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Keywords

episodic, semantic memory, hippocampus, navigation, preconfigured

Abstract

By linking the past with the future, our memories define our sense of identity. Because human memory engages the conscious realm, its examination has historically been approached from language and introspection and proceeded largely along separate parallel paths in humans and other animals. Here, we first highlight the achievements and limitations of this mind-based approach and make the case for a new brain-based understanding of declarative memory with a focus on hippocampal physiology. Next, we discuss the interleaved nature and common physiological mechanisms of navigation in real and mental spacetime. We suggest that a distinguishing feature of memory types is whether they subserve actions for single or multiple uses. Finally, in contrast to the persisting view of the mind as a highly plastic blank slate ready for the world to make its imprint, we hypothesize that neuronal networks are endowed with a reservoir of neural trajectories, and the challenge faced by the brain is how to select and match preexisting neuronal trajectories with events in the world.

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Memory does not pay much attention to dates—it skips years or stretches temporal distance.

Siegrfried Kracauer (1993, p. 50)

HUMAN MIND–CENTERED TAXONOMY OF MEMORY

The regularities and recurrences of our world make the past relevant to the future. For an organism trying to survive and prosper, regularities and consistencies in the organism’s niche allow for the adaptive generalization from the past to the current situation in order to optimize future behavior. Thus, the past, present, and future are intricately intertwined. Yet, for historical reasons, we give them special names—such as memory, learning, and planning, respectively—and search for their allegedly distinct brain mechanisms.

Memory is often used as a synonym for knowledge. Thus, all forms of brain activity that increase the knowledge base of an individual can be referred to loosely as memory. In everyday language, we refer to memory as something that we remember and thus “have in mind” and can consciously communicate to others. Early thinkers in psychology made efforts to delineate distinct forms of memory from the human mind’s point of view (reviewed in Squire & Dede 2015), rather than asking how memory systems evolve and what brain mechanisms support the seemingly different forms (Buzsáki 2019). Early taxonomies of memory have been separated into verbal declarative (or explicit) versus nondeclarative (or implicit) forms (Schacter 1987, Squire 1992). Although non-verbal forms are inaccessible to conscious recollection and support different needs of the organism, they can influence behavior, decision, and even mental life (Tulving & Schacter 1990).

Definitions are the ciphers of communication. They pin down or ground our concepts as completely as possible and are a prerequisite for communicating, testing, and challenging concepts. Despite the advances afforded by the memory taxonomies, language-dependent memory classification has some disadvantages. First and foremost, it inevitably creates a discontinuity between research in humans and in other animals. If conscious recollection and flexible verbal mediation are the acid test of certain forms of memory, this precludes or at least greatly curtails

their study in experimental animals (Tulving 2005). Second, even in humans, the postulated divisions may not map neatly onto physiological types. The same structures may participate in promoting the encoding, consolidation, reconsolidation, and recollection of memories but using different mechanisms at different times. Third, while separation of past, present, and future may feel intuitive, and terms such as memory, navigation, planning, and imagination evoke different things in most people's minds, brain mechanisms may not form such boundaries. For these reasons, the search for neuronal dynamic-based classification of memory types is warranted (Davachi 2006). However, only brain-based mechanisms can ground results found in humans and animals. This is not to say that the interaction between language and memory is not an important area to study. Quite to the contrary, this interaction remains the future frontier of our understanding of the human mind. The point we attempt to convey here is that it is possible and important to have an understanding of the neurophysiological basis of memory processes that is as free as possible from mind-based definitions and invocations of conscious accessibility and language output. We hope that examining and comparing the shared mechanisms across species will help us revisit and redefine our existing concepts.

Here we review research on declarative memory using a brain-based approach rather than a human mind-referenced approach. We focus on three hotly debated areas of memory research. First, we consider the relevance of animal research on memory mechanisms whose current definition involves consciousness and requires human language. Second, we discuss the relationship between exploration in physical space and exploration in mental space from a physiological perspective. Third, we contrast the dominant blank-slate idea of memory accumulation with an alternative hypothesis, which implies that learning is a selection or matching process between a large reservoir of internally generated neuronal patterns and world events. Additional comments and references for each section are available in the **Supplemental Text** and **Supplemental References**.

Intuitively, we can distinguish two types of memories that we can verbally declare: memories for events, referred to as episodic (or autobiographic) memory, and memories for facts, referred to as semantic memory (Squire 1992, Tulving 1972). Episodic events have a duration and take place somewhere. In contrast to this time-directed and segment-defined type of memory, semantic facts are abstracted punctate events; they define objects, living things, and facts in the surrounding world; and they do not need to be anchored in space and time (Squire 1992, Tulving 1972) (**Figure 1**) but rather represent general knowledge (Eichenbaum 2004) or a set of beliefs. Over the years, these definitions have been simplified to indicate that knowing "what" corresponds to semantic facts, and knowing "what" happened, "where," and "when" corresponds to episodic events.

What is the relationship between these two forms of declarable memories? One proposal is that semantic memories are gradually formed from multiple overlapping episodes with common items (junctions) among the episodes (Buzsáki 2005, Nadel & Moscovitch 1997). Accordingly, semantic memories do not emerge instantly but rather evolve through multiple recurring similar episodes, during which the temporal and spatial contexts of the multiple episodes sharing a common item are gradually stripped away and become invariant to the conditions that created them. Eating the first soufflé is a unique experience. After having many of them at different times and places, soufflé becomes a name for a particular dessert with specific significance or "meaning" (Nadel & Moscovitch 1997). Another suggestion is that the abstraction process occurs during sleep, when hippocampal neuronal assemblies active during the waking learning episodes are replayed numerous times and the dominant elements among these episodes are transferred to the neocortex, where they are categorized and stored as context-free semantic memories (Frankland & Bontempi 2005, McClelland et al. 1995, Nadel & Moscovitch 1997). This iterative episodic-semantic process is postulated to be the route for generating semantic knowledge in all mammals (Buzsáki & Moser 2013).

Consolidation: the process by which an initial memory trace stabilizes and becomes available for long-term retrieval

Reconsolidation: the process by which an existing memory trace restabilizes after having become labile

Matching: the process by which a preexisting neural state becomes associated with a novel circumstance or action

Supplemental Material >

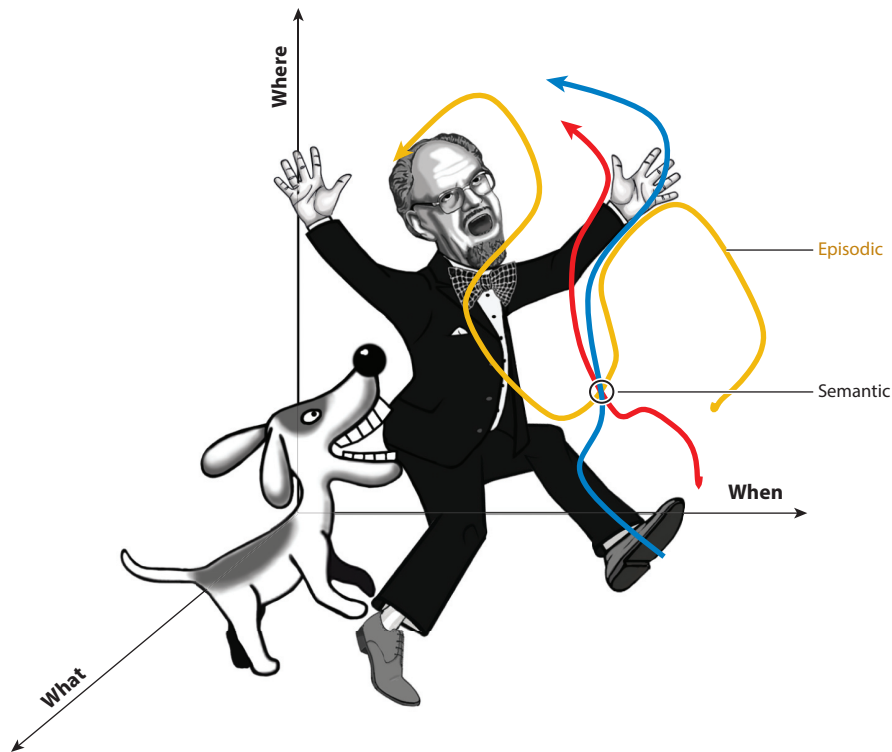


Figure 1

Spacetime representation of episodic and semantic memories. Episodic memory evolves in spacetime (where, when axes) with a corresponding neuronal trajectory (color lines). The trajectory is a vector that unfolds in spacetime (i.e., a segment with distance and duration). Only neuronal networks that generate such directional neuronal trajectories (as opposed to bidirectional correlations or associations) can support episodic memory. Three such trajectories (or episodes) are illustrated here. Intersection of multiple trajectories through the same space state can be considered as a node (*black circle*) or a snapshot in spacetime (context-free semantic memory). Figure adapted from Buzsáki (2019).

Yet, this hypothesis of semantic knowledge acquisition does not account for the fact that humans can use language to acquire facts and concepts instantly and without the need for direct personal experiences (an example would be the belief that “Instagram is a fast way of sharing pictures”). Does this language-dependent shortcut to new knowledge utilize the same brain mechanisms as the episode-dependent acquisition of semantic information? Imaging studies favor the hypothesis that abstractions derive from off-line integration of episodes. After a period of consolidation, but not when measured shortly after learning, multivariate patterns of blood-oxygen-level-dependent (BOLD) activity in human medial prefrontal cortex during memory retrieval show an overlapping pattern of activation for related experiences (Tomparry & Davachi 2017). Whereas these overlapping neural representations may represent the abstractions from episodic experiences that support semantic knowledge, other work has shown that children with hippocampal agenesis or early brain trauma acquire reasonable semantic knowledge of world facts and relations despite having a severe episodic memory deficit (Vargha-Khadem et al. 1997). Furthermore, there is evidence that acquiring semantic knowledge during normal development may occur prior to learning detail-rich episodic representations (Keresztes et al. 2018).

There is also ambiguity in the intuition-based definition of episodic memory. Consider the following two statements: The World Trade Center in New York City was destroyed on September 11, 2001. World War I started in Sarajevo on June 28, 1914. Both sentences list three items (an event, a place, and a date, although not a clear duration). Should these formally similar statements, when recalled consciously, be categorized as episodic or semantic memories? Whereas it is unlikely that the reader will have a personal recollection of the events of World War I, many readers experienced the September 11 event as first-person observants. It is an unforgettable life episode, an autobiographical event for many of us, embedded in a unique sequence structure. But if the ownership of memory is regarded as a key difference between the two statements (Tulving 1985), then the important issue to be raised is whether they involve the same or different neuronal networks and mechanisms. A possible grounding answer comes from brain lesion case studies. Patient H.M.'s pathology is often (mis)interpreted as the fact that he failed to learn novel facts and episodes after bilateral removal of his hippocampi, entorhinal cortices, and even parts of the amygdala but could remember most facts and life events happened prior to his brain surgery (Scoville & Milner 1957). In reality, there is no evidence that H.M. could recall any of his life experiences having himself as the participant observer. Instead of recalling first-person, self-referenced experiences, there is evidence that he reconstructed world events from learned associations of facts, dates, and places (Corkin 2013), just as we recite the event for the trigger of World War I.

Tulving, who coined the term “episodic” (Tulving 1972), placed a strong emphasis on the first-person (egocentric) involvement in episodic memory and called it auto-noetic (or self-knowing) experience (Tulving 1985). The collections of these first-person (experiencer)-viewed memories constitute the self (Tulving 2002), and they are distinct from events viewed from the perspective of an external (third-person) observer (e.g., one's birth place and birth date). Therefore, the key problem to be addressed is whether first-person and third-person events are coded and stored by the same or different brain mechanisms. The separation of self from others and the environment is pervasive in the animal kingdom, and its mechanisms can therefore be studied in small-brained animals. Below, we explain how this ego-versus-allo distinction relates to neuronal mechanisms.

MEMORY, NAVIGATION, AND THE HIPPOCAMPAL SYSTEM

Leading theories on the functions of the hippocampal system are based largely on two spectacular discoveries: the dramatic memory impairment after removal of the hippocampus and associated structures (Milner et al. 1998, Scoville & Milner 1957) and the observation that spiking of hippocampal neurons varies reliably with the spatial position of the animal (hence the hippocampal neurons are called place cells) (O'Keefe & Nadel 1978). The spatial navigation or cognitive mapping view of the hippocampal system (O'Keefe & Nadel 1978) was recently amplified by the discovery of grid cells in the entorhinal cortex (Hafting et al. 2005). Accordingly, the entorhinal cortex and the dorsal/posterior hippocampus generate interdependent maps or representations of the space in which the organism lives. Extensive series of elegant experiments have shown that the hippocampus, entorhinal cortex, and related structures deploy an arsenal of mechanisms for navigation by keeping track of direction, distance traveled, time passed, environmental boundaries, and locomotion speed (McNaughton et al. 1996, 2006). A third important branch of memory research was triggered by the discovery of long-term potentiation and depression (Bliss & Collingridge 1993). These discoveries launched decades of constructive debate about the primacy of spatial representation and memory (Eichenbaum et al. 1999, Olton et al. 1979) and the relationship between memory and synaptic plasticity (Bliss & Collingridge 1993).

A critical aspect of the continuing debate has revolved around the issue of whether the hippocampus and its allied structures constitute a relational memory system, with spatial memory

Place cells:

hippocampal neurons that become consistently activated in specific locations within the environment

Grid cells:

neurons whose increased firing at the apices of imaginary equilateral triangles on the floor of the environment marks the position of the animal

Cognitive map: the mental representation of a set of relationships

Spatial map: a representation of a set of places that are systematically related to each other in the Euclidian space

Remapping: the change in the physical location of peak firing of hippocampal place fields, or the change in firing rate within a fixed position

being merely one type of relational representation (Eichenbaum et al. 1999), or whether the exclusive or primary role of the hippocampus and entorhinal cortex is to support navigation and spatial memory. Most investigators agree that the hippocampus can represent both spatial and nonspatial information, but the key difference among approaches lies in the relationship between these two classes of information. Whereas memory theories view spatial and nonspatial features on an even footing, and therefore claim that hippocampal neurons can respond to both spatial and nonspatial inputs, the cognitive map theory “sees space as crucial and central, with other types of nonspatial information embedded in a primary spatial framework” (O’Keefe & Krupic 2021, p. 1427). Within a hippocampal cognitive map, place features are generated in the hippocampus “while nonspatial inputs are generated elsewhere and projected to the hippocampus, where they are embedded in place representations” (O’Keefe & Krupic 2021, p. 1428).

One might, of course, ask why geometric features cannot also be projected from other brain regions, as postulated for other modalities (Lisman et al. 2017). More importantly, we need to clarify in our descriptions whether the place field (the explanans) explains the place or whether the place (the explanandum) explains the place field. The spatial map is a description of the constellation of landmarks and not of the landmarks themselves. It is this constellation or set of relationships that is captured by the intended notion of the cognitive map, rather than concrete places per se.

Although a large and dynamically developing body of work supports the cognitive mapping theory, at least three levels of experimental observations challenge its exclusiveness. First, hippocampal lesions result in profound deficits in tasks in which the spatial relationships of room cues are not critical for learning (Clark & Isaacson 1965, Ross & Eichenbaum 2006), and medial temporal lobe damage in humans impairs the formation of novel relations, including new semantic associations (Keane et al. 2020). Second, there is no absolute link between the spatial map in the hippocampus and spatial learning. When rats are trained on a spatial task in a black box and tested in an identical but white box, most hippocampal neurons change their spatial relationship to both room cues and local landmarks (i.e., remapping); despite a new spatial map, navigational performance remains intact (Jeffery et al. 2003). In a complementary manner, when the temporal relationships among hippocampal neurons become scrambled at the theta oscillation timescale without affecting place fields, the animal cannot solve a spatial task (Robbe et al. 2006). Third, when rats are trained to run in a wheel between trials of a spatial alternation task—that is, their head remains at a fixed spatial position—the entire duration of the run is tessellated by sequential activity of neurons, as if the animal was navigating in the maze (Pastalkova et al. 2008). Finally, at one extreme, one could argue that if the sole function of the hippocampus is navigation, it remains to be explained why it has so many neurons and intricate circuits when spatial navigation can be effectively accomplished by insects with simple brains (Gallistel 1990). Thus, while these experiments and arguments demonstrate that an intact hippocampus is needed for nonspatial memory tasks as well, still little is known about how memory and navigation are related. The next section explores this relationship and how the context of space and time has become intertwined with episodic memory.

Types of Declarable Memories Are Related to Types of Navigation

From an evolutionary perspective, memory is a transmission mechanism gleaned from past experience to guide current and future behaviors rather than a storage of symbols of world events and facts. Therefore, memory-based planning evolves from mechanisms of interacting with the physical world, though disengaged from environmental and body cues. Within this framework, the brain substrates and the neuronal algorithms underlying navigation in real and mental space (i.e., mental time travel; Tulving 2002) are hypothesized to be the same (Buzsáki 2005, Buzsáki & Moser 2013) (**Figure 2**).

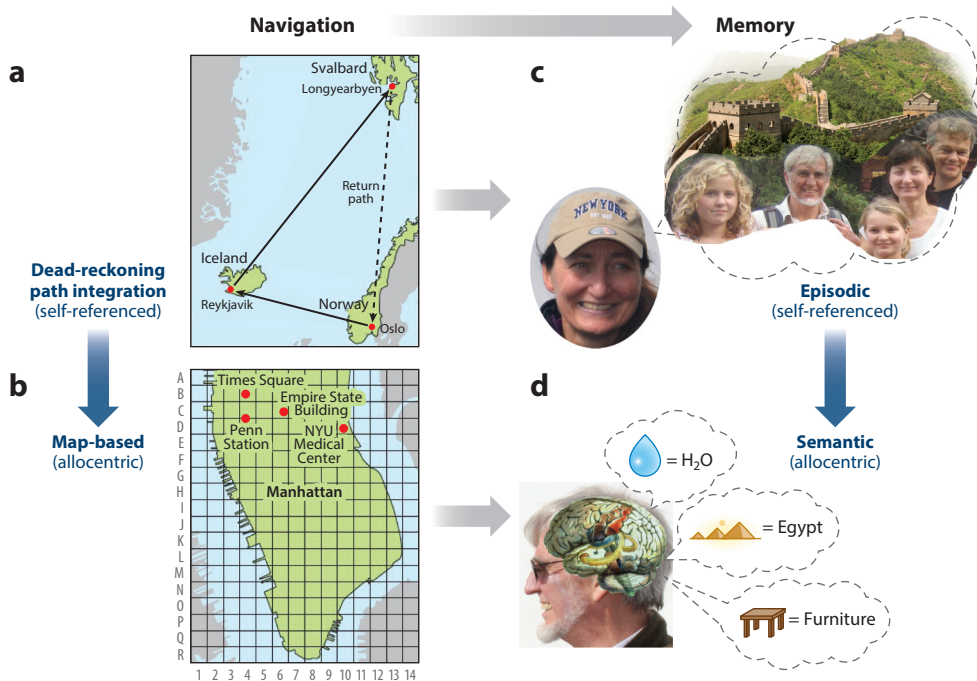


Figure 2

Relationship between navigation and declarative memory. (a) Path integration (also known as dead reckoning) is based on self-referenced information by keeping track of travel distances (time elapsed multiplied by speed) and direction of turns. Calculating translocation relative to the start location allows the animal to return to the start along the shortest (homing) path. (b) Map navigation is supported by the relationships among visible or otherwise detectable landmarks. A map is constructed by exploration (path integration). (c) Episodic memory is mental travel in time and space referenced to self. (d) Semantic memory is explicit representation of living things, objects, places, and events without temporal or contextual references. Semantic knowledge can be acquired through multiple episodes with common elements. We hypothesize that the evolutionary roots of episodic and semantic memory systems are the dead-reckoning and landmark-based forms of navigation, respectively. Figure adapted from Buzsáki & Moser (2013).

A map is only an aspect of navigation, one that provides static position information in an allocentric reference frame from the relationships among landmarks. The metric needed for the estimation of distances between landmarks arises from a second mechanism, known as self-referenced (or egocentric) navigation, based largely on path integration of motion and local cues. The essential components of the self-referenced navigation system are the initial reference position, head direction, locomotion speed, and elapsed time (McNaughton et al. 1996, 2006). Navigation is associated with sequentially organized neuronal assemblies of place cells and grid cells, and it is invariably linked to hippocampal theta oscillations, the cycles of which contain sweeps of neural sequences corresponding to segments of the animal's travel along past, present, and future locations (Dragoi & Buzsáki 2006, O'Keefe & Recce 1993, Skaggs & McNaughton 1996).

Internalization of Overt Navigation

There is a clear parallel between egocentric navigation and episodic memory, on the one hand, and map-based navigation and semantic memory, on the other (**Figure 2**). The composition of neuron

Path integration: vector summation of distances and angles from a given starting location

Neuronal trajectory: the path of the neuronal assembly vector; it can be matched to cognition or overt behavior such as the locomotion trajectory of the organism

Internalization: an evolutionary process by which external signal-dependent brain activity becomes independent from outside signals

types and neuronal trajectories in the entorhinal-hippocampal system may serve both path integration (Sargolini et al. 2006) and episodic memory. On the other hand, omnidirectional, context-free place cells determine each place in the environment explicitly, just as concept cells in humans become active in response to both observed and recalled specific objects or persons (Quiroga et al. 2005). A main difference is that mental navigation does not depend on immediate environmental or body-reafferent cues. It has been suggested that neuronal mechanisms, which initially depended on external cues in simple organisms, have become “internalized” (Buzsáki et al. 2014) in more complex brains so that self-organized brain activity can maintain neuronal trajectories. Without external constraints, disengaged processing in the brain can create an internalized virtual world and generate new knowledge through vicarious or imagined experience, tested against preexisting and stored knowledge.

It is important to emphasize that the suggested evolutionary continuity of navigation and memory does not imply that there are distinct mechanisms that developed sequentially. Instead, the mechanisms are strongly intertwined, and the degree to which they dominate depends on the level of brain complexity and the availability of external cues. More complex brains can rapidly acquire multiple representations, hold them as separate over longer timescales, and use them flexibly even in degraded conditions. Yet, the fundamental rules in simple and more developed brains remain the same.

Under the allocentric map-based navigation framework, a subset of hippocampal place cells should fire continuously as long as the rat’s head remains in the same location, while all other pyramidal neurons should remain silent. In contrast, if assembly sequences are generated by internal mechanisms, neuronal activity might instead change continually. **Figure 3** illustrates an experiment that compared these views by training rats to alternate between the left and right arms of a T maze and to run in a running wheel at the start area for 10 to 20 s at a constant speed while facing the same direction on each run (Pastalkova et al. 2008). The findings show that not a single neuron among the hundreds recorded fired continuously throughout the wheel running, thus marking the fixed x - and y -coordinates of the rat. Instead, spiking activity of pyramidal neurons displayed a continuous sequence, unique for left and right choices, from the water reward on one side of the maze, through wheel running, to the water reward on the opposite arm of the maze (Pastalkova et al. 2008) (**Figure 3**). In other words, the entire journey during a single trial from reward to reward, including running in the wheel, was associated with a unique neuronal trajectory of perpetually changing cell assemblies. As the animal’s body and head were not displaced while in the wheel, the interleaving activity of neurons did not meet the criteria for place cells. Instead, the neuronal trajectory served as a guide to select the correct future path from stored experience. In accordance with the rodent experiments, single-unit studies in human patients also revealed that retrieval of a memory is associated with reactivation of the same neurons that were active during learning (Gelbard-Sagiv et al. 2008), implying that the hippocampus and entorhinal cortex generate neuronal trajectories specific to different memory episodes and their free recall. These and related experiments support the view that navigation in the real world and in mental space is supported by the same hippocampal mechanisms (Fujisawa et al. 2008, Wang et al. 2015).

TIME REPRESENTATION AND TIME CELLS

The internalization of path integration may provide the needed spatial scaffolding for episodes. In addition, passage of time against a clock can be faithfully tracked by internally evolving neuronal trajectories that maintain information about past memories and planned goals (Itskov et al. 2011, Pastalkova et al. 2008). This prompted Eichenbaum (2014) to suggest that neuronal trajectories can offer the missing temporal context for episodic memory and to dub the hippocampal and

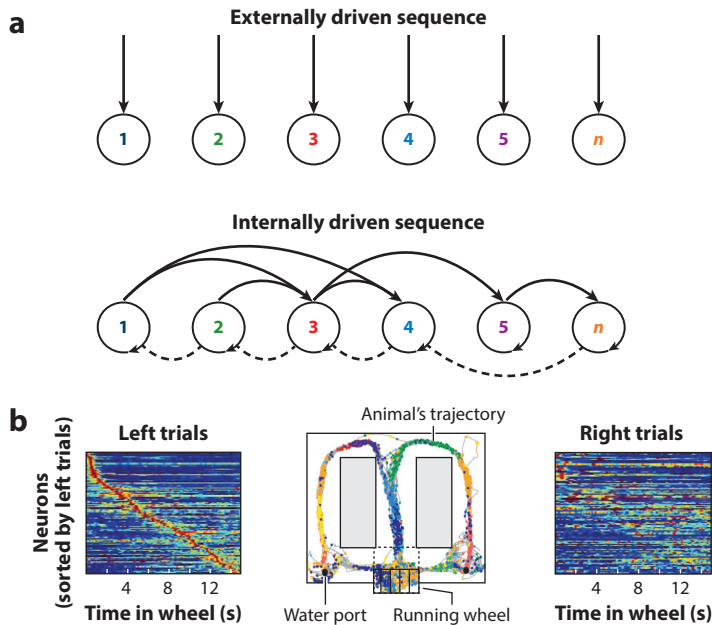


Figure 3

Cell assembly sequences track the “what” (i.e., which corridor), distance, and duration. (a) During physical travel, successive assemblies of neurons (1 to n) respond sequentially because of the changing constellation of environmental landmarks and/or proprioceptive information from the body (i.e., externally driven sequence) (*top*). During mental travel, sequential activation is supported by self-organized patterning (i.e., internally driven sequence) (*bottom*). (b) Sequential activation of neuronal assemblies in an episodic memory task. (*Middle*) The rat was required to run in a running wheel for 15 s before choosing either the left or the right arm of the maze based on the remembered last arm choice. It obtained a water reward if it chose the opposite of the previously chosen arm. The color-coded dots represent spike occurrences of simultaneously recorded hippocampal neurons. (*Left*) Normalized firing-rate profiles of neurons during wheel running, ordered by the latency of their peak firing rates during left trials (each line represents a single cell). (*Right*) Normalized firing rates of the same neurons during right trials. Note that an observer can infer the run duration (and distance) in the wheel as well as the future choice of the rat from the same sequential firing patterns of the neurons. Figure adapted from Pastalkova et al. (2008).

entorhinal neurons “time cells.” Time cells have time fields, analogous to place fields: “[T]ime cells may play a role in episodic memory by tagging when events occur in time, just as place cells map where events occur in space” (cited in Lisman et al. 2017, p. 1439). His group designed a series of experiments with the goal of dissociating duration-tracking from distance-tracking neurons. They trained rats to run on a treadmill for a target duration or a target distance. Spiking of most hippocampal and entorhinal neurons correlated with both duration and distance; that is, they fired reliably and repeatedly on subsequent trials at the same distance or at the same time from the beginning of the run. A minority of neurons was relatively selective for time spent on the treadmill, while the activity of an equally small fraction was better correlated with distance (Eichenbaum 2014, Kraus et al. 2013). Thus, for a moment it appeared that the neuronal mechanisms of episodic memory with its postulated “what,” “where,” and “when” components had finally been grounded (Eichenbaum 2014).

If the brain needed to store separate representations of every individual experience of our lifetime—that is, every combination of “what,” “where,” and “when”—the list would be extraordinarily long and would require an outsized storage capacity and an inefficiently long search time for

any given episode. An alternative solution is to store the “what,” “where,” and “when” components separately and recreate the original episode by re-embedding the “what” into the ordinal structure of “where” and “when” (Friston & Buzsáki 2016) (**Figure 1**), in a process similar to generating color by multiplying different portions of red, green, and blue wavelengths. Adding a time axis to the “what” is also appealing for defining first-person (egocentric episodic) versus third-person (allocentric semantic) memories, since the ego-versus-allo separation is inherently present in the concept of spacetime. This juxtaposition could be described as one between the idea that “every day I am getting closer to my grant deadline” (i.e., I am an inside actor, flowing with the local events toward a stationary “what”) and the idea that “my grant deadline is approaching” (i.e., I am a stationary observer and the “what” is moving toward me) (Boroditsky 2018).

An episode is an unfolding storyline in time, which we recall as a trajectory or sequence of events as a structure in space, whereas semantic memory is a frozen subspace of the trajectory with disconnected spatial-temporal history (**Figure 1**). The reference spaces can be small or large and can be nested inside one another (e.g., a drawer in a desk in a room in a house. . .). The self moving through space is a history or episode with both spatial and temporal adjacency relationships. If we assume this spatial and temporal coordinates framework, and add it to the coding of the “what,” we may conclude that neuroscience has identified a road map for uncovering the neurophysiological mechanisms of episodic memory and for understanding the global function of the hippocampal system. However, a careful scrutiny of **Figure 3** and related findings tells a different story.

Concepts of Space and Time in Memory Research

As was the case for memory, the concepts of space and time started out as vague ideas without clear definitions and boundaries that could be used to contrast our ephemeral lives to the vastness of the universe. Science has transformed and grounded these dimensionless concepts with the invention of measuring instruments, and it replaced space and time with their definable variants, distance and duration, quantified by the units of human-made instruments such as rulers and clocks, thereby giving them practical meanings. As a result, the abstract concepts of space and time, defined as independent a priori from each other and from everything else, have become axioms of human thinking. In today’s world it would be hard to imagine and organize human life without clocks, even though a few closed human societies have survived until this day without developing linguistic structures that relate to time (Sinha et al. 2011). Furthermore, in many languages, temporal words have a spatial sense as their primary meaning (as in the statement “the river is a two-day walk from here”) (Boroditsky 2018).

The appeal of space and time derives from the Newtonian framework of physics in which events take place in space and unfold on a timeline, in accordance with our definition of episodic memory (**Figure 1**). In our language-guided minds, time and space form the very basis of our imagination. Research in neuroscience continues to be performed and interpreted within the “container” framework of classical physics, even though in contemporary physics there is no longer space which “contains” the world, and there is no time “in which” events occur (Rovelli 2016). The space is the things themselves. When human-invented instruments are taken away, space and time revert back to dimensionless and ungrounded concepts. How are then nonhuman animals expected to represent space and time in their brains when they have no sensors for either space or time, and no clocks or rulers to inspect? By definition, space and time are immaterial, thus they cannot exert an impact on things, including the body and the brain. Furthermore, neither clocks nor brains “make” time (Buzsáki & Llinás 2017). Because space and time cannot be studied directly and cannot be derived from first principles, we should ask: Do place and time cells represent space and time out there, or are neurons or brain circuits expected to “make” distance and duration for brain computation?

In principle, subjective time can be related to neuronal activity, such as time cells or ramped increases or decreases in spiking activity. The succession and accumulation of spiking events allow the experimenter to compare the rate of change to units of a clock. However, these observations do not demonstrate that neuronal activity computes time per se. It has not been shown that neuronal circuits anywhere in the brain are dedicated to computing time as their sole and independent function. It is more likely that the alleged time cells and circuits compute specific functions that evolve sequentially and therefore correlate with the units of an instrument or other events. With careful investigations, neurons with suspected time-tracking features always turn out to compute something else (Leon & Shadlen 2003).

In light of these considerations, now we can ask again whether the three pillars of episodic memory (the “what” in space and time) are present in the hippocampus or anywhere else in the brain. The evolving neuronal trajectory (**Figure 3**) predicts the goal arm, distance run, and duration since the beginning of the experimenter-imposed delay. However, note that there is only a single neuronal measure, the sequential firing of neurons, and this measure has been interpreted in three different ways, depending on the experimenter’s preoccupation. Distance and duration are derived measures, equated via velocity. The brain receives constant information from speed/acceleration sensors, such as the vestibular apparatus and optic and haptic flow. These signals are mirrored by the firing rates of fast firing interneurons in the hippocampus and entorhinal cortex (called speed cells; Kropff et al. 2015). Why would brain circuits code for three separate variables when any two variables can be used to compute the third for free?

Merging the Past, Present, and Future

Several mechanisms support the sequential organization of neuronal activities and the speed by which they evolve. Brain rhythms have been postulated to serve such syntactic functions (Buzsáki 2019). In the hippocampal system, the most prominent rhythm is the theta oscillation, which coordinates spiking activity in both phase space and three-dimensional neuronal space (5–10 Hz; Buzsáki 2005) (**Figure 4**). First, unlike a single clock, theta waves show a systematic phase shift up to 270° in the CA1-CA3-dentate gyrus axis and different layers of the entorhinal cortex. Second, theta phase shifts 180° from the septal to the temporal pole of the hippocampus and in the corresponding dorsoventral axis of the entorhinal cortex (Patel et al. 2012). Third, activated neuronal assemblies during navigation and memory tasks oscillate faster than the local field potential (LFP) theta signal (O’Keefe & Nadel 1978, O’Keefe & Recce 1993, Pastalkova et al. 2008), and the oscillation frequency of the cell assemblies correlates inversely with the size of the place fields (Dragoi & Buzsáki 2006).

Because of the phase interference between the faster-oscillating cell assemblies and theta LFP, member neurons of the assemblies show a progressive backward phase shift of pyramidal cells’ spikes (phase precession; O’Keefe & Recce 1993). Although all active neurons in the hippocampal system are active in different phases (or times) of the theta cycle, their phase differences vary coherently in each theta cycle, even though the cycles dilate and compress dynamically as a function of the animal’s running speed (Geisler et al. 2007, Maurer et al. 2012) (**Figure 4**). As the rat passes through a sequence of place fields, portions of this sequence are reproduced in a compressed form within individual theta cycles (Dragoi & Buzsáki 2006, Samsonovich & McNaughton 1997, Skaggs et al. 1996) (**Figure 5**). Instead of a continuous representation of distance or duration, each theta cycle contains sweeps (or renewed neuronal trajectories) that correspond to overlapping spatial segments of the animal’s path, so that the animal’s past, current, and future positions can be inferred from spike contents in single theta cycles (**Figure 5**). At each cycle, this sweeping neuronal trajectory (corresponding to looking back and looking ahead) results in locations behind

Subjective time:
the feeling of change,
related to external
events or internal
sensation (e.g., hunger)

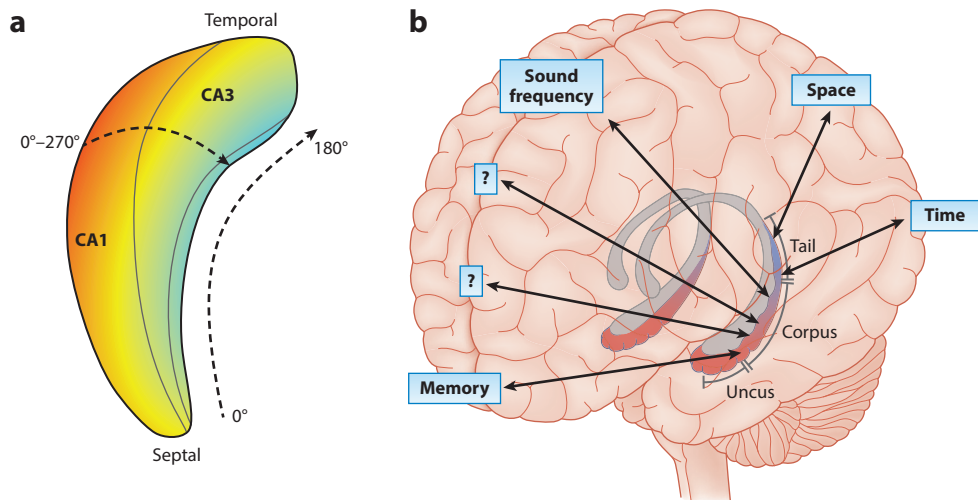


Figure 4

Theta phase dynamics evolve in neuronal space. (a) Theta oscillation is a traveling wave and shows systematic phase shift in both the septotemporal and the CA1-CA3-dentate gyrus axes (the color scale illustrates the phase offsets between regions). The hippocampal neurons are locked to local theta rhythm and show a phase shift up to 270° in the CA1-CA3-dentate gyrus axis and a 180° shift from the septal to the temporal pole. Panel adapted from Petersen & Buzsáki (2020). (b) The hippocampus communicates bidirectionally with the neocortex and performs the same kind of computation irrespective of the cortical inputs. The experimental design and the nature of the input, rather than neuronal computation per se, affect whether hippocampal neurons correlate with duration, distance, position, or metrics of other modalities. Panel adapted from Royer et al. (2010).

and in front of the animal being transiently represented. As the velocity of the rodent increases, the place field size of the neurons remains preserved, but larger segments of the paths are compressed into fewer theta cycle assemblies due to faster transitions between assemblies (Maurer et al. 2012). Thus, in the ambulating rat, speed affects the rate of change between assembly transitions (this is called speed gain). The primacy of phase, as opposed to time organization, can also be illustrated by displaying spiking activity as a function of travel distance, travel duration, or successive theta cycles (Buzsáki & Tingley 2018) (see **Supplemental Figure 1**).

Time-compressed reproductions of neuronal sequences do not require locomotion or external signals. In the absence of theta oscillations, when the animal stops moving or is engaged in consummatory behaviors, intermittent sharp wave-ripples (SPW-Rs; 110–200 Hz oscillations) occur in the hippocampus. These events are believed to be involved in various aspects of memory and are found in every mammal investigated to date, and they may serve identical functions (Buzsáki 2015). During SPW-Rs, a large fraction of neurons fire together, many of which correspond to the neurons that are active as place cells in the corridors of a maze (**Figure 5**). Prior to movement, the sequential order of neuronal firing is typically the same as the sequential firing on the track (i.e., forward). In contrast, at the end of the journey the neurons fire dominantly in reverse order to the animal's path (Diba & Buzsáki 2007, Foster & Wilson 2006), as if the hippocampus played a movie back for us on fast-forward or rewind to display sequential events that will evolve in the future or have already occurred in the past. The speed of replay during such SPW-R “virtual runs” corresponds to 8 m/s, which is 10–20 times faster than the average speed at which the rat runs through those place fields. This time scale is determined by the internal dynamics of hippocampal networks rather than by sensory inputs. Forward events before the run may serve to prime or

Supplemental Material >

Sharp wave-ripple (SPW-R):

a combination of sharp wave, reflecting afferent excitation, and ripple, a locally induced fast oscillation

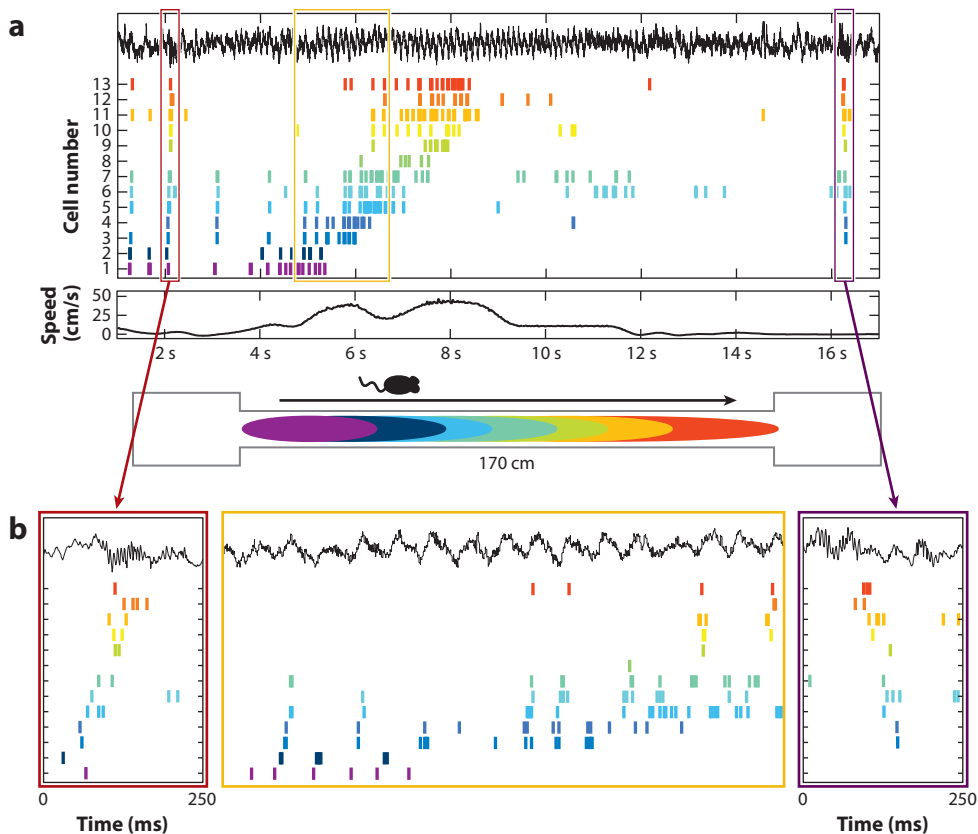


Figure 5

Time compression of neuronal assembly sequences. (a) Spike trains of 13 hippocampal neurons (*color ticks*) before, during, and after a single lap. The top black trace illustrates the local field potential; the bottom black line illustrates the locomotion speed of the rat. (b) Spike sequences within single theta cycles are compressed versions of the place field activity on the track (2-s segment highlighted in the yellow box). These theta sequences gradually shift as the animal moves from left to right down the track. On each end of the track (*red and purple boxes*), spiking during ripples reflects forward and reverse replay of the sequences on the track, respectively. Figure adapted from Diba & Buzsáki (2007).

potentiate neuronal circuits for action planning. Conversely, reversed replay events at the end of the run nonconsciously recapitulate the movement trajectory in the maze. Although a large body of experiments suggests that internally induced SPW-R events may serve both prospective and retrospective roles in cognition (i.e., prediction and postdiction; Diba & Buzsáki 2007, Pfeiffer & Foster 2013), we have no way to know what a rodent is thinking or experiencing when hippocampal SPW-Rs emerge.

However, during the past decade, work on human subjects has verified and expanded findings on experimental animals. Simultaneous intracranial recordings of ripples from the temporal lobe and the temporal association cortex showed that their coupling increased prior to successful verbal reports of recall in a paired associates memory task (Henin et al. 2020), replicating analogous findings in rats (Khodagholy et al. 2017). The incidence of SPW-R increases 1 to 2 s prior to the onset of free recall. The increase is content selective for faces and places, as detected through increased differential coupling between SPW-Rs and broadband activation at those neocortical recording

sites in the fusiform area and entorhinal and perirhinal cortices that preferentially responded to faces and places during a learning phase (Norman et al. 2019). Furthermore, spike sequences identified during memory formation are replayed in association with ripples during successful memory retrieval (Vaz et al. 2020), supporting observations in rodents that the neuronal trajectories active during learning are reinstated during SPW-Rs and provide the sought-after relationship between neural reinstatement and behavioral measures of memory recall.

Evidence for memory reinstatement in healthy humans has been seen using other methods, such as functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). Using fMRI, it has been shown that multivariate patterns that characterize a learning experience persist into postencoding rest periods, and their persistence relates to later memory for the preceding presented items as if the brain was prioritizing them in memory (Tambini & Davachi 2013, Tambini et al. 2010). In a recent study, the authors decoded each presented picture from patterns of MEG sensor activity (stimulus code) and searched for their spontaneous reoccurrence and sequential order during the 5-min brain idling epochs prior to recall. Importantly, the sequential order of the detected signals corresponded not to the order of the original stimulus presentation but to the subjective importance reported by the participants. The spontaneously reactivated compressed sequences were associated with a power increase at 100–180 Hz, which the authors tentatively source-localized to the hippocampus. The order of detected items within the temporally compressed patterns was dominantly in a forward direction, but in a second part of the study in which learning was rewarded, the sequences reversed their order, which was reminiscent of the forward-reversed replay sequences of hippocampal neurons in the rat (Liu et al. 2019) (**Figure 5**). Importantly, replay events have been associated with activity increases in the default mode network (Higgins et al. 2021, Kaplan et al. 2016), an indication that hippocampal SPW-Rs play a key role in the coordination of global-scale activity of the neocortex.

Internally organized neuronal trajectories are continuous within both theta cycles and SPW-Rs without clear boundaries of past, present, and future. Stated differently, mechanisms of postdiction and prediction are not so distinct in the brain. What appears to be postdiction (memory of the past) in the sequential activity of cell assembly sequences can also be called prediction (plans for future action). These neurophysiological findings echo similar recent thinking in psychology. Planning and recalling feel different: One relates to the subjective future, the other to the subjective past. Yet it has long been recognized that planned actions cannot be carried out unless the plan is kept in memory until its actions are completed. Planning thus can be referred to as “constructive” episodic memory (Schacter & Addis 2007) or “memory of the future” (Ingvar 1985, Schacter 2012). In support of this view, bilateral hippocampal damage can impair not only recalling the past but also thinking about one’s personal future and imagining new fictitious experiences (cf. Race et al. 2011, Squire et al. 2010). Accordingly, it has been shown that neural activation patterns during future planning largely overlap with activation patterns during memory retrieval tasks (Buckner & Carroll 2007, Hassabis et al. 2007, Schacter et al. 2012). These new findings are beginning to bring down the walls that have long stood between human invented terms and brain mechanisms.

CONSOLIDATION OF MEMORIES

A unique feature of declarative, particularly episodic, memory is that such knowledge can be acquired in a single trial and yet can last for a lifetime. This permanence is surprising in light of the constant reshaping of neuronal connection strengths in the brain (Ziv et al. 2013). One potential solution is a selection/consolidation process after learning. This can be achieved by retrieving and reconsolidating parts of the original memory trace (Dudai 2012, Nader et al. 2000). Alternatively, off-line nonconscious mechanisms might be at work. It has been suggested that hippocampal SPW-Rs during sleep represent the mechanism by which such selection, editing, and

maintenance occur (Buzsáki 1989). The recurrence of SPW-Rs and associated waking experience-related neuronal trajectories several thousand times a night offers a tentative explanation of the fact that episodic information can be remembered even after a single experience. During learning, when the theta rhythm is present, inputs from the neocortex bring about a transient change of synaptic strengths in the hippocampal circuits, where the learned information is temporarily held. This first stage is followed by a consolidation phase during which the wake-active neurons and synapses are repeatedly reactivated during SPW-Rs, often in concert with thalamocortical spindles and slow oscillations (Diekelmann & Born 2010). This way, the initially labile memories are distributed across the rest of the brain and consolidated into permanent forms (Buzsáki 1989, Cowan et al. 2020, Frankland & Bontempi 2005, McClelland et al. 1995).

The experiments summarized above suggest that spontaneous replay of neuronal sequences is more a reflection of the brain's "beliefs" woven from paths and events that have never been directly experienced than a veridical recapitulation of the world as presented to the sensory organs. The time-compressed theta and SPW-R events support an internalized vicarious trial-and-error process that can flexibly replay real or fictive alternatives to construct novel inferences; filter, re-order, and generalize them; and select an optimal action strategy without the need for movement-based exploration. SPW-Rs offer a putative mechanism for combining newly acquired and existing knowledge to influence choices, plan actions, facilitate generalization and abstraction, and, potentially, trigger creative thoughts (Buzsáki 2015, Joo & Frank 2018).

Recall of Memories Once or Multiple Times

The value of a memory is only as good as its retrievability. However, within a short-time segment, only limited aspects of the vast stored memories can surface to the level of awareness [it has to be "fished up, so to speak, from a reservoir" (James 1890, p. 1507)]. Just as in vision what we call seeing is reading brain computation of serial samples of a mere 5° of foveal views, retrieval of memory is scanning multiple limited segments of stored information and weaving them into a story. This hypothetic process is referred to by various terms, such as level of awareness, internal attention (Raichle 2015), working (short-term) memory (Baddeley 1992), or transient buffer (Baddeley 2012) (see **Supplemental Text** for further details). Only after this retrieval mechanism has occurred can the content of memory be consciously accessible to guide current and future behaviors. While working-memory representations typically vanish immediately after being transformed into action, with no further service to the organism, other information enters long-term storage, and with support from the hippocampus, this knowledge can then assist with multiple future actions, including creating novel ideas. From this goal-oriented perspective, distinguishing memory mechanisms based on their single utility or multiple utilities is perhaps more meaningful than distinguishing between working and episodic memories.

The new problem, therefore, is to understand the selection mechanism that promotes or prevents the perpetual consolidation/reconsolidation or postretrieval editing process (Dudai 2012, McKenzie & Eichenbaum 2011, Schiller et al. 2010), which includes the process of forgetting (Wixted 2004). Perhaps off-line computation, including sleep, is the key (see **Supplemental Text** for further discussion).

HIPPOCAMPAL SEQUENCE-BASED APPROACH TO EPISODIC MEMORY

If we remove space and time from the definition of episodic memory, we lose the economic advantage of storing the "what," "where," and "when" separately and reconstructing the original experience from their reinstatement. An alternative efficacious approach is to divide the labor

Theta rhythm:
a 4–9 Hz oscillatory pattern in the local field of the hippocampus when the animal is engaged in exploratory behaviors or rapid-eye-movement (REM) sleep

Supplemental Material >

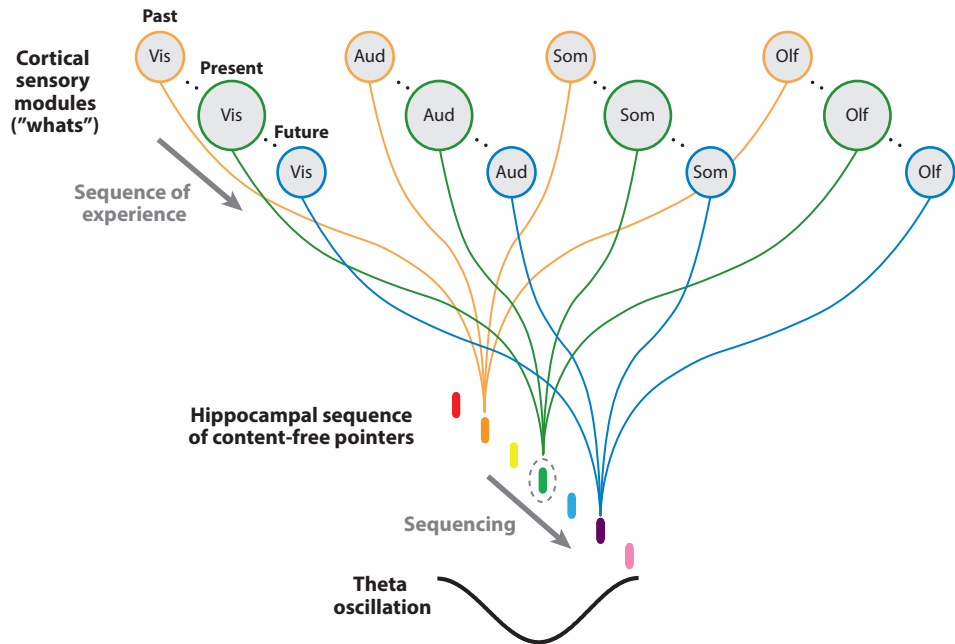


Figure 6

Brain mechanism–based view of episodic memory: the hippocampus as a sequential multiplexed pointer. Indices that point to cortical modules for different inputs are sequenced by evolving hippocampal activity patterns, thus preserving the directed ordinal structure over which experience occurred. Semantic content resides in cortical modules that are concatenated by the hippocampus during both encoding and recall. Abbreviations: Aud, auditory; Olf, olfactory; Som, somatosensory; Vis, visual. Figure adapted from Buzsáki & Tingley (2018).

between the “whats” and their sequential order. Under this new formulation, an episodic event is an ordered sequence of “whats.” Instead of storing a huge repertoire of unique events of our lives, each of which unfolds in postulated space and time coordinates (**Figure 1**), we can store the detailed content of the events in the neocortex, whereas the task of constructing and reconstructing the sequential order of episodes is left to the hippocampus. This task separation plays an analogous role to that of an index in a book, whereby each individual entry points to a cortical storage site in the neocortex from which semantic knowledge of the event can be retrieved (Teyler & DiScenna 1986). In our extension of the indexing hypothesis, the key function of the hippocampus is the sequential ordering of these “what” events. Instead of a static index that points to a cortical site, the neuronal trajectories in the hippocampal system form a sequential pointer (a directed sweep), which can scan through the relevant neocortical modules and concatenate semantic chunks into neuronal narratives for both encoding and retrieval (i.e., constructing episodes; **Figure 6**). Episodic storytelling to self (i.e., the process of thinking) or others is the process of making sense of real-world events and imagining causal order structures. In contrast to directionless associations, only directed narratives (**Figure 1**) reveal causal relations and inferences.

Perhaps the most fundamental physiological function of the hippocampus is directed sequence generation (**Figure 3**). It produces content-limited cell assembly sequences without encoding the details of particular events, and the sequences tile the gaps between events or places to be linked (a form of “hashing”; Friston & Buzsáki 2016). Navigation in the world or in mental space is inherently a directed succession of events. We walk through the events and with the assistance of

the hippocampus we piece together a storyline from scattered semantic fragments stored in the neocortex. Our subjective feeling of time may come from this vectorial ordering. The order of the recalled events may not correspond faithfully to the original but may be modified by the priorities set by previous experience and relationship to the events (Liu et al. 2019). As a result of such subconscious reordering by SPW-Rs, the replayed events may reflect the interpreted significance rather than the original sequence of events. In the proposed sequencing model, episodic memory is an ordered sequence of translationally invariant “whats” (Buzsáki & Tingley 2018). Sequencing or ordering can be viewed as a preconfigured syntactical operation, which, similar to language, can give rise to virtually unlimited constructs from limited numbers of “whats.” An implication is that after hippocampal damage the details of a situation can be recalled, but without the correct order of experienced events.

A wealth of work has already shown that the hippocampus is important for sequence memory. Behavioral work has shown that rats with hippocampal damage exhibit impaired memory for the order of odor stimuli, even though they maintain the capacity to recognize individual odors that have recently occurred (Fortin et al. 2002). Similarly, hippocampus-damaged amnesic patients have much less of a problem with recalling places, streets, and unique events separately than with remembering the sequential order in which the events occurred or constructing street routes for efficient navigation (Dede et al. 2016, Maguire et al. 2006).

Human imaging experiments have also provided support for a sequence-generator function of the hippocampus. Using fMRI, early work has shown that activation in the hippocampus during the encoding of a sequence of three items is related to subsequent memory for the order of the items but not the individual items (Tubridy & Davachi 2011). Further, a recent study showed that after learning a sequence of objects, when participants were viewing the same items embedded in distinct context sequences, hippocampal activation patterns diverged to reflect the distinct sequences and not the items (Hsieh et al. 2014). In general, the similarity in hippocampal activity patterns in humans has now been shown to reflect the proximity of events in both space and time, and it also appears to scale appropriately from short sequences to the unfolding of experiences over weeks. Greater temporal stability in hippocampal activity patterns was observed between items that were later subjectively judged as “close” as compared to “far,” even though the item pairs were separated by the same number of intervening trials in the task (Ezzyat & Davachi 2014). A series of experiments have shown that although time may correlate with experienced sequences, there are evident discontinuities at the boundaries between event sequences (Davachi & DuBrow 2015). Sequences encountered in the same context or event are better integrated in memory as measured by retrieval success, and these items appearing in the same context are later remembered as having appeared more closely together in time (DuBrow & Davachi 2013).

A recent study used GPS data and the time stamps of the snapshots taken automatically by a body camera that the participants wore over the course of 4 weeks. Subsequently, when participants were scanned using fMRI while recalling their real-life experiences, both the spatial and the temporal distance of two memories were correlated with hippocampal neural distance measures over various scales of magnitude (Nielson et al. 2015). In a virtual reality study, subjects navigated through the streets of a virtual town and were asked to recall whether two objects were close to each other or far apart. In this experiment as well, neural similarity scaled with the proximity of event memories in both spatial and temporal dimensions, supporting the notion of a common hippocampal coding mechanism for space and time (Deuker et al. 2016).

The hypothesis of a sequence-generator function of the hippocampus may resolve the apparent contradiction between the trace transfer and dual trace models of declarative memories. According to the trace transfer hypothesis, after learning the initial memory a trace resides in the hippocampus and is transferred over time to the neocortex (Frankland & Bontempi 2005, McClelland et al.

1995, Scoville & Milner 1957, Squire 1992). In contrast, according to the dual trace model, detailed information about episodes will be kept forever in both the hippocampus and the neocortex (Nadel & Moscovitch 1997). Under the sequence-generation hypothesis, the main preoccupation of the hippocampus is to concatenate content-containing events in the neocortex, rather than to compose a *de novo* trace of the entire novel experience in the hippocampus. This sequencing role of the hippocampus also remains a requirement for recalling ordered events forever.

According to this “search-engine” function, the neuronal trajectories of the hippocampus should covary with activities between modalities in the neocortex. The anatomical organization of the hippocampus is well suited for such a task. In contrast to the modularly organized neocortex, the hippocampus is fundamentally a single giant module with the most extensive recurrent excitatory system in the brain (Wittner et al. 2007). The strongly connected graph of the intrahippocampal circuit and the neuronal sequences selected from this large graph serve to combine and mix neuronal messages from wide areas of the neocortex, independently of their modalities and origin, and the hippocampus returns the computational results to these same neocortical areas by way of the entorhinal cortex and retrosplenial cortex (Witter et al. 2000) (**Figure 6**).

Overall, the physiological recordings and behavioral, lesion, and imaging experiments support the hypothesis that encoding and preserving the sequential order of experiences is a crucial function of the hippocampus. Learning the sequential order of events allows the brain to form predictions about the impending future and to plan upcoming actions accordingly.

NEURONS THAT WIRE TOGETHER FIRE TOGETHER: LEARNING AND MEMORY IN A PRECONFIGURED BRAIN

The burden of the inherited framework from philosophy and folk psychology in current neuroscience is perhaps nowhere more prominent than in the science of memory. A persistent tacit assumption is that each new learning changes network connectivity and dynamics in some brain circuit. According to this framework, brain complexity scales with the amount of learning. Although perhaps no neuroscientist would accept such adamant blank slate (or *tabula rasa*) view of the brain, we typically design our experiments and interpret the results within this framework (Buzsáki 2019). In its fundamental version, the blank slate model applied to neuronal networks assumes a collection of largely similar, randomly connected neurons with balanced excitatory and inhibitory connections. This view has been fueled by the ideas of equipotentiality (Lashley 1950) and equivalence of associability and, in contemporary neuroscience, by the dominance of Hebbian learning and plasticity (Hebb 1949). This view is perhaps most explicitly expressed by Alan Turing, the great pioneer of mind modeling: “Presumably the child brain is something like a notebook as one buys it from the stationer’s. Rather little mechanism, and lots of blank sheets” (Turing 1950, p. 456). As a result, artificial intelligence models built this way have an inconvenient bug known as “catastrophic interference” (McClelland et al. 1995): The constant adjustment of functional connectivity in the models following new learning can unpredictably erase all stored memories, an event real brains never experience.

This prevailing framework is surprising, given that brains have an evolutionary history in their natural niche and so they bring their explicit predispositions to any situation. Ethology and experimental psychology have produced ample demonstrations that organisms with both simple and complex brains are prepared to associate certain events, unprepared to associate others, and contra-prepared to associate still others (Seligman 1970). Because of such evolutionary bias, animals in laboratory situations often follow unexpected strategies and auto-shape persistent, energetically costly behaviors that seem irrational in the cost-benefit scheme defined by the experimenter (Breland & Breland 1961, Brown & Jenkins 1968). This should be a powerful message,

because physiological observations and interpretations can only be as relevant as the underlying behavior. If it takes thousands of trials for animals to learn an experimenter-designed paradigm, each animal may acquire it by adopting different strategies. Without a detailed analysis of behavior, we may come to believe that we are studying neuronal correlates of learning and memory, whereas in reality the observed neuronal events may simply reflect head turns, whisking, or heart rate changes (Krakauer et al. 2017, Vanderwolf 2003).

In contrast to this blank slate framework, recent research suggests that the brain's main preoccupation is to maintain a preconfigured internal dynamic (Buzsáki 2019)—sometimes referred to as an attractor, neural manifold, or schema (Hopfield 1982, McKenzie et al. 2014, Samsonovich & McNaughton 1997)—and to provide a stable and robust balance against competing needs, such as wide dynamic range, sensitivity, and plasticity. The brain, and particularly the hippocampus, perpetually generates and maintains a large reservoir of preconfigured neuronal sequences that are available for matching with new experiences (Battaglia et al. 2005, Buzsáki & Mizuseki 2014, Dragoi & Tonegawa 2011, Luczak et al. 2009, Tambini et al. 2010), rather than responding to stimuli impinging on our sensors all the time. The implication of this preexisting dynamic is that the pattern of neurons that will come to store the memory of an event will strongly depend upon existing patterns and may even *be* an existing pattern. In psychological terms, encoding in this inside-out framework always occurs upon a background of neuronal pattern retrieval. Metaphorically, the brain can be likened to a preconfigured dictionary with gibberish neuronal words, some of which may gain meaning as a result of experience. In this inside-out framework (Buzsáki 2019), learning is primarily a process of matching between the available neuronal trajectories and things and events in the world rather than a process of building up a novel pattern with each experience. Artificial neural networks that rely on such reservoir computing have been explored in liquid state machines and echo state networks (Maass & Markram 2004, Tanaka et al. 2019). Below, we review the few pieces of physiological evidence that have been gathered in support of this alternative perspective on learning and memory.

Work on sensory systems has already shown a strong resemblance of self-organized spontaneous patterns and stimulus-evoked responses (Stringer et al. 2019). In the visual cortex of cats and monkeys, imaging studies revealed that spontaneous activity often displayed patterns that closely corresponded to orientation maps evoked by stimuli. Moreover, trial-to-trial variability of the evoked activity could be predicted from the instantaneous state of ongoing cortical activity (Arieli et al. 1996). Similarly, in the auditory cortex, population firing rate vectors evoked by a variety of stimuli occupied a subset of a larger space outlined by spontaneous events (Luczak et al. 2009). Developmental studies in ferrets have shown that with experience, the statistics of the activity evoked by the experimental stimuli come to match those observed during spontaneous activity (Berkes et al. 2011). These results are consistent with the hypothesis that the preexisting patterns of activity that best reflect various aspects of our lived experience become preferentially reinforced and reinstated during future encoding moments as well as spontaneously, during sleep or in the absence of trigger stimuli. Such distinctions can be illustrated experimentally by the emergence of hippocampal place fields.

Contrasting Views on Place Field Induction in the Hippocampus

Ideas about the emergence of place fields range between two extremes. At one end is the assumption that environmental inputs, combined with Hebbian or other plasticity rules, give rise to new place fields (i.e., blank slate model). The observations that place fields of place cells and grid patterns of grid cells can be distorted, extended, or even split by changing the geometry of the

Preconfigured

dynamic: the set of activity patterns that emerge due to innate and fixed anatomy and to single-cell properties

Neuronal state:

neuron assemblies are in a perpetual change, which can be represented as a spatiotemporal vector or assembly sequence moving in state space

environment (Giocomo 2016, O'Keefe & Burgess 1996) are compatible with this view. Furthermore, the observation of remapping, with each environment represented by a different orthogonal map consisting of member neurons drawn randomly from the population (Kelemen & Fenton 2010, Muller et al. 1987, Samsonovich & McNaughton 1997), may be interpreted to support the blank slate model. The implication for memory research is that each situation is expected to be coded by orthogonal constellations of neuronal assemblies.

Interpretations at the other extreme assume that place fields are drawn from a preexisting reservoir in preconfigured hippocampal networks (i.e., preconfigured dynamic model). Support for the latter view comes from experiments that demonstrate that the place cell sequences in a novel environment can be predicted from similar but compressed sequences detected during SPW-Rs of pre-experience sleep (Dragoi & Tonegawa 2011, Farooq & Dragoi 2019, Grosmark & Buzsáki 2016). Furthermore, the observations that place fields typically emerge rapidly in both familiar and novel environments is compatible with the idea that learning occurs through a reassignment of existing patterns to novel situations (Sadtler et al. 2014, Tambini et al. 2010) rather than gradually over the course of several trials, as would be expected if incremental Hebbian plasticity were the mechanism of place cell induction.

Attempts to experimentally manipulate hippocampal pyramidal neurons also fall into such opposing views. In support of the equivalence of associability (blank slate) claim, elegant series of studies have shown that when any single CA1 pyramidal cell is injected with a strong intracellular or juxtacellular current, resulting in a large dendritic plateau potential, a new place field can be induced at any position of the mouse's path (Bittner et al. 2015, Milstein et al. 2020). These observations are interpreted by suggesting that any sensory input that occurs within a multi-second time window around the plateau potential can get strengthened and, therefore, induce a new place field. In contrast, other experiments are more compatible with the prewired model. The first study to test this hypothesis used long-term potentiation (LTP) of the CA3-CA1 connections (Dragoi et al. 2003) (**Figure 7**). LTP perturbation induced novel place fields and made existing place fields disappear. However, new fields tended to emerge in low firing rate neurons in locations associated with preexisting dormant activity; strong existing place fields could not be modified. In support of these findings, spatially uniform intracellular depolarization of silent CA1 pyramidal cells led to spatially tuned subthreshold response and place-field spiking (Lee et al. 2012).

When a handful of CA1 pyramidal neurons were optogenetically activated, pyramidal cell-interneuron couplings were immediately reorganized, and a fraction of directly stimulated and nonstimulated neurons gained new place fields. Importantly, the induced firing fields occurred in places already associated with sparse preexisting spiking activity. Furthermore, in the sleep prior to neural stimulation, neurons with newly expressed place fields already showed correlated firing with co-tuned peer neurons (McKenzie et al. 2021). These experiments demonstrate that novel place fields are unmasked from dormant place fields and that incorporation of synthetic signals is constrained by preexisting circuit dynamics. What might appear as a freshly created novel place field (i.e., information newly added to hippocampal circuits) may be more appropriately described as a selection process between preexisting internally organized neuronal trajectories and constellations of external inputs (Buzsáki 2019, Dragoi & Tonegawa 2011, Farooq & Dragoi 2019, McKenzie et al. 2021). More generally, the reorganization of hippocampal circuits is both constrained and guided by a backbone of a preconfigured repertoire of states (Battaglia et al. 2005, Buzsáki & Mizuseki 2014, Dragoi & Tonegawa 2011). In summary, the dormant-to-overt place field conversion may be the physiological mechanism for novel place field induction, and this process is more an unmasking of preexisting connections and partnership with other peers than the creation of a novel neuronal state due to some unique feedforward sensory drive.

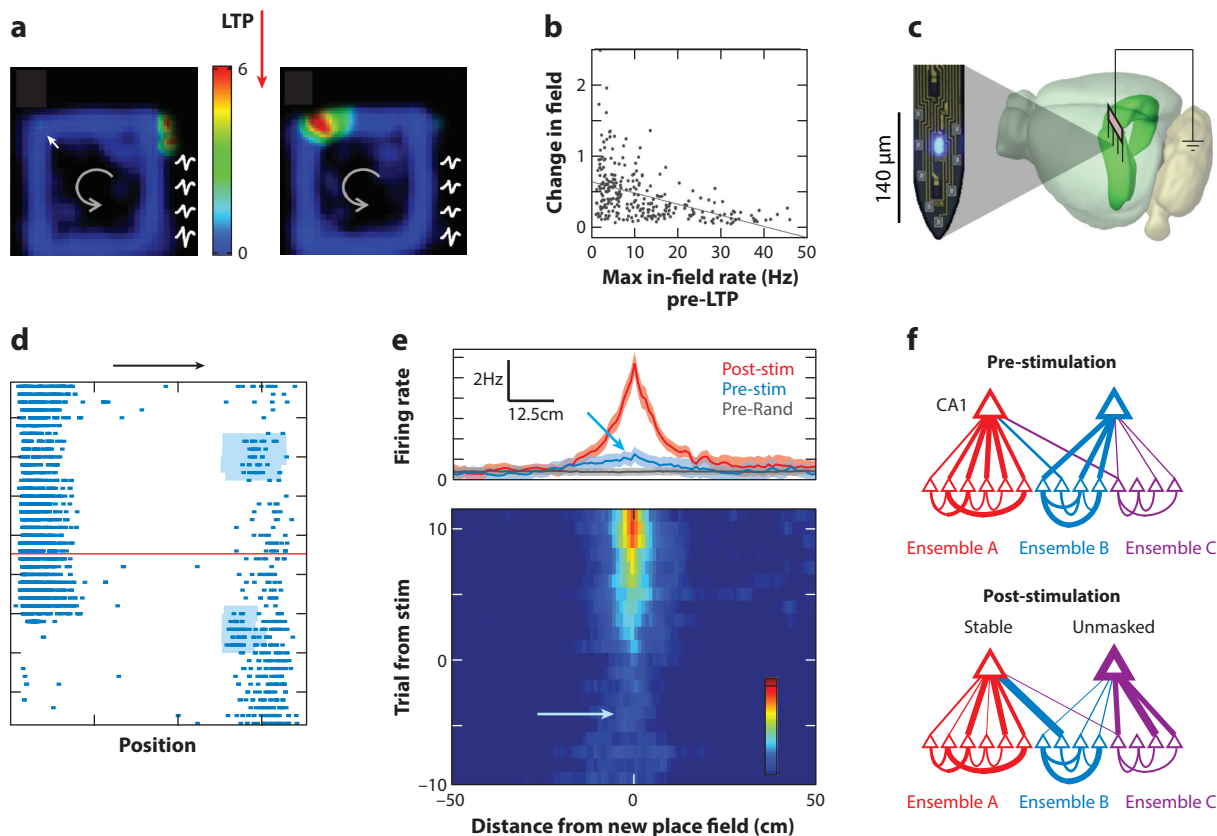


Figure 7

Hippocampal plasticity is constrained and predicted by existing dynamics. (*a*) Place field reorganization after the connections between hippocampal CA3 and CA1 neurons were altered by long-term potentiation (LTP) (*red arrow*). The white arrow shows weak firing of a CA1 pyramidal neuron in the location of the future, post-LTP place field (“ghost” field). (*b*) Most place field changes occurred in neurons with low pre-LTP firing rates. (*c*) Similar results were seen in an optogenetic version of the experiment where μ LED probes were used to drive small subsets of neurons in a fixed location on the track (*d*). The blue shading shows optogenetic stimulation of a synthetic place field of a CA1 neuron. The red line shows the separation between a morning and afternoon recording session. The arrow shows the running direction of the mouse down the 1.2-m track. (*e*) Like in the LTP experiment, new place fields emerged in locations with weak, preexisting drive (*blue arrows*). (*f*) Schematic depiction of how place fields reorganize after LTP or optogenetic stimulation. Before stimulation, neurons in CA1 (*top, triangles*) receive heterogeneous inputs from afferents tuned to places A, B, or C (ensembles A–C). Stimulation can both increase and decrease existing connections. CA1 neurons strongly associated with afferent ensembles will remain stable, while those with moderate associations to ensembles in a given environment may remap when some connections are strengthened (*purple*) and others are weakened (*blue*). Abbreviations: pre-Rand, random samples during pre-stimulation trials; stim, stimulation. Panels *a,b* adapted from Dragoi et al. (2003); panels *d,e* adapted from McKenzie et al. (2021).

A Continuum of Known and Unknown

From the perspective of independent or orthogonal maps, the minority of neurons active in multiple environments may be regarded as noise or imperfection in the system (Marr 1971). However, when other physiological features of this minority are considered, a different picture emerges. The default firing rates of this minority during sleep are also higher, and their individual place fields are larger, compared with those of the majority neurons with single place fields (Buzsáki & Mizuseki 2014). Furthermore, this minority of “generalizers” fires synchronously with other neurons more frequently across all brain states compared to the slower firing majority, has longer

Log-normal distribution:

a statistical distribution where the incidence of some measurement is normally distributed if a log transform is applied to the measured quantity

axons, and produces a stronger and more effective excitation in their targets (Ciocchi et al. 2015). As a result, in physiological time frames, such as theta oscillations and SPW-Rs, about half of the spikes in the hippocampus are contributed by this active minority, with the other half provided by the majority of neurons with no or a single place field. Calcium imaging in mice running in virtual reality has shown that these propensities of the hippocampal neurons remain stable across environments and also over weeks (Lee et al. 2020), despite considerable reorganization of the place fields (Ziv et al. 2013). Other features of neuronal organization echo similar heterogeneities (Koch & Laurent 1999). Both micro- and macroscopic anatomical organization and physiological features, such as axon conduction velocity, synaptic weight distributions, firing rates, spike transmission probability, and population synchrony span orders of magnitude, and their distributions typically obey a log-normal rule (Buzsáki & Mizuseki 2014).

In this autocratic brain organization, neurons at the two ends of the log-normal distribution of activity contribute to learning and memory differently. The more strongly connected, faster firing neurons have better reciprocal connections with the majority, share information among themselves, and generalize across situations, while the majority keep their independent solitude and elevate their activity only in unique situations. The seemingly distinct qualitative features of the two tails of these distributions are described by discrete words, such as familiar and novel, rigid and plastic, good-enough and precise. Yet, they are part of a continuum.

Every novel situation contains elements of familiarity. The preconfigured backbone of strongly interconnected and highly active member neurons enables the brain to regard no situation as completely unknown. That existing ensembles come to generalize to novel exemplars was demonstrated by McKenzie et al. (2014), who showed that when rats learn that particular objects are rewarded in a subset of locations, and later learn that new objects share the same reward associativity, the neurons that fired in response to the first objects rapidly generalize to the new problem at hand. Matching existing states to novel circumstances allowed for rapid learning, as large savings were observed between learning a first and a second set of objects (McKenzie et al. 2014). We put forward that any situation—novel or familiar—is matched by the brain's highest-probability neuronal state. Nothing is completely novel to the brain; it always guesses and compares.

Under the learning-by-matching hypothesis, the fundamental problem to solve is which pre-existing representation to instantiate. Multiple maps can exist for the same space and can switch rapidly (on the order of milliseconds) depending on task demands (Jackson & Redish 2007), thus allowing a physiological mechanism by which the brain's hypotheses about latent states can be brought to bear and then quickly rejected or retained. In this framework, instantiating a preexisting neural state in a novel situation amounts to categorizing the present together with the related past in which the same neural state was active.

From this inside-out perspective, brain correlates of newly acquired experience are not created and added to an ever-expanding memory store. The most important preoccupation of the brain is to maintain its own dynamic and a large vocabulary of reservoir states. Some of these available patterns become grounded by action-based calibration, so that an ever-growing fraction of the preconfigured neuronal trajectories gains utility or real-world meaning to the organism. In summary, we submit that learning is primarily a process of matching preexisting neuronal dynamics to events in the world.

CONCLUSIONS

As many aspects of neuroscience, learning and memory have been approached from the human mind's point of view. Because some forms of human memory engage the conscious realm, the major forms of memory have been traditionally divided into verbal declarative and nondeclarative.

As an alternative to this human mind–referenced approach, our review offers a brain-based understanding of memory with a focus on hippocampal physiology. From an evolutionary perspective, memory is a mechanism that guides current and future behaviors by selecting appropriate actions on the basis of past experience. Some forms of memory are useful only once (single-utility or working memory), whereas others are useful for a lifetime (multiple-utility or long-term memory). Aspects of these operations are supported by interlinked physiological mechanisms and brain states, such as waking learning and sleep-supported editing or consolidation.

Verbally declarable memories can be couched from the first-person (egocentric episodes) and third-person (allocentric semantic knowledge) perspectives. Since the separation of self from others and the environment is pervasive in the animal kingdom, this perspective allows for a forward strategy for studying memory in all animals, and it links episodic and semantic memories to egocentric (path-integration) and allocentric (map-based) forms of navigation, respectively. We suggest that disengagement (or internalization) from environmental and body-derived cues allows the hippocampal system in complex brains to perform vicarious or imagined navigation (mental time travel) and to evaluate what-if outcomes against preexisting and stored knowledge without the need for immediate physical action.

Navigation in real or mental space is a succession of events and is invariably linked to sequentially organized neuronal assemblies (trajectories) in the hippocampus and allied structures. We suggest that neuronal trajectories in the hippocampal system form a content-limited multiplexed pointer, which scans through the detail-rich neocortical modules and concatenates information chunks into sequences for both encoding and retrieval. Sequencing or ordering is a preconfigured syntactical operation, which, similar to language, can give rise to virtually unlimited constructs from limited numbers of semantic “whats.”

In contrast to the persisting view of the mind as a highly plastic blank slate, we hypothesize that the brain is endowed with a large repertoire of internally generated trajectories. Learning in this preconfigured model is a selection or matching process between best-fitting neuronal patterns and world events. Though the history of neuroscience has been grounded by the search for neural mechanisms underlying cognitive processes, we advocate a complementary inside-out perspective to discover the mental manifestations of fundamental biological processes.

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