Where next for the study of anhydrobiosis? Studies have largely relied on detecting gene upregulation upon exposure to desiccation. This approach will fail to identify constitutively expresssed genes that are important for anhydrobiotic survival but whose expression does not change during desiccation and rehydration. We still do not understand why some nematodes, for example, do not survive desiccation, while others can survive immediate exposure to extreme desiccation, and yet others require preconditioning at a high relative humidity. A comparative approach is likely to be informative, as has recently been published comparing the genomes of *P. vanderplanki* and its desiccation-intolerant relative *P. nubifer*.

Where can I find out more?

Barrett, J. (1982). Metabolic responses to anabiosis in the fourth stage juveniles of *Ditylenchus dipsaci* (Nematoda). Proc. R. Soc. Lond. B. *216*, 159–177.

Boschetti, C., Pouchkina-Stantcheva, N., Hoffmann, P., and Tunnacliffe, A. (2011). Foreign genes and novel hydrophilic protein genes participate in the desiccation response of the bdelloid rotifer *Adineta ricciae*. J. Exp. Biol. *214*, 59–68.

Crowe, J.H. (2014). Anhydrobiosis: an unsolved problem. Plant Cell Environ. *37*, 1491–1493.

Erkut, C., and Kurzchalia, T.V. (2015). The *C. elegans* dauer larva as a paradigm to study metabolic suppression and desiccation tolerance. Planta *242*, 389–396.

Gusev, O., Suetsugu, Y., Cornette, R., Kawashima, T., Logacheva, M.D., Kondrashov, A.S., Penin, A.A., Hatanaka, R., Kikuta, S., Shimura, S., *et al*. (2014). Comparative genome sequencing reveals genomic signature of extreme desiccation tolerance in the anhydrobiotic midge. Nat. Commun. *5*, 4784.

Perry, R.N., and Wharton, D.A. (2011). Molecular and Physiological Basis of Nematode Survival (CABI Publishing, Wallingford).

Potts, M., Slaughter, S.M., Hunneke, F.U., Garst, J.F., and Helm, R.F. (2005). Desiccation tolerance of prokaryotes: Application of principles to human cells. Integr. Comp. Biol. *45*, 800–809.

Tyson, T., O'Mahony Zamora, G., Wong, S., Skelton, M., Daly, B., Jones, J.T., Mulvihill, E.D., Elsworth, B., Phillips, M., Blaxter, M., *et al*. (2012). A molecular analysis of desiccation tolerance mechanisms in the anhydrobiotic nematode *Panagrolaimus superbus* using expressed sequence tags. BMC Res. Notes *5*, 68.

Wang, C., Grohme, M.A., Mali, B., Schill, R.O., and Frohme, M. (2014). Towards decrypting cryptobiosis - analyzing anhydrobiosis in the tardigrade *Milnesium tardigradum* using transcriptome sequencing. PLoS One *9*, http://dx.doi.org/10.1371/journal.pone.0092663.

Wharton, D.A. (2002). Life at the Limits: Organisms in Extreme Environments (Cambridge University Press, Cambridge).

Department of Zoology, University of Otago, P.O. Box 56, Dunedin, New Zealand.
*E-mail: david.wharton@otago.ac.nz

Primer

The hippocampus

James J. Knierim

The hippocampus is one of the most thoroughly investigated structures in the brain. Ever since the 1957 report of the case study H.M., who famously lost the ability to form new, declarative memories after surgical removal of the hippocampus and nearby temporal lobe structures to treat intractable epilepsy, the hippocampus has been at the forefront of research into the neurobiological bases of memory. This research led to the discovery in the hippocampus of long-term potentiation, the pre-eminent model of the cellular basis of memory. Furthermore, the discovery of place cells, head direction cells, and grid cells in the rodent hippocampal formation established a firm foundation for the notion that the hippocampus plays a critical role in memory formation by providing the brain with a spatiotemporal framework within which the various sensory, emotional, and cognitive components of an experience are bound together. This framework allows the experience to be stored in such a way that it can be later retrieved as a conscious recollection of that experience.

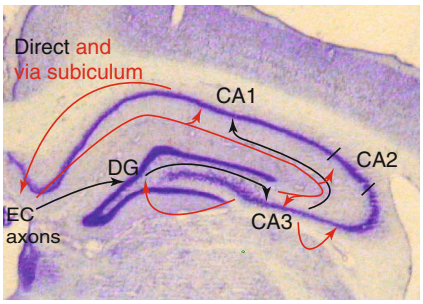
In this primer, I will first review the basic anatomy of the hippocampus, giving a historical overview of early conceptions of hippocampal circuitry and describing modern findings that are the inspiration of much current work on hippocampal physiology and function. Next, I will consider human and animal lesion studies, the results of which underlie our basic understanding that the hippocampus performs a critical function in the brain's ability to store and retrieve memories (particularly episodic memories in humans). Finally, I will review key aspects of hippocampal behavioral neurophysiology and relate them to current theories of hippocampal function.

Anatomy

Intrinsic circuitry

In humans, the hippocampus is an elongated structure buried deep within the medial temporal lobe. Its resemblance in gross dissection to a seahorse inspired its naming after this sea creature (genus *Hippocampus*). In rodents, the hippocampus is a relatively large, cashew-shaped structure lying just beneath the neocortex. A cross-section of its long axis reveals the classic, textbook depiction of the hippocampal anatomical connectivity, the so-called 'trisynaptic loop' (Figure 1). The entorhinal cortex provides the major cortical input to the hippocampus, with its strongest projections via the perforant path to the dentate gyrus (DG) region (Synapse 1). The DG projects to the CA3 region via the mossy fiber pathway (Synapse 2). CA3 projects to the CA1 region via the Schaffer Collateral pathway (Synapse 3). Finally, CA1 projects back to the entorhinal cortex, completing the loop. An important addition to the classic trisynaptic circuitry is that CA3 axons, in addition to their projections to CA1, send collaterals that make synapses onto other CA3 neurons. This recurrent collateral pathway inspired a number of influential theories of CA3 as an autoassociative memory system, displaying attractor dynamics that are critical for supporting a distributed memory.

The unidirectional circuitry of the trisynaptic loop was originally believed to be mainly contained within a cross-sectional slice (or



Current Biology

Figure 1. Coronal slice through the transverse axis of the hippocampus.
The black lines trace the classic 'trisynaptic loop'. The red lines depict other important pathways in the hippocampus, including the direct projections from entorhinal cortex (EC) to all three CA fields, the feedback to the EC via the subiculum, the recurrent collateral circuitry of CA3, and the feedback projection from CA3 to DG. For simplicity, many other details of the connectivity of the hippocampus are omitted.

lamella) of the hippocampus. The 'lamellar hypothesis' proposed that the hippocampus was structured as a stack of these lamellae, organized as independent, functional modules along the longitudinal axis of the hippocampus. Modern anatomical tracing studies, however, have revealed widespread connectivity along the longitudinal axis, showing that transverse slices (cross-sections, as in Figure 1) through the hippocampus are not functionally independent. The connectivity within the transverse axis is also more complex, with multiple, parallel processing circuits and feedback circuits. The entorhinal cortex projects not only to DG, but also directly to the CA3 and CA1 regions. CA3 provides a feedback projection to the DG, via the excitatory mossy cells of the dentate hilus, thus violating the earlier notion that hippocampal processing is exclusively unidirectional. Finally, recent experiments have fostered a new appreciation of the CA2 region, which has traditionally been considered a transition zone between CA1 and CA3: it is now clear that CA2 has its own functions and must be regarded as a distinct computational unit on par with CA3 and CA1.

Entorhinal inputs and outputs

The hippocampus receives major cortical input from the entorhinal cortex, which is composed of two distinct brain regions in rats. The medial entorhinal cortex (MEC), especially its most caudal regions, is associated with spatial processing regions of the brain, such as the retrosplenial cortex and the dorsal presubiculum (also called the postsubiculum). The lateral entorhinal cortex (LEC) is associated with high-order, item-recognition areas, such as the perirhinal cortex. Both regions receive input from the prefrontal cortex and olfactory cortex, and they also send projections to each other. The MEC and LEC projections to DG and CA3 overlap, appearing to target the same cells. Thus, DG and CA3 can combine the information conveyed by both inputs. In contrast, the projections to CA1 are segregated along the transverse axis, such that the part of CA1 close to the subiculum receives input from LEC and the part of CA1 close to CA2 receives input from MEC. The superficial layers of MEC and LEC project to the hippocampus (in general, layer II projects to DG and CA3, whereas layer III projects to CA1 and subiculum). The deep layers receive feedback from the hippocampus. Connections from deep to superficial layers, as well as the presence of basal dendrites of layer II/III neurons in deep layers, form a critical anatomical feedback loop that allows the hippocampal output to directly affect the neural processing of the hippocampal inputs.

Other cortical and subcortical connections

In addition to the major inputs from the entorhinal cortex, the hippocampus receives direct inputs from the perirhinal cortex and postrhinal cortex. It also receives major subcortical inputs from the medial septum (related to the strong theta rhythm in the hippocampus), locus coeruleus, raphe nucleus, nucleus reuniens, and amygdala. The CA3 and CA1 regions have a major output to the lateral septum via the fornix. CA1 also projects to the nucleus accumbens (ventral striatum), amygdala, and prefrontal cortex. This list is incomplete, and is presented here as an indication that the hippocampal anatomy is more complex than the classic trisynaptic circuit. The reader is referred to more complete anatomy reviews mentioned in the Further Reading list.

Longitudinal axis

As a final point of anatomy, there are major differences in connectivity patterns along the longitudinal axis of the hippocampus. In rodents, this axis is often referred to as the dorsal-ventral axis. The dorsal hippocampus is the most rostral part of the hippocampus. At more caudal levels, the hippocampus curves ventrally. The dorsal hippocampus receives inputs from the parts of the MEC with the finest resolution spatial cells. The ventral hippocampus is highly connected with the prefrontal cortex and the amygdala. In primates, the entire hippocampus is located ventrally in the medial temporal lobe and is arranged primarily in an anterior-posterior orientation. The anterior hippocampus of primates corresponds to the ventral hippocampus of rodents, and the posterior hippocampus of primates corresponds to the dorsal hippocampus of rodents. In rodents, the dorsal hippocampus and ventral hippocampus are differentially involved in spatial versus emotional memory and cognition. Because most single unit recording studies and many lesion studies in rodents are performed on dorsal hippocampus, and many primate studies concentrate on the anterior hippocampus (the homolog of ventral hippocampus in rodents), data that appear to show species differences between rodents and primates may actually reflect differences between the computational processes of dorsal (posterior) hippocampus versus ventral (anterior) hippocampus.

Hippocampal lesions

Human studies

There is a rich literature on the amnesic effects of hippocampal damage in humans. The hippocampus is highly susceptible to damage from epilepsy, hypoxia, ischemia, or encephalitis. The entorhinal cortex is typically the first region of the brain to show the plaques and tangles of Alzheimer's disease. Years ago, a number of epilepsy patients, including the famous H.M., had their hippocampus removed in an attempt to treat their debilitating seizures. Studies of these patient populations showed that a major function of the human hippocampus and its adjacent brain regions is to support the creation of new, declarative memories (memories that can be brought to conscious awareness and verbalized).

Declarative memory can be subdivided into two types: episodic memory and semantic memory. Episodic memory refers to a recollection about a specific event in one's past, tied to a specific time and place — for example "This morning, in my kitchen, I ate an egg for breakfast". Semantic memory refers to one's store of general knowledge about the world — for example "Eggs come from chickens and are a typical breakfast food". Many investigators believe that the hippocampus proper is particularly

crucial for forming new episodic memories, whereas other parts of the medial temporal lobe are more critical for forming new semantic memories. In support of this distinction, some patients who sustained hippocampal damage early in life have deficits in episodic memory, finding it difficult to remember events of their daily lives, but seem to have an intact semantic memory, being able to learn school subjects such as languages and acquiring factual knowledge within a normal range.

Patients with hippocampal damage can retain memories of events that occurred years prior to the onset of their brain damage. This sparing of remote memory has led to the notion of a consolidation gradient, whereby memories gradually become independent of the hippocampus as they are consolidated in other brain regions (presumably neocortex). Note that this phenomenon, called 'systems consolidation', differs from a related concept, called 'cellular consolidation', in which memories become resistant to change over time due to changes in gene expression and protein synthesis in individual neurons. Some investigators question whether the spared, remote memories of hippocampal patients carry the same richness of detail expected from a true episodic recall of the event, for example "I vividly recall my excitement at receiving a bicycle on my 10th birthday", as opposed to a more semanticized version of the event, such as "I know that I got a bicycle on my 10th birthday". This important question is still under intense debate.

A more recent twist was the discovery that these amnesic patients also displayed a deficit in their ability to imagine new experiences. When asked to describe an imaginary scenario, such as a day at the beach, hippocampal patients were able to mention the individual components associated with such an experience, such as the presence of sand, waves, seagulls, and so on, but were less able than control subjects to construct a detailed narrative, such as "I am lying on my back and feel the warmth of the sun on my face. I hear the sound of seagulls to my left. Behind me I hear a group of people playing volleyball". This inability to construct from its individual components a mental narrative of an imagined event may be related to the inability to reconstruct a mental narrative of an actual autobiographical event (episodic memory amnesia).

Animal studies

The literature on the effects of hippocampal lesions in experimental animals is controversial. Much work in recent decades has centered largely on the question of whether spatial learning is the primary (exclusive) deficit that results from hippocampal damage, or whether there might also be nonspatial deficits. The dominant test for hippocampal damage has been the Morris water maze. In the basic version of this task, rats are placed in a pool of opaque water and swim in search of a hidden escape platform, submerged just under the water surface, which is always located in a fixed position. Because there are no local cues available in the water, and because the rats are started from a new location each trial, the rats cannot use surface cues or a simple motor strategy to find the platform; instead they are presumably forced to rely on a spatial map strategy. Rats with hippocampal lesions have severe deficits in learning this task. Other tasks that are commonly used to test for hippocampal spatial deficits are the radial maze and contextual fear conditioning.

An early model of hippocampus-dependent learning in primates was the delayed nonmatch-to-sample task. In this task, monkeys are presented with a sample object; after a delay, they are required to choose between the sample object and a new object in order to obtain a reward. Subsequent work demonstrated that, under most conditions, the memory deficit resulted primarily from damage to the entorhinal and perirhinal cortex rather than the hippocampus proper. Other tasks that are not overtly spatial do appear to depend on the hippocampus. One example is Pavlovian trace conditioning, in which a temporal gap separates the offset of a conditioned stimulus, such as a tone, and the onset of an unconditioned stimulus, such as a puff of air to the eye. The hippocampus is required for a subject to learn to produce a conditioned response in trace eyeblink and trace fear conditioning. In contrast, when the unconditioned stimulus overlaps in time with the offset of the conditioned stimulus, called delay conditioning, the hippocampus is not required.

Physiology

A tremendous amount of information is known about the neurophysiology of the hippocampus. Most of this work has been done on rats, but research on mice is increasing at a fast pace. Rather less work has been done on other species, including rabbits, bats, birds, monkeys, and humans, but such research allows for important cross-species comparisons.

Place cells

The most famous and extensively studied correlate of hippocampal neural activity is the place cell (Figure 2). Pyramidal cells of the CA1, CA2, and CA3 regions, as well as granule cells of the DG, fire selectively when rats occupy one or more specific locations in an environment, called the 'place field' or 'firing field'. The discovery of these cells prompted the theory that the hippocampus forms a cognitive map of the environment. Although many descriptions of place cells state that they are controlled primarily by distal landmarks, this misconception has been overturned by numerous studies showing that salient local cues can tightly control place fields, even overriding the influence of distal landmark under certain conditions. The spatial firing of place fields can also be influenced by local boundaries and by self-motion cues, such as vestibular input, that support path integration.

It is increasingly clear that place cells are a heterogeneous population with varying functional properties. Under some circumstances, some place fields appear to encode location primarily based on distances to boundaries or discrete object landmarks; other place fields apparently derive their spatial specificity from path integration computations. Place cells in different parts of the hippocampus have different properties, especially when measured at the level of neural ensembles. Individual place fields

are larger in more ventral parts of the hippocampus compared to dorsal parts, consistent with the anatomical and functional differences described above. Thus, place cells receive input from multiple sources, including self-motion, boundaries, objects, odors, and head-direction. They appear to combine these disparate sets of cues to create a map of spatial context that is used to underlie flexible learning and cognition (see below).

Grid cells and boundary cells

Grid cells are not found in the hippocampus proper, but close by in the MEC and other extrahippocampal regions. Grid cells fire in multiple locations in an environment, which are arranged in a precise, hexagonal grid. It is thought by many investigators that grid cells are the fundamental unit for calculating a position signal based on self-motion, a process known as path integration. As MEC provides a major input to the hippocampus, the grid cells presumably play a major role in the spatial computations of the hippocampus. Early models assumed that grid cells provide the spatial input that drives the spatial selectivity of place cells, but recent evidence shows that disruption of grid cells can leave place cells largely intact. Moreover, inactivation of place cells causes disruption of the MEC grid cells. It is possible that boundary (border) cells, another class of MEC cells that fire selectively when the rat is located at or near the boundary of an environment, may provide information to support place cell firing, at least in small environments. Based on the anatomical feedback loops described above, the relationship between grid cells and boundary cells in MEC, and place cells in the hippocampus, probably cannot be described in a simple feedforward model, but rather the different types of cells affect each other in recursive processing loops.

Time and distance coding

Under certain conditions, such as when rats run in place in a running wheel during the delay period of a memory task, or when they are confined in a small space during such a delay period, hippocampal cells encode the time elapsed since the start of the epoch. If the firing of the cell is plotted as a function of time, some cells have a peak firing rate shortly after the start of the epoch, and other cells have peak firing rates at longer times. When firing rate is plotted as a function of time, these 'time fields' look just like place fields that are plotted as a function of location along a linear track. When rats run in place on a treadmill, some place cells also are affected by the virtual distance traveled on the treadmill.

It appears that the same pyramidal cells can encode time, distance, or location, depending on the conditions. Although these three properties are phenomenologically very distinct, current computational theories of path integration can provide a unifying framework. According to both continuous attractor theories and oscillatory interference theories, the same neural network can in principle produce all three properties depending on the precise nature of the inputs that update the system. If the network has some type of unvarying, periodic output, it will function as a clock (time cells); if the periodic output is modulated by the animal's speed of movement, it will function as an odometer (distance cells); if the periodic output is modulated by both speed and heading direction, it will function as a positioning system (place/grid cells).

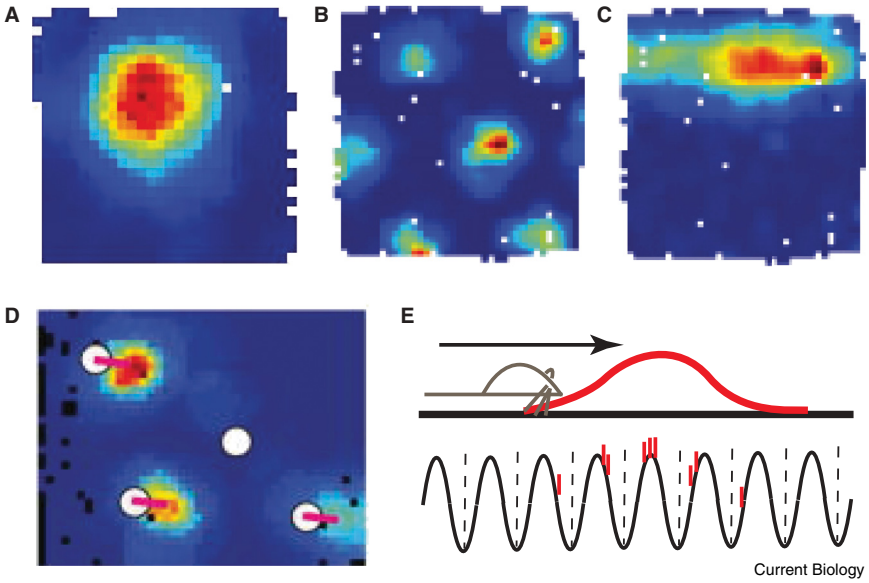


Figure 2. Behavioral correlates of hippocampal and medial entorhinal neurons.
(A) Place field recorded from a CA3 pyramidal cell (data provided by H. Lee). (B) Grid cell recorded from the MEC (data provided by F. Savelli). (C) Boundary cell recorded from the MEC (data provided by F. Savelli). (D) Object-vector cell recorded from CA1 (data provided by S. Deshmukh). The three firing fields of this cell maintain a similar direction and distance from 3 of the 4 objects in the environment (white circles). (E) Illustration of theta phase precession. The top depicts a place field (red) when a rat runs on a linear track. The bottom depicts eight cycles of the theta rhythm as the rat runs through the place field. Red tick marks indicate spikes. The spikes occur at a late phase of the theta cycle as the rat enters the field, and the spikes occur at increasingly earlier phases as the rat progresses through the place field.

Remapping

Only a fraction of place cells are active in a given environment, and this active subset changes when the animal enters a new environment. The activation of separate spatial maps in different environments or contexts is called 'remapping'. Even in the same environment, the place cell representations can remap in response to changes in the shape or color of the environment, changes in the task of the animal, or behavioral manipulations that disorient the animal. Remapping can take the form of a complete reorganization of place fields, with an independent set of active cells (called 'global remapping'). Alternatively, under some conditions, the place cells can alter

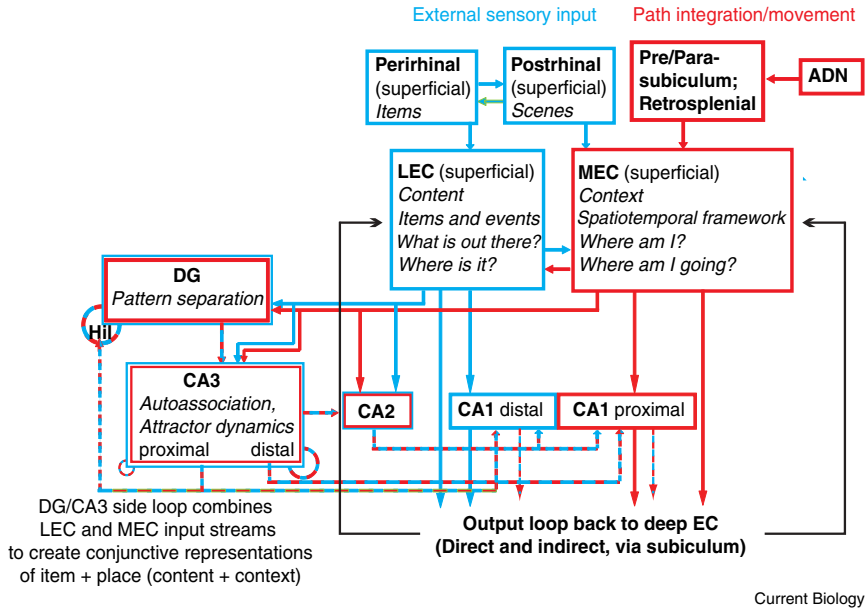


Figure 3. Anatomical model of information flow and functions of the hippocampal system in support of memory.

In this highly simplified schematic, the LEC pathway (blue) receives input from the perirhinal cortex (as well as other inputs, such as olfactory cortex). It is thought to convey information about individual items and events in the external world, including information about their spatial location. The MEC pathway (red) receives input from postrhinal cortex (parahippocampal cortex in primates) about scenes as well as information about self-movement, head direction, and path integration from presubiculum, parasubiculum, and retrosplenial cortex. Head direction input arrives via the anterior dorsal nucleus (ADN) of the thalamus. The DG and CA3 combine overlapping input from both pathways to store in memory conjunctive representations of the content of an experience within its spatiotemporal context. Putative attractor networks in CA3 support mnemonic computations associated with distributed memory systems, such as pattern separation and pattern completion. The output of the DG/CA3 processing loop is sent to CA1, both directly and indirectly via CA2, where it is compared with direct input from EC. The output of this comparison is fed back to the deep layers of EC, which distribute the information to other neocortical areas as well as back to the superficial EC layers, where it can influence the next stage of memory processing.

their firing rates substantially (in the extreme case shutting off entirely), but the firing fields of active cells remain in the same locations (called 'rate remapping'). Partial remapping can occur when some place fields remap and others do not.

The remapping phenomenon may reflect the ability of the hippocampus to support context-dependent memory. The creation of new maps for different environments, or different behavioral situations in the same environment, may allow the hippocampus to store the specific memories and behavioral contingencies specific to each situation. Because grid cells of the MEC do not share this remapping property, the creation of context-specific representations in the hippocampus may be the most important transformation that occurs between the spatial representations of the MEC and of the hippocampus.

Theta and large irregular activity

In rodents, the hippocampal EEG is dominated by a striking oscillation of approximately 8 Hz when the animal is locomoting, performing other investigatory behaviors, or is in the REM stage of sleep. Principal neurons and interneurons are strongly modulated by this theta rhythm, firing in bursts that are phase-locked to the theta rhythm. Place cells show a strong phenomenon called theta phase precession: as the rat runs through a place field, each theta-modulated burst of firing of the cell occurs at increasingly earlier phases of the theta rhythm. Because the phase of theta provides information about the precise location of the animal in the larger place field, the phase precession provides one of the more robust examples of a temporal code in the brain. Numerous models have been generated about the origin and functional significance of phase precession, including that it allows sequences of place fields to be recapitulated in a compressed sequence amenable to LTP mechanisms to encode a memory trace of the sequence.

When the rodent is engaged in nonexploratory behaviors, such as eating or grooming, and when it is in the slow-wave stage of sleep, the hippocampal EEG enters the 'large irregular activity' (LIA) mode. During this mode, intermittent bursts of synchronized neural activity cause large deflections in the EEG called sharp wave/ripples. The place cell activity during the sharp wave/ripples in slow wave sleep or quiet wakefulness recapitulate, on a very compressed time scale, the sequences of activity that the rat recently experienced during behavior — that is, the place cells fire in the same sequence as their place fields were experienced. This 'replay' is hypothesized to be involved in the systems consolidation process, as a mechanism whereby the events recently experienced by the animal are replayed to the neocortex in order to update the permanent, neocortical memory stores.

Nonlocal representations during behavior

When the rat is performing a behavioral task, the hippocampus generates brief (50–100 millisecond) sequences that represent locations away from the current location of the rat ('nonlocal representations'). These sequences can occur during sharp wave/ripples that are generated during behavior, for example at a reward site, and can take the form of sequences of locations that replay the animal's most recent trajectory, as well as the same trajectory played in reverse order.

Nonlocal representations can also be prospective in nature: when the animal is at the choice point of a maze, it sometimes performs a behavior called vicarious trial and error, moving its head back and forth as it appears to evaluate the different behavioral choices and potential

outcomes. Bursts of theta-related hippocampal activity can represent sweeps of spatial sequences that correspond to the animal's choices on the maze. In other cases, when the animal is about to make a trajectory to a known goal location, a hippocampal population burst can trace a precise route toward that goal from the animal's current location, before the animal begins its movement. These nonlocal sequence representations may be involved in the animal's planning of routes and evaluation of behavioral choices, and they may be a neurophysiological correlate of the functions of the hippocampus in 'imagining the future' discussed above.

Nonspatial firing

Although spatial location has been the most studied correlate of hippocampal cells, there are clearly nonspatial correlates of these cells as well. The presence of nonspatial firing is not surprising, given that the LEC input appears to encode local cues such as individual objects and odors. The temporal firing characteristics of hippocampal cells when they act as time cells have already been discussed. When objects are present in the environment or when the rats perform behavioral tasks with greater cognitive demands than a standard foraging task, hippocampal cells fire in complex ways related to the objects and the behavioral task parameters. When an object is moved in an environment, some hippocampal cells create a place field at the location previously occupied by the object, providing a putative memory trace of the former location of the object. Most, if not all, nonspatial firing correlates of place cells appear to be also dependent on spatial location. For example, place cells respond to a conditioned stimulus in a Pavlovian fear conditioning task, but only when the rat is within the place field of the cell. This conjunctive item plus place encoding may be a reflection of the hippocampus combination of its LEC and MEC inputs.

A spatiotemporal framework for organizing memories

After decades of debate regarding whether the hippocampus is primarily a spatial mapping system or a relational learning/declarative memory system, the field is converging on a consensus that the hippocampus supports episodic memory by combining a spatial/temporal signal (from the MEC) with a signal related to individual items experienced by the animal (from the LEC) to form a conjunctive representation of the individual items of an experience within the spatiotemporal context of that experience (Figure 3). Computational processes such as pattern separation in the DG allow the hippocampus to create distinct representations of similar experiences to minimize interference in the storage and recall of specific memories. Conversely, the recurrent collateral system underlies hypothesized attractor dynamics of the CA3 region that allows pattern completion, error correction, and generalization of memory retrieval cues, as well as competitive interactions to prevent memory interference. The spatiotemporal framework provided by the hippocampus allows the memories to be stored in a flexible manner such that they can be retrieved and utilized to guide behavior under disparate conditions unrelated to the original experience. This framework may also underlie the ability of humans to 'ponder the future' the same way that episodic memory allows 'mental time travel' to reconstruct a conscious memory and relive that experience in the mind.

FURTHER READING

Andersen, P., Morris, R., Amaral, D., Bliss, T., and O'Keefe, J. (Eds.) (2007). The hippocampus book. (Oxford: Oxford University Press).
Bonnevie, T., Dunn, B., Fyhn, M., Hafting, T., Derdikman, D., Kubie, J.L., Roudi, Y., Moser, E.I., and Moser, M.B. (2013). Grid cells require excitatory drive from the hippocampus. Nat. Neurosci. *16,* 309–317.
Buzsaki, G. (2006). Rhythms of the Brain (Oxford: Oxford University Press).
Colgin, L.L., Moser, E.I., and Moser, M.B. (2008). Understanding memory through hippocampal remapping. Trends Neurosci. *31,* 469–477.
Derdikman, D., and Knierim, J.J. (Eds.) (2014). Space, Time and Memory in the Hippocampal Formation (Vienna: Springer).
Deshmukh, S.S., and Knierim, J.J. (2013). Influence of local objects on hippocampal representations: Landmark vectors and memory. Hippocampus *23,* 253–267.
Deshmukh, S.S., and Knierim, J.J. (2011). Representation of non-spatial and spatial information in the lateral entorhinal cortex. Front. Behav. Neurosci. *5*, 69.
Eichenbaum, H. (ed.). (2015). Special Issue: Perspectives on 2014 Nobel Prize. Hippocampus *25(6).*
Eichenbaum, H., and Cohen, N.J. (2014). Can we reconcile the declarative memory and spatial navigation views on hippocampal function? Neuron *83*, 764–770.
Hassabis, D., Kumaran, D., Vann, S.D., and Maguire, E.A. (2007). Patients with hippocampal amnesia cannot imagine new experiences. Proc. Natl. Acad. Sci. USA. *104*, 1726–1731.
Hasselmo, M.E. (2012). How We Remember: Brain Mechanisms of Episodic Memory (Cambridge, Mass.: MIT Press).
Johnson, A., and Redish, A.D. (2007). Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. J. Neurosci. *27,* 12176–12189.
Jones, M.W., and McHugh, T.J. (2011). Updating hippocampal representations: CA2 joins the circuit. Trends Neurosci. *34,* 526–535.
Knierim, J.J., and Hamilton, D.A. (2011). Framing spatial cognition: neural representations of proximal and distal frames of reference and their roles in navigation. Physiol. Rev. *91,* 1245–1279.
Koenig, J., Linder, A.N., Leutgeb, J.K., and Leutgeb, S. (2011). The spatial periodicity of grid cells is not sustained during reduced theta oscillations. Science *332*, 592–595.
Macdonald, C.J., Lepage, K.Q., Eden, U.T., and Eichenbaum, H. (2011). Hippocampal "time cells" bridge the gap in memory for discontiguous events. Neuron *71*, 737–749.
McClelland, J.L., McNaughton, B.L., and O'Reilly, R.C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psychol. Rev. *102*, 419–457.
McNaughton, B.L., Barnes, C.A., Gerrard, J.L., Gothard, K., Jung, M.W., Knierim, J.J., Kudrimoti, H., Qin, Y., Skaggs, W.E., Suster, M. *et al*. (1996). Deciphering the hippocampal polyglot: the hippocampus as a path integration system. J. Exp. Biol. *199*, 173–185.
Moita, M.A., Rosis, S., Zhou, Y., LeDoux, J.E., and Blair, H.T. (2003). Hippocampal place cells acquire location-specific responses to the conditioned stimulus during auditory fear conditioning. Neuron *37,* 485–497.
O'Keefe, J., and Nadel, L. (1978). The Hippocampus as a Cognitive Map (Oxford: Clarendon Press).
O'Keefe, J., and Recce, M.L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus *3*, 317–330.
Pastalkova, E., Itskov, V., Amarasingham, A., and Buzsaki, G. (2008). Internally generated cell assembly sequences in the rat hippocampus. Science *321*, 1322–1327.
Pfeiffer, B.E., and Foster, D.J. (2013). Hippocampal place-cell sequences depict future paths to remembered goals. Nature *497,* 74–79.
Scoville, W.B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatry *20*, 11–21.
Squire, L.R., Stark, C.E., and Clark, R.E. (2004). The medial temporal lobe. Annu. Rev. Neurosci. *27,* 279–306.
Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W., and Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. Science *277,* 376–380.
Witter, M.P., and Amaral, D.G. (2004). Hippocampal formation. In The Rat Nervous System (3rd edition), G. Paxinos, ed. (Amsterdam: Elsevier) pp. 635–704.

Zanvyl Krieger Mind/Brain Institute, Johns Hopkins University, 3400 N. Charles Street, Baltimore, MD 21218, USA.
E-mail: jknierim@jhu.edu