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Branka Milivojevic and Christian F. Doeller

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THEORETICAL REVIEW

Mnemonic Networks in the Hippocampal Formation: From Spatial Maps to Temporal and Conceptual Codes

Branka Milivojevic and Christian F. Doeller

Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour

The hippocampal formation has been associated with a wide variety of functions including spatial navigation and planning, memory encoding and retrieval, relational processing, novelty detection, and imagination. These functions are dissimilar in terms of their behavioral consequences and modality of representation. Consequently, theoretical standpoints have focused on explaining the role of the hippocampal formation in terms of either its spatial or nonspatial functions. Contrary to this dichotomy, we propose that it is essential to look beyond these traditional boundaries between mnemonic and spatial functions and focus instead on the processes that these functions have in common. In this framework, we use electrophysiology data from the spatial domain to predict effects on the systems level, both in spatial and nonspatial domains. We initially outline the results of studies that have used findings from spatial navigation in rodents to predict the patterns of brain activity observable in people who are exploring virtual environments. We discuss how certain properties of space-defining neurons enable space to be represented as a mental map of interconnected locations, which are expressed at multiple spatial scales in separate modules in the hippocampal formation. We then suggest that memories are also organized in networks, characterized by mnemonic and temporal hierarchies. We finish by discussing how virtual-reality techniques can be used to create novel lifelike episodes allowing us to look at episodic memory processes while multivariate analysis tools can be used to explore the organizational structure of mnemonic networks.

Keywords: episodic memory, spatial memory, mnemonic resolution, temporal resolution, hippocampus

The hippocampal formation (HF) has been shown to be important for memory in humans and spatial navigation in rodents. Mainly due to methodological constraints, these two research fields have been developing with little overlap: research on memory functions of the HF has been primarily conducted on the systems level, while research on HF function in rodents has been conducted largely on the cellular level. However, advances in virtual-reality (VR) technology have made it possible to investigate spatial functions in humans, enabling us to start bridging the gap between cellular and systems-level organization of spatial cognition.

However, the gap between memory and space remains. The aim of this article is to discuss how we can bring what we know about

spatial processing from rodent research closer to the domain of memory in humans, thereby enabling us to develop novel testable hypotheses about mnemonic functions. To illustrate our approach and hypotheses, we limit ourselves to discussing only the most relevant literature, and refer the reader to other reviews for a more comprehensive overview of the literature (see e.g., Bird & Burgess, 2008; Buckner, 2010; Buzsáki & Moser, 2013; Corballis, 2013; Eichenbaum & Cohen, 2001; McNaughton, Battaglia, Jensen, Moser, & Moser, 2006; Nadel & Payne, 2002; Ranganath & Ritchey, 2012; Redish, 1999; Rissman & Wagner, 2012; Rudy & Sutherland, 1995; Smith & Mizumori, 2006; Tulving, 1983; Wang & Morris, 2010).

Spatial Representations in the Hippocampal Formation

Ever since Scoville and Milner (1957) published their seminal report on patient HM's severe memory impairments following bilateral resections of the hippocampus and surrounding medial-temporal-lobe (MTL) structures, it has been clear that the HF plays an essential role in memory formation and retrieval (Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Mishkin, Malamut, & Bachevalier, 1984; Nadel, Samsonovich, Ryan, & Moscovitch, 2000; O'Keefe & Nadel, 1978; Squire & Zola, 1996; Tulving, 1983).

Branka Milivojevic and Christian F. Doeller, Radboud University Nijmegen, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands.

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Correspondence concerning this article should be addressed to Branka Milivojevic, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: b.milivojevic@donders.ru.nl

However, an independent line of research in freely navigating rodents has demonstrated the existence of spatially tuned cells that represent an animal's current position in the environment (O'Keefe & Dostrovsky, 1971; see Figure 1A). These so-called place cells are hippocampal pyramidal neurons found in subfields CA1 and CA3 which signal the animal's position within an environment by selectively increasing their firing rate when the animal is traversing a specific place. The resulting spatial firing pattern is called a place field (O'Keefe & Dostrovsky, 1971). Place cells have also been identified in humans (Ekstrom et al., 2003), bats (Ulanovsky & Moss, 2007), and primates (Ono, Nakamura, Nishijo, & Eifuku, 1993).

Another spatially tuned cell type are grid cells, which are located one synapse upstream of the hippocampus in the medial entorhinal cortex (EC; Hafting, Fyhn, Molden, Moser, & Moser, 2005). These cells have multiple firing fields, arranged in a strikingly regular grid, which is defined by the vertices of tessellated, equilateral triangles (see Figure 1B). Grid cells have been initially observed in rats (Hafting et al., 2005) and, subsequently, also in

mice (Fyhn, Hafting, Witter, Moser, & Moser, 2008), bats (Yartsev, Witter, & Ulanovsky, 2011), and nonhuman primates (Killian, Jutras, & Buffalo, 2012).

On the population level, place and grid cells provide a map-like representation of the local environment and form the basis of the hippocampal-entorhinal navigation system (Buzsáki & Moser, 2013). Moreover, these cells are not limited to representing a particular location or grid of locations within only one environment as a new map is created whenever an animal enters a new environment. This so-called remapping allows the exact same place cells to code for multiple locations within different environments, while their place fields within any given environment are stable over time (Muller & Kubie, 1987).

In line with these electrophysiological findings, damage to the hippocampal formation impairs spatial memory both in rats (Morris, Garrud, Rawlins, & O'Keefe, 1982) and humans (Bohbot et al., 1998). Since invasive single-unit recordings in freely navigating humans are difficult, recent neuroimaging research with navigation in *virtual* environments is proving vital for systems-level investi-

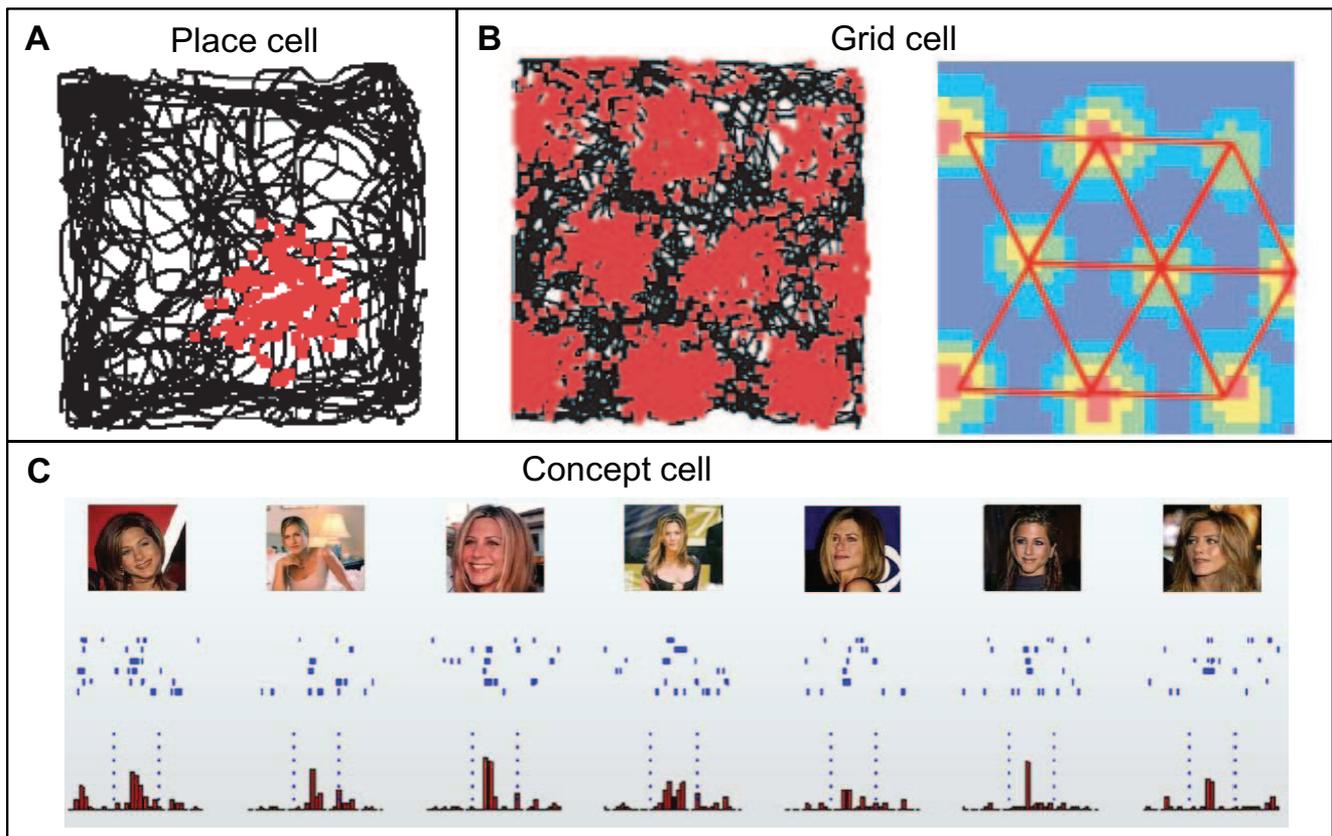


Figure 1. Example of a place field of a typical CA1 place cell. Red dots indicate action potentials superimposed on the animal's path (black line). B. Firing fields (left) and spatial autocorrelogram (right) of a typical medial entorhinal grid cell showing the characteristic hexagonal grid-like structure of the firing fields. C. Responses of a hippocampal cell in humans responding selectively to different images of the actress Jennifer Anniston. A and B adapted from "From Cells to Systems: Grids and Boundaries in Spatial Memory," by C. F. Doeller, C. Barry, & N. Burgess, 2012, *The Neuroscientist*, 18, Figure 1, p. 557. Copyright 2012 by Sage Publications. C adapted from "Invariant Visual Representation by Single Neurons in the Human Brain," by R. Quiroga, L. Reddy, G. Kreiman, C. Koch, & I. Fried, 2005, *Nature*, 435, Figure 7, Supplemental Material. Copyright 2005 by Nature Publishing Group.

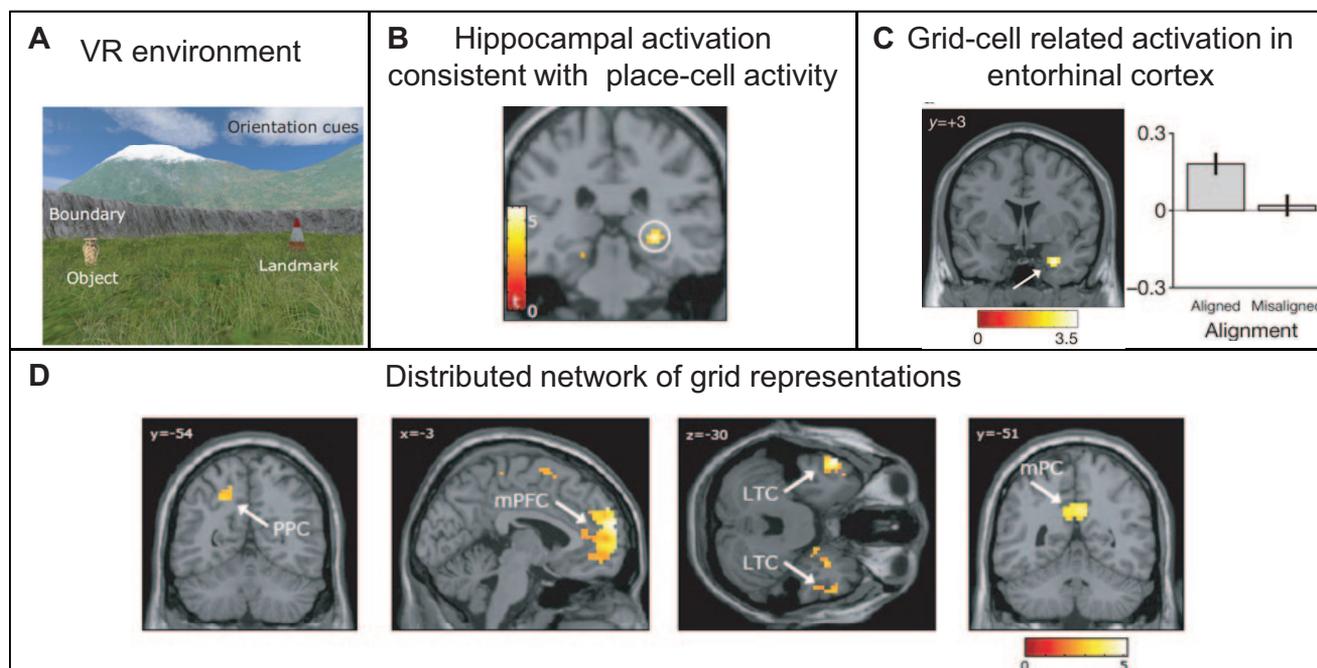


Figure 2. Spatial representations in humans consistent with population-level place and grid cell responses. A. Snapshot of a virtual-reality (VR) environment that participants explored, collecting and replacing objects found within the arena. B. Boundary-related hippocampal fMRI signal consistent with place-cell activity. C. Systematic difference of activity between runs aligned versus misaligned to the grid reflecting grid-related activation in the entorhinal cortex. D. Network of regions including posterior parietal cortex (PPC), medial prefrontal cortex (mPFC), lateral temporal cortex (LTC), and medial parietal cortex (mPC) showing grid-cell related response pattern. A and B adapted from “Parallel Striatal and Hippocampal Systems for Landmarks and Boundaries in Spatial Memory,” by C. F. Doeller, J. A. King, & N. Burgess, 2008, *PNAS: Proceedings of the National Academy of Sciences of the United States of America*, 105, Figures 1 and 2, p. 5916. Copyright 2008 by *Proceedings of the National Academy of Sciences USA*. C and D adapted from “Evidence for Grid Cells in a Human Memory Network,” by C. F. Doeller, C. Barry, & N. Burgess, 2010, *Nature*, 463, Figure 3, p. 659, and Figure 4, p. 660. Copyright 2010 by Nature Publishing Group.

gation of spatial representations in humans (e.g., Doeller, Barry, & Burgess, 2010; Doeller, King, & Burgess, 2008; Maguire et al., 1998; Wolbers, Wiener, Mallot, & Büchel, 2007).

Aiming to bridge the gap in what we know about spatial representations in rodents and humans, Doeller and colleagues (Doeller et al., 2008, 2010; Doeller & Burgess, 2008) have developed a VR object-location memory task that mimics rats’ foraging tasks (see Figure 2A for an illustration of the VR environment). They showed that systems-level fMRI responses in participants navigating a VR environment are consistent with the population response of place cells (Doeller et al., 2008) and grid cells (Doeller et al., 2010) in rodent HF (see Figure 2B for boundary-related hippocampal activation consistent with place-cell activity and Figure 2C for grid-cell related navigation effect). In this task, participants explore a circular VR environment and collect objects that at a later stage need to be re-placed at their original positions. Participants’ spatial memory performance was operationalized as the distance between the original and remembered locations.

By informing their fMRI model with predictions derived from single-cell recordings, Doeller et al. (2010) predicted that differences in activity between instances when the participants moved in alignment with the grid compared to the instances when the

movement was misaligned from the grid would reveal that grid-cell-like representations exist in the human brain (see Figure 2C for more details). Consistent with a population response of grid cells, they found systematic speed-dependent differences between aligned and misaligned movements in the EC, with a characteristic grid-related sixfold rotational symmetry of the fMRI response as a function of running direction. Moreover, they demonstrated that a wider network of regions, usually implicated in autobiographical memory and future thinking (entorhinal, posterior/medial parietal, medial prefrontal and lateral temporal cortices), is also sensitive to running direction and speed in a similar way as EC (see Figure 2D). These results provided systems-level evidence that grid-cell-like spatial representations exist beyond the EC. Since the effect was correlated with spatial-memory performance, these findings suggest that grid-cell representations might play an important role in memory formation.

Thus, in addition to the overlap between spatial and mnemonic representations in the HF, there is also substantial overlap in terms of the network of brain regions that seem to subserve both spatial cognition and nonspatial mnemonic processes (Burgess, Maguire, Spiers, & O’Keefe, 2001; Doeller et al., 2010; Renoult, Davidson, Palombo, Moscovitch, & Levine, 2012; Schacter, Addis, & Buck-

ner, 2007). Therefore, it could be possible that the distinction between nonspatial and spatial representational domains is not necessary to fully appreciate functional specialization of the HF (Bird & Burgess, 2008; Buzsáki & Moser, 2013; Eichenbaum et al., 1999; O'Keefe & Nadel, 1978; Redish, 1999). The same cells that code for animals' locations in space could also code for individual memories and the mechanisms that enable an animal to navigate through space may also enable it to navigate through the archive of its memories.

Bridging the Gap Between Memory and Space

In the current review, we consider it essential to look beyond the traditional boundaries between mnemonic and spatial functions of the HF, and focus instead on the processes that these functions have in common. In this framework, systems-level effects could be predicted based on cell-level data obtained using electrophysiological recordings. To develop this framework, we follow the lead of influential theories that explain episodic-memory function in humans in the light of place-cell properties in rodents (Bird & Burgess, 2008; Eichenbaum et al., 1999; O'Keefe & Nadel, 1978; Redish, 1999). Redish (1999), for example, discussed how sequential firing of place cells during navigation is conceptually similar to sequences of events in time that typify episodic memory.

We expand on this and similar theories by including grid cells (cf. Hasselmo, 2009), which also code for spatial information, and cells that code for nonspatial mnemonic information. Although electrophysiological data on nonspatial mnemonic functions on the single-cell level are rare (e.g., Quiñero, Reddy, Kreiman, Koch, & Fried, 2005; Rutishauser, Ross, Mamelak, & Schuman, 2010; Wood, Dudchenko, & Eichenbaum, 1999), we can, never-

theless, make systems-level predictions in the memory domain by using a combination of cell-level findings and system-level research with VR-based experiments in the spatial domain.

In accordance with two influential theories of hippocampal functioning (Eichenbaum & Cohen, 2001; O'Keefe & Nadel, 1978), we assume that both spatial and mnemonic information is organized via networks of interconnected representations. As such, our approach draws from O'Keefe and Nadel's (1978) spatial map theory and the relational memory theory proposed by Eichenbaum and Cohen (2001; Eichenbaum et al., 1999).

O'Keefe and Nadel (1978) proposed that populations of place cells provide an allocentric representation of space that is stored as an internal spatial-map-like guide that allows us to interact with and navigate in the world, resembling the cognitive map proposed by Tolman (1948). According to this view, when an animal is initially exposed to an environment, a spatial map-like representation is created in the hippocampus as a consequence of exploration of the environment (see Figure 3 for illustration), and items and events are then encoded onto this map, which forms their spatial context (O'Keefe & Nadel, 1978).

Eichenbaum and Cohen (2001; Eichenbaum et al., 1999) suggested that episodic memories are represented as a network of linked information. The links are thought to arise from an overlap between independent episodes. These points of overlap would be represented as hubs or nodes in that network (see Figure 3 for illustration). Those nodal representations would contain information which can be abstracted from the original episode, such as people, objects, landmarks, locations and perhaps even actions. As a parallel to spatial processing, a similar process of abstraction has been proposed to underlie formation of place fields in the spatial

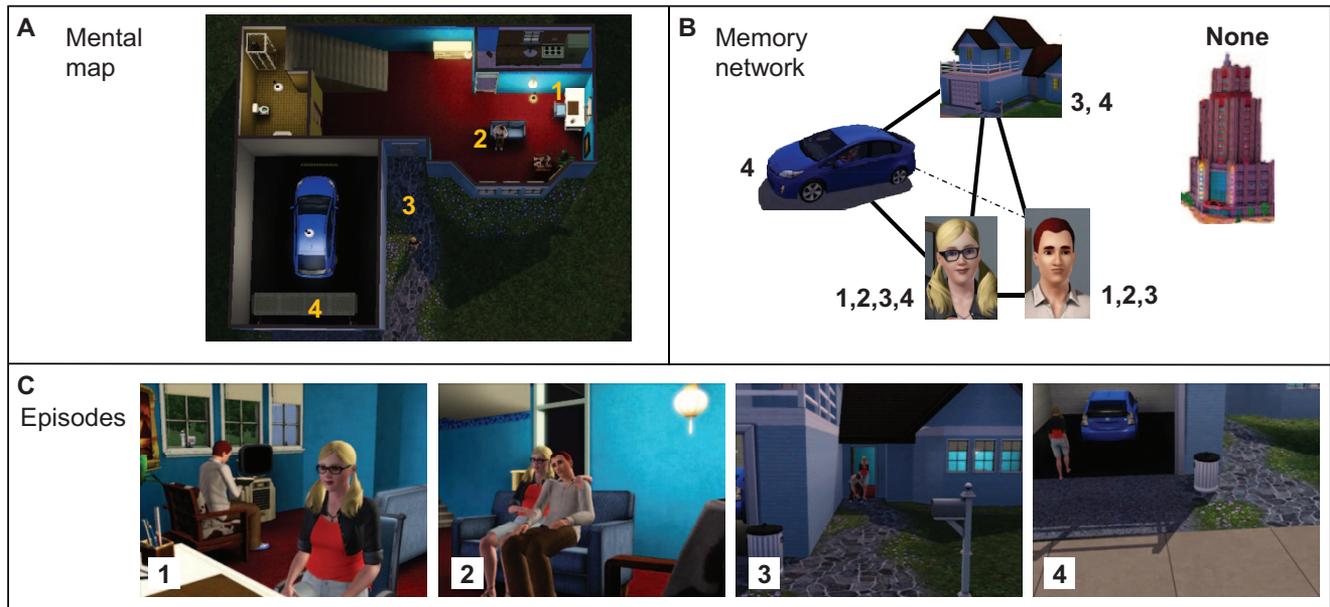


Figure 3. Illustration of types of information which may be extracted from individual episodes. A. Mental map-like representation of interconnected spatial locations. Labels 1, 2, 3, and 4 correspond to spatial locations of each episode (Part C). B. Mnemonic map of interconnected mnemonic items. Labels 1, 2, 3, and 4 correspond to which episode featured a particular mnemonic item. C. Snapshots of example episodes that contain different mnemonic items and occur in different spatial locations.

domain, because stable place fields are established through repeated visits to the same locations in space (Buzsáki & Moser, 2013).

Recent electrophysiology recordings in the human HF have revealed the presence of cells that might indeed code for information carried by the hypothesized nodes of a memory network (Quiari Quiroga, 2012; Quiari Quiroga et al., 2005). These so-called “concept cells” fire whenever a person consciously recognizes a familiar concept (see Figure 1C) irrespective of the modality of the percept (Quiari Quiroga et al., 2005). These cells have been found in the HF and amygdala (Mormann et al., 2008). Although not all of the visually responsive cells in the HF are invariant to low-level image differences (Steinmetz et al., 2011), an interesting question arises whether those cells that *are* invariant to low-level image differences may have similar underlying mechanisms as spatially tuned place and grid cells, but in the domain of memory rather than space (Quiari Quiroga, 2012).

Similarly to how place cells can have preferred place fields in different environments, the firing patterns of concept cells has been described as “sparse” in the sense that they fire in response to a small number of concepts rather than coding for only a single concept (Mormann et al., 2008; but see Plaut & McClelland, 2010). This form of conceptual coding is unlikely to reflect one-to-one mapping between individual cells and unitary concepts, and it is more likely that these concept cells are nodes within conceptual networks, which may themselves be partially overlapping (Waydo, Kraskov, Quiari Quiroga, Fried, & Koch, 2006). We propose that concept cells should also exhibit remapping, if the HF indeed codes for both space and mnemonic concepts in similar ways. Remapping may enable individual concept cells to respond to multiple independent concepts, the way the exact same place cell can code for different locations in different environments (Muller & Kubie, 1987). New concepts are likely to be integrated into already existing networks, provided that there is overlap between new events, and previously encoded events. However, if there is no overlap between previously encoded events and new events, pattern separation mechanisms in the HF may create a new independent network, similarly to the way a representation of a novel environment is established. Within the new network, the same cells could code for novel events and concepts, while remapping mechanisms would ensure that the two networks do not interfere with each other.

We propose that concepts arise through integration of mnemonic items, such as people, objects, landmarks, or locations, which appear in multiple individual episodes (see Figure 3). It is conceivable that the conceptual representations coded by these concept cells might be an intermediate form between purely episodic memories and already established semantic knowledge, which is represented outside of the HF (Patterson, Nestor, & Rogers, 2007). Furthermore, given that the hippocampus is not always needed for semantic knowledge acquisition (Vargha-Khadem et al., 1997), it is likely that this form of across-episode integration may not be the only route to semantic knowledge (see also Nadel et al., 2000, for discussion).

Nevertheless, there is increasing evidence that the HF subserves across-episode integration. For example, the HF seems to mediate inferential reasoning about relations between objects that were not directly encoded (Eichenbaum et al., 1999; Kumaran & McClelland, 2012; Kumaran, Summerfield, Hassabis, & Maguire, 2009;

Kumaran, 2012; Zeithamova, Dominick, & Preston, 2012) as well as learning regularities across episodes (Doeller, Opitz, Krick, Mecklinger, & Reith, 2005, 2006). Additionally, systems-level evidence in humans indicates that the HF may integrate novel information into pre-existing representational networks during encoding (Shohamy & Wagner, 2008; Staresina & Davachi, 2009; Zeithamova et al., 2012).

Mnemonic Resolution

But how are mnemonic concepts represented in the brain? We can gain insights into organization of mnemonic conceptual representations by translating what we know about spatial representations. In rodents, the size of place fields increases along the dorsal-to-ventral axis of the hippocampus (Kjelstrup et al., 2008). Similarly, the size of grid-cell firing fields and the spacing between the vertices of the grid increase along the dorsal-to-ventral axis of rodent medial EC (Hafting et al., 2005). Furthermore, grids cells are clustered into modules where cells with the same grid spacing and grid-field size appear within the same area of the medial EC, and discrete jumps in size can be seen between adjacent modules (Barry, Hayman, Burgess, & Jeffery, 2007; Stensola et al., 2012).

In humans, the hippocampus is sensitive to distances between places (Morgan, Macevoy, Aguirre, & Epstein, 2011) and some evidence suggests that smaller-scale detailed spatial representations may be encoded in the posterior hippocampus while large-scale representations of spatial context may be encoded in the anterior hippocampus (Nadel, Hoescheidt, & Ryan, 2013). Recent reviews have detailed the current state of knowledge regarding how functional specialization, anatomical properties (including amount of neurogenesis) and connectivity patterns (within the HF and beyond) differ between anterior and posterior hippocampus (Fanselow & Dong, 2010; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Ranganath & Ritchey, 2012). Despite these interesting models, distribution of spatial scales, particularly in the EC, is not fully understood in humans and more work is required.

In the way that spatial locations can vary in size, concepts can also vary in scope, and we suggest that mnemonic concepts are represented at multiple hierarchical levels (see Figure 4 for illustration). Conceptually comparable to the observed range of spatial scales, the representations of individual events (e.g., reading this article) would appear at the lowest level of such a mnemonic hierarchy and be represented by the “finest-scale” modules. Similarly, we would predict that “snapshots” or short segments of episodes (Figure 3C) would be represented at the lowest level of mnemonic hierarchy through activity of finest-scale modules. At the next level of mnemonic hierarchy, representations of conceptually narrower mnemonic items (e.g., reading articles) would be represented by “medium-scale” modules. These medium-scale modules would represent information which we could define as individual mnemonic items (specific individuals, objects, locations, landmarks or actions), abstracted from individual episodes from which they are acquired, and would form the nodes of the mnemonic network (Figure 3B, see also Figure 4).

The range of spatial scales observed in rats might imply (Stensola et al., 2012) that the hypothesized mnemonic hierarchy might

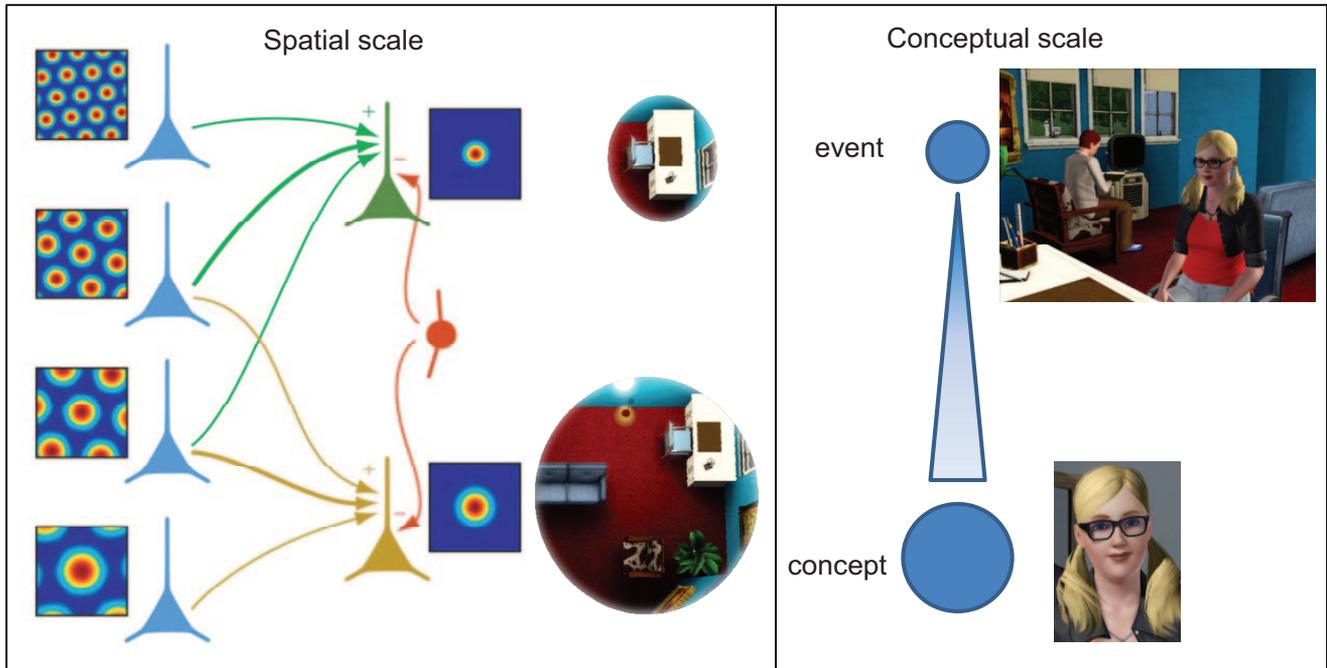


Figure 4. Illustration of spatial (left) and mnemonic or conceptual (right) scales. Different spatial scales have been observed for both grid cells in entorhinal cortex and place cells in the hippocampus. Smaller spatial scales code for smaller and more detailed sections of space (e.g., desk in the corner), while larger spatial scales code for larger sections but may lose details of the representations (e.g., desk or sofa or chair). In comparison, mnemonic scales may represent information at multiple levels, where a single event may be coded with considerable detail (smaller scale) while abstracted concepts may represent information which is repeated over multiple events. Left panel adapted from “From Grid Cells to Place Cells: A Mathematical Model,” by T. Solstad, E. I. Moser, & G. T. Einevoll, 2006, *Hippocampus*, 16, Figure 1, p. 1027. Copyright 2006 by John Wiley & Sons, Inc.

consist of several levels. We speculate that the next hierarchical level would represent information in “coarse-scale” modules and would be associated with reduced detail of those representations (e.g., reading activity in general). Such higher-level representations would entail loss of differences between individual mnemonic items and may represent conjunctions of any of the possible mnemonic items. If we consider the two characters from Figure 3, we may represent them as two individuals, or as one couple. Similarly, we may represent the house they live in as a particular location in space (lower-level representation) or as their home (a higher-level representation requiring associations between the house and the couple).

Note that the coarse module that represents the conjunction between the two individuals, and the house would do so by responding with the same pattern of neural activity to the house, the woman and the man, or any combination of the individual items. In contrast, a module that codes for the “couple” would respond with the same pattern of neural activity to the man or the woman, but not the house, and may be localized elsewhere in the HF. Place cells with firing patterns that differentiate between general and specific sets of circumstances (contexts) have been discussed by Smith and Mizumori (2006). They have shown that nonspatial contextual cues, such as task demands, have an effect on firing properties of place cells and changes to these contextual

cues can result in place-cell remapping (cf. Anderson & Jeffery, 2003). Furthermore, these contextual effects are evident at different spatial scales: Some cells are responsive at any location in the environment, as long as the rat is performing a particular task, while other cells are only responsive at a more spatially restricted location within the environment while the rat is performing the same task.

Although it is not clear whether such context-specific cells show any systematic distribution in the HF (Smith & Mizumori, 2006), evidence suggests that different levels of mnemonic hierarchies are represented in anatomically distinct areas of the HF. For example, it has been proposed that detailed forms of memory can be mapped to the posterior hippocampus (Poppenk et al., 2013) and other posterior MTL structures (Ranganath & Ritchey, 2012), while more abstract forms of memory can be mapped onto the anterior hippocampus (Poppenk et al., 2013) and other anterior MTL structures (Ranganath & Ritchey, 2012). This organizational principle may also, tentatively, relate to the proposed mnemonic resolution modules.

In addition to those coarser, higher-level, representations, frequently co-occurring finer-scale representations at a lower hierarchical level could become more closely linked in mnemonic networks. The effect of such stronger links may result in automatic reactivation of the representation of one mnemonic

concept when a related mnemonic concept is encountered (Schapiro, Kustner, & Turk-browne, 2012; Zeithamova et al., 2012). Considering the example episodes from Figure 3C, frequent co-occurrence of the male and female characters may result in both higher-level representation of them as a couple and in closely linked representations of these two characters. This linkage between the two characters may result in an automatic reactivation of one when the other is encountered. On the neural level, this automatic reactivation would result in activation of neural patterns corresponding to both of the mnemonic concepts simultaneously in the fine-scale modules. The coactivation of the same neural patterns may further strengthen connections between the cells that code for these mnemonic concepts. As mentioned earlier, commonly co-occurring mnemonic concepts may result in formation of a new mnemonic concept that would represent the co-occurring mnemonic concepts at a coarser mnemonic resolution (for similar discussion, see Kumaran & McClelland, 2012). The neural representation of this higher-level concept of the two characters as a couple would be distinct from the lower-level concepts of the two individual characters, and it remains a possibility that the higher-level conceptual similarity could exist in the absence of lower-level automatic reactivation, or automatic reactivation could be mediated through the higher-level concept. Therefore, multiple mnemonic concepts that share a higher order conceptual representation would all activate the neural pattern corresponding to that higher order conceptual representation, while neural patterns corresponding to lower-level conceptual representations would remain dissimilar.

Temporal Resolution

In addition to the location where a particular episode occurred, encoding information about the time of events is a hallmark of episodic memory (Howard & Kahana, 2002; MacDonald, Lepage, Eden, & Eichenbaum, 2011; Staresina & Davachi, 2009; Tulving, 1983), and the hippocampus has been hypothesized to represent the spatiotemporal context of events (Buzsáki & Moser, 2013; Eichenbaum & Cohen, 2001; Eichenbaum et al., 1999; Hasselmo, 2009; Howard & Kahana, 2002; O'Keefe & Nadel, 1978; Smith & Mizumori, 2006; Tulving, 1983). Furthermore, there is both systems-level (Lehn et al., 2009; Staresina & Davachi, 2009) and cell-level (MacDonald et al., 2011) evidence that the hippocampus plays a crucial role in bridging temporal gaps between events. MacDonald et al. (2011) demonstrated that cells coding for temporal information also show evidence of remapping or changes in firing preferences depending on situational context, akin to spatial remapping of place cells.

We propose that if temporal coding in the hippocampus is indeed similar to spatial coding, various temporal resolutions should also map onto modules in the HF, which were discussed above. Temporal context is thought to be encoded in a similar way as spatial context (Buzsáki & Moser, 2013). According to this theory, sequences of events in an episode, like the sequences of spatial locations during navigation, are coded by cell firing that occurs at troughs of theta-rhythm cycles. At each cycle, neurons corresponding to past, present and future positions within a sequence will fire at the phase of the theta cycle before its trough, at its trough, and after its trough, respectively (Buzsáki & Moser,

2013; Lisman & Jensen, 2013). As the animal moves through the field, the phase, at which each cell fires, shifts—a phenomenon called theta phase precession (O'Keefe & Recce, 1993). Since smaller place fields can be traversed faster than large ones, systematic oscillatory differences between finer-scale and coarser-scale modules would be expected. Indeed, entorhinal neurons along the dorso-ventral axis differ in frequency of subthreshold membrane potential oscillations (Giocomo, Zilli, Fransen, & Hasselmo, 2007), as predicted by the oscillatory interference model (Burgess, Barry, & O'Keefe, 2007), and hippocampal theta activity changes along the dorso-ventral axis (Patel, Fujisawa, Berenyi, Royer, & Buzsáki, 2012; Schmidt et al., 2013). We would predict that the temporal sequence of events could also be represented at coarser and finer scales, which could be coded by different oscillatory dynamics. Coarser temporal scales may be useful for coding sequences of events in a global sense, while finer temporal scales may be useful for coding sequences of detailed, short-lasting, events (Buzsáki & Moser, 2013). In that sense, coarser and finer temporal scales may enable compression and expansion of the level of detail that is available in episodic memories, as suggested by Poppenk et al. (2013).

Quantifying Memory Networks

Although the notion of a memory network may not be novel, the organizational structure of such networks is largely unknown and recent technological advances have made it possible to explore how such networks are organized. Namely, VR technology has progressed immensely and VR-development kits can be used to develop games, as well as animated movie scenes or virtual environments. These sorts of technological advances enable researchers to create virtual environments in which participants can navigate (Burgess et al., 2001; Doeller et al., 2008; Ekstrom et al., 2003; Maguire et al., 1998). But VR methods can also be used to create novel virtual events that participants can encode for the first time during the experimental session, thereby allowing us to track the development of spatial and mnemonic representations in realistic settings at the same time.

In conjunction with VR techniques, multivariate pattern analysis (MVPA) methods and fMRI adaptation/repetition suppression (Grill-Spector, Henson, & Martin, 2006) can be used to examine the informational content of stimuli. MVPA analyses gain power by taking into account the patterns of activation across multiple voxels and therefore become more sensitive at discriminating between conditions than univariate analyses techniques. This is particularly relevant if one is interested in quantifying the organization of *distributed* mnemonic networks. Application of MVPA methods have steadily gained in popularity since Haxby et al. (2001) showed evidence that representational content can be used to differentiate visual categories in distributed ventral visual-stream brain regions beyond the areas previously related to face and scene processing (Epstein & Kanwisher, 1998; Kanwisher, McDermott, & Chun, 1997). Despite the fact that spatial coding in rodent HF is not topographically organized and distribution of place and grid cells are likely to be uniformly distributed throughout hippocampus and medial EC, respectively, previous MVPA studies have shown that it is possible to decode participants' location within VR

(Hassabis et al., 2009). Furthermore, MVPA decoding of mnemonic representations in the HF has also been successful (Chadwick, Hassabis, Weiskopf, & Maguire, 2010; Polyn, Natu, Cohen, & Norman, 2005).

One type of MVPA analysis is representational similarity analysis (RSA). This is a computationally simple yet powerful approach that examines data for similarity of activation patterns (i.e., correlations between voxel-wise activation patterns) between two conditions or trial types. Unlike machine-learning MVPA methods, which aim to classify a trial as belonging to one of a small number of conditions, RSA allows researchers to examine neural similarity between multiple conditions. In other words, it allows us to use the data to reveal systematic relationships between conditions, rather than defining a priori categories of interest. This type of analysis has been used extensively to map areas that are involved in representation of various object categories (Kriegeskorte, Mur, & Bandettini, 2008) but can also be used to investigate the representational similarity of mnemonic representations (Schaapiro et al., 2012; Xue et al., 2010).

Questions for Future Research

The approach we have outlined in this article could potentially be used to investigate the organization of mnemonic networks in novel ways. Several questions of interest that arise from the discussion above are outlined here:

1. *Is mnemonic information represented at different resolutions in the human hippocampal formation?* In the spatial domain, locations in space are represented at multiple spatial resolutions. Such different spatial-resolution modules are observed in distinct regions in the HF. It is of considerable interest to determine whether mnemonic resolution can also be mapped onto distinct modules in the HF. By answering this question we can also determine whether there are hierarchies of mnemonic conceptual representations in the human brain.
2. *Is episodic temporal information represented at different resolutions in the human hippocampal formation?* The relationship between spatial and temporal resolution is also of considerable interest. If different spatial-resolution modules exist in the human brain, do similar modules represent shorter and longer time scales of remembered episodes? If this is indeed the case, then we can begin to investigate how information is integrated at multiple time scales.
3. *What is the nature of information encoded by nodal representations?* We have related nodal representations to concept cells in the HF. Electrophysiological recordings suggest that people and landmarks are represented by such concept cells. It would be of considerable interest to determine if other types of information, such as objects, locations and actions, are also represented by nodal representations in the HF. MVPA techniques might be suitable to test this question by tracking characters, locations, landmarks, objects and actions in VR environments.
4. *How is novel information integrated into mnemonic networks?* The question of how novel items are integrated into existing mnemonic networks remains open. In the spatial domain, place cells prefer to maintain a representation of known environments, even if the experienced environments are slightly different from the familiar ones, a phenomenon called attractor dynamics (Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005). Translating this to human memory might mean that novel mnemonic items may be preferentially integrated into existing networks, until such time that sufficient quantity of novel information may lead to the development of a new mnemonic network. Tracking the emergence of such network representations could provide novel computational principles of memory organization in the brain. Likewise, electrophysiological studies could investigate whether concept cells in humans remap, like place cells in rats do.

In summary, we have outlined a framework on mnemonic networks that builds on previous theories and studies in freely moving rodents, showing that spatially tuned neurons in the HF provide a map-like representation of locations, expressed at multiple spatial scales. We propose that mnemonic networks (a) share representational structure with the neural machinery involved in spatial navigation and (b) map onto separable representational modules in the human HF, characterized by varying mnemonic and temporal resolution. Realistic, life-like scenarios implemented using virtual reality technologies in combination with novel multivariate analysis tools could potentially reveal new insights into the organizational structure of such mnemonic networks.

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