


REVIEW ARTICLE

Hippocampal interlamellar cell–cell connectome that counts

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Abstract

The hippocampus is regarded as a cognition hub, particularly for learning and memory. Previously, neuronal mechanisms underlying various cognitive functions are delineated with the lamellar hippocampal circuitry, dentate gyrus–CA3 or CA2–CA1, within the transverse plane. More recently, interlamellar (often referred to as longitudinal) projections have received intensive attention to help understand signal convergence and divergence in cognition and behavior. Signal propagation along the longitudinal axis is evidenced by axonal arborization patterns and synaptic responses to electro- and photo-stimulation, further demonstrating that information flow is more enriched in the longitudinal plane than the transverse plane. Here, we review the significance of longitudinal connections for cognition, discuss a putative circuit mechanism of place coding, and suggest the reconceptualization of the hippocampal circuitry.

KEYWORDS

feedforward network, longitudinal connection, place coding, spatial memory, synaptic plasticity

1 | INTRODUCTION

Learning and memory are essential cognitive functions of the brain. Signal processing for learning and memory is considered to be largely shaped by the lamellar hippocampus circuitry. To date, most circuit mechanisms underlying cognitive functions have been intensively studied in the lamellar segment of the hippocampus, with multi-synaptic formation from the dentate gyrus (DG) to the cornu ammonis 3 (CA3) or CA2 regions and the CA1 region (Andersen et al., 1969, 1971; Sloviter & Lomo, 2012; Steffenach et al., 2002). Incoming information from the entorhinal cortex layer II (ECII) enters the DG through the perforant path in each lamellar segment. The segmental circuitry ends when the axonal fibers of CA1 pyramidal cells approach the subiculum and then terminate at the ECV (Bliss & Lomo, 1973; Witter et al., 1989; Yang et al., 2004) (Figure 1). Such a

lamellar circuit provides an attractive opportunity to examine fundamental issues in neuroscience, such as the formation of learning and memory, the relationship between networks and functions, and hippocampus-related disorders. A single hippocampal lamellar organization appears to suffice to delineate the entire entity of information processing for hippocampus-related cognitive functions. Accordingly, it is believed that the malfunction of the lamellar circuit is a root cause of various neurological and psychiatric diseases (Irving & Harvey, 2014; Kandel & Spencer, 1961; Noh et al., 2019; Sloviter, 1994).

Many hippocampal neurons have projections to neighboring hippocampal lamellae, yet these have often been overlooked in previous studies. The significance of these longitudinal connections to hippocampal functions has not been intensively tested due to (1) a strong belief in the lamellar hypothesis and (2) the scarcity of

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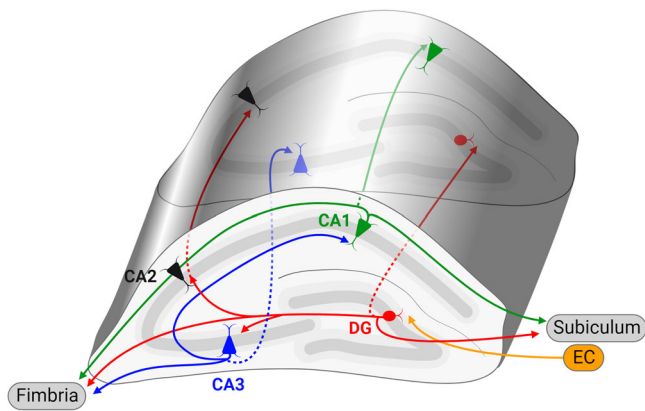


FIGURE 1 Schematic illustration of the hippocampal lamellar and interlamellar connections. Multisynapses are formed mainly by the DG, CA3, CA1, and EC regions within the hippocampal lamellae. Information from the ECII enters the DG through the perforant path. DG granule neurons project to CA3 pyramidal neurons, of which axons approach CA1 pyramidal cells often through the CA2. The lamellar circuitry ends when CA1 pyramidal cells project to the subiculum, terminating at the ECV. The longitudinal connections (partial-dotted lines) indicate synaptic projections between neurons across the hippocampal lamellae. The colors indicate representative neurons and their projections: red, DG; blue, CA3; black, CA2; green, CA1; orange, EC. Adapted from previous studies (Andersen et al., 1969, 1971; Bliss & Lomo, 1973; Choi et al., 2021; Pak et al., 2022; Sloviter & Lomo, 2012; Steffenach et al., 2002; Strange et al., 2014; Sun et al., 2018; Witter et al., 1989; Yang et al., 2014). CA3, cornu ammonis 3; DG, dentate gyrus; EC, entorhinal cortex layer.

techniques to identify escapable interlamellar axons. Thus, the cellular mechanisms responsible for behavioral and physiological outcomes have been explained merely in terms of the lamellar circuitry. Moreover, interlamellar axons easily escape detection, mainly because they are too thin to be visualized and are weakly identified via classical staining and electrophysiological methods (Choi et al., 2021; Yang et al., 2014). Along with previous studies that have observed the presence of interlamellar axons (Amaral & Witter, 1989; Claiborne et al., 1986; Henze et al., 2000), there are several lines of anatomical and electrophysiological evidence showing connections between hippocampal regions, such as CA1-CA1, CA3-CA3, and DG-DG connections (Choi et al., 2021; Pak et al., 2022; Strange et al., 2014; Sun et al., 2018; Yang et al., 2014). In this review, we describe the anatomical and physiological aspects of interlamellar networks along the longitudinal axis, which corresponds to the septotemporal (or dorsoventral) axis in rodents and the anterior-posterior axis in primates (Table 1).

2 | DG NETWORK

Being innervated by ECII-originating axonal fibers, DG is the first hippocampal station in the cortico-hippocampal network (ECII-DG-CA3 [or CA2]-CA1-subiculum) (Blaabjerg & Zimmer, 2007; Kohara et al., 2014;

Swanson et al., 1978). The DG consists of three distinct layers: the molecular, granule cell, and polymorphic layers (including the adult-born granule cell layer and dentate hilus) (Amaral et al., 2007). The molecular layer is a cell-sparse layer that is mostly composed of the dendrites of DG granule cells (DGGCs). The somata of granule cells are densely packed in the granule cell layer. Neurons in the molecular and granule cell layers receive inputs from both the EC and dentate hilus (a part of polymorphic layers) and then send signals back to the dentate hilus and further CA3 or CA2 region up to the CA1 (Blaabjerg & Zimmer, 2007; Kohara et al., 2014; Swanson et al., 1978). The dentate hilus in the polymorphic cell layer has two major types of neurons: GABAergic interneurons and glutamatergic mossy cells (Amaral, 1978; Amaral et al., 2007). Interneurons and glutamatergic neurons in the molecular and granule cell layers interact with the dentate hilus along the septotemporal axis, providing an associational projection between DG-DG segments (Amaral & Witter, 1989; Buckmaster et al., 1996; Sloviter, 1994). To date, most interlamellar connections in the DG are thought to be mediated by the dentate hilus.

2.1 | Interlamellar connection and signal transfer in the DG

Studies using Golgi and *Phaseolus vulgaris* leucoagglutinin (PHA-L) staining methods show that DG-originating mossy fibers target multiple hippocampal subfields, such as the CA1, CA2, and CA3 regions and the DG. These mossy fibers often stretch up to 2 mm (Amaral & Witter, 1989; Andersen et al., 1971; Tamamaki & Nojyo, 1991). Some DG-originating mossy fibers in the septal region seem to make interlamellar projections to the temporal area of the CA1 region (Amaral & Witter, 1989; Henze et al., 2000). A recent study with cell type-specific transgenic mouse lines demonstrates that DG axons in the septal area send monosynaptic projections to CA2 pyramidal cells lamellarly and further extend their axon bundles toward the temporal area interlamellarly (Kohara et al., 2014). This finding agrees with a much earlier observation of the DG-CA2 projection along the septotemporal direction using a PHA-L staining method in rats (Amaral & Witter, 1989). These studies suggest that signals coming into the DG may not remain within a single hippocampal lamella, but propagate across the hippocampal lamellae.

Previous anatomical studies have also suggested a notion that some axonal collaterals of DG mossy fibers likely project to the granule cell layer along the septotemporal axis of the hippocampus (Claiborne et al., 1986; Petersen et al., 2013b; Scharfman & Pierce, 2012). Electrical activation of the perforant path causes signals to spread longitudinally through DG neurons, and navigation into a novel space alters theta and gamma synchrony across the longitudinal hippocampus (Lomo, 2009; Pare & Llinas, 1994; Penley et al., 2013). Furthermore, optogenetic activation of the DG in the septal hippocampus results in neuronal activation in the temporal DG and vice versa from the temporal to the septal DG (Kheirbek et al., 2013). These data suggest the presence of a DGGC-DGGC connection along the longitudinal axis (Figure 2). A more recent study using two-photon axon imaging confirms the presence of

TABLE 1 Key studies of interlamellar connections in the hippocampus

Interlamellar connection	Method	Species	References		
From	To	Finding	Method		
DG	DG	Electrical activation of the perforant path causes signals to spread longitudinally over DG neurons	Multiple field potential recordings with <i>ex vivo</i> whole-brains	Guinea pigs	Pare and Linas (1994)
DG	DG	Stimulation of the septal DG activates the intermediate and septal DG	Extracellular field recording	Rabbits	Lomo (2009)
DG	DG	DG granule cells project to neighboring granule cells longitudinally	Optogenetics and IHC staining	Transgenic mice	Kheirbek et al. (2013)
DG	DG	DG-DG granule longitudinal connections possess LTP	Whole-cell recording	Mice	Choi et al. (2021)
DG	CA2	DG granule cells project functional synapses to CA2 pyramidal cells longitudinally	Whole-cell recording with glutamate uncaging	Mice	Pak et al. (2022)
CA3	CA3	Synchronous neuronal firing spread throughout the disinhibited longitudinal CA3 region	Field potential, extra- and intracellular recordings	Guinea pigs	Miles et al. (1988)
CA3	CA3	CA3-CA3 axonal projection at the septo-temporal level	HRP staining	Sprague-Dawley rats	Ishizuka et al. (1990)
CA1	CA1	Electrical stimulation at septal hippocampus results in excitatory response in more temporal CA3 and CA1 regions.	Local field potential recording <i>in vitro</i>	Guinea pigs	Bartlesghi et al. (1983)
CA1	CA1	Being evoked at medial EC, electrical responses of CA1 cells propagate along longitudinal axis	Multiple field potential recordings with <i>ex vivo</i> whole-brains	Guinea pigs	Pare and Linas (1994)
CA1	CA1	Longitudinal connection between CA1s	PHA-L staining	Sprague-Dawley rats	Cenquizca and Swanson (2007)
CA1	CA1	CA1 pyramidal cells project functional synapses to CA1 pyramidal cells longitudinally	Extracellular field recording, whole-cell recording with glutamate uncaging	Sprague-Dawley rats	Sun et al. (2018); Yang et al. (2014)

Abbreviations: CA1, cornu ammonis 1; CA2, cornu ammonis 2; CA3, cornu ammonis 3; DG, dentate gyrus; EC, entorhinal cortex; HHC, immunohistochemistry; HRP, horseradish peroxidase; PHA-L, Phaseolus vulgaris leucoagglutinin.

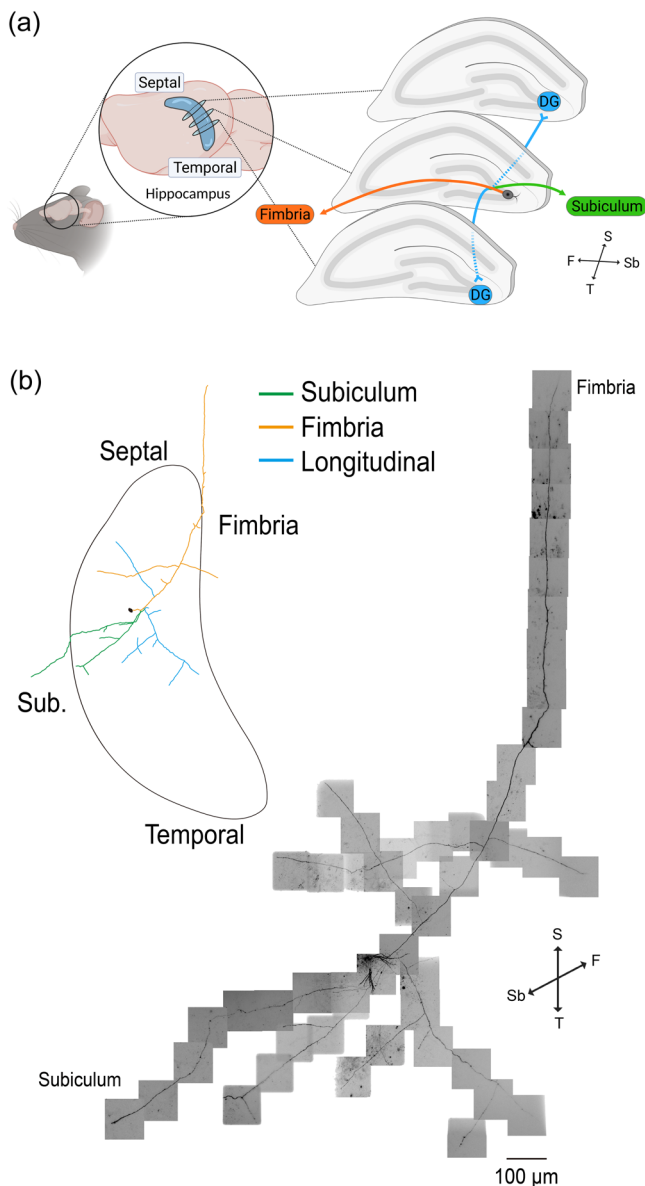


FIGURE 2 A three-dimensional model for the axonal projections of DG granule neurons. (a) Three major projection patterns of the DG neurons are shown: cyan, longitudinal axons to neighboring DG neurons in both septal and temporal directions; orange, axons to fimbria; green, axons to subiculum. (b) Heterogeneous axonal arborization of DG granule neurons. Three major axonal projections from a DG granule neuron stained with Alexa Fluor 594: fimbria via CA3 neurons (orange), subiculum (green), and longitudinal axons (cyan). Adapted from Choi et al. (2021). CA3, cornu ammonis 3; DG, dentate gyrus; F, fimbria; S, septal; Sb or Sub, subiculum; T, temporal.

direct and bidirectional longitudinal axons between granule cells in the DG (Choi et al., 2021; Pak et al., 2022). The primary axon of a DG granule cell heading to the CA3 region bifurcates to the longitudinal direction. Longitudinal axons have denser varicosities and are thinner than the primary axons that head toward the CA3 area, suggesting heavy synaptic weight and rapid signal transfer along the longitudinal axis (Table 2). At the circuit level, enhanced synaptic excitability and plasticity are observed

in the DG-DG network (Table 3) (Pak et al., 2022). In local field recordings with longitudinal hippocampal slices, the longitudinal DG-DG connection shows more robust synaptic efficacy and long-term potentiation (LTP) than the transverse network, implicating a pivotal role of longitudinal axons in the regulation of cognition and behavior (Pak et al., 2022).

2.2 | Roles of the DG-DG network in disease models

Several lines of evidence have suggested that the DG network is involved in epileptic seizures. Early studies have shown that epileptic seizures generate in the DG network, thereby giving rise to increased excitability and synchrony in the brain (Sloviter, 1991, 1994; Zappone & Sloviter, 2004). Indeed, upon the incidence of an epileptic seizure, enlarged varicosities in the longitudinal DG-DG (but not DG-CA3) axons likely contribute to increased excitability, leading to a promotion of electrical spread through the longitudinal network (Choi et al., 2021). In the meantime, both the enlarged varicosity of DG-DG axons and epileptic responses are prevented by the systematic application of antiseizure drugs, such as a muscarinic antagonist and GABA_AR enhancer.

The other study demonstrates a correlation between anxious behavior and the longitudinal DG-DG network (Pak et al., 2022). Abnormal anxiety levels caused by noise-induced hearing loss or chronic restraint stress are related to increased synaptic responsiveness and altered plasticity in the longitudinal DG network. More interestingly, anxiety is not closely correlated with synaptic activity in the transverse DG-to-CA3 network. It seems that anxiety-like behavior is attributable to a hyperexcitable input/output function in the DG-DG network, which is accompanied by impaired long-term synaptic plasticity (Pak et al., 2022). These data show that synaptic hyperexcitability of the DG-DG network leads to enhanced electrical spread to several cortices sequentially and/or simultaneously throughout the brain, thereby promoting the generation and/or development of abnormal behavioral traits, such as epileptic seizure and increased anxiety.

3 | CA3 NETWORK

CA3 is situated in the middle of the intrahippocampal pathway, receiving monosynaptic inputs from the ECII and DG. The CA3 region comprises a class of pyramidal cells with dendrites located in the following layers: (1) the stratum lacunosum moleculare (SLM) of the distal apical dendrites, largely having inputs from ECII; (2) the stratum radiatum (SR) extending adjacent to the DG hilus and receiving inputs from mossy fibers, commissural fibers, and neighboring CA3 neurons; (3) the stratum lucidum, which contains numerous synapses with DG cells in the form of a thorny excrescence; (4) the stratum pyramidale, which mainly consists of a cell body layer; and (5) the stratum oriens (SO), where CA3 axons and basal dendrites sprout and receive inputs from recurrent/commissural fibers. In the lamellar view, CA3 primary axons have three to eight collaterals, known as Schaffer collaterals. These multiple branches terminate in various hippocampal stations of

TABLE 2 Axonal arborization for principal and longitudinal axons in the DG, CA1, and CA3.

Region	Axonal type	Length (μm)	Thickness (ratio PA:LA, PA = 1)	Varicosity density	References
DG	PA	Cell body to fimbria: 1150 ± 219 (C57BL/6 J mice: Whole hippocampus)	1:0.4–0.5	1.39 ± 0.31 (Whole) 0.85 ± 0.29 (Slices) (#/100 μm)	Choi et al. (2021)
	LA	432 ± 256 (C57BL/6 J mice: Whole hippocampus)		6.57 ± 1.20 (Whole) 3.78 ± 0.50 (Slices) (#/100 μm)	
CA1	PA	>1000 (C57BL/6 J mice: Slices)	1:0.6–0.8	7.30 ± 1.56 (Slices) (#/100 μm)	Yang et al. (2014)
	LA	375 ± 22 (C57BL/6 J mice: Slices)		19.76 ± 3.01 (Slices) (#/100 μm)	
CA3	PA	All visible PAs per neuron: 280–1670 (SD rats: Slices)	1:0.08–0.5	Few varicosities found (not specified)	Ishizuka et al. (1990)
	LA	Unknown		14.2 ± 2.2 (Bunch of slices) (#/100 μm)	

Note: In the subregions of the hippocampus, the PAs are longer and thicker than the LAs. PAs have sparser varicosities than LAs.

Abbreviations: CA1, cornu ammonis 1; CA3, CA3, cornu ammonis 3; D, Sprague Dowley; DG, dentate gyrus; EC, entorhinal cortex; LA, longitudinal axon; PA, principal axon; Slices, hippocampus slice preparations; Whole, whole hippocampus preparation.

the CA1, CA2, DG hilus, subiculum, and fimbria of commissural fibers (Andersen et al., 1973; Le Duigou et al., 2014; Ishizuka et al., 1990; Li et al., 1994).

3.1 | Interlamellar connection and signal transfer in the CA3

Schaffer collaterals approach the CA1 along the transverse and longitudinal axes (Hjorth-Simonsen, 1973; Ishizuka et al., 1990; Li et al., 1994). They have different gradients of septotemporal projections depending on the lamellar location of CA3 cells (along the proximodistal axis), as shown in studies with HRP and PHA-L axonal tracers (Amaral & Witter, 1989; Ishizuka et al., 1990). CA3 neurons project to the CA1 both septally and temporally. Specifically, proximal CA3 neurons (situated adjacent to the DG) preferentially project septally, whereas distal CA3 neurons (situated adjacent to the CA2 region) preferentially extend temporally. This interlamellar projection of CA3 pyramidal neurons in a septotemporal gradient manner has been confirmed by single-cell staining with biocytin (Li et al., 1994). Accordingly, when the CA3 is electrically stimulated, neural responses propagate to the neighboring CA3 region along the septotemporal axis (Bains et al., 1999; Bartesaghi et al., 1983; MacVicar & Dudek, 1980; Miles et al., 1988; Miles & Wong, 1983). Meanwhile, lesion in a CA3 region results in the disappearance of electrical responses in the neighboring CA3 region (Bains et al., 1999).

Spatial and nonspatial information is conveyed along the septotemporal axis of the CA3 region (Hampson et al., 1999; Kjelstrup et al., 2008). These interlamellar connections are analogous to the neural network through which CA3 pyramidal cells send axonal collaterals to neighboring CA3 cells or themselves, forming associative and recurrent networks, respectively (Amaral & Witter, 1989; Le Duigou et al., 2014; Miles & Wong, 1986; Montgomery et al., 2001; Sloviter, 1994; Steffenach et al., 2002). This feature is known to be involved in enhanced signal reverberation and synchrony (Kandel & Spencer, 1961; Miles & Wong, 1983).

3.2 | Roles of the interlamellar CA3 network

There are currently three plausible lines of evidence delineating the roles of the interlamellar CA3 network in cognition and behavior. First, the interlamellar CA3-CA3 network generates ensemble firings for promoting synchronized signal cascades throughout the brain. The neuropathological etiology underlying epileptogenesis seems to be regulated by the activity of the interlamellar CA3 (Stasheff et al., 1989; Traub & Wong, 1982). Synaptically paired CA3-CA3 pyramidal cells show N-methyl-D-aspartate receptor (NMDAR)-dependent long-term synaptic plasticity, which often promotes the redistribution and reversibility of synaptic strength (Bains et al., 1999; Debanne et al., 1998, 1999; Montgomery et al., 2001; Selig et al., 1999). Synchrony through recurrent connection promotes

TABLE 3 Synaptic efficacy and plasticity in DG, CA1, and CA3.

Region	Input-output function	Connection	Short-term plasticity (paired-pulse interval)	Long-term plasticity	References
DG	Transverse < longitudinal (local field recording)	Perforant path to DG Longitudinal DG to DG	PPF (50 ms) PPF (50–100 ms) PPD (500–750 ms)	Weak LTP (Tetanus: 100 Hz × 4) LTD Strong LTP (Tetanus: 100 Hz × 4)	Pak et al. (2022); Petersen et al. (2013a)
CA1	Transverse < longitudinal (local field recording and glutamate uncaging)	Schaffer collateral to CA1 Longitudinal CA1 to CA1	PPF (50–200 ms) Unknown	Robust LTP (Tetanus: 100 Hz × 2) Robust LTD (1 Hz pp-LFS or DHPG) Robust LTP (Tetanus: 100 Hz × 2) No LTD (1 or 5 Hz LFS, 1 Hz pp-LFS, or DHPG)	Nanou et al. (2016); Sun et al. (2018); Yang et al. (2014)
CA3	Unknown	Mossy fiber to CA3 Associational CA3 to CA3	PPF (50 ms) PPF (50 ms) with small 1st EPSC PPD (50 ms) with large 1st EPSC	Robust LTP and LTD MF-CA3 and CA3-CA3 (with different mechanisms)	Debanne et al. (1996, 1998); Harris and Cotman (1986); Henze et al. (2002); Pak et al. (2022); Son and Carpenter (1996); Zalutsky and Nicoll (1990)

Note: In DG granular and CA1 pyramidal cells, the synaptic input-output functions of the DG-DG and CA1-CA1 network are steeper than those of the perforant path and the Schaffer collateral pathway, respectively. All types of connections show both PPF and PPD over various inter-pulse intervals, but preferentially PPD in the DG, PPF in the CA1 region, PPF in the mossy fibers to CA3, and PPD in CA3 to CA3. LTP is shown in all subregions, whereas LTD is uncertain or absent in the longitudinal network.

Abbreviations: CA1, cornu ammonis 1; CA3, cornu ammonis 3; DG, dentate gyrus; DHPG, (RS)-3,5-Dihydroxyphenylglycine, a selective group I mGluR agonist; EPSC, excitatory postsynaptic current; LFS, low-frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; PPD, paired-pulse depression; PPF, paired-pulse facilitation.

ensemble firings in the entire CA3 network, leading to orchestral spikes throughout the brain (de la Prida et al., 2006; Miles & Wong, 1983; Wittner & Miles, 2007). Second, the interlamellar CA3-CA3 network may be involved in the manifestation of spatial and nonspatial memories. Anatomical segregation along the longitudinal axis allows spatial and nonspatial information to be processed differently in a task-relevant manner (Hampson et al., 1999; Moser & Moser, 1998). Accordingly, an anatomical lesion of longitudinally connected CA3 axons impairs the retention of spatial memory (Steffenach et al., 2002). Third, the CA3 participates in pattern separation (e.g., discrete representation of complex episodic memory) and completion (e.g., a retrieval process of previously stored information) (Leutgeb et al., 2007; Rolls, 2013; Yassa & Stark, 2011). In particular, the longitudinal and recurrent CA3-CA3 network may be primarily accountable for pattern separation due to the intrinsic properties of the CA3 network in which associational axons of CA3 pyramidal neurons flow out of the lamella, venturing toward the neighboring CA3.

Also, CA3 recurrent connection can be suitable for dealing with the reverberation of information transfer largely mediated by a “feedback” mechanism. Signals initiated by a single CA3 neuron have profound synchrony through the recurrent synapses, promoting orchestral firings in the entire CA3 network. Such simultaneously reverberating firings enable CA3 neurons to readily retrieve the spatiotemporal context of previously stored information, as previously suggested (Neunuebel & Knierim, 2014; Rolls, 2013). The roles of interlamellar CA3 in cognition and behavior remain to be further investigated for better clarification.

4 | CA2 NETWORK

The CA2 is centrally interposed between the CA3 and CA1. In general, CA2 pyramidal cells have a similar appearance to other pyramidal neurons of the CA1 and CA3 (Chevalyere & Siegelbaum, 2010; Tamamaki et al., 1988). CA2 cells are unique in their size, membrane properties, and apical dendrite characteristics. For instance, CA2 cells have larger somata, lower input resistance, and slower after hyperpolarization than CA1 cells, and they lack thorny excrescences on their apical dendrites, which are seen in CA3 cells. In the lamellar view, the CA2 receives strong ipsilateral synaptic inputs from the ECII/III, but weak inputs from the CA3. It also receives contralateral inputs from the CA3 and CA2 and then sends monosynaptic outputs to the CA3 and CA1 (Bartasaghi & Gessi, 2004; Chevalyere & Siegelbaum, 2010; Hitti & Siegelbaum, 2014).

4.1 | Interlamellar network in the CA2

An interlamellar projection from the DG to CA2 is first proposed in a study using the PHA-L staining method. This is later verified using genetic and optogenetic tools (Amaral & Witter, 1989; Kohara et al., 2014). As aforementioned, DG-originating mossy fibers in the septal hippocampus form synapses in the CA2 lamellarly and then

extend to neighboring CA2 regions toward the temporal hippocampus interlamellarly. Furthermore, it has been observed that an interlamellar connection originates from septal CA2 neurons and extends to temporal CA1 neurons has been observed (Meira et al., 2018). This interlamellar connection may indicate a higher chance of synaptically paired recordings from the CA2-CA1 region in longitudinal slices compared to transverse slices. Thus, the paired rate of CA2-CA1 connection in transverse slices is similarly as low as the rate of synaptically paired CA3-CA1 neurons, possibly due to the septotemporal projections of CA3/CA2 neurons to CA1 neurons (Chevalyere & Siegelbaum, 2010; Ishizuka et al., 1990). Although the CA2 network is known to be involved in social memory (Hitti & Siegelbaum, 2014), other roles of the longitudinal CA2 network in cognition await further investigation.

5 | CA1 NETWORK

CA1 pyramidal cells are situated between the CA2 and subiculum. They have a similar somata shape and dendritic arborization pattern as CA3 and CA2 pyramidal cells (Amaral & Witter, 1989). The SLM of the CA1 distal apical dendrite is synaptically connected to the ECIII, and the SR of CA1 apical dendrites receives monosynaptic inputs from both the ipsilateral and contralateral CA3. The SO, where basal dendrites and axons sprout, is located nearby the pyramidal cell layer. In the lamellar view of CA1 axonal outputs, CA1 pyramidal cells project to the subiculum that, in turn, gives rise to a projection to the ECV (Amaral & Witter, 1989; Feng et al., 2000).

5.1 | Interlamellar connection and signal transfer in the CA1

The interlamellar network of the CA1 region is first identified using an extracellular local field recording (Raisman et al., 1966). Later, further electrophysiological evidence of a CA1-CA1 network is provided using an evoked field potential recording (Bartasaghi et al., 1983). Electroencephalogram unit recordings also show that signals in the CA1 region propagate along a longitudinal axis in an animal model with lesion-induced seizures (Buzsaki et al., 1991). When stimulated at the EC, responses of CA1 cells propagate along both the transverse and longitudinal axes in an ex vivo whole-brain preparation (Pare & Llinas, 1994). Consistent with data from electrophysiological studies, an anatomical study using PHA-L axonal staining suggests a longitudinal connection between CA1 cells (Cenquizca & Swanson, 2007). This CA1-CA1 connection promotes theta and gamma synchrony across the longitudinal axis (Patel et al., 2012; Penley et al., 2013). Recently, a direct synaptic connection between CA1 pyramidal neurons has been observed along the longitudinal axis using a photo-stimulated glutamate uncaging technique (Figure 3) (Sun et al., 2018; Yang et al., 2014). In an ex vivo whole hippocampus preparation, researchers observe that the primary axonal fiber toward the subiculum bifurcates to

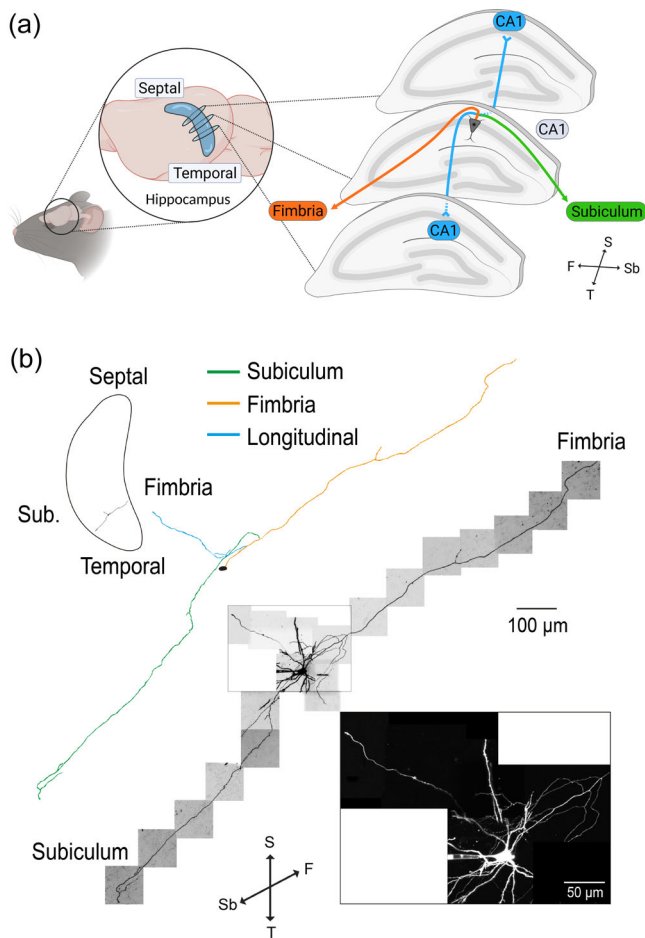


FIGURE 3 Three-dimensional model of axonal projections of CA1 pyramidal neurons. (a) Three major projections of CA1 neurons are shown: cyan, longitudinal axons to neighboring CA1 neurons in both the septal and temporal directions; orange, axons to the fimbria; green, axons to the subiculum. (b) Three major axonal projections from a DG granule neuron stained with Alexa Fluor 594. Adapted from Yang et al. (2014). CA1, cornu ammonis 1; DG, dentate gyrus; F, fimbria; S, septal; Sb or Sub, subiculum; T, temporal.

produce longitudinal axons that often extend up to $\sim 400 \mu\text{m}$. These longitudinal axons are thinner and have denser varicosities than the primary axons, which likely promote rapid electrical spread along the septotemporal plane of the CA1. Given the longitudinal connection between CA1 neurons and the direct connection between the CA1 and the EC, CA1 activity does not necessarily require prior activation of DG, CA3, or CA2 (i.e., EC-CA1-CA1-EC).

5.2 | Roles of the interlamellar CA1 network in information processing

Roles of the interlamellar CA1-CA1 network have been proposed in the context of epileptic seizure activity, learning and memory, and time-to-space conversion underlying perception. First, the CA1 interlamellar network is considered a potential locus for hippocampal

epilepsy. Epileptic responses are synchronized along the entire length of the hippocampus via the longitudinal projection of CA1 neurons (Umeoka et al., 2012). Lamellar cuts at the middle of the longitudinal pathway effectively prevent the induction of epileptic responses in the human hippocampus (Shimizu et al., 2006). Similarly, the interlamellar network within the CA1 region has been proposed as a key factor in the development of epilepsy (Shao & Dudek, 2004). Recent studies provide an anatomical substrate for rapid signal transfer across the lamellae. The longitudinal axons of CA1 cells have thinner axons and denser varicosities than their transverse axons. These properties likely enable signals to propagate rapidly along the longitudinal axis. Moreover, the multiple (as viewed in the denser varicosities) axonal targets successively recruit a large population of neighboring cells, thereby affecting the wide areas of the hippocampus. These studies implicate a significant role of the interlamellar CA1 network in the propagation of epileptiform activities.

Second, a recent study has demonstrated robust long-term synaptic plasticity in the longitudinal CA1 network using an *in vivo* extracellular field recording and glutamate uncaging (Sun et al., 2018). The CA1-CA1 network exhibits NMDAR-dependent LTP, suggesting a bidirectional connection both toward the septal and temporal CA1 regions. The presence of a pronounced LTP in the CA1-CA1 connection implies an essential role in learning and memory circuitry.

Third, linearly connected neurons along the longitudinal CA1 network enable spatial representation for long-lasting preservation of sequentially incoming signals (Yang et al., 2014, 2018). In this regard, the CA1 longitudinal system participates in a “feedforward” function of information flow. Feedforward processing appears to be important for encoding time-varying sensory information and later spatially presenting it for sensory perception (Yang et al., 2016, 2018). As aforementioned above, serially connected feedforward circuits of the CA1 may serve as a mnemonic buffer that transforms the temporal sequences of incoming inputs into spatial representations. Such a transformation hypothetically requires incoming signals to be amplified by synchronization with brain oscillation, the so-called “clock signal.” The combination of signal amplification and synchronization allows the feedforward network to transform temporally sequenced signals into a spatial pattern.

6 | PERSPECTIVE: A ROLE OF INTERLAMELLAR CONNECTIONS IN PLACE CODING

It is well-established that ensemble discharge required for place coding takes place in the DG, CA3, CA1, and sensory cortices (Feldman, 2009; Hensch, 2005; Kjelstrup et al., 2008; M. Lee et al., 2021; Park et al., 2011; Senzai & Buzsaki, 2017; Yang et al., 2011). There are several lines of evidence for the involvement of interlamellar connections in a circuit mechanism by which such ensemble activities are executed during spatial navigation. Space-responding cells are featured by ensemble firings in several areas of

the hippocampus and quickly remapped in different environments (Park et al., 2011). Also, space-responding cells appear to exist along the longitudinal axis of the hippocampus (Kjelstrup et al., 2008; Senzai & Buzsaki, 2017). It is supported by a finding that surgical lesions of the longitudinal connection impair spatial memory (Steffenach et al., 2002). According to these previous studies, place coding can be shaped by intrinsic connections along the longitudinal plane of the hippocampus. Interestingly, the septal hippocampus is finely tuned to place coding, while the temporal hippocampus broadly responds to spatial navigation (Fanselow & Dong, 2010; Hauser et al., 2020). This functional compartmentalization may be explained by a circuit mechanism by which interlamellar connections contribute to place coding.

Given a certain relationship between longitudinal circuitry and spatial navigation, here, we propose a putative model of the activation pattern of place cells along with the interlamellar connection in the hippocampus. For example, the activity of place cells is illustrated in the context of a rodent roaming around a square box to search for food (Figure 4). Suppose three parts of the hippocampus (septal, intermediate, and temporal) and the rodent moves sequentially from position A to B and C where it reaches the food, completing a trajectory movement. A space-encoding signal (or firing) corresponding to position A (cyan color) in the septal place field diffusely propagates toward the intermediate (or more temporal) region of the hippocampus. In a sequence, another space-encoding signal from position B (magenta color) in the septal region disperses into the intermediate region along the longitudinal axis. These two discrete space-encoding signals in the septal

hippocampus would be merged to display a new activation pattern (blue color) in the intermediate hippocampus. Finally, when the rodent finds the food at position C, the other space-encoding signal (yellow color) in the septal place field is transmitted to the intermediate region, forming another new pattern of a place field (red color). As space-encoding signals that are formed in the intermediate (cyan, blue, and red colors) move further toward the temporal region, a more diffused representation (gray-blue color) would be produced in the more temporal hippocampus possibly by “interlamellar connections” (Jung et al., 1994; Kjelstrup et al., 2008; Komorowski et al., 2013). That being said, trace information (A-B-C) can be held in a form of the mnemonically relayed and broadly turned ensemble firings in the temporal hippocampus, therein undergoing a signal transformation of temporally sequenced signals to a spatial pattern.

This model cannot be merely due to the interlamellar connectivity of each hippocampal station, but also the different properties of septal and temporal hippocampal cells, such as the neurotransmitter receptor density, gene expression, neurogenesis, intrinsic connectivity, and extrinsic synaptic sources (Amaral et al., 1991; Amaral & Witter, 1989; Anacker & Hen, 2017; Edelman & Lessmann, 2018; Ishizuka et al., 1990; Keinath et al., 2014; Kempadoo et al., 2016; A.-R. Lee et al., 2017; Lein et al., 2007; Martens et al., 1998; Yang et al., 2015). Nonetheless, the interlamellar connectome can significantly contribute to the effective execution of place cells in light of energy efficiency to avoid an unnecessarily long loop via transverse circuitry. Further investigation is required to obtain empirical evidence to support this hypothesis.

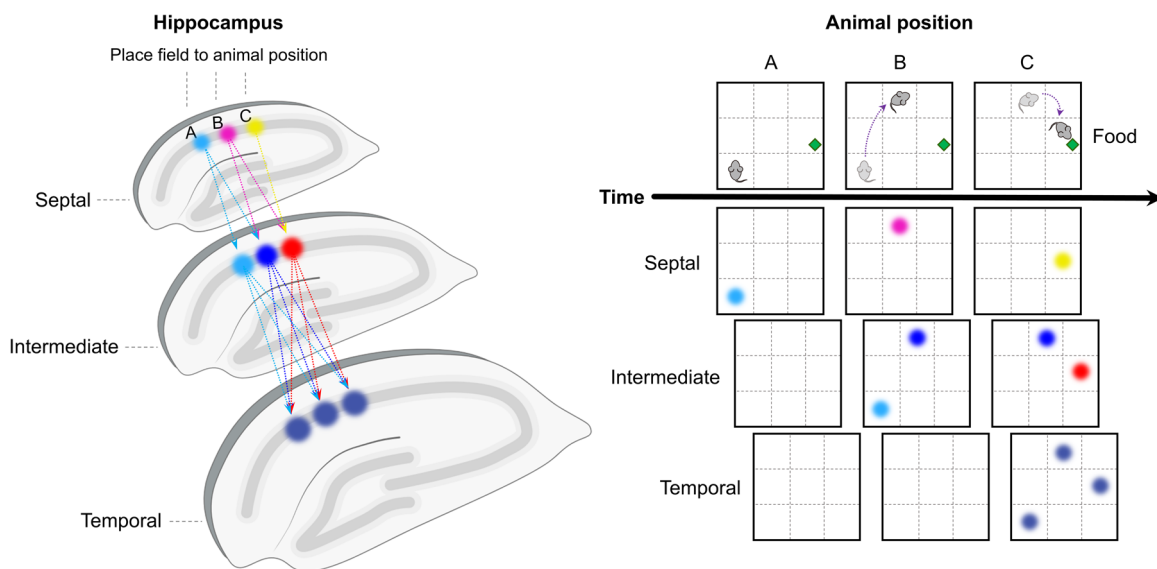


FIGURE 4 A putative model of the activation pattern of place cells along an interlamellar axis. The activity pattern of place cells is illustrated in the context wherein a rodent roams around a square box to find food (green rhombus). In this model, when the space-encoding signals move from the septal to temporal region, a more diffused representation can be produced after the signals are broadly tuned in the more temporal hippocampus through interlamellar connections, creating a new and wider form of a place field pattern. Cyan magenta yellow key (CMYK) color model: red, a mixture of yellow and magenta; blue, a mixture of magenta and cyan; gray-blue, a mixture of cyan, blue and red. Implied from previous studies (Choi et al., 2021; Jung et al., 1994; Kjelstrup et al., 2008; Komorowski et al., 2013; Pak et al., 2022; Sloviter & Lomo, 2012; Steffenach et al., 2002; Strange et al., 2014; Sun et al., 2018; Yang et al., 2014).

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