Hippocampus at 25

COMMENTARY

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Abstract

The journal Hippocampus has passed the milestone of 25 years of publications on the topic of a highly studied brain structure, and its closely associated brain areas. In a recent celebration of this event, a Boston memory group invited 16 speakers to address the question of progress in understanding the hippocampus that has been achieved. Here we present a summary of these talks organized as progress on four main themes that address this question: (1) Understanding the hippocampus in terms of its interactions with multiple cortical areas within the medial temporal lobe memory system, (2) understanding the relationship between memory and spatial information processing functions of the hippocampal region, (3) understanding the role of temporal organization in spatial and memory processing by the hippocampus, and (4) understanding how the hippocampus integrates related events into networks of memories.

Keywords:

hippocampus, place cells, declarative memory, navigation, memory integration, time cells

Hippocampus has just passed its twenty-fifth year of publication. Over this period Hippocampus has published both research papers and reviews that present and discuss discoveries at every level of analysis, from molecular and cellular underpinnings of plasticity to many new insights from neuroimaging about functional organization of the human hippocampal region. On May 24-25, 2016, the Charles River Association for Memory (CRAM), an informal meeting of memory researchers and students in the Boston area, hosted a celebration of this anniversary with a focus on a review of progress and highlights of current research on the hippocampus and memory. At this meeting 16 speakers reviewed progress in understanding the hippocampus and associated brain areas, each from their own perspective, and updated the audience on recent findings from their laboratories. While there was no pre-planned organization of specific topics, the contents of the talks converged on four main themes that reflect areas of major current research towards understanding hippocampal mechanisms and function, and here we share our views on progress in these themes with the readers of Hippocampus.

Understanding the hippocampus in terms of its interactions with multiple cortical areas within the medial temporal lobe memory system.

Charan Ranganath critically evaluated the idea that the hippocampus and medial temporal lobe (MTL) cortex form a memory system that is anatomically and functionally separate from the surrounding neocortex. He presented the “PMAT” framework as an alternative view, in which there is no division between MTL and extra-

MTL cortical regions. Instead, analyses of functional and structural connectivity across species support a distinction between posterior medial (PM) and anterior-temporal (AT) cortico-hippocampal systems (Ranganath & Ritchey, 2012; Ritchey et al., 2015; Maass et al., 2015). Ranganath presented evidence showing that connectional differences between the PM and AT networks give rise to different functional characteristics. The research suggests that regions within the PM and AT networks are more functionally similar to other nodes in the same network—both in terms of recruitment during memory tasks and in terms of information encoded on single learning trials—than they are to regions within the other network (Ritchey et al., 2014; Wang, Ritchey et al., 2016). Ranganath described evidence for specialized coding of object information in the AT system and spatial and temporal context in the PM system in fMRI studies of spatial working memory (Libby et al., 2014) and temporal order (Hsieh et al., 2014). Finally, he presented quantitative evidence showing that the PMAT framework better accounted for intrinsic functional connectivity and task-related activity than did the MTL memory system framework.

Whereas studies of amnesia are often assumed to reflect strict localization of memory processes, the PMAT framework explains MTL amnesia as a disconnection syndrome, in which the PM and AT networks are isolated from input coming from other sensory, motor, and associative networks. PMAT additionally explains how neocortical damage in Alzheimer's Disease and Semantic Dementia differentially affect episodic and semantic memory, despite common areas of MTL damage (e.g., LaJoie et al., 2014).

Ranganath closed by highlighting the fact that PMAT can explain the same findings as memory systems models, but it can also account for findings by **Cohen** and others implicating the hippocampus in perception, language, and action. Ranganath further speculated that there could be more than two cortico-hippocampal networks. The broader implication is that the hippocampus might implement a common computation, but the functional correlates would depend on which networks are interfacing with the hippocampus during the task.

Digging more deeply into the cortical area that provides the most direct interface between the hippocampus and surrounding cortex, **Menno Witter** focused on new discoveries about interactions between lateral and medial subdivisions of the entorhinal cortex (LEC and MEC respectively; Witter et al., 2000). Although different division schemes with more subdivisions have been proposed, particularly in primates, recent functional connectivity data indicate that also in humans, a functional dichotomy may exist. This is thus in line with what has been proposed largely based on anatomical, electrophysiological and behavioral data obtained in rodents and to some extent in non-human primates. One might thus be tempted to consider the entorhinal cortex essentially as a 'twin structure' where the siblings show different phenotypes. Witter summarized briefly the 'traditional arguments' on which the subdivision between LEC and MEC was based, cytoarchitectonic differences blended with differences in hippocampal projection patterns, and major cortical connections. The latter, in particular, seem to be reflected well in the different functions acclaimed to be mediated by one or the other subdivision. Cortical connectivity of MEC is characterized by connections with areas such as the presubiculem, parasubiculum, retrosplenial cortex and postrhinal

cortex, all areas that are considered to belong to the 'spatial processing domain' of the cortex (Ranganath's PM system). In contrast, LEC is characterized by connectivity with olfactory areas, insular, orbitofrontal and perirhinal cortices (the AT system). These areas are likely more involved in processing of object information, attention and motivation.

Witter subsequently presented data on the neuronal composition and connectivity of the intrinsic networks in LEC and MEC, concluding that until recently, only neurons in layer II were reported to differ with respect to electrophysiological properties. In view of the dominance of inhibitory connectivity between stellate cells in layer II of MEC, members of his group studied local connectivity between principal neurons in layer II of LEC. Comparable to what was reported for MEC, also in LEC, fan cells are mainly indirectly connected by way of fast spiking interneurons. In MEC, layer II cells that project to the hippocampus express the molecular marker reelin, and this is also true for LEC layer II hippocampal projection neurons.

In contrast, preliminary data indicate that LEC and MEC might show differences in their interneuron network. Furthermore, genetic and developmental data indicate that the two might originate from different parts of the pallium. Together these data indicate that LEC and MEC are indeed two different cortical entities within the hippocampal region but their precise relationship is still unclear. How these components interact is key to understanding the integration of information across functional streams of information processing performed by the hippocampal formation.

David Amaral discussed several remaining challenges in understanding the relationship between the hippocampal formation and the rest of the brain. He first

focused on the development of these interactions. While there have been indications for some time that the hippocampal formation develops far earlier than other neocortical regions (Kostovic et al., 1993), there is actually very little published information on the development of hippocampal connections. Amaral (Amaral et al., 2014) demonstrated that entorhinal connections with the rest of the nonhuman primate hippocampal formation are well established by birth; even the topographic and laminar relationships are largely in place. While there are technological impediments for studying the developments of these connections in the human brain, Amaral indicated that new lipophilic dyes (Jensen-Smith et al., 2007) may facilitate examination of connectivity in the human hippocampal formation. He described ongoing studies in his laboratory to chart pathways emanating from the entorhinal cortex in the fetal monkey brain which indicate that many of these pathways are established at least by the end of the second trimester.

Another issue raised by Amaral was plasticity following early damage to the hippocampal formation. He summarized a series of studies carried out with Pierre Lavenex and Pamela Banta-Lavenex (Lavenex et al., 2006, Lavenex et al., 2007). Rhesus monkeys were tested in an open field octagonal maze that could evaluate local cue versus spatial relational learning. Animals who received complete bilateral lesions of the hippocampal formation as an adult were essentially at chance in performing this task. Even a "control" animal who turned out to have a bilateral, presumably ischemic, partial lesion of CA1 was unable to accomplish the task. However, another group of rhesus monkeys who sustained bilateral hippocampal lesions at two weeks of age were unimpaired at the task when tested as adults. This finding is reminiscent of studies in

human children who maintained the ability to learn new semantic information despite early damage to the hippocampus (Vargha-Khadem et al., 2003). Amaral pointed out that ongoing studies indicate that these early hippocampal lesions markedly changed the organization of the adjacent amygdala and presumably compensatory changes in this or other brain regions enabled the performance of a "hippocampal dependent" task without a hippocampus.

Amaral emphasized the extreme paucity of neuroanatomical information of the human brain and suggested that differences between what is known from the rodent and what actually occurs in the human may have profound influence on how the field views the function and pathology of the hippocampal formation. He highlighted the very dramatic differences in the cytoarchitectonic organization of the CA1 region and pointed to previous research (Ishizuka et al., 1995, Vargha-Khadem et al., 2003, Altemus et al., 2005) that used intracellular staining techniques to demonstrate the difference in the morphology of CA1 pyramidal cells in the rat and monkey hippocampus. Even greater differences would be expected in the human brain but the morphology of human CA1 pyramidal neurons have not been adequately studied. He also highlighted some potential differences in the connectivity of the human hippocampal formation. While the rodent has massive commissural connections between the dentate gyrus and hippocampus, these are largely missing in the monkey brain (Amaral et al., 1984). And available electrophysiological evidence suggests that this is also the case in the human brain (Wilson et al., 1990) which may have important implications for the understanding of the propagation of temporal lobe seizures. He concluded that while much has been

learned about the neuroanatomy of the hippocampal formation, much remains to be learned that can benefit from the development of new techniques.

Understanding the relationship between memory and spatial information processing functions of the hippocampal region.

In 2014, Brenda Milner won the Kavli Prize in Neuroscience for the discovery of global amnesia following hippocampal region damage and John O'Keefe both shared the Kavli Prize, and won both the Nobel Prize in Physiology and Medicine along with Edvard and May-Britt Moser, for discoveries of position coding neurons in the hippocampal region. These discoveries highlighted two prominent, and superficially disconnected perspectives on the hippocampus that emerged from different approaches and have yet to merge in a single conception about the fundamental mechanisms and functions of the hippocampal system (Eichenbaum & Cohen, 2014; Schiller et al., 2015).

Supporting the view that the hippocampus plays a general role in memory, cognitive neuroscience studies following on the observations on amnesia due to hippocampal damage in humans have shown that the hippocampus is critical to memory and is activated when humans encode and retrieve memories, and these studies have shown that the particular form of memory supported by the hippocampus is characterized by memory for facts and events (declarative memory). **Neal Cohen** argued that declarative memory involves a fundamentally relational (or associative or contextual memory) system, representing the relations among the constituent elements of experience, whether those relations are spatial, temporal, or associative/contextual (Konkel et al., 2008). The critical role of hippocampal-dependent relational memory can

be documented even at the shortest timescales. For example, in a series of studies of spatial reconstruction performance, where the spatial positions of a set of 5 or fewer objects must be reconstructed after a delay of just 4 sec, patients with hippocampal amnesia made 40x as many “swap errors” (relational errors) as did normal controls (Watson et al., 2013); normal controls showed strong correlation of hippocampal volume with spatial reconstruction task swap errors, even stronger than the correlation with classic long-(20-30min) delay neuropsychological tests; and normal controls showed an even stronger correlation between swap errors and (micro)structural integrity of the hippocampus measured with MR elastography (Schwarb et al., 2016).

What is hippocampal memory for? It is used in service of many things: not only conscious recollection or explicit remembering, but also a huge set of cognitive operations and behavioral repertoires that seem to stretch the definition of memory, including cognitive mapping/spatial navigation, inferential reasoning, future imagining, creative thinking, critical aspects of language, decision-making and adaptive problem-solving, and, active learning, active exploration, and memory-guided choice behavior (Cohen, 2015).

The critical role of the hippocampus in active exploration and active learning can be seen in work in which participants either moved a viewing window to see and study objects to be remembered for later, or else saw the exact same physical stimuli passively when someone else guided the viewing window. Subsequent memory was superior for the active vs passive condition, performance depended on “revisitation” of previously viewed objects and such revisitations activated the hippocampus and its functional connections to a larger cortical network, and patients with hippocampal

amnesia showed very few revisitations and failed to show the advantage of active vs passive viewing (Voss et al., 2012). Likewise, taking advantage of our eye movement measures of memory, we found that viewing behavior during the study phase of the spatial reconstruction task tied relational memory to active exploration and active learning: measures of the entropy vs orderliness of transitions among successive fixations during study of the objects predicted swap (relational) errors in subsequent reconstruction performance. Such lines of work emphasize the critical role of relational memory in choice behavior and action, regardless of timescale, permitting memory to guide behavior that in turns shapes behavior, both in the moment and into the future.

In contrast to this general role of the hippocampus in memory and instead supporting the view that the hippocampus plays a specific role in spatial cognition and navigation, a large body of research on the firing properties of hippocampal neurons in rodents has confirmed and extended the observation of robust spatial firing properties of hippocampal region neurons, leading to the view that the hippocampus forms a cognitive map of physical space and supports navigational computations. **John O'Keefe** argued that cognitive map theory postulates that the hippocampus provides the rest of the brain with a map of a familiar environment; the map is composed of a set of place representations connected together according to rules which represent the distances and directions amongst them. These distance and direction vectors are derived from the animal's movements in that environment.

The existence of hippocampal signals coding for location, direction, distance and speed of movement provide support for the theory. The primary behavioral test for hippocampal function is the Morris water maze navigational task that requires the

animal to approach a hidden platform in a water pool from different directions on each trial. The drawbacks of the water maze are that it is difficult to score performance and choice at any point in the maze independent of prior choices. O'Keefe described a new land- based version of the water maze which overcomes these drawbacks. His "honeycomb maze" consists of 37 octagonal platforms arranged in an octagonal pattern. Each platform is fixed to the top of a pneumatic tube allowing it to be raised and lowered independently of the others. 16 rats were trained to navigate to a specific goal platform from any location on the maze. At each location the animal stood on one of the platforms and was offered a choice of two neighboring platforms and its task was to choose the one which had the smallest angle with the direction of the goal. The animal was rewarded when it reached the goal but not elsewhere.

Control rats learned the task quickly and their performance was affected by three variables: it deteriorated as the angle between the two platforms decreased, as the distance of the choice point from the goal increased as predicted by Hull's goal gradient effect, and as the angle between the direction of the correct platform and the direction to the goal increased as predicted by Dashiell's goal direction factor. Although the percentage of correct choices decreased as the direction of the correct platform deviated from the goal direction, performance still remained above chance at all angles showing that animals are capable of determining which of 2 platforms has the smaller angle to the goal direction. O'Keefe interprets these findings as evidence that the hippocampus is capable of vector computations.

Edvard Moser outlined evidence that the brain's representation of space relies on a plethora of interconnected cell types whose firing is tuned to specific spatial

features (Hafting et al., 2005; Rowland et al., 2016). This extended network spans multiple brain areas, most notably the hippocampus (place cells) and the medial entorhinal cortex (grid cells, border cells, head direction cells and speed cells).

Spatially-modulated cells do not respond linearly to individual physical features of the sensory world. Instead it has been proposed that spatially-tuned patterns of cell activity arise as the result of network computation of the incoming multisensory information. Attractor network properties, which depend on specific connections between specific classes of cells, may be crucial to the formation of grid patterns, and grid cells, along with border cells, may be critical for the formation of place cells in the hippocampus (Rowland et al., 2016). Therefore, understanding the topology of the network and how it is assembled is fundamental to understanding how specific spatially-tuned firing emerges.

Investigating the emergence of spatially-tuned firing during development has been a valuable tool to this end. Tetrode recordings in young rats have shown that place, border and head direction cells exhibit adult-like features from the onset of spatial navigation, whereas the regular firing of grid cells emerges at the end of a protracted period during postnatal development. This protracted period coincides with the structural and functional maturation of layer II microcircuit of the medial entorhinal cortex, and specifically with the maturation of excitatory-driven fast spiking interneurons (Langston et al., 2010, Couey et al 2013). Moser showed data suggesting that manipulation of the rearing environment during this period may influence how fast animals acquire grid maps at adult age, although the data also show that maturation of grid cells is surprisingly robust to experience (rearing in a sphere disrupted grid-like

firing on the first few exposures to an outside environment at adult age but then it recovered).

The robustness to experience points to the importance of maturational factors in the development of the entorhinal-hippocampal circuit. However, surprisingly little is known about the structural maturation of this system, and the role that early excitatory activity in the different components of the network exert on its structural maturation and connectivity. Moser presented preliminary data suggesting that maturation follows the entorhinal-hippocampal circuit, from MEC layer II through CA3 to CA1 and to MEC layer V. Within MEC, the circuit developed from dorsal to ventral. The stages of the circuit are interdependent in the sense that maturation of one step is necessary for the next. Stellate cells (in the dorsal MEC) were the first to be born, and to mature, in the MEC, and activity of these cells was necessary for the maturation of all other elements of the MEC and hippocampus circuit. Moser also talked about the origin of the speed-cell signal (Kropff et al., 2015), which was hypothesized, based on preliminary data, to originate in the mesencephalic locomotor region, more specifically the penunculopontine nucleus, reaching the MEC via connections to the medial septum – diagonal band. A full characterization of the development of the spatial firing properties of neurons in this system promises new insights into how spatial information processing is organized by interactions between components of the system during development and experience.

Elizabeth Buffalo discussed her non-human primate model as a possible direction for highlighting common fundamental features of memory and spatial cognition. Motivated by research in amnesic patients with damage to medial temporal lobe

structures, research in nonhuman primates has focused mostly on the mnemonic functions of the hippocampus and associated cortices. By contrast, neurophysiological studies in rodents have primarily emphasized the spatial representations of the hippocampal formation. In her talk, Beth Buffalo argued that we should carefully consider the role eye movements play in modulating neural activity in the primate hippocampal formation. One striking difference between rodents and primates is in the way in which information about the external world is gathered. While rodents typically gather information by moving to visit different locations in the environment, primates often use eye movements to visually explore an environment, and our visual system allows for inspection of our environment at a distance (see Cohen, above). Buffalo presented data which demonstrated that eye movements affect primate neural activity in a way that is comparable to rodents' movement through space.

Using a free-viewing paradigm in monkeys, research in the Buffalo lab has identified spatial representations in neurons in the primate entorhinal cortex that reflect eye movements (Killian et al., Nature, 2012; Killian et al., PNAS, 2015). These representations include entorhinal grid cells and border cells, as well as saccade-direction cells, a potential analog to rodent head-direction cells. In addition, research in the Buffalo lab has identified theta-band oscillations in the primate hippocampus that are modulated by visual exploration. In particular, saccades serve to reset the ongoing hippocampal theta-band oscillation, perhaps as a way to optimize the processing of incoming information (Jutras et al., 2013; Jutras et al., 2014; see also Hoffman et al., 2013).

The Buffalo lab has also trained monkeys to use a joystick to navigate virtual environments, performing tasks of free-foraging and a virtual Morris water maze task of spatial memory. Preliminary data from these studies suggest that virtual navigation elicits theta-band oscillations in the primate hippocampus as well as spatial representations that reflect the maneuvers made by the monkey. Buffalo presented data demonstrating that primate hippocampal neurons show selectivity for aspects of behavior in virtual navigation including turning behavior and velocity modulation (Browning et al., 2016). Ongoing studies in the Buffalo lab utilize novel behavioral tasks and novel virtual environments to further probe the nature of hippocampal representations, with the goal of testing the overarching hypothesis that the hippocampal formation contributes to a general map of cognition, which involves space and time along with other dimensions by which cognition can be organized.

Another view on reconciling the spatial and memory views was offered by **Lynn Nadel**, who argued that first emerged out of the disagreement between human and monkey/rat data on hippocampal lesions. In the 1960s work on the patient H.M. indicated that the human hippocampus was critical for memory, but early animal models of amnesia following hippocampal damage failed initially to replicate the memory impairment. In H.M., the damage was most severe at the anterior (ventral in rats) end of the hippocampus, whereas most rat studies focused on the dorsal (posterior in humans) hippocampus. The first hint of a resolution based on the distinction of function along the long axis of the hippocampal region came from single-unit studies in rats showing that place cell field size varied along the longitudinal axis – small at the dorsal end, larger at the ventral end (Jung, Weiner and McNaughton, 1994). Work in humans

has recently suggested that the posterior/dorsal hippocampus represents spatial details while the anterior/ventral hippocampus seems to represent entire locations or contexts (Nadel, Hoscheidt and Ryan, 2013).

Work on entorhinal cortex (Stensola et al. 2015) made a crucial contribution by showing that grid cells along the axis react differentially to a remapping situation (compression of the experimental apparatus). Grid cells at the dorsal end retained spatial resolution but those at the ventral end did not, they instead retained context representation. These network-level effects show that while cells along the axis are all 'mapping space' they nonetheless have somewhat different functions reflecting a grain difference (cf. Poppenk et al., 2013). Further work on the differential function of areas along the long axis of the hippocampal region may lead to a deeper insight about spatial and memory processing.

Understanding the role of time in spatial and memory processing by the hippocampus

In addition to a strong role for space, recent work has highlighted multiple ways in which temporal organization is represented within, and influences, memory representations. Different lines of study have discovered firing sequences compressed over very brief periods that recapitulate temporally organized firing patterns observed during behavioral events, described the coding of sequential moments over the course of seconds in temporally structured experiences, and identified a key role for extended time in linking memories and influencing the strength of memories.

György Buzsáki described sharp wave ripples (SWRs) of the hippocampus, a local field potential phenomenon that involves synchronous population activity of the

hippocampus that “replays” sequences of spiking activity that recapitulate recent experiences. Sharp wave ripples occur during ‘off-line’ states of the brain, associated with consummatory behaviors and non-REM sleep, and are influenced by numerous neurotransmitters and neuromodulators. SWRs arise from the excitatory recurrent system of the CA3 region and the sharp wave ripple-induced excitation brings about a fast network oscillation (ripple) in CA1.

The spike content of sharp wave ripples is temporally and spatially coordinated by a consortium of interneurons to replay fragments of waking neuronal sequences in a compressed format. Thus, while classic hippocampal place cells activate sequentially as an animal traverses locations in space, elements of the sequence of activations are reproduced in brief form during subsequent SWRs. Given that sharp wave-ripples are involved in constructing both retrospective and prospective information, Buzsáki hypothesized that they are critical for maintaining the cognitive map. According to this hypothesis, disrupting neuronal activity specifically during sharp wave ripples should result in an altered representation of space coded by place cells.

To test this hypothesis Buzsáki’s group trained mice to learn every day a new set of three goal locations on a multi-well maze. As the mouse learned, sharp wave ripples occurred regularly at the goal locations. They aborted them in real time by optogenetic silencing of a small subset of CA1 pyramidal neurons. Following learning, control (non-illuminated and random delay-silenced) place cells maintained the location of their place fields during learning and showed increased spatial information content. In contrast, the place fields of SWR-silenced place cells shifted after learning, and their spatial information was unaltered. Sharp wave ripple silencing did not impact the firing rates or

the proportions of place cells. Optogenetic silencing of place cells at random delays after SWRs did not affect their spatial properties as compared to non-illuminated controls. These observations indicate that sharp wave ripple-associated spiking activity is necessary to maintain stable hippocampal place fields and preserve the cognitive map.

These findings demonstrate that spiking of recently active place cells during sharp wave ripples is critical for maintaining place field stability in the hippocampal CA1 region while the animal learns a new configuration of the hidden reward locations in that environment. During each session, place fields ‘re-stabilized’ during the learning trials. Silencing pyramidal neurons during SWRs in the goal areas prevented them from becoming part of the re-stabilized map. These results support the hypothesis that sharp wave ripples are essential for the maintenance of the cognitive map.

The firing patterns in sharp wave ripples reflect sequences of locations that have recently occurred during movement, raising the question of how the hippocampus incorporates information about periods when an animal is immobile at a location in between movement events. **Loren Frank** addressed the question of whether and how the hippocampus constructs a representation of current position in the absence of movement. Frank and colleagues showed that a specific subset of neurons in the CA2, CA3 and CA1 subregions demonstrates remarkably specific place-related activity during immobility (Kay et al., 2016). They first identified these neurons in hippocampal area CA2 and found that spike-triggered analysis of immobile periods indicated that these neurons associate with a specific hippocampal LFP pattern Frank termed an N-wave: a ~200 ms, low frequency positive "wave" detectable in CA3 and DG LFP. They then

found that putative interneurons located throughout the hippocampus also associate with the N-wave and further that CA1 and CA3 principal neurons associating with the N-wave also show profound location specificity during immobility. These findings identify a hippocampal network pattern, distinct from both hippocampal theta and sharp-wave ripples, which operates during immobility. The association of this pattern with spatially specific firing indicates that the hippocampus actively represents current position during immobility. Their results also demonstrate rapid switching between representation of current position and sharp wave ripple-associated representations of past ("replay") and potential ("preplay") navigational experience.

Howard Eichenbaum described a different role for time in the firing patterns of hippocampal principal cells that occurs during ongoing behavior. He outlined evidence of hippocampal "time cells" in studies where animals repeat specific temporally-structured experiences. In these studies he and others (Eichenbaum, 2014) have described neurons that fire reliably at a succession of specific moments in temporally structured episodes, much like place cells fire at specific locations in spatially structured environments. In one study his group recorded as rats ran on a treadmill during the delay period of a T-maze delayed alternation task and observed that some hippocampal neurons fired at specific brief periods during wheel running. In this study running on a treadmill that strongly maintains the animal's head and body location, thus distinguishing temporally modulated activity from changes in location as an animal runs through space (Kraus et al., 2013). In addition, by varying the speed of the treadmill they disentangled neural activity associated with elapsed time from that associated with distance traveled while running in place, and found that some cells coded only time,

others coded only distance, and most encoded time and distance to different extents. In a second study, they also identified memory-specific time cell sequences in head-fixed animals performing a non-spatial delayed matching to sample task,

Eichenbaum argued that these findings combined with many other studies provide abundant evidence that hippocampal neurons fire in specific moments in temporally structured experiences, along with or independent of spatial influences, as shown both by distinguishing spatial and temporal influences and by holding location and behavior constant (Eichenbaum, 2014). These studies indicate that the properties of hippocampal time cells parallel those of place cells. Just as place cells are guided by local spatial cues, time cells are guided by temporal cues (the length of an interval; MacDonald et al., 2011). Time cells and place cells both also encode specific stimuli and behavioral actions (MacDonald et al., 2011; Kraus et al., 2013). Like place cells, time cell activation patterns predict memory success and memory choices (Pastalkova et al., 2008).

In addition, Eichenbaum presented evidence that the medial entorhinal cortex also represents moments in time and is critical to time cell sequences in the hippocampus. His group finds that grid cells in the medial entorhinal cortex and elsewhere fire at specific moments in time (as well as with distance run) during treadmill running and, similar to the multipeaked spatial firing patterns of grid cells observed as animals explore space, many entorhinal grid cells also have multipeaked temporal firing patterns (Kraus et al., 2015). Furthermore, Eichenbaum presented preliminary evidence that brief optogenetic inactivation of a large portion of the medial entorhinal cortex disrupts time cell sequences in the hippocampus. These complementary findings

indicate that space and time are processed together in the hippocampus and medial entorhinal cortex.

Alcino Silva examined how temporal coding over long periods (minutes to hours) can link memories for related experiences. He argued that, although real world learning often requires the association of information across time, where one memory becomes associated or linked to another minutes, hours or even days apart, little is known about the molecular, cellular and circuit mechanisms that link or connect memories across time (Silva et al., 2009; Rogerson et al., 2014. Recent studies, including experiments that addressed the mechanisms that determine which neurons go on to encode a given memory (i.e., memory allocation; Han et al., 2007, 2009; Silva et al., 2009, propose that learning triggers the activation of the transcription factor CREB, and a subsequent temporary increase in neuronal excitability. This, in turn biases the allocation of a subsequent memory to the neuronal ensemble encoding the first memory, such that the recall of one memory increases the likelihood of recalling the other memory. Accordingly, studies with head mounted fluorescent microscopes and TetTag mice show that the overlap between the hippocampal CA1 ensembles activated by two distinct contexts acquired within a day is higher than when the two contexts are separated by a week, and that this CA1 ensemble overlap is associated with behavioral linking of the two contextual memories, so that the recall of one context triggers the recall of the other (Cai et al., 2016). Importantly, older mice, known to have lower CA1 excitability, do not show the overlap between CA1 neuronal ensembles, or the behavioral linking of memories across time. However, increasing cellular excitability with a chemogenetic approach (DREADD), and activating a common ensemble of CA1

neurons during two distinct context exposures, rescued the CA1 neuronal ensemble overlap deficit as well as the behavioral linking of memories in aging mice. Remarkably, recent studies have also implicated the CA1 region in human relational memory, suggesting that the studies in mice reflect general mechanisms of memory linking. Disruption of these mechanisms may result in source and relational memory problems associated with psychiatric problems, including schizophrenia, and major depression.

In addition, two other talks focused on how information encoded during an experience can persist for varying periods of time. **Richard G M Morris** emphasized that a memory trace may be encoded and stored within long-term memory, but this is no guarantee that the information will be retained for a long time. For some years, his group has been investigating the idea that neural activity happening some time before or for a period after an encoding experience can contribute to memory retention – the flow of experience. Instead of such neural activity serving to interfere with memory stability, it may sometimes trigger neuromodulatory transmission that activates an intracellular cascade potentiating the memory of events occurring around the same time. In this connection, it is notable that the retention of episodic-like memory is enhanced, in humans as well as in animals, when something novel happens shortly before or after encoding. Could it be that novelty serves to activate this same biochemical cascade whose outcome is enhanced stabilization of recently potentiated synapses? This idea is integral to the “synaptic tagging and capture” theory of lasting long-term potentiation and, with it, of the very types of synaptic plasticity widely thought to underlie memory traces.

Using an everyday memory task for mice, Morris' lab group sought the neurons mediating an apparently dopamine-dependent enhancement of memory retention by novelty, previously thought to originate exclusively from the tyrosine hydroxylase-expressing (TH+) neurons in the ventral tegmental area (VTA). He reported that neuronal firing in the locus coeruleus (LC) is especially sensitive to environmental novelty. Anatomical studies showed that LC-TH+ neurons project more profusely than VTA-TH+ neurons to the hippocampus. Further, optogenetic activation of LC-TH+ neurons mimics the novelty effect, and this novelty-associated memory enhancement was unaffected by inhibition of VTA neurons. Surprisingly, three effects of LC-TH+ photoactivation are sensitive to dopamine D1/D5 receptor blockade and resistant to noradrenergic-receptor blockade – memory enhancement, potentiation of synaptic transmission, and enhancement of long-term potentiation, in area CA1 in vitro. It seems, therefore, that LC-TH+ neurons can mediate post-encoding memory enhancement in a manner consistent with the release of dopamine in hippocampus (Takeuchi et al, Nature, 2016, in press).

Lila Davachi presented results from functional imaging experiments in humans demonstrating that multivariate hippocampal activation patterns that characterize one experience can persist into post-encoding time periods (Tambini et al, 2010; Tambini and Davachi, 2013; Tompary et al, 2015). Individual differences in the persistence of hippocampal activation patterns relates to subsequent memory in that they predict later memory for the representations encountered during the task. Furthermore, memory-associated hippocampal patterns persist into active time periods as well. In one experiment Davachi's group had participants doing 'math' instead of resting and showed

that CA1-VTA connectivity that was present during the associative encoding task and predictive of later associative memory also persisted into the subsequent unrelated MATH task. Furthermore CA1-VTA connectivity during the unrelated math task also predicted later associate memory independently from what was seen during encoding (Tompary et al, 2015). Davachi also presented data showing that post-encoding manipulations (in fear conditioning and reward learning) can alter the subsequent consolidation of conceptually related representations via a retroactive selective memory enhancement (Dunsmoor et al, 2015). These latter findings bear resemblance to Morris' tag and capture hypothesis derived from animal models.

In addition, Davachi suggested if patterns representing past experiences persist into the future that they might influence how new information is encoded. She outlined preliminary data that shows that hippocampal (and whole brain) patterns of activity measured during emotional encoding bleeds ~ 30 minutes forward into a neutral encoding block and changes both behavior, by enhancing the encoding of the neutral scenes (makes them stronger in memory as if they were emotional), and brain patterns which look more similar to emotional encoding brain patterns than neutral brain patterns.

Davachi concluded that these findings parallel in humans key observations from studies on aspects of temporally persistent activity in animals. The persistence of hippocampal brain patterns (in particular in CA1) is related to hippocampal replay in sharp wave ripples as well as to Silva's new data on overlapping hippocampal ensembles representations that are acquired close in time. Also, the retroactive memory effects of VTA activation and emotional experiences are likely related to Morris' tag and capture hypothesis and new findings. Davachi suggested two distinct

mechanisms for temporal integration (Davachi and DuBrow, 2015) that are in the field right now: (1) For experiences that occur close in time, ongoing hippocampal patterns may involve overlapping neural ensembles and this context signal can promote their associative retrieval or integration. (2) For experiences that are very far apart in time (minutes, hours, days), reactivation of the prior event can promote the integration of new events into old memory patterns.

Understanding how the hippocampus integrates related events into networks of memories.

Lynn Nadel introduced the critical importance of integrating memories acquired at different times in his comments on consolidation and reconsolidation of memories. He argued that current questions about consolidation emerged because the initial idea that the hippocampus is in some sense a temporary memory system has been overturned, and we now understand that the recall of relatively detailed remote memories requires hippocampal involvement (cf. Nadel et al., 2000; Ryan et al., 2001). This shift was reflected in Multiple Trace Theory (Nadel & Moscovitch, 1997), which raised the possibility that reactivating an apparently consolidated memory might plausibly change it. Work in his lab on episodic memory reconsolidation (Hupbach et al, 2007, 2008, 2009) showed that memories can be changed, and has now explored some of the factors controlling what Nadel thinks is actually memory “updating”. Context seems particularly important, as does the nature of the reactivation. In a recent fMRI study his group has shown that when reactivation robustly activates a brain network indicative of the retrieval of extensive detail one sees very little updating – it appears

that vividly retrieved memories are more readily distinguished from the current situation, hence less likely to be conflated.

Alison Preston emphasized that learning events do not occur in isolation; rather, how we learn in the present is often influenced by what we have experienced in the past. The recent findings on interactions between experiences that occur close in time, as discussed above, is one way in which past experiences influence new memories. Beyond the role of time, work in Preston's laboratory has shown that new events that relate to past experiences in context trigger reactivation of existing memories in both neocortex and CA1, a striking parallel to recent findings from the Silva group (Schlichting, Zeithamova, & Preston, 2014; Zeithamova, Dominick, & Preston, 2012). Reactivated memories may then be modified to accommodate the new information. Such integration of past and present experience can promote the formation of abstract knowledge that represents the relationships among distinct learning events (Schlichting, Mumford, & Preston, 2015). In a series of human neuroimaging studies, the Preston group has shown that integrated memories that span experiences support novel behavior across a variety of tasks and cognitive domains, including inferential reasoning, concept formation, and generalization (Schlichting & Preston, 2015).

Preston highlighted an important role for anterior hippocampus and posterior medial prefrontal cortex (mPFC) in memory integration. Preston's group has shown that increased hippocampal-mPFC engagement and connectivity during events overlapping with existing memories promotes both new learning and inference (Zeithamova et al., 2012). Interactions between these regions during rest periods following overlapping event encoding further benefit memory for the overlapping content, indicating that offline

periods and consolidation more generally plays an important role in memory restructuring (Schlichting & Preston, 2014; Schlichting & Preston, In press).

Memory integration can also be shown at a representational level within anterior hippocampus and posterior mPFC. Distributed activation patterns within these regions become more similar for events that share common features (Schlichting et al., 2015), and come to reflect memory schemas that guide decisions in novel learning contexts (Molitor et al., 2015). Moreover, mPFC mediates updating of hippocampal representations when environmental goals change. Through interactions with mPFC, anterior hippocampal schemas reflect the changing relevance of individual event features, prioritizing features that are most relevant for the current task goal.

The notion that new learning interacts with existing memories is by no means new; yet, the neural mechanisms and behavioral implications of memory integration are not well understood. Collectively, Preston's work on this topic provides a mechanistic account of how past and present experience dynamically interact, leading to the formation of adaptive memory representations that anticipate future use. The results suggest that mPFC biases reactivation toward behaviorally relevant memories, promoting updating of hippocampal representations to reflect the general principles that are shared among specific events (Schlichting & Preston, 2015). More broadly, these findings indicate that integrated hippocampal representations support a host of flexible behaviors beyond the domain of episodic memory.

Stephan Heckers considered what we know about the hippocampus with regard to understanding schizophrenia. Schizophrenia is one of several neuropsychiatric disorders characterized by abnormalities of hippocampal structure and function. In

contrast to the longstanding interest in exploring the cerebral cortex as the neural basis for schizophrenia, studies of the hippocampus did not begin until 1985 (Bogerts et al., 1985). Since then, postmortem studies of hippocampal structure and gene expression and increasingly sophisticated in-vivo studies of hippocampal structure and function have provided convincing evidence for a role of the hippocampus in the disease mechanism of psychotic disorders (Heckers and Konradi, 2010).

Smaller hippocampal volume is the most robust structural brain change in schizophrenia, with an effect size exceeding 0.5 (Adriano et al., 2012). There is significant interest in identifying the anatomical pattern of this volume change. While there is some evidence for greater volume changes in subfield CA1, there is now also emerging evidence for greater changes in the anterior (uncus) compared to the posterior hippocampus (Strange et al., 2014)

Most neuropsychiatric disorders that are characterized by a volume reduction of the hippocampus (e.g., AD, epilepsy, amnesia) are associated with significant loss of hippocampal principal cells (i.e., the glutamatergic, excitatory pyramidal cells). The volume change in schizophrenia, however, is not due to a loss of pyramidal cells (Konradi et al., 2011). In contrast, there are significant decreases in the protein and gene expression of subsets of hippocampal interneurons. Two types, the parvalbumin-positive and the somatostatin-positive interneurons are particularly affected, leading to an abnormal balance of excitation and inhibition (Heckers and Konradi, 2010; Konradi et al., 2011).

Recent neuroimaging studies have provided compelling evidence that the baseline activity of the anterior hippocampus is increased and that the recruitment

during task performance is impaired in schizophrenia (Heckers et al., 1998) (Schobel et al., 2009). This affects relational memory specifically, resulting in decreased performance on associative and transitive inference tasks (similar to those employed by Preston) in the early as well as later stages of schizophrenia (Armstrong et al., 2012a; Armstrong et al., 2012b; Ongur et al., 2006). These findings highlight the importance of linking the information processing functions of the hippocampus to cellular and structural abnormalities in mental disorders.

Issues of 25 years ago, current understandings, and future challenges

We have come a long way in the last 25 years. Where do we stand and where are we headed? Although there is not a full consensus on the following points, the following are some of the common threads that cut across the themes outlined above and, combined with the themes outlined above and recent findings by other investigators, these new understandings indicate that we have moved on from questions about what role the hippocampus plays to deeper, recently emergent questions about mechanisms of information processing in the hippocampal system:

1. 25 years ago it was about the fundamental role of the hippocampus in consolidation as a temporary store, but now it's about integrating the coding of new events with past and succeeding events. **Nadel** (above) directly addressed this issue in his work (Nadel & Moscovitch, 1997), and the findings on the phenomenon of reconsolidation are now widely interpreted as a result of successful or failed integration of new memories within an existing network

(Morris et al., 2006; Hardt et al., 2010; Mckenzie & Eichenbaum, 2011; Dudai, 2012). Evidence for the integration of memory representations in the hippocampus is now well established in studies on the acquisition and expression of related memories in humans (**Preston**, above; Milivojevic & Doeller, 2013; Collin et al., 2015; Constantinescu et al., 2016) and animals (**Silva, above;** Mckenzie et al., 2014). The integration process is strongly influenced by the salience of succeeding new experiences (**Morris, Davachi,** above). Furthermore the role of the hippocampus in memory integration extends to the expression of integrated memories in on-line processing, associated with guiding of choice behavior in the context of spatial navigation, inferential reasoning, planning, and more.

2. In studies on rodent models, 25 years ago it was about spatial coding as the predominant feature of hippocampal neuronal activity, but now temporal organization is also a prominent dimension of hippocampal representations of ongoing experience (**Eichenbaum,** above; Pastalkova et al., 2008; Naya & Suzuki, 2011; Allen et al., 2016), post-encoding stabilization (**Buzsaki**, above; Carr et al., 2011; Wikenheiser & Redish, 2015a), linking memories across experiences (**Frank, Davachi,** above), and planning (**Cohen**, above; Diba and Buzsáki, 2007; Pfeiffer & Foster, 2013; Wikenheiser & Redish, 2015b).
3. 25 years ago it was about the hippocampus itself or the hippocampal region as a whole, but now it's about how the hippocampus interacts with other areas within the medial temporal lobe and elsewhere. As outlined by **Ranganath** (above), emerging evidence has allowed us to trace specific processing pathways by

which hippocampal representations facilitate learning of high-level knowledge about people, things, and their spatial, temporal, and situational relationships in a given context. Within such schemes the hippocampus is recognized as a "hub" between a system that originates in the classic "where" stream and processes spatial organization and movement through the organization, and a system that originates in the "what" stream and processes high order representations of events. The idea that the hippocampus is the convergence site for these systems (Davachi, 2006; Eichenbaum et al., 2007) takes on new importance as we recognize interactions in both directions between the hippocampus and these streams (Rowland et al., 2016; Knierim et al., 2103; Keene et al., 2016) and between the streams directly (**Witter**, above). The interactions between these areas may support all manner of organization in memory, including organization by time (**Eichenbaum**, above) and abstract dimensions (Constantinescu et al., 2016).

4. 25 years ago it was about whether the hippocampus is specialized for spatial memory and navigation (**O'Keefe, Moser**, above) or supports a broader role in memory (**Cohen**, above; Squire & Wixted, 2011). But now it's about identifying the breadth of dimensions by which the hippocampal region organizes representations of experience and the range of behavioral repertoires it enables. In addition to spatial dimensions, other dimensions by which the hippocampal region maps cognition include egocentric visual space (**Buffalo, Cohen**, above), social relations (Tavares et al., 2015), object associations (**Cohen, Preston, Heckers,** above), temporal relations (**Cohen, Silva**, **Davachi, Eichenbaum,**

above), and conceptual space (Buzsáki and Moser, 2012; Constantinescu et al., 2016). Furthermore, space as well as non-spatial dimensions may be mapped along a continuum of the resolution of detail of events within the long axis of the hippocampal region, from specific memories and particular places in the dorsal (rats)/posterior (humans) hippocampus to generalized memories in the ventral/anterior hippocampus (**Nadel, Preston**, above; Brun et al., 2008; Kjelstrup et al. 2008; Royer et al., 2010; Komorowski et al., 2013; Collin et al., 2015; Schlichting et al., 2015).

The themes and threads presented here set some of the challenges in our next decades of exploring the hippocampus.

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References

Adriano F, Caltagirone C, Spalletta G. 2012. Hippocampal volume reduction in first-episode and chronic schizophrenia: a review and meta-analysis. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry 18(2):180-200.

Allen TA, Salz DM, McKenzie S, Fortin NJ. 2016. Nonspatial Sequence Coding in CA1 Neurons. J Neurosci. 36(5):1547-1563.

Altemus KL, Lavenex P, Ishizuka N, Amaral DG. 2005. Morphological characteristics and electrophysiological properties of CA1 pyramidal neurons in macaque monkeys. Neuroscience 136:741-756.

Amaral DG, Insausti R, Cowan WM. 1984. The commissural connections of the monkey hippocampal formation. J Comp Neurol 224:307-336.

Amaral DG, Kondo H, Lavenex P. 2014. An analysis of entorhinal cortex projections to the dentate gyrus, hippocampus, and subiculum of the neonatal macaque monkey. J Comp Neurol 522:1485-1505.

Armstrong K, Kose S, Williams L, Woolard A, Heckers S. 2012a. Impaired associative inference in patients with schizophrenia. Schizophrenia Bulletin 38(3):622-629.

Armstrong K, Williams LE, Heckers S. 2012b. Revised associative inference paradigm confirms relational memory impairment in schizophrenia. Neuropsychology 26(4):451-458.

Bogerts B, Meertz E, Schonfeldt-Bausch R. 1985. Basal ganglia and limbic system pathology in schizophrenia. A morphometric study of brain volume and shrinkage. Archives of General Psychiatry 42(8):784-91.

Browning Y, Jutras MJ, Morrisroe K, Lewis C, Fries P, Stieglitz T, Fairhall A, Buffalo EA. 2016. Spatial representations in the monkey hippocampus during free-foraging in virtual reality. Society for Neuroscience abstract, San Diego, 2016.

Brun VH, Solstad T, Kjelstrup KB, Fyhn M, Witter MP, et al. 2008. Progressive increase in grid scale from dorsal to ventral medial entorhinal cortex. Hippocampus 18:1200–1212.

Buzsáki G, Moser EI. 2013. Memory, navigation and theta rhythm in the hippocampal-entorhinal system. Nat Neurosci. 16(2): 130-138.

Cai DJ, Aharoni D, Shuman T, Shobe J, Biane J, Song W, Wei M, Veshkini M, La-Vu M, Flores S, Lou J, Kim I, Sano Y, Kamaga M, Zhou M, Baumgaertel K, Lavi A, Tuszynski M, Mayford M, Golshani P, Silva AJ. 2016. A shared neural ensemble links distinct contextual memories encoded close in time. Nature 534:115-118.

Carr MF, Jadhav SP, Frank LM. 2011. Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. Nat Neurosci 14(2):147-153.

Cohen NJ. 2015. Navigating life. Hippocampus, 25: 704-708.

Collin SH, Milivojevic B, Doeller CF. 2015. Memory hierarchies map onto the hippocampal long axis in humans. Nat Neurosci 18:1562-1564.

Constantinescu AO, O'Reilly JX, Behrens TEJ. 2016. Organizing conceptual knowledge in humans with a grid like code. Science 352:1464-1468.

Couey JJ, Witoelar A, Zhang SJ, Zheng K, Ye J, Dunn B, Czajkowski R, Moser MB, Moser EI, Roudi Y, Witter MP. 2013. Recurrent inhibitory circuitry as a mechanism for grid formation. Nat Neurosci. 16(3): 318-324.

Eichenbaum H, Yonelinas AR, Ranganath C. 2007. The medial temporal lobe and recognition memory. Annual Review of Neuroscience 30:123-152.

Eichenbaum H, Cohen NJ. 2014. Can we reconcile the declarative memory and spatial navigation views of hippocampal function? Neuron 83:764-770.

Davachi L. 2006. Item, context and relational episodic encoding in humans. Current Opinion in Neurobiology 16:693-700.

Davachi L, DuBrow, S. 2015. How the hippocampus preserves order: the role of prediction and context. Trends in cognitive sciences 19(2): 92-99.

Diba K, Buzsáki G. 2007. Forward and reverse hippocampal place-cell sequences during ripples. Nat Neurosci. 10(10): 1241-1242.

Dudai Y. 2012. The restless engram: consolidations never end. Annual review of neuroscience 35:227–247

Dunsmoor JE, Murty V, Davachi L,Phelps EA. 2015. Emotional learning selectively and retroactively strengthens episodic memories for related events, Nature. 20(7547):345-8.

Eichenbaum, H. 2014. Time cells in the hippocampus: A new dimension for mapping memories. Nature Reviews Neuroscience. 15:732-744.

Eichenbaum H and Cohen NJ (2014) Can we reconcile the declarative memory and spatial navigation views of hippocampal function? Neuron 83:764-770.

Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. 2005. Microstructure of a spatial map in the entorhinal cortex. 436(7052): 801-806.

Han J-H, Kushner SA, Yiu AP, Cole CJ, Matynia A. Brown RA, Neve RL, Guzowski JF, Silva AJ, Josselyn SA. 2007. Neuronal competition and selection during memory formation. Science, 316: 457-460.

Han J-H, Kushner SA, Yiu AP, Hsiang H-LL, Buch T, Waisman B, Bontempi B, Neve RL, Frankland PW, Josselyn SA. 2009. Selective erasure of a fear memory. Science 323:1492-1496.

Hardt O, Einarsson EO, Nader K (2010) A bridge over troubled water: reconsolidation as a link between cognitive and neuroscientific memory research traditions. Annual review of psychology 61:141–167.

Heckers S, Konradi C. 2010. Hippocampal pathology in schizophrenia. In: Swerdlow NR, editor. Current Topics in Behavioral Neurosciences: Behavioral Neurobiology of Schizophrenia and Its Treatment. New York: Springer. p 529-553.

Heckers S, Rauch SL, Goff D, Savage CR, Schacter DL, Fischman AJ, Alpert NM. 1998. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. Nature Neuroscience 1(4):318-323.

Hoffman KL, Dragan MC, Leonard TK, Micheli C, Montefusco-Siegmund R, Valiane TA. 2013. Saccades during visual exploration align hippocampal 3-8 Hz rhythms in human and non-human primates. Front Sys Neurosci. 2013 Aug 30, 7:43.

Hsieh LT, Gruber MJ, Jenkins LJ, Ranganath C. 2014. Hippocampal activity patterns carry information about objects in temporal context. Neuron. 81(5):1165-1178.

Hupbach A, Gomez R, Hardt O, Nadel L. 2007. Reconsolidation of episodic memories: a subtle reminder triggers integration of new information. Learn Mem. 14(1-2):47-53.

Hupbach A, Hardt O, Gomez R, Nadel L. 2008. The dynamics of memory: context-dependent updating. Learn Mem. 15(8):574-9.

Hupbach A, Gomez R, Nadel L. 2009. Episodic memory reconsolidation: updating or source confusion? Memory. 17(5):502-10.

Ishizuka N, Cowan WM, Amaral DG. 1995. A quantitative analysis of the dendritic organization of pyramidal cells in the rat hippocampus. J Comp Neurol 362:17-45.

Jensen-Smith H, Gray B, Muirhead K, Ohlsson-Wilhelm B, Fritzsch B. 2007. Long-distance three-color neuronal tracing in fixed tissue using NeuroVue dyes. Immunological investigations 36:763-789.

Jung MW, Wiener SI, McNaughton BL. 1994. Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. J Neurosci. 14(12):7347-56.

Jutras MJ, Fries P, Buffalo EA. 2013. Oscillatory activity in the monkey hippocampus during visual exploration and memory formation. Proc Natl Acad Sci U S A 110(32): 13144-13149.

Jutras MJ, Buffalo EA. 2014. Oscillatory correlates of memory in non- human primates. Neuroimage. 85 Part 2; 694-701.

Kay K, Sosa M, Chung JE, Karlsson MP, Larkin MC, Frank LM. 2016. A hippocampal network for spatial coding during immobility and sleep. Nature. 531(7593):185-90.

Keene C, Bladon J, McKenzie S, Liu C, O'Keefe J, Eichenbaum H. 2016. Complementary functional organization of neuronal activity patterns in the lateral and medial entorhinal cortex. J Neurosci 36:3660-3675.

Killian NJ, Potter SM, and Buffalo EA. 2015. Saccade direction encoding in the primate entorhinal cortex during visual exploration. Proc Natl Acad Sci U S A. 112(51):15743-15748.

Killian NJ, Jutras MJ, Buffalo EA. 2012. A map of visual space in the primate entorhinal cortex. Nature 491:761-764.

Kjelstrup KB, Solstad T, Brun VH, Hafting T, Leutgeb S, et al. 2008. Finite scale of spatial representation in the hippocampus. Science 321:140–143

Knierim JJ, Neunuebel JP, Deshmukh SS. 2013. Functional correlates of the lateral and medial entorhinal cortex: objects, path integration and local-global reference frames. Philos Trans R Soc Lond B Biol Sci. 369:1635

Komorowski RW, Garcia CG, Wilson A, Hattori S, Howard, MW, Eichenbaum, H. 2013. Ventral hippocampal neurons are shaped by experience to represent behaviorally relevant contexts. J Neurosci 33:8079-8087.

Konkel A, Warren DE, Duff MC, Tranel D, Cohen NJ. 2008. Hippocampal amnesia impairs all manner of relational memory. Frontiers of Human Neuroscience, 2: 15.

Konradi C, Yang CK, Zimmerman EI, Lohmann KM, Gresch P, Pantazopoulos H, Berretta S, Heckers S. 2011. Hippocampal interneurons are abnormal in schizophrenia. Schizophrenia Research 131(1-3):165-73.

Kostovic I, Petanjek Z, Judas M. 1993. Early areal differentiation of the human cerebral cortex: entorhinal area. Hippocampus 3:447-458.

Kraus BJ, Robinson RJ II, White JA, Eichenbaum H, and Hasselmo ME. 2013. Hippocampal 'time cells': Time versus path integration. Neuron 78: 1090-1101.

Kraus BJ, Brandon MP, Robinson II RJ, Connerney MA, Hasselmo ME, Eichenbaum H. 2015. During running in place, grid cells integrate elapsed time and distance run. Neuron 88:578-589.

Kropff E, Carmichael JE, Moser MB, Moser EL. 2015. Speed cells in the medial entorhinal cortex. Nature. 523(7561): 419-424.

La Joie R, Landeau B, Perrotin A, Bejanin A, Egret S, Pélerin A, Mézenge F, Belliard S, de La Sayette V, Eustache F, Desgranges B, Chételat G. 2014. Intrinsic connectivity identifies the hippocampus as a main crossroad between Alzheimer's and semantic dementia-targeted networks. Neuron. 81(6):1417-28.

Langston RF, Ainge JA, Couey JJ, Canto CB, Bjerknes TL, Witter MP, Moser EI, Moser EB. 2010. Development of the spatial representation system in the rat. Science 328(5985): 1576-1580.

Lavenex P, Lavenex PB, Amaral DG. 2007. Spatial relational learning persists following neonatal hippocampal lesions in macaque monkeys. Nat Neurosci 10:234-239.

Lavenex PB, Amaral DG, Lavenex P. 2006. Hippocampal lesion prevents spatial relational learning in adult macaque monkeys. J Neurosci 26:4546-4558.

Libby LA, Hannula DE, Ranganath C. 2014. Medial temporal lobe coding of item and spatial information during relational binding in working memory. J Neurosci. 34(43):14233-14242.

MacDonald CJ, Lepage KQ, Eden UT, Eichenbaum H. 2011. Hippocampal “time cells” bridge the gap in memory for discontiguous events. Neuron 71:737-749.

Maass A, Berron D, Libby LA, Ranganath C, Düzel E. 2015. Functional subregions of the human entorhinal cortex.Elife. Jun 8;4. doi: 10.7554/eLife.06426.

McKenzie S, Eichenbaum H. 2011. Consolidation and reconsolidation: Two lives of memories? Neuron 71: 224-233.

McKenzie S, Frank AJ, Kinsky NR, Porter B, Rivière PD, Eichenbaum H. 2014. Hippocampal representation of related and opposing memories develop within distinct, hierarchically-organized neural schemas. Neuron 83:202-215

Milivojevic B, Doeller CF. 2013. Mnemonic networks in the hippocampal formation: from spatial maps to temporal and conceptual codes. J Exp Psychol Gen. 142:1231-1241.

Molitor, R. J., Schlichting, M. L., Mack, M. L., Guarino, K. F., McKenzie, S., Eichenbaum, H., & Preston, A. R. (2015). Schema representations in hippocampus and medial prefrontal cortex support generalization in novel contexts. Paper presented at the Annual Meeting of the Society for Neuroscience, Chicago, IL.

Morris RGM, Inglis J, Ainge JA, Olverman HJ, Tulloch J, Dudai Y, Kelly PAT. 2006. Memory reconsolidation: sensitivity of spatial memory to inhibition of protein synthesis in dorsal hippocampus during encoding and retrieval. Neuron 50:479–489.

Nadel L, Moscovitch M. 1997. Memory consolidation, retrograde amnesia and the hippocampal complex. Curr Opin Neurobiol. 7(2):217-27.

Nadel L, Samsonovich A, Ryan L, Moscovitch M. 2000. Multiple trace theory of human memory: computational, neuroimaging, and neuropsychological results. Hippocampus. 10(4):352-68.

Nadel L, Hoscheidt S, Ryan LR. 2013. Spatial cognition and the hippocampus: the anterior-posterior axis. J Cogn Neurosci. 25(1):22-8.

Naya Y, Suzuki WA. 2011. Integrating what and when across the primate medial temporal lobe. Science 333, 773-776.

Ongur D, Cullen TJ, Wolf DH, Rohan M, Barreira P, Zalesak M, Heckers S. 2006. The neural basis of relational memory deficits in schizophrenia. Archives of General Psychiatry 63(4):1268-1277

Pastalkova E, Itskov V, Amarasingham A, Buzsáki G. 2008. Internally generated cell assembly sequences in the rat hippocampus. Science 321:1322-1327.

Pfeiffer BE, Foster DJ. 2013. Hippocampal place-cell sequences depict future paths to remembered goals. Nature. 497(7447):74-79.

Poppenk J, Evensmoen HR, Moscovitch M, Nadel L. 2013. Long-axis specialization of the human hippocampus . Trends Cogn Sci. 17(5):230-40.

Ranganath C, Ritchey M. 2012. Two cortical systems for memory-guided behaviour. Nat Rev Neurosci. 13(10):713-726.

Ritchey M, Libby LA, Ranganath C. 2015. Cortico-hippocampal systems involved in memory and cognition: the PMAT framework. Prog Brain Res. 219:45-64.

Ritchey M, Yonelinas AP, Ranganath C. 2014. Functional connectivity relationships predict similarities in task activation and pattern information during associative memory encoding. J Cogn Neurosci. 26(5):1085-1099.

Rogerson T, Cai DJ, Frank A, Sano AJ, Shobe J, Lopez-Aranda MF, Silva AJ. 2014. Synaptic tagging during memory allocation. Nat Rev Neurosci 15(3):157-169.

Rowland DC, Roudi Y, Moser MB, Moser EI. (2016) Ten years of grid cells. Annu Rev Neurosci. 2016 Mar 9. [Epub ahead of print]

Royer S, Sirota A, Patel J, Buzsáki G. 2010. Distinct representations and theta dynamics in dorsal and ventral hippocampus. J. Neurosci 30(5): 1777-1787.

Ryan L, Nadel L, Keil K, Putnam K, Schnyer D, Trouard T, Moscovitch M. 2001. Hippocampal complex and retrieval of recent and very remote autobiographical memories: evidence from functional magnetic resonance imaging in neurologically intact people. Hippocampus 11(6):707-14.

Schlichting, M. L., Mumford, J. A., & Preston, A. R. (2015). Learning-related representational changes reveal dissociable integration and separation signatures in the hippocampus and prefrontal cortex. Nat Commun, 6, 8151.

Schlichting, M. L., & Preston, A. R. (2014). Memory reactivation during rest supports upcoming learning of related content. Proc Natl Acad Sci U S A, 111(44), 15845-15850.

Schlichting, M. L., & Preston, A. R. (2015). Memory integration: neural mechanisms and implications for behavior. Curr Opin Behavioral Sciences, 1, 1-8.

Schlichting, M. L., & Preston, A. R. (In press). Hippocampal-medial prefrontal circuit supports memory updating during learning and post-encoding rest. Neurobiol Learn Mem.

Schlichting, M. L., Zeithamova, D., & Preston, A. R. (2014). CA1 subfield contributions to memory integration and inference. Hippocampus.

Schlichting ML, Zeithamova D, Preston, AR. 2014. CA1 subfield contributions to memory integration and inference. Hippocampus 24(10):1248-1260.

Schiller D, Eichenbaum H, Buffalo EA, Davachi L, Foster DJ, Leutgeb S, and Ranganath C. 2015. Memory and space: Towards an understanding of the cognitive map. Journal of Neuroscience 35:13904-13911.

Schobel SA, Lewandowski NM, Corcoran CM, Moore H, Brown T, Malaspina D, Small SA. 2009. Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. Archives of General Psychiatry 66(9):938-46.

Schwarb H, Johnson CL, McGarry MD, Cohen NJ. 2016. Medial temporal lobe viscoelasticity and relational memory performance. Neuroimage. 132:534-541.

Silva AJ, Zhou Y, Rogerson T, Shobe J, Balaji J. 2009. Molecular and cellular approaches to memory allocation in neural circuits. Science 326(5951): 391-395.

Squire LR, Wixted JT. 2011. The cognitive neuroscience of human memory since H.M. Annu Rev Neurosci 34:259-288.

Strange BA, Witter MP, Lein ES, Moser EI. 2014. Functional organization of the hippocampal longitudinal axis. Nat Rev Neurosci 15(10):655-69.

Stensola T, Stensola H, Moser MB, Moser EI. 2015. Shearing-induced asymmetry in entorhinal grid cells. Nature. 518(7538):207-12.

Takeuchi T, Duszkiewicz AJ, Sonneborn A, Spooner PA, Yamasaki M, Watanabe M, Smith CS, Fernández G, Deisseroth K, Greene RW and Morris RGM. 2016. Locus coeruleus and dopaminergic consolidation of everyday memory. Nature, in press.

Tambini A, Davachi L. 2013. Hippocampal multi-voxel encoding patterns persist into post-encoding rest. Proceedings of the National Academy of Sciences 110(48):19591-6

Tambini A, Ketz N Davachi L. 2010. Enhanced brain correlations during rest are related to memory for recent experiences. Neuron. 65:280-290. (Video abstract link: http://www.cell.com/neuron/abstract/S0896-6273%2810%2900006-1)

Tavares RM, Mendelsohn A, Grossman Y, Williams CH, Shapiro M, Trope Y, Schiller D. 2015. A Map for Social Navigation in the Human Brain. Neuron 7:231-243.

Tompary A, Duncan K, Davachi L. 2015. Consolidation of associative and item memory is related to post-encoding functional connectivity between the ventral tegmental area and different medial temporal lobe subregions during an unrelated task. J Neurosci. 35 (19): 7326-31.

Vargha-Khadem F, Salmond CH, Watkins KE, Friston KJ, Gadian DG, Mishkin M. 2003. Developmental amnesia: effect of age at injury. Proc Natl Acad Sci U S A 100:10055-10060.

Voss JL, Warren DE, Gonsalves BD, Federmeier KD, Tranel D, Cohen NJ. 2012. Spontaneous revisitation during visual exploration as a link among strategic behavior, learning, and the hippocampus. Proceedings of the National Academy of Sciences USA, 108: E402-E409.

Wang SF, Ritchey M, Libby LA, Ranganath C. 2016. Functional connectivity based parcellation of the human medial temporal lobe. Neurobiol Learn Mem. 2016 Jan 19. pii: S1074-7427(16)00017-4. doi: 10.1016/j.nlm.2016.01.005. [Epub ahead of print]

Watson PD, Voss JL, Warren DE, Tranel D, Cohen NJ. 2013. Spatial reconstruction by patients with hippocampal damage is dominated by relational memory errors. Hippocampus, 23: 570-580.

Wikenheiser AM, Redish AD. 2015a. Hippocampal theta sequences reflect current goals. Nat Neurosci. 18(2):289-294.

Wikenheiser AM, Redish AD. 2015b. Decoding the cognitive map: ensemble hippocampal sequences and decision making. Curr Opin Neurobiol 32:8-15.

Wilson CL, Isokawa M, Babb TL, Crandall PH. 1990. Functional connections in the human temporal lobe. I. Analysis of limbic system pathways using neuronal responses evoked by electrical stimulation. Experimental brain research 82:279-292.

Witter MP, Wouterlood FG, Naber PA, Van Haeften T. 2000. Anatomical organization of the parahippocampal-hippocampal network. Ann N Y Acad Sci. 911:1-24.

Zeithamova, D., Dominick, A. L., & Preston, A. R. (2012). Hippocampal and ventral medial prefrontal activation during retrieval-mediated learning supports novel inference. Neuron, 75(1), 168-179.