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Cellular components and circuitry of the presubiculum and its functional role in the head direction system

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Abstract

Orientation in space is a fundamental cognitive process relying on brain-wide neuronal circuits. Many neurons in the presubiculum in the parahippocampal region encode head direction and each head direction cell selectively discharges when the animal faces a specific direction. Here, we attempt to link the current knowledge of afferent and efferent connectivity of the presubiculum to the processing of the head direction signal. We describe the cytoarchitecture of the presubicular six-layered cortex and the morphological and electrophysiological intrinsic properties of principal neurons and interneurons. While the presubicular head direction signal depends on synaptic input from thalamus, the intra- and interlaminar information flow in the microcircuit of the presubiculum may contribute to refine directional tuning. The interaction of a specific interneuron type, the Martinotti cells, with the excitatory pyramidal cells may maintain the head direction signal in the presubiculum with attractor-like properties.

Keywords Postsubiculum · Hippocampus · Patch clamp · Microcircuit · Head direction

The presubiculum is a distinct area in the parahippocampal region

The presubiculum is a cortical region of the hippocampal-parahippocampal formation in the brain's temporal lobe (Fig. 1a). The hippocampus is subdivided into dentate gyrus, Ammon's Horn (CA3, CA2, CA1), and subiculum; the parahippocampal area is its continuation, composed of presubiculum, parasubiculum, entorhinal (medial and lateral parts), peri- and postrhinal cortices (Fig. 1b; Witter and Amaral 2004; Van Strien et al. 2009). The presubiculum corresponds to Brodmann's areas 27 and 48 (Brodmann 1909), following the temporoventral-to-septodorsal hippocampal axis in rodents. The most dorsal part, corresponding to Brodmann's area 48, is also called "postsubiculum" (Brodmann 1909; Rose and Woolsey 1948; Blackstad 1956)

and can be distinguished based on differences in afferent and efferent connectivity (van Groen and Wyss 1990a, b). Following the proximo-distal axis of the hippocampus (from dentate gyrus to subiculum), the presubiculum is located next to subiculum and is followed by the parasubiculum (Fig. 1a); these three areas are classically grouped together as the "subicular complex." The retrodorsal part of the presubiculum is bordered by the retrosplenial cortex.

The six-layered cytoarchitectonic organization of the presubicular cortex (Fig. 1b) marks an abrupt transition from the cloud like organization of the subiculum (but see layers in O'Mara et al. 2001; Ishihara and Fukuda 2016). Afferent axon terminals are numerous in the dorsal part of the presubiculum. An "extremely dense plexus formed by [] many afferent axons" (Cajal 1899) in superficial layers distinguishes the presubiculum from the neighboring subiculum and parasubiculum and defines the dorsal limit of the presubiculum, towards the neighboring retrosplenial cortex (Fig. 1c; Cajal 1899; Blackstad 1956). The transition from pre- to parasubiculum can also be identified with a specific marker of presubicular layer 2, calbindin (Boccara et al. 2010, 2015; Preston-Ferrer et al. 2016). Layer 2 of the presubiculum is densely packed with small neuronal cell bodies, whereas the cellular density of the superficial layers 2/3 in the adjacent parasubiculum is more homogeneous (Ishihara and Fukuda

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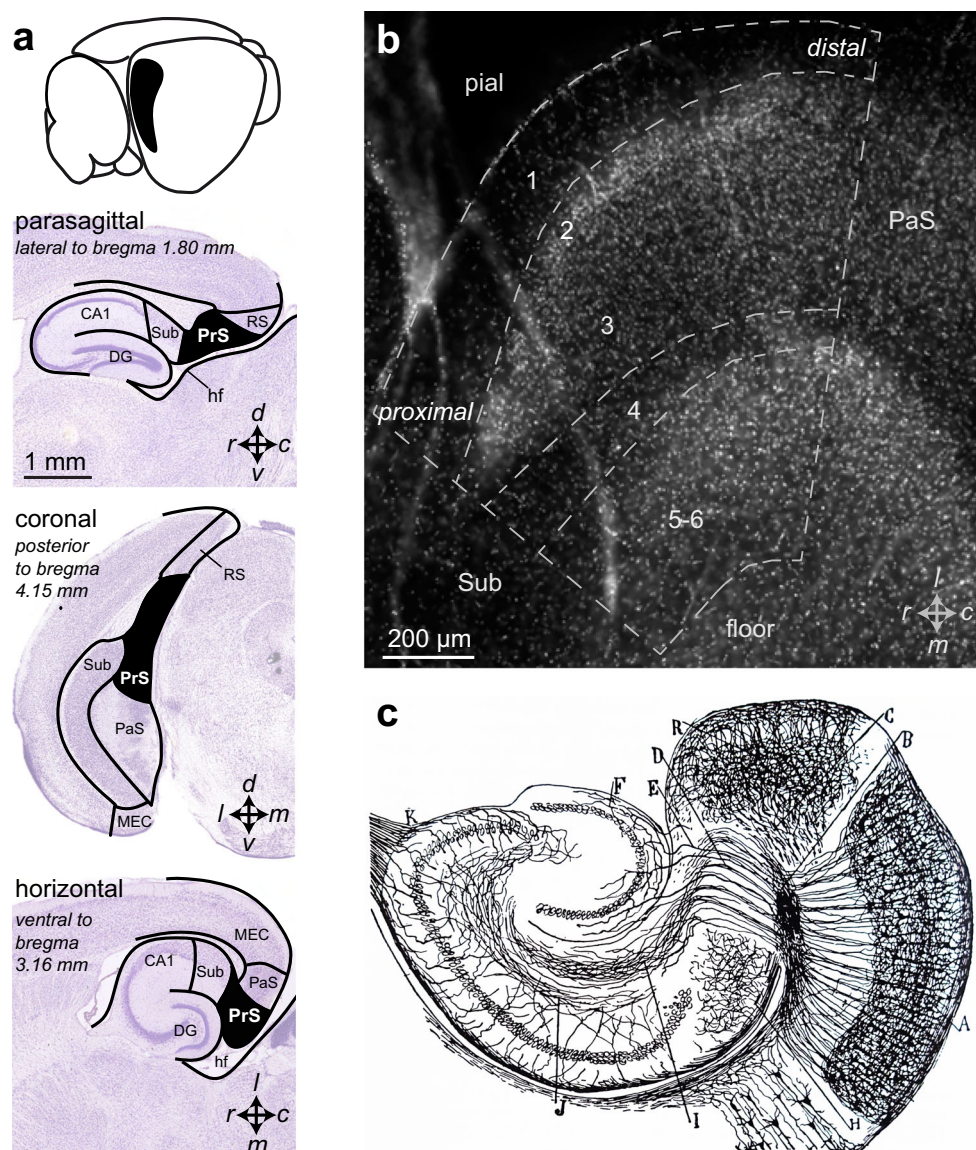


Fig. 1 Anatomy of the presubiculum. **a** Drawing of the brain from a top-caudal-lateral perspective shows the position of the presubiculum in black. Below, the presubiculum is highlighted in black in the different sections from parasagittal (**a'**), coronal (**a''**) and horizontal (**a'''**) slices processed with Nissl staining (modified from Paxinos and Franklin 2013; with permission). **b** Horizontal section of the presubiculum showing layers 1 to 6; modified from Simonnet et al. (2013), with permission. hf hippocampal fissure; DG dentate gyrus; MEC medial entorhinal cortex; PaS parasubiculum; PrS presubiculum RS retrosplenial cortex; Sub subiculum; d dorsal; v ventral; m medial; l lateral; r rostral; c caudal. **c** Figure 493 from Ramón y Cajal (1899). The original drawing by Santiago Ramón y Cajal is conserved at the Legado Cajal, Instituto Cajal, Consejo

Superior de Investigaciones Científicas-CSIC/Spanish National Research Council, Madrid, Spain. Original legend: Horizontal section through the medial entorhinal area and Ammon's horn immediately ventral to the place of the dorsal hippocampal commissure in a 15-day-old-mouse. Golgi Staining. A, medial entorhinal area; B, convergence site for ventral fascicles of the perforant path; C, afferent bundles to the presubiculum; D, perforant fibers; E, fibers to the dentate gyrus; F, fibers ending in the dentate gyrus; H, alvear temporoammonic path and the plexus it generates in the subiculum; I, plexus formed by perforant fibers in the stratum lacunosum moleculare of Ammon's horn; J, collateral plexus in Ammon's horn; K, fimbria; R, deep plexus of the subiculum

2016). Cajal (1899) noted that the characteristic afferent fiber plexus avoided the dense presubicular layer 2 (Fig. 1c), an observation that holds true also for virally labeled thalamic axon terminals that project densely to presubicular layers 1 and 3 but tend to avoid layer 2 (Simonnet et al. 2017).

The six layers of the presubiculum appear in a specific and unique manner during development. Radial migration of

neuronal progenitors from the ventricular zone shapes laminar compartments (Angevine and Sidman 1961; Rakic 1974), before subsequent changes generate the adult cortical organization. Cortical areas may be classified according to the development of their laminar organization and their aspect in the adult stage (Lorente de No 1933; Filimonoff 1947). Historical anatomical studies group hippocampus and subiculum

together as the archicortex, a part of the allocortex, with an incomplete structure both during developmental and adult stages (Cortex Incompletus, less than six layers), as opposed to the Isocortex (Cortex Completus, with six layers). In some studies, the presubiculum was grouped together with the entorhinal area and termed periarthicortex (part of the Periallocortex or Cortex Intermedius), an intermediate region undergoing structure changes during development before reaching the adult stage (Lorente de No 1933; Filimonoff 1947). While these early classifications were based solely on anatomy, they already distinguished the presubiculum from neighboring structures. The development of the presubiculum is indeed peculiar. It develops late compared to the entorhinal cortex and its deep layers appear at the same time as the neighboring subiculum (Bayer 1980). In the adult, it is interesting to see the presubiculo-subiculum transition in horizontal slices where presubicular deep layers appear as a continuation of the subiculum (Fig. 1a). Brodmann, in his studies on Marsupials, described this transition as an “abrupt interruption of layer II-V at the beginning of the subiculum, with only layer I and VI continuing into Ammon’s horn in greatly widened form” (Brodmann 1909). Immunohistochemistry for various substances and markers now allows precise mapping of the border between the presubiculum and subiculum. There is a conspicuous absence of GluR1 immunoreactivity in the presubiculum (Ishihara and Fukuda 2016). On the other hand, acetylcholinesterase staining is strongly present in superficial layers of presubiculum (Slomianka and Geneser 1991), as well as staining for vesicular glutamate transporter 2 (VGluT2) (Ishihara and Fukuda 2016).

Head directional coding by the presubiculum

The hippocampus and parahippocampal regions are important for spatial orientation in rodents (O’Keefe and Nadel 1978; Jarrard 1993; Buzsáki and Moser 2013), non-human primates (Robertson et al. 1999; Killian et al. 2012) and humans (Maguire et al. 2000; Wolbers et al. 2007; Doeller et al. 2010; Jacobs et al. 2013). The presubiculum, more specifically, is involved in head direction coding (Wiener and Taube 2005; Taube 2007; Finkelstein et al. 2015). Extracellular recordings in freely moving rats have shown that up to 50–60% of neurons in the dorsal presubiculum discharge according to the animal’s directional heading (Ranck 1984; Taube et al. 1990a; Taube 2007; Boccara et al. 2010; Tukker et al. 2015; Preston-Ferrer et al. 2016). Each head direction (HD) cell has one preferred direction, defined as the one with the highest firing rate. The basal firing rate is close to zero and increases with a triangular or Gaussian distribution of frequencies around the preferred direction (Blair and Sharp 1995; Taube 1995). The whole HD cell population allows a complete representation of horizontal head orientations. Each neuron has a stable tuning curve, with

variable maximal firing rates across different neurons (from 5 to 115 Hz). Interestingly, HD cell discharge persists without adaptation as long as the preferred direction is maintained (Taube et al. 1990a), contrasting with the transient firing at stimulus onset during other forms of sensory information processing (Gabernet et al. 2005; Whitmire and Stanley 2016; Lampl and Katz 2017). Unlike a compass, head direction cells are not sensitive to the geomagnetic field but depend on visual landmarks for anchoring their preferred direction in a given environment (Sharp et al. 2001a). Rotation of the major polarizing visual cue within an environment leads to a corresponding shift of the preferred direction (Taube et al. 1990b). Head direction cell firing does not change in the absence of visual landmarks but preferred direction is susceptible to drift over time. Visual cues are therefore used to anchor but not to generate the head direction signal. Other sensory inputs such as auditory or olfactory inputs may also participate in anchoring HD signals but visual inputs are exerting greater control (Goodridge et al. 1998). Motor activity seems to improve signal quality but is not necessary for its generation: restraining an animal reduces peak firing rates but does not abolish head direction cell activity (Taube et al. 1990b).

The presubiculum is not the only area signaling head direction. The circuit involved in generating and maintaining the head direction signal also includes the dorsal tegmental nucleus (DTN) (Sharp et al. 2001b), lateral mammillary nucleus (LMN) (Stackman and Taube 1998), anterior dorsal thalamic nucleus (ADN) (Taube 1995), lateral dorsal thalamus (LDN) (Mizumori and Williams 1993; Shires et al. 2013), retrosplenial cortex (both granular and agranular regions) (Cho and Sharp 2001; Jacob et al. 2017) and entorhinal cortex (Sargolini et al. 2006) (Simplified circuit diagram, Fig. 2a).

The role of the presubiculum in the brain-wide HD circuit

The head direction signal is thought to originate in a subcortical attractor network structure, within the tegmento-mammillary circuit (Sharp et al. 2001a; Bassett et al. 2007). Several studies have suggested that its generation is based on head movement information of vestibular origin while other sensory systems may contribute additional information to increase stability and precision (Stackman and Taube 1997; Muir et al. 2009). In brief, vestibular angular head velocity signals are converted to a head directional signal by the DTN and LMN (Clark and Taube 2012). From the LMN, the head direction signal is then relayed via the ADN sending projections to the retrosplenial cortex (van Groen and Wyss 1990c; Shibata and Honda 2012) and presubiculum (van Groen and Wyss 1990b; Shibata and Honda 2012). Functionally, the ADN is a critical relay in the head direction circuit, as its lesion disrupts head direction cells in cortical areas, including

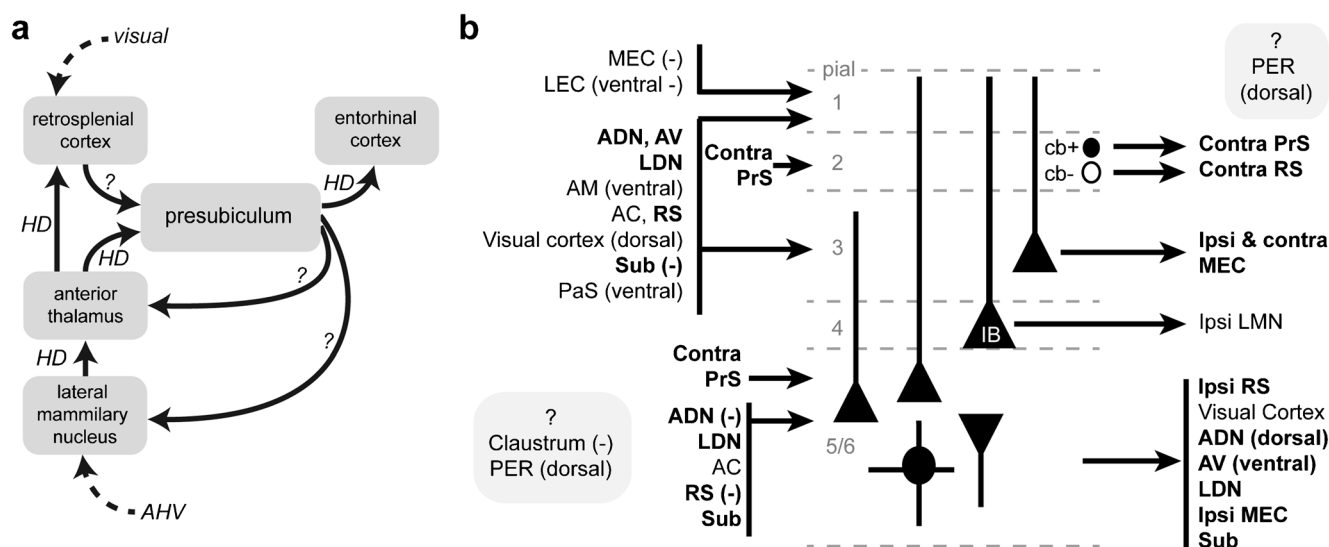


Fig. 2 Main circuit connections of the presubiculum. **a** The head direction (HD) signal is generated in interactions between the lateral mammillary nucleus and the dorsal tegmental nucleus, from an angular head velocity signal of vestibular origin. HD information is conveyed via the anterior thalamus to the presubiculum. Layer 3 presubicular neurons convey the HD signal to the entorhinal cortex. The nature of the feedback signal to the lateral mammillary nucleus carried by layer 4 neurons and the nature of the feedback signal to the thalamus via layer 5/6 neurons still needs to be clarified. The presubiculum also receives projections from the retrosplenial cortex that might update the HD signal with information of

the presubiculum (Goodridge and Taube 1997), parasubiculum and entorhinal cortex (Clark and Taube 2012). Indeed, head direction cells in the presubiculum seem to be monosynaptically driven by those in the ADN (Peyrache et al. 2015). Their main inputs probably come from thalamic cells with identical or similar tuning, although the degree of convergence of thalamic to presubicular head direction cells and presubicular interneurons has yet to be tested directly. While thalamic neurons signal HD with an anticipatory time interval of 25–40 ms (Blair and Sharp 1995; Taube and Muller 1998), presubicular neurons signal the current HD.

In rodents, the directional signal in presubiculum is coherently present before the opening of the eyes in the second postnatal week, indicating that vision is not necessary for the development of directional tuning, even though it later becomes crucial for anchoring the HD signal to the environment (Bjerknes et al. 2015; Tan et al. 2015). The presubiculum is one entry point of visual information into the head direction processing system and plays a significant role in refining the signal with visual information. The presubiculum receives direct visual information from primary and secondary visual cortices (Vogt and Miller 1983) and indirect visual information from the retrosplenial cortex (Vogt and Miller 1983; van Groen and Wyss 1990c; Jones and Witter 2007; Sugar and Witter 2016). By its direct projections to the ADN (van Groen and Wyss 1990b; Ishizuka 2001; Yoder and Taube

2011) and LMN (Allen and Hopkins 1989; Gonzalo-Ruiz et al. 1992; Yoder and Taube 2011), the presubiculum may be a crucial node to combine visual landmark information with head direction signals and send feedback to the subcortical generators of the head direction signal (Fig. 2). Lesions of the presubicular cortex impair the visual landmark control of a cell's preferred direction in the ADN (Goodridge and Taube 1997) and LMN (Yoder et al. 2011) and in the entire interconnected circuit. The role of presubicular projections to the retrosplenial cortex (Wyss and van Groen 1992) and LDN (van Groen and Wyss 1990a, b) are still unclear. The LDN is described as part of the somatosensory system (Bezudnaya and Keller 2008), but despite reciprocal connections with the presubiculum (Golob et al. 1998) head direction signal dependence upon somatosensory inputs has not been reported.

The presubiculum integrates head direction and visual information before relaying the signal to the entorhinal-hippocampal network (Yoder et al. 2011, 2015). Three lines of evidence underscore the organizational relation between head direction, grid and place cell signals. First, ontogeny of spatial representations indicates that presubicular, vestibular-based directional signals may be instrumental for the subsequent development of grid cells and place cells (Langston et al. 2010; Wills et al. 2010). The presubicular projections to the medial entorhinal cortex (Honda and Ishizuka 2004) originate from head direction cells (Tukker et al. 2015; Preston-Ferrer et al. 2016), thus

providing a source of head directional input likely crucial for grid cell generation in the medial entorhinal cortex (Bonnevie et al. 2013; Winter et al. 2015). Second, head direction cells, grid cells and place cells are all influenced by visual landmarks. Rotation of a visual landmark produces an equivalent rotation of preferred direction, grid and place field (Knierim et al. 1995; Sargolini et al. 2006). Lesions of anterior thalamus and presubiculum degrade CA1 place cell information content and place fields of presubiculum-lesioned animals shift unpredictably and are poorly controlled by visual landmarks (Calton et al. 2003). Lesion of the LMN degrades the angular disambiguation by place cells of visually identical compartments (Harland et al. 2017). Last, the head direction coding in the presubiculum and its consequences on the whole hippocampal-parahippocampal function are important for the animal's behavior. Presubicular lesions, similar to hippocampal lesions, impair spatial learning and memory (Taube et al. 1992).

Afferent and efferent connectivity, cellular physiology and morphology across presubicular layers

The anatomical organization and cellular properties of presubicular neurons may account for some aspects of the processing of head orientation signals. Here follows a layer-by-layer description of afferent and efferent projections and neuronal firing patterns across the presubicular cortex. An overview of the presubicular connectivity is given in Table 1, Table 2 and Fig. 2.

The presubicular layers were initially described by Ramón y Cajal according to their neuronal content and density (Cajal 1899). Cajal's description still holds true, both for non-human primate and rodent presubiculum. Layers 1, 2 and 3 are classically grouped together as the superficial layers and layers 5 and 6 as deep layers (Fig. 1b). Anatomical modules have been described in superficial layers during early postnatal stages in mouse (Nishikawa et al. 2002), in adult rats (Ray et al. 2017) and in adult monkeys (Ding and Rockland 2001).

Superficial layers

Presubicular layer 1, the thin molecular layer immediately below the pial surface, is almost devoid of neurons, containing only a small number of putative interneurons (Cajal's "short axon cells") and glial cells. It is, as for all cortical areas, an input layer targeted by long-range inputs as well as by local dendritic inhibition (Nassar et al. 2015; Simonnet et al. 2017).

Presubicular layer 2 is a layer with densely packed pyramidal and fusiform cells (Cajal 1899). Its thickness is similar to that of layer 1. The main inputs to layer 2 originate in the contralateral presubiculum (van Groen and Wyss 1990a;

Shibata 1993; van Groen and Wyss 1995) via commissural fibers (Honda et al. 2008) and some fibers come from the subiculum and claustrum (van Groen and Wyss 1990a; Wang et al. 2017). Axon terminals of long-range retrosplenial and thalamic afferents tend to ramify in layers 1 and 3 but rather avoid the cell bodies of layer 2 (van Groen and Wyss 1990b; Shibata 1993; Shibata and Honda 2012, 2015). Whether these afferents contact layer 2 cell dendrites extending in other layers (layer 1 or 3) remains unknown. In the most dorsal part of mouse presubiculum, layer 2 cell bodies clearly form clusters that are separated by fiber stripes (Slomianka and Geneser 1991). About one third of these clustered neurons in layer 2 are Calbindin positive and project to the contralateral presubiculum. Calbindin-negative neurons project to the contralateral retrosplenial cortex (Preston-Ferrer et al. 2016). The presence of two or more cell populations in layer 2 could account for the diversity of their electrophysiological properties, with firing patterns that may be regular spiking, irregular spiking or initially bursting (Abbasi and Kumar 2013). Layer 2 cells are poorly sensitive to head direction (Preston-Ferrer et al. 2016), possibly due to the lack of anterior thalamic input. Interestingly, however, layer 2 neurons, while poorly modulated by head direction, can be entrained by theta oscillations (Preston-Ferrer et al. 2016). Theta oscillations are prominent in the hippocampal-parahippocampal region during exploration, and acetylcholine modulation from the septum is a major player in hippocampal theta rhythm (Vandecasteele et al. 2014). Septal fibers target the MEC and parasubiculum but less so the presubiculum (Gonzalez-Sulser et al. 2014). In contrast to other areas involved in space coding within the hippocampal and parahippocampal area, only few head direction cells of the presubiculum are modulated by theta oscillations (Boccaro et al. 2010; Tukker et al. 2015; Preston-Ferrer et al. 2016). Although it was suggested that layer 2 neurons could be grid cells or border cells (Boccaro et al. 2010), their role in spatial navigation remains to be determined.

Presubicular layer 3 is larger than layer 2, however with a much lower neuronal density (Cajal 1899). Layer 3 neurons are mostly small regular spiking pyramidal neurons (Abbasi and Kumar 2013; Simonnet et al. 2013; Huang et al. 2017; Peng et al. 2017), with relatively homogeneous electrophysiological properties in rat and mouse (Fig. 3; Simonnet et al. 2013, 2017). Most of layer 3 pyramidal neurons are head direction cells (Tukker et al. 2015; Preston-Ferrer et al. 2016), inheriting their tuning properties via direct synaptic contacts from anterior thalamic head direction cells (Peyrache et al. 2015; Simonnet et al. 2017). Layer 3 pyramidal cells also receive direct input from axons originating in the retrosplenial cortex that make synaptic contacts on their proximal dendrites (Kononenko and Witter 2012). The kind of information carried by these afferent signals and how they influence firing of layer 3 cells is still unknown. Other inputs to layer 3 come from the lateral thalamus (van Groen and

Table 1 Presubiculum receives inputs from:

	Afferent?	References	From which hemisphere(s)?	To dorsal/ventral PrS?	Layer(s) receiving axons
Thalamus					
ADN	Main input	van Groen and Wyss (1990a, b, 1995); Shibata (1993); Shibata and Honda (2012); Simonnet et al. (2017)	Ipsilateral	More to dorsal than to ventral PrS	Mainly layer L1, L3, L4, few in deep layers
AV	Main input	van Groen and Wyss (1990a, 1995); Shibata (1993); Shibata and Honda (2015)	Ipsilateral	AVp and AVm both project to dorsal and ventral PrS. Topographic projections	AVp targets L1 and L6. AVp targets L1, L3 and L5 (Shibata and Honda 2015)
AM	Yes	van Groen and Wyss (1990a); van Groen et al. (1999); Shibata (1993)	Ipsilateral	Ventral	Sparse, mainly in L5 and L1 (van Groen et al. 1999)
LDN	Main input	van Groen and Wyss (1990a, b); van Groen and Wyss (1992)	Ipsilateral	Dorsal and ventral PrS with laminar differences. Topographic projections	L1, L3, L4, with axon bundles coursing from L3 to L1; In ventral PrS, axons target mostly deep layers
Cingulate cortex	Yes	Vogt and Miller (1983); Jones and Witter (2007)	Mostly ipsilateral	Dorsal (ACd and ACv) > intermediate (ACd and ACv) > ventral (ACv); Caudal ACv targets dorsal PrS preferentially; Rostral ACv target intermediate and ventral PrS (Jones and Witter 2007)	ACd and ACv send axons to L1 and L3 mainly but also L5.
RS	Main input	Vogt and Miller (1983); van Groen and Wyss (1990a, b, c); Jones and Witter (2007); Sugar and Witter (2016)	Mostly ipsilateral	RSv and RSd target dorsal and ventral PrS; Caudal RSv and rostral RSd project to dorsal PrS only (van Groen 1990a, Jones and Witter 2007)	RS L5 neurons (van Groen 1990a) project to L1, L3 and deep layers of PrS (van Groen 1990a; Jones and Witter 2007; Sugar and Witter 2016)
Orbitofrontal cortex	Yes	Kondo and Witter (2014)	Ipsilateral	Dorsal and ventral with laminar differences	Caudal VO projects to superficial layers of dorsal PrS and deeper layers of ventral PrS.
Visual cortex	Yes	Vogt and Miller (1983)	Ipsilateral	Dorsal	L1 and L3 receive visual cortex inputs
Hippocampus	Unclear	van Groen and Wyss (1990a); Cenzuzca and Swanson (2007); Honda and Shibata (2017)	In rats, van Groen (1990a) reported retrogradely labeled pyramidal and non-pyramidal neurons in CA1 from dorsal PrS injections. In rats, Cenzuzca and Swanson (2007) described no projection from CA1 to PrS. Honda and Shibata (2017) described no projection in rats but some in rabbits.		

Table 1 (continued)

	Afferent?	References	From which hemisphere(s)?	To dorsal/ventral PrS?	Layer(s) receiving axons
Subiculum	Main input	Sorensen and Shipley (1979); van Groen and Wyss (1990b); Funahashi et al. (1999); Kim and Spruston (2011); Honda and Shibata (2017)	Ipsilateral	Dorsal and ventral	Terminals in L1, L3 and most of all in L5–6; From distal Subiculum (Kim and Spruston 2011)
Para-hippocampal region	Main input	Honda et al. (2008); Preston-Ferrer et al. (2016)	Bilateral with distinct patterns	Dorsal and ventral	Received in L2 and L5 from bilateral L2 and ipsilateral L5
PaS	Yes	van Groen and Wyss (1990a, b); Köhler (1985); Honda and Shibata (2017)	Bilateral	Ventral	Superficial layers
MEC	Yes	Wyss (1981); Funahashi and Stewart (1997); van Groen and Wyss (1990a, b); Honda and Shibata (2017)	Ipsilateral	Ventral	Sparse projections to L1 (Wyss 1981)
LEC	Yes	Wyss (1981); Honda and Shibata (2017)	Ipsilateral	Ventral	Sparse projections to L1
PER	Yes	Kosel et al. (1983); van Groen and Wyss (1990a, b)	Ipsilateral	Dorsal	?
POR					
Clausttrum	Yes	van Groen and Wyss (1990); Wang et al. (2017)	Dorsal and ventral; sparse projections	?	

Afferent connectivity pattern to the presubiculum. To our knowledge, areas not listed in this table do not project to the presubiculum. Main inputs send significant projections to the PrS and the others are secondary; however, very few functional studies have been done to define the significance of each one of the presubicular inputs described here. “Ipsilateral” means that at least ipsilateral projections have been reported

Table 2 Presubiculum sends projections to:

	Efferent?	References	Targeted hemisphere(s)?	From dorsal/ventral PrS?	Layer(s) of origin?
Thalamus	LMN Yes	Allen and Hopkins (1989); Gonzalo-Ruiz et al. (1992); Yoder and Taube (2011); Huang et al. (2017)	Ipsilateral only	Dorsal and ventral	Big pyramidal neurons form L4 or upper deep layer
	ADN Main output	van Groen and Wyss (1990a, b); Ishizuka (2001); Yoder and Taube (2011); Huang et al. (2017)	Ipsilateral	Dorsal only. Topographic projections (van Groen and Wyss 1990b)	Deep layers (Yoder and Taube 2011; Huang et al. 2017), L6 (van Groen and Wyss 1990b)
	AV Main output	van Groen and Wyss (1990a); Ishizuka (2001); Dillingham et al. (2015)	Ipsilateral	Ventral only	Deep layers, L6 (Van Groen and Wyss 1990a)
	LDN Main output	van Groen and Wyss (1990a, b); Ishizuka (2001)	Ipsilateral	Dorsal and ventral PrS	Deep layers
Retrosplenial cortex	Main output	Vogt and Miller (1983); van Groen and Wyss (1990a, 1992); Honda et al. (2011); Preston-Ferrer et al. (2016)	Bilateral	Topographic projections. Mainly dorsal, few projections from ventral. Topographic projections: rostral → caudal	Neurons in L2 and L5 project to ipsilateral RSV-b; L2 calbindin negative neurons project preferentially to RS
	Yes	Preston-Ferrer et al. (2016)	Ipsilateral	Dorsal	Deep layers project to primary and secondary visual cortex
Visual cortex	Yes	Vogt and Miller (1983)	Ipsilateral	Dorsal	Deep layers, at least layer 5 pyramidal neurons
Subiculum	Yes	Funahashi et al. (1999); Honda et al. (2011)	Ipsilateral	Ventral and intermediate	Deep layers project to primary and secondary visual cortex
Para-hippocampal region	Main output	Honda et al. (2008); Honda et al. (2011); Preston-Ferrer et al. (2016)	Bilateral	Dorsal and ventral	L2 project to contralateral and ipsilateral L2 and L5; L5 projects ipsilaterally only
					, mainly to L5, with few ascending projections to L2; Contralaterally projecting neurons are mostly L2 calbindin positive cells
PaS	Yes	Köhler (1985); van Groen and Wyss (1990a, b); Honda et al. (2011)	Bilateral (van Groen and Wyss 1990a, b)	Dorsal PrS projects to ventral PaS (van Groen and Wyss 1990b)	Superficial layers of PrS project to PaS, mostly to superficial layers
MEC	Main output	Swanson and Cowan (1977); Beckstead (1978); Köhler (1984, 1985); Bartsaghi et al. (1988); van Groen and Wyss (1990a, b); Honda and Ishizuka (2004); Kononenko and Witter (2012); Canto et al. (2012); Rowland et al. (2013); Honda and Shibata (2017); Huang et al. (2017)	Bilateral with layer specificity. PrS may be the only commissural input to MEC (Bartsaghi et al. 1988)	Topographic projections: Septal PrS projects to lateral MEC. Temporal PrS projects to medial MEC. Projection patches in entorhinal cortex (see Köhler 1984, 1985);	L3 projects bilaterally to MEC; Deep layers project ipsilaterally only
LEC	Yes	van Groen and Wyss (1990b); Honda and Ishizuka (2004)	Ipsilateral	Dorsal	Deep layers may send a few terminals to LEC L1 (Honda and Ishizuka 2004)
PER	Yes	van Groen and Wyss (1990a, b)	Bilateral	Dorsal PrS project to PER	?
POR					

Efferent connectivity pattern from the presubiculum. To our knowledge, the presubiculum does not project to areas not listed in this table. “Main output” indicates that the presubicular projections to these areas are significant. “Ipsilateral” means that at least ipsilateral projections have been reported. “Ipsilateral only” means that the presence of contralateral projections have been checked and excluded. AC anterior cingulate cortex (*d* dorsal, *v* ventral) = infradiata, ADN anterodorsal thalamus, AM antero-medial thalamus, AV antero-ventral thalamus (*p* parvocellular, *m* magnocellular), *DTN* dorsal tegmental nucleus, *L* layer, *LDN* latero-dorsal nucleus of the thalamus, *LEC* lateral entorhinal cortex, *LMN* lateral mammillary nucleus, *MEC* medial entorhinal cortex, *PaS* parasubiculum, *PER* perirhinal cortex, *POR* postrhinal cortex, *PrS* presubiculum, *RS* retrosplenial cortex (*d* dorsal, *v* ventral), retrosplenial cortex: nomenclature of Jones and Witter (2007); *RSv-a* = 29a & 29b = RSG = RGA, *RSv-b* = 29c = RGb, *Rsd* = 29d = RSA = Rdg, *Sub* subiculum, *Sup* superficial layers, *VO* ventral orbitofrontal cortex

Wyss 1990b; Shires et al. 2013). The layer 3 head direction signal is directly sent to the ipsilateral medial entorhinal cortex (Tukker et al. 2015; Preston-Ferrer et al. 2016). Ipsilateral and contralateral projections to the MEC (Köhler 1984, 1985; Caballero-Bleda and Witter 1993, 1994; Honda and Ishizuka 2004; Huang et al. 2017) may originate from different neurons and 20–30% of ipsilaterally projecting neurons may be GABAergic (van Haeften et al. 1997; Huang et al. 2017).

Layer 4

Layer 4 in parahippocampal cortices had been named “lamina dissecans” (literally meaning “splitting layer”) and described as a neuron-free layer with only fibers and glial cells (Rose 1926; Lorente de No 1933), separating superficial layers (1, 2 and 3) from deep layers (5 and 6). However, in the presubiculum, layer 4 may rather be considered as a thin layer lying below the lamina dissecans, containing big pyramidal neurons (Lorente de No 1933) projecting to the LMN (Table 2; Fig. 3). These neurons, identified using retrograde labeling (Yoder and Taube 2011; Huang et al. 2017), form a distinct population of intrinsic bursting neurons (Simonnet et al. 2013; Huang et al. 2017). From our work with combined retrograde labeling and recording of intrinsic firing patterns, we suggest that the intrinsically generated bursting behavior defines the subpopulation of pyramidal cells projecting to the LMN (Huang et al. 2017). The functional definition may be more meaningful than the definition of layer 4 as being located at a specific depth from the pial surface. Due to the curved nature of the presubiculum, the absolute depth and width of layer 4 may vary between its proximal and distal portion and

as a function of the slicing angle. The 600- μ m-deep limit between superficial and deep layers may approximate the border between deep and superficial layers in most cases (Peng et al. 2017). It leaves layer 4 undefined, however, which may explain why intrinsic bursting neurons have been reported in either superficial or deep layers of the presubiculum (Peng et al. 2017). Presubicular bursting neurons may be strongly or weakly bursting (Menendez De La Prida et al. 2003) and intrinsically, bursting neurons may differ from the initially bursting neurons reported in layers 2 and 3 of the presubiculum (Abbasi and Kumar 2013). Different types and spatial distributions of ion channels could underlie the different bursting behaviors (Menendez De La Prida et al. 2003). With their fast integrative properties and bursting behavior, layer 4 cells are good candidates to rapidly signal the fast visual update (< 80 ms) of the head direction signal directly to the generating area of the head direction signal, i.e., the lateral mammillary nucleus (Zugaro et al. 2003; Yoder et al. 2015). In the future, it will be important to identify the input signals received by presubicular layer 4 neurons, from long-range afferents or locally from layer 3 neurons.

Deep layers

The deep layers of the presubicular cortex in rodents can be divided in layer 5, containing large to medium sized pyramidal cells and layer 6, containing smaller fusiform and pyramidal cells (Cajal 1899). Deep layers may even be subdivided into three sublayers (5, 6, 7) in the primate presubiculum (Ding 2013). There is still little data addressing whether the morphological and electrophysiological

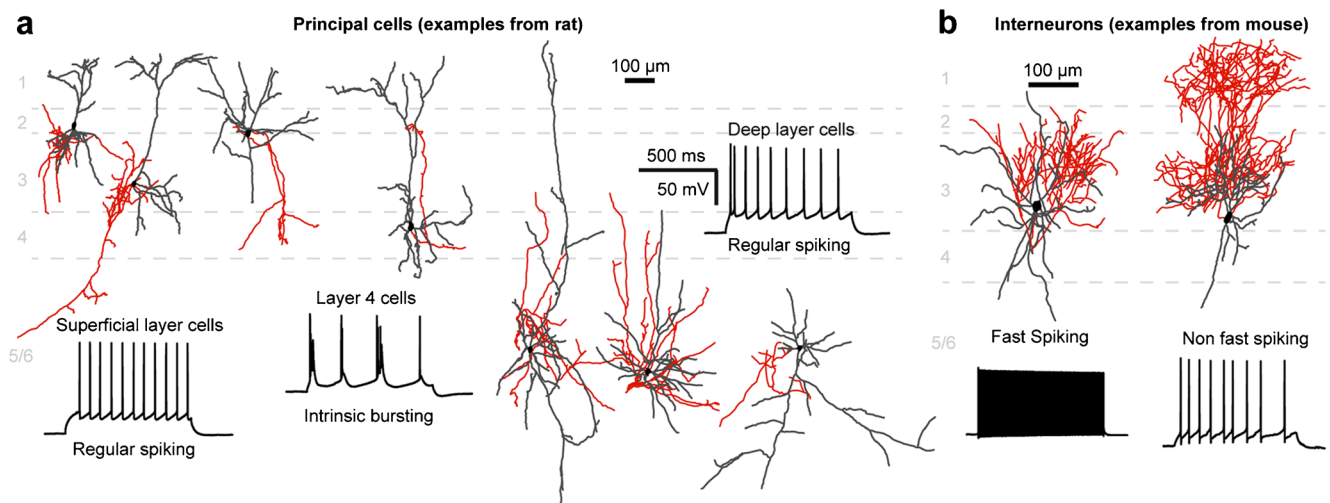


Fig. 3 Morphologies and firing patterns of principal neurons and interneurons in the presubiculum. **a** Examples of principal neurons and their representative firing patterns (reproduced with permission from Simonnet et al. 2013). Regular spiking neurons found in the presubiculum can be non-adapting (example from a superficial layer cell)

or adapting (example from a deep layer cell). **b** Parvalbumin (PV) expressing fast-spiking interneuron and Martinotti type low-threshold spiking interneuron with its non-fast spiking firing pattern (from Nassar et al. 2015). Axons in red, dendrites in black. Scale bars for time and voltage apply to all electrical traces

properties of neurons follow the laminar structure in deep layers, partly because of the difficult distinction between sublayers 5 and 6. The first recordings of head direction signals in the presubiculum were largely obtained from deep layers (Ranck 1984; Taube et al. 1990a). From more recent work using tetrode and juxtacellular recordings, head direction cells are also found in deep layers and additionally, in superficial layers (Boccara et al. 2010; Preston-Ferrer et al. 2016). The vast majority of deep layer neurons in slice recordings discharge with a regular spiking firing pattern, which seems compatible with the non-adapting HD cell firing (Fig. 3; Simonnet et al. 2013; Huang et al. 2017; Peng et al. 2017). Upper layer 5 (Honda et al. 2011) contains mostly pyramidal neurons with high input resistance making them easily excitable; deeper fields seem much more heterogeneous: neurons can be pyramidal, inverted pyramidal and multiform and their intrinsic properties are more diverse (Simonnet et al. 2013). Describing neurons defined by their projection targets might help to better understand the structure and function of deep layers. Deep layer cells projecting to the anterior thalamus differ from layer 4 LMN projecting cells (Yoder and Taube 2011) with distinct electrophysiological properties (Huang et al. 2017). Identifying other projecting neurons in deep layers, including those targeting the ipsilateral medial entorhinal cortex (Honda and Ishizuka 2004), subiculum (Funahashi et al. 1999), retrosplenial cortex (Vogt and Miller 1983; van Groen and Wyss 1990c), or visual cortex (Vogt and Miller 1983), might help to untangle the diversity of neuronal properties in deep layers. Deep layers receive less long-range afferent axons than the superficial layers and are therefore not a major input layer of the presubiculum. For example, afferents from thalamic nuclei or cingulate cortices project densely to superficial layers and sparsely to deep layers. Even so, some afferents target deep layers, as those from CA1 (in the rabbit, but not in rat, Honda and Shibata 2017), the subiculum (Köhler 1985; van Groen and Wyss 1990b; Funahashi et al. 1999) and contralateral presubiculum (van Groen and Wyss 1990a). While neurons in layer 3 and layer 4 seem to have unique targets (MEC and LMN, respectively) and rather homogeneous properties, neurons in layer 2 as well as in deep layers have multiple projection targets and also more heterogeneous cellular properties. The cellular diversity within presubicular layers might therefore match the diversity of their projection targets. Even so, multiple projections by specific cell types are not excluded.

Presubicular interneurons

The presubicular cortex contains ~11% of GABAergic neurons. GABAergic neurons constitute 80% of cells in layer 1

but less than 15% in the other layers (Nassar et al. 2015). The interneuronal diversity in the presubiculum matches that of other cortical areas, including parvalbumin (PV) positive fast spiking basket cells and somatostatin (SST) positive low threshold spiking Martinotti-like cells (Fig. 3). As in canonical cortical areas, interneurons may provide local inhibitory control via perisomatic or dendritic inhibition. Interestingly, a subpopulation of interneurons with intermediate, quasi fast-spiking firing patterns exists as well and some GABAergic neurons express both PV and SST (Nassar et al. 2015). Whether interneurons possess specific features according to their laminar position or whether they preferentially target specific neurons within the microcircuit remains to be determined.

Intra-presubicular excitatory and inhibitory connectivities

Both interlaminar and intra-laminar excitatory connections have been described in the presubiculum (Funahashi and Stewart 1997; Peng et al. 2017; Simonnet et al. 2017). Many descending projections emerge from superficial layers and contact neurons in deep layers (Funahashi and Stewart 1997; Honda et al. 2008). In contrast, excitatory activity does not seem to be transferred from deep to superficial layers, which is consistent with the low number of ascending axonal collaterals (Funahashi and Stewart 1997) and results from anterograde and retrograde tracings (Honda et al. 2008). Axonal tracings of single layer 5 neurons showed that these cells have diverse projection patterns including long septo-temporal intra-presubicular projections (Honda et al. 2011). Different types of projections have been highlighted: some restricted to deep layers, hypothesized to send feedback information and others covering the whole presubicular plate, thought to regulate the temporal dynamics within a widespread neuronal population in the presubiculum (Honda et al. 2011).

Most of the intra-laminar connectivity is inhibitory. Excitatory cells preferentially contact local interneurons that inhibit excitatory cells and other inhibitory cells in return (Peng et al. 2017; Simonnet et al. 2017 for SST interneurons; Nassar et al. 2018 for PV interneurons). More recurrent excitatory connections were found in deep layers than in superficial layers (Peng et al. 2017), which might favor synaptic burst initiation in deep layers (Funahashi and Stewart 1997).

Mechanisms underlying head direction-related firing

Persistent firing of single neurons is a hallmark of the head direction system. Could it rely on the intrinsic properties of head direction cells? This possibility was put forward by

Yoshida and Hasselmo (2009) showing that in the presence of Carbachol, depolarizing current injections can trigger persistent firing, due to the activation of a calcium-sensitive non-selective cationic current (I_{CAN}). This was observed in the majority of both superficial and deep layer presubicular neurons tested. Persistent sodium currents may also help the generation of repetitive firing (Bean 2007). A TTX-insensitive Na current in neurons of superficial layers of presubiculum, with particularly slow kinetics and presumably expressed at some distance from the soma, could support sustained firing in the axon (Fricker et al. 2009). It could also participate in non-linear input integration, allowing amplification of excitatory inputs in dendrites, similar to or complementary to NMDA plateau potentials (Major et al. 2013). The prolongation of the decay of large dendritic EPSPs or spine potentials may support the presubicular coding of stable head positions.

The mechanism for persistence of directional firing could also rely on network properties that guarantee a localized static activity profile in the network. Head direction neurons maintain firing even in the absence of external activation, forming a coherent ensemble, with a correlated discharge of neurons with similar preferred head directions (Sharp et al. 2001a; Taube 2007; Peyrache et al. 2015). Theoretical models have therefore suggested that HD neurons are linked together to form an attractor network, with strong excitation between cells with similar tuning (Skaggs et al. 1995; Blair 1996; Redish et al. 1996; Zhang 1996; Goodridge and Touretzky 2000; McNaughton et al. 2006; Knierim and Zhang 2012). Excitatory-excitatory connections are scarce in the presubiculum (Peng et al. 2017; Simonnet et al. 2017) but their number may be sufficient for recurrent excitation among neurons with similar directional tuning. Hence, depending on the exact hardwiring, a 2% connectivity may account for mutual excitation between neurons coding for preferential directions that are apart by 7° or less. Global feedback inhibition seems important to limit the overall network activity (Zhang 1996; McNaughton et al. 2006).

The emergence of direction-selective persistent activity may also be achieved independently of excitatory-excitatory connections. For the generating circuit of the head direction signal, the reciprocal DTN-LMN network, an alternative continuous attractor network model without recurrent excitation has been suggested. In this spiking neuron model, a self-sustained hill of persistent activity, encoding a maintained head direction, is achieved through recurrent cross-inhibition, in combination with an external excitation (Song and Wang 2005).

We recently suggested that in the presubiculum, the dynamic interactions of a specific interneuron type, the Martinotti cells, with excitatory pyramidal cells, may

support head direction signals (Simonnet et al. 2017). Direct excitation of layer 3 pyramidal neurons by thalamic inputs and a high local inhibitory recurrent connectivity are important features for autonomous attractor dynamics to emerge. Pyramidal cells excite and recruit local Martinotti type interneurons following sustained high frequency firing, through strongly facilitating synapses (Fig. 4). Martinotti cell inhibition plays a dual role, dependent on spike-timing. In pyramidal cells that drive Martinotti cell firing, precisely timed recurrent inhibition helps sustain rather than inhibit firing. However, Martinotti cells exert lateral inhibition in pyramidal cells with a different phase. The recruitment of Martinotti cells requires persistent firing of one set of head direction cells, which is why they should be most active while the head is maintained in a constant direction, a prediction that still awaits experimental evidence. Based on data from our paired recordings in slices (Fig. 4), presubicular pyramidal cell and Martinotti-cell interactions were simulated in a firing rate model. The model, a modified attractor network without recurrent excitation between pyramidal cells, showed that inhibitory feedback activated at high firing frequencies could maintain a coherent activity bump, even in the absence of external input (Simonnet et al. 2017). The facilitating synaptic dynamics of Martinotti-cell recruitment therefore seem crucial to maintain a good coherence of the system over time.

The firing of another interneuron type, the fast spiking PV interneurons, is positively modulated by angular head velocity (Tukker et al. 2015; Preston-Ferrer et al. 2016). Angular velocity cells increase their firing rate during fast head turns. This is a hallmark of neurons in vestibular nuclei but what is the origin of the presubicular angular velocity signal? The input-specific adapting synapse dynamics of PV interneurons, together with a convergent wiring of thalamic directional input onto PV cells, could provide the ingredients for the local reconstitution of an angular velocity signal in the presubiculum. PV cells are activated rapidly by thalamic excitation, with depressing dynamics, as shown from optogenetic activation of thalamic fibers in the presubicular slice (Nassar et al. 2018). Therefore, synaptic excitation of PV cells will be strong and maintained only during fast head turns, when the set of active synapses continuously changes, driving continuous PV firing, despite depressing synapse dynamics. The complementary timing of the recruitment of MC and PV cells (Fig. 4) resembles that of onset-transient and late-persistent interneurons in the hippocampus and neocortex (Pouille and Scanziani 2004; Isaacson and Scanziani 2011). In the presubicular head direction network, PV interneuron activation will fade away during maintained directional heading, when the activity-dependent feedback inhibition by MC cells kicks in (Fig. 4).

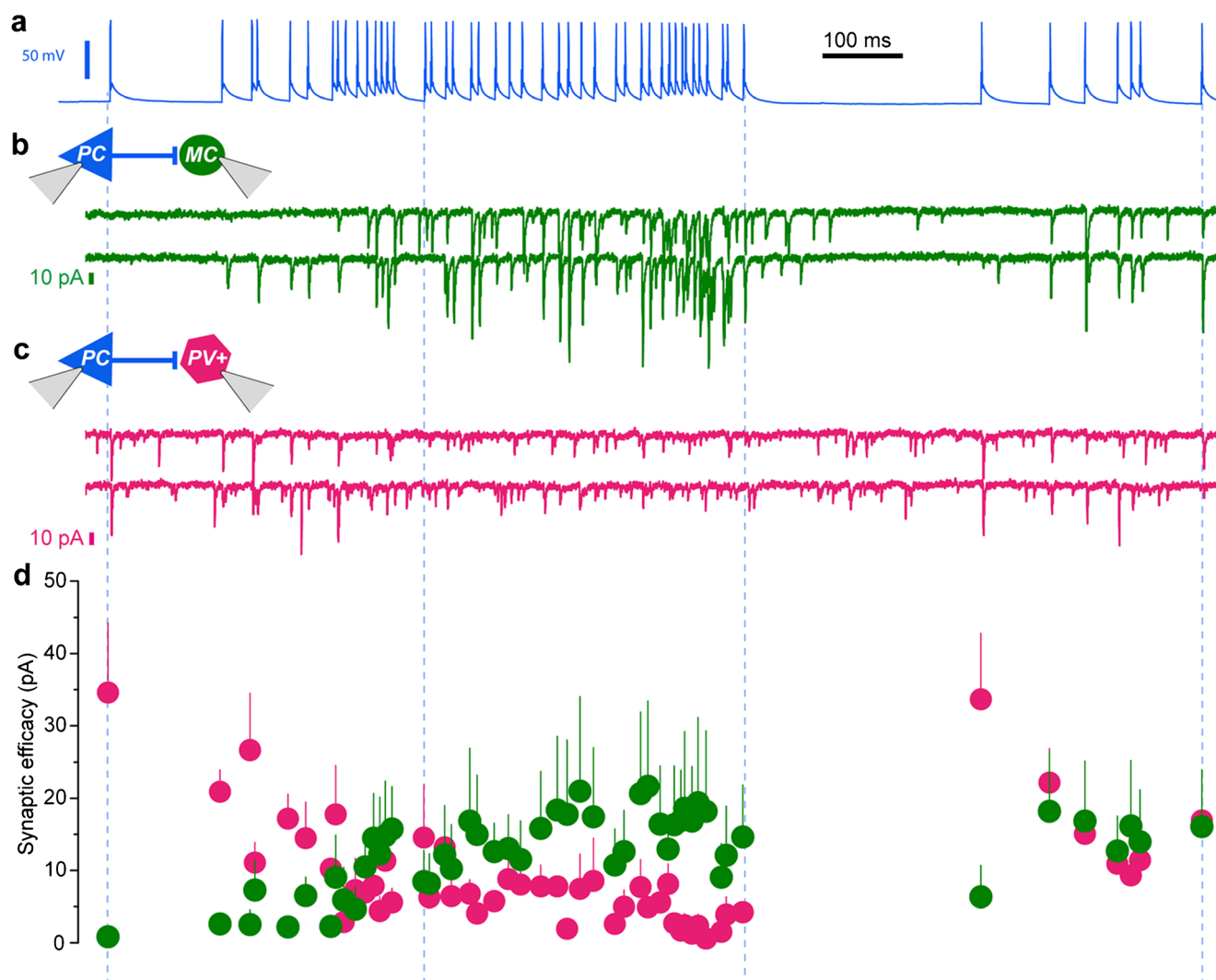


Fig. 4 Synaptic responses to HD spike train in Martinotti vs parvalbumin (PV) expressing cells. **a** Head direction firing pattern injected in a pyramidal neuron. **b** The recordings from a postsynaptically connected Martinotti cell show EPSCs in response to the spike train, with facilitating dynamics. **c** The recording from a postsynaptically connected parvalbumin positive fast-spiking neuron also shows EPSCs in response

to the same spike train but with depressing dynamics. **d** Summary graph of the average efficacy of evoked EPSCs for the Martinotti cells (in green; $n = 5$ pairs) and the average efficacy of evoked EPSCs in parvalbumin positive cells (in pink; $n = 5$ pairs). Note how the first spike evoked the largest response in PV cells, while Martinotti neurons did not respond to the first spike. (From Simonnet et al. 2017)

Future challenges

Defining the cellular components of the presubiculum, their anatomy and their physiology, has led to increased knowledge of this transitional cortical region. To understand the function of the circuitry, it will be important to elucidate how each population participates in information processing. Powerful molecular tools to target specific neuronal populations are becoming available and will need to be integrated in a system level approach and behavioral readout of the head direction signal. In vivo studies are needed to determine what kind of information different neurons code for the following: Which neurons are grid cells or border cells or conjunctive cells? Where are theta modulated cells? How do the different

subtypes of interneurons participate in signal processing? Electrophysiological and anatomical data available for Martinotti cells need to be extended to other types of interneurons such as PV and VIP cells and complemented by cell-type specific behavioral investigations. Molecular markers for principal neurons are still scarce; more of them should be identified, to better define the tuning properties for different head direction cells in different presubicular layers and with different projection targets. The diversity of the neuronal populations of the presubiculum requires more work to untangle the dense web of their connections, locally and across the brain. Eventually, new hypotheses need to be tested by manipulating the activity of defined presubicular cell populations.

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