Chapter 4

A Role for the Longitudinal Axis of the Hippocampus in Multiscale Representations of Large and Complex Spatial Environments and Mnemonic Hierarchies

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Abstract

The hippocampus is involved in spatial navigation and memory in rodents and humans. Anatomically, the hippocampus extends along a longitudinal axis that shows a combination of graded and specific interconnections with neocortical and subcortical brain areas. Functionally, place cells are found all along the longitudinal axis and exhibit gradients of properties including an increasing dorsal-to-ventral place field size. We propose a view of hippocampal function in which fine-dorsal to coarse-ventral overlapping representations collaborate to form a multi-level representation of spatial and episodic memory that is dominant during navigation in large and complex environments or when encoding complex memories. This view is supported by the fact that the effects of ventral hippocampal damage are generally only found in larger laboratory-scale environments, and by the finding that human virtual navigation studies associate ventral hippocampal involvement with increased environmental complexity. Other mechanisms such as the ability of place cells to exhibit multiple fields and their ability to scale their fields with changes in environment size may be utilized when forming large-scale cognitive maps. Coarse-grained ventral representations may overlap with and provide multi-modal global contexts to finer-grained intermediate and dorsal representations, a mechanism that may support mnemonic hierarchies of autobiographical memory in humans.

Keywords: hippocampus, longitudinal axis, dorsoventral, ventral, place cell, grid cell, multiple place fields, interneuron, gamma oscillations, large environment, complexity, spatial navigation, spatial memory, multi-scale representations, CA3, memory hierarchies

1. Introduction

The hippocampus is one of the most studied brain structures in humans and animals. Most work has focused on its dorsal subdivision and little is known, functionally and theoretically, of the entire structure along its longitudinal, dorsoventral axis. In this chapter, we review the recent literature and propose that the longitudinal axis of the hippocampus may be crucial to support multi-scale mnemonic hierarchies. We further propose that, in the rodent, this axis may be crucially involved in spatial navigation in large and complex environments.

The hippocampus is an elongated bilateral C-shaped structure with a dorsal to ventral longitudinal axis which corresponds to some extent to the posterior to anterior axis in humans [1]. Cell structure and function, and intrinsic trisynaptic circuitry, are conserved along the longitudinal axis, although there are differences in subfield composition. Patterns of gene expressions along the axis suggest molecularly defined dorsal, intermediate, and ventral domains each containing further subdomains showing gradual or sharp transitions. The dorsal and ventral regions of the structure exhibit differing cortical and subcortical connectivity. For example, the dorsal hippocampus receives visual and spatial information from the anterior cingulate and retrosplenial cortices via the medial entorhinal cortex, whereas the ventral hippocampus has major connections with the prefrontal cortex, amygdala, and hypothalamus (**Figure 1**). Interestingly, most of this connectivity is gradated, and in the case of structures with which dorsal and ventral connect contiguously, such as the medial entorhinal or prefrontal cortices, there can be transitional areas of overlapping inputs from both poles. The demarcated genetic domains and differing connectivity of the long axis have led to the hypothesis that the dorsal and ventral regions may be functionally distinct. In this model, the dorsal region mediates spatial and declarative memory, while the ventral region is involved in regulating emotional responses (see [2] for review). However, the presence of smooth graded transitions of connectivity within the long axis may suggest a more complex functional gradient.

Spatially-tuned "place cells" involved in navigation are found all along the dorsal to ventral axis with gradually increasing place field sizes. Compared to the wealth of knowledge available on dorsal hippocampal place fields, relatively few studies have examined the functional correlates of place fields in the intermediate and ventral hippocampus. Most lesion, electrophysiological, and pharmacological studies have found a role for dorsal but not ventral hippocampus in spatial navigation. It is clear however that the computations involved in small visually-accessible spaces may be fundamentally different from that in larger, more complex memory-based spaces (see [3] for Review). Interestingly, however, as will be reviewed below, spatial deficits associated with the rodent ventral hippocampus have been mostly observed in open environments such as the water maze. In addition, several human studies involving spatial navigation or scene recollection using fMRI showed that the posterior hippocampus (dorsal) is always activated, whereas the anterior hippocampus (ventral) is mostly activated in more complex tasks. Taken together, the rodent and human literature suggest that although the dorsal hippocampus alone is sufficient for simple spatial processing, more complex spatial processing, such as navigating in larger or cluttered environments, requires coordination along the entire hippocampal long itudinal axis.

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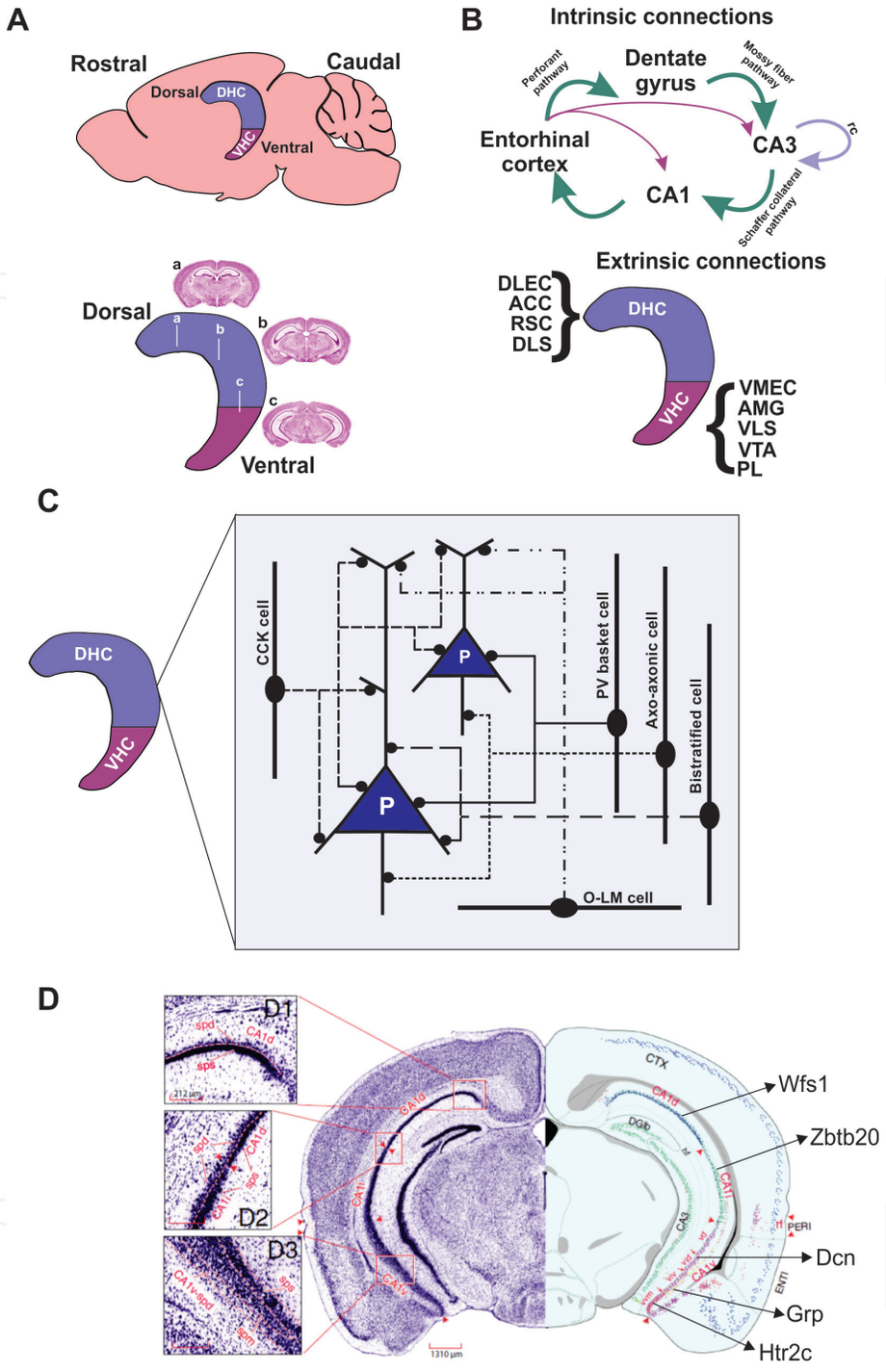

Figure 1. A) Schematic representation and photomicrographs of cresyl violet-stained coronal sections along the longitudinal axis of the hippocampus in rodents. The most rostral sections (e.g. a) contain the dorsal hippocampus (DHC) only. In contrast, more caudal sections contain ventral (VHC) and intermediate (not shown) subdivisions of the hippocampus. B) Simplified representation of intrinsic (upper panel) and extrinsic (lower panel) connectivity along the dorsoventral axis of the hippocampus. Abbreviations: entorhinal cortex (EC), dorsolateral band of the entorhinal cortex (DLEC), anterior cingulate cortex (ACC), retrosplenial cortex (RSP), dorsal part of the lateral septum (DLS), ventromedial band of the entorhinal cortex (VMEC), amygdala (AMG), ventral part of the lateral septum (VLS), ventral tegmental area (VTA), prelimbic cortex (PL). C) Schematic summary of the main synaptic connections between pyramidal cells (P) and several classes of interneuron, see ref. [83]. D) Distributions of five marker genes (arrows), Wfs1, Zbtb20, Dcn, Htr2c, and Grp reveal three molecular domains of the CA1 subfield (CA1d, dorsal; CA1i, intermediate; and CA1v, ventral HC), adapted from Ref. [8].

There is currently very little known about how spatial cells generate a cognitive map of large, cue rich, natural environments in which cues are functionally relevant. Such navigation is likely supported by a multi-scale memory system in the hippocampus and associated structures. In this view, finer grain dorsal place fields preferentially encode important locations such as burrows or reward sites with enhanced details, whereas global representations, as well as less important spatial areas, encode broader ventral place fields. Dynamic scaling of place fields in response to changes in environment size, and increased density of place fields at important locations or landmarks would also be important mechanisms contributing to such a multi-scale representation (See [4] for Review). Moreover, because dorsal place cells can exhibit multiple fields in larger environments their representation of the larger space may include robust redundancies that can be disambiguated by specific overlapping large ventral place fields. In this fashion, different sub-populations of place cells along the longitudinal axis may be involved in tracking and triangulating multiple goal positions in large environments containing multiple sub-regions.

Several human studies proposed a role for the dorsoventral axis in declarative memory [5]. The dorsal hippocampus is involved in recollection of specific details of an event, whereas ventral areas are involved in the global essence, schema, or "gist" of the event. This is consistent with the idea of "nested hierarchies" or memory "chapters" in which more global / general events and lifetime periods (ventral) overlay and confer meaning to more specific episodic events and details (dorsal). However, we will argue below that while specialization may result from the longitudinal organization of the hippocampus, it is not its primary purpose. Rather, we propose that complexity (as applied to memory or space) determines the extent to which specific levels of the structure are involved and how they interact.

2. Hippocampal long-axis anatomy and connectivity

Since its first anatomical description by Julius Caesar Arantius in 1587 [6], the hippocampus (HC) has been shown to have a rich and well-structured anatomical organization and specific connectivity pattern with distinct brain areas. Based on differences in its inputs, Cajal and Lorente de Nó suggested that the structure could be subdivided into functionally distinct subregions along its longitudinal axis [7]. Subsequent studies using modern tracing techniques have demonstrated that the connections between the HC and other brain areas were indeed topographically organized, supporting the idea of a modular organization. The dorsoventral axis of the HC (also referred to as septo-temporal or longitudinal axis in the rodent) can be subdivided into dorsal (septal), intermediate and ventral (temporal) portions based on variation in entorhinal inputs, subcortical projections, and gene expression. A number of excellent reviews describe the details of this organization [1, 2, 8–10]. Historically, significant emphasis has been placed on the notion that the dorsal hippocampus (DHC) supports spatial learning and that the ventral hippocampus (VHC) is primarily involved in emotional and motivational processes [1, 2, 5]. However, evidence for multiple levels of anatomical and functional organization along the longitudinal axis may change this dichotomous view towards an integrated, more holistic theory of the hippocampal function, as is reviewed below.

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2.1. Intrinsic connectivity

The HC is a dorsoventrally elongated structure (**Figure 1A**) that includes the dentate gyrus (DG), the cornu ammonis (CA) fields CA1, CA2, and CA3, or HC proper, and the subiculum (Sub). The main excitatory synaptic pathway within the HC, referred to as the trisynaptic circuit (**Figure 1B**), receives its inputs from the superficial layers of the entorhinal cortex via the perforant path to the DG. The DG projects to the CA3 region, which in turn projects to CA1. The CA1 region projects back to the deep layers of the entorhinal cortex, closing the circuit [7]. As such, the hippocampus may be seen as a computational cul-de-sac receiving, processing and returning information from and to the entorhinal cortex. Strong experimental evidence has implicated the trisynaptic circuit in spatial navigation and memory processing, but how exactly the HC encodes locations and events at the network level along the long axis is not yet fully understood. Seminal studies have shown that the entorhinal cortex provided a first level of short-range longitudinal integration through its connection with DG [11].

The CA1 projection to the subiculum follows a transverse topography. In an arrangement that minimizes axonal overlaps, CA1 pyramidal neurons located close to CA2 send projections to the most distal portion of the subiculum, whereas CA1 cells further away from CA2 project across the CA1/subicular border to more proximal portions of the subiculum [12]. Evidence for local connections within CA1 revealed that the majority of the projections from pyramidal neurons travel a relatively short distance along the dorsoventral axis, suggesting that distant dorsal and ventral CA1 levels may not have robust intrinsic associational excitatory connections [13, 14]. However, this does not exclude the possibility for significant multi-synaptic interactions between CA1 neurons along the longitudinal axis. For example, CA1 neurons that project to the subiculum send axon collaterals to the stratum oriens of longitudinally nearby CA1 cells. Importantly, CA1 neurons project longitudinally broadly to the subiculum, making this structure another site for dorsoventral integration [14]. Further studies are needed to clarify whether these fibers make contact with CA1 pyramidal neurons.

CA3 pyramidal neurons are connected with the ipsilateral CA1 field through Schaffer collaterals, and with contralateral CA1 and CA3 neurons through commissural fibers. Postsynaptic targets from CA3 to CA1 comprise both interneurons and pyramidal cells [15]. CA3 projections to CA1 significantly extend dorsoventrally, both in rats and monkeys, providing a strong opportunity for longitudinal integration [16]. Interestingly this pattern of projection seem to be ordered: CA3 neurons located close to the DG (proximal) preferentially project to dorsal portions of CA1, distal CA3 neurons tend to project to ventral CA1 [17]. CA3 neurons also project heavily to each other, forming an associational recurrent network (**Figure 1B**). Specifically, CA3 pyramidal cells located close to CA1 (mid and distal portions of CA3) project prominent fibers along the dorsoventral axis of CA3 [17, 18]. These studies suggest that the longitudinal component of the CA3 to CA1 projection and associational connections within CA3 may provide a significant means for integration of information along the dorsoventral axis of the HC. This raises the possibility that CA3 could coordinate the activity of dorsal and ventral CA1 networks that are activated during spatial navigation and memory.

Oscillatory activity patterns are thought to be involved in the transmission and integration of information. It has been reported that gamma oscillations dynamically coordinate the activity of CA3-CA1 networks in DHC during performance of a hippocampus-dependent memory task, and gamma waves are coherent along the dorsoventral axis [19]. Gamma rhythms could also coordinate the activity between HC and entorhinal cortex along the axis [20] and may serve to control the timing of information flow throughout the HC. Evidence suggests that gamma rhythm generation in the CA3-CA1 regions does not require external inputs and results from the interaction between CA3 pyramidal neurons and interneurons [21]. This conclusion holds for sharp wave ripple oscillations as well [22]. Although GABAergic interneurons represent only about 10% of the total hippocampal neuronal population, they strongly influence the activity of the pyramidal cells (**Figure 1C**). The parvalbumin (PV)-expressing basket cells, which innervate perisomatic regions, proximal dendrites, and axon initial segments of pyramidal neurons, represent about 20% of all GABA-containing interneurons [23] and are key to the generation of gamma oscillations [24]. They are unevenly distributed along the longitudinal axis [25] but form an extensive, mutually interconnected interneuron network along that axis. For instance, a PV-containing basket cell in the CA1 region labeled with biocytin can provide divergent outputs to 60 other PV-expressing basket cells [15]. In contrast, a single inhibitory cell in CA3 contacts about 1000 postsynaptic pyramidal cells within a limited zone of innervation, suggesting that it can synchronize the activity of many local pyramidal cells [26]. In addition to the PV-expressing basket cells, the HC also contains basket cells expressing vasoactive intestinal polypeptide (VIP) and/or cholecystokinin (CCK). Note that the CA1 subfield contains more than 21 types of interneurons in addition to pyramidal cells. CCK-expressing basket cells share similar features to PV-expressing basket cells, however, most CCK cells are regular-spiking and form much smaller intrahippocampal networks than PV cells [27, 28]. CCK-containing cell ensembles are highly sensitive to neuromodulators and the disruption of this system has been associated with disorders such as anxiety [29]. These studies indicate that the inhibitory networks along the dorsoventral axis of the HC can support large-scale oscillations (e.g. gamma, sharp wave ripple, theta) and long-range information gating [25, 30]. This may provide the precise temporal structure necessary for dorsoventral ensembles of pyramidal neurons to perform specific functions, such as memory formation and complex spatial navigation [31]. However, although our understanding of the physiology of interneurons has advanced substantially, the exact longitudinal connectivity within and across different classes of interneurons is not yet well understood. A comprehensive understanding of the dialog between interneuron networks and pyramidal neurons along the longitudinal axis of HC may provide important insights into its function.

2.2. Extrinsic connectivity

It is generally thought that the dorsal-ventral organization of the HC corresponds to that of the entorhinal cortex (reviewed in Ref. [32]). DHC is preferentially connected to the dorsolateral portion of the medial entorhinal cortex, which conveys proprioceptive information to the HC, a modality thought to be critical for spatial navigation [33, 34]. In contrast, VHC has strong connections to the ventromedial part of the medial entorhinal cortex, which is modestly modulated by spatial information [35] (**Figure 1B**). Both lateral (LEC) and medial (MEC)

entorhinal cortex feature 3 bands (medial, intermediate and lateral) which further differentiate their interactions along the longitudinal axis of HC. The medial band of the LEC receives strong inputs from VHC, while the medial band of the MEC receives projections from both DHC and VHC. The lateral band of the LEC projects to the DHC. Unlike the medial entorhinal cortex, which contains grid cells, the lateral entorhinal cortex does not display spatial tuning and is thought to provide multi-sensory contextual inputs to spatial navigation computations [36, 37]. Overall, these observations indicate that the MEC provides spatial information to the DHC, whereas the LEC provides non-spatial information to the VHC. It also shows that the band-like structure of the entorhinal cortex and its non-uniform interactions with the longitudinal axis of HC may act as a site of interaction and integration along that axis. However, it is important to emphasize that the organization of HC-entorhinal cortex connectivity follows a gradual transition along the longitudinal axis, which does not support the often dichotomous view of a dorsal-ventral functional differentiation.

Prefrontal cortex projections to the entorhinal cortex are also topographically organized [38]. Infralimbic (IL) and prelimbic (PL) areas of prefrontal cortex influence the VHC via projections to the ventromedial parts of the entorhinal cortex. In contrast, anterior cingulate and retrosplenial cortices influence the DHC through their projections to the dorsolateral parts of the entorhinal cortex. The IL and PL are involved in emotional regulation and memory [39, 40] while the retrosplenial cortex is involved in spatial navigation [41] (**Figure 1B**). Generally, studies have shown that the medial prefrontal cortex is involved in predictive and adaptive behavior [42]. Some neurons in the PL/IL area represent the motivational salience of places and have place cell-like spatial activity, while others reflect the specifics of the rat trajectory [43]. Ventral CA1 is directly connected to the PL as shown by retrograde labeling, indicating that VHC is able to directly influence neural activity in PL. Importantly, transient deactivation of the PL-VHC circuit impairs spatial learning in the water maze [44, 45]. Anterior insula, the high-order interoceptive cortex, is also connected with the VHC [46]. It is has been reported that the anterior insula is involved in context-drug association [47] indicating that VHC may also play a role in drug addiction.

The connections between the different dorsoventral levels of the hippocampus and subcortical areas have been described in detail. For instance, most of the projections from the amygdala to the hippocampal formation terminate in the VHC and in entorhinal regions that are interconnected with VHC rather than in the DHC [48]. Moreover, VHC is connected predominantly to the caudomedial part of the nucleus accumbens whereas DHC is connected to the lateral and rostral portions of this nucleus [49]. The dorsal part of the lateral septum is mainly connected to DHC whereas its ventral part is more connected to VHC [50]. The amygdala, ventral striatum, and lateral septum are involved in motivation and emotional processing [51–53]. Interestingly, it has been reported that striatal neural ensembles reactivated during post-learning sleep, which may contribute to learning and memory consolidation [54, 55].

Altogether, these studies point to a complex heterogeneous pattern of inputs and outputs that led some to propose that the longitudinal axis is composed of "modular" sections, specialized for specific functions. An alternative hypothesis is that, in fact, there are no specialized modules

along the longitudinal axis, at least not computationally. The longitudinal axis may be a site of interaction between various streams of information emanating from the processing of complex information, with longitudinal interneurons "orchestrating" the information flow.

2.3. Neurochemical and genetic differences

The differential connectivity seen along the longitudinal axis of the HC is also mirrored neurochemically (**Figure 1D**). For instance, the monoamine systems tend to primarily project to the VHC. Serotonin and norepinephrine innervation are greater in VHC than DHC [56–59]. Dopaminergic input of the ventral tegmental area (VTA) to the HC is stronger in VHC [60–62]. Recent evidence shows that the VTA reactivates during sleep, suggesting that it may continue to modulate the HC during memory consolidation [63]. It is well-known that dopaminergic signaling plays an important role in novelty-related modulation of hippocampal memory. For example, dopamine D1/D5 receptor activity in DHC regulates synaptic plasticity and memory consolidation [64] and dopamine released from the locus coeruleus into the DHC promotes spatial learning and memory [62, 65]. Other differences have been established. Parvocellular vasopressin neurons of the suprachiasmatic nucleus project mainly to the VHC [66]. Cholinergic input from the fornix innervates more strongly DHC [67]. VHC, *in vitro*, has a weaker GABAergic synaptic inhibition response to Schaffer collateral stimulation when compared to DHC [68]. Interneurons containing calretinin, nitric oxide synthase, and somatostatin are more common in VHC than DHC [69]. Interneurons containing calretinin play a crucial role in the generation of rhythmic hippocampal activity by controlling other interneurons terminating on different dendritic and somatic compartments of pyramidal cells [70]. Molecular studies performed in the HC have also revealed differential gene expression along its dorsoventral axis. For example, the expression of neurotrophin-3, which is associated with neurogenesis, is higher in DHC than VHC; while VIP-positive interneurons are more common in the VHC [71]. Similarly to interneurons containing calretinin, VIP-expressing interneurons can be subdivided into distinct classes depending on the selectivity of their projections to other cells [72]. Serotonin receptors are more numerous in the VHC [73], in particular serotonin receptor 3A (5-HT3AR) [74]. In contrast, histidine decarboxylase, the enzyme responsible for the synthesis of histamine, is predominant in DHC, but not in VHC [74]. Functionally, the infusion of histamine into DHC improved both reference and working memory, while histamine in VHC produced only a working memory improvement [75].

Functional differentiation along the dorsoventral axis of the HC could be related to a corresponding differentiation in the glutamatergic system's function. Studies have indeed found a lower expression of both NMDA receptor and AMPA receptor subunits in VHC compared to DHC [76]. A dorsoventral differential expression in GABAA receptor subunits has also been reported. The expression for α1, β2, and γ2 subunits was lower, whereas α2 and β1 subunits were higher, in the VHC compared to DHC [77]. These functional differences of the glutamatergic and GABAergic systems could explain differences in long term potentiation (LTP, a cellular correlate of learning and memory) induction observed along the septotemporal axis. In VHC, the magnitude of LTP in response to afferent stimulation is smaller

than LTP elicited in the DHC [78]. Interestingly, exposure to acute stress or increased corticosterone levels enhanced LTP in the VHC through the activation of a mineralocorticoid receptor [79]. Finally, interesting variation in the expression of HCN1 and HCN2 channel subunits across the dorsal-ventral hippocampal axis have been observed in CA1 pyramidal neurons [80]. The expression for HCN2 subunit in dendrites was lower in VHC, whereas HCN1 was higher, compared with DHC. In addition, the differential expression for HCN subunits was correlated with the functionally augmented H-conductance gradient observed in VHC neurons, which could explain why CA1 neurons in VHC are more excitable than DHC CA1 neurons [81, 82].

Overall, these findings suggest that the HC exhibits multiple micro and macro domains distributed along its longitudinal axis. The VHC, but not DHC, seems to be strongly modulated by diverse neurotransmitter systems that can influence numerous neural processes involved, for instance, in learning and memory. Moreover, the ventral CA1 neurons target cortical and subcortical brain areas that mediate a variety of functions such as cognitive control, decision making, motivation, reward processing and hormonal regulation. The VHC is thus well positioned to play a broader role than DHC in interfacing hippocampus-related functions with other computations in the brain. We postulate that this interface, and hence dorsoventral coordination, is likely to be more active when tasks are complex and heavily rely on memory. More studies on hippocampal architecture are needed to advance our understanding of how different hippocampal domains process information and can be coordinated during behavior and memory-related processes.

3. Functional organization of the hippocampal long-axis

All levels of the longitudinal axis of the HC include place cells exhibiting firing fields at specific locations within the environment. We will first review the properties of these cells, we will then examine how manipulations of the dorsal and ventral regions of the HC impact spatial navigation and memory in different types of environments.

3.1. Place cell properties and gradated field size along the longitudinal axis

Place cells, discovered by O'Keefe and Dostrovsky in 1971, are pyramidal neurons within the HC that exhibit so called "complex spikes" and become active when an animal moves through a particular place within a given environment. The regions in which a place cell fires is that cell's "firing field" or "place field." Place cells are non-topographic in that neighboring cells are as likely to have nearby place fields as distant ones [18, 19]. Although place fields will remain stable when an animal is removed and then later replaced in an environment, only about half of them will still exhibit spatial firing in a new environment, often at positions unrelated to their former locations [84]. This shift in place field locations is known as "global remapping" and also occurs if all cues are removed from a familiar environment [85]. It is important to note that spatial cues can be multimodal i.e. visual, olfactory, auditory [86], and if only some cues are removed or other subtle changes are made to the environment, place fields remain spatially stable but exhibit changes in their

overall firing rate ("rate-remapping"). Accordingly, a subpopulation of place cells can be thought to form a dynamic cognitive map of an environment [87]. Place cells are present in all parts of the trisynaptic circuit (CA1-3, and DG) and although they are traditionally thought to possess a single place field, they may exhibit multiple fields [24, 88–90]; see **Figure 2A**. For example, DG place cells have multiple fields even in small environments (~1 meter) and the firing rates of these cells are sensitive to even small changes in the environment. CA1 and CA3 cells generally have a single field in small environments, although around 20% are thought to exhibit two fields [7]. Interestingly, in a larger than usual open-field environment (180 × 140 cm), dorsal CA1 and CA3 place cells exhibited multiple fields [88], although CA3 fields were generally singular on an 18 m linear track [91]. This finding suggests that space may be coded differently in a narrow 1D walkway than in an open 2D field, an idea that is supported by the fact that many CA1 place cells fire in only one direction when an animal traverses a 1D walkway, but are omnidirectional in an open 2D space [92]. In another study, dorsal CA1, CA3, and DG cells generally had multiple fields in a large 4 × 4 m environment, but not as many as would be predicted for such a large space [93]. This may be due to the exact proximal-distal DHC locations from which these cells were recorded suggesting that this proximal-distal axis may represent an additional functional gradient within the HC related to the number of fields a place cell exhibits [21].

Grid cells in the medial entorhinal cortex also possess multiple fields, however, these fields are evenly distributed in a hexagonal lattice and the scale, relative orientation, and offset of grid firing patterns are generally conserved across environments [94]. It has often been suggested that with the extensive hippocampal to entorhinal cortex connections, there may be a role for grid cells in shaping the spatial selectivity of place fields along the dorsoventral axis [20, 95]. However, studies demonstrating that medial septum inactivation as well as lesions to the head direction system disrupt grid cell but not place cell functions, suggest that this is not entirely the case [23, 70]. Moreover, place fields mature before grid cell firing patterns are established, suggesting that place cells may be established in the absence of grid-like firing [96]. Instead, place cells and grid cells are likely complementary and interacting representations that work in concert to support the reliable coding of large-scale space [12, 32]. Grid field size and spacing increases along the dorsoventral axis of the medial entorhinal cortex in several discrete steps, in contrast to the apparently smooth gradient of increasing place field sizes found along the dorsoventral axis of CA1/CA3.

Seminal studies identified place fields in both DHC and VHC, although ventral place cells were less common and had larger and less spatially selective place fields [26, 97] (**Figure 2A**). More than 20 years later, relatively few studies have further compared dorsal and ventral place fields. A recent study revealed a gradient of increasing place field size from the dorsal through intermediate to ventral regions of the longitudinal axis in CA3 in an 18 meter long one-dimensional track [91]. In this study, place field diameters ranged quasi-linearly from smaller than 1 meter in dorsal CA3 to about 10 meters near its ventral pole. Ventral place fields were often less defined than dorsal fields in terms of shape and in-field firing rate. Whereas dorsal firing fields were generally ovoid with symmetrical bands of diminishing firing rate, ventral fields show irregular edges and multiple firing rate peaks. However, the increased size and reduced spatial selectivity of ventral place cells do not necessarily indicate

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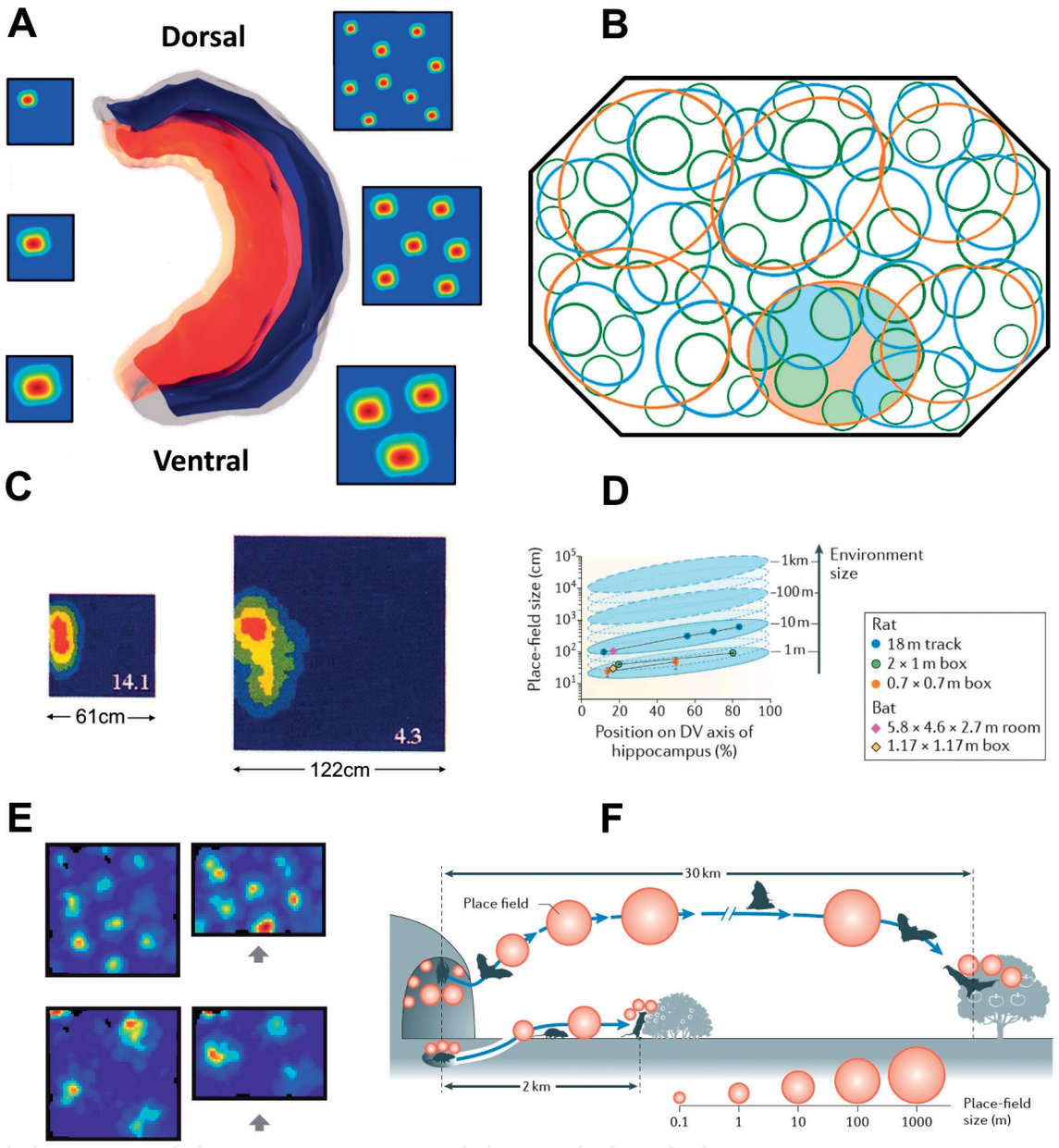

Figure 2. Possible mechanisms involved in a spatial representation of large-scale space. A) a 3D rendering of the hippocampal longitudinal axis. An individual place cell from the dorsal, intermediate, and ventral regions exhibits a single place field in a small environment (left), and multiple place fields in a large environment (right) see Ref. [127]. B) Large environment populated with overlapping small, medium and large place fields from the dorsal, intermediate, and ventral regions respectively. The shaded area shows a large ventral place field overlapping multiple intermediate and dorsal fields. C) Experimental data showing that an individual place field increases in size when the environment dimensions are enlarged, adapted from Ref. [128]. D) Data pooled from multiple experimental studies is extrapolated to predict that the up-scaling of place fields along the hippocampal long axis will hold over a continuum of environmental sizes. The ellipses depict a 10-fold gradient of spatial scales found along the dorsoventral hippocampal axis (x-axis) plotted against place field size (left y-axis) in different sized environments (right y-axis). The vertical-shift between the different ellipses represents the place field of the same neuron increasing with environment size, adapted from Ref. [4]. E) Experimental data showing that smaller-scale dorsolateral grid cells in the medial entorhinal cortex only show minimal rescaling associated with environmental compression (upper panel), whereas larger-scale ventromedial grid cells re-scaled completely to cover the re-sized environment (lower panel), adapted from Ref. [129]. F) Depiction of how the home range of a bat or rat may be represented at multiple spatial scales. Smaller more dorsal place fields encode a higher-resolution representation of important locations such as the home area or food sites. Larger more ventral place fields encode a lower-resolution representation of less important "travel" areas, adapted from Ref. [4].

a reduction in spatial precision. Instead, the gradient of place field size along the longitudinal hippocampal axis may signal a shift from sparse to distributed coding and may suggest a role for ventral cells in spatial context processing and generalization [13]. This may explain why aged rats and humans, who are thought to rely more on DHC than VHC, perform poorly in memory tasks that require contextual reminders [98, 99].

We propose a functional organization of the hippocampal long axis in which a continuous gradient of place field size implements a representation of space at multiple scales and levels of detail. Each environment may be mapped and landmarks triangulated by ensembles of overlapping place fields located at all levels along the axis, each with different remapping properties, size, and number of irregularly spaced subfields. Grid cell and border cell inputs would provide a metric framework on which these ensembles would depend, helping to anchor place fields and reduce drift in open areas of the environment [28]. These ensembles may be strengthened and consolidated during sleep. Individual place cells would be involved in multiple ensembles, and it is likely that multiple ensembles would be active simultaneously, adding redundancy as well as potentially coding different aspects of an environment. Concurrently, larger ventral place fields would overlap with and bind together smaller dorsal fields and may play a particularly important role in navigating through larger, more complex environments.

3.2. Dorsal and ventral hippocampal functions

The traditional view has been that lesions or inactivation of the DHC but not VHC result in spatial learning and memory deficits, whereas targeted disruption of the VHC but not DHC attenuates fear responses in anxiogenic paradigms [9, 10, 17, 31]. However, most laboratory-scale environments used for testing spatial learning and memory in rodents may lack the size and complexity to properly engage the VHC. For example, lesions to the DHC but not the VHC consistently impaired spatial memory performance in radial-arm and T-maze tasks which consist predominantly of narrow bidirectional walkways [17, 64, 100, 101]. Interestingly, VHC inactivation produced a spatial performance deficit in a circular open field (1.8 m diameter) in which the rat had to learn sequences of reward locations, but only when small or large obstacles were introduced to the maze [102]. The obstacles are likely to have increased the complexity of the environment requiring greater involvement of the hippocampal circuitry, especially the ventral levels. Effects of ventral lesions have also been reported, albeit inconsistently, in the water maze, an open circular environment of about 1.5 to 2 meters in diameter. Although the water maze is relatively large, it still could be in sufficient to require the engagement of ventral place fields most of which may be about 5.5 meters in diameter [91]. Also, because swimming is generally stressful to rodents, the spatial navigation involvement of the VHC in this task cannot easily be dissociated from its involvement in fear. Moreover, the water maze constitutes a “vista space” in which the entire environment, spatial cues, and target destination can be perceived at all times. The VHC may be more involved in spatial navigation in more complex “environmental spaces” which contain multiple regions that cannot be visually apprehended without considerable movements and require more planning, decision points, and integration of information over time (see [3] for review). Clearly, more studies in positively rewarded large-scale and complex environments are necessary to further understand the respective roles of the dorsal and ventral hippocampal poles.

In earlier work, DHC lesions were shown to produce a spatial deficit comparable to total hippocampal lesions in both the working memory and reference memory versions of the water maze, whereas VHC lesions had no effect. In addition, retrieval of a spatial memory could be achieved with about 70% of the DHC in normal rats, whereas 20% of the dorsal region was sufficient for acquisition [29, 31, 103, 104]. In another study, lesions of DHC but not VHC mildly impaired both working memory and reference memory in the water maze, compared to full HC lesions, suggesting that spatial learning and memory in this task may engage both the dorsal and ventral regions [15, 17]. Further evidence for the involvement of the entire axis in navigation comes from a study in which reversible inactivation of either DHC or VHC produced comparable retrieval deficits when delivered just before a probe trial, however only dorsal inactivation had an effect when delivered before training [105]. These results suggest that although spatial memory can be acquired by dorsal circuits, it can be less efficiently acquired with ventral ones, and retrieval of such a memory engages both DHC and VHC if it was acquired with a fully functional HC. Two more studies found similarly that VHC lesions produced spatial deficits in the water maze, although not as severe as those associated with dorsal lesions [106, 107]. Finally, a recent study found that large DHC and VHC lesions which each included at least part of the intermediate hippocampus resulted in a double dissociation in the water maze [108]. When the lesions were made before any experience, rats with ventral lesions could learn the position of a platform both in the original pool, and in a second novel pool, whereas rats with dorsal lesions could not. Intriguingly, when the lesions were made after training in the original pool, only rats with dorsal lesions could learn the platform position in the new environment. This suggests that the VHC may have a specific role in spatial learning in a novel environment. Together these studies suggest that the VHC may be involved in storing, retrieving, and comparing memories of varying sized and shaped environments.

These finding in rats may be closely related to findings in humans that suggest that the anterior hippocampus, the human analogue of VHC, is important for spatial context differentiation [109]. Indeed, human navigation studies often involve larger and more complex environments than the mazes traditionally used in rodent experiments. Although responses to spatial manipulations usually involve the posterior hippocampus (PHC), the human analogue to the dorsal hippocampus, the anterior hippocampus (AHC) is often also involved. For example, accurate wayfinding activated PHC in subjects navigating a route through a virtual town, but subjects that navigated best also activated AHC [110]. Another study involved learning to navigate through three virtual mazes consisting of interconnected corridors of increasing sizes followed by recalling which images of landmarks belonged to which of the three mazes [111]. While the PHC was activated during the traversal of all three mazes, the AHC was only involved when navigating through the largest and most intricate maze. A number of seminal human fMRI studies have measured hippocampal activation in licensed London taxi drivers, who are required to train over 4 years to learn the complex layout of London's streets [112–115]. Interestingly, these drivers had greater gray matter volume in PHC and less in AHC compared to matched controls [112, 113]. Taxi drivers were significantly more knowledgeable about London landmarks and their spatial relationships than controls. However, they were significantly worse at forming and retaining new associations involving visuo-spatial information, suggesting that these may involve the AHC [113, 114]. A follow-up study demonstrated that

the taxi driver's ability to form associations between visual stimuli was intact, the impairment being specific to acquiring new information containing a spatial component [115]. Another study has shown that both imagination and 1-week recall of scenes engage AHC, suggesting its role in scene construction [116]. In contrast, recall of scenes after a 30-minute delay elicited significantly less activation of the AHC and was more associated with PHC activation. Recall of longer-term spatial memories may require activation of more "global" levels of autobiographical memory (see Section 5), which may explain the involvement of the AHC.

There is strong evidence that lesioning VHC in rodents attenuates fear response in a number of anxiogenic paradigms including light/dark exploration, hyponeophagia, open field exploration, and the elevated plus maze [10, 117, 118]. It is therefore possible that VHC lesions could attenuate anxiety in the water maze resulting in improved performance which may compensate for any spatial impairments resulting from the lesions. In fear conditioning experiments, dorsal lesions impair the retention of contextual fear but not cued fear [119, 120]. Ventral lesions attenuate conditioned freezing in response to cued fear as well as contextual fear, although a more consistent response to contextual fear is observed after dorsal lesions [120–123]. Subsets of neurons in CA1 of the VHC fire differently in places associated with elevated anxiety or during goal approach [124]. Ventral neurons that show anxiety-related firing typically project to the prefrontal cortex, whereas neurons that show goal-directed firing usually target the nucleus accumbens. Ventral hippocampal neurons that are most active during behavioral tasks and sharp wave ripples triple-project to prefrontal cortex, amygdala, and nucleus accumbens. This last finding suggests that VHC cells may be conjunctive, with the potential to encode both spatial and affective properties of an environment.

In sum, both human and rodent studies suggest that spatial processing involves the activation of the DHC, and that the VHC becomes involved when more spatial processing is required, for example in larger and more complex spaces or when forming new spatial associations. Moreover, the widespread connectivity of the VHC to regions such as the medial prefrontal cortex may be critical for processes involved in navigating large-scale space such as route planning and wayfinding. The ability of ventral place cells to encode both spatial and affective components may suggest its role in sensing and avoiding danger. It is therefore important that more studies examine the properties and function of these larger ventral place fields while simultaneously recording dorsal place fields during spatial navigation through large and complex environments (see [125, 126] for example environments). Similarly, the effects of DHC and VHC lesions or inactivation need to be examined in the context of much larger and more complex spatial navigation tasks. In the next section we will argue that a multi-scale memory system incorporating the entire longitudinal axis of the hippocampus is critical for supporting spatial representations in such large-scale complex environments.

4. Navigating in large-scale complex space

Wild animals often traverse large and sometimes dynamic expanses of complex cue-rich space. We next examine what is currently known about navigating in such large natural environments. Mechanisms such as the dynamic scaling of place and grid fields in response to environment

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size and level of details may play a role in forming efficient large-scale representations of space. An environmental-scale representation may consist of a collection of smaller detailed spatial maps linked together through a coarser more global representation. The ability of grid cells to form a contiguous pattern between environments may be involved in forming this global map. Additionally, ventral place fields or specialized subsets of goal-sensitive neurons may facilitate the transition between sub-sections of the larger environment. The ability of place cells to exhibit multiple place fields in larger environments may be a critical mechanism for forming a multi-scale representation of complex large space. Important locations such as burrows or reward sites may be preferentially encoded with finer grained dorsal place fields, whereas large ventral fields with their connectivity to brain areas involved in fight or flight may be preferred in more exposed travel areas. However, the overlapping of dorsal to ventral representations in both small and large environments may facilitate different kinds of spatial processing. The multiple fields exhibited by hippocampal place cells could be flexibly recombined to form a complex spatial representation similar to that of a "megamap" which could simultaneously encode non-spatial information [130]. We propose that multiple overlapping megamaps consisting of different place-field scales along the hippocampal long axis simultaneously encode an animal's environment.

4.1. Differences between laboratory-style and natural environments

Most of what is known about spatially-tuned cells in the brain has been learned while recording from rodents moving through small, highly controlled, and often highly symmetrical environments. Most unit-recordings are made while an animal explores or forages in small otherwise empty boxes or cylinders typically between 40 cm and 1.5 m across [13, 97, 131], or on linear tracks [90, 91]. As discussed in the previous sections, most hippocampal lesion or inactivation studies also take place on narrow walkways or in relatively small open environments [17, 108]. The advantage of such environments is that they allow the experimenter to study sub-components of behavior by controlling the information that is available to solve the task. However, these environments, most of which are vista-space paradigms where the entire environment, cues, and target destination can be perceived at all times, limit our understanding of more complex large-scale navigation. It has been established that place cells, border cells, grid cells and head direction cells are all active in these types of environment and together facilitate the creation and maintenance of cognitive maps. However, how these neuronal mechanisms operate in larger spaces, such as rodents natural habitats is unknown. For example, Norway rats typically have a home range of around 250 m^2 [132] but have been reported to roam up to 2 km in a night [133]. Environmental spaces of that scale will contain large numbers of vista areas that cannot be simultaneously perceived. Navigating between different areas would require a number of processes that are not recruited in laboratory settings such as planning and maintaining routes out of sensory range, being able to take unplanned shortcuts, and wayfinding new routes around obstacles or other changes in the environment [3]. The vastly increased spatial scale involved in this type of navigation likely means that the VHC would be much more involved. Larger ventral place fields may therefore have a role both in covering spaces with its large place fields as well as overlapping and giving context to more-dorsal smaller fields (See **Figure 2B**).

In addition to an increase in spatial scale, the fundamental structure of natural space is vastly different from that found within the mazes and environments typically used in the laboratory. Whereas experimental settings generally contain a relatively small number of highly controlled distal and/or local visual cues, natural environments are comparatively cue-rich with an abundance of visual, auditory, and olfactory cues as well as irregular terrain. These differences could have profound effects on the way hippocampal place cells function. For example, dorsal place fields were shown to be significantly smaller when rats ran along a track that contained a rich set of somatosensory and olfactory cues compared to the same cells recorded on a featureless running track [134]. Consequently, place cells may function quite differently in a natural setting, in fact, dorsal place cells recorded in the laboratory may be larger than they would be in natural settings because of a lack of fine details to encode. In addition, the environments used in laboratories are almost always symmetrical whereas perfect symmetry is less common in natural environments. Grid cells fire in regular hexagonal bands in boxes and cylinders but non-hexagonal firing patterns have been shown in irregularly shaped environments [135]. Natural environments often have very asymmetrical and complex boundaries and it is unclear how grid and border cells would function in these conditions. Furthermore, HC cells may also respond to environmental changes. For examples, dorsal place fields have been shown to enlarge as well as drift when recorded in darkness [136]. Animals likely build up detailed cognitive maps of their habitat over the course of their lifetime and can undoubtedly use other navigation strategies when traversing less familiar regions (see [4, 137]).

Electrophysiology in freely moving rodents has historically been limited to small laboratory-style environments because data transmission has required a ceiling mounted tether. One technical innovation that may open the door to larger-scale recordings is the emergence of wireless electrophysiological recording systems. Although the current generation of wireless devices has some limitations, such as battery life, overheating, and the combined weight of the drive and implant which often is carried on the animal's head, these devices will undoubtedly help elucidate the role of dorsal and ventral place fields in navigating larger-scale and complex environments. An interesting question is whether laboratory rodents born and raised in small home-cages have the full capability to encode and navigate in large environments. Wild-born animals may have the ability to more rapidly and comprehensively form large-scale spatial representations and may be better candidates for these types of studies [4]. It is currently unknown how animals generate a cognitive map of large complex environments, although some pertinent work will be reviewed next.

4.2. Potential mechanisms involved in a large-scale spatial representation

The dynamic nature of individual place cells is likely to play a role in creating a large-scale spatial representation. A number of studies have shown that place field size scales with environment size. Place fields recorded in a 60 cm^2 environment were 60% larger in a 120 cm^2 environment [128] (**Figure 2C**). In another study, place field size increased by 30% on average when rats were transferred from a 68 cm diameter cylinder to a 150 × 140 cm^2 square box. This also resulted in the place cells exhibiting multiple fields [131]. It has been suggested that this

re-scaling of place fields would hold over a continuum of environmental sizes, and that all neurons along the hippocampal longitudinal axis may scale their place-field sizes simultaneously as environmental size changes [4] (**Figure 2D**). Place cells in DHC also respond to environmental parameters such as the amount of local detail and the position of their field relative to environmental features [134, 136]. Place field size changes have also been reported when objects or cues are added to, removed from, or shifted within an environment. For example, place cells become larger and less stable when visual and odor cues are removed from a familiar environment [138]. Adding or removing objects from the environment led to partial remapping of place fields, and the size of place fields decreased when objects were present [139]. Finally, place fields tended to be smaller at locations close to the walls or local cues during exploration of an open-field [140]. This flexibility in matching place field size to environment size and to the density of local spatial details may be even more pronounced in larger, more cue-rich environments and may constitute an important mechanism for representing space at that scale. Moreover, although these studies exclusively looked at dorsal place cells, it is likely that ventral place fields also exhibit similar properties especially considering their connectivity to grid cells in the ventromedial entorhinal cortex which have also been shown to exhibit environmental compression.

The dorsal to ventral hippocampal long axis has topographical connections originating from the dorsolateral to ventromedial extent of the medial entorhinal cortex [141]. Grid cells exhibit hexagonal lattices of firing fields which, unlike place cells, occur in several modules of discretized field size and spacing [129]. Smaller scale grid cells are found more dorsolaterally in the medial entorhinal cortex and share connections with the DHC, whereas larger scale grid cells, shown to be up to 10 ten times larger, are found more ventromedially and share connections with the VHC [142]. Individual grid cells exhibit similarly sized fields when recorded in different environments [143]. In contrast, when an environment increases in size in the presence of an animal, grid spacing was shown to increase transiently, perhaps as a consequence of grid cells being anchored to environmental boundaries, but then reverted to the original grid spacing shortly thereafter [144, 145]. In addition, a study that included recordings of grid cells along the dorsolateral to ventromedial extent of the medial entorhinal cortex showed a functional dissociation with environmental compression [129]. Smaller-scale grid cells showed minimal rescaling of about 20% when the environment was reduced in size. In contrast, the larger-scale grid cells rescaled completely so that the same fields exhibited in the original environment were maintained, albeit with reduced grid-field distances in the compressed direction (See **Figure 2E**). This result suggests that these larger-scale grid cells may have a role in facilitating the formation of new and unique representations for novel environments. Another possibility is that these cells, in concert with the larger ventral place fields, may preferentially encode larger and more complex environments. VHC place fields may also share this property so that rather than re-scaling to 30–60% of the extension of an environment as reported in DHC cells [128, 131] they may rescale completely with changes in the environment size. The ability to dynamically change grid field size could be particularly useful when traversing natural environments which often contain regions of different sizes. Several models have suggested that grid cells could play a central role in a large-scale spatial representation. Theoretically, two grid cells with different scales could together represent a

coding range that is much larger than the individual grid wavelengths producing a highly precise estimate of position [146, 147]. This combinatorial grid code hypothesis proposes that the function of grid cells is to efficiently encode very large environments. However, although possible, it seems unlikely that the medial entorhinal cortex would circumvent the hippocampus in situations involving large-scale navigation given that fMRI studies consistently demonstrate robust hippocampal activation in large-scale spatial navigation paradigms [110, 111, 148]. Therefore it is more likely that place and grid cells have complementary roles in supporting the reliable encoding of large-scale space [12]. Environments that contain multiple interconnected compartments can be used to compare local and global representations. Dorsolateral grid cells initially represented two identical and connected maze compartments with identical but disjointed sets of fields. However, with repeated experience in the maze the grid cell representation spanned both compartments, and thus provided a global representation of the apparatus [149]. In contrast, dorsal place fields continued to exhibit fragmentation across multiple interconnected identical compartments arranged in parallel even when tested for a comparatively larger number of sessions [150]. A different subset of place cells may encode each locality within a larger environmental space, whereas grid fields may be contiguous between localities representing both the environment and a metric of the movement of the animal through space.

When thought about in these terms, spatial representations of very large environments may be a collection of DHC-bound detailed spatial maps linked together by coarser more global representations involving the VHC. There is indeed some evidence for compartmentalization of larger spaces from studies with humans. For example, participants in a virtual reality navigation study performed better at pointing to previously learned targets if their body or pointing targets were aligned with the local reference frame [151]. Interestingly, performance was further increased when the participant's body or current corridor was parallel or orthogonal to a global reference frame instead of oblique. These findings suggest an influence of both local and global frames of reference on recall of a multi-scale spatial environment.

Graph theory has provided an interesting set of tools to formalize the integration of interconnected representations of space [152, 153]. In graph-like structures, local positional information is represented by nodes that are interconnected with edges. The *Network of Reference Frames* theory [153] expands this concept and proposes that graphs are superseded by reference frames that each represents a vista space of variable size with an independent coordinate system and orientation. Reference frames are interconnected by edges that describe the perspective shift required to move between them. These theories very effectively model tasks such as traversing rooms and corridors in a building, or streets in a city. Larger open spaces such as a field or park would have to be represented by multiple overlapping graphs or reference frames. While interesting, the neural representation of graph-like structures is still unclear. As previously mentioned, grid cells may form a global representation responsible for connecting smaller detailed spatial maps. Grid cell's connection and conjunction with head direction and border cells may enable them to make the translation and rotations necessary for connecting nodes. Another possibility is that the VHC forms a coarser representation that overlaps with different independent local DHC representations. Alternatively, specialized route and goal- distance and

direction cells may have a role in connecting independent representations. For example, neurons in the parietal cortex fire in relation to route traversals in rats [154]. Route- and goal-sensitive neurons have also been demonstrated in the hippocampus of both rats and bats. In rats traversing a maze in which two partially overlapping routes led to the same goal location, 95.8% of dorsal place cells that fired were active on only one of the routes [155]. Goal-directed firing has also been shown in a subset of ventral CA1 neurons [124]. A subpopulation of CA1 neurons exhibited angular tuning to goal direction and/or goal distance in bats flying in complex trajectories towards a spatial goal [156]. Goal direction cells also fired towards a familiar but hidden goal, and this tuning did not change if the bat flew different routes to the goal. It would be interesting to record CA1 neurons along the extent of the hippocampal long axis while rats explored a large open space containing multiple "cities" each consisting of a different arrangement of interconnected local compartments. This paradigm would allow for a comparison of global and local representations, and rewards sites located within the cities would enable the examination of the route- and goal- tuning of neurons. Such a multi-scale task may help assess whether the mechanisms discussed in this section are involved in a large-scale spatial representations.

4.3. A multi-scale memory system for representing complex large-scale space

A multi-scale memory system utilizing the entire hippocampal longitudinal axis may use finer grained dorsal place fields to encode important locations such as burrows or reward sites with enhanced spatial details, whereas ventral place cells may be used to represent less important travel areas and to form a coarser, overlapping global representation [4] (**Figure 2E**). Several studies have reported increased density of dorsal place cells at salient reward-related locations within an environment [157–159]. For example, some DHC cells tend to cluster around the location of the hidden platform in the water maze [159] and respond to a shock-associated tone only when the animal is in that cell's place field [160]. Additionally, a subset of VHC CA1 neurons showed increased firing rate with increased anxiety in the open arms of an elevated plus maze [124]. These results in the rodent suggest that multiple overlapping dorsal and ventral representations would enable both fine- and coarse-grained representations to be simultaneously utilized in the same space, together with saliency and emotional information. The fine/coarse grain encoding of space is supported in humans by a fMRI study in which participants learned the positions of objects in relation to room geometry in a virtual environment [148]. The subjects were then required to position the objects onto a 2D overview of the environment and were given a positional granularity assessment of fine-, medium-, or coarse–grained, or failed, dependent on distance between their placement and the true positional pattern of the objects. The highest activation in the PHC (analogous to DHC in rats) was for fine-grained representations, and in the intermediate hippocampus for medium-grained representations. Although activation of the AHC (analogous to VHC in rats) did not significantly differ across fine-, medium-, or coarse-grained representations, it was significantly correlated with the number of coarse environmental representations encoded. This study suggests that dorsal, intermediate, and ventral representations occur simultaneously fulfilling the particular spatial processing needs as required.

A number of studies have demonstrated that hippocampal place cells exhibit multiple irregularly–spaced place fields in larger environments (see 3.1). One possibility is that at least some of these irregular fields may be dynamic, potentially changing their position, size, or firing rate in response to familiarization or changes to the environment. In addition, there may be some inherent interaction between the multiple fields exhibited by individual place cells and the phenomenon of "preplay" of future trajectories of the animal over short distances [161, 162]. Many attractor models have provided useful insights into how place cells represent an environment [163–165] but these models have been largely based on the assumption of a single spatial field per place cell. However, a recent model accounts for place cells exhibiting multiple fields and introduced the concept of a "megamap," in which place cells are flexibly recombined to represent a large space [130]. This flexibility gives the megamap a large representational capacity while enabling the hippocampus to represent multiple learned memories. Importantly, non-spatial information can be simultaneously encoded at no additional cost. Another feature of the megamap is that an underlying network of place cells is able to robustly encode any location in a large environment given a weak or incomplete input signal. We propose that any spatial environment is a priori represented by multiple megamaps consisting of different ensembles of place cells along the hippocampal longitudinal axis. These maps would encode different types of spatial and non-spatial information, and would be selectively activated by the demands of each task. For each map, ventral place fields would overlap with many dorsal place fields providing specific contextual and affective information to the map as well as facilitating a coarser representation of space when required (see **Figure 2B**). Dorsal place fields would cluster around task specific objects and cues increasing spatial resolution in these regions. Together, the dorsal-to-ventral components of a megamap would allow for its use in complex and large environments.

Although little is known about how the extended hippocampal system supports spatial representations of large-scale and complex space, some of the mechanisms discussed in this section, such as multiple place fields per neuron, are likely involved. It remains to be determined whether the multiple fields exhibited by place cells differ from each other in some quantitative manner such as in firing rate, size, or modulation by theta or sharp wave ripple oscillations. Do ventral place cells provide a secondary level of spatial processing when more complex spatial navigation or recollection are required, or are they specifically active when a coarse-grained representation is needed? Are grid cells part of a more global cognitive map which connects separate spatial reference frames? Are dorsal place fields more functionally important when navigating corridors and small rooms than during exploration of a large open space? Recording dorsoventral hippocampal place cells as well as grid cells while an animal navigates between discretized local spatial representations, such as small single-entrance mazes, nested within a larger more open environment may answer some of these questions. Studies that simultaneously record from the dorsal and ventral hippocampus during different types of experiences may also be critical. It may be that, to truly understand hippocampal function, some new recording probes are needed, capable of simultaneously recording from multiple points along its longitudinal axis. Moreover, although some studies have produced computational models of spatial representation and memory consolidation that include both DHC and VHC [32, 37, 166, 167], more work in this area is also required.

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Finally, the gradated spatial representations along the dorsoventral axis of the hippocampus may go beyond purely spatial processes and help explain the mechanisms of mnemonic hierarchies in declarative memory.

5. Mnemonic hierarchies in declarative memory

The human hippocampus is critical for the encoding and recall of episodic memories. Humans with hippocampal damage exhibit anterograde and temporally graded retrograde amnesias. There is evidence from human studies that episodic memory is encoded in complex mnemonic hierarchies in which lower-order categorical and specific events are nested within multiple layers of higher-order memories of extended lifetime periods (See [168]). The AHC has been associated with recollection of more global, "gist-like," higher order episodic memory, whereas the PHC has been associated with retrieving more categorical and specific episodes. Augmenting this view, we suggest that global and specific memories are not encoded within one particular segment of the axis but instead are distributed along the entire HC, as will be reviewed below.

5.1. Functional segregation of the hippocampal long axis in humans

In addition to the spatial studies already discussed in this chapter [110, 111, 148, 151], human fMRI studies have also shown other types of posterior and anterior hippocampal dissociations related to novelty [169, 170], encoding and retrieval [171], and vestibular and visual processing (see [5] for a review). Of specific relevance are findings that show PHC activation associated with recall of detailed or localized information, and AHC activation associated with more schematic, or "gist" recollection. One measure of gist memory consists in abstracting over large sets of items to create category-consistent false alarms which have been associated with activation of the AHC [172]. In contrast, recollection of detailed contextual information has been associated with PHC activation [173]. Additional indirect evidence comes from studies in participants with Post Traumatic Stress Syndrome who exhibit volume loss in the PHC and an increased reliance on AHC-dependent gist memory for more detailed recollection [174, 175].

There is also evidence that the recollection of detailed individual events is associated with PHC activation, whereas more comprehensive "global" multi-event narratives require AHC activation. In one study, participants watched realistic, life-like videos showing individual events that could be integrated into narratives in order to experimentally simulate processes involved in episodic memory formation [176]. These narratives were gradually built up by presenting seemingly unrelated events which were linked by subsequent events enabling both direct and inferred associations. Recollection of individual event-pairs was associated with PHC activation. When multiple event-pair associations were recalled, the intermediate hippocampus was involved if the events were not connected via inference, whereas recall of the same events pairs that included all the possible associations preferentially activated the AHC. Intriguingly, these findings suggest that the multi-event narrative was simultaneously

represented at multiple "narrative scales" along the hippocampal long axis. Other studies have also reported intermediate and AHC activation during inference or as a result of making new connections between associations [177, 178]. The simultaneous hierarchical encoding of memory along the hippocampal long axis would provide both the ability to recall separate events as well as to integrate multiple experiences into a more global memory representation. The AHC would maintain this more global representation and would therefore be involved in integrating new inferences or connections between events. Representing events at multiple scales may provide an effective way for a context or schema to improve recall and protect against loss of event details [176]. Similarly, a spatial representation encoded at multiple scales along the hippocampal long axis may improve navigation performance and help to prevent the loss of local spatial details.

5.2. Multi-scale models of declarative memory

Some have proposed a model of hippocampal long axis function in which the PHC and AHC have separate specializations [5]. In this view, the AHC and PHC constantly index information from different regions with which they are connected, each interaction changing the dynamics of the circuit. The relatively low volume of the DG in AHC would bias it towards pattern completion, whereas its higher relative volume in PHC would promote pattern separation. These biases, as well as the influence of graded entorhinal cortex connectivity would produce sharp PHC representations (high match specificity) and broader AHC representations (low match specificity). In this model, the AHC might retain links between principals, actions and setting of an event, whereas the PHC might retain the exact spatial and temporal context of the event even if this information is tangential to the episode's theme. This division of hippocampal function is compatible with the concept of "nested hierarchies" in autobiographical memory in which more abstract and longer lasting life periods (anterior) nest with less abstract and shorter autobiographical episodes (posterior).

It is likely that the relationships between autobiographical periods and specific episodes are characterized by many associations so that a given memory could be part of multiple autobiographic periods which themselves could be contained in multiple "Life Chapters" [168, 179]. Life chapters are major components in this hierarchical autobiographical knowledge structure that reflect extended time periods, typically spanning months to years, such as an individual's childhood or career [168, 179, 180]. As with nested hierarchies, one could predict that the AHC would have a functional role in the recollection of broader-scaled life chapters and the PHC would be more involved in recalling finer-grained episodes. However, it has been shown that the AHC is activated during the search and retrieval of specific episodic memories and that the PHC is associated with subsequent elaboration and reliving of the memory [181]. Although the memories accessed in this study were prompted by simple thematic cues such as "kiss" or "party", it is thought that the first level of entry of searching autobiographical knowledge is by searching more general and abstract autobiographical knowledge of extended life events. However, because the recollection of a memory was shown to involve both the AHC and PHC, the different scales of memory may not be restricted to specific sections of the longitudinal axis. This idea is further supported by the

fact that recollection of two-week-old as well as 10-year-old memories activated both the PHC and AHC [182].

To summarize, autobiographical memory in humans, similar to spatial representation in rodents, may consist of simultaneous overlapping fine- to coarse-grained representations along the hippocampal longitudinal axis. These graded representations may relate to a multilayer memory hierarchy in which lower-order categorical and specific memory episodes are nested within multiple higher-order life chapters. There is evidence that the PHC and AHC may be more active when retrieving and encoding lower-order and higher-order components of this memory hierarchy, respectively. However, additional evidence of whole-hippocampal activation during recall in general suggests that autobiographical memory may be distributed along the entire hippocampus.

6. Conclusion/summary

The hippocampal long axis consists of multiple interacting levels working together to generate complementary representations along a functional fine to coarse gradient. In this integrated model of hippocampal function, the extrinsic connectivity along the longitudinal axis enables the hippocampus to incorporate input from a wide range of brain regions. It is likely that the intrinsic interactions between the longitudinal regions of the hippocampus occur via selective excitatory connections, such as in CA3, and via interneuronal connections, especially during oscillatory episodes and it is important that more work be done to elucidate this inter-region connectivity within the long axis. Although there is compelling evidence that the VHC becomes more active during spatial navigation in larger and more complex environments, more work also needs to be done to record simultaneously at different longitudinal levels in tasks in which complexity and environmental size are systematically varied. This type of realistic navigation may rely on a number of additional mechanisms such as re-scaling of place and grid field representations with environment size, increased number of active place fields per neuron, the clustering of finer-scale place cells in important regions of the environment, and the existence of overlapping fine-to-coarse scale representations in all environments. Multi-scale models of autobiographical memory in humans describe a similar hierarchy of overlapping fine-to-coarse representations along the hippocampal longitudinal axis. Although the PHC and AHC may perhaps specialize in encoding and retrieving information from the lower- and higher-order divisions of these memory hierarchies respectively, there is evidence that encoding and recollection involves the entire extent of the hippocampus.

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