampal neural activity in animals and humans have revealed a clear and specific role of the hippocampus in the processing of non-spatial information. Here this evidence is reviewed in support of the notion that the hippocampus organizes the contents of memory in space, in time, and in networks of related memories.

Keywords Non-spatial memory · Hippocampus · Neural activity · Relational memory · Episodic memory

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The distinction in hippocampal function between non-spatial and spatial aspects of memory became prominent with the publication of O’Keefe and Nadel’s (1978) landmark book in which they argued that the hippocampus is dedicated to cognitive mapping, defined by them as the organization of events in physical space (p. 1). Their principal evidence supporting this hypothesis was a set of tables indicating a

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Curr Topics Behav Neurosci (2018) 37: 101–117

DOI 10.1007/7854_2016_450

Published Online: 28 September 2016

large proportion of then existing publications reporting deficits following hippocampal damage on spatial as compared with a much smaller proportion of studies reporting deficits in non-spatial memory. These findings were complemented by a description of prominent electrophysiological correlates of spatial behavior, including a prominent theta rhythm during movement through space and especially the observation of hippocampal principal neurons that fire when animals occupy a particular location in the environment (place cells), that could reflect a mapping of space.

Since that time, the issue of whether the hippocampus processes non-spatial information has been debated, and has received considerable attention in many experiments. In studies on humans, there is overwhelming evidence that patients with hippocampal damage are impaired in tasks that require memory for specific non-spatial stimuli, such words or pictures, presented visually or orally, and therefore without any demand for remembering where the items were seen or any other aspect of space (Squire et al. 2004). Correspondingly, many functional imaging studies have reported hippocampal activation associated with memory for non-spatial stimuli, most typically when items are associated with memory for the spatial (e.g., Davachi et al. 2003) or non-spatial (Henke et al. 1997; Zeineh et al. 2003; Preston et al. 2004; Qin et al. 2009) context in which they were experienced (for reviews see Davachi 2006; Diana et al. 2007; Eichenbaum et al. 2007).

In animals, the situation is less clear, and here is where the story gets interesting. In O'Keefe and Nadel's (1978) review, few studies reported effects of hippocampal damage on classical or instrumental conditioning or discrimination learning, leading to their conclusion that the hippocampus is not involved in non-spatial memory. This conclusion seemed to be confirmed by later studies using the Morris water maze to show that hippocampal lesions impair learning guided by distal spatial cues but not learning guided by a local visual cue (Morris et al. 1982) and studies using fear conditioning to show that hippocampal lesions impair conditioning to a spatial context but not conditioning to an auditory cue (Phillips and LeDoux 1992). However, there are many exceptions that challenge any simple view about non-spatial conditioning and discrimination learning. For example, a form of classical conditioning where a brief "trace" interval is inserted between the non-spatial conditioning and unconditioned stimuli makes the task hippocampal-dependent (Solomon et al. 1986). In the classic spatial alternation task, animals with hippocampal damage can solve the problem when they can alternate continuously but fail when a brief delay is inserted between alternations (Ainge et al. 2007a, b). In both conditions the spatial cues and any demands for spatial cognition per se are identical—they differ only in the demand to remember across a delay. Showing how complicated the findings can be in any particular formal behavioral paradigm, one study described impairment, no effect, or even facilitation of simple odor discrimination learning in rats with hippocampal system damage (Eichenbaum et al. 1988).

In studies on non-spatial recognition memory in animals, the story is, again, complicated. This story begins with Mishkin's (1978) discovery that large medial temporal lesions impair visual object recognition in the delayed non-matching to

sample (DNMS) task, where a single novel object is viewed as the sample, then following a delay, at test monkeys are rewarded for choosing a different novel stimulus over the sample. However, in contrast to the devastating effects of large medial temporal lobe removal, lesions limited to the hippocampus in monkeys had a much less severe effect (Zola et al. 2000) or no effect (Murray and Mishkin 1998). Similarly, in rats, selective hippocampal lesions do not impair object-cued DNMS performance (Mumby 2001; but see Clark et al. 2001), whereas damage to the neighboring perirhinal cortex results in severe DNMS deficits in both monkeys and rats (see Eichenbaum et al. 2007; Squire et al. 2007).

The studies showing remarkably little impairment in non-spatial recognition memory are countered by a different pattern of results revealed using a naturalistic test of recognition memory that measures preferential exploration of objects. In humans and monkeys, subjects are initially allowed to visually explore a novel picture, then following a delay, are shown the same picture and another novel picture. Without any reinforcement, subjects preferentially view the novel picture, and, importantly, this novelty preference depends on the pictures being presented in the same background visual context showing that the picture memory is context dependent (Bachevalier et al. 2015). Hippocampal damage severely impairs this preferential viewing effect (Nemanic et al. 2004; Zola et al. 2000), and the deficit occurs only in context-dependent recognition (Bachevalier et al. 2015). In rodents, subjects initially explore duplicates of a novel three-dimensional object in a familiar environment and then, following a delay, are presented with one of those objects and a new object replacing one of the duplicates. Most studies have reported no effect of hippocampal damage, but hippocampal lesions do impair preferential exploration of a familiar object in a novel place in the familiar environment, or a novel spatial context, and preferential viewing of an earlier explored object over a more recently explored object (Eacott and Norman 2004; Langston and Wood 2010). There are some observations of deficits in novel object preference in mice with knockout of the NMDA receptor (Rampon et al. 2000), and in rats with extensive hippocampal damage (Broadbent et al. 2004), or at very long delays (Clark et al. 2000), and most impressively, during temporary inactivation of the hippocampus (Cohen et al. 2013; Cohen and Stackman 2015). These variable findings on non-spatial recognition memory suggest that there may be more than a single strategy that can support recognition, with one strategy dependent on the hippocampus and another that can be supported by other structures or systems, and whether or not a hippocampal-dependent strategy is critical depends on task demands.

Guided by several findings in humans suggesting a distinction between recognition supported by mere familiarity with a recently experienced stimuli contrasted with recollection of the experience with the stimulus study event (Yonelinas 2001), we addressed the possibility of dual mechanisms supporting recognition by developing a variant of the DNMS task designed to distinguish familiarity-like and recollection-like strategies in rats. Our approach adopted a signal detection analysis in which performance on recognition memory judgments is characterized by the Receiver Operating Characteristic (ROC) function that generates separate indices of the contributions of recollection and familiarity in humans (Yonelinas 2001). To

perform this analysis in rats, we modified the standard DNMS protocol to initially present, as a list of sample stimuli, odor cues taken randomly from a pool of familiar odors. Then, following a delay, animals were presented with the “old” stimuli (same odors as the samples) and equal number of “new” stimuli (other odors from the pool) sequentially (Fortin et al. 2004). The resulting ROC curve was very similar to functions observed in humans, indicating the contributions of both familiarity-like and recollection-like processes. Moreover, even when the overall recognition performance (measured by percent correct which combines the contribution of recollection and familiarity) was equivalent in these conditions, normal rats exclusively used recollection whereas rats with hippocampal damage exclusively relied on familiarity. This double dissociation of strategies unequivocally shows that the hippocampus supports a recollection-like process, while sparing familiarity for the same stimuli. These results provide an explanation for the mixed pattern of findings on hippocampal damage and recognition memory in DNMS and preferential exploration paradigms, suggesting that differences in the memory demands of these tasks drives performance that depends on a hippocampal-dependent recollection-like or can be supported by a hippocampal-independent familiarity-like processes (see Sauvage et al. 2008, 2010). An alternative explanation of the specific role of the hippocampus in recollection is that the hippocampus is necessary only for the development and expression of strong memories (Squire et al. 2007). A potential reconciliation of these perspectives is that recollection involves memories that typically contain vivid associations (e.g., Davachi et al. 2003; Quin et al. 2009).

1 What Is the Nature of Memory Representation that Supports “Recollection” of Non-spatial Stimuli?

Many studies in rodents, monkeys, and humans have described hippocampal neuronal activity associated with a broad range of non-spatial stimuli and behavioral events. In rodents, hippocampal neurons have been reported to fire associated with visual, tactile, olfactory, and auditory cues in a broad range of learning and memory paradigms (Eichenbaum et al. 1999; Eichenbaum 2004, 2010; see below). These findings join with many other reports of hippocampal neural activity associated with combinations of specific stimuli, match/non-match stimulus comparisons, and the locations of these events in animals performing recognition memory tasks (Wood et al. 1999; Weibe and Staubli 1999; Deadwyler et al. 1995; Otto and Eichenbaum 1992). The extent to which non-spatial and spatial cues are represented depends on the context of behavioral demands (Muzzio et al. 2009).

Also, a large fraction of hippocampal neurons in monkeys fire associated with learned associations between specific visual stimuli and eye movement responses (Wirth et al. 2003). Similarly, a large fraction of hippocampal neurons in monkeys respond to visual stimuli modulated by their familiarity in the naturalistic recognition task described above (Jutras and Buffalo 2010). Furthermore, multiple studies have reported that hippocampal neurons in humans also respond to visual stimuli

and their responses are modulated by familiarity in recognition tasks (Fried et al. 1997) and distinguish the stimuli that are recalled from those forgotten (Rutishauser et al. 2008). Hippocampal neuronal responses also predict memory for learned verbal paired associates (Cameron et al. 2007). Human hippocampal neurons exhibit sparse and distributed coding of individual remembered stimuli (Wixted et al. 2014) and many hippocampal neurons generalize across closely related stimuli (Quiroga et al. 2005; Krieman et al. 2000a) and fire while the subject is imagining a cued stimulus (Krieman et al. 2000b).

In addition, hippocampal neurons signal learned behavioral actions. Lenck-Santini et al. (2008) described hippocampal neurons that fire during learned “jump” responses, reminiscent of Ranck’s (1973) pioneering descriptions of a variety of “behavioral correlates” of hippocampal neurons in rats, later attributed to the location where those behaviors occurred, even though these responses are not explained fully by location alone. These reports of activity associated with specific behavioral actions were preceded by other pioneering observations of hippocampal neuronal activity modeling the conditioned eyeblink response in rabbits (Berger et al. 1983; Hattori et al. 2015), and short-latency auditory-driven responses of hippocampal neurons in rats classically conditioned to seek food upon presentation of a tone stimulus (Olds et al. 1972). In sum, there is considerable variation in the types of non-spatial and spatial information encoded in hippocampal neural activity patterns, leading to the conclusion that hippocampal neuronal activity in rodents and monkeys is “high-dimensional” in the sense that hippocampal neurons exhibit considerable mixed selectivity to multiple relevant non-spatial and spatial dimensions that are salient in a large range of memory tasks (see Mckensie et al. 2014).

The observations discussed above do not directly shed light on how hippocampal neuronal firing patterns specifically support recollection of episodic memories. Next I will further focus on my proposal, made some time ago (Eichenbaum et al. 1999), that the hippocampus contributes to recollective memory by constructing relational representations that bind elements of memories and link memories via their common elements, composing a “memory space” that supports both spatial and non-spatial dimensions of memory organization. According to this view, the representational schemes that underlie relational processing are: (1) the representation of events as objects within the context in which they occur, (2) the representation of episodes as the flow of events across time, and (3) the interleaving of events and episodes into relational networks, supporting the ability to draw novel inferences from memory (Eichenbaum 2004). Here I will review some of the older and more recent findings that support this perspective, focusing on non-spatial aspects of relational memory representations and activity patterns of neurons in the hippocampus that may support these representations.

Representation of events as objects in context. As introduced above, several studies have shown that hippocampal damage causes deficits in the spontaneous preference for exploring familiar objects in new locations or in new environmental contexts, even when preference for novel objects in familiar locations is preserved. Similarly, the hippocampus is essential to recognizing and discriminating objects only when object representations and associations are context dependent (Butterly

et al. 2012; Bachevalier et al. 2015). These findings are complemented by several reports that hippocampal neuronal activation that occurs during the exploration of specific objects is embedded within the spatial firing patterns (place fields) of those neurons. For example, following tone-cued fear conditioning, hippocampal neurons come to be driven by the conditioned tone stimulus when the animal is within the place field of that neuron (Moita et al. 2003). Also, in rats performing a variant of the novel object exploration task, hippocampal neurons fired associated with specific objects and their familiarity embedded within the spatial firing patterns (place fields) of these neurons (Manns and Eichenbaum 2009). In rats performing a context-guided object-reward association task, hippocampal neurons fire when animals sample specific objects within particular locations and spatial contexts (Fig. 1; Komorowski et al. 2009). Similarly, after training on somatosensory or auditory discrimination tasks, hippocampal neurons encode tactile and auditory cues along with the locations where they were experienced and rewarded (Itskov et al. 2011, 2012; Vinnik et al. 2012).

Parallel studies using fMRI have shown that specific stimuli are encoded within spatial context in the human hippocampus. For example, when human subjects recall imagined scenes that applied to specific verbal items, the hippocampus was activated only when the subjects recalled the item and scene (Davachi et al. 2003). Also,

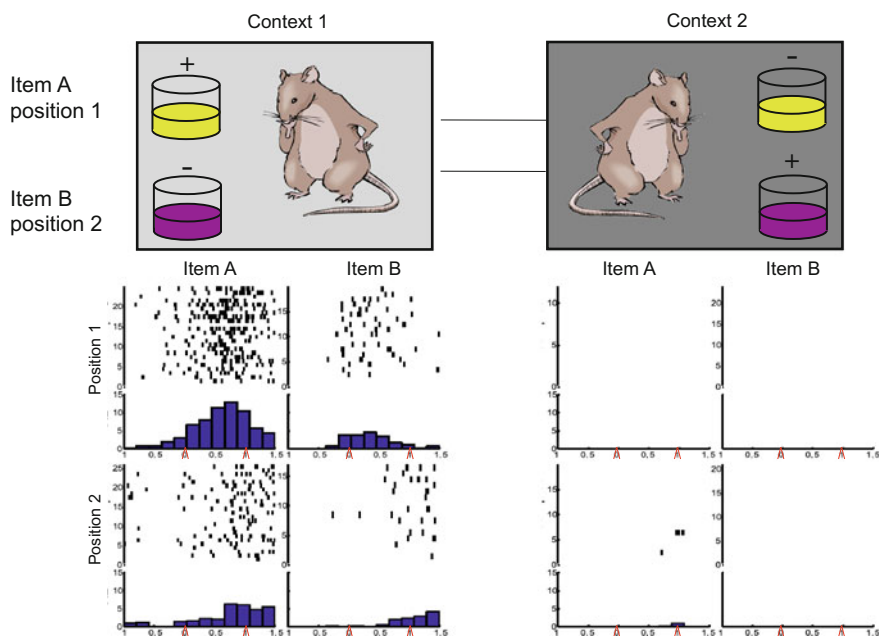


Fig. 1 An example CA1 neuron that fires as a rat samples a specific odor located in a particular position within one spatial context. *Top* The rat performs a context-guided odor association task in which object A, not B, is rewarded in Context 1 whereas object B, not A, is rewarded in Context 2. *Bottom* Rasters and summary histogram of firing rates during object sampling (between red arrows) (from Komorowski et al. 2009)

studies on humans indicate that hippocampal damage eliminates the preferential viewing of locations in a scene where objects were previously observed and are now absent (Ryan et al. 2000), and correspondingly, activation of the hippocampus in normal subjects that predicted subsequent successful object-location memory by preferential viewing (Hannula and Ranganath 2009). Also, humans with hippocampal damage are impaired in memory for the locations of multiple objects, and in particular, most errors are due to “swapping” objects between locations (Watson et al. 2013). Together, these findings indicate a specific role for the hippocampus in the organization of non-spatial objects within a spatial context. Notably, even though the representations of non-spatial stimuli described here are embedded within spatial contexts, these paradigms described above do not involve demands for navigation by body movements through space, as is the focus of much current research on the role of the hippocampus in spatial aspects of memory (Hartley et al. 2014). Instead, these tasks simply require identifying objects within their spatial context.

1.1 Representations of Episodes as Sequences of Events

Additional recent evidence indicates that another non-spatial aspect of memory processing supported by the hippocampus involves the organization of events in time. In humans, there is considerable evidence that hippocampal damage results in deficits in memory for the order of events even when memory for the events is intact, and evidence from imaging studies that the hippocampus is activated during the encoding and retrieval of the order of events in memories, independent of memories for the events themselves (reviewed in Eichenbaum 2013, 2014). Similarly, selective hippocampal lesions result in impairments in memory for the order of studied non-spatial stimuli, even when memory for the stimuli themselves is spared (Fortin et al. 2002; Kesner et al. 2002a, b; Ergorul and Eichenbaum 2004).

There is also growing evidence that memory for the flow of events in experiences is mediated directly by representations of time and order by hippocampal neurons. Thus, recently it has become clear that the same hippocampal principal neurons that are place cells can also represent time independent of place (Eichenbaum 2013). An early study showed that ensemble activity patterns of CA1 neurons gradually change during while rats sampled sequences of odors, and this signal of continuously evolving temporal context predicted success in remembering the odor sequence (Manns et al. 2007). Confirming these findings in a functional imaging study in humans, Ezzyat and Davachi (2014) reported that pattern similarity in hippocampal activation signaled temporal proximity of associated objects and this signal was correlated with memory performance.

In addition, several other studies have identified hippocampal principal neurons that fire at a particular moments in time of a temporally structured event, composing temporal maps of specific experiences. Across these studies, the location of the animal is held constant or firing patterns associated with elapsed time are distinguished from those associated with spatial and behavioral variables, and the firing

patterns of these cells are dependent on the critical temporal parameters that characterize the task. Because these properties parallel those of place cells in coding locations in spatially structured experiences, we called these neurons “time cells” (MacDonald et al. 2011), even though these neurons are the same cells that exhibit spatial firing specificity in other circumstances.

Time cells have now been observed in several behavioral paradigms, including during delay periods in maze tasks in which rats alternate goals (Gill et al. 2011; Pastalkova et al. 2008; Kraus et al. 2013; Fig. 2), bridging temporal gaps between associated non-spatial cues (MacDonald et al. 2011), during the delay period in a non-spatial matching to sample task (MacDonald et al. 2013), and throughout trials in trace eyelid conditioning (Modi et al. 2014). Importantly, in some of these studies, the animal is immobilized and thus space plays no role in ongoing behavior or memory whatsoever (MacDonald et al. 2013; Modi et al. 2014; Naya and Suzuki 2011). The findings of these studies establish a broad scope of temporally structured episodes in which the hippocampus encodes the temporal organization of specific experiences. Confirming these results in a functional imaging study in humans, Hsieh et al. (2014) reported that pattern similarity in hippocampal activation signaled the combination of object and temporal context information in sequence learning. Furthermore, some of the studies in animals have closely linked the emergence of time cells sequences to the encoding of specific memories and to subsequent memory accuracy (Gill et al. 2011; Modi et al. 2014; MacDonald et al. 2013), thus indicating a causal role of time cell firing patterns to memory performance.

The role of the hippocampus in organizing events in time extends even to spatial memories and spatial representations. Thus, for example, while the hippocampus is required for accurate delayed alternation in a T-maze, the hippocampus is not

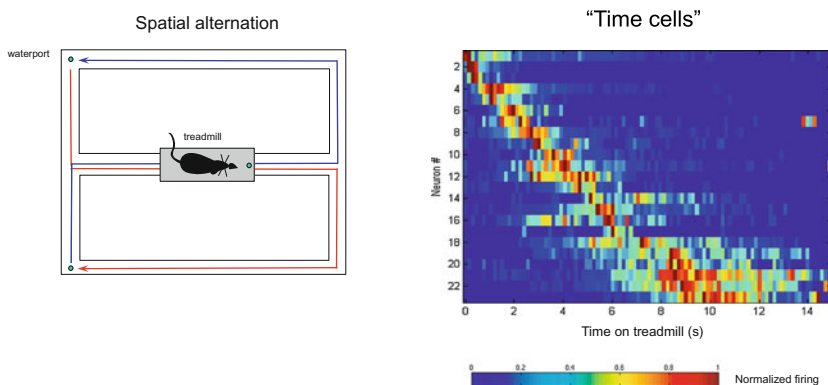


Fig. 2 Hippocampal time cells during the period when a rat runs in place while performing a spatial alternation task. *Left* The spatial alternation task with treadmill in the center of the maze stem. *Red and blue lines* indicate alternate right-turn and left-turn paths. *Right* ensemble firing rate mapping where each row represents the normalized average firing rate of a neuron (see cell numbers on Y-axis) over the 15 s treadmill run. Note that each cell fires during a specific moment of treadmill running and the entire period of running is filled with time-specific representations (from Kraus et al. 2013)

required for animals to learn to turn in one direction in a T-maze or even to alternate left and right turns if allowed to alternate continuously (O’Keefe and Nadel 1978). Consider that the demands for using spatial representations are equivalent in all these versions of T-maze learning. That is, to distinguish left and right turns at a choice point, and one could perform all these tasks based on the same egocentric or allocentric spatial representations. The difference between these tasks is a demand for memory for time, specifically remembering which turn was last performed, only in delayed alternation and not in learning a consistent turn direction or in continuous alternation. Correspondingly, the spatial firing patterns are different depending on which memory is current—place cells fire differentially depending on whether the animals is in the midst of a left-turn or right-turn trial even in the portion of maze where these routes overlap (Wood et al. 2000). The differentiation of spatial representations that is dependent on the ongoing temporal context occurs both in versions of the task where the hippocampus is required and in those where it is not required, and these context-dependent firing patterns predict accurate memory performance (Robitsek et al. 2013).

Also, the representation of temporally ordered sequences of events by the hippocampus extends to monkeys and humans. In monkeys, hippocampal neuronal activity signals elapsed time in a memory delay between associated objects (Naya and Suzuki 2011). In humans, hippocampal neurons fire in sequence associated with learning (Paz et al. 2010) and memory (Gelbard-Sagiv et al. 2008) of the flow of events experienced in movie clips.

The significance of prominent temporal representation as an aspect of non-spatial coding in the hippocampus is high in two ways. First, as introduced by Tulving (1984) episodic memories are defined by a temporal organization that embodies the temporal organization of events in personal experiences. We know that the hippocampus is critical to episodic memory and to memory for the temporal order of events, even when space is not relevant. Now the existence of time cells provides a mechanism by which the hippocampus organizes memories for events in time. Second, the existence of time cells offers a parallel temporal organizing mechanism to the spatial organizing mechanism offered by place cells. Therefore, the hippocampus could support representations of episodes by mapping objects and events within a framework of space and time, conferring upon those memories connections that reflect the spatial and temporal associations between distinct but related events (Eichenbaum 2013, 2014).

1.2 Representation of Memories Linked into Relational Networks

Since the work of Piaget (1928) we have known that memories are not stored in isolation but rather are integrated into organizations of and personal experiences that I call relational networks. In early work on the role of the hippocampus in building relational networks, Bunsey and Eichenbaum (1996) examined the

capacity of rats to link overlapping stimulus associations into relational networks. They trained rats on associations between pairs of odors that shared a common element (A–B and B–C) and then tested for the existence of the relational network that (A–B–C), but assessing knowledge about the indirectly related elements (A–C). Normal rats showed they had developed the relational representation, but animals with hippocampal lesions did not. Subsequently, Dusek and Eichenbaum (1997) showed that normal rats can also learn a series of overlapping stimulus choice problems (choose A over B, B over C, C over D, D over E), and show acquisition of a hierarchical relational representation (A over B over C over D over E) by accurate transitive choices (e.g., B over D). Again the hippocampus was required for the relational judgment. Similarly, rats with hippocampal damage are impaired in learning a circular organization of relations among non-spatial stimuli (A over B over C over A; Dusek and Eichenbaum 1998). Notably, none of these tasks involves spatial organizations.

In more recent work, Tse et al. (2007) showed that when rats learn to find distinct food flavors in specific designated locations within an open field, they develop an organized representation of the spatial relations among the objects in a particular environment and rely on the hippocampus for rapid assimilation of new flavor-place associations within the relational representation (or schema). McKenzie et al. (2013) explored the neural basis for the development and elaboration of a spatial schema in which rewards could be found at multiple locations. They reported that hippocampal neurons encode the animal's approach to multiple reward locations and rapidly assimilate and reorganize the overall network representation to accommodate the new reward locations. These studies focus on the spatial organization of non-spatial events, and demonstrate a key role for the hippocampus in interleaving non-spatial memories within a spatial relational representation.

In a more ambitious study where rats learned multiple context-dependent object-reward associations, McKenzie et al. (2014) characterized the neural ensemble representations as a hierarchy of relations among non-spatial and spatial dimensions of events, including the identity of the objects, their reward assignments, the positions within a context in which they were experienced, and the spatial context in which they occurred. These findings revealed the overall structure of the relational representation of all of the events in the task, such that non-spatial features of events (object identifies and reward valences) were embedded within spatial organization (positions) in separate schemas for each context (Fig. 3). Furthermore, after initial learning the initial set of object-reward associations, new object associations were rapidly assimilated into the relational structure that was established by initial learning. In addition, within the overall hierarchical representation, items that had common reward associations in particular positions had strongly similar representations, indicating close associations between objects that were never experienced together. This aspect of the relational representation likely supports the capacity to make novel inferences between those indirectly related objects.

In parallel studies Preston and colleagues (2004) have explored role of the hippocampus in forming relational representations in humans. In their paradigm, subjects learn overlapping pairwise associations between visual objects (e.g., A–B

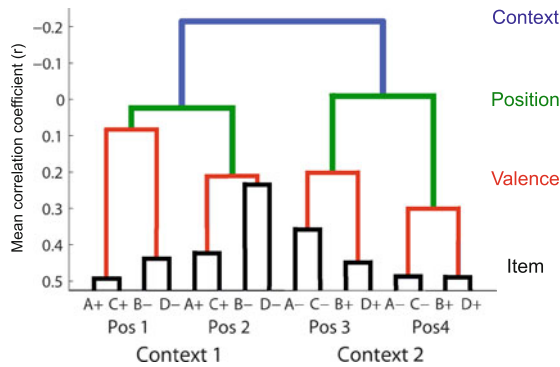


Fig. 3 A dendrogram showing the hierarchy of representational distances measured as correlations between simultaneously recorded neuronal population vectors associated with spatial (context and position) and non-spatial (reward valence and object identity) dimensions in animals performing the same task as show in Fig. 1 where they chose between stimuli A versus B on some trials and between C versus D on other trials. Each type of trial is composed as a specific stimulus (A or B), reward value (+ or -), position (Pos) and context shown on X-axis (from Mckenzie et al. 2014)

and B–C) from which they can make inferences between indirectly related elements (A–C), demonstrating the acquisition of a simple relational network that interleaves the overlapping memories and links all three elements (similar to Bunsey and Eichenbaum 1996). Furthermore they showed that, the learning of the second, overlapping pair (B–C) reinstates the hippocampal representation of the earlier learned pair (A–B) and that this content-specific hippocampal activation signaled subsequent success on the inferential judgment (Zeithamova et al. 2012). These findings indicate that the development of relational networks depends upon reinstatement of related networks into which the new information is assimilated, and shows that the subsequent interleaved network supports novel inferences from memory. Recently, Wimmer and Shohamy (2012) have reported parallel findings of hippocampal activation associated with reward values shared between indirectly associated stimuli. In addition, it is notable that the relational network in this paradigm organized neither by space or time, but rather simply by associative links among the elements. These findings extend the scope or relational dimensions supported by the hippocampus to the most fundamental of all dimensions, simple associations between objects.

2 Conclusions—The Role of the Hippocampus in Non-spatial Aspects of Memory

The findings describe above clearly implicate the hippocampus in non-spatial memory processing, including in several studies where space plays no role in memory performance (e.g., Bunsey and Eichenbaum 1996; Alvarez et al. 2002;

Fortin et al. 2004; Naya and Suzuki 2011; Zeithamova et al. 2012). At the same time, the evidence that the hippocampus encodes memories of non-spatial events in isolation from the context and other events is weak. In the view of this investigator, these observations support the idea that the role of the hippocampus is precisely to link event memories with relational representations that are organized by space, time, and associative networks.

Even in seemingly simple memory tasks that require only recognition of individual objects, I believe that relational memory is involved. Consider, for example, the experiment using ROC analysis of odor recognition. It would seem that this task simply requires recognition of individual odors independent of other stimuli, their locations, or their temporal order. But consider further that all of the odors were generally familiar; in each testing session, the sample stimuli were a subset of odors from a pool and odors were presented in different lists many times across testing sessions. Therefore, the memory demand on each test was not, "Have you ever experienced this odor?", but rather, "Was this odor on the list today?". The task thus requires memory for stimuli in the context of the current study list, much as memory for highly familiar words in standard recognition tests in humans demands not a judgment about whether the each word has been seen before, but rather was it on the study list in this experiment (see also Butterly et al. 2012). In my view, the demand for hippocampal function in "recollection" depends on the extent to which performance normally benefits by memory of items in the context of the study experience.

This perspective on the role of the hippocampus in non-spatial memories is supported by a comparison of the kinds of errors made in recognition memory following damage to the hippocampus versus prefrontal cortex in rats. In the ROC paradigm described above, hippocampal and prefrontal lesions both cause selective impairment in the recollection-like component of recognition. However, further inspection of the nature of the impairment indicates a key distinction in these impairments. Hippocampal lesions result in a reduction in the "hit" rate, that is, an increase in errors in which the subject declares stimuli experiences as samples as "new" (Fortin et al. 2004). This kind of error is, of course, what one expects in amnesia caused by hippocampal damage. However, prefrontal lesions do not affect the hit rate, but instead elevate the rate of "false alarms," errors in which items that did not appear in the sample list are declared "old" (Farovik et al. 2008). This kind of error reflects a deficit in distinguishing the source of odor memories as on the current study list as opposed to those on earlier study lists. Thus, prefrontal damage does not cause impairment in odor memory per se, but rather a loss of memory for the study list source or context. These findings indicate that rats do indeed normally benefit from relating individual odor memories to the context of the current study list, and these results suggest that memory for the study items in that context underlies recollection-like performance in rats.

Here I have argued that the role of the hippocampus is to organize memories in context, in order, and in relational networks. The organization can map onto space, but can also map onto time, or onto an associational structure that is neither time nor space. It may be that the hippocampus serves more in the organizational role

than the representation of the items themselves, as suggested by some studies that describe hippocampal representation as including the organization alone without item coding (Naya and Suzuki 2011) or as a hierarchical organization with the organization at the top of the hierarchy and object dimensions at the bottom (Mckenzie et al. 2014; Manns and Eichenbaum 2009; Fig. 3). To the extent that organization proves to be the predominant role of the hippocampal representations across paradigms, we might best think of the hippocampus as fundamentally like the orchestra leader whose role it is to organize the performance of musicians who sit in different places and play in a distinct sequence. From this perspective, the division between spatial and non-spatial aspects of hippocampal memory is, in my view, not the most useful compartmentalization of hippocampal function. Rather, I suggest a shift to thinking of a distinction between the contents of memories, the objects and events that occur, and the organization of memories, in dimensions of space, time, associative networks, and perhaps more dimensions by which elements of memories are connected.

Acknowledgments NIMH MH094263, MH51570; MH52090, MH095297; ONR MURI N00014-0-1-0936.

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