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Navigating the Circuitry of the Brain's GPS System: Future Challenges for Neurophysiologists

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Abstract

The discovery of the brain's navigation system creates a compelling challenge for neurophysiologists: how do we map the circuitry of a system that can only be definitively identified in awake, behaving animals? Do grid and border cells in the entorhinal cortex correspond to the two classes of principal cell found there, stellate and pyramidal cells? In the hippocampus, does the diversity seen in pyramidal cell subtypes have functional correlates in the place cell system? How do interneurons regulate the activity of spatially tuned principal cells in the hippocampal and entorhinal circuits? Here, we discuss recent literature relating the cellular circuitry of these circuits to *in vivo* studies of the brain's navigation system, and the role that interneurons have in regulating the activity of principal cells in these circuits. We propose that studying *in vitro* models of neuronal oscillations in the entorhinal cortex and hippocampus can provide useful insights for bridging the gap in understanding that exists in relating *in vivo* and behavioral studies to circuit function at the cellular level.

Keywords

interneurons; hippocampus; oscillations

INTRODUCTION

The ultimate aim of neuroscience is often stated as understanding how the brain gives rise to human consciousness, a problem that has troubled philosophers throughout human history. In the 17th century, René Descartes famously argued, through the idea of dualism, that the mind was separate from the brain although thankfully this position has not proved too discouraging to modern neuroscientists. In seeking to relate neuronal physiology to cognition and behavior, we must ask which hypotheses can be formulated that allows us to address the brain-mind problem (Eccles, 1951). This year, the neuroscience community celebrates as the 2014 Nobel Prize in Physiology or Medicine was awarded to John O'Keefe, May-Britt Moser and Edvard Moser for their work in formulating such hypotheses and demonstrating how neurons in the hippocampus (O'Keefe and Dostrovsky, 1971; O'Keefe,

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1976) and entorhinal cortex (Fyhn et al., 2004; Hafting et al., 2005; Sargolini et al., 2006) provide the physiological substrate through which animals perceive their position in space.

The discovery of place cells in the hippocampus (O'Keefe and Dostrovsky, 1971), along with grid cells in the medial entorhinal cortex (mEC; Hafting et al., 2005) presents physiologists with a compelling challenge: how do we map the circuitry of a system that can only be definitively identified in awake, behaving animals? What cell types are involved? What are the local targets of the reciprocal connections between the mEC and hippocampus? How do place and grid cells integrate into the local circuitry and how do interneurons regulate their activity? The answers to these questions will yield important insights into neurophysiology that will likely be applicable to multiple brain systems.

In our research group, we seek to unravel the circuitry of the cortex and hippocampus at the cellular level, with a focus on how interneurons integrate into developing networks. In the CA1 region of the hippocampus alone, there are at least 20 different interneuron subtypes (Klausberger and Somogyi, 2008), each exerting a unique influence on information processing and circuit function. Understanding how interneurons control the output of principal cells is essential if we want to take the next step in solving the brain-mind problem, and link behavioral and *in vivo* studies to neuronal circuit function at the cellular level. Much of the diversity of hippocampal interneurons is genetically determined early in gestation and, while they all use a common neurotransmitter, GABA, each subtype predictably expresses a variety of Ca-binding proteins or neuropeptides (Tricoire et al., 2011). It is through learning what makes each interneuron subtype unique that we will gain not just a better grasp of physiology, but also the knowledge needed to develop new, targeted strategies for manipulating neuronal circuits to improve outcomes in pathophysiological and mental health disorders.

COMPONENTS OF THE NAVIGATION SYSTEM

The first challenge in unravelling the circuitry of the hippocampal formation navigation system is to identify the key cell types in both hippocampus and mEC. In the mEC, pure grid cells are mainly located in layer 2 while neurons in deeper layers have more complex spatial responses (Sargolini et al., 2006). Layer 2 and 3 of the mEC are unusual in that they possess two different types of principal cells, stellate cells and pyramidal cells (Germroth et al., 1989; Alonso and Klink, 1993), although the distinction between these two groups is not always clear (Canto and Witter, 2012). Principal cells in layers 2 and 3 of the mEC send two main projections to the hippocampus, targeting both the dentate gyrus (DG) and stratum lacunosum-moleculare in CA1 (although other projections also exist; see review by Canto et al., 2008). A simplified schematic of the connections between the hippocampus and entorhinal cortex is shown in Figure 1.

Recent studies of entorhinal projections to the hippocampus show that, in layer 2, calbindin-positive pyramidal cells target CA1 and the contralateral mEC, while calbindin-negative stellate cells project principally to the DG (Varga et al., 2010; Kitamura et al., 2014; Ray et al., 2014). Evidence suggests that layer 2 stellate cells are more likely to be grid cells (Domnisoru et al., 2013; Schmidt-Hieber and Hausser, 2013), although a later study

suggested that layer 2 grid cells were mostly pyramidal cells, while layer 2 border cells were mostly stellate cells (Tang et al., 2014). As pyramidal cells and stellate cells appear more as a continuum of morphologies than distinct classes in the mEC (Canto and Witter, 2012), it is possible that their functions will not parse as cleanly as experimenters would hope for (a familiar problem for those working with interneurons!). Just as genetic approaches have revolutionised our ability to study interneuron subtypes, these methods are now being used to provide important clues about the divergent nature of seemingly homogenous pyramidal cell populations (e.g., Lodato et al., 2014; Zeisel et al., 2015). Separating function based on principal cell morphology would be an important step in understanding the circuitry of the brain's spatial navigation system, but we also need to discover how interneurons control their output. Do these cells receive different inputs from within and outwith the local entorhinal circuit? Interestingly, calbindin-positive contralateral mEC-projecting principal cells of the mEC receive inputs from CCK-positive basket cells while calbindin-negative ipsilateral DG-projecting principal cells do not (Varga et al., 2010). Unlike fast-spiking PV-positive basket cells, CCK basket cells integrate inputs over a long time window and their outputs have a high failure rate coupled with asynchronous release, allowing them to integrate inputs from different sources and provide a more “tonic” form of inhibition to their targets (Armstrong and Soltesz, 2012). By selectively targeting contralateral-projecting principal cells (and presumably also those projecting to CA1), CCK basket cells may coordinate spatial information flow between hemispheres and that feeding back from CA1, whilst sparing projections to DG. In addition to connections between entorhinal principal cells and CCK basket cells, it is likely that other differences in connectivity with local interneurons exist that have yet to be discovered. With two readily distinguishable classes of principal cell, the mEC provides a useful model for studying differences in connectivity that likely also apply to other regions where principal cells may, at least superficially, appear more similar.

ARE ALL PYRAMIDAL CELLS MADE EQUALLY?

With just a single layer of principal cells, the hippocampus is a region where the principal cells within each subfield appear somewhat uniform. While place cells were first described in CA1 (O'Keefe and Dostrovsky, 1971), they can also be found in both DG and CA3 (Jung and McNaughton, 1993; McNaughton et al., 1983; O'Keefe, 1976). One common observation from *in vivo* electrophysiological studies in the hippocampus is that only a minority of principal cells in all subfields display spatial firing preferences (Leutgeb et al., 2007; O'Keefe, 1976; O'Keefe and Dostrovsky, 1971). Are there qualitative differences between principal cells that have spatial preferences and those that do not? Perhaps not: recent findings suggest that, given a sufficiently large environment, all CA1 pyramidal cells would exhibit spatial preferences (Rich et al., 2014).

There is a large body of evidence to suggest that pyramidal cells in the hippocampus vary both morphologically and functionally, especially along the radial axis (deep to superficial) where, for example, superficial CA1 pyramidal cells are enriched for calbindin whilst those close to stratum oriens are not (reviewed by Slomianka et al., 2011). Within CA1, fast-spiking parvalbumin-expressing basket cells preferentially target deep pyramidal cells, but more frequently receive excitatory inputs from superficial pyramidal cells (Lee et al., 2014).

Furthermore, PV-positive basket cells preferentially innervate pyramidal cells that project to the amygdala, demonstrating remarkable heterogeneity within the CA1 microcircuit (Lee et al., 2014). In addition to differences in connectivity, CA1 pyramidal cells also display morphological heterogeneities: surprisingly, the axon of more than half of all pyramidal cells arises from a basal dendrite and not the soma (Thome et al., 2014) and, in some cases, can even arise from the apical dendrite (Lorincz and Nusser, 2010). But do these differences have any bearing on the spatial navigation system? It would appear that the radial position of pyramidal cells is important, as deep pyramidal cells in CA1 are more likely to have place fields than those located superficially (Mizuseki et al., 2011), and CA1 pyramidal cells can be functionally split into two groups based on their behavior during linear track running (Senior et al., 2008).

The existence of different pyramidal cell subtypes raises the question of whether it is appropriate to treat pyramidal cells as a homogenous group when studying any aspect of physiology, be it synaptic plasticity, the connectivity between principal cells and interneurons, or projections to other hippocampal subfields. One of the key challenges to physiologists is to determine whether these functionally distinct populations of place cells correlate with morphologically distinct groups of principal cells observed throughout the hippocampus. As well as studying the behavior of principal cells during spatial navigation, uncovering the role of interneurons in controlling this circuit is essential for understanding the system as a whole, as is clearly demonstrated by the study of CA1 PV-positive basket cell connectivity from the Soltesz group (Lee et al., 2014).

INTERNEURONS: ESSENTIAL REGULATORS OF NETWORK ACTIVITY

While comprising only a small percentage of cortical neurons, inhibitory interneurons play a fundamental role in coordinating network activity. A multitude of interneuron subtypes exist, each with unique morphological and physiological specialisations that allow them to occupy a specific niche in mediating the activity of neuronal circuits (Freund and Buzsaki, 1996; McBain and Fisahn, 2001; Klausberger and Somogyi, 2008). While it would be expected that interneurons contribute to pacing rhythmic activity during spatial navigation, some interneurons in CA1, DG and the subiculum also show spatial selectivity, and are able to carry similar amounts of spatial information as principal cell place fields (Ego-Stengel and Wilson, 2007; Wilent and Nitz, 2007). Instead of merely being driven by place cells, CA1 interneurons can have complimentary (i.e., inverse) firing fields to place cells, even when those neurons are connected monosynaptically (Hangya et al., 2010), implying that interneurons may have an important role for shaping place fields through disinhibitory mechanisms.

The spatially tuned interneurons in CA1 observed by Hangya et al. (2010) were proposed to be perisomatic-targeting interneurons based on their fast-spiking properties, although some dendrite-targeting hippocampal interneurons also exhibit similar firing properties (Tricoire et al., 2011). Interestingly, in the mEC feedback inhibition plays a role in generating grid fields (Pastoll et al., 2013) but parvalbumin-positive interneurons (a group that includes perisomatic-targeting cells) do not possess grid-like firing fields (Buetfering et al., 2014).

This suggests that there may be different cellular mechanisms for generating hippocampal place fields and entorhinal grid fields.

Identifying cells based purely on extracellular firing properties cannot definitively separate them and, as has been discussed elsewhere (Gloveli, 2010), determining the role that non-fast spiking interneurons have in spatial navigation is needed for a complete understanding of the circuitry. This is particularly challenging as place cells are generally identified through *in vivo* extracellular recordings, making it difficult to definitively characterise their morphology unless juxtacellular labelling techniques are also employed. Conversely, while *in vitro* slice experiments easily allow identification of cell morphology and connectivity, one obviously loses the ability to identify spatially tuned neurons. A possible solution to the problem of identifying functionally related neurons *in vitro* is through the study of neuronal oscillations.

NEURONAL OSCILLATIONS: LINKING *IN VITRO* MODELS TO *IN VIVO* STUDIES?

Neuronal oscillations arise from the synchronous activity of networks of neurons, and are categorised by frequency band, e.g. slow oscillations (<1 Hz), theta oscillations (4–10 Hz) and gamma oscillations (30–90 Hz; reviewed by Buzsaki and Draguhn, 2004). Theta oscillations are typically observed during movement, both in the hippocampus (Vanderwolf, 1969; Ranck, 1973; O'Keefe, 1976) and entorhinal cortex (Mitchell and Ranck, 1980). Gamma oscillations, often occurring nested within theta oscillations, are believed to be important for working memory, representation of spatial sequences, and long-range synchronisation between different brain regions (for reviews, see e.g., Colgin and Moser, 2010; Lisman, 2010; Buzsaki and Wang, 2012).

Both gamma and theta oscillations appear to be important for the hippocampal spatial navigation system. When a rat runs on a linear track, groups of CA1 place cells representing the animal's movement trajectory will fire on the same theta cycle (Skaggs et al., 1996; Dragoi and Buzsaki, 2006). The timing of place cell firing relative to the theta oscillation systematically shifts during sequential theta cycles, a phenomenon known as phase precession (O'Keefe and Recce, 1993), which can also be observed in some interneurons (Ego-Stengel and Wilson, 2007). CA1 pyramidal cells can be split into two functional groups that, during spatial navigation, show different theta phase precession during nested gamma oscillations cycles (Senior et al., 2008). The timing of place cell spikes relative to theta oscillations may encode important information about the animal's position in space (O'Keefe and Burgess, 2005), and the coupling of theta and gamma rhythms seems to be important for communication between the hippocampus and entorhinal cortex (Buzsaki and Moser, 2013; Colgin, 2013). The hippocampal theta rhythm can also coordinate gamma oscillations in multiple neocortical locations (Sirota et al., 2008), and theta oscillations link the hippocampus and prefrontal cortex during learning tasks (Brincat and Miller, 2015). Clearly, understanding the cellular mechanisms that generate these oscillations will yield important insights into the circuitry of hippocampal formation and how it communicates

with the rest of the brain. Useful mechanistic insights into how oscillations are generated can be gained through use of *in vitro* slice models.

HIPPOCAMPAL GAMMA OSCILLATIONS

Perhaps the most studied hippocampal oscillation *in vitro* is the gamma oscillation, where persistent gamma oscillations can be evoked through bath application of carbachol (Fisahn et al., 1998) or kainate (KA) (Traub et al., 2003). Transient periods of gamma oscillations can also be evoked through pressure-application of small volumes of KA in stratum radiatum, both in CA3 (Gloveli et al., 2005) and CA1 (Chittajallu et al., 2013). The carbachol model generates gamma oscillations by activating cholinergic systems that exist *in vivo* but are typically severed during slice preparation, whereas the kainate model likely triggers a generalised depolarisation, providing enough excitatory drive to bring some neurons to threshold and trigger network oscillations. Although these models induce gamma oscillations by different methods, they demonstrate a propensity for hippocampal circuitry to oscillate within this frequency range. Indeed, while we use the term ‘gamma oscillation’ to refer to any oscillation in the 30 to 90 Hz range, it is clear that the term covers multiple oscillations with unique generators that co-exist within the hippocampus (Buzsaki and Wang, 2012).

The key test of whether these *in vitro* systems are reliable models of *in vivo* gamma oscillations is whether they replicate essential features of the oscillation and provide mechanistic insights that can be verified *in vivo*. In CA3, these models do indeed recapitulate the main features of gamma oscillations observed *in vivo*; *in vitro* models show that individual pyramidal cells have a low firing probability during gamma (Fisahn et al., 1998; Hajos et al., 2004; Gloveli et al., 2005), which is also seen *in vivo* (Csicsvari et al., 2003; Senior et al., 2008). *In vitro* studies also predicted that fast-spiking, perisomatic targeting basket cells were essential for generating gamma oscillations (e.g. Hajos et al., 2004; Mann et al., 2005), which was confirmed *in vivo* using optogenetic activation of parvalbumin-expressing interneurons (Cardin et al., 2009).

In CA1, gamma oscillations can be slow, originating from CA3, or fast, originating from mEC (Colgin et al., 2009); if grid cells and place cells are not successive stages of an information processing stream (Bush et al., 2014) then studying the mechanisms that allow either fast or slow gamma rhythms to dominate in CA1 could yield insights into how grid cell and place cell circuits interact. In CA1, fast-spiking basket cells drive slow gamma oscillations only in the pyramidal layer and not in more superficial layers *in vivo* (Lasztoczi and Klausberger, 2014), and we recently uncovered potential cellular mechanisms generating basket cell-independent gamma oscillations using an *in vitro* model, with axo-axonic, bistratified, and putative trilaminar cells all providing attractive candidates for driving this form of gamma oscillation (Craig and McBain, 2015; see Fig. 2A).

OSCILLATIONS IN THE mEC

Gamma oscillations can be modelled in the mEC using *in vitro* slices, which, similar to CA1, also reveals different oscillators with distinct peak frequencies (Middleton et al.,

2008). Another useful oscillation for studying entorhinal-hippocampal dynamics is the slow oscillation, which occurs throughout the cortex during slow wave sleep, marked by transitions between synchronous bursts of activity (Up states) and periods of relative quiescence (Down states) (Steriade et al., 1993). In the mEC, *in vivo* studies show that persistent Up states can increase the firing of neurons in CA1 (Hahn et al., 2012). Up-Down states (UDS) in the mEC also occur spontaneously *in vitro* (Fig. 2B) where they are balanced by the interneurons targeting GABA_A receptors and terminated by GABA_B receptors (Mann et al., 2009), with post-synaptic GABA_B receptors essential for afferent-evoked termination of the Up state (Craig et al., 2013). Like gamma oscillations, the activity of fast-spiking interneurons seems to be important for maintaining UDS *in vitro* (Tahvildari et al., 2012); this study found that pyramidal cells fired more than stellate cells during mEC Up states, paralleling *in vivo* observations that grid cells are more strongly theta-locked than border cells (Tang et al., 2014). Further work in understanding the mechanisms of UDS generation in the mEC has shown that Up states are suppressed by dopamine (Mayne et al., 2013).

Inputs to the mEC arriving in layer 1 may be responsible for terminating Up states (Craig and McBain, 2014), but it is not yet clear which cells in the mEC drive hippocampal oscillations. Does the hippocampal drive from persistent Up states (Hahn et al., 2012) and fast gamma oscillations (Colgin et al., 2009) in the entorhinal cortex arise from separate circuits or the same group of cells? We cannot assume that these are governed by principal neurons, as the hippocampus and entorhinal cortex share reciprocal inhibitory projections (Melzer et al., 2012). Given the large amount of interconnectivity between these regions, understanding how network activity is generated within both of these networks and how they are functionally linked will be a key milestone in fully describing the circuitry of the brain's spatial navigation system.

CHALLENGES FOR THE FUTURE?

Neurophysiologists are making good progress in understanding the cellular circuitry that generates gamma oscillations but to fully map the circuitry of the hippocampal formation's navigation system, a slice model of theta oscillations, with both fast excitatory and inhibitory neurotransmission intact, would be incredibly helpful. Optogenetic activation of mEC neurons at theta frequencies induces field oscillations which also show nested gamma activity (Pastoll et al., 2013), and isolated whole hippocampi spontaneously generate theta oscillations *in vitro* (Goutagny et al., 2009). These approaches may provide a way to determine which cell types generate, and are driven by, theta oscillations.

The major focus on understanding the brain's spatial navigation system, and memory processes, has been on the hippocampus and entorhinal cortex. However, it has long been known that cells in the subicular complex are spatially tuned (e.g., Taube et al., 1990; Sharp and Green, 1994), and both fast and slow gamma oscillations can be generated intrinsically in this region (Jackson et al., 2011). While it is often assumed that the subiculum acts merely as a relay for hippocampal output, theta oscillations can be generated in the subiculum and travel "backward" through CA1 to CA3 (Jackson et al., 2014), calling into question the assumptions about unidirectional information flow through the hippocampus. Furthermore,

we recently found that removing the subiculum actually increased the peak frequency of gamma oscillations in CA1 (Craig and McBain, 2015), and anatomical studies are starting to reveal the nature of the subicular projections to CA1 (Sun et al., 2014). Discovering what role the subicular complex plays in hippocampal information processing remains a key challenge, and may help us to move beyond the trisynaptic pathway paradigm to gain a fuller understanding of all hippocampal functions, from spatial navigation and beyond.

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FIGURE 1.

Simplified schematic showing connections between entorhinal cortex, subiculum and hippocampal subfields. For clarity, CA2 and the pre- and para-subicular connections, as well as connections with the contralateral hippocampal formation, have been excluded. Green arrows mark excitatory connections and red arrows mark inhibitory connections.

FIGURE 2.

A, Neurolucida reconstruction of fast-spiking basket cells from (top) CA3 and (bottom) CA1, with whole cell current-clamp recording of cell firing and extracellular field potential from stratum radiatum during kainate-evoked hippocampal gamma oscillations. Adapted from Craig and McBain (2015) with permission. B, Neurolucida reconstructions and simultaneous whole cell current-clamp recordings from a layer 1 putative neurogliaform cell (top trace) and layer 3 pyramidal cell (bottom trace) in medial entorhinal cortex, displaying spontaneous Up and Down states. Trace on right shows area in red box on an expanded time scale. Taken from M Craig (unpublished observations).