



Relational memory and the hippocampus: representations and methods

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Since the discovery of the importance of the hippocampus for normal memory, considerable research has endeavored to characterize the precise role played by the hippocampus. Previously we have offered the relational memory theory, which posits that the hippocampus forms representations of arbitrary or accidentally occurring relations among the constituent elements of experience. In a recent report we emphasized the role of the hippocampus in all manner of relations, supporting this claim with the finding that amnesic patients with hippocampal damage were similarly impaired on probes of memory for spatial, sequential, and associative relations. In this review we place these results in the context of the broader literature, including how different kinds of relational or source information are tested, and consider the importance of specifying hippocampal function in terms of the representations it supports.

Keywords: hippocampus, relational memory, memory representations, amnesia

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CHARACTERIZING THE FUNCTIONAL ROLE OF THE HIPPOCAMPUS

That the hippocampus plays a critical role in memory has been clear since the documenting of severe amnesia following temporal lobe resection in patient H.M. (Scoville and Milner, 1957). Since that time, an extraordinary amount of research has been directed at characterizing the functional role the hippocampus plays in memory, leading various authors to emphasize, among other things, spatial memory or **cognitive mapping** (O'Keefe and Nadel, 1978), **declarative memory** (Cohen, 1984; Cohen and Eichenbaum, 1993; Squire et al., 2004), **explicit memory** (Graf and Schacter, 1985), **recollection** (Aggleton and Brown, 2006; Ranganath et al., 2004), and **relational memory** (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001). Our own work has focused on the profound deficits observed on tests of relational memory in amnesia consequent to hippocampal damage (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001; Hannula et al.,

2006, 2007; Konkel et al., 2008; Ryan and Cohen, 2003; Ryan et al., 2000).

THE HIPPOCAMPUS AND ALL MANNER OF RELATIONAL MEMORY

In a recent paper (Konkel et al., 2008) we tested the idea that the hippocampus is critical in memory for all manner of relations among the perceptually distinct elements of experience, providing evidence for this claim in the finding that hippocampal amnesia was associated with deficits in memory for spatial, sequence (temporal), and associative (co-occurrence) relations among items. This finding is noteworthy because prior studies of hippocampal-dependent memory have tended either to examine memory for only a single type of relation or conflated multiple kinds of relations. Only by employing a procedure in which each of several kinds of relational memory could be tested separately, using the same materials, were we able to examine fairly whether the hippocampal role extended to all types of relations or whether instead some types are special.

need
examples
of
elements

Declarative memory

Memory for facts and events, to be contrasted with procedural memory, which supports the ability to acquire and express skills (or the difference between “knowing that” and “knowing how”). **The nature of declarative representations, thought to be fundamentally relational and flexible,** makes it possible for such memory to be consciously accessed and “declared”.

Explicit memory

A kind of memory based on explicit remembering or conscious recollection of some prior learning episode, or the kind of memory test that requires explicit remembering; usually defined in contrast to implicit memory, involving the ability of behavior to be influenced by previous experience without requiring the individual to consciously recollect the prior experience.

Recollection

A process that results in the retrieval of additional information about a particular item from memory beyond its oldness; this information could be some detail of the study experience such as the color of the font of the item or its location on the screen, or some internal state at study time, such as what the item reminded you of.

Relational memory

Memory for relations among the constituent elements of experience, providing the ability to remember names with faces, the locations of various objects or people, or the order in which various events occurred. Can be contrasted to item memory, i.e., of the individual elements themselves. The hippocampus is required for memory for arbitrary or accidentally occurring relations.

Place cells

When an animal is exploring its environment, principal neurons of the hippocampus fire preferentially in particular regions of the environment corresponding to the neurons’ “place fields”; in this way, a set of such neurons can represent the entire environment. The “places” are represented relationally, in terms of the relations among elements in the environment.

Source memory

Memory for information about an item beyond the item itself; i.e., its various relations to other elements of the event. In laboratory experiments, this usually refers to the particular location of an item on the computer screen, the color of the font or format in which the item is displayed, or the voice or identity associated with some piece of presented information.

ARE SOME TYPES OF RELATIONAL MEMORY SPECIAL?

In contrast to a view emphasizing all manner of relations, some “limited-domain accounts” (see Cohen and Eichenbaum, 1993) have focused exclusively or primarily on one or another particular type of relations. Perhaps the best example is the spatial memory or cognitive mapping theory of hippocampus (O’Keefe and Nadel, 1978), based initially on the discovery in the hippocampus of what were called **place cells** (cells that fire preferentially when the animal is in one or another particular location) (O’Keefe and Dostrovsky, 1971). Many studies have gone on to report spatial correlates of hippocampal activity or **hippocampal dependence of spatial memory performance, based on allocentric spatial relations,** not only in animals but also in humans (see Bird and Burgess, 2008; **Table 1**). But both the animal and human literatures are now filled with numerous findings from other studies documenting hippocampal involvement in relational tasks with no critical spatial component (see Cohen et al., 1999; Eichenbaum and Cohen, 2001; **Table 1**), making it difficult to reconcile a solely spatial account of hippocampal function. This also applies to other limited-domain accounts; any evidence that supports a given limited account (e.g. spatial maps) contradicts a different limited account (e.g. associative memory) while evidence for the latter similarly contradicts the former.

More modern variants have shifted the debate to whether **one particular type of relation is “special” or critical in hippocampal function.** For the spatial mapping hypothesis, for example, Bird and Burgess (2008) have suggested that **spatial maps represented in the hippocampus allow for the construction/reconstruction of mental images which, the authors believe, mediate episodic recollection.** It is extraordinarily difficult to assess whether **spatial or some other type of representation is somehow more fundamental,** providing the basis for gaining access to the full range of relational information for which the hippocampus is involved. But it is entirely feasible to assess whether there are any functional implications of the “specialness” hypothesis, i.e., any differences manifested in the relationship of hippocampus to performance. That is, moving beyond the question of whether the hippocampus is engaged by and critical for all manner of relations, **we can ask whether memory for one or another type of relations is disproportionately dependent on the hippocampus,** and whether memory for various relations is statistically dependent on any particular type of relational memory.

TESTING MULTIPLE RELATIONS OR MULTIPLE SOURCES OF INFORMATION ABOUT ITEMS

Critical tests and advancement of theories in this area require assessing multiple kinds of relations, or multiple sources of information about the to-be-remembered items (or **source memory**), in order to determine whether there are meaningful distinctions to be drawn among them. **The most powerful way to test this is through comparison of multiple types of relations within a single paradigm for the same participants.** But this criterion has rarely been met. A small number of studies (see **Table 1**) have tested multiple types of relational memory in either the same paradigm or the same subjects. Some fMRI studies have expressly attempted to compare spatial memory to other types of relations. While some (e.g. Kumaran and Maguire, 2005; Ryan et al., 2009) **have found more hippocampal activity in the spatial than other putatively relational conditions,** others (e.g. Kohler et al., 2005; Uncapher et al., 2006) have not.

But, critically, of all the studies attempting direct comparisons, only those by Staresina and Davachi (2008), Uncapher et al. (2006), and Konkel et al. (2008) compared more than one type of relational memory or association to memory for the items themselves within the same paradigm and subjects. **Staresina and Davachi (2008) showed participants nouns on a colored background and asked them to make a mental image of the object in that color and make one of two different judgments about the image while fMRI activity was recorded.** At test, participants made an old/new item judgment followed by forced-choice decisions about the color in which the item was presented and the type of judgment they made at the time they generated an image. Findings showed that the hippocampus exhibited little activity when only the item was remembered, more activity when in addition the color or task judgment was remembered, and the most activity when both color and task judgments were remembered for the item. By contrast, the perirhinal cortex, thought to be involved in memory for items and for intra-item binding (binding *within* items), showed activity both for trials when the item alone was later correctly remembered and when the item and color were later correctly remembered. Also using a subsequent memory analysis with yes/no item recognition and forced-choice source judgments, Uncapher et al. (2006) had participants make a living/non-living judgment on words in **one of four colors located in one of four quadrants on the screen.** They found that the hippocampus was more active when both sources were later remembered than if only one were remembered, whereas the perirhinal cortex was

Table 1 | A selection of neuroimaging and MTL lesion studies that tested memory for associations, spatial locations, sequences, or some combination thereof. For neuroimaging studies, the result column lists the active MTL regions for the listed contrast (or reduction in activity as noted).

Study	Materials	Lesion/ Neuroimaging	Analysis	Result
Spatial Task Only				
Bayley and Squire (2005)	Apartment layout	Lesion	No comparison group used	Patients impaired
Cansino et al. (2002)	Pictures of common objects in an array	fMRI	SM: SC > SI	No MTL activity
Cansino et al. (2002)	Pictures of common objects in an array	fMRI	Ret: SC > SI	H, Ph
Crane and Milner (2005) expt. 1	Physical toys placed in an array	Lesion	Trials to criterion	Patients impaired
Crane and Milner (2005) expt. 2	Physical toys placed in an array	Lesion	Trials to criterion, placement accuracy	Patients impaired
Hannula and Ranganath (2008)	3D pictures rendered in an array	fMRI	C > I for each phase of WM task	H, Pr at sample and probe phase
Hannula and Ranganath (2008)	3D pictures rendered in an array	fMRI	Matching > mismatching > incorrect for each phase of WM task	H at probe phase
Hartley et al. (2003)	Virtual environment	fMRI	Searching > route following	H
Maguire et al. (2006)	Virtual recreation of London	Lesion	Navigation efficiency	Patient impaired on some routes
Pine et al. (2002)	Virtual environment	fMRI	Searching > route following	H
Ryan et al. (2000)	Scenes	Lesion	Relational eye-movement effect	Patients impaired
Spiers and Maguire (2006)	Virtual recreation of London	fMRI	fMRI activity collected during navigation	H
Associative Task Only				
Davachi et al. (2003)	Words	fMRI	SM: SC > SI	H, Ph
Davachi and Wagner (2002)	Word triplets	fMRI	Enc: relational > item processing	H
Davachi and Wagner (2002)	Word triplets	fMRI	SM: 3 words from triplet > 1 or 2	H in relational but not item condition
Giovanello et al. (2004)	Word pairs	fMRI	Ret: associative > item pair	H
Giovanello et al. (2003)	Word pairs	Lesion	Associative, item pair, or single item recognition	Patients impaired on associative test
Graf and Schacter (1985)	Word pairs	Lesion	Stem completion and cued recall	Patients impaired on cued recall
Hannula et al. (2007)	Face-scene pairs	Lesion	Associative recognition and relational eye movement effect	Patients impaired
Haskins et al. (2008)	Word pairs	fMRI	SM: increasing familiarity in unitization or associative condition	Pr
Henke et al. (1997)	Face-scene pairs	PET	Enc: associative or item encoding	H, Ph
Henke et al. (2003)	Face-profession pairs	fMRI	Enc: faces and profession > face alone	H (reduction)
Henke et al. (2003)	Face-profession pairs	fMRI	Ret: face and profession block > face only block (associative test for both)	H, Pr
Prince et al. (2005)	Word pairs and word-font pairs	fMRI	Associative hit > miss at encoding and retrieval	H
Ranganath et al. (2004)	Words presented in one of two colors	fMRI	SM: SC > SI	H, Ph

(Continued)

Table 1 | *Continued.*

Study	Materials	Lesion/ Neuroimaging	Analysis	Result
Associative Task Only				
Ranganath et al. (2004)	Words presented in one of two colors	fMRI	SM: increasing item familiarity	Pr
Staresina and Davachi (2006)	Words presented with colored backgrounds	fMRI	SM: recalled words > SC > SI	H
Staresina and Davachi (2006)	Words presented with colored backgrounds	fMRI	SM: SC > SI for recall and recognition	Pr
Turriziani et al. (2004)	Male and female faces and professions	Lesion	Single face, face-face, and face-profession recognition	Patients equally impaired at associations
Sequence Task Only				
Kumaran and Maguire (2006)	Pictures of objects arranged in quartets	fMRI	Half-repeated sequence > repeat or scrambled sequences	H
Kumaran and Maguire (2006)	Pictures of objects arranged in quartets	fMRI	Half repeated or scrambled sequences > repeated sequences	Pr
Schendan et al. (2003)	Numbers indicating which of four buttons to press	fMRI	Embedded sequence > random sequence block	H
Multiple Tasks				
Hannula et al. (2006) expt. 1	Objects within a scene	Lesion	Continuous recognition for scenes, detecting objects shifted within a scene	Patients impaired at detecting shifts
Hannula et al. (2006) expt. 2	Face-scene pairs	Lesion	Associative recognition	Patients impaired
Holdstock et al. (2005)	Various	Lesion	Variety of yes/no, AFC, and recall item, spatial, and sequence tasks	Patient is impaired at all recall tasks, spatial and sequence tasks, and some item recognition tasks
Holdstock et al. (2002)	Various	Lesion	Variety of yes/no, AFC, and recall item and spatial tasks	Patient is impaired at all recall tasks, spatial tasks, and yes-no recognition
Kohler et al. (2005) expt. 1	Pairs of line drawings in an array	fMRI	Ret: swapped locations or rearranged pairs > repeated pairs	H
Kohler et al. (2005) expt. 2	Line drawings	Intentional encoding	Ret: new items > old items	Pr
Kroll et al. (1996) expt. 1	Two-syllable words	Lesion	Continuous recognition of new words, words made of repaired syllables, or words with one previously seen syllable	Left-hemisphere lesion patients impaired
Kroll et al. (1996) expt. 2	Various kinds of drawings of faces	Lesion	Recognition of repeated faces or faces with repaired features	Patients impaired
Kumaran and Maguire (2005)	Spatially and socially arranged networks of friends	fMRI	Mentally traveling through a social or spatial network or making judgments about friends' faces or homes	Hippocampal activity was only above baseline in the spatial network condition
Mayes et al. (2004)	Various	Lesion	Variety of item recognition, within-domain (e.g. face-face) and between-domain (e.g. face-word) associative recognition, spatial, and sequence tests	Patient is impaired on between-domain associative, spatial, and sequence recognition

(Continued)

Table 1 | Continued.

Study	Materials	Lesion/ Neuroimaging	Analysis	Result
Multiple Tasks				
Olson et al. (2006)	Line drawings in an array	Lesion	Working memory task for items, occupied locations, or the conjunction of the two	Patients were impaired at the conjunction
Pihlajamäki et al. (2004)	Line drawings in an array	fMRI	New object in array > baseline repeated array	H, Ph, Pr
Pihlajamäki et al. (2004)	Line drawings in an array	fMRI	Items shifted locations in array > baseline repeated array	H, Ph
Ryan et al. (2009)	Pictures in an array	fMRI	Ret: judging which of two pictures was to the right of the other or more realistic; which of two objects is typically above the other or more expensive, or which of two unstudied pictures is typically in front of the other or is softer	Hippocampal activity was above baseline in every condition; it was highest in the spatial conditions
Multiple Tasks within Paradigm within Participants				
Konkel et al. (2008)	Triplets of computer-generated patterns	Lesion	Item, associative, spatial, and sequence tests	Patients impaired at sequence, associative, and spatial tasks
Staresina and Davachi (2008)	Words presented on one of four colored backgrounds	fMRI	SM: correct color or correct color and task > item only or correct task	Pr
Staresina and Davachi (2008)	Words presented on one of four colored backgrounds	fMRI	SM: both color and task correct > color or task correct > item only	H
Uncapher et al. (2006)	Words in one of four font colors in an array	Participants made a living/non-living judgment on each word	SM: both color and location correct > color or location correct	H
Uncapher et al. (2006)	Words in one of four font colors in an array	Participants made a living/non-living judgment on each word	SM: both color and location correct = color or location correct = item only correct	Pr

SM, subsequent memory; SC, source correct; SI, source incorrect; Ret, retrieval time; Enc, encoding time; H, hippocampus; Ph, parahippocampus; Pr, perirhinal cortex; C, correct; I, incorrect; WM, working memory.

what is SM exactly?

- The "subsequent memory paradigm" is an analysis tool to identify brain activity elicited during episodic encoding that is associated with successful subsequent retrieval.

- The 'subsequent memory effect' may be defined as significantly greater activation of a particular brain region during memory encoding for trials in which later retrieval was successful compared to that in trials in which later retrieval was unsuccessful.

equally active regardless of whether any source was remembered so long as the item was correctly remembered. Konkel et al. (2008) tested the necessity of the hippocampus for a variety of relations by showing patients with hippocampal amnesia triplets of computer-generated patterns presented sequentially in one of three screen locations. After each study block, participants were tested either on the spatial locations of a triplet, the temporal sequence of a triplet, or the co-occurrence of items in a triplet (associative memory), each tested in a manner independent of the other forms of relational information, and were tested for memory of the items themselves. We found that patients with

damage limited primarily to the hippocampus showed disproportionately impaired memory for each kind of relation, compared to that of comparison participants, despite relatively intact item memory. Patients with more extensive damage, extending into MTL cortical regions, performed at floor levels on the item task as well. Moreover, correlational analyses performed on the various relational memory performances of comparison participants showed statistical interdependencies, with no special dependency on any particular type of relation. Thus, in none of these studies was there evidence for any particular type of relation being "special".

how exactly?

Unitization

The fusing, blending, or configuring of multiple aspects of a sensory array into a single-item representation; thought to be accomplished by cortical regions outside of the hippocampus [such as in the fusiform face area (FFA) for faces, and the perirhinal cortex for some complex objects], and less flexible and less relational than hippocampal representations of multiple objects.

HIPPOCAMPUS AND REPRESENTATION

Some accounts of the hippocampus have emphasized the nature of the processing it supports in the act of remembering, such as recollection (Aggleton and Brown, 2006; Ranganath et al., 2004; see reviews by Diana et al., 2007; Eichenbaum et al., 2007); this focus is particularly apparent in the neuroimaging literature, where the ability to image active processes in the brain may encourage such an approach. Our own work has instead focused on the representations of experience that the hippocampus supports. Our earliest proposals about declarative memory (Cohen, 1984; Cohen and Eichenbaum, 1993) emphasized the storage of the outcomes of processing, representing facts and events in highly linked, flexible networks. Our subsequent proposals, describing relational memory theory, characterized declarative memory as being fundamentally relational, representing all the various arbitrary or accidentally occurring relations among the (perceptually distinct) constituent elements of experience, again in highly flexible networks (Cohen and Eichenbaum, 1993; Cohen et al., 1997; Eichenbaum and Cohen, 2001; Ryan and Cohen, 2003). The long-lived appeal of the spatial memory/cognitive mapping theory of hippocampus (O'Keefe and Nadel, 1978) may be the clarity of its proposal about hippocampal representation – it is an allocentric map of the environment, representing the relations among the various stimuli in the environment, with flexible navigable links among the elements in the map (see Bird and Burgess, 2008 for an up-to-date version).

In our view the hippocampus represents experience as nodes within a multi-dimensional representation space (also see Eichenbaum, 2004), with each axis or dimension representing a different domain of information (not just x,y space, or just space and time). Various relations among items (spatial, sequential/temporal, etc.) are captured within the n -dimensional space. Information from the various processing streams arrives via inputs from earlier cortical areas (such as perirhinal and parahippocampal cortex), activating relevant nodes within the representational space (shown as several distinct representation planes in Figure 1). Inputs to the hippocampus also cause reactivation of related information via relational links with associated nodes. To the extent that the model is reflective of physiology, “place cell” activity can be understood as reflecting a subset of the more general, relational memory space where the critical dimensions are the axes of space. Not only are the “places” to which hippocampal neurons preferentially fire represented relationally, but when tested under circumstances that emphasize things other than spatial navigation

these neurons represent other types of relations. Thus the nodes that were thought to reflect spatial memory under one testing condition can reflect various types and combinations of relational information, including expressly non-spatial relations, reflecting the different aspects of the n -dimensional space. This view was captured by Eichenbaum and Cohen (1988) in their suggestion that these hippocampal neurons should be called “relational cells” rather than the narrower construal of place cells. This framework offers an account of why patients with hippocampal amnesia still have access to the products of sensory processing, and exhibit memory for and priming of individual items, but are unable to place these products in the multi-dimensional space that allows the items to be relationally bound to one another and flexibly connected to previously existing memories. And, critically, it explains why their relational memory is impaired for all manner of relations without any “special” deficit for any particular kind of relation.

FUTURE DIRECTIONS

Many other important issues about memory and the MTL, not covered by this review, warrant further research. One important issue is the potential division of labor in memory within the MTL (see Aggleton and Brown, 2006; Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007; Mayes et al., 2007; Squire et al., 2004). There is considerable empirical support for differential functions of the hippocampus versus surrounding MTL cortices, for relational memory versus item memory respectively, but their exact roles and their interactions remain underspecified. Another important issue that complicates work in this area concerns the definition of “items” as opposed to “relations” or “sources”. For example, the same stimulus information could be seen as the item or as the context depending on instructions and allocation of attention (see Diana et al., 2007). Moreover, two portions of the sensory array might be considered part of the same one object or as part of multiple separate objects. We (Cohen et al., 1997; Eichenbaum et al., 1994) and others (Diana et al., 2007; Mayes et al., 2007; Moses and Ryan, 2006) have noted that multiple sensory features can be fused, blended, configured, or unitized into a single item representation by structures outside of the hippocampus, such as the MTL cortices, obviating the need for hippocampal-dependent relational memory. However, it is difficult to know *a priori* when fused or unitized representations might be in play, although such representations are thought to be less flexible than relational representations (Cohen et al., 1997; Eichenbaum et al., 1994; Haskins et al., 2008). It will be critical to develop methods for acquiring independent evidence of

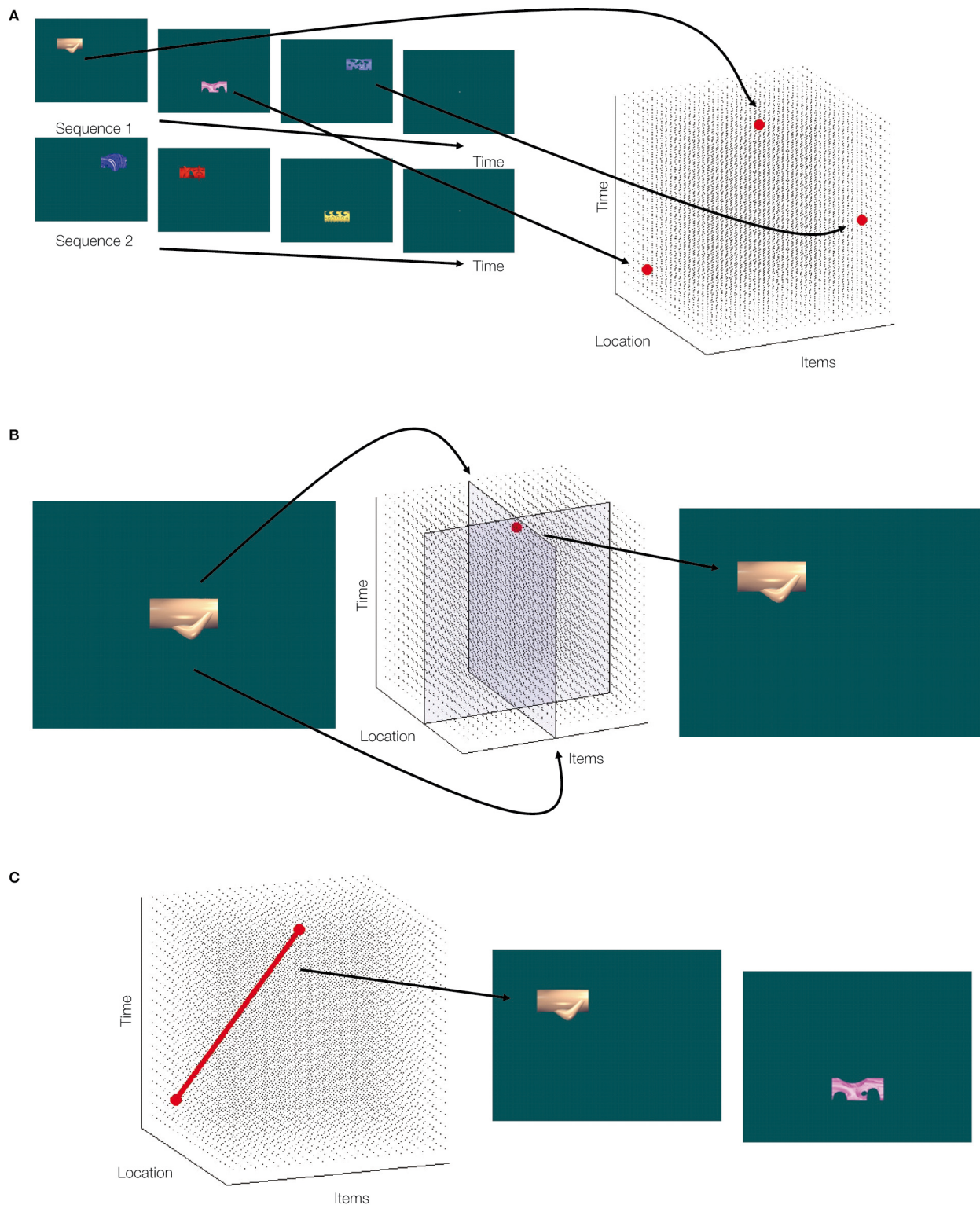


Figure 1 | A schematic of the putative hippocampal representation.

(A) At encoding (illustrated with stimuli from Konkel et al., 2008), items are encoded into a multi-dimensional representational space according to aspects such as time and location, thereby capturing all the various types of relations among items. **(B)** When relational or source memory is tested via recognition

(e.g., where was this item studied?), the item together with the source probe constrains or limits the space to be searched, aiding retrieval of the relevant information (i.e., activation of the relevant node). **(C)** Activation of a given node in the space may also lead to reactivation of related nodes (here, retrieving the next item and location in the sequence).

such representations in action. Finally, hippocampal representations themselves require further exploration: Are the various dimensions in the hippocampal representation independent, or do they covary? What determines the strengths of various links in the multi-dimensional space? These and other questions will keep memory research focused on the hippocampus for years to come.

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