Overview

Hippocampus

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Damage to the hippocampus and related brain regions causes a profound amnesic syndrome, in which patients are unable to form new memories about their experiences and about facts about the world. A number of theories have been proposed to explain hippocampal function. The theories that are currently most influential propose that the hippocampus is the substrate of declarative or episodic memory and that the hippocampus is the neural locus of a cognitive map. Anatomical, physiological, and behavioral studies of the hippocampal system have enabled a rich understanding of a number of general principles of information processing and storage in the brain. In this article, we describe key anatomical and physiological features of hippocampal function as well as the most influential theories of hippocampal function. © 2012 John Wiley & Sons, Ltd.

How to cite this article:
WIREs Cogn Sci 2012, 3:231–251. doi: 10.1002/wcs.1164

INTRODUCTION

Imagine life without the memories that largely define who we are. Imagine not remembering intimate moments and arguments with family and close friends. Imagine having an electrifying conversation with a stranger in a coffee shop, walking out of the shop, and immediately not remembering the conversation, the stranger, or the ambiance in which it happened. Damage to a brain structure called the hippocampus leads to precisely this kind of memory loss.[1] The role of the hippocampus in memory has made it one of the most studied structures in the brain. These studies have not only generated great insight into the nature of memory, but they have also revealed a host of general principles underlying brain function.

A number of early electrophysiological discoveries, such as the identification and characterization of specific inhibitory[2] and excitatory synapses,[3] as well as the demonstration of long-term plasticity at these synapses,[4] were made in studies of the hippocampal formation. These phenomena were later shown to be present throughout the brain. A prime reason for the special utility of the hippocampus for such electrophysiological studies is that the principal cells of the hippocampus and the dentate gyrus (the pyramidal cells and granule cells, respectively) are arranged in a single, dense layer, with synaptic inputs well segregated into layers above and below the principal cell layer. This arrangement facilitates the electrical stimulation of well-defined inputs and the identification of sources and sinks in the extracellular recordings[5] (Figure 1).

In addition to cellular neurophysiology, the hippocampus has played a major role in the discovery of principles of systems, computational, and cognitive neuroscience. Single neuron recordings from the hippocampus of awake, freely moving rats led to the discovery of place cells,[8,9] neurons that selectively fire at specific spatial locations in a given environment. This discovery opened up avenues for understanding the role of single neurons in spatial navigation and in high-order cognition.

The hippocampus thus occupies a prominent place in studies of brain function at multiple levels. In this article, we describe aspects of hippocampal anatomy, physiology, and function. The *Anatomy* and *Physiology* sections highlight the features relevant to understanding hippocampal function at the level of systems and cognitive neuroscience.

ANATOMY

The hippocampus, with its unique anatomy and laminated structure, has long fascinated neuroanatomists.[10] It derives its name from the similarity of

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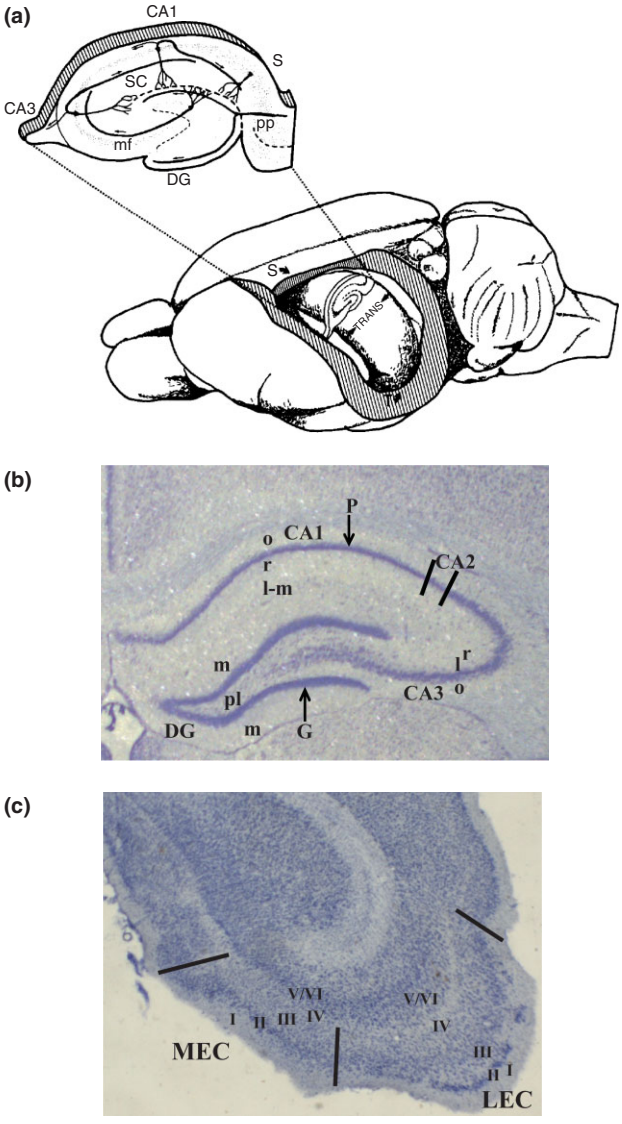

FIGURE 1 | Hippocampus anatomy. (a) Position of the hippocampus in the rat brain. The drawing depicts a rat brain after the neocortex overlying the hippocampus was removed to reveal the position and the shape of hippocampus. S: septal pole of hippocampus; T: temporal pole; TRANS: transverse axis, orthogonal to the septotemporal axis. Inset shows enlargement of a section along the transverse axis, with the 'trisynaptic pathway'.[6] CA1, CA3: areas CA1 and CA3 of the hippocampus, DG: dentate gyrus, mf: mossy fibers, pp: perforant path, S: subiculum, sc: Schaffer collaterals. (Reprinted with permission from Ref 7. Copyright 1989 Elsevier Limited) (b) Nissl stained coronal section of the rat brain showing the hippocampus. CA1, CA2, CA3: areas CA1, CA2, and CA3 of the hippocampus; DG: dentate gyrus; G: granule cell layer of the dentate gyrus; l: stratum lucidum of CA3; l-m: stratum lacunosum-moleculare; m: molecular layer of DG; o: stratum oriens; p: pyramidal cell layer; pl: polymorphic layer of DG, also referred to as the hilus; r: stratum radiatum. (c) Nissl stained coronal section of the rat brain showing medial (MEC) and lateral (LEC) entorhinal cortex. Layers I–VI are marked.

the shape of the human hippocampus to the sea horse (genus *Hippocampus*). Different subregions of the hippocampus, the CA1, CA2, and CA3 fields, derive their names from an even older name for the structure, the *cornu ammonis* (horn of Amun, an ancient Greek god). Together with the dentate gyrus (DG) and parahippocampal regions, including the subiculum, presubiculum, parasubiculum, and the entorhinal cortex (EC), the hippocampus is thought to play a key role in memory and navigation.

As the hippocampus has been studied most extensively in the rat, both anatomically and physiologically, we limit the anatomical descriptions in this article primarily to the rat hippocampus. The rat hippocampus is an elongated, C-shaped structure extending from the septal nuclei at the rostral–dorsal–medial end, bending over and around the diencephalon, into the temporal lobe at the caudal–ventral–lateral end (Figure 1(a)). The major axis of the hippocampus is thus referred to as the septotemporal (also called the dorsal–ventral or longitudinal) axis, and the orthogonal axis is referred to as the transverse axis. In primates, the posterior hippocampus corresponds to the septal (dorsal) hippocampus of rats, whereas the anterior hippocampus corresponds to the temporal (ventral) hippocampus of rats (for comparison of hippocampal neuroanatomy in rats, monkeys and humans, see Ref 11).

Information Flow in the Hippocampal Formation

Using the anatomical and physiological evidence available at the time, Andersen et al.[6] formulated the lamellar hypothesis, which proposed that the synaptic connections between the subregions of the hippocampal formation are mostly limited to a thin slice (lamella) orthogonal to the septotemporal axis. Thus, a transverse strip of hippocampus was thought to possess the entire 'trisynaptic pathway',[6] which comprises the EC axons and terminals connecting to DG, DG connections to CA3, and CA3 connections to CA1. According to this view, the hippocampus was organized along the septotemporal axis as a stack of such lamellae, each operating as a mostly independent functional unit. Later anatomical evidence showed that, apart from the mossy fibers connecting DG to CA3, all pathways in the hippocampal formation are more divergent along the septotemporal axis than suggested by the lamellar hypothesis.[7] Furthermore, the synaptic connectivity within the hippocampal formation is much more complex than the classic 'trisynaptic pathway,' with a number of parallel input pathways and feedback pathways (Figure 2). Thus,

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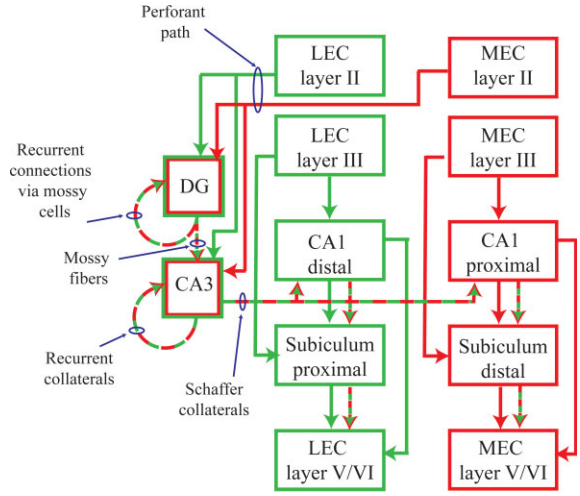

FIGURE 2 | Information flow in the hippocampal formation. LEC receives major input from perirhinal cortex, which is part of the ventral 'what' pathway, while MEC receives major input from postrhinal (parahippocampal) cortex. The projections from LEC and MEC layer III to CA1 and subiculum remain segregated along the transverse (proximal-distal) axis of the hippocampus, whereas the projections from LEC and MEC layer II to the DG and CA3 converge onto the same anatomical regions. See text for details.

although the notions of the hippocampal lamella and the simple, trisynaptic circuit had become ingrained in the textbooks, these concepts have been replaced by a more complex view of hippocampal connectivity and circuitry (reviewed in Ref 12).

In the following paragraphs, we describe the major cell types and synaptic connectivity thought to underlie the flow of information through the hippocampus. Figure 1 shows various subregions of the hippocampus and entorhinal cortex. The EC, divided into medial (MEC) and lateral (LEC) areas, is a gateway for the majority of the cortical input to the hippocampus. It has six well-defined layers. The neurons in layers II and III send major inputs to the hippocampus, DG, and the subiculum, and the neurons in layers V and VI receive feedback from CA1 and subiculum.[13,14]

Granule cells, the principal neurons in the DG, form a horizontal U- or V-shaped layer, with dendrites that extend into the molecular layer and receive excitatory inputs from layer II EC neurons via the perforant path. In a typical, coronal section through the septal hippocampus, the two arms of this U or V are referred to as the upper and the lower blades, with the upper blade being more dorsal of the two. The deeper layer of the DG, called the polymorphic cell layer (or hilus), has a variety of neurons. Mossy fibers (the axons of granule cells) give rise to collaterals that synapse onto some of the neurons in the polymorphic cell layer, including the mossy cells. Mossy cells are glutamatergic neurons that project back onto the granule cells and inhibitory interneurons along the septotemporal axis.[15] Thus, the granule cells and mossy cells form both disynaptic and trisynaptic feedback loops. The functions of these feedback loops are presently unknown.

CA3 pyramidal neurons, which form a well-defined cell layer starting in between the upper and lower blades of the DG, receive inputs from the mossy fibers as well as from the EC layer II neurons via the perforant path. CA3 pyramidal cells make two major projections within the hippocampus. The recurrent collateral system comprises CA3 axons that make synapses onto other CA3 pyramidal cells. Collaterals of the same axons that form the recurrent collateral system also project forward to the CA1 region in a pathway called the Schaffer collateral system. The Schaffer collaterals show a topographical organization in their projections along the transverse axis of CA1. To understand these projection patterns, it is necessary to introduce the anatomical terminology with which the cells along the CA layer are described in terms of their proximity to the DG. Cells that are closer to the DG are called proximal, whereas cells that are farther away are called distal. Distal CA3 pyramidal cells project preferentially to proximal CA1 cells, at levels more temporal to the cells of origin, while proximal CA3 neurons project more to distal CA1 cells at levels more septal to the cells to origin (Figure 3(a)). CA1 also receives inputs from the EC that correspond to the proximal-distal organization of the Schaffer collaterals. Unlike CA3 and DG, where the inputs from the medial EC (MEC) and the lateral EC (LEC) are distributed equally along the transverse axis, MEC layer III neurons project to proximal CA1 while LEC layer III neurons project to distal CA1.[13,14] Thus, proximal CA1 receives primarily input from the MEC and from distal CA3, whereas distal CA1 receives primarily input from LEC and proximal CA3 (Figure 3(a)). Because LEC and MEC are thought to convey fundamentally different types of information to the hippocampus,[16–20] and proximal and distal CA3 are also thought to perform different computational processing,[21,22] it is likely that the proximal and distal regions of CA1 are functionally distinct.[23]

The subiculum also shows the same type of segregation along the proximal distal axis, as LEC layer III projects to proximal subiculum and MEC layer III projects to distal subiculum. Back projections from CA1 and subiculum to layers V and VI of EC, in turn, maintain this topography, with proximal CA1 and distal subiculum projecting to MEC and distal CA1 and proximal subiculum projecting to LEC.[14] This anatomical segregation implies that there are two

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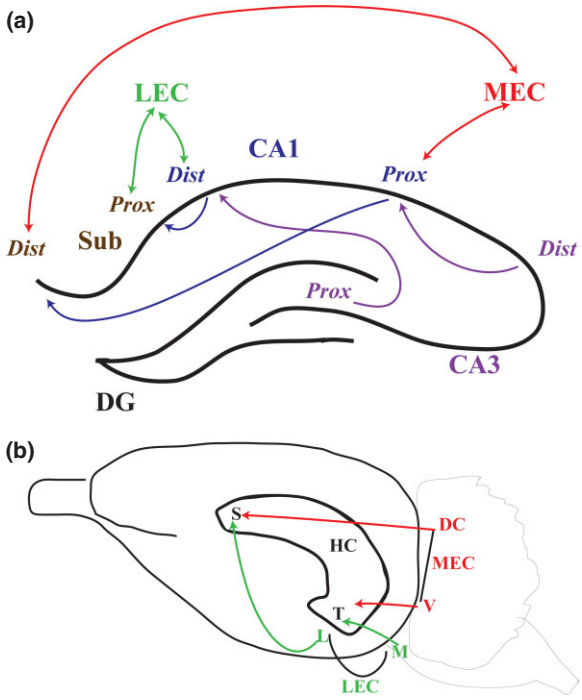

FIGURE 3 | Segregation of projections to hippocampus along the proximal-distal and septo-temporal axes. (a) Schematic showing segregation of inputs to proximal and distal portions of CA1 and subiculum. Arrowheads represent the direction of information flow. Note that LEC and MEC also project directly to all parts of the DG and CA3 regions, but these connections are omitted for simplicity. (b). Schematic showing topographical projection of LEC and MEC inputs to the hippocampus. The lateral (L) part of LEC (near the rhinal sulcus) and the dorsocaudal (DC) part of MEC project to the septal (S) region of the hippocampus (HC), while the medial (M) part of LEC and the ventral (V) part of MEC project to the temporal (T) region of the hippocampus.

distinct processing streams through the hippocampal formation, one that is associated with MEC inputs (thought to relay spatial information based on path integration) and the other associated with LEC inputs (thought to relay information about objects and external landmarks). These streams become mixed in the DG and CA3 regions, but remain relatively segregated in the direct, bidirectional projections among the EC, CA1, and subiculum regions (Figure 2). The functional relevance of this anatomical organization is unknown, but it implies that the DG/CA3 regions are involved in combining these input streams in a way that is critical for memory representation.

Input Gradients along the Septotemporal Axis of the Hippocampus

Entorhinal projections to the hippocampal formation show a topographical gradient along the septotemporal axis of the hippocampus. Cells located laterally in LEC and dorso-caudally in MEC project to septal levels of the hippocampus, while those located medially in LEC and rostro-ventrally in MEC project to the temporal levels of the hippocampus[14,24] (Figure 3(b)). Thus, just as there is an anatomical organization of projections along the transverse axis, there is a corresponding level of organization along the septotemporal axis of the hippocampus. Other differences between the septal and temporal halves of the hippocampus in terms of anatomical connectivity, cell physiology, and behavioral effects of lesions suggest that the septal (dorsal) and temporal (ventral) parts of the hippocampus subserve different functions[25] (but see Refs 26 and 27). Figure 2 summarizes the information flow within the hippocampal formation.

Functional Implications of Anatomical Differences between Hippocampal Subregions

The numbers of neurons in different regions and the connectivity patterns between regions have led to hypotheses about the nature of information processing in different regions. About 300,000 neurons from EC project to approximately 1,000,000 granule cells in DG. In comparison, CA3 has approximately 250,000 pyramidal neurons and CA1 has 400,000.[12,28] The relatively small number of EC neurons projecting onto a larger number of DG granule cells has led to the hypothesis that DG performs pattern separation, by creating sparse, nonoverlapping representations from EC input. In contrast, CA3 pyramidal neurons, with their extensive recurrent connectivity, are thought to perform pattern completion from DG and/or EC inputs, allowing recall of memories from degraded or incomplete inputs.[29–31] Recurrent connectivity within CA3 may also play a role in one-trial learning and sequence learning[30,32–36] (see *Hippocampal Function* section). Finally, CA1 pyramidal neurons receive inputs from CA3 as well as EC, and thus can compare the recalled information from CA3 with current input from EC.[36–38]

PHYSIOLOGY

In this section, we review the physiological properties of the hippocampus that are thought to be important for its function in memory and navigation.

Single Cell Physiology

The principal neurons in CA1 and CA3, the pyramidal cells, appear as complex spiking cells in extracellular recordings. The term complex spiking refers to the fact that these neurons sometimes fire a burst of action

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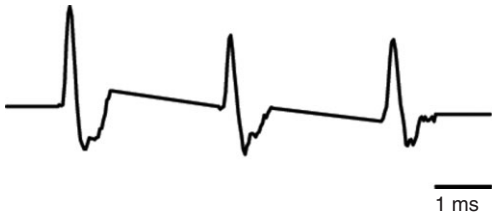

FIGURE 4 | Complex spike in the hippocampus. Extracellular recordings of action potentials from a cell recorded in vivo are shown here. Negative is up. Notice how the amplitude of the action potential drops during a burst, while the interspike interval remains around 3 ms. The number of spikes during a burst is variable.

potentials that are separated by a short interspike interval (a complex spike) (Figure 4). Interneurons do not fire complex spikes.[39,40] Complex-spike bursting may be a mechanism that allows a cell to increase its drive on a downstream target by summating the excitatory postsynaptic potentials (EPSPs) of the target.[41]

Place Cells

When rats explore an environment, the activity of the complex-spike cells is closely related to the rat's location[8,9] (Figure 5). These neurons are thus called place cells, and their discovery was the inspiration for O'Keefe and Nadel's[42] cognitive map theory of the hippocampus. The spatial selectivity of place cells is robust to the loss of individual sensory stimuli, even to the extent that many place cells fire at the same location in the dark as in the light.[9] Some neurons, called 'misplace cells', combined both spatial and nonspatial parameters, in that they fired most strongly at a spatial location when the rat 'sniffed in a place, either because it found something new there or failed to find something that was usually there' (Ref 9, p. 78). We shall come back to these cells later.

Properties of place cells in the rodent hippocampus have been extensively characterized in the last 40 years. The place fields of neurons recorded in a given environment are distributed over the entire environment[43] (Figure 5), although behaviorally significant parts of the environment, such as the walls[44] or the location of a goal,[45,46] might be overrepresented. While foraging for food in open environments, where the rat can approach most of the place fields from a variety of directions, the place fields are mostly nondirectional; that is, the place cell fires at its place field regardless of the direction in which the rat moves through the field.[47] On a radial arm maze[48] or a linear track,[49] on which the rat moves through a location in only two directions, the place fields show directional properties, in that they fire more strongly when the rat runs through the field in one direction compared to the opposite direction. Similarly, when the rat follows a route between points of interest (e.g., reward locations) in an open environment, a higher proportion of neurons show directional firing than when the rat is foraging for randomly distributed reward in the same environment.[50] When the rat runs along a stereotyped path, it always passes through spatial locations in a sequence (points A–B–C–D–E while running from left to right, and the reverse sequence E–D–C–B–A while running from right to left). The entire path can thus be represented by a sequence of neurons activating as a function of distance from the left or right side. The directional properties of the place cells under these conditions are, at first sight, inconsistent with cognitive map theory,[42] which proposes that place cells represent spatial locations in a holistic map of an environment. However, if the two (forward and backward) trajectories of the rat are represented by two different maps, this apparent directionality simply becomes a byproduct of the rat using one map to traverse one direction and another to traverse in the other. This phenomenon may explain why the same location on the drive from home to work and on the return drive, just on the other side of the yellow line, can seem very different from each other. However, although place-field directionality is an area of active study, there is no conclusive explanation for this phenomenon at present.

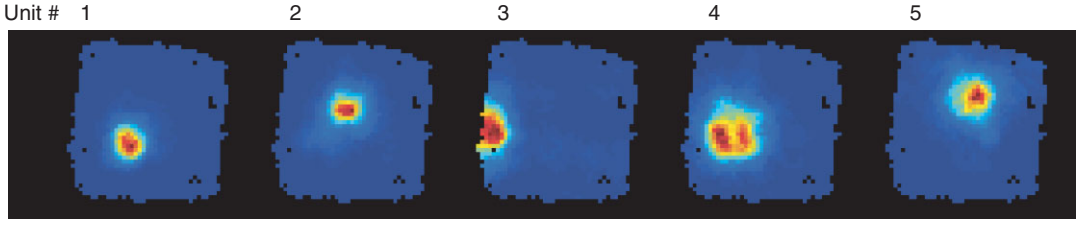

FIGURE 5 | Place cells. The five squares represent the 5 ft^2 box in which the rat was foraging, with the pattern of activity (firing rate map) of each of the five simultaneously recorded place cells (units) shown in one square each. Colors represent the firing rates of the neurons in different locations in the box, with a firing rate of 0 Hz represented by blue and the highest firing rate for the given neuron represented by red. Notice that the five neurons have different preferred firing locations within the box.

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Functional Inputs to the Hippocampus from MEC

What are the inputs to the hippocampus that contribute to the generation of the spatial representation? Animals use self-motion (idiothetic) cues as well as external sensory cues to navigate. Path integration, or dead reckoning, is the integration over time of one's speed and direction of travel in order to calculate an estimate of one's current location. This location estimate can be relative to the starting point (e.g., a homing vector) or to some other stable reference point (e.g., a point on an allocentric map). Idiothetic information consists of motion information derived from vestibular inputs, motor efference copy, and proprioceptive inputs. Optic flow information is also typically included as idiothetic information, as it can be used to estimate velocity.

Two cell types in hippocampus-associated areas are thought to be the result of path integration computations. These are the head direction cells, first discovered in the postsubiculum,[51,52] and the grid cells in the MEC.[53,54] A head direction cell fires when the rat's head points in a certain direction, regardless of its location, and a population of head direction cells represents the entire 0–360° range (Figure 6). The head direction cell system is thought to integrate an angular velocity signal to calculate momentary head direction, and thus allows the rat to keep track of the direction it is heading at any given moment, serving the role of an 'internal compass'. The grid cell system is thought to integrate a linear velocity signal to create a periodically repeating, spatial signal. That is, a grid cell fires whenever the rat is at a vertex of a regular, tessellating grid made of equilateral triangles, like a piece of 'graph paper' on which to plot the animal's trajectory (Figure 7(a)). MEC also has conjunctive grid by head direction cells,[55] indicating interactions between the spatial and head direction systems. Neighboring grid cells fire at locations offset from each other, while showing the same orientation and spacing between the grid vertices (Figure 7(b)). This pattern of activity of the grid cell population ensures that all spatial locations in the environment are represented in the MEC.

The path integration information described above appears to enter the hippocampus via MEC. MEC projects to the hippocampus in a topographical manner, with dorsocaudal MEC projecting to septal hippocampus and ventral MEC projecting to temporal hippocampus (described in the *Anatomy* section). The spacing between vertices of a grid cell increases as a function of the location of the grid cell along the dorso-ventral axis in MEC[54,56] (Figure 7(b) and (c)), and correspondingly, place field size of a single place cell in the hippocampus increases as a function of the location of the place cell along the septotemporal axis of the hippocampus.[57,58]

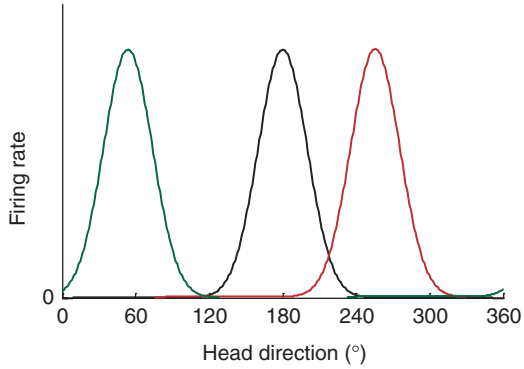

FIGURE 6 | Head direction cells. The plots show schematic representations of the firing rates of three head direction cells as a function of the direction of the rat's head. Each head direction cell has a preferred head direction at which it maximally fires, and the preferred directions of the head direction cell population cover the entire 360° range.

In any inertia-based system such as path integration, errors in estimating the instantaneous speed and direction accumulate as an increasing error in the estimate of current location. These accumulating errors can be countered by occasionally realigning the path-integrator-based estimate of current location to an estimate based on allothetic information. Accordingly, external sensory cues exert a strong control over the place cells and grid cells. O'Keefe and Conway[59] recorded place cells in a T maze with four prominent cues along the curtained periphery. They showed that the place fields rotated with the external cues. Similarly, place fields from rats foraging in a cylinder rotate with the cue card hung on the wall of the cylinder.[60] Information from various sensory modalities can be used as allothetic cues by the rat.[59,61] Head direction cells and boundary-sensitive cells[62–64] are thought to mediate the binding of the grid cells and place cells to the spatial landmarks of the external world.[65]

Functional Inputs to the Hippocampus from LEC

Projections from LEC to hippocampus may be the source of nonspatial information that becomes incorporated into the spatial map provided by place cells. LEC is part of the brain's ventral, 'what' pathway, and it gets inputs from the perirhinal cortex,[16] which is implicated in object identity and novelty detection. Evidence for representation of nonspatial information in LEC is starting to accumulate. LEC neurons do not show spatial selectivity under behavioral paradigms usually

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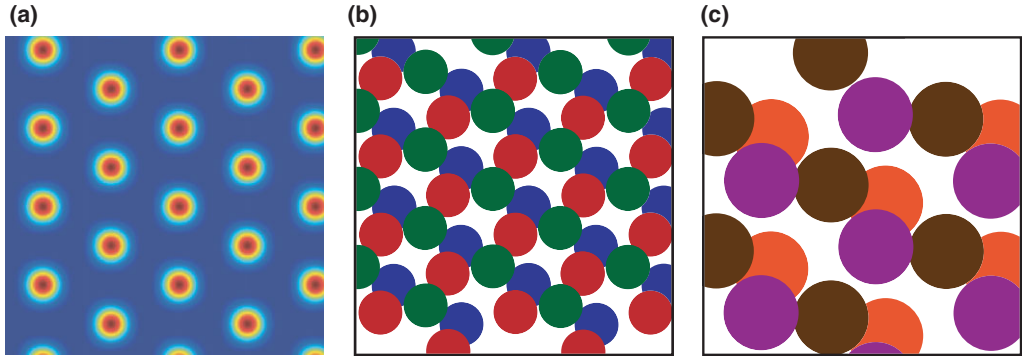

FIGURE 7 | Grid cells. (a) Firing rate map of a simulated grid cell. See Figure 5 for explanation of how a firing rate map is generated. The grid cell fires when the rat is at regularly spaced vertices of a tessellating grid of equilateral triangles. (b) Neighboring grid cells fire at locations offset from each other, while maintaining a similar inter-vertex spacing and orientation. The 3 colors represent the vertices of three different grid cells. (c) Grid cells recorded from the part of MEC more ventral than the grids cells shown in (b). Notice how both the inter-vertex spacing as well as the size of the vertices is larger than those in (b).

used for monitoring spatial selectivity in the hippocampus.[17,18] Under these conditions, the hippocampus and MEC show strong theta oscillations associated with locomotion and exploratory activity, while LEC does not show strong theta oscillations.[19] Furthermore, LEC neurons show object-related firing when rats forage in an open field in the presence of discrete objects,[20] consistent with its proposed role in nonspatial information processing.

There is ample evidence for the representation of discrete, nonspatial information embedded in the spatial framework of the hippocampus. Early studies recording from hippocampal neurons in freely moving animals investigated spatial[8] as well as nonspatial[39] correlates. Further explorations of place cells revealed some cells that encoded a conjunctive representation of nonspatial and spatial information. These so-called misplace cells fired when a rat encountered an unexpected object in a particular location or failed to receive an expected reward in a particular location.[9] The hippocampus also shows conjunctive representations of spatial and nonspatial variables when the rats perform nonmatch-to-sample tasks using odors. For example, the firing rates of some cells are modulated by odor identity and odor match/nonmatch, as well as by location.[66,67] In a fear conditioning task, place cells develop responses to an auditory conditioned stimulus, but only when the stimulus is delivered when the rat is in the place field of the cell.[68] In a two-chamber, odor-discrimination task, the proportion of neurons discriminating between the odors presented within a particular location increased as the rat learned the task.[69] In a simple task in which rats encountered multiple objects along a circular track, spatial location was the primary variable represented in the hippocampal pyramidal neuron population and object identity was a secondary variable that modulated the primary, spatial representation.[70] Taken together, these studies show that nonspatial information is represented within the context of a robust, spatial representation in the hippocampus. The conjunctive representation of spatial + nonspatial information may be a key contribution of the hippocampus to support episodic memory (see *Hippocampal Function* section).

In addition to providing nonspatial information about local objects, the LEC also appears to carry a spatial signal that is related to these local landmarks.[20] A small fraction of LEC neurons appear to fire in spatially discrete locations that are at a distance from the objects, but this spatial signal apparently requires the presence of objects. Other LEC neurons fire at the previous locations of objects after the objects are moved to new locations, as if they have a 'memory' for the previous object locations. Thus, the LEC does not have a purely nonspatial representation, but may create a spatial representation based on the allothetic information provided by local landmarks.

Spatially Selective Neurons in Other Animals

A variety of species show spatial correlates similar to rats, indicating the prevalence of the neural representations of space. Mice[71] and bats[72] have place cells in the hippocampus and grid cells in MEC.[73,74] Primates, including humans, also have spatial representation in the hippocampus. Ono et al.[75] demonstrated putative place cells in the monkey hippocampus when the monkey moved itself in a motorized cab in two-dimensional space. This study also reported conjunctive representations of spatial and nonspatial stimuli in the hippocampus. Ludvig et al.[76] recorded place cells from the hippocampus of freely moving squirrel monkeys, confirming

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that primates have spatial representations in the hippocampus similar to rodents under analogous behavioral conditions. Rolls et al.[77] reported a novel spatial response in the monkey hippocampus. These neurons, called spatial view cells, fired when the monkey looked at a specific spatial location, regardless of where the monkey was located. Spatial firing correlates have also been observed in the hippocampus of humans navigating in a virtual environment.[78] Studies on London taxi drivers show that increased navigational expertise is associated with an increase in the volume of the posterior hippocampus (the equivalent of dorsal hippocampus in the rat, which contains the most spatially specific place cells).[79] In addition, the hippocampus of the right hemisphere is selectively active when these taxi drivers mentally imagine driving specific routes through London.[80] Conversely, damage to area CA1 leads to profound impairment in place learning in humans.[81] These results implicate the hippocampus in navigation and place representations across species.

Temporal Code in the Hippocampus

Distinct patterns in the hippocampal local field potential (LFP) are associated with distinct behaviors in rats. Theta oscillations (6–10 Hz) accompany exploratory activity and the rapid eye movement (REM) phase of sleep, while large irregular activity (LIA) is associated with immobility, slow-wave sleep, and nonexploratory behaviors, such as eating or grooming[82] (Figure 8). In recent years, many advances in our understanding of hippocampal function have come from relating the firing of hippocampal neurons to various aspects of the LFP.

Theta Modulation of Single Neuron Activity in the Hippocampus

Both principal cells and many interneurons of the hippocampus are strongly modulated by the ongoing theta rhythm when the rat explores an environment. Place cells show a particularly intriguing relationship with LFP theta oscillations. As the rat passes through the place field of a cell, the neuron fires in bursts that occur at earlier and earlier phases of the LFP theta cycle[49] (Figure 9). This modulation of the preferred theta phase of a neuron by the rat's location in the neuron's place field is known as phase precession. All phase-precessing neurons in CA1 fire in the same phase of theta as the rat enters the place field of the neuron. This stereotypic theta phase precession organizes the spikes of neurons with overlapping place fields in a temporal order within a single theta cycle, such that a neuron with a place field earlier in the rat's trajectory will fire earlier within the theta cycle than the neuron with a place field later in the rat's trajectory[83] (Figure 10(a)). This ordering of place cell spikes within a cycle, in addition to firing rate, can be used to predict the spatial location of a rat better than just the firing rates of the simultaneously recorded neurons.[49] Theta phase precession is an example of a temporal code, where information is stored in the relative time of firing of neurons, in contrast to a rate code, where the number of spikes per unit time carries information about the represented variable (space, in this case). Phase precession ensures that the interval between spikes of neurons with overlapping place fields falls within the range of intervals conducive to plasticity.[49,83] The fixed lag between the spikes of neurons that follow each other in the given environment could play a role in strengthening the synapses between them, thereby encoding learned spatial sequences and allowing future locations to be predicted from the current location, based on past experience.[84–86]

Organization of Hippocampal Single Unit Activity during Ripples

High frequency oscillations, called ripples, are observed during LIA and may play a role in organizing patterns of neuronal activity. Large, rapid (50–100 ms) deflections called sharp waves are seen in CA1 LFPs during slow wave sleep and awake immobility, drinking, grooming, and eating (Figure 8). Ripples (100–200 Hz) are typically observed as riding on top of the sharp waves. Large numbers of CA1 and CA3 neurons fire during sharp waves, phase locked to the negative phase of the ripples.[88]

Patterns of activity of hippocampal neurons during ripples have been implicated in mnemonic processes. Hippocampal neurons active during exploration are more likely to be active during ripples in a rest session following the exploration, and they show a tendency to 'replay' the sequence they participated in during behavior[89,90] (Figure 10). These replay events repeatedly activate sequences associated with an experience, within the timescale conducive for induction of synaptic plasticity,[91] and are thought to play a role in encoding and subsequent stabilization of memories. Memory consolidation theory (reviewed in Ref 92) states that memories are transferred from the hippocampus to the cortex, over time. Consistent with this hypothesis, there are temporal correlations between hippocampal ripples and cortical spindles, and corresponding correlations between single units in hippocampus and cortex.[93] This hippocampus-triggered activation of cortical neurons may lead to modification of the cortical circuitry during ripple-spindle events, such that the hippocampal

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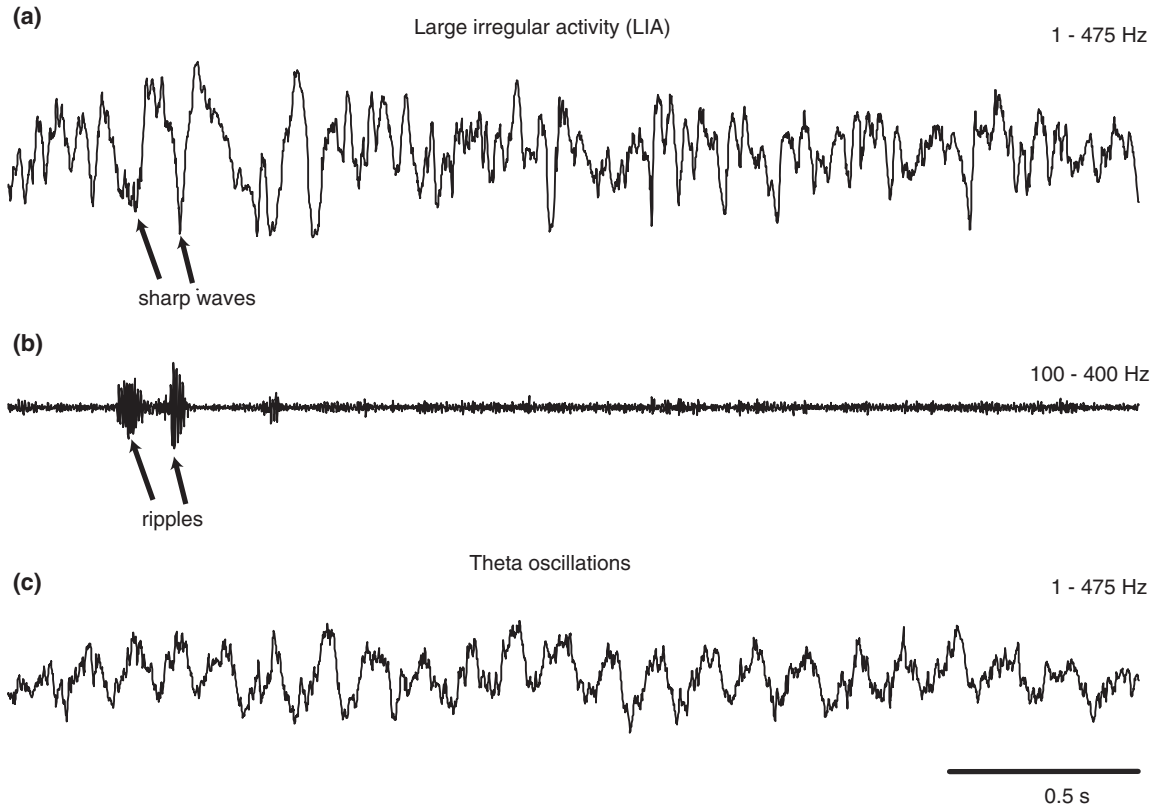

FIGURE 8 | Local field potentials show different patterns corresponding to different behavioral states. (a) Large irregular activity seen during immobility, slow-wave sleep, and nonexploratory behaviors. Two of the sharp waves observed during this epoch are marked. (b) High frequency ripples recorded simultaneously as the trace in (a), from an electrode in the CA1 pyramidal cell layer, where the ripple amplitude is strongest. (c) Theta oscillations observed during locomotion. Bandpass frequencies for each of the three traces are shown at the upper right corner of each trace.

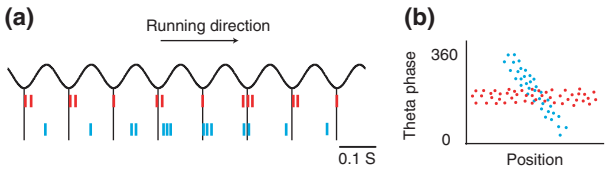

FIGURE 9 | Theta phase locking and theta phase precession. (a) Schematic showing theta oscillations in the LFP, and simultaneously recorded spikes of theta phase locking (red) and theta phase precessing (cyan) neurons while the rat runs on a linear track. Vertical lines mark locations of valleys in the LFP oscillations, for ease of identifying the phase of the theta cycle when the neurons fired. (b) Distribution of theta phase at which the two neurons fire as a function of position. The red neuron fires in approximately the same phase of theta in each cycle, while the cyan neuron fires in earlier and earlier phases of theta as the rat traverses through the place field of this neuron. Data from multiple runs on a linear track are used to generate phase precession plots like this. Hippocampal place cells show theta phase precession, while interneurons tend to show theta phase locking.

memory trace now has a cortical counterpart. The strengthening of the cortical memory trace may correspondingly allow the retrieval of the memory to become less dependent on the hippocampus.

Plasticity in the Hippocampus

Memory can be described as the accurate storage and recall of information by the brain. Changes in synaptic efficacy are thought to be a major mechanism of information storage, ever since Cajal hypothesized that neurons communicate with each other at the synapses.[10] Hebb[94] postulated a formal hypothesis for synaptic plasticity that stated: 'When an axon of cell A is near enough to excite a cell B and repeatedly and persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased' (p. 62). Bliss and Lømo[4] demonstrated this 'Hebbian plasticity' in perforant path to DG granule cell synapses in the hippocampus of anesthetized rabbits. They showed that high frequency stimulation (15 or 100 Hz) led to an increased efficacy of synaptic transmission, which lasted for prolonged periods of time. This came to be called long-term potentiation (LTP). LTP was later demonstrated in the DG mossy fiber to CA3 pyramidal cell synapses and in the CA3 Schaffer collateral to CA1 pyramidal cell synapses in hippocampal

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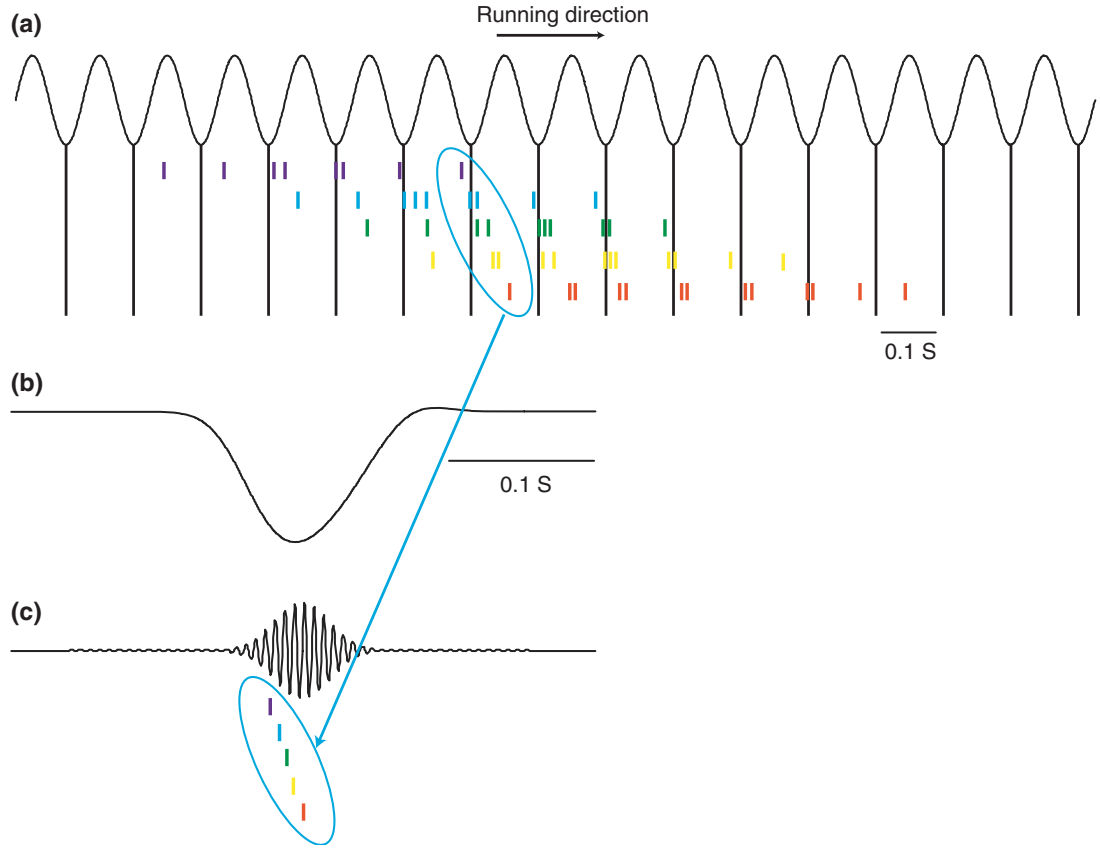

FIGURE 10 | Temporal ordering of place cells during behavior and ripples. (a) Schematic showing the relative timing of firing of place cells with partially overlapping place fields on a linear track. LFP theta oscillations are shown on top, and spikes of different neurons in different colors are shown below. Theta phase precession organizes the firing of neurons such that neurons with place field centers earlier in the rat's trajectory fire earlier within the theta cycle than the neurons with place field centers later in the rat's trajectory. This ensures that neurons maintain similar relative timing of firing over multiple theta cycles.[87] (b) and (c) Sharp waves (b) and ripples (c) are observed during awake immobility or slow wave sleep after the behavior. During these sharp wave–ripple epochs, a large number of CA1 and CA3 neurons tend to fire. Their order of firing within a ripple event tends to replay the order observed during the preceding behavior session.

transverse slices[95] (Figure 11(a) and (b)), as well as in numerous brain areas outside the hippocampal formation. The hippocampal slice preparation has been used extensively for studying synaptic plasticity. The NMDA (N-methyl D-aspartate) subtype of glutamate receptor, which is a dual voltage- and ligand-(glutamate) gated Ca^{2+} channel, is critical for the induction of LTP at many synapses, including the perforant path-DG synapse and the Schaffer collateral-CA1 synapse. At the resting membrane potential, the pore of the NMDA receptor is blocked by Mg^{2+} ions, such that release of glutamate by a presynaptic cell is insufficient, by itself, to open the channel. Rather, the postsynaptic cell has to be depolarized in order to electrostatically repel the Mg^{2+} ion from the channel, at the same time that glutamate is bound to the receptor, in order for the channel to open. This characteristic gives the NMDA receptor the properties of a coincidence detector of both presynaptic (glutamate release) and postsynaptic (depolarization) activity, thus satisfying the major requirement of Hebb's postulate. (It is important to note, however, that not all forms of LTP require the NMDA receptor. For example, LTP at the mossy fiber-CA3 synapse does not depend on NMDA receptors, but are instead controlled by opioid receptors, providing them with different computational properties that are under investigation.[96])

Information can also be stored by reducing the efficacy of synaptic transmission. Dunwiddie and Lynch[97] showed that low frequency stimulation (1 Hz) can lead to long term depression (LTD) at Schaffer collateral/commissural to CA1 pyramidal cell synapses in hippocampal slices (Figure 11(a) and (c)). Taken together, LTP and LTD allow for bidirectional modulation of synaptic strength as a function of experience (or history) of the synapse.

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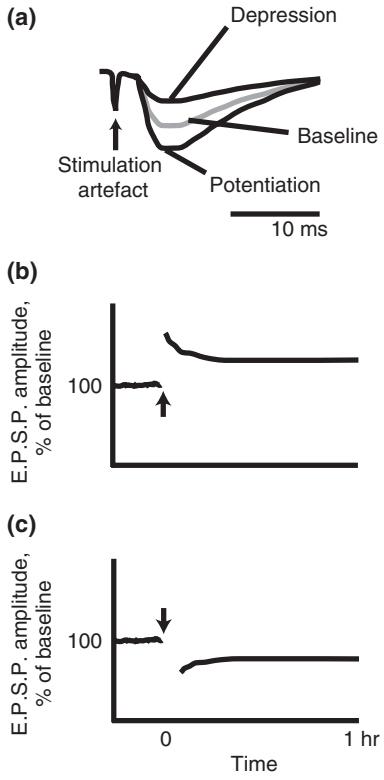

FIGURE 11 | Long term potentiation (LTP) and depression (LTD). (a) Schematic showing excitatory postsynaptic potentials (EPSPs) recorded in response to electrical stimulation of the presynaptic axons. The waveforms show a stimulation artefact corresponding to the test stimulus applied to the presynaptic axons followed by EPSPs. The gray line shows baseline EPSP recorded before induction of LTP or LTD, while the black lines show the changed amplitude of EPSP after induction. LTP induction protocols give rise to a larger EPSP amplitude (potentiation), while LTD induction protocols give rise to a smaller EPSP amplitude (depression). These changes last for prolonged periods of time (hours to days). (b) and (c) Schematics showing EPSP amplitude as a function of time. Arrowheads indicate timing of LTP inducing stimuli in (b) and LTD inducing stimuli in (c). Low frequency stimuli used in LTD induction typically last a few minutes, and hence there is a temporal gap between the pre- and post-stimulus amplitudes in (c).

Hebb's rule requires a cell to repeatedly and persistently take part in firing another cell to induce synaptic potentiation between those cells. In order to maintain this causal relationship between the presynaptic cell driving the postsynaptic cell, the presynaptic cell must fire before the postsynaptic cell to induce LTP. Levy and Steward[98] showed this temporal relationship in the perforant path to DG granule cell synapse. In addition, they showed that if the postsynaptic cell fires before the presynaptic cell, there is synaptic depression. This bidirectional plasticity, dependent on the relative timing of pre- and postsynaptic cells, is now generally called spike-timing dependent plasticity and has become an important area of investigation of neural plasticity mechanisms.[99,100] In the hippocampus, these mechanisms are thought to play an important role in the formation and storage of representations of sequential experiences.[35,84–86]

Evidence linking synaptic potentiation and depression to learning and memory is accumulating. For example, rates of acquisition and forgetting of spatial memory and rates of induction and duration of LTP show similar changes with aging,[101] demonstrating a correlational, if not a causal, relationship between LTP and memory. Further evidence for a role of synaptic plasticity in memory comes from experiments using pharmacological or genetic means to disrupt plasticity, and studying the effect of this disruption on memory. The NMDA antagonist AP5 blocks spatial but not visual discrimination learning in the water maze[102] at intrahippocampal concentrations that block hippocampal LTP in vivo and in vitro, implicating the NMDA-receptor-dependent form of LTP in the hippocampus in spatial memory. Kentros et al.[103] showed that the NMDA antagonist, CPP, interferes with the long term stabilization of newly acquired place fields in the hippocampus. Place fields in a familiar environment were unaffected by CPP, and new place fields formed in a new environment under the influence of CPP, indicating that LTP was not required for the creation of a new spatial representation. However, the new place cells were not stable when the animal was re-exposed to the novel environment; rather, the hippocampus created a different representation of the same environment, as if the animal's second visit was actually to another novel environment. Thus, the long-term stabilization of new place fields was selectively affected by CPP, without hindering the formation of the place fields in new environments. This result indicated that NMDA-dependent plasticity may play a selective role in binding the internal, spatial representation of the hippocampus to the external sensory cues that define a particular environment or context.

The preceding studies showed evidence of a relationship between NMDA receptors, LTP, and learning, but these experiments were not specific to the hippocampus. Newer studies have restricted the extent of NMDA receptor deletion to specific subregions of the hippocampus. These studies further bolster the claim of involvement of hippocampal LTP in memory, by countering the possibility that the deficits in memory observed in prior studies were caused by changes in extrahippocampal structures. For example, mice with NMDA receptor subtype NR1 knockout in CA3 pyramidal cells showed deficits in LTP at the

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CA3 recurrent synapses. Unlike animals with systemic blockage of NMDA receptors, however, these animals showed more subtle learning deficits. They learned the spatial version of the water maze task, but when only a subset of the spatial cues present during training were available in a probe test, the mutant mice performed worse than the controls. In parallel, CA1 place fields showed a similar degradation of their spatial selectivity in the presence of partial cues.[104] This deficit in performance in the presence of only a subset of cues implicates LTP at the CA3 recurrent synapses in the phenomenon known as pattern completion, in which a memory can be recalled based on partial or degraded retrieval cues.[29–31]

Adult Neurogenesis in the Dentate Gyrus

Neurogenesis, the formation of new neurons from precursor cells, is a form of plasticity distinct from synaptic plasticity discussed so far. The DG is one of only two brain areas in mammals that show neurogenesis throughout the adult life span,[105,106] contrary to the long-held belief that no new neurons could be generated in the adult brain. Adult neurogenesis in DG is thought to play a role in learning and memory, as well as pattern separation.[107] At present, however, it is not known what specific role these adult-born granule cells play, and why the computational processing of the dentate gyrus appears to require a constant supply of newborn neurons, contrary to almost every other region of the brain.

Pathological Plasticity: Kindling

So far, we have seen different forms of plasticity thought to be involved in brain function. However, uncontrolled plasticity can lead to pathological conditions. One of the animal models for epilepsy uses a phenomenon called kindling. Epilepsy is characterized by recurrent, spontaneous seizures caused by highly synchronized activity in the brain. The hippocampus (and other medial temporal lobe structures) is often a focus of epilepsy. In fact, patient H.M., the most studied amnesic (see *Hippocampal Function* section), had temporal lobe epilepsy, for which he received the bilateral temporal lobe resection that unexpectedly caused his amnesia.[1] Repeated electrical induction of seizures in brain areas such as the hippocampus leads to an increase in epileptic responses to the stimulation over time.[108,109] This phenomenon is referred to as kindling, because of its analogy to starting a large fire by lighting small twigs.[110] If this stimulation is continued further, the animals are said to be 'over-kindled,' and they start showing spontaneous seizures. Many of the molecular players involved in synaptic plasticity, including the NMDA receptor described above, are also involved in kindling (reviewed in Ref 111).

HIPPOCAMPAL FUNCTION

Over the years, investigators have assigned to the hippocampus a variety of functions, including attention, emotion, olfaction, memory, and navigation. Space limitations preclude a description of all proposed theories, and we shall concentrate on the theories that are currently most influential: the hippocampus as the substrate of declarative or episodic memory,[112,113] the hippocampus as a cognitive map,[42] and theories related to these two.

The Hippocampus and Memory

Scoville and Milner's[1] report that damage to the hippocampal formation leads to a profound amnesia was a starting point for understanding the role of the hippocampal formation in memory. They reported that patients with extensive medial temporal lobe damage 'appear to forget the incidents of their daily life as fast as they occur' (p. 15). The short-term memory of these patients seemed to be intact, but they forgot events after a short period of time or as soon as they were distracted. H.M., one of the patients in this study, showed an inability to form new memories about facts and events (anterograde amnesia). He also displayed a partial retrograde amnesia, such that he could remember events in his early childhood much better than events that occurred three years prior to the surgical procedure in which his hippocampus was removed. Later, H.M. was shown to be capable of procedural[114] and perceptual[115] learning, without any conscious memory of the preceding training trials. For example, over the course of repeated trials, H.M. learned to draw a line between two outlines of a star while looking at the drawing through a mirror, which is a skill that requires practice, even from control subjects. This learning persisted over days, although H.M. never recalled from trial to trial having ever performed the task before. Similarly, H.M. learned to identify drawings of objects with many of the contours missing, without remembering having seen the objects before. These phenomena, and similar findings from other amnesics, formed the basis of the hypothesis that there are multiple forms of memory, of which the hippocampal formation is involved in only a subset.[112,114,115] Attempts to characterize the properties of hippocampus-dependent learning have led to a number of important theories about the function of the hippocampus.

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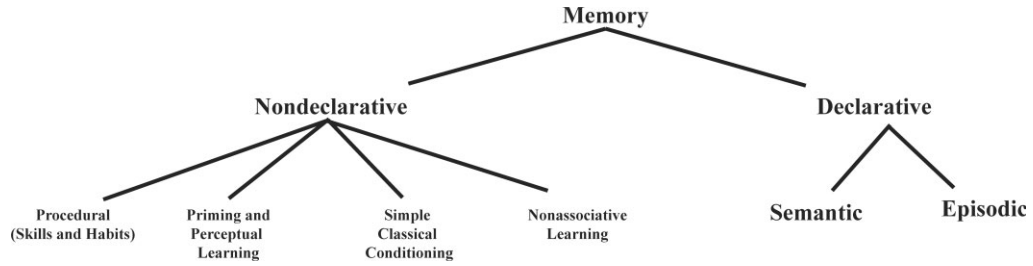

FIGURE 12 | Classification of memory.[117]

Declarative Memory

Memories can be categorized as nondeclarative ('knowing how') or declarative ('knowing that')[116] (Figure 12). Nondeclarative memory is concerned with skilled behavior and the ability to respond appropriately to stimuli after conditioning or habit learning. In contrast, declarative memory stores representations of facts (semantic memory) and events (episodic memory) that can be recalled consciously and verbalized. Semantic memory is a memory of a fact, independent of the event that occurred when the memory was acquired, whereas episodic memory is a conscious recollection of an autobiographical event within a spatiotemporal context from a person's past. A defining aspect of both these forms of declarative memory is that they can be 'declared', whereas nondeclarative memory refers to changes in behavior or perception, without a conscious recollection. For example, 'I know that balance is critical while riding a bicycle' is a semantic memory, 'I lost my balance and fell in the roadside puddle the first day I was learning to ride the bicycle' is an episodic memory, while the actual motor skill of riding the bicycle is a nondeclarative memory.

Declarative memory theory proposes that different types of memory are processed and stored in different memory systems in the brain, and the medial temporal lobe system, which includes the hippocampal formation, is involved in declarative memory.[112,117] The declarative memory theory also proposes that the role of the hippocampal formation in declarative memories is time-limited, to account for the fact that patients with total anterograde amnesia (because of damage to the hippocampal formation) display a time-limited, graded, retrograde amnesia.[118] That is, their memories of events that occurred long before their hippocampal damage are stronger than their memories for events that occurred more recently before that damage. Nonhuman primates and other animals have also been reported to show a similar gradient in retrograde amnesia, as recent memories for learning that occurred right before hippocampal damage are affected more than remote memories.[119]

Standard consolidation theory and its variants propose that the hippocampus is required for the rapid learning of declarative information, but that over time, the memory trace is 'transferred' from the hippocampus to the neocortex.[92,120] The sharp wave/ripple complexes discussed above have been postulated to play a role in this consolidation.[121] In contrast, multiple trace theory proposes that the retrograde amnesia gradient results from different memory strengths associated with repeated reactivations of older memories, such that they are more robust to hippocampal insult than newer memories.[122] In this view, the hippocampus is always required for the robust details of normal episodic memory, but other brain regions, in the absence of a functional hippocampus, can subserve a more limited form of memory that supports the recall of some aspects of an experience but not at the same level of detail as a normal episodic memory. Although not yet providing conclusive answers, the standard consolidation theory and the multiple trace theory provide distinct predictions (e.g., whether there is a distinction between retrograde amnesia for episodic vs. semantic memories), and these predictions are under investigation.[123] In recent years, the very existence of robust, temporal gradients of hippocampus-dependent memories has been called into question by some investigators.[124] These questions are complex, given that (a) there are molecular processes of consolidation ('cellular consolidation' and 'reconsolidation') that may occur in parallel with the putative 'systems consolidation' addressed by the standard consolidation theory and (b) memory systems (e.g., semantic vs. episodic; recognition vs. recall) may differ with respect to the existence and/or time course of consolidation. These topics will continue to generate new experiments and debate.[123–127]

Episodic Memory

While declarative memory theory states that the hippocampus (along with entorhinal, perirhinal, and parahippocampal cortices) plays a role in episodic as well as semantic memory, there is evidence that the anatomical substrates of the two forms of memory can

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be dissociated. Vargha-Khadem et al.[128] showed that amnesics who suffered bilateral hippocampal damage early in life 'before they acquired the knowledge base that characterizes semantic memory' (p. 376) showed profound deficits in episodic memories, while having near normal semantic memories later in life. That is, they were able to learn language and learn many of the facts that all schoolchildren master, but their ability to recall specific events from their own lives was severely impaired. Thus, while the hippocampus is critical for episodic memories, semantic memories might rely on other structures in the medial temporal lobe in humans[128,129] and monkeys.[130] Other investigators counter, however, that because the hippocampus and medial temporal lobe structures are richly interconnected, these results are better understood as reflecting quantitative, rather than qualitative, differences in the roles played by these structures in episodic vs. semantic memory.[131]

Episodic-like Memory in Animals

Although it is difficult to test the conscious, autonoetic aspect of episodic memory (and semantic memory) in nonverbal animals, it is possible to ask whether the other functional correlates of episodic memory can be seen in animal behavior. Episodic memory in humans can be characterized as a conjunctive memory for *what* happened, *where* it happened, and *when* it happened. Animals can be tested on their performance of tasks that require memory for all three of these aspects, and this animal analog of human episodic memory has been termed 'episodic-like memory.' In an early demonstration of episodic-like memory in animals, Clayton and Dickinson[132] allowed scrub jays to store perishable worms and nonperishable peanuts in two distinct trays. When allowed to search shortly after caching the food, the jays searched more for the worms, which they preferred over peanuts. However, if they were allowed to search only after the interval in which they knew the worms would decay (and thus become unpalatable), they searched more for peanuts. Thus, the jays were aware of *when* and *where* they had stored the worms and the peanuts (*what*), and they used the information to direct their choice of food. Scrub jays also show the ability to keep track of who was watching when. Dally et al.[133] allowed a bird (the storer) to cache the food in tray 1 in the presence of observer A and in tray 2 in the presence of observer B. If observer A was present during recovery, the storer recached more items from tray 1, but if observer B was present during recovery, it did so from tray 2. This result indicates that the storer knew, and kept track of, which observer was watching when it was storing in the two trays. These memories satisfy the criteria of what, where, and when for being episodic-like memories.

Episodic-like memory has been demonstrated in other animal species, specifically great apes and rats. Analogous to scrub jays, chimpanzees and bonobos also remembered how long ago perishable but preferred (fruit juice ice cube) and nonperishable (grape) foods were hidden from them. They chose the ice cube after a short interval, but chose the grape after intervals long enough for the ice cube to have melted.[134] Babb and Crystal[135] taught rats that the food with distinctive flavor gets replenished after a long but not a short delay, while regular food does not get replenished on the same day. After training, the rats sampled the locations of food with the distinctive flavor more frequently after a long delay as compared to a short delay. When one of the two distinctively flavored food types was devalued either by satiation (i.e., feeding the same food type before trial) or by simulating poisoning (with lithium chloride injection right after eating the food type), the rats went to the location of the nondevalued food, as compared to the location of the devalued food. Thus, the rats were capable of using what (food type), where (location of different food types), and when (time after last test) information, characteristic of episodic-like memory.

The two parallel input streams (Figure 2) may be involved in providing the hippocampus with two of the three components of episodic-like memory.[36,70] The MEC may provide the spatial framework, and the LEC may provide the external sensory input corresponding to the content of an experience. The DG and CA3 regions, in turn, may be the locations where these two streams of information are combined into conjunctive representations of the 'what' and 'where' components of experience, which may be a necessary step before the memories can be stored in such a way that they can later be retrieved as an episodic memory.

Physiological Signatures of Components of Episodic-like Memory

A number of physiological studies have demonstrated that hippocampal cells are capable of encoding the three components of episodic-like memory. For example, place cells encode the conjunctions of 'what' and 'where' information.[9,68,69] Timing information is also represented in some forms by the hippocampus, such as in the representation of spatiotemporal sequences.[35,83–85,136,137] The CA3 region in particular may be crucial for one-trial learning, which is a key component of episodic memory. CA3 place fields rapidly store information about the spatiotemporal sequence of place fields, starting with the first exposure to an altered environment.[35,36] Similarly,

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mice with selective deletion of NMDA receptors from CA3 pyramidal neurons[104] are deficient in LTP at the CA3 recurrent synapses and show deficits in the rapid learning of new locations in the water maze task.[34] In humans, hippocampal neurons that respond during an experience are selectively reactivated when the person consciously recalls the experience.[138] Thus, although the precise relationship between these firing properties and episodic(-like) memory remains to be determined, it appears that the firing properties of hippocampus neurons are well-suited to subserving this form of memory.

Relational Learning Theory

In an attempt to operationally define declarative memory in terms applicable to animal studies, Cohen and Eichenbaum proposed relational learning theory, which posits that declarative memory involves the encoding of relations between different items. At the time of retrieval, these encoded relations play a role in flexible access to the information under conditions that may be different from the original learning conditions.[139,140] Storing the relationships between facts and events allows for the flexible use of contents of the declarative memories across a broad range of situations . Further refinements to this theory were proposed to account for the relationship between episodic and semantic memories. While episodic memories are memories of unique experience, semantic memories are generalized facts gleaned from aspects common to multiple experiences. According to this theory, episodic memory stores information about the sequences of events (and items) that constitute an episode, and semantic memory is derived from elements that overlap across multiple episodes, which appear as nodes in a relational network.[141] These nodes thus become 'timeless', in the sense of not being bound to a single episode during which they were acquired, and they allow the subject to compare and contrast memories and hence make inferences from indirectly related events. This idea of timeless nodes in a relational network is analogous to the generalization from multiple similar experiences implicit in semantic memory.

Evidence for relational processing comes from studies in animals as well as humans. For example, Bunsey and Eichenbaum[142] showed that rats can draw *transitive inference* from learned associations. For example, if 'A implies B' and 'B implies C', then the rats can infer 'A implies C'. Similarly, rats can draw *symmetric inference*, that is, after being taught 'A implies B', they infer 'B implies A'. Both the transitive inference and symmetric inference are consistent with relational processing, as they require flexible utilization of learned relationships. Bilateral hippocampal lesions abolished this relational processing, while keeping the learning about stimulus associations like 'A implies B' intact, indicating the role of hippocampus in relational processing (see Ref 143 for alternative interpretation of transitive inference results).

Configural Association Theory

If the same stimulus predicts two different outcomes depending on the context, simple stimulus-reward associations are insufficient to account for the complex relationships between stimuli and responses. For example if a tone (T) and a light (L) predict a reward on their own, but not when presented together, a strategy based on representations of individual sound and light stimuli will fail when faced with sound and light together (as that will signal the reward even more strongly than either stimulus alone). This problem can be solved by treating a combination of sound and light as a single stimulus, and associating it with presence or absence of reward (i.e., T = reward, L = reward, TL = no reward). Sutherland and Rudy[144] hypothesized that the hippocampus builds and stores configural associations between stimuli. To account for the experiments that showed that animals with hippocampal damage were capable of solving configural association tasks under some conditions, this theory was modified to state that neocortex is the site for storing configural associations, but the hippocampal formation increases the saliency of configural associations and speeds up storage of these associations in the neocortex.[145]

Cognitive Map Theory

Tolman[146] proposed that in the course of exploring an environment, rats construct a 'cognitive map' of the environment in their brains. This map can be utilized later for finding an efficient path to a new goal when the need arises. O'Keefe and Nadel[42] hypothesized that this cognitive map resides in the hippocampus. According to this theory, the hippocampus is 'the core of a neural memory system providing an objective spatial framework within which the items and events of an organism's experience are located and interrelated'[42] (p. 1). External stimuli and internal states that constitute an event or an experience are organized within the spatial framework encoded by the hippocampus, in such a way to produce context-dependent and flexible learning that is distinct from the rigid, inflexible learning systems of other brain areas. Further, the organization of nonspatial variables in the context of space and time was proposed to underlie episodic memory in humans.[42]

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Physiological Evidence for the Role of Hippocampus as a Cognitive Map

Animal (especially rat) studies have produced substantial amount of evidence for cognitive map theories. Hippocampal lesions lead to impairment of spatial navigation, but not cue-based learning.[147] Place cells[8] in the hippocampus, along with head direction cells[52] and grid cells[53,54] in the structures upstream to the hippocampus (described in the *Physiology* section), are consistent with the role of the hippocampal formation and related structures in creating the spatial framework. Similarly, humans show a space-related signal in medial temporal lobe structures, complementing the evidence from animal studies.[78–80,148,149] Furthermore, conjunctive representations of spatial and nonspatial variables in the hippocampus[66–70] point to the storage of events and items in the context of a spatial framework hypothesized by O'Keefe and Nadel.[42] Episodic memory, which entails a conscious memory of events in one's past, is retrieved by 'mental time travel',[150] which 'often involves a covert reconstruction of a spatially organized complex scene'[151] (p. 262), even when the specific detail recalled is not overtly spatial. The encoding of nonspatial information in the context of spatial information may indicate why episodic memory recall often involves reconstruction of space while recalling who said what after which event.[151] Thus it is possible to explain episodic memory within the framework of the cognitive map theory.[42]

CONCLUDING REMARKS

The theories of hippocampal function differ on the nature of information that is explicitly represented in the hippocampus. For example, is space the primary variable encoded in the hippocampus as claimed by the cognitive map theory, or is space simply a good, and ubiquitous, example of the type of relational processing that relational learning theory proposes as the fundamental characteristic of the hippocampus? After years of investigation and debate on these questions, evidence is converging in support of a number of common threads among these theories, including the notions of hippocampus-dependent learning being flexible and crucial for episodic memory. Hippocampal anatomical and physiological features like CA3 recurrent connectivity and rapid plasticity provide substrates for the requisite, one-trial nature of episodic memory. The parallel streams of input to the hippocampus appear to provide the substrate for both spatial and nonspatial inputs to the hippocampus, allowing the formation of context-specific, conjunctive representations of what, where, and when that seem to be crucial for episodic memory. Field potentials, such as the theta rhythm and sharp wave/ripple complexes, appear to reflect population-level processing that segments hippocampal processing into discrete, temporally ordered sequences that promote the storage and consolidation of these sequences of experience into long-term memory. Further understanding of the role of hippocampus in memory requires a more detailed study of the anatomical and physiological substrates of memory. For example, understanding the nature of information that is conveyed to the hippocampus by its inputs,[20,54] and how this information is processed in different subregions of the hippocampus,[152–154] will aid in understanding the nature of hippocampal computation. Similarly, although much is known about synaptic plasticity in the hippocampus and the need for hippocampal plasticity in memory, the details of mechanisms underlying memory formation and retrieval still need to be worked out. Functional studies, involving combinations of ensemble recording to understand what a large number of simultaneously recorded neurons are doing,[155] intracellular recordings to understand the subthreshold events,[156] and rapid, localized disruption/manipulation techniques using optogenetics will help understand the network interactions underlying memory formation and retrieval. As seen from the historical evidence, such studies in the hippocampus will also reveal general principles of information processing that are relevant for numerous neural systems.

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