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Citation	Neuroscience Research. 143; 1-12
Published	2019-07
Type	Journal Article
Textversion	Publisher
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DOI	10.1016/j.neures.2018.08.002

Matsumoto, N., Kitanishi, T., & Mizuseki, K. (2019). The subiculum: Unique hippocampal hub and more. *Neuroscience Research*. 143, 1–12. https://doi.org/10.1016/j.neures.2018.08.002

The subiculum: unique hippocampal hub and more

Running head: Uniqueness of subiculum

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Key words: subiculum, oscillations, place cells, membrane potentials

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Acknowledgments:

This work is supported by JSPS KAKENHI (18H05137, 17K19462, 16H04656, 16H01279, (K.M.), 17H05575, 17H05977, 17K14939 (T.K.), 17J10860 (N.M.)), Daiichi Sankyo Foundation of Life Science (K.M.), the Naito Foundation (K.M.), Mochida Memorial Foundation for Medical and Pharmaceutical Research (K.M.), Astellas Foundation for Research on Metabolic Disorders (K.M.), SEI Group CSR Foundation (K.M. and T.K.), the Asahi Glass Foundation (K.M.), Hokuto Foundation for Bioscience (K.M.), Toray Science Foundation (K.M.), Life Science Foundation of Japan (K.M. and T.K.), Shimadzu Science Foundation (K.M.), the Tokyo Biochemical Research Foundation (K.M.), Brain Science Foundation (K.M.), the Ichiro Kanehara Foundation for the Promotion of Medical Science & Medical Care (K.M.), the Uehara Memorial Foundation (K.M.), the NOVARTIS Foundation (Japan) for the Promotion of Science (K.M.), Futaba Electronics Memorial Foundation (K.M.), the Osaka City University (OCU) Strategic Research Grant 2017 for basic researches (K.M.), the Japan Prize Foundation (T.K.), the Sumitomo Foundation (T.K.), Takeda Science Foundation (T.K.), Narishige Neuroscience Research

Foundation (T.K.), the Nakajima Foundation (T.K.), and the Osaka City University (OCU) Strategic Research Grant 2017 for young researches (T.K.).

The authors declare that there are no competing financial interests.

Abstract

The hippocampal formation, which comprises the hippocampus proper, dentate gyrus, and subiculum, is crucial for learning, memory, and spatial navigation. Historically, most studies have focused on the hippocampus proper and dentate gyrus; however, recent evidence has highlighted the substantial contribution of the subiculum to interregional communication and behavioral performance. Moreover, various network oscillations in the subiculum appear to be crucial for cognitive functions. The subiculum shows complicated spatial representation during exploratory behavior, suggesting that the subiculum does not simply relay hippocampal information to the target regions but it functions as a unique computational unit. The network mechanism underlying the uniqueness of the subiculum awaits further investigation.

1. Introduction

The hippocampal formation, which is generally defined as the region comprising the dentate gyrus, hippocampus proper (hereafter, the hippocampus), and the subiculum (van Strien et al., 2009) (Fig. 1A-1B), is crucial for episodic and spatial memory. The dentate gyrus and hippocampus process information consisting of mnemonic components by incorporating entorhinal inputs and then distributing the information to various brain areas (Buzsáki, 1996; Hunsaker and Kesner, 2018). Nevertheless, the mechanisms through which such multimodal hippocampal information is transferred to downstream brain areas remain elusive. The subiculum receives direct synaptic inputs from the hippocampal CA1 area and projects to various cortical and subcortical areas (see Section 2.3). This widespread projection pattern implies that the subiculum plays a crucial role in organizing hippocampal output (McNaughton, 2006). Moreover, the many features that distinguish the subiculum from the CA1 area, including its laminar structure (Section 2.1), cellular composition (Section 2.2), synaptic plasticity (Section 3), behavioral roles (Section 4), neural oscillations (Section 5.1), and spatial/non-spatial representations (Section 5.2), suggest that the subiculum has a unique function in information processing. Despite the postulated importance of the subiculum, considerably fewer studies have investigated subicular function compared with hippocampal function. Here we review the latest studies of this poorly-understood brain area to shed light on its fundamental function.

2. Anatomy: cellular and circuit infrastructure of the subiculum

2.1 Structure

The subiculum has a three-layered appearance comprising a molecular layer, a pyramidal cell layer, and a polymorphic layer (O’Mara, 2005; O’Mara et al., 2001) (Fig. 1C). The molecular layer is the most superficial (closest to the hippocampal fissure) layer and is continuous with the *stratum radiatum* and the *stratum lacunosum-moleculare* of the adjacent hippocampal CA1 area. The subicular pyramidal cell layer, which is flanked by the molecular and the polymorphic layers, is thicker than the hippocampal pyramidal cell layer. As its name suggests, this layer consists largely of pyramidal cells but with looser cell packing than in the *stratum pyramidale* of the hippocampus. The polymorphic layer is located deeper (*i.e.*, closer to the alveus) than the pyramidal cell layer and is continuous with the *stratum oriens* of the CA1 area. Recent immunohistochemical investigation further characterized the internal structure of the subiculum (Ishihara and Fukuda, 2016), dividing it into proximal (closer to CA1 area) and distal (further from CA1 area) subfields based on differential cytoarchitecture and immunoreactivity for calbindin (Fujise et al., 1995). The proximal subiculum can be further subdivided into five layers along the superficial-deep axis based on expression of proteins, including neuron-specific nitric oxide synthase (nNOS) and Purkinje cell protein 4 (Ishihara and Fukuda, 2016). The subiculum exhibits a unique gene expression pattern in embryonic (Sheppard et al., 1995) and postnatal animals (Cembrowski et al., 2018; Lein et al., 2004; Roy et al., 2017), but to date, there is no widely-accepted molecular marker that identifies the whole subiculum.

2.2 Cell types and morphology

The principal cell type in the subiculum is pyramidal cells. Using single-cell labeling, Harris *et al.* (2001) revealed the dendritic and axonal morphology of subicular pyramidal cells. Most subicular pyramidal cells have a single primary apical dendrite with its first major branch point at the superficial edge of the pyramidal cell layer. The branches of the apical dendrites climb through the molecular layer, with many reaching the hippocampal fissure. Regardless of soma location, the basal dendritic arbors are similar across subicular pyramidal cells in their total arbor size and number of branches. Further, both apical and basal dendrites have numerous dendritic spines.

Subicular pyramidal cells have axon collaterals that reach the alveus. Most also have axonal collaterals that climb into the apical dendritic region through the pyramidal cell layer. These collaterals have multiple varicosities both in the pyramidal cell layer and the apical dendritic region, suggesting that subicular pyramidal cells make synaptic contacts within the subiculum (Harris et al., 2001). Indeed, multiple whole-cell recordings have demonstrated extensive recurrent connections within the subiculum (Böhm et al., 2015). The axon collaterals extending obliquely across the cell layer toward the CA1 area or presubiculum are thought to project outside of the subiculum (Harris et al., 2001).

Subicular pyramidal cells are classified into at least two types based on their firing responses to intracellularly injected depolarizing current: the neurons that fire multiple action potentials within approximately 20 ms of pulse onset (Staff et al., 2000) are called intrinsically bursting neurons (mostly located in the deep cell layer), whereas neurons that discharge a single spike or train of action potentials with spike frequency adaptation are called regular-spiking neurons (mostly located in the superficial layer) in rodents (Behr et al., 1996; Harris et al., 2001; Harris and Stewart, 2001a; Knopp et al., 2005; Mattia et al., 1997; Menendez de la Prida, 2006; Menendez de la Prida et al., 2003; Staff et al., 2000; Stewart and Wong, 1993; Taube, 1993; Wellmer et al., 2002) (Fig. 1C) and humans (Wozny et al., 2005). The proportion of intrinsically bursting neurons is higher in the distal subiculum than in the proximal subiculum (Cembrowski et al., 2018; Jarsky et al., 2008) (Fig. 1C). There is recurrent connection both among regular-spiking neurons and intrinsically bursting neurons (connection probability: 4.7%, regular-spiking to regular-spiking neurons; 3.7%, bursting to bursting neurons). Regular-spiking neurons also innervate bursting neurons, but not *vice versa* (connection probability: 7.3%, regular-spiking to bursting neurons; 0%, bursting to regular-spiking neurons) (Böhm et al., 2015) (Fig. 1C). When sinusoidal currents with constant amplitudes are applied to subicular neurons, both regular-spiking and intrinsically bursting neurons exhibit theta-frequency membrane resonance (Wang et al., 2006), similar to CA1 pyramidal cells (Zemankovics et al., 2010) and medial entorhinal stellate cells (Giocomo et al., 2007). These two neuron types differ in their dendritic morphology, projection targets, expressed receptors, and pharmacological responsiveness (Graves et al., 2012; Kim and Spruston, 2012).

In vitro intracellular recordings have provided detailed characterizations of subicular intrinsically bursting and regular-spiking neurons. The bursting neurons accompany fast after-hyperpolarization following serial spikes, which is related to the lack of accommodation and enable the neurons to incessantly discharge. On the other hand, both fast and Ca^{2+}-dependent slow after-hyperpolarization follow a series of action potentials in regular-spiking neurons, which might allow for accommodation of a series of spikes (Behr et al., 1996). The bursting neurons receive greater tonic inhibition than regular-spiking neurons, suggesting that GABAergic inhibition may shape subicular output patterns (Panuccio et al., 2012). Another study demonstrated serotonin-induced reduction in the number of spikes in the burst and an increase in membrane conductance in subicular bursting neurons (Behr et al., 1997). Both calcium and sodium conductance are involved in the bursting firing of subicular pyramidal cells (Cooper et al., 2005; Jung et al., 2001; Mattia et al., 1997; Menendez de la Prida, 2006; Stewart and Wong, 1993; Taube, 1993; Wellmer et al., 2002). Using depolarizing current pulses, intrinsically bursting neurons can be further classified as “strong bursting” or “weak bursting” according to whether they repetitively burst or exhibit a single burst followed by regular-spiking action potentials (Menendez de la Prida, 2006). Regular-spiking neurons can be further classified as “tonic” or “adaptive” based on the degree of spike frequency adaptation (Menendez de la Prida, 2006). The impact of activity of intrinsically bursting neurons on postsynaptic neurons is dependent on their firing patterns, as bursting neurons may depolarize postsynaptic neurons via facilitating or depressing synapses. By contrast, the impact of activity of regular-spiking neurons on postsynaptic neurons is relatively constant because they do not show prominent bursting activity. Therefore, intrinsically bursting neurons and regular-spiking neurons may have distinct roles in information transfer depending on the properties of the synapses made between these neurons and postsynaptic neurons. It remains to be explored what kind of information is transferred from what type of subicular neurons to what downstream neurons/regions via what type of synapses.

Interneurons are also present in the subiculum. Relative to the divergent types of interneurons that have been characterized in the hippocampus and neocortex based on their electrophysiological properties, morphology, and Ca^{2+}-binding proteins, subicular interneurons are poorly characterized (Greene and Totterdell, 1997; Kawaguchi and Hama, 1987a; Knopp et al., 2008; Köhler et al., 1985; Seress et al., 1993; Soriano et al., 1993; Wang et al., 2017). Approximately 60% of putative GABAergic interneurons in the subiculum exhibit a fast-spiking firing pattern (Böhm et al., 2015). Fast-spiking, non-pyramidal cells are present in the pyramidal cell layer (Greene and Totterdell, 1997; Kawaguchi and Hama, 1987b; Menendez de la Prida et al., 2003), whereas chandelier cells are present in the molecular layer (Soriano et al., 1993). Based on Ca^{2+}-binding proteins, parvalbumin-positive cells are mainly located in the pyramidal cell layer, whereas the majority of calretinin-positive cells are in the pyramidal cell layer and the molecular layer (Knopp et al., 2008). Some somatostatin-positive interneurons in the polymorphic layer express nicotinic acetylcholine receptor alpha2 subunits (Chrna2), which are reminiscent of oriens lacunosum-moleculare interneurons in the dorsal CA1 area (Leão et al., 2012; Nichol et al., 2018). Another cell type, called membrane potential oscillation cells, fires action potentials interspersed with membrane potential oscillations in reaction to depolarizing current pulses (Menendez de la Prida et al., 2003). Most of the membrane potential oscillation cells are morphologically indistinguishable from pyramidal cells (Menendez de la Prida et al., 2003).

2.3 Projections

Afferents

The subiculum is primarily innervated by the CA1 area and entorhinal cortex (Amaral et al., 1991; O'Mara, 2005; Witter, 2006) (Fig. 1D). The projection from the CA1 to the subiculum within the transverse plane shows similar topographical organization as the CA3-to-CA1 projection. Neurons in the distal (*i.e.*, far from the dentate gyrus along the pyramidal cell layer) CA1 area have strong connections with neurons in the proximal (*i.e.*, close to the dentate gyrus) subiculum, whereas neurons in the proximal CA1 area project to the distal subiculum neighboring the presubiculum (Amaral et al., 1991; O'Mara, 2005; Witter, 2006). This precise topographic projection from the proximal CA1 area to the distal subiculum requires teneurin-3 (Berns et al., 2018). The axons of CA1 neurons have been shown to terminate in the subicular pyramidal cell layer and a deep portion of the subicular molecular layer (Amaral et al., 1991). The subiculum also receives major inputs arising from layer III of the medial and lateral entorhinal cortices (Honda et al., 2012). The projection from the entorhinal cortex to the hippocampal formation is segregated: Layer III entorhinal neurons project to the CA1 area and the subiculum, whereas layer II stellate cells project to the dentate gyrus, CA3, and CA2 areas (Behr et al., 1998; Honda et al., 2012; Steward and Scoville, 1976; Tamamaki and Nojyo, 1993; Witter, 1993; Wyss, 1981). Layer II pyramidal cells in the medial entorhinal cortex, which are called island cells, densely project to the CA1 area and modestly project to the subiculum (Kitamura et al., 2014). Afferent subicular excitation by the CA1 area and medial entorhinal cortex exhibit cholinergic modulation (Kunitake et al., 2004).

The ventral and medial parts of the anterior thalamic nuclei (*i.e.*, the anteroventral and anteromedial thalamic nuclei), but not the dorsal part (*i.e.*, the anterodorsal thalamic nucleus), might project to the temporal subiculum (Shibata, 1993; but see Jankowski et al., 2013; Mathiasen et al., 2017), suggesting that the subiculum receives theta-modulated head-direction signals in the anteroventral thalamic nucleus (Clark and Taube, 2012; Jankowski et al., 2013; Tsanov et al., 2011). Moreover, the subiculum is innervated by the basal amygdala (Cembrowski et al., 2018) and the nucleus reuniens of the thalamus (Wouterlood et al., 1990).

Efferents

The dorsal subiculum has been shown to have substantial efferent projections to various cortical and subcortical areas (Fig. 1D). The efferent projection arising from the rat dorsal subiculum reaches several cortical areas, including the retrosplenial cortex, medial prefrontal cortex, entorhinal cortex, perirhinal cortex, and postrhinal cortex (Aggleton and Christiansen, 2015; Honda and Ishizuka, 2015; Kinnavane et al., 2018; Kloosterman et al., 2003; Swanson and Cowan, 1977; Tamamaki and Nojyo, 1995; Witter, 2006; Witter et al., 1990). Moreover, neurons in the rodent dorsal subiculum innervate subcortical regions such as the hypothalamic nuclei (Kishi et al., 2000), nucleus accumbens (Groenewegen et al., 1987), midline thalamic nuclei (Namura et al., 1994), and lateral septum (Namura et al., 1994). Dorsal subicular neurons also project to the anteromedial and anteroventral thalamic nuclei and the mammillary bodies predominantly via the fornix in rodents (Bubb et al., 2017; Christiansen et al., 2016; Dillingham et al., 2015; Ishizuka, 2001; Kinnavane et al., 2018; Namura et al., 1994; Witter et al., 1990; Wright et al., 2010).

Accumulating evidence indicates that the subiculum also sends backward projections to the CA1 area (Berger et al., 1980; Harris and Stewart, 2001b; Köhler, 1985; Seress et al., 2002; Shao and Dudek, 2007; Sun et al., 2014; Xu et al., 2016). In line with this finding, some nNOS-immunoreactive pyramidal neurons in the subiculum innervate the CA1 area (Seress et al., 2002). Moreover, the dorsal subiculum innervates adult-born granule cells in the dentate gyrus (Deshpande et al., 2013), suggesting a potential impact on newborn granule cells involved in memory and emotion (Aimone et al., 2011; Nakashiba et al., 2012; Sahay et al., 2011a, 2011b; Santarelli et al., 2003).

The efferent projections from the subiculum are topographically organized along the proximodistal and dorsoventral axes. Individual subicular pyramidal cells exhibit a lower degree of axonal collateralization than CA1 pyramidal cells and project to only one or a few target brain areas (Naber and Witter, 1998). For instance, the dorsal-distal subiculum preferentially projects to the retrosplenial cortex, dorsal presubiculum, and medial entorhinal cortex, whereas the dorsal-proximal subiculum targets the nucleus accumbens, perirhinal cortex, prelimbic cortex, and lateral entorhinal cortex (Naber and Witter, 1998). The topographic projection from the subiculum to the parahippocampal areas becomes adult-like by postnatal day seven in rats (O'Reilly et al., 2013). Such a projection pattern that is widespread as a whole subiculum, but target-specific as individual projection neurons, implies that the subiculum plays a role in distributing distinct types of information to specific downstream target areas.

The subiculum adjoins the presubiculum (van Strien et al., 2009), which has a six-layered appearance (Honda et al., 2011, 2008; Honda and Ishizuka, 2004; Peng et al., 2017; Simonnet et al., 2013). The dorsal part of the presubiculum is often called the postsubiculum in rodents (Ding, 2013; Taube, 2007). While the subiculum has many unidirectional efferents, connections between the presubiculum/postsubiculum and their target regions are mostly reciprocal (Ding, 2013). For instance, the rat postsubiculum has reciprocal connections with the primary and secondary visual cortex (Vogt and Miller, 1983). Therefore, visual information of external landmarks may be transferred to the postsubiculum via the visual cortex, calibrating postsubicular head-direction signals (Knierim and Zhang, 2012; Yoder et al., 2011).

3. Synaptic plasticity

Synaptic plasticity, the activity-dependent plastic modification of synaptic transmission, is an important cellular learning process. The well-known forms of synaptic plasticity are the long-lasting increase (Bliss and Lømo, 1973) and decrease (Dudek and Bear, 1992; Mulkey and Malenka, 1992) in synaptic weights, which are called long-term potentiation (LTP) and long-term depression (LTD), respectively. CA1-to-subiculum synapses are known to exhibit both types of synaptic plasticity (Behr et al., 2009; O'Mara et al., 2000). Neurotransmission between CA1 and subicular pyramidal cells is mediated via presynaptic glutamate and postsynaptic AMPA-type and NMDA-type glutamate receptors (Behr et al., 1998). LTP is induced by high-frequency stimulation of the CA1-to-subiculum pathway both *in vitro* (Boeijinga and Boddeke, 1996) and *in vivo* (Commins et al., 1998). At synapses from CA1 neurons onto regular-spiking subicular neurons, LTP is induced by a postsynaptic mechanism based on postsynaptic NMDA-receptor activation. By contrast, at synapses from CA1 neurons onto bursting subicular neurons, LTP is suggested to necessitate presynaptic NMDA-receptor activation and subsequent presynaptic Ca^{2+}-influx (Behr et al., 2009).

Low-frequency stimulation that induces LTD at CA3-to-CA1 synapses or has little effect on these synapses rather result in moderate, late-developing LTP at CA1-to-subiculum synapses (Anderson et al., 2000; Huang and Kandel, 2005). This form of LTP is facilitated by β-adrenergic receptors *in vitro* (Huang and Kandel, 2005) and can be inhibited by acute stress *in vivo* (Macdougall and Howland, 2013). While these studies monitored population responses measured as field excitatory postsynaptic potentials, whole-cell recordings from single neurons have successfully induced CA1-subiculum LTD, which relies on postsynaptic muscarinic acetylcholine receptors and intracellular Ca^{2+} (Li et al., 2005). Bursting and regular-spiking neurons show distinct forms of synaptic plasticity in response to low-frequency stimuli at CA1-subiculum synapses. Low-frequency stimuli induce NMDA-receptor-dependent LTD in bursting cells and metabotropic glutamate receptor-dependent late-onset LTP in regular-spiking cells, both of which require postsynaptic Ca^{2+}-signaling (Fidzinski et al., 2008). The polarity of this bidirectional synaptic plasticity in subicular neurons is modulated by muscarinic acetylcholine receptors and voltage-gated L-type Ca^{2+} channels (Shor et al., 2009).

Cell-type specificity is an intriguing feature of subicular synaptic plasticity. As described above, bursting neurons and regular-spiking neurons have distinct molecular mechanisms for inducing synaptic plasticity and may show opposite polarity (*i.e.*, either LTP or LTD) in response to the same stimulation frequency. Such properties indicate that a single input pattern from upstream areas can regulate the synaptic strength of bursting and regular-spiking neurons in different ways. Because these two types of principal neurons preferentially project to different sets of target areas (Kim and Spruston, 2012), this simultaneously-occurring, distinct synaptic plasticity may flexibly change the output balance of the subiculum from one set of projection targets to another set of targets. Moreover, the involvement of the neuromodulatory system, including acetylcholine and noradrenaline, may ensure that such synaptic plasticity only occurs under specific neuromodulatory/behavioral states, such as learning or stress.

In addition to the synaptic plasticity, there is non-synaptic plasticity that is mediated by metabotropic glutamate receptors, acetylcholine receptors, or brain-derived neurotrophic factor (BDNF) in the subiculum (Graves et al., 2016; Moore et al., 2009). For example, BDNF enhances and depresses intrinsic excitability in subicular bursting and regular-spiking neurons, respectively (Graves et al., 2016). This variety of synaptic/non-synaptic plasticity suggests that the subiculum not only relays information from the hippocampus but may also actively participate in the processing of information in a unique manner.

4. Behavioral function: contribution to memory

Selectively lesioning the subiculum with minimal damage to the adjacent hippocampus is technically challenging, and only a handful lesion studies are available. One of the first lesion studies on the rodent subiculum investigated allocentric spatial memory in a water maze test (Morris et al., 1990). A neurotoxic lesion of either the subiculum or the hippocampus impaired the acquisition of spatial navigation, suggesting that both areas are necessary for allocentric spatial learning (Morris et al., 1990). A series of lesion studies on the dorsal subiculum further suggested the contribution of the subiculum to memory of idiothetic (*i.e.*, self-motion) cues and spatial novelty (Potvin et al., 2010, 2007) as well as visual pattern separation (Potvin et al., 2009). Interestingly, lesion of either the subiculum or the hippocampus often impaired spatial memory to a similar degree, while concurrent lesion of both areas induced a more severe deficit than a single-area lesion (Morris et al., 1990; Potvin et al., 2007). This additive impairment suggests that the subiculum serves a unique spatial function that cannot be explained by a role merely as a downstream region of the hippocampus (Lever et al., 2009; Olson et al., 2016). Recently, an optogenetic study of dorsal subiculum-specific Cre transgenic mice revealed that the pathway from CA1 to dorsal subiculum to medial entorhinal cortex is crucial for hippocampus-dependent memory retrieval, but not for encoding (Roy et al., 2017). In contrast, the direct pathway from CA1 to medial entorhinal cortex is essential for memory encoding, but not for retrieval (Roy et al., 2017).

5. Physiology: neural correlates of cognitive functions

5.1 Neural oscillations

The hippocampus exhibits various types of extracellular neural oscillations including theta, gamma, and sharp wave/ripples (Bieri et al., 2014; Buzsáki, 2015, 2002; Chrobak and Buzsáki, 1996; Colgin, 2015; Colgin et al., 2009; Colgin and Moser, 2010; Igarashi et al., 2014; Kitanishi et al., 2015; Mizuseki et al., 2009; Mizuseki and Buzsaki, 2013). Each type of oscillation is tightly coupled with animal's behavior and sleep/wake cycles (Buzsáki, 2015, 2002; Colgin and Moser, 2010; Mizuseki and Miyawaki, 2017). These oscillations reflect gross electrical activity in the local network and typically accompany neuronal firing phase-locked to the ongoing oscillations. The synchronous firing of a neuronal population aligned to a certain oscillation potently excites postsynaptic neurons, thereby facilitating interregional transmission (Fell and Axmacher, 2011). Either during or over the course of learning a memory task, interregional oscillatory interactions are dynamically regulated in the hippocampus and parahippocampal areas (Kemere et al., 2013; Montgomery and Buzsáki, 2007; Yamamoto et al., 2014). Moreover, synaptic plasticity in the CA1 area regulates the development of phase-locked firing along a type of gamma oscillations inherited from the upstream CA3 area during a novel experience (Kitanishi et al., 2015), suggesting that synaptic plasticity controls interregional information transfer by regulating oscillatory interactions (Kitanishi et al., 2017).

Like the hippocampus, the subiculum also shows theta oscillations (Bullock et al., 1990), gamma oscillations (Chang and Huerta, 2012), and sharp wave/ripples (Anderson and O'Mara, 2003; Chrobak and Buzsáki, 1996) *in vivo* (Fig 2A). Moreover, accumulating evidence suggests that the subiculum may play a role in the generation of these oscillations. Theta oscillations (4–10 Hz) are generally associated with alert exploratory behavior and rapid eye movement (REM) sleep (Anderson and O'Mara, 2003; Buzsáki, 2002; Chang and Huerta, 2012), and are thought to be unidirectionally transmitted from the CA3 area to the downstream regions, CA1 area, and subiculum via an excitatory feedforward pathway. However, in isolated whole hippocampal preparation and during REM sleep *in vivo*, spontaneously generated theta oscillations within the subiculum are signaled backward to CA1 and CA3 areas, presumably through long-range GABAergic feedback projection (Jackson et al., 2014). How these distinct types of theta oscillations are organized remains to be elucidated. Interestingly, there is a greater increase in theta power in the subiculum when mice explore a novel object than a familiar object, which is not the case in the CA1 area (Chang and Huerta, 2012). In the hippocampus of freely-behaving animals, the spike timing of place cells progressively advances to earlier phases of extracellular theta cycles as the animal walks through the cell's place field, a phenomenon that is referred to as theta phase precession (O'Keefe and Recce, 1993). The place field and theta phase precession are striking substrates of rate and temporal code of space, respectively, although it is still debated whether the two codes are intrinsically coupled (Harris et al., 2002; Mehta et al., 2002) or definitely independent (Huxter et al., 2003; Souza and Tort, 2017). Subicular principal cells show theta phase precession similar to the CA1 area (Kim et al., 2012).

In addition, the subiculum shows gamma oscillations in behaving rodents (Chang and Huerta, 2012). It has been suggested that the subiculum is the third spontaneous gamma generator in the hippocampal formation, in addition to the CA3 area and the entorhinal cortex because gamma oscillations have been observed even in the isolated subiculum (Jackson et al., 2011). Subicular gamma oscillations have at least two frequency bands that are distinctly modulated by theta oscillations: slow gamma oscillations (25–50 Hz) are mediated through excitatory and inhibitory mechanisms, whereas fast gamma oscillations (100–150 Hz) require rapid and strong local inhibition in the subiculum (Jackson et al., 2011; Menendez de la Prida, 2003). Whether subicular gamma oscillations mediate information flow from the hippocampal formation to multiple cortical and subcortical efferent areas is yet to be investigated.

Sharp wave/ripples occur in the hippocampus primarily during consummatory behavior, immobility, and slow-wave sleep (Buzsáki, 2015). Population bursts generated in recurrent CA3 circuits produce large transient field excitatory postsynaptic potentials in the termination zone of CA3 axons, such as the CA1 *stratum radiatum* and *stratum oriens*, that are observed as sharp waves (Buzsáki, 2015). Large depolarizations in CA1 pyramidal and inhibitory neurons induce a dynamic interaction among the activated neuronal ensemble, which consequently produces high-frequency (150–250 Hz) periodic field potentials—called ripples—in the *stratum pyramidale* (Stark et al., 2014; Ylinen et al., 1995). These sharp wave/ripple complexes are implicated in memory replay during sleep (Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994) and during quiet wakefulness (Diba and Buzsáki, 2007; Foster and Wilson, 2006; Jadhav et al., 2012; Kudrimoti et al., 1999; Malvache et al., 2016). The content of such replay spans spatial (Lee and Wilson, 2002), episodic-like (Takahashi, 2015), and emotional modalities (Girardeau et al., 2017; Wu et al., 2017). Sharp wave/ripples are also reported in the output structures of the hippocampal formation, including the subiculum, presubiculum, and entorhinal cortex, of behaving rats (Anderson and O'Mara, 2003; Chrobak and Buzsáki, 1996) and can be observed in the subiculum of horizontal brain slices (Maslarova et al., 2015). *In vitro* electrophysiology has revealed that some subicular cells are activated before CA1 sharp wave occurrence (*i.e.*, 'preceding' activity), while some others are activated after sharp waves (*i.e.*, 'following' activity) (Norimoto et al., 2013).

Surgical incision of the CA1-to-subiculum connection abolished the “following” but not “preceding” subicular activity (Norimoto et al., 2013). These results suggest that the subiculum is involved in both the generation and propagation of sharp wave/ripple complexes.

In contrast to extracellular studies, intracellular recordings—such as whole-cell recording and sharp electrode recording—enable us to investigate intracellular correlates of extracellular oscillations. Specifically, *in vivo* whole-cell recordings have demonstrated membrane potential dynamics at various frequency bands in the hippocampus, namely sub-theta (~3 Hz) (Matsumoto et al., 2016), theta (Harvey et al., 2009), gamma (Penttonen et al., 1998), and ripples (English et al., 2014). In the subiculum, whole-cell and juxtacellular recordings in awake mice have revealed that, during CA1 ripples, bursting neurons and regular-spiking neurons are activated and inhibited, respectively, indicating that bursting neurons are preferentially used to output information during ripple events (Böhm et al., 2015). The intracellular dynamics of subicular neurons for other types of oscillations remain unknown.

5.2 Single-cell representation

One of the most striking firing patterns in the hippocampal formation occurs in spatial representation. The best characterized neural substrate of spatial representation is hippocampal place cells, which fire whenever an animal crosses a certain place in the environment (O’Keefe and Dostrovsky, 1971). Each of the hippocampal CA1, CA2, and CA3 areas has a different type of place coding (Alvernhe et al., 2008; Barnes et al., 1990; Hussaini et al., 2011; Lee et al., 2004a, 2004b; Lee and Knierim, 2007; Leutgeb et al., 2005, 2004; Mankin et al., 2015; Mizuseki et al., 2012; Park et al., 2011; Vazdarjanova and Guzowski, 2004).

Subicular neurons have also been shown to encode an animal’s location in the environment (Fig. 2B). Approximately half of subicular pyramidal neurons show stable spatial firing across multiple light-dark transitions, suggesting that these neurons use egocentric cues to maintain their spatial representation (Brotons-Mas et al., 2010). In addition to rate coding, a fraction of subicular neurons is phase-locked to extracellular theta oscillations (Anderson and O'Mara, 2003) and exhibits robust theta phase precession (Kim et al., 2012).

The spatial code in the subiculum differs from that in the hippocampus in many ways. Subicular neurons generally have lower spatial selectivity (Barnes et al., 1990) and multiple place fields (Kim et al., 2012), contain a stronger directional signal (Sharp and Green, 1994), and rarely remap in two geometrically and visually distinctive contexts (Brotons-Mas et al., 2010; Sharp, 2006, 1997). Moreover, subicular neurons predict an animal's future location earlier than hippocampal neurons (Sharp, 1999). The spatial firing properties of subicular neurons are different along the proximodistal axis: neurons in the distal subiculum exhibit higher firing rates and spatial coherence as well as larger firing field sizes than those in the proximal subiculum (Kim et al., 2012; Sharp and Green, 1994). This proximal-distal difference in subicular firing may reflect the topographically biased inputs from the CA1 area and medial/lateral entorhinal cortices (Knierim et al., 2006). While hippocampal spatial codes are known to differ along the dorsoventral axis (Royer et al., 2010; Strange et al., 2014) and superficial-deep axis (Danielson et al., 2016; Geiller et al., 2017; Mallory and Giocomo, 2018; Mizuseki et al., 2011), how subicular spatial codes are organized along these axes remains unknown. Although some studies have classified subicular pyramidal units into bursting cells and non-bursting (*i.e.*, presumably, regular-spiking) cells (Anderson and O'Mara, 2003; Gigg et al., 2000; Sharp and Green, 1994), similar to *in vitro* experiments (Menendez de la Prida, 2006), no differences in spatial firing properties between these two cell types have been found

(Sharp and Green, 1994).

Besides place code, the dorsal subiculum represents other spatial and non-spatial properties including physical boundaries in a context (Brotons-Mas et al., 2017; Lever et al., 2009), the current axis of direction of movement (Olson et al., 2016), novel objects (Chang and Huerta, 2012), rewards (Martin and Ono, 2000), and working memory (Deadwyler and Hampson, 2004). These findings are briefly summarized below.

Based on computational models of the formation of hippocampal place fields, boundary vector cells that fire maximally when an environmental boundary is perceived at a certain distance and allocentric direction from the animal were predicted to exist (Barry et al., 2006). Later, the existence of such boundary vector cells was experimentally demonstrated by extracellular recordings from the dorsal subiculum (Lever et al., 2009) (Fig. 2B). Similarly, a portion of subicular cells demonstrate barrier-associated firing when a square open field is divided into four sub-chambers by inserting barriers. These neurons are called barrier-related cells (Brotons-Mas et al., 2017). When human subjects are located near physical boundaries in a virtual environment, strong theta oscillations are observed in the subiculum (Lee et al., 2018), which may reflect the firing of a neuronal population representing the physical boundaries. A recent study further demonstrated the role of the subiculum in the axis of travel (Olson et al., 2016), showing that approximately 9% of neurons in the dorsal subiculum discharge when an animal runs in a specific direction—as well as in the 180° opposite direction—in a complicated maze with multiple interconnected tracks (Fig. 2B). This axis-tuned neural activity is lost in an open arena, and thus, thought to encode track segment orientation relative to physical boundaries. The subicular axis-tuned cells are distinct from head-direction cells abundant in parahippocampal areas (*i.e.*, presubiculum, parasubiculum, and medial entorhinal cortex) because the head-direction cells in these areas typically represent only one orientation and maintain their directional tuning in an open arena (Boccara et al., 2010; Peyrache et al., 2017, 2015; Simonnet et al., 2017; Taube et al., 1990a, 1990b; Tukker et al., 2015).

One of the characteristic features of subicular spatial coding is multiplexed, conjunctive representation of space. While conjunctive spatial representations exist in the CA1 area (Acharya et al., 2016) and medial entorhinal cortex (Sargolini et al., 2006), the subiculum has a greater variety of such representations. For instance, axis-tuned neurons conjunctively encode routes and environmental boundaries (Olson et al., 2016), and boundary vector cells represent relationships among distance, allocentric direction, and boundary (Lever et al., 2009). Moreover, many place-tuned neurons in the subiculum also have directional selectivity (Sharp and Green, 1994), and subicular neurons with multiple place fields can be regarded as multiplexed place cells (Kim et al., 2012). As unitary spatial components such as place, head direction, distance, and boundary are all encoded in one synapse upstream of the subiculum (*i.e.*, the CA1 area and entorhinal cortex), a unique role of the subiculum may be integrating various information into a compressed spatial code that can be efficiently read out by downstream areas (Kim et al., 2012). Through such integration, the subiculum may support spatial navigation, particularly in a large, complicated natural environment, that requires efficient binding of multiple types of spatial information.

In line with previous behavioral research (*e.g.*, Potvin et al., 2010), it has been shown that when mice perform a novel object recognition task some subicular units fire at a higher rate for novel objects than familiar ones (Chang and Huerta, 2012; but see Anderson and O'Mara, 2004). Another example of non-spatially tuned neurons is related to reward. One-third of subicular neurons exhibit an anticipatory increase in firing in response to predictable rewards delivered by electric stimulation of the medial forebrain bundle, whereas a greater proportion of accumbens cells reacts in advance of rewards by increasing or decreasing their firing rates (Martin and Ono, 2000). However, such reward-related firing in the subiculum is absent when food is used as a reward (Barnes et al., 1990; Sharp and Green, 1994) presumably because food is a less powerful reward than direct stimulation of the medial forebrain bundle. It has also been shown that the subiculum and CA1 area fire in a shared but complementary manner when rats perform a delayed non-matching-to-place task with a retention delay varying from 1 to 30 s (Hampson et al., 1999). The firing response of the dorsal subiculum was associated with delays shorter than 15 s, whereas dorsal CA1 neurons responded to longer delays (Deadwyler and Hampson, 2004), suggesting the complementary contribution of these two regions to working memory.

As summarized in this section, the spatial code in the subiculum shares some similarities with the hippocampal code, but contains more compressed, conjunctive representation. Moreover, the subiculum shows a variety of non-spatial code. As the literature on the subiculum grows, a more unified view of some of the apparently distinct subicular codes may emerge. Alternatively, the disparate subicular firing patterns may represent the fundamental heterogeneity of the subicular network function. In any case, there is extensive room for further research on this intriguing brain region.

6. Summary and future perspectives

Here, we reviewed the anatomy, plasticity, behavioral role, and activity patterns of the subiculum. While the subiculum has become a brain region of increasing research attention, there are many intriguing questions about the subiculum that remain to be answered. We herein suggest possible future perspectives.

(1) Input: A variety of information (*e.g.*, space, time, object, novelty) is represented in the CA1 area and medial/lateral entorhinal cortices, which are one synapse upstream of the

subiculum. Determining what type of information in what upstream areas is transmitted to what parts/cells of the subiculum would help to comprehensively understand the network mechanisms of the subiculum.

(2) Intrinsic computation: The subicular pyramidal cells exhibit several forms of synaptic plasticity and form recurrent circuits. These network properties imply that the subiculum actively modifies and integrates inputs from upstream regions. Revealing what intrinsic computations are performed and, as a consequence, how neuronal information is distributed in bursting/non-bursting cells along the proximal-distal and superficial-deep axes would be a key step in uncovering the fundamental function of the subiculum.

(3) Output: The subiculum projects to multiple brain regions, but individual subicular neurons project to only one or a few of these target regions. Such a widespread, but specific, projection pattern raises the possibility that the subiculum sends distinct types of information to specific target areas. Revealing what information is output to what projection targets at each behavior/sleep state is crucial for understanding the impact of the hippocampal formation on downstream targets.

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Figure Legends

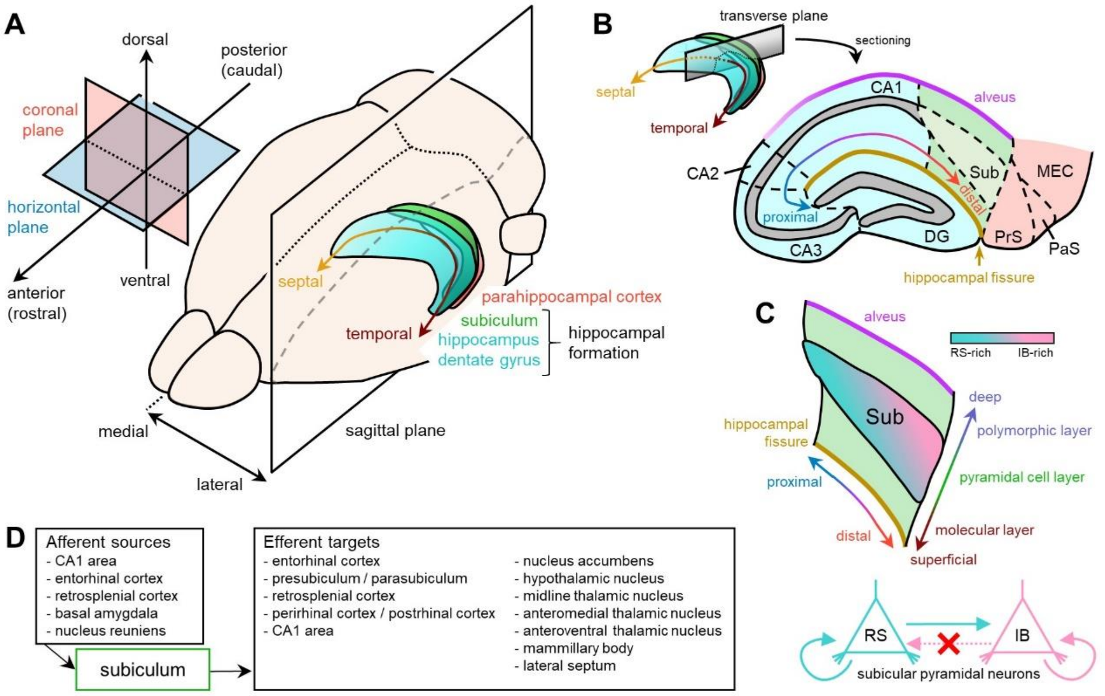

Figure 1. Anatomy of the rat subiculum. *A*, Diagonal view of the rat brain. The hippocampal formation (*green* and *pale blue*) and parahippocampal cortex (*red*) are inside the brain. The hippocampal formation includes the hippocampus (*pale blue*), dentate gyrus (*pale blue*), and subiculum (*green*). Three representative reference axes and corresponding cardinal planes are shown: the anteroposterior (rostrocaudal (in rat)), dorsoventral, and mediolateral axes are perpendicular to the coronal, horizontal, and sagittal planes, respectively. The hippocampal formation has a C-shaped curve; the end closer to the septum is referred to as the septal pole, whereas the end abutting on the temporal lobe is called the temporal pole. Note that the hippocampal dorsal and ventral horns correspond to the septal and temporal poles, respectively, in rodents (McNaughton, 2006; Strange et al., 2014). *B*, An example transverse section of the dorsal hippocampal formation and parahippocampal cortex. The hippocampus, dentate gyrus, subiculum, and parahippocampal cortex (such as presubiculum, parasubiculum, and medial entorhinal cortex) are shown. The hippocampus is further subdivided into the CA1, CA2, and CA3 subareas. In the hippocampus, the proximodistal axis is defined in accordance with the proximity of the dentate gyrus. The hippocampal fissure, or the hippocampal sulcus (*gold*), isolates the CA1 area and subiculum from the dentate gyrus. The alveus (*purple*) is composed of white myelinated axonal fibers of hippocampal and subicular pyramidal neurons. Note that the transverse plane is perpendicular to the septotemporal (longitudinal) axis shown as a *yellow*-to-*brown* line. *C*, The subiculum has a three-layered appearance including a polymorphic layer, pyramidal cell layer, and molecular layer. The

molecular layer is closest to the hippocampal fissure. The subicular pyramidal cell layer is flanked by the molecular layer and the polymorphic layer. The polymorphic layer is nearer to the alveus. The superficial and deep layers are defined by their proximity to the hippocampal fissure and alveus, respectively. Within the subicular pyramidal cell layer, more regular-spiking neurons (*pale blue*) are located in a more superficial and proximal subfield, whereas more intrinsically bursting neurons (*pink*) are located in a deeper and more distal subfield. There is recurrent circuitry within regular-spiking and bursting neurons. Regular-spiking neurons make synapses with bursting neurons but not *vice versa* (Böhm et al., 2015). *D*, Interregional projections from and to the dorsal subiculum are shown. *Abbreviations*: Sub, subiculum; DG, dentate gyrus; PrS, presubiculum; PaS, parasubiculum; MEC, medial entorhinal cortex; RS, regular-spiking neurons; IB, intrinsically bursting neurons.

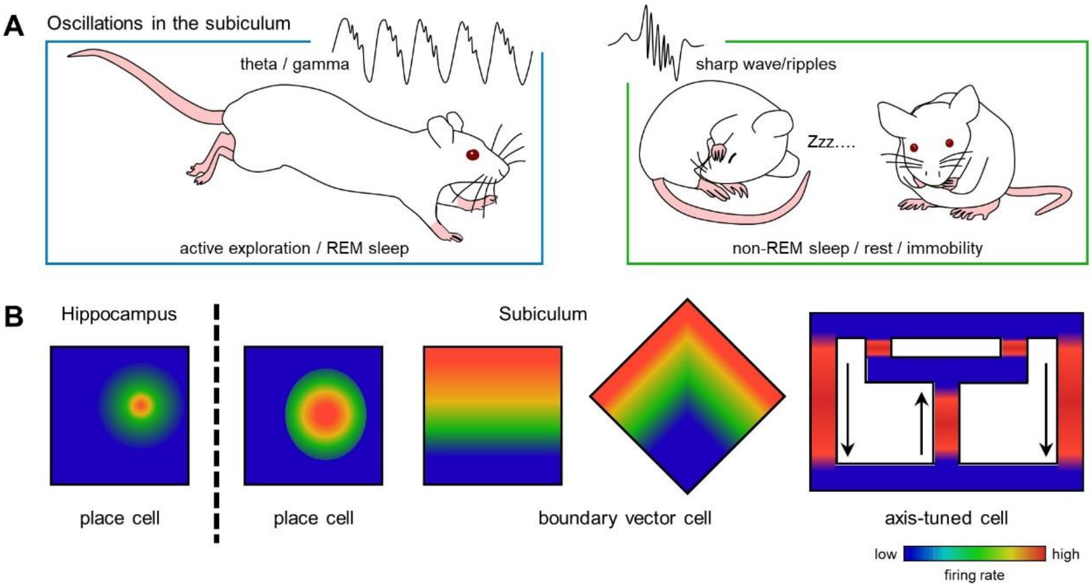

Figure 2. Physiology of the rat subiculum. *A*, Extracellular oscillations in the rodent subiculum. Theta and gamma oscillations are observed during active exploration and REM sleep, whereas sharp wave/ripple complexes are observed during non-REM sleep, rest, and immobility. *B*, Comparison of firing maps between hippocampal and subicular spatial cells. A hippocampal place cell in a square open arena (left-most panel), a subicular place cell (second panel), a subicular boundary vector cell (Lever et al., 2009) (third panel), a boundary vector cell in a different environment (Lever et al., 2009) (fourth panel), and a subicular axis-tuned cell (Olson et al., 2016) (fifth panel). The arrows in the fifth panel indicate the animal's direction of movement. Warm and cold colors indicate high and low firing rates, respectively. *Abbreviations*: REM, rapid eye movement.