Dori Derdikman · James J. Knierim
Editors

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Preface

The pace of discovery in the field of hippocampal research is accelerating at a remarkable rate. It is very difficult for new students joining a laboratory, or for researchers outside the field, to get up to speed on the latest findings and trends. With this in mind, we invited prominent authors to write a selection of chapters, which together would encompass many of the exciting aspects of our evolving field of the hippocampal formation. In such an endeavor, there is always a trade-off between depth and breadth, and we decided to restrict the scope of the book to research that primarily centers around the neurophysiology of hippocampal processing in behaving animals, primarily rodents (which, not coincidentally, is our particular area of research). As a result, many of the relevant interesting subjects related to the hippocampal formation were left out of the volume. Specifically, we have not included chapters related to the dramatically growing field of human learning and memory in the hippocampus. Furthermore, originating from a systems neuroscience background, we did not put much emphasis on cellular and molecular phenomena, such as LTP and LTD. Moreover, our book has been biased towards aspects which involve the analysis of behavior, with much less emphasis on currently popular fields such as the connectome in the hippocampus or elsewhere. For a relatively recent coverage and review of all aspects of the hippocampal formation, we highly recommend *The Hippocampus Book* (*2006*). We also regret that the book does not have a detailed coverage of the anatomy of the regions we are interested in and refer the reader to the chapter written by Witter and Amaral (2004). We believe that this volume is a great addition to current literature by describing the explosion of new results in our field in recent years. As portrayed in the introduction, the book contains 19 chapters outlining the various inputs into the hippocampus, the diverse functions of the hippocampus, and the outputs from the hippocampus, with particular emphasis on the various functional cell types in this and adjacent regions, some of them recently discovered, such as grid cells and time cells.

We would like to take this opportunity to pay tribute to one of the original leaders of place cell research, Robert Muller, who passed away this year. Along with his colleagues at SUNY Downstate, Jim Ranck and John Kubie, Bob published some of the seminal work on place cells. They introduced the now ubiquitous

random-foraging task to simplify the behavior of the animal and to ensure behaviorally homogeneous sampling of the environment. Their pair of papers in 1987 left little room for the place-cell skeptics at the time to explain away the spatial correlates of these cells as being confounded by spatially correlated cues or behaviors. They also coined the term "place cell remapping," a phenomenon that is still under intense investigation and that is thought by many to underlie the hippocampal contribution to context-dependent memory. In addition to his many important contributions, Bob and the SUNY Downstate group trained some of the best of the next generation of researchers. He also was the initial inspiration to study place cells for one of us (JK), who, as a graduate student thinking about new avenues of research for postdoctoral training, attended a seminar by Bob and immediately became entranced by these amazing cells that seemed to offer an unparalleled, physiological window into high-order cognitive processes. Traces of Bob's work and legacy will be found throughout this volume.

We would greatly like to thank the authors of the chapters of this book, who have been extremely cooperative along the way in submitting the chapters and bearing with our comments and corrections. We would also like to thank the editors at Springer, Amrei Strehl, Wilma McHugh, and Karthik Kannan, who have suggested to us the whole project and who have assisted us with it all along the way. And finally, we would like to thank our families—Geeta, Ruti, Zohar, Shira, and Itamar, for their support and their willingness to bear with our extremely overloaded schedules, partly a result of working on this book.

Haifa, Israel — Dori Derdikman
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Contents

Introduction: A Neural Systems Approach to Space, Time, and Memory in the Hippocampal Formation

1

Dori Derdikman and James J. Knierim

In the span of 19 years between 1957 and 1976, three discoveries catapulted the hippocampus and medial temporal lobe to the forefront of research on the neural mechanisms of learning and memory. In 1957, Scoville and Milner (1957) reported the fascinating case study of the famous patient H.M., who lost the ability to form new declarative memories after undergoing bilateral removal of the hippocampus and adjacent cortical structures. In 1973, Bliss and Lomo (1973) discovered long-term potentiation (LTP) in the hippocampus of rabbits, providing a putative cellular mechanism for the storage of memories. And in 1976, following up on a short communication published a few years earlier (O'Keefe and Dostrovsky 1971), John O'Keefe described neurons in the hippocampus that were selectively active when a rat occupied a specific location in its environment (O'Keefe and Dostrovsky 1971; O'Keefe 1976). The discovery of these *place cells* and the subsequent publication of O'Keefe and Lynn Nadel's (1978) extraordinarily influential book, *The Hippocampus as a Cognitive Map,* generated a new field of research that has blossomed into one of the most important systems for understanding cognition at the level of neural circuitry and systems.

O'Keefe and Nadel's theory (at least as originally presented in their book) is often misconstrued as pertaining only to spatial learning and navigation, with limited relevance to the types of amnesia associated with hippocampal damage in humans (e.g., H.M.). Although spatial representation and mapping are indeed at the heart of the theory, its reach extends beyond these domains. Cognitive map theory is explicitly a theory of episodic memory, as evidenced by this one-sentence summary from the first paragraph of the book: "We shall argue that the

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hippocampus is the core of a neural memory system providing an objective spatial framework within which the items and events of an organism's experience are located and interrelated" (O'Keefe and Nadel 1978, p. 1). In the popular conception of the theory, this sentence would end with a period after the phrase "spatial framework." However, just as central to the theory is the remainder of the sentence: the spatial framework embodied by place cells is the organizing scaffold used by the brain to bind together ("interrelate") the "items and events of experience." This framework allows the flexible retrieval of memories for use in situations that differ from the original learning situation, in contrast with the nonflexible learning associated with nonhippocampal structures (in modern days associated with other brain systems such as the striatal habit learning system). O'Keefe and Nadel's book primarily centers on spatial learning in the rat, but later chapters expand the theory to human episodic memory and language.

In the years since its publication, *The Hippocampus as a Cognitive Map* has generated at least as much controversy as it has inspired some of the most seminal research in systems neuroscience. After many years and many debates, a consensus may be emerging about the role of the hippocampus as part of a larger network of brain areas that interact to store and retrieve memories and guide memory-driven thoughts and actions. Via the medial entorhinal cortex (MEC), the hippocampus receives inputs from regions that encode spatial variables, such as location and head direction, and that appear to use strategies such as path integration, discussed later in this book, to update a representation of the animal's current position and heading (Quirk et al. 1992; Fyhn et al. 2004; Hafting et al. 2005; Sargolini et al. 2006; McNaughton et al. 2006). Via the lateral entorhinal cortex (LEC), the hippocampus receives inputs from brain regions that appear to encode individual items related to the external world (Hargreaves et al. 2005; Bussey et al. 2005; Norman and Eacott 2005) (Fig. 1.1). The medial and lateral processing streams converge in the dentate gyrus (DG) and CA3 regions of the hippocampus, where they are thought to be combined into conjunctive representations of "what + where" (object + place; item + source; event + context) that are stored as a distributed memory in an associative network that allows complete memories to be recalled and brought to consciousness when presented with partial or degraded retrieval cues (McNaughton and Morris 1987; McNaughton et al. 1989; Rolls and Treves 1998; Redish 1999; Knierim et al. 2006; Manns and Eichenbaum 2006; Ranganath 2010; Eichenbaum et al. 2007). The hippocampus is also connected with a number of other brain areas that use these memories to guide specific behaviors. In this book, prominent investigators review recent research into the types of inputs that the hippocampus receives via its medial and lateral entorhinal inputs and their afferent structures, the types of processing intrinsic to the hippocampus that are thought to underlie its mnemonic processing, and the interactions with brain regions that are thought to be more directly involved in the control of behavioral output and cognitive control.

This introductory chapter provides a brief (and necessarily selective) history of the major themes of research on hippocampal place cells [see also reviews by Muller (1996), Best et al. (2001), Anderson et al. (2007)] and a brief overview of hippocampal anatomy. We then provide a summary of the themes that run

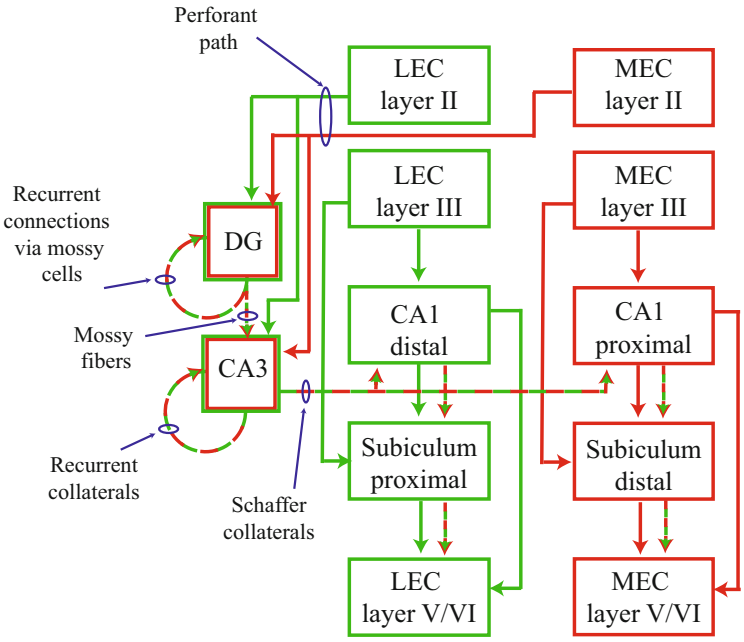

Fig. 1.1 Parallel processing streams from the entorhinal cortex through the hippocampus. In this simplified schematic, the substantial cross talk between the input streams is not shown for simplicity. Layer III of the lateral and medial entorhinal cortex regions sends outputs to segregated portions of CA1 along the transverse (proximal-distal) axis of the hippocampus. CA1 returns projections to the deep layers of the entorhinal cortex, both directly and indirectly through distinct regions of the subiculum. Layer II of the lateral and medial entorhinal cortex sends projections to the DG and CA3 regions, where the input streams are intermixed. The presumed conjunctive representations of the two inputs are merged with the segregated input in CA1. *LEC* lateral entorhinal cortex, *MEC* medial entorhinal cortex, *DG* dentate gyrus (From Deshmukh and Knierim. *Hippocampus*. WIREs Cogn Sci 2012 doi:10.1002/wcs.1164)

throughout the various chapters of the book, to give the reader an overview of the organization of the book and an appreciation of how the various chapters relate to each other. These chapters address overlapping concepts that form the intellectual framework of much current research on the role of the hippocampus in neural processing of space, time, and memory.

1.1 Short Historical Overview

1.1.1 What Cues Drive Place Cells?

Early research on place cells was devoted to understanding the cues that the cells used to determine their spatially restricted firing fields. By intentionally minimizing local spatial cues, investigators showed that place cells were under the control of

distal visual landmarks when these landmarks were rotated as a whole (O'Keefe and Conway 1978). However, removal of the cues or turning off the lights showed that the cells did not require these distal landmarks to display their spatially specific firing (O'Keefe and Speakman 1987; Quirk et al. 1990; Markus et al. 1994). Thus, place fields were not a simple correlate of a spatially biased, local sensory cue (such as an odor at a specific location) or a specific external landmark. Rather, they represented a more abstract conception of space unrelated to any specific sensory input [see Knierim and Hamilton (2011), for a review]. Furthermore, different subsets of hippocampal neurons demonstrated place fields in different environments or in the same environments in which the spatial cues or nonspatial task demands were sufficiently altered (Kubie and Ranck 1983; Muller and Kubie 1987; Bostock et al. 1991; Markus et al. 1995). This phenomenon was termed "remapping," and it is thought to underlie the role of the hippocampus in discriminating similar memories as well as in supporting context-specific memories (Knierim 2003; Nadel et al. 1985).

Not long after the publication of O'Keefe and Nadel's book, Ranck (1985) reported another class of spatially selective cells that fired when an animal's head pointed in a particular direction in allocentric space. These *head direction cells* appeared to act as an azimuthal compass. Like place cells, they were controlled by distal landmarks but were not dependent on the presence of these landmarks to fire in a directionally specific manner (Taube et al. 1990a, b). Vestibular lesions abolished the tuning properties of these cells (Stackman and Taube 1997), consistent with models that proposed that angular velocity signals were the primary drive that updated the directional signal (McNaughton et al. 1991; Skaggs et al. 1995; Zhang 1996; Blair 1996; Redish et al. 1996). The head direction cells were subsequently shown to be intimately related to place cells, as rotations in the preferred directions of their tuning curves were tightly coupled to identical rotations of place cells (or place field remapping in some cases), even in the presence of stable, spatial landmarks (Knierim et al. 1995, 1998).

In addition to the influence of external sensory cues, the work of McNaughton and colleagues emphasized the importance of self-motion (idiothetic) cues in driving place cell responses (McNaughton et al. 1996). McNaughton's initial theoretical work suggested that the cognitive map was formed by associating place cells that represented "local views" at a given location with the body movements that linked these views (McNaughton et al. 1989). Later work suggested that the body movement cues were the primary drive upon place cells, allowing these cells to perform a path integration (dead reckoning) computation by integrating a movement vector (speed and direction) over time to produce a spatial signal (McNaughton et al. 1996; Samsonovich and McNaughton 1997). External sensory inputs were required to keep the internal, cognitive map from drifting relative to the external world and to allow the animal to localize itself when entering a familiar environment. Redish, Touretzky, and colleagues suggested that these operations (path integration and representations of external sensory landmarks) occurred in inputs upstream of the hippocampus, and the job of the hippocampus was to integrate these two types of inputs (Redish and Touretzky 1997; Redish

1999). A similar dichotomy between internal and external navigation systems appeared in O'Keefe and Nadel's book.

In addition to external landmarks and idiothetic cues, O'Keefe and Burgess (1996) demonstrated that the boundaries of an environment exert a profound control over the location-specific firing of place cells. As the four walls of a chamber were stretched/compressed to change the geometry between squares and rectangles, the place fields stretched/compressed accordingly or remapped. Burgess and colleagues formulated a "boundary vector cell" model that not only explained the existing data but successfully predicted how cells would respond to new manipulations (O'Keefe and Burgess 1996; Burgess et al. 2000; Hartley et al. 2000; Barry et al. 2006). The model predicted the existence of boundary-related cells, which were subsequently discovered in a number of brain regions (Lever et al. 2009; Savelli et al. 2008; Solstad et al. 2008; Boccara et al. 2010). Lever et al. (2002, also O'Keefe 1979) reported that some place cells maintained their locations relative to the local boundaries of a recording box when the box was shifted relative to the spatial cues in the laboratory frame of reference. This dominance of the local reference frame over the global during relative translations was demonstrated conclusively by a number of subsequent experiments (Knierim and Rao 2003; Siegel et al. 2008; Yoganarasimha and Knierim 2005). Similarly, new experiments that increased the salience of local surface cues to match that of the distal landmarks began to show that these local cues could control the place fields as strongly, or even more strongly, than the global cues (Young et al. 1994; Shapiro et al. 1997; Zinyuk et al. 2000; Knierim 2002; Brown and Skaggs 2002). New investigations into the three-dimensional structure of place fields in animals that normally navigate on surfaces vs. animals that navigate in true, three-dimensional volumes add further, intriguing complications to the nature of hippocampal spatial cues (Taube 2011; Hayman et al. 2011; Yartsev and Ulanovsky 2013). Thus, local cues, global cues, environmental boundaries, and self-motion cues all interact to drive place cells, with some sets of cues having dominance over others depending on the specific circumstances.

1.1.2 The Contributions of Hippocampal Inputs and Subfields

The confusion wrought by the various types of cue control over place cells seems intractable until one considers that the large majority of studies concentrated primarily on the CA1 region of the hippocampus. CA1 is many synapses removed from the primary sensory regions that initially encode the changes to the sensory environment and the animal's movements through the environment. To understand the computational functions of the place cells, it is necessary to understand explicitly the properties of its input and output regions. Initial investigations into the entorhinal inputs to the hippocampus had been done in early years (Barnes et al. 1990; Quirk et al. 1992; Frank et al. 2000), but few follow-up experiments were done. However, in 2004–2005, two papers from the lab of May-Britt Moser and Edvard Moser stunned the neuroscience community by reporting the presence

of the remarkable *grid cells* in the MEC (Fyhn et al. 2004; Hafting et al. 2005). These papers were quickly followed by other reports that the MEC contained head direction and boundary-related activity and that they were part of a network of brain areas with similar properties (Sargolini et al. 2006; Boccara et al. 2010). These areas were immediately hypothesized to be involved in path integration computations (Hafting et al. 2005; O'Keefe and Burgess 2005; McNaughton et al. 2006), perhaps fulfilling the roles envisioned early on by O'Keefe and Nadel and by Redish as providing the path integration or internal navigation system inputs to the hippocampus. At the same time, the LEC was shown to be devoid of location-specific firing correlates (Hargreaves et al. 2005). It was hypothesized that the LEC conveyed information about specific items and objects to the hippocampus. Thus, the spatial and nonspatial firing properties of hippocampal cells may be explained by the different types of information conveyed by the two primary inputs to the hippocampus.

Although early work on place cells reported that CA3 and CA1 had place fields, most papers failed to report robust, qualitative difference between the properties of the cells in these regions [with the exception of McNaughton et al. (1983)]. However, in 2004, the Knierim, Moser, and Guzowski labs published four papers showing clear differences in the ensemble responses of CA3 and CA1 to environmental changes (Lee et al. 2004a, b; Leutgeb et al. 2004; Vazdarjanova and Guzowski 2004). These differences were interpreted in terms of computational theories of autoassociation, pattern completion/separation, and sequence encoding in the recurrent collateral system of CA3 (Guzowski et al. 2004; Knierim et al. 2006). Since then, studies have begun to detail the different functional correlates of CA3 and CA1, as well as the correlates of the dentate gyrus and subiculum regions, many using genetic techniques to specifically alter the functions of discrete hippocampal subfields (Sharp 1999; Nakazawa et al. 2003; Wilson et al. 2005; Leutgeb et al. 2007; Nakashiba et al. 2009).

1.1.3 Nonspatial Firing of Place Cells

For many years after the discovery of place cells, a debate raged about whether space was the only correlate of hippocampal cells, or whether these cells also encoded nonspatial variables (Shapiro and Eichenbaum 1999; O'Keefe 1999). Although running direction and speed were known to modulate place cells (McNaughton et al. 1983; Wiener et al. 1989), these can be considered spatial variables. Numerous studies now show that nonspatial variables are encoded by hippocampal cells, but it appears that these nonspatial variables typically (perhaps always) are encoded as a modulation of the underlying spatial firing field of the cell. Odors, objects, conditioned stimuli, and operant behaviors have all been shown to modulate the firing of a place cell when the rat is within its place field (O'Keefe and Dostrovsky 1971; Wood et al. 1999; Wiebe and Staubli 1999; Manns and Eichenbaum 2009; Komorowski et al. 2009). Of special interest has been the so-called splitter cell phenomenon, in which the firing rate through a place field

can be modulated as a function of the upcoming goal of the rat's current trajectory (prospective coding) or as a function of the starting point of the current trajectory (retrospective coding) (Wood et al. 2000; Frank et al. 2000; Ferbinteanu and Shapiro 2003). More recently, the encoding of time has been explored in hippocampal cells, demonstrating sequential firing of cells when the animal runs in place or is confined to a small place during a delay interval (Pastalkova et al. 2008; MacDonald et al. 2011). Under certain conditions, it has been shown that the cells fire at a specific duration, but that this time signal is also modulated by a location or distance signal (MacDonald et al. 2011; Kraus et al. 2013). Time coding is one of the most important new functions associated with hippocampal cells, as it may provide new insight into how the hippocampus underlies the temporal components of episodic memory as well as providing insight into how the same neural architecture can compute such diverse output signals as time, distance, and position.

1.1.4 Hippocampal Oscillations, Replay, and Nonlocal Representations

The hippocampal theta rhythm has been investigated for many decades, and it plays a prominent role in O'Keefe and Nadel's book. Theta is present when animals are engaged in exploratory behaviors, such as moving, sniffing, and whisking (Vanderwolf 1969; O'Keefe and Nadel 1978; Buzsaki 2002). Place cells are strongly modulated by the theta rhythm, and O'Keefe and Recce (1993) discovered the phenomenon of *theta phase precession*, one of the premier examples of a temporal code in the central nervous system. Gamma rhythms are also prominent in the hippocampus, and theta-gamma coupling has been investigated as a mechanism, whereby spikes are packaged and sequentially organized to allow for coordinated information transfer and processing within the hippocampal system (Jensen and Lisman 2005; Lisman and Redish 2009; Colgin et al. 2009). When animals are asleep, inactive, or performing non-exploratory behaviors (e.g., eating or grooming), the hippocampal EEG is dominated by large, irregular activity, punctuated by sharp wave/ripple (SWR) events (O'Keefe and Nadel 1978; Buzsaki 1986). Wilson and McNaughton (1994) showed that during SWRs in slow-wave sleep, place cells fire in bursts of activity that replay, at a compressed time scale, the activity of place cells that had been active when the animals were running minutes before. Since then, many studies have investigated these nonlocal representations (i.e., representations not of the current location of the animal, but of some other sequence of locations away from the animal's current position) during both sleep and awake activity [e.g., Hoffman and McNaughton (2002), Dragoi and Buzsaki (2006), Diba and Buzsaki (2007), Johnson and Redish (2007), Davidson et al. (2009), Carr et al. (2011), Jadhav et al. (2012)]. These events are a major model system of the neural basis of systems consolidation, reward learning, and vicarious trial and error.

1.1.5 Place Cells and LTP

Given the strong connection between LTP, memory, and the hippocampus, it is perhaps surprising that few direct studies of the relationship between LTP and place cells appeared before 1998. Kentros et al. (1998) showed that NMDA receptor activity was not required for the initial formation of place fields, but was required for the long-term binding of the place cell map to a given environment. Previous work on the relationship between LTP and place fields centered on aged animals, who show abnormalities in spatial learning, LTP, and place cell firing properties (Barnes et al. 1997; Barnes 2003; Wilson et al. 2005). Place cells remain one of the most important model systems for understanding the cognitive changes that accompany the normal aging process. Conversely, studies of place field formation in pups (Langston et al. 2010; Wills et al. 2010; Scott et al. 2011) and adult neurogenesis in the DG (Gould et al. 1999; Aimone et al. 2006) have become important models of the development of cognitive learning systems. In normal adult animals, numerous studies have followed the Kentros et al. study and investigated explicitly the relationship between LTP and place cells. These studies include knockout mice with altered NMDA subunits or other LTP-related genes in different hippocampal subfields (McHugh et al. 1996; Rotenberg et al. 2000; Nakazawa et al. 2004; McHugh et al. 2007) and studies that artificially stimulated hippocampal cells to induce LTP and create new place fields (Dragoi et al. 2003). Other studies of learned sequences of place fields have interpreted changes in place fields in terms of spike-timing dependent plasticity (Mehta et al. 1997, 2000; Lee et al. 2004a; Lee and Knierim 2007), a form of long-term potentiation and long-term depression that relies on the precise timing relationships of presynaptic and postsynaptic neural firing.

1.1.6 The Hippocampus and the Rest of the Brain

A major trend in systems neuroscience over the past decade or so has been the investigation of how different brain systems and brain regions interact to support perception, cognition, and behavior. Much recent work in the hippocampus has correspondingly focused on its relationship to other brain regions in the support of memory and behavior. Prominent are the interactions with the prefrontal cortex, amygdala, striatum, and parietal cortex (Save and Poucet 2000; Moita et al. 2003, 2004; Jones and Wilson 2005; Hyman et al. 2005; Nitz 2009; van der Meer et al. 2010; van der Meer and Redish 2011). A major component of these studies is the realization that there are functional gradients along the dorsal-ventral axis of the hippocampus (corresponding to the posterior-anterior axis in primates) and that regions of the hippocampus along this axis are connected differentially with these extrahippocampal systems (see below, and Fig. 1.2). An understanding of the relationship between this longitudinal axis of the hippocampus and functional connectivity with extrahippocampal structures will provide great insight in the future into the general computational function of the hippocampal system.

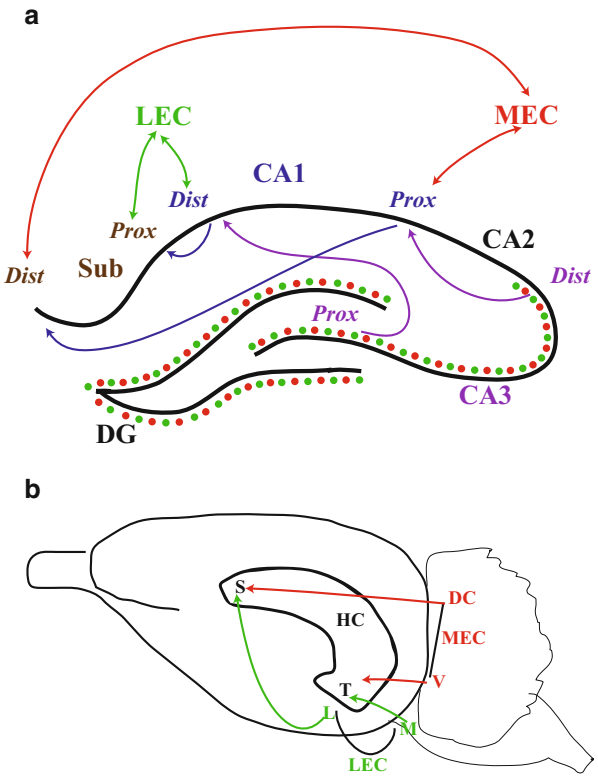

Fig. 1.2 (**a**) Transverse axis of the hippocampus. *Arrows* show the direction flow of information from the segregated regions along the transverse (proximal-distal) axis. The terms proximal and distal refer to distance from the dentate gyrus along the pyramidal cell layer. Direct projections from LEC and MEC target different regions of CA1, and the return projections are also segregated. Proximal CA3 projects to distal CA1, which projects to proximal subiculum. Distal CA3 projects to proximal CA1, which projects to distal subiculum. The *red* and *green dots* indicate that the perforant path projections from the MEC and LEC to DG and CA3 are not segregated along the transverse axis (*arrows* of perforant path projection to CA3 and DG are not shown in this panel). (**b**) Longitudinal (septal-temporal) axis of the hippocampus. The dorsocaudal MEC projects to the septal (dorsal) hippocampus, whereas the ventral MEC projects to the temporal (ventral) hippocampus. The lateral band of LEC projects to the septal (dorsal) hippocampus, whereas the medial band of LEC projects to the temporal (ventral) hippocampus (Modified from Deshmukh and Knierim. *Hippocampus*. WIREs Cogn Sci 2012 doi:10.1002/wcs.1164)

1.2 Short Anatomical Overview

A detailed description of hippocampal anatomy is well beyond the scope of this chapter. Readers can find detailed descriptions in Witter and Amaral (2004) and in Amaral and Lavenex (2007). We describe here, in a highly simplified form, three basic organizing principles of hippocampal anatomy that are relevant for the chapters of this book (1) parallel processing streams via the MEC and LEC,

(2) organization along the transverse axis, and (3) organization along the longitudinal axis.

1.2.1 Parallel Processing Streams

The hippocampus receives its major cortical input via the MEC and the LEC (Fig. 1.1). These areas are the terminal regions of two anatomically defined processing streams that are relatively segregated in terms of their connectivity patterns, although there is a substantial cross talk between the two streams (Burwell 2000). The MEC receives input from the postrhinal cortex (parahippocampal cortex in primates), which receives input primarily from visuospatial regions. In primates, the parahippocampal region contains the parahippocampal place area, which responds to the images of visual scenes (Epstein et al. 1999). The MEC is also heavily interconnected with the presubiculum, parasubiculum, and retrosplenial cortical regions. These regions, associated with the head direction cells of the anterior dorsal thalamus, contain head direction cells, place cells, border cells, and grid cells. In contrast, the LEC receives major input from the perirhinal cortex, which is associated with the processing of complex objects. The perirhinal cortex receives input from unimodal sensory areas (Burwell 2000). Both the LEC and MEC receive major inputs from the olfactory system. This anatomical segregation has been characterized as underlying functional processing streams related to what vs. where, self vs. other, cue vs. action, content vs. context, or internally generated self-motion vs. external sensory inputs (Manns and Eichenbaum 2006; Knierim et al. 2006; Lisman 2007; Knierim et al. 2014).

1.2.2 Transverse Axis

The hippocampal transverse axis refers to the cross-sectional cut through the hippocampus containing the classic trisynaptic loop circuitry from the DG to CA3 to CA1 (Fig. 1.2a). Although the classic textbook notion of hippocampal connectivity emphasizes this simple, feedforward circuit, there are parallel pathways and feedback circuits along the transverse axis that are presumably just as important. The entorhinal cortex makes direct projections to all three regions (as well as the subiculum, which is a major output region of the hippocampus). Layer II of the EC projects to DG and CA3, whereas Layer III projects to CA1 and subiculum. Both LEC and MEC project to the same parts of DG and CA3; thus, the cells in DG and CA3 presumably are able to form conjunctive representations of the two types of inputs encoded by the two input streams. In contrast, the MEC projects primarily to the proximal half of CA1 (close to CA3), whereas the LEC projects primarily to the distal half of CA1 (close to the subiculum) (Steward 1976). The granule cells of the DG project to the CA3 region, as well as to the cells of the dentate polymorphic layer (the hilus). CA3 and the hilar mossy cells send feedback projections to the granule layer (Scharfman 2007). CA3 sends feedforward

projections to CA1 (the Schaffer collaterals) as well as feedback connections to itself (the recurrent collaterals). The proximal part of CA3 (close to the DG hilus) has a smaller proportion of recurrent collaterals than the distal part of CA3 (close to CA1) and projects primarily to distal CA1 (i.e., the LEC-recipient zone) (Ishizuka et al. 1990; Witter et al. 2000). The distal part of CA3 has a greater density of recurrent collaterals than the proximal part and projects primarily to proximal CA1 (i.e., the MEC-recipient zone) (Ishizuka et al. 1990; Witter et al. 2000). CA1 sends outputs to the subiculum and to the deep layers (V and VI) of LEC and MEC. These return projections respect the same proximal-distal segregation patterns as the input connections. (Relatively little is known about the CA2 region that forms a small strip of cells in between CA1 and CA3, although recent work is beginning to appreciate that this region is not simply a transition zone between CA1 and CA3.) This brief description of the transverse circuitry indicates that the main processing loop in the hippocampus is much more complicated than standard textbook descriptions of the hippocampal slice preparation, and a full understanding of hippocampal processing and computation will require a detailed description of the functional roles of each connection in this circuit.

1.2.3 Longitudinal Axis

The longitudinal axis refers to the dorsal-ventral (also known as the septal-temporal) axis of the hippocampus (Fig. 1.2b). In primates, this axis corresponds to the posterior-anterior axis, as the rat dorsal hippocampus corresponds to the primate posterior hippocampus and the rat ventral hippocampus corresponds to the primate anterior hippocampus. There are a number of functional dissociations along this axis. Physiologically, place fields grow larger as one moves from dorsal to ventral (Jung et al. 1994; Kjelstrup et al. 2008). Lesion studies demonstrate that the dorsal hippocampus is more involved in precise spatial localization tasks, whereas the ventral hippocampus is more involved in contextual tasks and emotional processing (although these dissociations are not absolute) (Moser and Moser 1998; Ferbinteanu et al. 1999; de Hoz et al. 2003). Corresponding to these functional gradients, the dorsal hippocampus is preferentially connected to retrosplenial cortex (Witter and Amaral 2004) and the high-resolution grid cells of the dorsocaudal MEC (Dolorfo and Amaral 1998), whereas the ventral hippocampus is preferentially connected to the prefrontal cortex, amygdala, and the low-resolution grid cells of the ventral MEC (Dolorfo and Amaral 1998). The dorsal hippocampus is also connected with the lateral band of the LEC, whereas the ventral hippocampus is connected preferentially with the medial band of the LEC (Dolorfo and Amaral 1998). Presently, little is known about the functional correlates of these bands in the LEC.

1.3 Organization of the Book

Many themes pass as common threads throughout the chapters of this book. In this section we shall highlight some of these themes and point to the chapters in which they are discussed.

1.3.1 Main Cell Types

As mentioned above, ***place cells*** were discovered in the 1970s, by O'Keefe and Dostrovsky (1971). Many of their characteristics are described throughout the chapters of this book: Chap. 14 discusses issues related to the computation of place cells; Chap. 9 portrays remapping of place cells; Chap. 16 discusses the similarities and differences between place cells of different species; Chap. 4 describes interactions between head direction cells and place cells; Chap. 5 describes the relationship between grid cells and place cells; Chap. 8 describes the involvement of path integration in the generation of place cells; Chap. 11 discusses the temporal aspects of place cells; Chap. 12 describes the relations between oscillations and place cells; Chap. 13 describes how place cells could be related to memory from the concept of replay; Chap. 10 describes splitter cells; and Chaps. 17–19 describe the readout of place cells in other brain regions outside the hippocampus.

Head direction cells were discovered in the decade following the discovery of place cells (Ranck 1985), suggesting for the first time that there may be more than one cell type related to the cognitive map of space. Head direction cells are described in depth in Chap. 4. Their connection to grid cells is described in Chap. 5, and theoretical issues related to head direction cells are discussed in Chap. 14.

Grid cells were discovered more recently by Hafting et al. (2005). The hexagonal patterns formed by their firing fields have generated an extreme interest in the scientific community. Although the characteristics of grid cells are not as thoroughly investigated as the characteristics of place cells, the large fraction of chapters in this volume discussing grid cells demonstrates the enthusiasm this new cell type has caused. Chapter 5 describes the phenomenology of grid cells; Chap. 14 describes theoretical aspects of grid cells and their relation to place cells; Chap. 16 deals with comparative aspects across species; Chap. 4 describes interactions between head direction cells and grid cells; Chap. 6 deals with the relationship between grid cells in the MEC and cell phenomenology in the LEC; Chap. 7 discusses modulation of grid cells by cholinergic input; Chap. 9 discusses the relationship between remapping in grid cells and place cells; Chap. 8 discusses grid cell models in the context of path integration; and Chap. 12 deals with the relationship between grid cells and neuronal oscillations.

Shortly following the discovery of grid cells, ***border/boundary cells*** were discovered in the entorhinal cortex (Savelli et al. 2008; Solstad et al. 2008). Interestingly, these cells were actually predicted from theoretical models of place cells,

called "boundary vector models," (Barry et al. 2006) and were also found in the subiculum by the same authors who created the models (Lever et al. 2009). See Chaps. 5 and 16 for discussion on these cells.

Recently there has been some evidence that in certain behavioral tasks, hippocampal cells can encode time (Pastalkova et al. 2008; MacDonald et al. 2011). These cells were thus termed ***time cells***, in analogy with place cells. The temporal aspects of hippocampal encoding are described in Chap. 11.

Finally, ***spatial view cells*** have been described in the monkey and human literature (Rolls et al. 1997; Ekstrom et al. 2003). These cells fire whenever the animal looks at a certain position in space, and their characteristics are described in Chap. 16.

1.3.2 Navigation

It is generally accepted that the brain areas involved in the formation of place cells, head direction cells, and grid cells are related to navigation. However, there are many open questions. For example, what components of navigation are related to the different brain areas? What does it mean to host a *cognitive map* in our brain, aiding us in navigation? When do we decide to read out information from this system while in navigation? Classical studies, such as those of Packard and McGaugh (1996), have suggested a dissociation between different brain areas involved in different styles of navigation. For example, it has been suggested that the striatum is more involved in rigid or "taxon-like" navigation, in which behavior is dominated by "left" and "right," while the hippocampus is involved in flexible, "maplike" functions, allowing the animal to perform shortcuts while navigating, in the spirit of the original cognitive map suggested by Tolman (1948) and discussed by O'Keefe and Nadel (1978). Issues related to the hippocampal formation and navigation are discussed in many chapters. Chapter 2 discusses the pivotal role of the parietal cortex in navigation; Chap. 14 discusses the question of how SLAM (Simultaneous Localization and Mapping, a concept studied intensively in the robotics literature) may be implemented in the brain; and Chap. 8 discusses the path integration mechanism of navigation.

1.3.3 Memory

Since the seminal work of Scoville and Milner (1957) on H.M., the role of the hippocampus in memory has not been much disputed. However, for many years it has been unclear how to reconcile this role and the role of the hippocampal formation in navigation, as manifested by the discovery of place cells. Part of the solution emerged from the understanding that hippocampal cells encode more than only *place* (Shapiro and Eichenbaum 1999). Rather, in some situations, they seem to encode also the *time* and the *content* of events (see Chap. 11). As portrayed in some chapters of this book, there are many indications that hippocampal formation

cells in general, and place cells in particular, encode many aspects of the world in addition to solely place: Chap. 11 shows that in some situations place cells become time cells; and Chap. 10 describe how place cells may encode past or future, and not only the present. Chapter 9 also discusses how place cells may encode time over long intervals. In addition, many chapters discuss the relationship of the hippocampal formation to memory: Chaps. 3 and 6 describe object memory; Chaps. 12 and 13 relate oscillations to memory; Chaps. 14 and 8 discuss attractor models of memory; and Chaps. 17–19 discuss the relationship of the hippocampus to other memory systems. As described in many of these chapters, the involvement of place cells and other types of cells in the encoding of time and content, in addition to position, suggests that such cells are part of a mechanism of episodic memory, as suggested by Tulving (1983).

Another theme which is related to associative memory, and which runs through many chapters of this book, is the distinction between pattern completion and pattern separation. Pattern completion is the ability of a network to retrieve a complete, stored representation in response to partial or degraded input cues. Pattern separation is the ability of a network to transform similar input patterns into output patterns that are less similar (more orthogonal) than the inputs, in order to reduce interference between the patterns. See a more detailed definition of these terms and their relation to memory in Chaps. 9, 15, and 17.

1.3.4 Parallel Streams

Classic work in the visual system has suggested that there are two major streams for processing information: the dorsal "where" stream and the ventral "what" stream (Ungerleider and Mishkin 1982; Kravitz et al. 2011, 2013). There are anatomical indications that these streams project differently into the hippocampal formation (as discussed above). Chapter 3 discusses the dissociation between the perirhinal and postrhinal cortices, and Chap. 5 discusses the LEC and its distinction from the MEC.

1.3.5 Remapping

When passing from one environment to another, place cells sometimes show dramatic changes in their firing pattern. The question of which change in the environment induces a change in the firing pattern of place cells, and which does not, was a subject of many studies. The term *remapping* has since been used also for describing changes in other cell types, such as head direction cells and grid cells during transformations in the environment. Remapping is discussed in many chapters of this book (see Chaps. 5, 8–11, 13, and 16).

1.3.6 Comparative Issues

The rat is no doubt the major animal model used in this type of hippocampal research. Recently, due to advances in genetic techniques, there is increasing research performed in mice as well. However, a major question is to what extent these results, obtained in rodents, translate to other species, especially to other mammals. Specifically, we are also interested to know whether humans have similar mechanisms as those described in the rat. Chapter 16 in the book contains a detailed discussion of the little that is known about how the results in rats translate to other species. The chapter contains detailed tables outlining similarities and differences between results in different species. Among other things, the chapter describes recordings of place cells and grid cells in bats and discusses their implications for major theories in the field. In addition, other chapters, such as Chaps. 2 and 11, touch on these comparative issues.

1.3.7 Path Integration

Path integration is proposed to be a major explanation of how place cells, head direction cells, and grid cells are formed. The basic idea is that self-motion cues, such as the vestibular senses, optic flow, and proprioception, provide information about velocity that is integrated over time to yield an estimate of position. The advantage of path integration is that it can be used for constant updating of position without the necessity of computing continuously the complex associations between each location of an environment and arbitrary spatial landmarks. The disadvantage is that path integration accumulates error, and thus, the position signal needs to be anchored on occasion to absolute estimates of position obtained from external senses. Chapters 4, 8, and 10 discuss these issues.

1.3.8 Modeling: Attractor Vs. Oscillatory Interference

The generation of the types of cells described in this book is a matter of heated debate. There are two major classes of theories that account for the generation of grid cells and place cells. The first class of theories suggests that grid cells are formed from combinations of two oscillations generating beats. Major proponents of this theory advocate for it in Chap. 12. The second class of theories suggests that grid cells are formed through network interactions in an attractor-based model. Major proponents for this theory advocate for it in Chap. 16. There have also been attempts to reconcile and merge these theories, such as that by Hasselmo and Brandon (2012). Both classes of theories are discussed and compared in depth in Chaps. 8 and 14, where the advantages and disadvantages of these two modeling attitudes are compared. Although all present theories have gaps and inconsistencies, they are fruitful in that they generate many testable predictions, pointing out important issues in this growing field of research.

1.3.9 Phase Precession and Oscillations

There is an intimate relationship between local field potential oscillations and the activity of the cells described here. The rat's hippocampus and associated structures contain characteristic oscillations, such as a prominent 5–12 Hz theta oscillation, gamma waves, and ripples. The different cell types in this region are characteristically locked to different phases of the theta oscillation. In addition, some cells perform *phase precession*, which means that the phase of their spikes relative to the theta wave becomes earlier and earlier as the rat progresses through the field of the place cell or grid cell. These issues are discussed in depth in Chaps. 12 and 16 and can be found in many of the other chapters in the book, such as Chaps. 5, 6, 9, 13, 17, 18, and 19.

1.3.10 Objects

The classical description of place cells and other types of cells in this system relates to the position of the self in the environment. However, if these regions are also involved in the coding of the general spatial environment, an interesting question is how is the position of other objects encoded. Is their position encoded in the same reference system in which the self is coded, or are there dedicated regions for encoding object position? These questions, in our view, need to still be clarified. A discussion of related questions can be found in Chaps. 3, 6, and 11.

1.3.11 Modulation of Hippocampus

In addition to the "canonical" neurotransmitters, glutamate and GABA, the hippocampus is modulated by a plethora of neuromodulators, such as dopamine, acetylcholine, serotonin, and cannabinoids. While there are general roles of these modulators in the context of the whole brain, it is of interest to investigate what are the specific roles of such modulators in the hippocampal formation. For example, how are theta waves in the hippocampus affected by the cholinergic projection from the medial septum to the hippocampus? A discussion of hippocampal modulation can be found in Chap. 7, with additional discussion of different forms of hippocampal modulation also in Chaps. 9, 12, 17, and 18.

1.3.12 Adult Neurogenesis

Although only dealt with in one chapter (Chap. 15), we believe adult neurogenesis is a major issue in hippocampal research. There are two main regions in the brain in which such adult neurogenesis occurs in large quantities, the olfactory bulbs and the dentate gyrus in the hippocampal formation. The rareness of this phenomenon in the brain suggests that adult neurogenesis must have a functional role that is critical

for the computations performed by these two regions. Thus, it is imperative to understand this role and the connection of this phenomenon to the function of the different cell types in the hippocampal formation.

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Part I

Hippocampal Inputs

The Posterior Parietal Cortex: Interface Between Maps of External Spaces and the Generation of Action Sequences

2

Douglas A. Nitz

Abstract

In primates as well as rodents, the posterior parietal cortex maps spatial relationships having both egocentric and external frames of reference. In this chapter, the form in which rat posterior parietal cortex neuronal activity maps position within trajectories through the environment is considered in detail and compared to the forms of spatial mapping observed for neurons of the hippocampus and entorhinal cortex. Evidence is presented to indicate that posterior parietal neurons simultaneously map positions both within and across segments of paths through an environment. It is suggested that the specific nature of posterior parietal cortex mapping of space serves, in part, to transition knowledge of position in the environment, given by hippocampus and entorhinal cortex, into efficient path-running behavior via projections to primary and secondary sensory and motor cortices. Posterior parietal cortex activity is also hypothesized to play a role both in driving trajectory dependence of hippocampal place cells and in anchoring spatially specific hippocampal and entorhinal cortical activity to the boundaries of the observable environment.

2.1 Introduction

Defined by a structure of afferent and efferent connections largely common to rodents and primates, the posterior parietal cortex (PPC) is home to neurons whose dynamics reveal many of the fascinating forms by which spatial relationships are mapped in the brain. PPC is an "associative" subregion of the neocortex, receiving afferents from nearly all primary and secondary sensory cortices and interconnected with a large number of other cortical regions considered to be associative. Based on its interconnections with other regions of the cortex, the PPC has been described as

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a cortical "hub," mediating a relatively high proportion of shortest-path connections between other structures (Bullmore and Sporns 2012).

In both rodents and primates, the effects of PPC damage on perception and/or the dynamics of PPC neurons lead to the exciting conclusion that this brain area is critical not only for registering simple spatial relationships (e.g., the position of a saccade target relative to the fovea) but also for simultaneously registering much more complex relationships (e.g., the position of a saccade target in the context of associated eye-in-head, head-to-trunk, and hand-to-eye positions). Damage to this region of the brain in humans is associated with the phenomenon of hemineglect, implicating it in the generation and perception of both personal and object spaces as well as spatial attention (e.g., Rafal 1994; Pouget and Driver 2000). Recordings of PPC neurons in monkeys implicate it in a range of functions including planning of body movements as they relate to each other and to the environment and in mental rotation (e.g., Crowe et al. 2005; Cohen and Andersen 2002). Dynamics of PPC neurons in rats have received far less attention, but, nevertheless, implicate it in registering the animal's environmental position in multiple reference frames simultaneously (Nitz 2012).

The hippocampus, as can be seen in many of the chapters in this volume, is also robustly capable of mapping complex spatial relationships, and, in fact, the single most dominant feature driving hippocampal activity appears to be the animal's position within environmental boundaries. Nearly all work employing recordings of hippocampal neurons has been carried out in rodents where it is more feasible to permit free movement about an environment. As such, while PPC function across species will be considered, this chapter will apply greater focus to findings concerning the activity of PPC neurons in rodents, usually rats, taking highly organized trajectories through the space of a recording environment. In the process, there will be an emphasis on how the form of spatial mapping of environmental position in the PPC of navigating rodents differs from and complements that observed for hippocampal neurons. Based on the spatial firing properties of PPC neurons, the structure of PPC efferents, and by comparison to the firing properties of hippocampal neurons, evidence will be presented to indicate that (1) PPC neurons map positions within both egocentric and non-egocentric frames of reference; (2) such spatial maps scale flexibly with changes in the size of an environment; (3) individual PPC neurons can differentially map position in multiple reference frames simultaneously; and (4) PPC is a critical player in the transformation of spatial cognition into planned motor action.

2.2 Afferents and Efferents of the Posterior Parietal Cortex

The posterior parietal subregion of rat neocortex can be clearly defined according to its cortical and thalamic afferents. PPC borders rostrally with somatosensory cortex, caudally with secondary visual cortex, and medially with retrosplenial cortex (Reep et al. 1994; Kolb and Walkey 1987). Thalamic inputs arise from the lateral dorsal and lateral posterior subregions (Reep et al. 1994). Critically, the

sources of thalamic input to PPC distinguish it from bordering cortical regions. Rostrally, somatosensory cortex is innervated by efferents of the thalamic ventrobasal nucleus, while PPC is not. Similarly, lateral geniculate nucleus projects to secondary visual cortex, but not to the PPC. Finally, retrosplenial cortex, on PPC's medial border, differs from PPC in receiving afferents from anterior thalamic nuclei (Reep et al. 1994).

Cortical afferents to the PPC define it as a true "association" cortex and largely parallel to those observed for primate PPC. Afferents arise from secondary auditory, visual, and somatosensory cortices (Reep et al. 1994), making the PPC a hub for multimodal integration. An excellent example of such integration in action is found in parietal subregion VIP of the monkey, where neurons are activated both by touch to particular regions of the head and visual stimuli that appear near that region of the head (Avillac et al. 2005). Accordingly, PPC lesions in the rat impair relational learning involving multimodal sensory stimuli (Robinson and Bucci 2012).

PPC also receives extensive afferents from other "association" cortices. Such afferent sources include the orbitofrontal cortex (Reep et al. 1994), perhaps explaining the modulation of saccade-related activity by reward for neurons in subregion LIP (Platt and Glimcher 1999). A rather restricted region of dorsal frontal cortex often referred to, in the rat, as Fr2, M2, or medial precentral cortex (MPC) projects to the PPC. Recent work examining spiking dynamics of neurons in the MPC (Sul et al. 2011; Erlich et al. 2011) suggests that this region is analogous to premotor regions of the primate cortex with neural activity often related either to specific current actions or, more abstractly, to upcoming actions (Averbeck et al. 2003). Finally, PPC receives afferents from retrosplenial, perirhinal, and postrhinal cortices (Burwell and Amaral 1998a, b; Reep et al. 1994). As will be discussed, it is through connectivity with these structures that the unique form by which PPC maps spatial relationships between the rat and positions along trajectories it takes through an environment may find interaction with hippocampal and entorhinal cortex networks whose activity patterns typically map position within the space of the observable boundaries of the environment. In this respect, it is notable that neurons whose firing rates are tightly tuned to the animal's head orientation relative to the observable environment (a.k.a. "head-direction cells") are found in great numbers in both the retrosplenial cortex (Cho and Sharp 2001) and in the lateral dorsal thalamic nucleus (Mizumori and Williams 1993), the primary source of thalamic input to the PPC. The directional tuning of such cells is, under normal circumstances, aligned to environment boundaries in the same way that the spatially specific activity patterns of hippocampal and entorhinal cortex neurons are (Knierim et al. 1998; Hafting et al. 2005; Taube et al. 1990). That is, tuning of head-direction cells is aligned, or takes reference, to what is usually referred to as the allocentric frame of reference. Note, however, that the term allocentric can, strictly speaking, be applied to any non-egocentric frame of reference including subregions of an environment defined by a trajectory. Thus, head-direction neurons within retrosplenial cortex and lateral dorsal thalamus are anatomically positioned to mediate interactions between spatial maps of environmental position in

hippocampal and entorhinal networks with any of the many egocentric and allocentric mappings of spatial relationships found in PPC.

PPC efferents reach many of the same regions from which the PPC receives afferents. Such projections include those to lateral dorsal and lateral posterior thalamus, secondary sensory cortices, and retrosplenial, perirhinal, postrhinal, and medial precentral cortices (Burwell and Amaral 1998a; Nitz 2009). PPC efferents also reach the thalamic reticular nucleus, the zona incerta, and the superior colliculus. In the freely behaving rat, the activity of some neurons of the superior colliculus, medial precentral cortex, and the PPC itself is tightly related to specific locomotor actions such as left and right turns (McNaughton et al. 1994; Cooper et al. 1998; Nitz 2006; Whitlock et al. 2012; Sul et al. 2011; Erlich et al. 2011).

Thus, the PPC gains afferents from sensory and motor regions of the neocortex as well as brain regions associated, in rodents and primates, with mapping of an animal's position in the space of the environment, the so-called allocentric or world-centered space. The PPC provides efferents to these same cortical subregions. Based on this remarkable connectivity structure, it is reasonable to conclude that PPC computes relationships among sensory inputs, motor actions, and their relationships to specific positions in both egocentric and allocentric spaces. However, the number of possible combinations of such variables and their relationships to specific spatial frames of reference and to each other is seemingly endless; neuroscience is likely just "scratching the surface" with respect to revealing specific computations that the PPC accomplishes and the forms they take in the electrical dynamics of PPC neurons.

2.3 Contrasting Methods for Examining Posterior Parietal Cortex Function

A variety of experimental approaches have been brought to bear on PPC function. The result is a complex array of published work implicating PPC in motor control (e.g., Mountcastle 1995), decision-making (e.g., Shadlen and Newsome 2001), attention (e.g., Colby and Goldberg 1999), spatial mapping of sensory stimuli (e.g., Mountcastle et al. 1975), navigation (e.g., Kolb and Walkey 1987), numerosity (e.g., Tudusciuc and Nieder 2009), reward processing (e.g., Platt and Glimcher 1999), generation of a body schema (e.g., Avillac et al. 2005), processing of topological relationships (e.g., Goodrich-Hunsaker et al. 2005), multimodal sensory association (e.g., Robinson and Bucci 2012), mental rotation (e.g., Crowe et al. 2005), object-centered spatial mapping (e.g., Chafee et al. 2005; Crowe et al. 2010), and even imagination (Hassabis et al. 2007).

Yet, for practical reasons, experimental approaches to determining PPC function (lesion, electrophysiology, imaging) cannot be applied equally across rats, humans, and nonhuman primates, in which PPC function has most often been examined. Practical limitations also dictate large differences in the types of tasks, behaviors, and actions that are used to reveal correlates of PPC neural activity or cognitive capabilities lost subsequent to PPC damage. For example, PPC activity during free

locomotion through an environment has been examined only in rodents. As a result, most, but not all (e.g., Bremmer et al. 2002), other work entails some form of head restraint and a "clamp" on responses of the vestibular system which potentially have a strong impact on PPC activity. Work in monkeys allows great precision in sensory stimulus presentation and rendering of motor actions to be combined with examination of PPC activity at the level of single neurons (i.e., with high spatial and temporal resolution). And, of course, it is only in humans that a request to "...imagine you are lying on a sandy beach in a tropical bay. Describe what you can see, hear, smell, and feel in as much detail as possible..." can be granted during PPC imaging (Hassabis et al. 2007).

The ultimate outcome of applying qualitatively different approaches to examining PPC functions remains to be determined. Certainly, different approaches allow more, different PPC functions to be revealed and several of these are considered in the succeeding sections. At the same time, different approaches may, somewhat inadvertently, provide strong evidence for certain PPC functions. For example, a role for PPC in mapping object-referenced space finds support in studies of hemineglect in humans (Driver et al. 1994), in monkeys performing tasks explicitly demanding perception of object spaces (Chafee et al. 2005), and in rats traversing paths through an environment (Nitz 2006). However, it is also clear that segregation in approach can be detrimental. In particular, hypotheses concerning the form and function of hippocampal interactions with PPC are constrained by the fact that hippocampal activity is almost always considered with reference to allocentric space (in rats) and PPC activity is almost always considered with reference to egocentric spaces such as the position of a stimulus relative to the position of the hand, eye, or head (in monkeys). One can easily miss the fact that both structures have in common a dependence of activity on the trajectory of the animal (e.g., Wood et al. 2000; Frank et al. 2000; Nitz 2006) and that PPC activity can map position in allocentric spaces (Nitz 2006; Chafee et al. 2005; Freedman and Assad 2006; Snyder et al. 1998). As a result, it is difficult to know whether PPC function differs considerably in rodents versus primates in line with possible differences in which senses dominate their assessments of spatial relationships or whether PPC function in rodents and primates is largely similar. The advent of head-restrained recordings in rodents during volitional movement through virtual reality environments may soon provide an opportunity for more direct comparisons (Harvey et al. 2009; Ravassard et al. 2013).

2.3.1 The Perspective from Human Work

The perceptual phenomena of hemineglect stand as the most impactful in revealing PPC function in higher cognitive processes in humans (Vallar 1998). The basic finding, neglect or even lack of awareness of the side of the body or visual field contralateral to the lesion, demonstrates that PPC is a critical determinant of what subset of sensory information reaches the level of conscious perception at any given time. Certain postures, for example, a turn of the head to the right in a left-field

hemineglect subject, can reduce the degree of neglect (i.e., the probability of detecting something in the left visual hemifield; Karnath et al. 1991). Such change in posture is, presumably, reflected in signaling from the proprioceptive and/or vestibular systems, suggesting that the PPC integrates proprioceptive, vestibular, and visual information as they relate to personal space. Hemineglect experiments were also among the first to demonstrate that PPC plays a role in mapping not only egocentric space but also the allocentric space defined by the shapes of objects (Driver et al. 1994). More recently, in an experimentally complementary fashion, the advent of fMRI has afforded the chance to add to the list of higher cognitive functions that appear to depend on PPC function in humans. Based on such work, the PPC appears to be involved in episodic memory (Addis et al. 2012), mental rotation (Richter et al. 1997), navigation (Spiers and Maguire 2007), imagination (Hassabis et al. 2007), and assessment of numerosity (Hayashi et al. 2013). Yet, while such work can direct future experimentation in important ways, it may also fall short of defining forms by which these processes are carried out in brain electrical activity. Beyond rough temporal correlation, the mechanisms by which activity patterns of PPC find interaction with activity patterns of other structures such as the hippocampus are perhaps best revealed in experiments employing multiple single-neuron recordings in behaving animals.

2.3.2 The Perspective from Monkey Single-Neuron Recordings

The vast majority of work in monkeys centers on action potential firing dynamics of individual PPC neurons. Early work of this type began in the laboratory of Vernon Mountcastle who remarked that PPC, in contrast to somatosensory cortex, had "...neurons that were active if and only if the animal "had a mind" to deal with the stimulus in a behaviorally meaningful way!" (Mountcastle 1995). Thus, already, at very early stages of single-neuron recordings in behaving animals, it was clear that PPC responses to sensory stimuli and correlations to motor acts were context dependent, with "context" sometimes being defined by rather abstract concepts such as intent as opposed to more palpable, though complex, relationships (contexts) such as position of the eyes, hand, and head to each other.

Examining PPC activity at the single-neuron level, a number of major advances have been made both with respect to concrete variables (e.g., relationship of eye, hand, and target positions) and with respect to more abstract variables such as object space. Critical among these findings have been as follows (1) the identification of PPC subregions; (2) the discovery of working memory or "delay" activity; (3) the relation of PPC activity to accumulation of evidence relevant to decision-making; (4) characterization of the complex forms by which PPC can map the position of a target in multiple egocentric frames of reference simultaneously; and (5) the demonstrations that PPC neuron activity can reflect position along mentally travelled paths, positions in object space, and conjunctions of egocentric and allocentric spatial relationships. The final two items in this list are those most

relevant to examining the role of the PPC as it relates to function of the hippocampus and are considered in more detail below.

2.3.3 Gain Fields and the Encoding of Multiple Spatial Relationships Simultaneously

A common structure for PPC recording experiments involves assessment of activity during a delay phase in a task demanding movement to a target; such work clearly shows that PPC subregions, aside from differences in anatomical connections, also differ according to the specific effector (e.g., eye versus hand) used to enact a movement to a target. Area LIP neurons, for example, are active primarily with respect to eye movements, while parietal reach region (PRR) neurons are active primarily when movement of the hand to a target is demanded (Cohen and Andersen 2002). Recent work (Murata et al. 2000) suggests that AIP neurons map spatial configurations of the hand necessary to grasp specific types of objects (i.e., movement of the digits relative to each other). Subregion VIP appears to be dominated by sensory responses to both tactile and visual stimuli (Colby and Duhamel 1996).

Interactions between these subregions appear to be organized according to the spatial frame of reference across which the activity of PPC neurons is organized or "tuned." In both LIP and PRR, for example, a target in the environment impacts neuronal spiking activity according to its position in an eye-centered frame of reference (Cohen and Andersen 2002). PRR activity tuned to target position in this eye-centered frame of reference is modulated in absolute degree by the position of the hand relative to the eye. That is, the target positions associated with maximal and minimal activity remain the same, but the absolute degree of activity at that target position, and others, is altered. Such modulation is often referred to as a "gain field" and, in effect, permits PPC neurons to simultaneously encode position of a target stimulus in multiple egocentric reference frames (e.g., relative to the head as well as relative to position on the retina; see Fig. 2.1). In this scenario, subpopulations of LIP and PPC neurons can maintain seemingly permanent activity relationships to each other wherein the groups of neurons tuned to the same eye-centered position of a target will always be most active relative to all otherwise-tuned neurons whenever a target falls in their preferred location. Across that same group of active neurons, different members will be most or least active according to the position of the hand relative to the eye such that all possible combinations of target-to-eye and hand-to-eye relationships are accompanied by different PPC firing patterns. Gain fields produced by eye and head position relative to the trunk and even the orientation of the head relative to the world have also been described (Brotchie et al. 1995; Snyder et al. 1998).

Different research groups differ in their assessment of the particulars by which PPC neurons can map combinations of spatial relationships (see, e.g., discussion of basis functions in Avillac et al. 2005). However, it is clear that identification of the spatial frame of reference and the extent to which other spatial relationships change

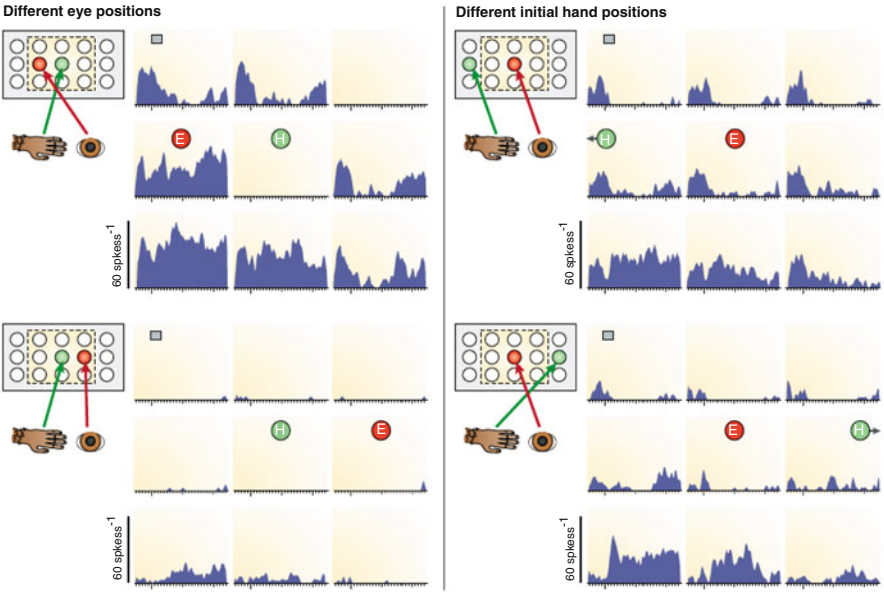

Fig. 2.1 A monkey faced a test panel that contained touch-sensitive buttons. Within each button was a red and a green light-emitting diode (LED). The monkey looked at the button that was illuminated with the red LED and pushed the button that was illuminated by the green LED. The source location of an auditory signal (300 ms burst of noise) was used to instruct the animal as to the target location for a reach. After a delay, the red and green LEDs were extinguished and the monkey reached towards the remembered location of the auditory target. Each of the four panels contains a schematic that shows variations of eye position and initial hand position. Head position is the same in all conditions. The *circles* indicate the relative position of each button assembly and the *dotted square outlines* a grid of potential sensory-target locations. The *red circle* indicates the button that the monkey fixated. The *green button* indicates the button that the monkey initially pressed. Next to each schematic are the response profiles for a single parietal reach region (PRR) neuron. Each was generated from data obtained when the monkey was participating in the variant of the reach task that is shown in the schematic. The spike-density histograms, aligned relative to the onset of the sensory cue, are arranged as a function of target location. The *circled "E"* and the *circled "H"* indicate the location of the monkey's eye position and initial hand position, respectively. The *grey bar* indicates the time of cue onset and the duration of the cue. Among the eight possible target locations, maximal activity is always observed when the target is to the southwest irrespective of starting eye and hand positions. Thus, the neuron is said to have, by default, a head centered frame for its spatially-specific activity (i.e., for the changes in response strength associated with the eight different target sites) However the magnitude, or "gain," of the overall pattern is strongly influenced by eye position such that the neuron's responses are informative of the target position relative to both the head and the eye. Figure reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience 3(7): 553–62 © 2002

the "gain" on spatially tuned PPC activity are absolutely critical to understanding the function of the PPC in mediating complex spatial relationships. In the case of PPC activity fixed to an eye-centered frame of reference, but gain modulated by position of the head and eye (together gaze position) relative to the trunk, one even finds a plausible explanation for the fact that gaze to the right (of the trunk) in a left-

field hemineglect subject enhances detection of stimuli in the left hemifield (Karnath et al. 1991; Pouget and Sejnowski 1997).

2.3.4 Posterior Parietal Cortex Activity in Nonhuman Primates Maps Non-egocentric Spaces

Finally, it is important to consider work examining the extent to which PPC activity in monkeys maps position in non-egocentric spaces. This aspect of PPC activity both broadens the range of functions for which one can consider PPC a participant and, in turn, broadens the range of possible interactions between PPC and hippocampus that are plausible. The issue has not been examined extensively, yet one can already compose an impressive list of rather abstract spaces across which specific PPC firing patterns are clearly observed. The available data indicate the following (1) that PPC neurons can map position in object space (Chafee et al. 2005); (2) that numerosity is differentially encoded in the activity of PPC neurons along a single continuum (Tudusciuc and Nieder 2009); (3) that orientation of the head relative to the "world" (the space of the recording room) can change the "gain" on PPC subregion 7a activity patterns which, at the same time, are based in an eye-centered reference frame (Snyder et al. 1998); and (4) that subregion LIP neurons can undergo alterations in the shape of their eye-centered patterns of spatial activity according to task rules that define two arbitrary spaces spanning opposite sides of an invisible line (Freedman and Assad 2006). Work directly demonstrating that PPC subregion 7a neurons can map object space (Crowe et al. 2008) has also revealed that the same population of neurons map position in both egocentric (retinal) and object frames of reference depending on task phase. That is, subregion 7a is identified as a potential locus for the transformation of ego- to object-centered frames of reference.

2.3.5 Posterior Parietal Cortex Lesion Studies in Rats

Prior to 2006, one could count on one hand the number of publications concerning the activity of PPC neurons in rats (Chen et al. 1994a, b; McNaughton et al. 1994; Qin et al. 1997). Prior to this, and for the same time period over which major advances were made in understanding hemineglect and the dynamics of monkey PPC neurons (and even their relation to each other), a large number of experiments examined the impact of PPC lesions on perception and behavior, particularly navigational behavior. A full rendering of findings from such work is beyond the scope of the present work (for review see Kesner 2009; Save and Poucet 2009; Reep and Corwin 2009), but it is useful to touch upon those that yield contrast to the effects of hippocampal lesions and those which implicate PPC function in the processing of allocentric spatial relationships.

The classic navigational task, the Morris water maze, demands mapping of position in allocentric space and has been the subject of many PPC lesion

experiments. As reviewed by Save and Poucet (2009), the results are largely mixed, with some groups reporting mild effects of PPC lesions on finding a submerged platform according to its place relative to distal cues defining the space of the experimental room (e.g., Kolb and Walkey 1987; Save and Poucet 2000). Larger deficits have been reported as well, particularly in studies wherein PPC lesions encompassed its more lateral reaches (Hoh et al. 2003; DiMattia and Kesner 1988). In contrast, hippocampal lesions robustly impair performance (e.g., Morris et al. 1990). Some evidence suggests that interaction between PPC and hippocampus is critical in solving the Morris water maze. Rogers and Kesner (2007) made either ipsilateral or contralateral unihemispheric lesions of hippocampus and PPC. Deficits in a dry-land version of the Morris water tank test were found only for the contralateral group suggesting that interaction between these two structures is a critical component of navigation in world-centered spaces.

PPC lesions more consistently result in deficits on tasks considered to test egocentric spatial cognition, but a close look at the findings suggests that the deficits cannot, at least simplistically, be explained by a failure to recognize the positions of environmental stimuli relative to self (e.g., to a position on the retina) nor a failure to differentially enact movements relative to the self (e.g., to make a left versus right turn). PPC-lesioned rats are somewhat impaired in their ability to move directly to a target without motor error (Kolb and Walkey 1987) and without abnormal variability in trajectory (Foreman et al. 1992). PPC lesions also impact performance on "egocentric" versions of Hebb-Williams mazes (Rogers and Kesner 2007) and in blind rats traversing Lashley III mazes (Pinto-Hamuy et al. 2004).

However, PPC rats are largely unimpaired at altering trajectory to reach a visible target (Kolb and Walkey 1987). Thus, PPC lesions do not impact the basic process of generating an appropriate egocentrically referenced movement (left or right to the present direction of motion) to a target that resides in a separate (retinal) egocentric frame of reference. Instead, deficits appear under conditions wherein a series of choices (left turn versus right turn versus straight) defining a path to a goal must be learned. While learning such a path can be accomplished by integration of egocentric, kinesthetic information across time, it is also possible that efficient route running involves learning the shape of the route itself and understanding the positions within it as contrasted to simply learning a series of locomotor behaviors. As will be discussed later, PPC activity more accurately reflects the former than the latter (Nitz 2006, 2009; Whitlock et al. 2012). Thus, it is distinctly possible that PPC lesion-induced deficits in labyrinth-style maze performance actually reflect a deficit in mapping of position in an alternate allocentric space, that defined by the correct route.

Some lesion work more directly evidences a role for rat PPC in processing of non-egocentric spatial relationships, thus supporting the preceding argument and the aforementioned role of PPC in mapping non-egocentric spaces in primates. Relatively early work indicated that PPC was critical in responding to object-in-place paired associates (Save et al. 1992; Long and Kesner 1998; Rogers and Kesner 2007) with object-only and place-only responses left intact; note that

"place," in this case, refers to the allocentric space defined by the boundaries of the observable environment. In contrast to the mixed results for the classic Morris water maze task, two studies employing a "proximal cues" version of the task found a clear impairment following PPC lesions (Kolb and Walkey 1987; Save and Poucet 2000). In each study, a visual cue or constellation of cues was placed within the borders of the water tank and, from trial to trial, bore a specific spatial relationship to the site of the submerged platform. The results suggest that the PPC, like hippocampus, plays a role in mapping positions in allocentric space, but that the two regions differ in mapping spatial relationships among proximal versus distal landmarks. Notably, proximal versus distal visual cue sets have been shown to define different navigational strategies during performance of the Morris water tank task (reviewed in Knierim and Hamilton 2011). Finally, PPC mapping of non-egocentric spatial relationships was also evidenced in recent work wherein lesioned rats were tested for their ability to recognize changes in the topology of objects spread about an open environment. When the positions of two objects in a four-object set (arranged as a square) were exchanged, PPC-lesioned, but not hippocampal-lesioned, animals failed to recognize the change, yet did recognize change under conditions where the distance between two objects in a two-object set was altered. The combined results are not easily explained as a change in the egocentrically based views from specific allocentric positions. Instead, the data suggests that intact PPC function is required to appreciate the topological relationships of all items to each other.

2.4 Dynamics of Rat Posterior Parietal Cortex Neurons in Freely Navigating Rats

As considered previously, neurophysiological experiments carried out in freely behaving animals permit one to examine PPC activity under more naturalistic conditions, specifically those in which (1) task-specific actions involve coordination of the entire body's musculature, (2) vestibular information is permitted to vary over a broad range (it is effectively clamped in most recording experiments in primates), and (3) extensive traversal of environmental space is possible (allocentric space is also clamped in most primate recording experiments). Of course, all three such conditions are exactly those required to reveal, in all their wonderful specificity, the most robust firing correlates of hippocampal and entorhinal cortex neurons, namely, the position and/or head orientation of the animal relative to the space of the observable environment (O'Keefe and Dostrovsky 1971; Terrazas et al. 2005; Foster et al. 1989).

And so, recording studies in rodents represent an opportunity to understand how the PPC, hippocampus, and entorhinal cortex complement each other both in mapping spatial relationships and in guiding navigation. There are, however, few such studies, perhaps due, in part, to the idea that the PPC primarily maps egocentric spatial information, but perhaps also in part to the fact that the spatial firing correlates of PPC neurons in freely behaving animals do not present themselves in

the obvious manner of hippocampal place cells, thalamic and entorhinal cortex head-direction cells, and entorhinal cortex grid cells. A downside of the freely behaving animal is that it often behaves freely. While spatially tuned place cell, grid cell, and head-direction cell activity are relatively immune to perturbation by modest changes in the animal's motor behavior, PPC activity appears particularly sensitive to variability in motor behavior. As such, extracting the spatial firing correlates of PPC neurons in freely behaving animals usually demands close monitoring of motor behavior [see Whitlock et al. (2012) for an excellent example], some degree of constraint on the trajectories and associated action sequences that an animal can take through any given environmental space, and/or behavioral "filtering" of positional tracking data to extract time periods associated with less variable behavior.

Though the number of studies employing such controls is not great (certainly less than 10), there are several basic features of PPC activity that permit direct comparison to the firing properties of place cells, head-direction cells, and grid cells. First, spatial firing correlates to specific frames of reference (egocentric and allocentric) have been identified. Second, there appears to be a small population of head-direction cells. Third, a gain field-like mechanism appears to permit mapping of multiple spatial relationships. However, it is also the case that, compared with structures such as hippocampus, the form of spatial activity patterning by PPC neurons is fundamentally different as are the core sources from which spatially specific activity arises. These components of PPC spatial activity are considered in more detail below.

2.4.1 Frame(s) of Reference

An early publication examining the firing behavior of PPC neurons in behaving rodents emphasized their correlation to specific locomotor actions taken by the animal (McNaughton et al. 1994). Nearly half of all PPC neurons in this study were found to exhibit either increased or decreased firing across portions of an eight-arm maze associated with turning (left versus right) and/or forward motion. Various combinations of correlates were observed. Neurons firing over maze sections associated with left turns as well as straight-run sections were observed as were neurons with more specific activity correlations (e.g., activity increases only over right-turn maze sections). Left- and right-turning and straight-running behavior reflect motion of the animal relative to itself and can, theoretically, be registered as series of whole-body proprioception, optic flow patterns, and/or vestibular system responses. As such, the work's main conclusion was that PPC contained a robust and redundant egocentric representation of the rat's state of motion. However, the authors were careful to note exceptions to the rule, neurons whose movement correlates appeared to depend on spatial context (e.g., which of all possible turn sites were associated with a given neuron's activation) and/or the nature of the preceding movement (e.g., a neuron sensitive to forward motion following right, but not left, turns). This seminal finding was strongly supported

in two subsequent studies (Nitz 2006; Whitlock et al. 2012), but, in each case, evidence was presented to further indicate that spatial context and/or context given by preceding or subsequent movements is a strong determinant of PPC firing activity in behaving animals.

Nitz (2006, see also Nitz 2009) examined PPC activity during traversals of multiple complex routes and found evidence that PPC activity correlates go well beyond what can be accounted for by egocentrically defined motion. Following a similar categorization protocol to that of the McNaughton et al. (1994) study, a similar proportion of neurons having left-turn, right-turn, and/or straight-run activity correlates were observed. However, the multiple paths used in this study permitted a broader analysis of the effect of context given by spatial position and movement sequence. Position of a movement in a sequence was shown to be a strong determinant of action-specific activity. For example, neurons having, on average, a tendency to fire strongly during execution of a left turn were highly variable in the strength of such firing across 10–12 different left-turn sites (Fig. 2.2). Follow-up analyses of the same data (Nitz 2009) demonstrated that the degree of variability in action-specific activity is great enough that any two regions of a track associated with the same action (e.g., execution of a right turn) can easily be dissociated by the activity patterns of just 50 PPC neurons. In fact, even single neurons may exhibit distinct firing increases over a subset of track sections associated with the three possible actions (left turns, right turns, straight runs), yet, through complete inactivity, distinguish these sections from others associated with the same actions (Fig. 2.3). In sharp contrast to the impact of context given by movement sequence, spatial context given by distal cues defining the environment's boundaries (i.e., the allocentric space) was nearly without impact on PPC firing patterns. When a path of a given shape was traversed from different start and end points in the allocentric space, path-position-specific firing rates of PPC neurons were unchanged. Hippocampal place cells, under the same circumstances, reflected the change in allocentric positions taken during path running by exhibiting differential patterns for the two path placements. Together, the findings strongly support a model in which, during traversal of a familiar path, the tendency for PPC neurons to exhibit an activity correlate to an egocentrically defined motion is so distorted by the context of that motion's position in a sequence that a mapping of position in the space of the route is derived. That is, PPC neurons map position in the rather abstract space defined by the route itself which is composed of the series of inflection points in behavior (starts, stops, turns) and the straight-run spaces that separate them.

More recently, Whitlock et al. (2012) examined firing patterns of PPC neurons during random-walk foraging periods in an open environment and during traversal of a regular series of turns and straight runs defined by boundary walls. By examining in detail the motion of the animal during the random-walk period, the authors were able to show that a subset of PPC neurons, in freely behaving animals, can robustly map egocentrically defined motions through correlation to both linear and angular velocity. Yet, the same neurons, under conditions of track running, switched completely, now reflecting the spatial structure defined by the required

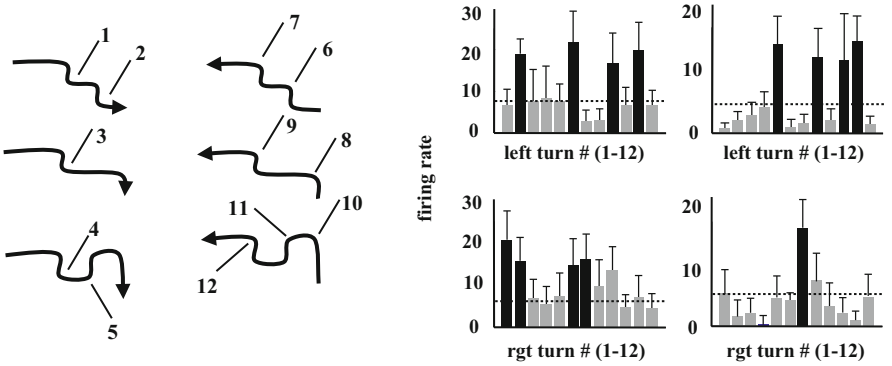

Fig. 2.2 Mean firing rates across 12 different *left or right turns* for four PPC neurons recorded during inbound and outbound traversals of the three path shapes given at *left* (*numbers* mark the site of 12 different *left turns*. Adapted with permission from Neuron 49(5):747–756 © 2006

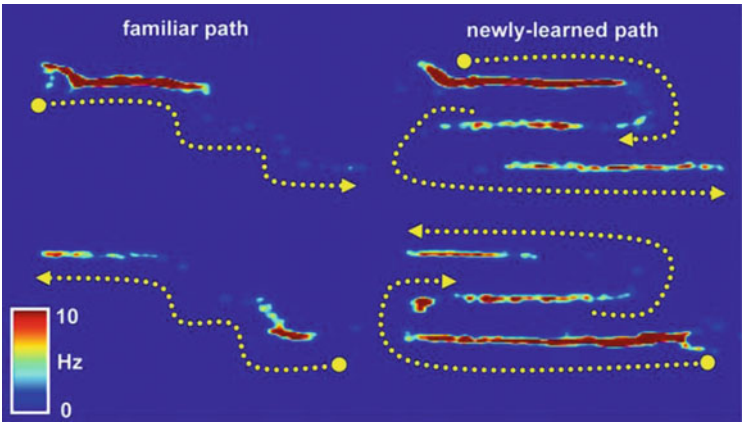

Fig. 2.3 Firing rates for a single PPC neuron across four different trajectories through space. The neuron fires strongly across all straight-run segments between the start point and the first right turn and also at some, but not all, *left and right turns*. Adapted with permission from Neuron 49 (5):747–756 © 2006

movement sequences. PPC activity patterns on the track persisted when the track was placed in a different allocentric space; entorhinal cortex grid cell patterns remapped in response to this change. The result clearly demonstrates that the network formed by PPC neurons in the rat is both capable of generating a representation of motion relative to the self (as in the result obtained during random foraging) and a spatial representation having an allocentric frame of reference (as in the result obtained during track running). During track running, the spatial reference frame for PPC neurons (the shape of the track irrespective of its place in the larger environment) is fundamentally different from that governing the spatial firing of entorhinal grid cells (position in the larger environment). That the same

network can map both egocentric and allocentric spaces parallels work in monkeys, mentioned earlier, where the task was to identify the position of a visual stimulus (a small square) relative to the position of an object (an upside-down T), irrespective of that object's position on the retina. Here, PPC activity initially reflected the position of the stimulus and object relative to the retina (i.e., was egocentrically framed), but later (within 100 ms) activity transitioned to better reflect position of the stimulus relative to the allocentric space defined by the object (Crowe et al. 2008).

2.4.2 Registering Position in Multiple Spaces

Spatial cognition is, at times, exceptionally complex. One can easily realize, for instance, the layout of a route and/or position within a route as they relate to position in the space of the observable environment and as they relate to positions on a physical map. Understanding how the brain registers such externally referenced spatial relationships based on egocentrically referenced sensory information may not only be key to understanding efficient and intelligent interaction with the environment but may also reveal mechanisms by which novel spatial relationships may be imagined.

Determining how such higher-level spatial relationships are encoded remains a challenge, yet recent findings reveal some of the forms by which neural activity can map multiple spatial relationships. Hippocampal neurons, for instance, can map an animal's position in two allocentric frames of reference. In one form of such encoding, hippocampal place cells maintain their positional firing correlates within the space of the arena but alter their in-field firing rates according to the differential positioning of that same arena within the larger, inaccessible environment defined by distal visual cues (Leutgeb et al. 2005). This form has been referred to as "rate remapping" [see Leutgeb and Leutgeb (2014)]. A second form is observed for a bounded environment that rotates within a larger environment defined by distal visual cues. Here, a relatively rapid exchange of two different place cell mappings is observed (Kelemen and Fenton 2010) with one mapping reflecting position in the bounded environment and the other position in the larger environment.

The forms by which PPC maps multiple spatial relationships have been examined most extensively in the monkey where it is possible to tightly control egocentrically defined spatial relationships among hand, eye, head, torso, and environmental stimuli. Here as well, one finds that one form of multiple-space encoding involves alterations in absolute firing rate for neurons which, nevertheless, maintain consistency in the egocentrically defined positions associated with their peak firing (Cohen and Andersen 2002). That is, the pattern of relative firing across positions is maintained, while the absolute rates at each position vary, a phenomenon termed a "gain field." A second form by which multiple relationships are mapped is through coexistence, in the same PPC subregions, of neurons having activity aligned to different frames of reference (e.g., neurons with eye- versus head-centered frames of reference in subregion LIP in response to auditory targets).

Recent work examining PPC and hippocampal activity in rats traversing squared spiral tracks provides a new understanding of how multiple allocentric and egocentric spatial relationships are simultaneously mapped. PPC neurons were recorded during traversal of squared spiral tracks each composed of five loops with each loop composed of four straight-run segments; right or left turns defined the beginning and end of each segment (Nitz 2012). The structure of the tracks was such that the animal was always in at least four allocentric positions (1) somewhere between two turns, (2) somewhere within the space of a single loop, (3) somewhere in the space of the full route (all loops and segments), and (4) somewhere in the space of the larger environment defined by distal visual cues. Of course, each track position was also associated with either straight-running or turning behavior and so the presence or absence of firing correlates to egocentrically defined motion could also be examined.

By distinct forms, PPC neurons mapped all three allocentric frames of reference associated with the squared spiral track structure and, in addition, were indicative of the animal's egocentrically defined state of motion. Despite repetition in the action sequences required to traverse each of the four path segments of a loop, a majority of PPC neurons exhibited significant differences in the pattern of firing seen across those segments and/or in the magnitude of firing across those segments (Fig. 2.4, upper plots). At the next largest spatial scale, that of loops, essentially the opposite phenomenon was observed. Firing patterns across loops, themselves constructed of four consecutive segment patterns, were recursive, exhibiting highly correlated contours that were spatially adapted to match differences in loop length. Mapping of position across the largest spatial scale, the full route, was also observed. While loop-to-loop firing patterns were highly correlated, the magnitudes of loop-based firing patterns changed as a function of loop position in the full route. For most neurons, linear trends of increasing or decreasing activity between the start and end points of the full spiral track were observed.

The overall result, simultaneous mapping of three allocentric spaces, is revealed in a covariance matrix based on the positional firing rates of 180 neurons recorded during traversal of a squared spiral track requiring right turns for inbound runs (Fig. 2.4). In this figure, pattern recurrence is color mapped (blue, low; red, high). All loop start and end points are marked with black brackets, and start and end points for the four segments of loop 1 are marked with blue brackets. Transitions in PPC firing patterns across adjacent track positions can be discerned by examining how quickly red values transition to blue values over the space perpendicular to the central diagonal. Each corner of the track is associated with a "pinch point" where such transition happens quickly (black arrow) compared to straight-run sections where transitions are more gradual (double black arrow). The difference is likely explained by changes in the animal's state of motion which persists across the longer straight-run sections. Strong pattern recurrence is also seen across loops and is observed as the red color mapping found across the central diagonal of each rectangular section outlined by the brackets of any two loops. Such a diagonal is marked by a black line for the loop 1 versus loop 2 portion of the matrix. While recurrence was, to some extent, also seen for analogous positions of different

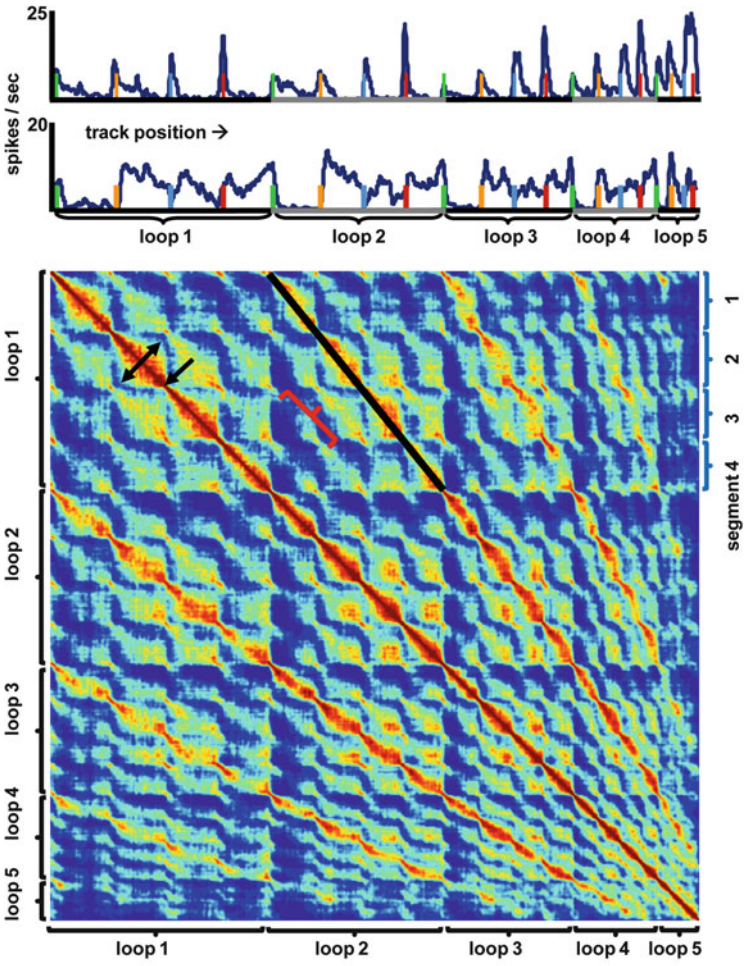

Fig. 2.4 *Top panels*—Firing rates 2 PPC neurons across linearized spiral track (actual track structures at bottom of figure). *Bottom panel*—Covariance matrix for 180 PPC neurons recorded during traversal of a squared spiral track. Pattern covariance among the 180 neurons is mapped (*blue*-low, *red*-high) for all possible combinations of track position

segments, its magnitude was much reduced owing to greater overall differences in pattern across segments (see, e.g., the loop 1, segment 2 versus loop 2, segment 3 as marked by the black bracket). The increased strength of recurrence across loops as compared to segments occurs despite the fact that both loops and segments are identical in the required behavioral sequence. Modulation of PPC activity according to a third allocentric space, the full route, is more subtle but can be observed as a degradation in the degree of recurrence as the separation between two

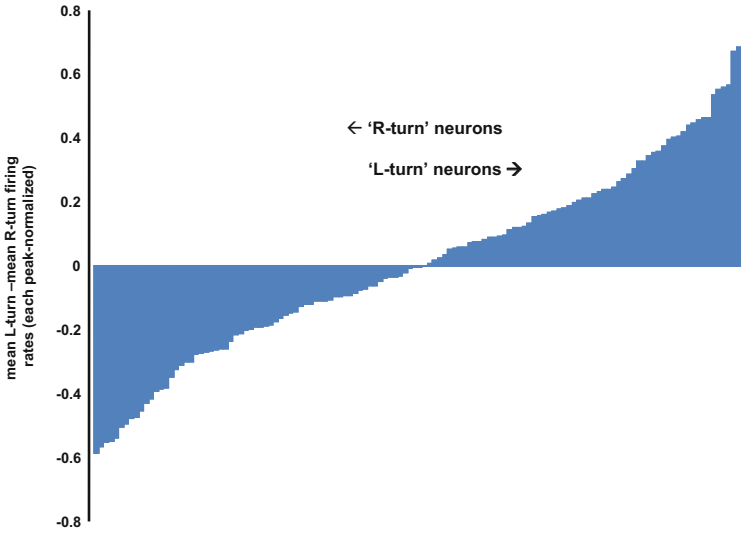

Fig. 2.5 Difference in mean firing rate across all left versus all right turns for 130 PPC neurons recorded during traversal of left-turning and right-turning squared spiral tracks (means based on 20 turns each). Firing rates for each turn were normalized to the maximum value prior to subtraction. Individual neurons are sorted by left-turn versus right-turn preference

loops becomes greater (compare, e.g., loop 1 versus loop 2 recurrence versus loop 1 versus loop 4 recurrence).

Finally, under the same conditions, a clear mapping of the egocentrically defined state of motion of the animal is still contained in the population neurons active at any given moment. As already stated, the covariance matrix reveals that different populations of neurons map straight-run versus turn sections of the squared spiral track. Left-turning versus right-turning status is given by the population of neurons most active at turn sites. Figure 2.5 depicts mean activity differences for left-turning versus right-turning track regions for 130 PPC neurons recording while running both the L-turning and R-turning versions of the squared spiral track. To eliminate track position as a determinant, mean firing rate across all 20 corners of each track was determined for each neuron (each value normalized to the maximum value for any of the 40 possible corners). Across the 130-neuron population considered, L- versus R-turn differences in firing rate were greater than 25 % for 40 % of all neurons (including those active mainly on straight-run sections).

Thus, the observed PPC population firing rate vectors are not driven solely by correlation to the animal's egocentrically defined state of motion and can instead be said to reflect the animal's position in the allocentric frames of reference defined by the segment, loop, and route spaces. Theoretically, any brain region receiving PPC efferents could extract position in each reference frame as well as the animal's egocentrically defined locomotor state through identification of the most active and

least active cells at any given time and through sensitivity or insensitivity to the absolute firing rates among that same set of cells. The fourth allocentric space, defined by the position of the track relative to distal visual cues, is not a major determinant of PPC firing patterns as rotation of the track relative to such cues does not strongly impact the observed track-based firing patterns (Nitz 2012 supplemental figures; data not shown here). Instead, this allocentric frame of reference is tightly mapped in the spatially specific patterns of hippocampal neurons (Nitz 2011).

2.5 Complementary Roles of Hippocampus and Posterior Parietal Cortex in Mapping Space and in Navigation

Several fundamental features of hippocampal and PPC spatially specific activity patterns are suggestive of their different roles in navigation and, in addition, the possible forms of interaction between these structures. As considered earlier, the most obvious anatomical pathways by which interactions may take place include the retrosplenial, perirhinal, and postrhinal cortices. Although spatial firing correlates for neurons in each of these regions have been observed (Cho and Sharp 2001; Hargreaves et al. 2005; Furtak et al. 2012), it is not at all clear what roles these structures might play as they relate to hippocampal and PPC function.

Before beginning a more detailed consideration of the contrasting and/or complementary roles of PPC and hippocampus, it is perhaps worth recalling a number of remarkable parallels found for basic features of spatial mapping associated with each region. First, both structures accomplish an allocentric mapping of position in the world based on egocentrically framed sensory information. Second, the spatially specific firing patterns in each region are both trajectory specific. That is, firing patterns associated with crossing of any given space may differ according to the specific trajectories taken to reach that space or the specific trajectories taken from that space (Frank et al. 2000; Wood et al. 2000; Ferbinteanu and Shapiro 2003; Nitz 2006; Harvey et al. 2012). Third, as discussed, both regions are capable of using a gain field-like mechanism to encode multiple spatial relationships simultaneously (Leutgeb et al. 2005; Nitz 2012). Finally, in both structures, dependence of spatially specific firing on the direction of movement through a given space is not observed under conditions wherein no organized path is utilized (i.e., in standard free-foraging tasks in open arenas; Whitlock et al. 2012; Markus et al. 1995).

2.5.1 Fluid Transfer of Spatial Cognition into Action and Attention for Action

As discussed earlier, mapping of allocentric spaces by hippocampal and PPC neurons appears to lie at the end point of neural processes achieving integration of self-motion across time. The activity patterns among medial entorhinal grid cells (Hafting et al. 2005) appear capable of specifying the location of any hippocampal

neuron's place-specific activity (Fyhn et al. 2004; see also McNaughton et al. 2006). Within the entorhinal cortex itself, it appears that self-motion integration (direction and speed across time) drives the differential activation of grid cells whose firing peaks bear a constant spatial relationship to each other [Sargolini et al. (2006), see Derdikman and Moser (2014)].

In the PPC, integration of self-motion in the service of creating an allocentric mapping of space is carried out in a fundamentally different way. Self-motion is not mapped onto a static two-dimensional map as in the entorhinal cortex. Instead, mapping of position in the allocentric space defined by a route appears to arise as a perturbation of individual cell firing correlates to forward, left-turning, or right-turning motion (McNaughton et al. 1994; Nitz 2006, 2012; Whitlock et al. 2012; see also Figs. 2.1 and 2.2). The degree of perturbation extends significantly to the large majority of PPC neurons such that only in a minority of PPC neurons is firing reliably related to a single motor act (Whitlock et al. 2012). For this reason, PPC firing patterns can truly be described as mapping the space of a route in a way that is not epiphenomenal to the actions executed at different points along that route (Nitz 2006). Thus, aside from differences in spatial frame of reference, a critical difference between hippocampal and PPC maps for allocentric spaces is that the latter derive directly from a base of activity strongly modulated by the animal's locomotor state. It is presently unclear whether modulation of PPC activity in this manner reflects input from local or retrosplenial head-direction neurons whose activity may be modulated by angular velocity or whether it reflects efference copy of action-related activity patterns in the medial precentral cortex (Erlich et al. 2011).

Because PPC activity maps allocentric position in a route-based frame of reference and, at the same time, reflects the egocentrically framed locomotor state of the animal, it stands as an ideal signal for transitioning spatial information into current and planned motor action. Structures mapping allocentric position in the world, such as the hippocampus and entorhinal cortex, can gain access to (i.e., influence) this process through projections to the retrosplenial, perirhinal, and postrhinal cortices (Burwell and Amaral 1998a, b). PPC likely accomplishes the transition to action through dense efferent connectivity to the medial precentral region just rostral to the primary motor cortex and lateral to the anterior cingulate (Nitz 2009). This region has analogy to primate premotor cortices both in its projections to primary motor cortex (Gu et al. 1999) and in containing populations of neurons with activity correlates to either current or planned actions (Erlich et al. 2011; Sul et al. 2011). PPC also maintains relatively dense projections to the primary and secondary sensory cortices and to the superior colliculus (Nitz 2009). Through such connections, PPC is ideally positioned to simultaneously guide attentional processes such that, during rapidly paced path running, detection of sensory cues relevant to precise timing of locomotor actions is facilitated.

2.5.2 Decision-Making in Navigation

The striking difference in the frame(s) of reference mapped by hippocampal and PPC firing patterns is perhaps a clue to their complementary functions in navigation. In the real world of both humans and rats, travel between locations is not accomplished by direct (i.e., straight-line) paths, but most often demands movement along nondirect paths involving turns and intersections. Spatial firing patterns of PPC neurons reflect progress through such routes (Nitz 2006, 2009). Hippocampal firing patterns reflecting position or positions within the full, observable environment are ideally suited to specifying which path, among several possible, to take from any given location to reach a target location. Such specification could take the form of activation of PPC neuron subpopulations whose activity sequences accompany progression through the chosen path and could represent the neural mechanism underlying most navigational decision-making. The entorhinal cortex would appear to be a candidate region to serve as an intermediary in this respect based on the path-position-specific patterns of activity it generates (Frank et al. 2000).

As discussed in the preceding section, the activation of PPC neurons registering path position may, in turn, lead to the specification of appropriate motor planning in regions such as the medial precentral cortex. In this respect, it is worth noting that choice of a path as a whole is likely preferential to a system wherein the appropriate direction of travel and locomotor actions are computed for all path positions. Association of entire paths with specific world-centered positions allows left-turning, right-turning, and straight-run behaviors to be planned in advance within a system of neurons concurrently encoding locomotor actions. In addition, the added step of remapping world-centered positional information into route-centered positional information may serve the purpose of creating generic PPC representations of path segments that are common to many otherwise differently shaped paths taken in different regions of the environment. Indeed, PPC neurons appear to maintain activity correlates to components of differently shaped paths that bear analogy to each other. For example, Fig. 2.3 depicts a PPC neuron that maintains activation between the start-point and first right turn of four different routes despite differences in orientation of the trajectories relative to the space of the environment and despite the fact that the same neuron fires weakly across other straight-run sections. Remarkably, such activity exhibits a high degree of adaptation to the changing lengths of path components, a feature also seen for the PPC firing patterns observed across loops of squared spiral tracks.

2.5.3 Anchoring

Several properties of spatial firing in hippocampus and entorhinal cortex indicate that their maps of allocentric space become "anchored" to the space of the observable environment at at least one time point following introduction to that environment. In fact, repeated reanchoring events appear to be necessary to avoid noise in spatial signaling arising from errors in self-motion integration (Hafting et al. 2005).

It is well known that both hippocampal and entorhinal cortex firing fields rotate in lock step with distal visual cues that define the space of the environment (Muller and Kubie 1987; Hafting et al. 2005). Furthermore, networks of neurons in each of these structures sometimes undergo what has been termed "global remapping" of place-specific firing patterns in response to alterations in the structural appearance of the environment (Leutgeb et al. 2005; Derdikman and Moser 2010). Here, the place-specific firing patterns among a group of hippocampal neurons are altered wholesale such that some neurons with place fields cease firing, formerly silent neurons may exhibit firing fields, and the spacing of place fields for any two active neurons is altered in a random fashion. The spacing of grid nodes for any pair of entorhinal cortex neurons remains the same, but the orientation of their grid axes relative to the environment is altered (Hafting et al. 2005). Such global remapping of place-specific activity implies that different maps of the environment can be anchored to the same environmental space. Recent data suggest that different hippocampal activity may even undergo repeated reanchoring events to two different allocentric frames of reference (Kelemen and Fenton 2010).

The mechanism by which spatial firing maps of these two regions are anchored to the spatial arrangement of distal visual cues remains to be determined and represents an important gap in current knowledge of hippocampal function. The process demands a conversion of egocentric to allocentric information and is likely carried out based on the relative positions of at least two distal visual cues egocentrically referenced to the animal's direction of gaze. This presumption is based on the fact that such relationships are uniquely related to specific positions in the allocentric space defined by the environment provided that there has been an accounting for the direction of gaze relative to the trunk. Supporting a role for the PPC in providing this type of spatial information, PPC neurons of the monkey have been shown to map the egocentric position of attended visual stimuli (Mountcastle et al. 1975; Brotchie et al. 1995; Colby and Goldberg 1999), including their depth (Bhattacharyya et al. 2009). Activity of the same neurons carries information as to the position of gaze relative to the trunk (Brotchie et al. 1995). Evidence that rat PPC neurons encode similar information is lacking. Nevertheless, the available data at least suggest that the PPC is ideally suited to participate in the process of anchoring hippocampal and entorhinal cortex maps to the space of the environment that their activity patterns encode. Indeed, lesion of the PPC results in impaired updating of hippocampal place cell firing patterns following rotation of distal visual cues that define the allocentric space of a high-walled environment (Save et al. 2005). In this respect, the specific role of the PPC likely occurs through interaction with retrosplenial and postrhinal cortices. In the former, neurons sensitive to locomotor behavior coexist with neurons sensitive to allocentrically referenced head orientation (Cho and Sharp 2001). In the latter, neurons with sensitivity to locomotor state appear to coexist with neurons mapping object position in allocentric space (Furtak et al. 2012). Thus, each structure appears capable of relating egocentric spatial information to the allocentric space of the observable environment.

2.5.4 Trajectory-Encoding in Hippocampus and PPC

An unsolved problem regarding hippocampal function in mapping allocentric space concerns the mechanisms allowing for the modulation of place-specific activity based on the trajectory used to reach a given space or the trajectory to be taken from a given space (Wood et al. 2000; Frank et al. 2000). The answer to the question is central not only to understanding influences on the hippocampal map for space but also to the nature of episodic memory since trajectory-specific spatial activity is an obvious candidate mechanism for differentiating two episodes sharing a common subset of experience.

As has been discussed extensively in this work, the spatially specific activity patterns of PPC neurons robustly map position within a trajectory. A corollary of this is that the output of the PPC contains the information necessary to differentially drive hippocampal and entorhinal cortex neurons according to trajectory. While it remains to be shown that PPC is critical to the generation of trajectory-specific activity in hippocampus, two findings suggest that it is. First, medial entorhinal cortex, anatomically intermediate to PPC and hippocampus, contains neurons that exhibit "path-equivalent" activity patterns; the same path taken from different starting points in the larger environment yields the same spatial firing pattern (Frank et al. 2000; see also Derdikman et al. 2009). Thus, medial entorhinal cortex is positioned to provide a PPC-like input reflecting path position to the hippocampal subregions it innervates. Second, recent data (Singer et al. 2010) demonstrate that identity in the shape of two paths strongly impacts the size of hippocampal place fields as well as the likelihood that hippocampal firing patterns will recur over a wider range of allocentric positions than is normally observed. This effect was also observed in work by Nitz (2011) in which hippocampal place fields were recorded in animals traversing the same squared spiral tracks depicted in Fig. 2.4. Notably, place field expansion and recursion beyond the normal range was organized according to the loops composing the track, the very same space over which recursion of PPC firing patterns was observed. Thus, for the same track-running environment, PPC and hippocampal neuron firing patterns were parallel in differentiating one-track dimension (squared spiral segments) and generalizing across another (loops).

Finally, speaking again to the potentially complementary nature of hippocampal and PPC spatial firing properties, it is possible that the route-centered mapping observed for PPC neurons could initially develop based on hippocampal input. As stated, route-centered mapping appears to arise as a modulation of PPC activity correlates to specific, egocentrically referenced, locomotor states. When the degree of modulation reaches a high level (e.g., Fig. 2.2), a mapping of route space has, for all intensive purposes, been generated. Hippocampal activity specific to positions in environmental space also discriminates positions in a route by virtue of the fact that the route exists in the environmental space. In the experiments of Nitz (2006, 2012), all routes were first learned under conditions wherein the track structure occupied the same positions in the space of the environment, as would almost always be the case in the real world. Thus, under such conditions, hippocampal activity is suited

to the job of differentiating PPC activity according to world-centered position. Evidence to this effect is given in the data of Burke et al. (2005) suggesting that superficial PPC neurons, untested in the Nitz (2006) publication, are tuned to the space of the environment. While plausible, this explanation for PPC route-based activity pattern fails to account for the ultimate independence of PPC route-based activity from world-centered position.

2.6 Summary

Close examination and comparison of hippocampal and PPC spatially specific firing properties reveals that the two structures share many attributes. Both structures yield activity patterns that map allocentric space, albeit in very different reference frames. In both cases, gain modulation of place-specific activity yields the ability to map multiple allocentric spaces, and their relationships to each other, simultaneously. Finally, trajectory-specific activity is observed for both PPC and hippocampus, though only in PPC is such activity independent of world-centered position. The primary differences between these structures are their frames of reference for spatially specific activity, the presence/absence of activity related to locomotor state, and, of course, their afferent/efferent connectivity with other structures. Considering the similarities and differences, it appears that the two structures play complementary roles both in mapping spatial relationships and in translating spatial cognition into action (i.e., into navigational behavior). Both trajectory dependence of activity and anchoring of activity to the appropriate frame of reference could arise, via intermediary structures, as an interaction between hippocampus and PPC. It is through the study of spatially specific activity in these intermediary structures, such as retrosplenial and postrhinal cortex, that a much more complete picture of the neural mechanisms subserving spatial awareness will be obtained.

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Perirhinal and Postrhinal Functional Inputs to the Hippocampus

3

Jonathan W. Ho and Rebecca D. Burwell

Abstract

There is widespread agreement that perirhinal (PER) and postrhinal (POR) cortices are essential for episodic memory. The conventional view is that PER provides object information, and POR provides spatial and contextual information to the hippocampus through different information streams to support episodic memory. There is, however, considerable integration across these two information streams. Moreover, PER and POR also participate in non-mnemonic cognitive processes. PER is necessary for object recognition memory and is involved in high-level perceptual processing that conjoins elemental features to represent unique objects and items. POR represents the spatial layout of the current context, including objects and patterns located in that context, and then monitors the context for changes. Such object and pattern information in POR most likely arrives via a direct PER to POR pathway. Thus, the PER provides object information to both the POR and to the hippocampus, but for different purposes. Object information in POR would be used to represent and update the spatial layout of physical features of the local environment and for forming contextual associations. Such contextual information from the POR together with object and item information from the PER are made available to the hippocampus for associative learning and episodic memory.

3.1 Introduction

There is widespread agreement that the hippocampal formation and nearby parahippocampal structures are essential for episodic memory. There is less agreement about whether these regions also participate in other cognitive processes. Yet,

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in order to remember events, we need to perceive the event and attend to certain aspects of the episode. What regions are most likely to provide the interface between perception and memory and attention and memory? The parahippocampal region includes two structures organized near the rhinal sulcus, the perirhinal cortex (PER) and the postrhinal cortex (POR), that exhibit structural and connectional homology across rodent and monkey brains based on established criteria (Campbell and Hodos 1970). Anatomical, experimental lesion and electrophysiological evidence suggest these two regions provide gateways for perception and attention into the hippocampal memory system.

3.2 Overview of the Anatomy of the Perirhinal and Postrhinal Cortices

The PER in both rodents and monkeys comprises two subregions, areas 35 and 36. In the rat the two regions are narrow, rostrocaudally oriented strips of cortex with area 36 lying dorsal to area 35 (Fig. 3.1a). Neuroanatomical studies of PER, including cytoarchitecture, histochemistry, and connections, suggest the rostral border with insular cortex arises at the caudal limit of the claustrum (Burwell 2001). The placement of this border is consistent with traditional definitions of the insular cortex as overlying the claustrum (Rose 1928). The most rostral part of PER area 35 is bordered ventrally by piriform cortex. At caudal levels, piriform cortex is replaced by the lateral entorhinal area (LEA) to form the ventral border. The dorsal border of PER area 36 is with ventral temporal cortex. This dorsally adjacent region goes by different nomenclatures depending on the atlas consulted. At rostral levels, area 35 lies ventral to the fundus of the rhinal sulcus and area 36 lies above. More caudally, area 35 encompasses the fundus and area 36 lies above it. The most caudal portion of the PER consists mainly of area 36, which also lies above the rhinal sulcus (Burwell 2001).

The POR, in its current form, was defined in 1995 (Burwell et al. 1995). It occupies all that was formally the caudal portion of perirhinal and/or ectorhinal cortex, depending on the atlas. Unfortunately, most rodent atlases persist in using the old nomenclature. The border between the PER and the POR usually coincides with the caudal limit of the angular bundle. In coronal sections, the white matter forming the angular bundle at this level has an elongated teardrop-shaped appearance. In atlases that have not adopted the newer nomenclature, the POR is roughly equivalent to the combination of regions designated as PER 35 and 36 (or PER and ectorhinal) caudal to this landmark (Lein et al. 2007; Paxinos and Watson 2006; Swanson 2004). The POR lies entirely dorsal to the caudal extension of the rhinal sulcus. At this level the rhinal sulcus is occupied by the entorhinal cortex (Dolorfo and Amaral 1998b). The ventral borders of the POR with medial entorhinal area (MEA) are consistent with the description by Insausti et al. (1997) and Dolorfo and Amaral (1998b).

Functional anatomical studies show that the unimodal and polymodal associational inputs to the PER and POR are very different (Burwell and Amaral 1998a).

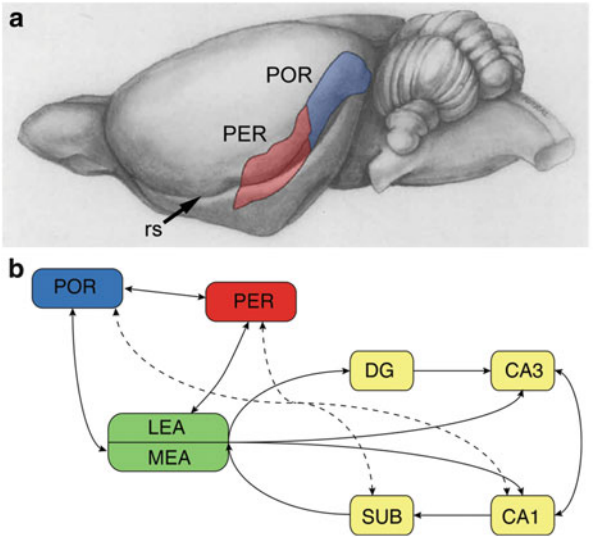

Fig. 3.1 Rodent perirhinal (PER) and postrhinal (POR) cortices. (**a**) Three-quarter view showing the locations of the PER (*red*) and POR (*blue*). (**b**) Simplified schematic connections among the PER, POR, lateral (LEA) and medial (MEA) entorhinal cortex, and hippocampal structures. The schematic includes the hippocampal formation (structures in *yellow*) and the parahippocampal region (structures in *red*, *blue*, and *green*). Note that the perirhinal and postrhinal cortices (PER and POR) have reciprocal connections with CA1 and the subiculum. Other abbreviations: *DG* dentate gyrus, *CA1 field CA1*, *CA3* field CA3, *SUB* subiculum. Figures adapted from Burwell and Agster (2008) and Burwell et al. (1995)

In rodents, although input from all modalities targets all parts of the PER, there is a topography of unimodal association inputs. Somatosensory, auditory, and visual inputs preferentially target rostral, mid-rostrocaudal, and caudal area 36, respectively, and olfactory input preferentially targets area 35 (Burwell 2001). Whereas the PER receives input from multiple sensory modalities, the POR is dominated by input from secondary visual cortex and visuospatial areas, including retrosplenial and posterior parietal cortices. The PER and POR also preferentially target different parts of the hippocampal formation.

The current view of the hippocampal formation emphasizes that spatial and nonspatial information are transmitted through different parahippocampal pathways (Fig. 3.1b) (Eichenbaum et al. 2007; Knierim et al. in press; Naber et al. 1997). Spatial information originating in multiple cortical regions converges on the POR (parahippocampal cortex (PHC) in the primate brain) and is transmitted to the hippocampal formation through the MEA (Burwell and Amaral 1998b; Suzuki and Amaral 1994). Likewise, nonspatial or item information converges on the PER and is then transmitted to the hippocampal formation through a pathway that includes the LEA. Both the PER and the POR project directly to the hippocampal field CA1 and the subiculum, although they terminate at different proximodistal levels (Naber et al. 1997, 2001).

The segregation of spatial and nonspatial information may be overemphasized in both anatomical and functional descriptions of the PER and POR. For example, in addition to its MEA projection, the POR also targets caudal LEA (Burwell and Amaral 1998b). Moreover, the LEA and MEA in both rats and monkeys are interconnected (Chrobak and Amaral 2007; Dolorfo and Amaral 1998a). Finally, in both species, the PER located in the nonspatial pathway is robustly and reciprocally connected with the POR/PHC in the spatial pathway (Burwell and Amaral 1998b; Suzuki and Amaral 1994).

3.3 Functions of the Perirhinal Cortex

The hippocampus was implicated in memory in the 1950s by Milner and colleagues (Scolville and Milner 1957; Milner and Penfield 1955). Object recognition memory tasks were commonly used as a standard test for declarative memory, and early investigations suggested a central role of the hippocampus for object recognition memory. It was not until the 1980s that neocortical regions emerged as contributing to object recognition memory (Murray and Mishkin 1986; Zola-Morgan et al. 1989). Ensuing human clinical cases and animal lesion studies rapidly established that severe impairments in object recognition memory tasks occurred with PER damage and not hippocampal damage. Subsequent neuropsychological research into the neural bases of declarative memory has since included the PER as a focus for memory research.

3.3.1 Perirhinal Cortex and Object Recognition Memory

Recognition memory is the judgment of prior occurrence of an item or event (Mandler 1980). Object recognition memory tasks such as the delayed nonmatch-to-sample (DNMS) task can be solved on the basis of familiarity, i.e., context-free judgment of prior occurrence. DNMS tasks usually comprise two phases. In the sample phase, the subject is presented with the sample object. Following a delay, in the test phase the subject is presented with a copy of the now familiar sample object and a novel object. According to the nonmatch-to-sample rule, the subject must displace the novel object to obtain a reward. Correct displacement of the novel object implies that the subject recognizes the familiar object.

Experimental lesions to PER in rats and monkeys were shown to impair object recognition memory in DNMS tasks (Meunier et al. 1993; Mumby and Pinel 1994). The rat version of the DNMS task, however, required months of training (Mumby and Pinel 1994; Rothblat and Hayes 1987). Consequently, a variant of DNMS tasks, the spontaneous object recognition (SOR) task (Fig. 3.2), invented by Ennaceur and Delacour (1988), has become the preferred experimental paradigm to investigate neurobiological mechanisms of recognition memory in rodents. The SOR task follows the general framework of DNMS tasks except that no pretraining is required. Instead, the task relies on rats' innate preference for novelty in a familiar

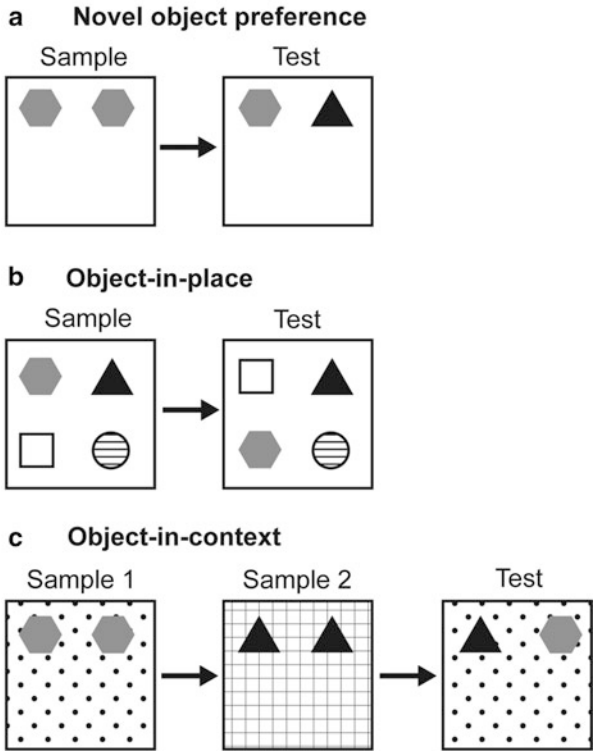

Fig. 3.2 Spontaneous object recognition (SOR) tasks. SOR tasks have been used to test recognition memory for single items and for spatial and contextual associations between objects. Experiments are carried out in an open-field arena that minimizes the availability of external visual cues. Objects are "junk" objects (e.g., candle sticks) or constructed of Duplo™. (**a**) In the novel object preference task, rats demonstrate recognition memory for familiar items (*grey hexagon*) by preferentially exploring the novel object in the test phase (*black triangle*). (**b**) In the object-in-place task, rats demonstrate recognition memory for familiar spatial associations between objects by preferentially exploring the objects that switched places (*white square* and *grey hexagon*). (**c**) In the object-in-context task, rats encounter two pairs of objects in different contexts (sample 1 and 2). Contexts are manipulated by carrying out the sample phases in different rooms or by altering the interior of the test arenas. Recognition memory of the familiar object-in-context construct is expressed by preferential exploration of the object that is incongruent with the context in the test phase (*black triangle*)

environment (Ennaceur and Delacour 1988). Performance is quantified by measuring the ratio of exploration of the novel and familiar objects (Fig. 3.2a). As no pretraining is necessary, experiments using SOR tasks as paradigms of object recognition memory can be completed in a matter of weeks. SOR tasks used to investigate mnemonic functions of PER explicitly use objects that share as few common features as possible in order to decouple mnemonic from perceptual demands. Thus, behavioral deficits in these conditions are considered to be a result of recognition memory impairments. The novel object preference version of the

SOR task has been used to test recognition memory for single objects (e.g., Dix and Aggleton 1999), but the SOR task paradigm is powerful in that it can also be used to assess recognition memory that involves associations of objects in place and objects in context (Dix and Aggleton 1999; Norman and Eacott 2005) (Fig. 3.2b, c).

Experimental lesions of PER severely impair object recognition memory in SOR tasks (Winters et al. 2004; Ennaceur et al. 1996), but this does not reflect a general memory deficit as PER lesions have no effect on pure spatial memory tasks (Winters et al. 2004). In contrast, hippocampal damage impaired spatial memory, but not object recognition memory (Forwood et al. 2005; Winters et al. 2004; but see Broadbent et al. 2010). Also, addition of PER damage to fornix transection did not exacerbate spatial memory impairments (Ennaceur and Aggleton 1997; Ennaceur et al. 1996). Transection of the fornix has been shown to produce deficits similar to hippocampectomy. Together, these findings demonstrate a double dissociation of PER and hippocampus for object recognition memory and spatial memory such that PER is necessary for object recognition memory, but not spatial memory, and the hippocampus is necessary for spatial memory, but not object recognition memory.

Object recognition paradigms are not limited to short duration delays. Rats demonstrate robust recognition memory with delays up to 24 h between encoding and testing. Under certain conditions, rats show object recognition memory up to 3 weeks after encoding indicating that PER is necessary for very long-lasting object memory (Mumby et al. 2007). Pharmacological techniques have shed light on the time course and phases of object recognition memory. Inactivation of PER using lidocaine, a sodium channel blocker, impaired encoding, early consolidation, and retrieval of object recognition memory (Winters and Bussey 2005b). In addition, local infusions of pharmacological antagonists have shown that shorter-term and longer-term object recognition memories are qualitatively independent processes supported by different neurotransmitter systems and synaptic plasticity mechanisms (Brown et al. 2012).

PER-dependent recognition memory is not limited to three-dimensional objects. PER receives multimodal input, and it is not surprising that PER would support recognition memory and discrimination learning for stimuli presented in various sensory modalities. Indeed, PER is necessary for odor recognition memory (Otto and Eichenbaum 1992; Feinberg et al. 2012), and PER neurons in rats performing an odor recognition task fired to nearly all the events in a trial (Young et al. 1997). PER is also necessary for integrating information across visual and tactile modalities (Winters and Reid 2010). Processing of auditory stimuli is also sensitive to PER damage under some conditions. PER damage impairs conditioning to auditory stimuli when the stimuli are complex, but not when the stimulus is a simple continuous tone (Kholodar-Smith et al. 2008a, b; Bang and Brown 2009). Rats also show robust object recognition memory of at least 1 h for two-dimensional visual images (Forwood et al. 2007) and for objects viewed behind a clear Perspex screen (Winters and Reid 2010). Importantly, PER damage impairs recognition memory under conditions in which stimuli are purely visual

allowing findings from rodent models to be better compared to those in human studies.

3.3.2 Perirhinal Cortex and Recency

Although experimental lesion studies are useful for assessing contributions of particular brain regions to specific functions, electrophysiology is more useful for understanding how information might be processed. Neuronal activity recorded in monkey anterior temporal lobe, including PER, suggested a mechanism capable of supporting recognition memory (Brown et al. 1987; Fahy et al. 1993). The proposed mechanism was neuronal response decrements to item repetition. Electrophysiological recordings in anterior temporal lobe were carried out in monkeys performing a serial visual recognition task in which individual novel and familiar images were repeatedly presented. Over half the recorded neurons were visually responsive, firing to the presentation of an image; some fired to multiple images and others to a few images. The firing rates of 38 % of the visually sensitive neurons in PER were maximal to the initial presentation of an item but significantly reduced to subsequent presentations (Xiang and Brown 1998). Therefore, information concerning familiarity and recency of an item can be inferred at the single neuron level when comparing the firing rate between the first presentation of an item and its subsequent presentation (Fahy et al. 1993; Xiang and Brown 1998). Neurons that responded maximally to unfamiliar objects but decreased firing rates in response to highly familiar objects carried information concerning relative familiarity; these neurons were termed "familiarity neurons." Some neurons fired maximally to the initial presentation of an item regardless of whether it was unfamiliar or highly familiar and were significantly reduced to the repeated presentation; these neurons were termed "recency neurons." Hence, recency neurons carry information on whether a given item was encountered recently regardless whether it was novel or familiar. A third type of neuron recorded in monkey PER responded maximally to an unfamiliar stimulus and briefly to a highly familiar stimulus; these neurons were termed "novelty neurons" (Xiang and Brown 1998). Together "familiarity" and "novelty neurons" are informative of the relative familiarity of an item, and "recency neurons" provide temporal information about items. Neurons that possess similar patterns of firing to item repetition to those recorded in the monkey have been recorded in rat PER (Zhu et al. 1995a). Burke et al. (2012), however, concluded that the relative familiarity of objects did not alter neuronal firing in rat PER. The absence of any neuronal decrements to familiar objects in Burke et al. (2012) may be explained, however, by differences in task design. In Burke et al. (2012), rats were trained to complete laps on a circular track containing objects to obtain a food reward. In their paradigm, the presentation of the objects was not closely controlled making it difficult to correlate changes in neuronal activity with the encountered objects. In serial recognition tasks in which repetition-sensitive neurons have been recorded in rats (Zhu et al. 1995a), behavior

and presentation of objects were closely controlled allowing precise correlation of neuronal activity with image presentation.

Rat imaging studies quantifying c-fos activity as a marker of neuronal activation to presentation of novel and familiar images have complemented electrophysiological evidence for neuronal response decrements signaling relative familiarity (Wan et al. 1999; Zhu et al. 1995b; Albasser et al. 2010). c-fos activity can be quantified by labeling its protein product, Fos, by standard immunohistochemical techniques. Using a "paired viewing procedure" in rats, novel and familiar images were presented to each eye. As visual information from each eye crosses to the opposite hemisphere, the effects of image familiarity on PER neuronal activity can be compared within an animal. Presentation of novel images increased neuronal activation compared with familiar images (Wan et al. 1999; Zhu et al. 1995b; Seoane et al. 2012; Warburton et al. 2003) consistent with electrophysiological recordings in rats and monkeys (Brown et al. 1987; Fahy et al. 1993; Xiang and Brown 1998; Zhu et al. 1995a). Moreover, successful object recognition memory in a modified SOR task was associated with increased PER neuronal activation (Albasser et al. 2010) demonstrating a correlational relationship between high neuronal activity in PER and preferential novelty exploration. In vivo pharmacological manipulations further strengthen the relationship between differential neuronal activity in PER to signal novelty and familiarity. Systemic injection of scopolamine, a cholinergic antagonist, disrupted increased neuronal activation to novel visual stimuli as measured by Fos staining and impaired object recognition memory in vivo (Warburton et al. 2003). Local infusion of antisense Fos oligodeoxynucleotide into PER disrupted differential Fos expression to novel and familiar visual stimuli and disrupted consolidation processes for longer-term object recognition memory in vivo (Seoane et al. 2012). Together, these studies (Albasser et al. 2010; Seoane et al. 2012; Warburton et al. 2003) complement electrophysiological and lesion data suggesting that a mechanism in PER centered on differential neuronal activity to item repetition is a potential mechanism underlying object recognition memory.

3.3.3 Perirhinal Cortex and Visual Perception

The current view of PER function is not restricted to a mnemonic role. PER is posited to function in visual perceptual processing in addition to object recognition memory given the pattern of impairments under certain conditions in discrimination tasks and its anatomical position at a high level in the ventral visual stream (Murray et al. 2007; Bussey and Saksida 2002; Cowell et al. 2010; Murray and Wise 2012).

Electrophysiological recordings in rats support a specialized role of PER in object information processing (Burke et al. 2012; Deshmukh et al. 2012; Zhu et al. 1995a). When rats encountered objects while navigating a circular track, a large proportion of recorded neurons in PER fired selectively when the animal was close to an object; this pattern of activity was termed the cell's "object field" (Burke et al. 2012). Some cells had multiple "object fields" and fired close to an object

regardless of its identity suggesting that neuronal activity in "object fields" reflected processing of object information. Nonspecific activity was observed when rats navigated an empty track with no objects, supporting the lack of spatial information processing in the PER (Burwell et al. 1998). Thus, in comparison with hippocampal place fields that are modulated by the location of the animal (Muller 1996), PER "object fields" are modulated by the presence of objects. Similar object-related firing activity was seen in PER when rats foraged in an open arena containing objects (Deshmukh et al. 2012; see Deshmukh and Knierim 2014). These properties of PER cells with multiple object-related firing fields reported in independent laboratories strengthen the role of PER in processing information about objects in some capacity, e.g., perceptual processing in which objects are represented through the conjunction of its features (Murray et al. 2007).

The proposal that the PER participates in visual perceptual processing can be traced to an experimental lesion study in monkeys performing modified match-to-sample tasks in which mnemonic demands were minimized (Eacott et al. 1994). Monkeys with PER damage were impaired when trial unique images from a large pool were used, but the impairment was mitigated when the pool of images was reduced to four; the PER-lesioned monkeys were also impaired when the discriminability of the images was reduced. Eacott et al. (1994) argued that the large number of trial unique images increased the probability that images would share common features. Thus, each image had to be precisely represented to protect from interference by other images. When the pool of images was small, less precise representations of the images were sufficient for successful performance. Based on the pattern of impairments, Eacott et al. (1994) posited that the PER is necessary for the accurate representation of visual stimuli in order to prevent interference from other similar visual stimuli.

In complex discrimination problems, a feature (A) can be a component in two different compounds with different outcomes: rewarded (AB+) and unrewarded (AC−). Hence, objects that predict different outcomes may share elemental features. This property of constituent features shared across objects in discrimination problems has been termed "feature ambiguity" (Bussey and Saksida 2002). Bussey and colleagues proposed the perceptual/mnemonic feature conjunction (PMFC) connectionist model of PER function to explain the selective deficits following PER damage in object discrimination under conditions in which discriminanda have overlapping features (Bussey and Saksida 2002; Murray et al. 2007). In the PMFC connectionist model, the ventral visual stream is considered as a continuum representing increasingly complex representations. Representations of object features and their conjunctions are arranged hierarchically such that simple features of objects are processed and stored in caudal areas and increasingly complex conjunctions of features are processed and stored rostrally, ultimately in the PER. Thus, the PMFC connectionist model would predict deficits associated with PER damage on match-to-sample tasks in Eacott et al. (1994) and in two-choice visual discrimination tasks in rats in which ambiguity of the discriminations were manipulated (Eacott et al. 2001). In Eacott et al. (2001), PER lesions impaired discriminations that required the conjunction

of features; lesions were without effect on simple discriminations that could be solved on the basis of individual features. The PER also seems necessary for tasks that require unitizing simple stimuli, such as lights and tones (Campolattaro and Freeman 2006a; Nicholson and Freeman 2000). Interestingly, PER damage impaired the simultaneous but not the serial version of feature positive discrimination learning, which requires disambiguation of overlapping stimulus elements (Campolattaro and Freeman 2006b). These findings are all consistent with a role for the PER in the PMFC connectionist model in representing a conjunction of features as a unique stimulus. Other evidence in monkeys also implicated PER specifically for discriminations that require associating individual features to represent an object as a whole (Bussey et al. 2002). According to the PMFC connectionist model, discriminations soluble on the basis of elemental features are not sensitive to PER lesions, but can be supported by visual areas outside the PER. Indeed, monkeys with damage to the middle temporal gyrus were impaired on a simple color discrimination task and monkeys with bilateral damage to PER were unimpaired (Buckley et al. 1997).

Studies in rats provide additional evidence for the PER as a site for perceptual processing of complex object representations. Effects of PER damage were examined in an SOR task that assessed the effect of varying the level of feature ambiguity, i.e., overlap of features between the novel and familiar objects on object recognition memory (Norman and Eacott 2004). At the lowest feature ambiguity level, objects were "junk" objects (e.g., bottles and candlesticks) that shared fewest common features. For the medium feature ambiguity level, the novel and familiar objects were both constructed of Duplo™ (large Lego bricks) in a configuration to maximize the discriminability of the two objects. Although different numbers and types of Duplo™ blocks were used for the novel and familiar object, each object shared the inherent features of the blocks and was therefore considered more ambiguous in terms of features compared with "junk" objects. In the highest feature ambiguity condition, the novel object was reconfigured using the same number and constituent blocks as the familiar object so both objects shared the most features. PER lesions produced a delay-dependent impairment in the lowest feature ambiguity condition and severity of the impairment increased with increasing ambiguity of the novel and familiar objects; at the highest ambiguity level, PER-lesioned rats were impaired in all delays including the shortest delay of 1 min (Norman and Eacott 2004). When objects were highly discriminable, PER lesions resulted in a delay-dependent impairment indicative of a mnemonic impairment. Increasing feature ambiguity, however, increased the severity of the recognition memory impairment implicating PER in high-level visual perception as well as mnemonic function.

The PMFC connectionist model was modified to account for object recognition memory impairment in PER-lesioned animal models by introducing a function in which the representation at a given level in the continuum including PER could be sharpened with experience (Cowell et al. 2006). Computer simulations of the modified PMFC connectionist model simulated the forgetting curve of object recognition memory typical of increasing delay and list lengths in delayed match- and nonmatch-to-sample tasks in experimental animal models (Cowell et al. 2006).

Moreover, removal of the layer in the model that corresponded with the PER exacerbated the delay and list-length-dependent reduction in recognition memory score consistent with the pattern of impairment in experimental animal lesion models (Mumby and Pinel 1994; Mishkin 1978; Norman and Eacott 2004).

Perceptual processing by PER is not generalized for all difficult visual discriminations, but only for discriminations requiring the configuration of multiple features that together form a gestalt representation of a stimulus (Eacott et al. 2001; Norman and Eacott 2005). PER had no role for fine discriminations of single features (Eacott et al. 2001) or a conjunction between an object and context (Norman and Eacott 2005). POR instead was necessary for familiarity discriminations in recognition memory that involved a conjunction of objects in context (Norman and Eacott 2005). Using a zero delay SOR task designed to minimize the mnemonic component of the task, Bartko et al. (2007a) tested the role of the PER within the hierarchical continuum of the PMFC connectionist model. In the zero delay SOR task, rats explored two identical sample objects in the sample phase; immediately after the sample phase, the test phase commenced in which varying levels of feature ambiguity were tested where the novel object varied in feature ambiguity with the familiar object. Control rats with intact PER successfully discriminated by preferentially exploring the novel object at all levels of feature ambiguity; PER lesions impaired discrimination only when the familiar and novel objects shared the most features in the highest feature ambiguity condition. To preclude any mnemonic contributions even at a zero delay, a spontaneous oddity preference task was performed that consisted of a single test phase in which three objects were presented simultaneously (Bartko et al. 2007a). Two objects were identical and the third "odd" object varied in similarity from sharing few features (low feature ambiguity) to sharing the most features (high feature ambiguity) with the other objects. Oddity judgments were expressed as preferential exploration of the "odd" object. As rats had all the information from the three objects available simultaneously for comparison, any impairment was interpreted as a perceptual processing deficit [but see (Suzuki 2009, 2010)]. Similar to the pattern of impairment in the zero delay SOR task, PER lesions impaired discrimination only in the highest ambiguity conditions (Bartko et al. 2007a). Furthermore, PER lesions impaired configural object recognition further supporting a perceptual role for PER in forming complex conjunctive representations (Bartko et al. 2007b).

There are reports in rodent models, however, arguing against a role of PER in high-level perceptual processing consistent with original accounts in clinical cases where medial temporal lobe damage resulted in severe memory impairments in the absence of perceptual deficits. Clark et al. (2011) argued against a perceptual function of PER in an elegantly designed two-choice visual discrimination task. In this task, PER-lesioned rats were trained to similar levels as sham-operated control animals on a basic discrimination problem. After successful learning, the image pair was morphed resulting in discrimination trials of varying degrees of difficulty. These trials were then interleaved with the well-learned baseline discrimination trials. Performance of rats with PER lesions did not differ from sham-operated controls across any level of discriminability even in the highest level of

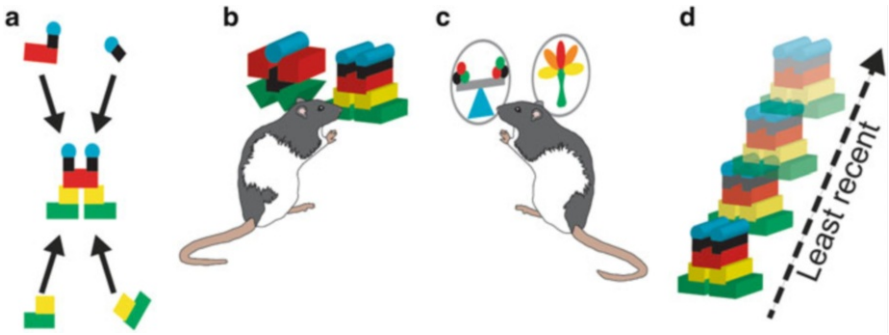

Fig. 3.3 Perirhinal cortex (PER) processes object information. (**a**) PER is necessary to form conjunctions of features into unique representations. (**b**) Such representations can be used for object recognition memory, discrimination, and disambiguation of three-dimensional objects. (**c**) Similar to **b**, the PER also processes information about two-dimensional images. (**d**) PER signals recency information about objects

feature ambiguity; PER lesions did, however, impair object recognition memory (Clark et al. 2011). In a separate study, PER-lesioned rats performed to similar levels compared to sham-operated controls in a configural discrimination task but were impaired in an object recognition memory task (Aggleton et al. 2010).

Although the reports (Aggleton et al. 2010; Clark et al. 2011) described above argue against a role of PER in high-level visual perceptual processing, the balance of the experimental lesion evidence supports a role for the PER in visual discrimination under conditions of high feature ambiguity when a conjunction of features is necessary to form an accurate representation of a unique stimulus (Fig. 3.3) (Bartko et al. 2007a, b; Norman and Eacott 2004). Tasks that can be solved using elemental features do not require PER, instead relying on visual ventral stream structures upstream of the PER that are sufficient to represent less complex stimuli.

3.3.4 Summary of Perirhinal Functions

Experimental lesions have established the canonical role of PER in object recognition memory. A mechanism in PER centered on response decrements is hypothesized to have the necessary speed, capacity, and properties to signal information on familiarity and recency of single items (Bogacz and Brown 2003). Additionally, this mechanism would be metabolically advantageous. In normal daily life many items will be familiar. Therefore, decremental neural activity for signaling familiarity would reduce energy demands of the system. Novel items may generate interest to the individual (e.g., a new source of food) requiring more processing and increased neuronal activity to engage the appropriate behavioral response. Evidence is available to support PER as a memory store. If PER functions as a locus of storage, then experimental lesions to this brain region should cause retrograde and anterograde amnesia. Both retrograde (Mumby et al. 2002; Wiig

et al. 1996) and anterograde (Barker and Warburton 2011; Winters et al. 2004) object recognition memory deficits have been reported in experimental lesion models in rats. Synaptic plasticity (e.g., long-term potentiation or long-term depression) is thought to be one of the underlying mechanisms of learning and memory (Lynch 2004; Martin et al. 2000). Indeed, pharmacological and genetic manipulations in PER block synaptic plasticity and impair object recognition memory (Barker et al. 2006; Warburton et al. 2005; Griffiths et al. 2008; Winters and Bussey 2005a).

A complementary view of PER function is visual perceptual processing for representations at the object level. The PMFC connectionist model (Bussey et al. 2002; Cowell et al. 2006; Murray et al. 2007) has been posited with the aim of unifying increased severity of recognition memory and discrimination impairments in conditions of high feature ambiguity in PER-lesion models. As such, the PMFC connectionist model interprets single item recognition memory impairments from PER damage not as forgetting or lack of encoding but interference of the fragmented or impoverished memory trace that would otherwise be protected by an intact PER (McTighe et al. 2010; Bussey and Saksida 2002; Cowell et al. 2006, 2010). Related views are that the PER is necessary for unitizing stimuli, e.g., lights and tones (Campolattaro and Freeman 2006b), or for encoding associative information about a cue, e.g., its relationship to reward or work schedules (Liu and Richmond 2000).

Evidence from experimental lesion studies and electrophysiological recordings is consistent with a role for PER in both a perceptual representational and a mnemonic framework. The consistent theme is the role of PER in object information processing whether for discrimination or recognition memory (Fig. 3.3). Electrophysiological recordings should be carried out in PER while rats perform visual discrimination and object recognition memory tasks in which feature ambiguity is varied. Any neuronal activity correlating with the level of feature ambiguity would support a role of PER for complex feature conjunctions and provide evidence that this brain region is capable of housing perceptual and mnemonic mechanisms.

3.4 Functions of the Postrhinal Cortex

Given that the POR is interconnected with anatomical regions implicated in the processing of spatial and visuospatial information, the first experimental lesion studies attempted to dissociate its functions from those of the PER. A reasonable hypothesis was that hippocampal-dependent spatial tasks, for example, the Morris water maze and contextual fear conditioning, would be sensitive to POR damage, but not to PER damage. Contrary to predictions, PER and POR damage resulted in deficits in contextual learning (Bucci et al. 2000, 2002; Burwell et al. 2004a), but not spatial navigation in the Morris water maze in studies using pigmented rats (Burwell et al. 2004b; Machin et al. 2002; Futter et al. 2006). This pattern of results suggested that spatial learning is qualitatively different from contextual learning and requires different brain regions and different processing abilities. Thus, when

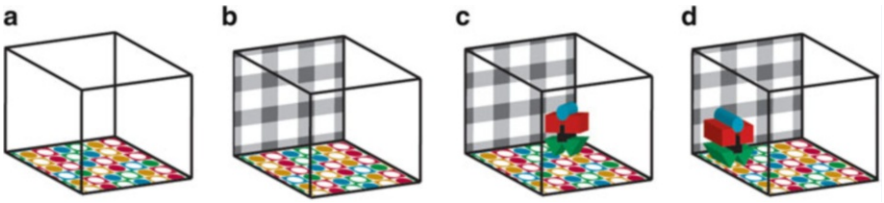

Fig. 3.4 Postrhinal cortex (POR) and processing of information in the local context. (**a**) POR encodes features of local contexts, such as a small room with a pattern on the floor. (**b**) POR signals changes such as an altered pattern on the wall. (**c**) POR also appears to encode the spatial layout of objects in the local context. (**d**) POR may also signal when there are changes in the spatial layout of objects, e.g., the transition from **c** to **d**

path integration is intact, animals might be able to complete a navigation task, but not able to process complex information about the local environment, e.g., information about patterns, objects, and the appearance of boundaries in an enclosed chamber.

3.4.1 Postrhinal Cortex and Context

Experimental lesion studies have demonstrated that the POR is necessary for processing information about objects when combined with places and contexts (Fig. 3.4). This was demonstrated in an SOR task (Fig. 3.2c) in which rats first explore two identical objects (A) that are presented in context 1 and then two different identical objects (B) in a second context (2) that differs by the interior of the testing arena. In the test phase, one copy of each of the objects (A and B) is presented in the context 1 (Norman and Eacott 2005). Normal rats will preferentially explore object B because this object is out of context compared with object A. In Norman and Eacott (2005), rats with POR damage were impaired in this task, suggesting a role in recognizing objects in different contexts. Rats with POR damage were not impaired in the standard SOR task (novel object preference task) for object recognition memory.

Based on the contextual fear learning and object-context recognition studies, one possibility is that the POR relies on information arising from the PER to process object and pattern information about the physical features of the local environment. By this view, POR is in a position to combine incoming spatial information from retrosplenial and posterior parietal cortices with incoming item, object, and pattern information from the PER to represent the spatial layout of items in the physical local context. If this is the case, one would expect to observe neuronal selectivity in POR that links objects to places. Neuronal activity was recorded in the POR in a bowtie-shaped maze during performance on an object discrimination task in which a pair of objects was presented on one side of the maze or the other (Furtak et al. 2012). With two pairs of objects and two locations in which objects were presented, it was possible to identify object-place conjunctive selectivity. As

predicted, a large proportion of POR cells exhibited object-place conjunctions. Another similar proportion of POR cells exhibited selectivity for particular locations in which objects appeared, regardless of the identity of the object in the location. Interestingly, some cells showed location or object-location selectivity during the stimulus presentation epoch when the rat was in the center of the maze viewing objects in particular locations at a distance. This phenomenon is reminiscent of monkey electrophysiology studies in which parahippocampal view cells were identified (Rolls et al. 1997) and of findings in human imaging studies in which a functionally defined parahippocampal locations show increased activity when individuals were viewing scenes or places (Epstein et al. 1999). The authors of the latter study suggest that the parahippocampal place area is involved in encoding new perceptual information about the spatial layout of scenes.

3.4.2 Postrhinal Cortex and Attention

In addition to representing the spatial layout of objects and patterns in the local context, some evidence suggests that the POR modulates attention to changes in the environmental context. For example, in rodents, damage to the POR impaired attentional orienting in a conditioned orienting task (Bucci and Burwell 2004). In a human imaging study, Yi and Chun (2005) reported that activity attenuates for repeated scenes in the parahippocampal place area. Decreases in activity were observed only when subjects attended the scenes during initial and repeated presentations. Electrophysiological studies in monkeys show that neuronal activity in the PHC is modulated by changes to stimuli in the periphery (Sato and Nakamura 2003) and by changes to the local context (Vidyasagar et al. 1991). These studies suggest a role in stimulus driven, bottom-up attention consistent with the notion that the POR and PHC automatically monitor the local environmental context for changes.

The first electrophysiological study of the rodent POR neuronal correlates employed a spatial task that had been used extensively for studies of hippocampal place cell properties in which double rotations of cues were carried out in a four-arm radial maze (Burwell and Hafeman 2003). The maze was defined by multisensory proximal (or local) cues and distal (or global) visual cues. Proximal cues consisted of visual, tactile, and olfactory cues located on the maze arms. Distal cues consisted of highly salient visual cues located on curtains surrounding the maze. On recording days, rats were run in three conditions. For the first and third baseline conditions, proximal and distal cues were organized in the standard configuration. In the second condition, the proximal and distal cues were each rotated 90° in opposite directions around the center of the maze. Hippocampal place fields recorded in this task can be controlled by either proximal or distal cues (Shapiro et al. 1997; Tanila et al. 1997). A signature of hippocampal place fields in this task is that after a place field has rotated in concordance with a rotation of either the proximal or distal cues, the field will normally return to the original location when the rotated cues are returned to the original configuration. POR neurons recorded in

this task responded quite differently. Although the majority of POR neurons appeared to form place fields using standard criteria, the fields tended not to rotate with either proximal or distal cues. Moreover, in the second baseline condition, these fields did not return to the configuration observed in the first baseline. POR neurons appeared to remap or adopt new spatial correlates, with each manipulation of proximal and distal cues. In addition, nearly all postrhinal place fields exhibited split or multiple subfields—also different from hippocampal place fields. Together with other available evidence, this study suggested that the POR might have a role in monitoring visuospatial changes in environmental stimuli as opposed to processing visual cues for purposes of navigation. In other words, POR cells appeared to participate in higher-level perceptual or attentional functions, at least in that task.

The studies reviewed so far suggest that the POR encodes new information about the spatial layout of the physical environmental context. This is consistent with the view that the POR is also monitoring the spatial layout for new information or changes. Recently, we demonstrated that cells in the POR do signal the onset of changes to the local context (Kent and Burwell 2012). We recorded single units in the POR during performance on a biconditional discrimination task using an apparatus that permits automated back projection of images to the floor of the maze. In this task, the pattern on the floor determines which of two embedded two-dimensional images is rewarded. For example, if the floors are either dotted or striped and the images are a star and a circle, the star would be correct on the dotted floor and the circle would be correct on the striped floor. The beginning of a trial is signaled by the appearance of a floor pattern and the animal must approach the center of the bowtie-shaped maze accompanied by the offset of white noise. After a variable delay, the images appear, and the animal must approach the image associated with the floor pattern. We observed POR cells that signaled the onset of white noise, floors, and image, consistent with a role in attention.

In the biconditional discrimination task described above, Kent and Burwell (2012) also observed POR cells that signaled a particular image, but only when it appeared on a particular floor pattern. This could be interpreted as signaling "what-which," a gestalt representation of an object in context, as described by Eacott and colleagues (Norman and Eacott 2005; Eacott and Gaffan 2005). In Norman and Eacott (2005), POR damage selectively impaired memory for objects in context when tested in a spontaneous object exploration task.

Available anatomical and functional evidence suggests that object information in the POR arrives directly from the PER. We suggest that the PER provides object information to both the POR and the hippocampus, but for different purposes. Object information in the POR would be used to represent and update the spatial layout of the features in the current context, including items, objects, and patterns (Fig. 3.4). Object information in the hippocampus would be used in associative learning and episodic memory.

3.4.3 Summary of POR Functions

We have suggested a model in which the POR (and PHC) encodes representations of specific contexts, monitors the current context, and updates the context representation when a change occurs (Furtak et al. 2012). By this model, the POR (1) combines spatial information with object and pattern information to form representations that link objects to places, (2) collects those item-place associations into representations of specific contexts including the spatial layout of features and items, (3) automatically monitors the current context for alterations, and (4) updates the representation of the current context with identified changes. The spatial information most likely arises from retrosplenial and posterior parietal cortices, whereas the information about individual items arises from the PER. The attentional functions would arise from interactions with posterior parietal cortex as well as the lateral posterior nucleus of the thalamus.

The POR representation of the local context would be available to other brain regions to support a number of functions, e.g., recognition of an object in a location or to guide behavior appropriate to context. It may also be that the POR signals the PER when alterations to the current context involve individual objects or patterns, resulting in further processing of the item by the PER.

3.5 Interactions Among Structures of the Hippocampal System

What information do the PER and the POR provide the hippocampus? Consistent with other proposals (Eichenbaum et al. 2007; Knierim et al. 2006; Knierim et al. in press), at the simplest level, we suggest that the PER provides information about individual items to the hippocampus. This would include not just visual cues but also discrete olfactory, tactile, and auditory cues, especially cues that have complex perceptual or associative properties. The POR provides a representation of the local context that includes the spatial layout of items and patterns. The hippocampus then forms representations of events and episodes and locates the episodes in place and time (Fig. 3.5).

Lesions to rat PER impaired object-in-place recognition memory (Barker et al. 2007). Object-in-place recognition memory can be tested using the object-in-place SOR task (Dix and Aggleton 1999) (Fig. 3.2b). In this task, rats bind object information with spatial information to form associations between the objects and their relative positions, and object-in-place memory is expressed as preferential exploration of the most salient novel spatial configuration of objects (Fig. 3.2b). Therefore, this task cannot be solved on the basis of familiarity of the objects alone nor the familiarity of the locations that are occupied as the identity of the objects and the occupied locations do not change. Rats must instead form an association between the objects and their relative positions. PER lesions impaired object-in-place recognition memory (Barker et al. 2007) leading to the possibility that the spatial relationship between objects is processed and stored within PER. The lack of

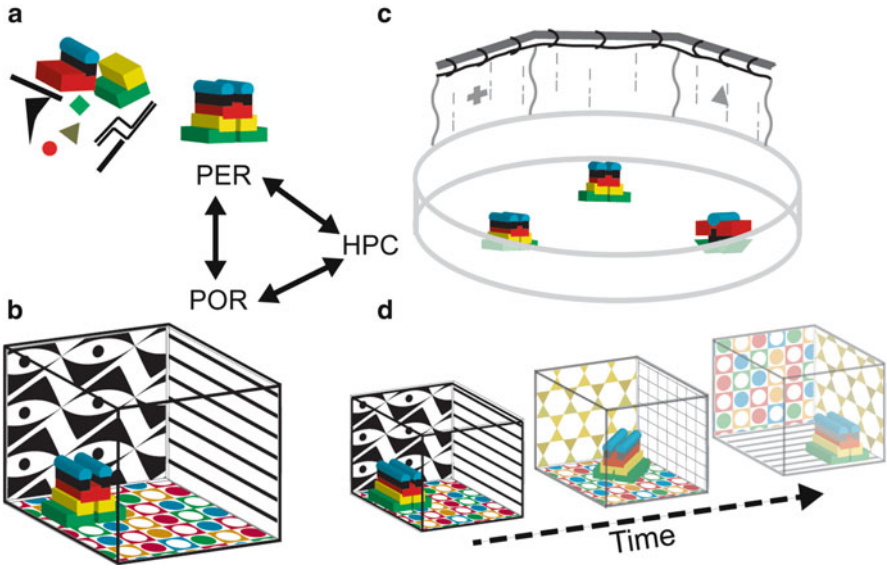

Fig. 3.5 Interactions among PER, POR, and hippocampus (HPC) for episodic memory. Hippocampus can process PER object information and POR contextual information in parallel. (**a**) Gestalt representations of complex objects are formed and housed in PER. (**b**) The spatial layout of object and pattern information is unitized in a contextual frame in POR and provided to the medial entorhinal area and the hippocampus. (**c**) Object information is available to hippocampus and the lateral entorhinal area from PER for accurate allocentric spatial information processing. (**d**) The hippocampus indexes the contexts supplied by POR and PER in a temporal framework for episodic memory

spatial information processing in PER (Burke et al. 2012; Burwell et al. 1998; Deshmukh et al. 2012; Hargreaves et al. 2005), however, argues against the notion that PER combines spatial information with object information. Furthermore, quantification of c-fos activity as a marker of neuronal activity implicated a role not of PER but of the hippocampal formation in signaling novel constellations of familiar images (Wan et al. 1999). Indeed, damage to hippocampus alone and disconnection of hippocampus from PER impaired rats in the object-in-place task prompting the hypothesis that an integrated network involving PER and hippocampus is necessary for forming representations of objects and their relative positions (Barker and Warburton 2011). The PER-hippocampal network for object-in-place associations proposed by Barker and colleagues (Barker et al. 2007; Barker and Warburton 2011), however, might be incomplete when spatial properties of POR are considered. c-fos imaging showed that POR was activated more to novel constellations of familiar objects (Wan et al. 1999) and electrophysiological recordings have demonstrated neural correlates of object-location conjunctions in POR (Furtak et al. 2012). Thus, the PER-hippocampal network proposed by Barker and colleagues (Barker et al. 2007; Barker and Warburton 2011) necessary for object-in-place representations should be modified to include the POR. Further

disconnection studies would establish the role of POR within a PER-hippocampal network for object-in-place recognition memory.

Although PER and hippocampus have been doubly dissociated along a nonspatial/spatial dichotomy (Ennaceur et al. 1996; Winters et al. 2004), there are reports that PER damage can impair performance in spatial memory tasks (Liu and Bilkey 1998a, b, c, 1999, 2001). A possible explanation to resolve these inconsistencies lies within the perceptual processing viewpoint of the PER (Bussey and Saksida 2002; Murray et al. 2007). The behavioral deficits in PER-lesioned animals are not thought to be a deficit in spatial information processing per se as PER lacks spatial processing properties (Burwell et al. 1998; Deshmukh et al. 2012; Hargreaves et al. 2005), but are thought to arise in situations when distal complex or ambiguous cues must be used to solve the spatial task (Aggleton et al. 2004). Thus, the requirement of PER in spatial tasks can be explained within its role in the PMFC connectionist model to provide accurate representations of cues to hippocampus for a more detailed cognitive map. Modulation of hippocampal place fields by PER lesions and effects of nonspatial object information provide evidence for this hypothesis as PER lesions destabilized place fields in the CA1 subfield of dorsal hippocampus (Muir and Bilkey 2001). The presence of objects in a testing arena increased the number and reduced the size of hippocampal place cells; moreover, these modulations in number and size of hippocampal place fields were recorded in the CA1 subfield that receives direct PER and LEA projections (Burke et al. 2011). Together, these findings implicate PER in providing detailed object information to hippocampus for a more detailed cognitive map.

PER is also necessary for forming temporal relationships between objects (Barker and Warburton 2011). Recency judgments of objects require an integrated network consisting of the PER and hippocampus as impairments resulting from disconnection of these two brain structures were the same as that resulting from damage to either region alone (Barker and Warburton 2011). “Recency cells” in PER signal whether an item has been encountered recently regardless of whether it is novel or familiar (Xiang and Brown 1998; Zhu et al. 1995a). Thus, temporal information relating to a specific item is available upstream in PER and must be further processed in hippocampus. An alternative hypothesis is that the hippocampus provides a temporal framework upon which PER simply provides object information (Fig. 3.5). “Time cells” recorded in the hippocampus are thought to form a temporally ordered structure upon which events are mapped (MacDonald et al. 2011; see Eichenbaum et al. 2014). Anatomical studies show direct connections from PER to field CA1. This direct connection allows the possibility that object information from PER can be indexed within a hippocampal temporal framework to form temporal associations among objects.

There is general agreement that both spatial and contextual information are provided to the hippocampus through a pathway that includes the POR. At the same time, the hippocampus has been implicated in contextual fear conditioning and in configural learning. How should this apparent discrepancy be understood? Based on Nadel and Wilner’s (1980) dual process theory of context representations, Rudy (2009) has suggested that the PER and POR support elemental

representations of context, whereas the hippocampus supports a hierarchical representation. By this view, representations of individual items in PER and POR are each associated with a context, whereas the hippocampus binds the individual elements and the current context into a single representation that is associated with an event. Experimental lesion and electrophysiological studies do suggest that context is processed differently by PER, POR, and the hippocampus; however, the elemental versus hierarchical views do not explain all the data.

Two primary differences between hippocampal and cortical contributions to context emerge from the experimental lesion literature. First, pretraining lesions of the PER or POR reliably impair contextual fear conditioning (Bucci et al. 2000, 2002; Burwell et al. 2004b). Pretraining hippocampal lesions, however, cause minor if any impairment (Maren and Fanselow 1997; Frankland et al. 1998; Wiltgen et al. 2006; Richmond et al. 1999; Biedenkapp and Rudy 2009). Second, PER or POR posttraining lesions impair contextual fear conditioning up to 100 days after training (Bucci et al. 2000, 2002; Burwell et al. 2004a; Corodimas and LeDoux 1995). The effects of posttraining lesions of the hippocampus are time limited and have diminished effects 50–100 days after training (Anagnostaras et al. 1999; Maren et al. 1997). Electrophysiological studies also differentiate hippocampus from adjacent cortical structures. For example, neither the PER nor the POR exhibits place fields in a paradigm used in hippocampal physiology studies (Burwell and Hafeman 2003; Burwell et al. 1998; Shapiro et al. 1997; Fyhn et al. 2004; Hargreaves et al. 2005). Both the hippocampus and the POR exhibit item-location conjunctions. In a biconditional discrimination task in which the place determined which of two odors would be rewarded, hippocampal cells developed odor-place conjunctions over time, perhaps as a consequence of associative learning (Komorowski et al. 2009). POR cells also exhibit object-location conjunctions in a visual discrimination task, but the time course of such conjunctions has not been examined (Furtak et al. 2012).

Based on the above review, we suggest a slightly altered view of the dual process of context representations proposed by Rudy (2009). We suggest that the POR represents context by binding information about individual elements arising from the PER with location information arising from the retrosplenial and posterior parietal cortices to encode the spatial layout of items and patterns in the local environment. This representation of context would be available to multiple brain regions including the hippocampus for purposes of episodic memory and associative learning.

Conclusion

Available evidence suggests that object information in the POR most likely arrives via a direct PER to POR pathway. We suggest that the PER provides object information to both the POR and to the hippocampus, but for different purposes. Object information in the POR would be used to represent and update the spatial layout of physical features of the local environment, including objects and patterns located in that context. Information in POR is then available to hippocampus for episodic memory. The parallel object information flow from

PER to hippocampus is for the purpose of associations of objects (but not limited to visual stimuli) across domains (space and time) for complex representations of detailed allocentric spatial information as well as episodic memory.

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Head Direction Cells: From Generation to Integration

4

Shawn S. Winter and Jeffrey S. Taube

Abstract

To maintain spatial orientation and guide navigation, an animal must have knowledge of its location and displacement of distance and direction from that location. Cells within the hippocampal formation and connected structures are spatially correlated to location and direction. Specifically, head direction (HD) cells discharge as a function of the directional heading of an animal, independent of their location or behavior. HD cells are found in many brain regions, but the classic circuit involved in generating, updating, and controlling their responses originates in the dorsal tegmental nucleus and projects serially to the lateral mammillary nucleus, anterior thalamic nuclei, and post- and parasubiculum and terminates in the entorhinal cortex. The HD signal is generated by self-movement cues, with the vestibular system playing a critical role. However, HD cells become strongly controlled by environmental cues, particularly visual landmarks. HD cells provide a continuous signal that an animal will use to guide its behavior and maintain orientation. Information provided by HD cells may be critical for generating the grid cell, but not for the place cell signal. Collectively, information from HD, place, and grid cells provide a complete representation of the animal's orientation in space.

4.1 Introduction

The ability to maintain spatial orientation and guide navigation throughout the environment is fundamental to survival. Spatial processing is necessary to locate resources such as food, shelter, or access to a mate. Spatial disorientation can result from various sources of brain damage that produce a heterogeneous set of cognitive impairments. For example, impairments in attention (i.e., hemispatial neglect),

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memory (i.e., Alzheimer's disease or Korsakoff's syndrome), or spatial processing (i.e., vestibular damage or heading disorientation) can all lead to spatial disorientation (Aguirre and D'Esposito 1999). To better understand the mechanisms through which these forms of cognitive impairments cause spatial disorientation, we must better understand how spatial information is processed in the brain.

In order to maintain orientation, two sources of spatial cues are available—environmental and self-movement cues. Environmental cues arise from sensory stimuli that are external to the organism, often referred to as allothetic cues, and can engage multiple sensory modalities such as vision, olfaction, or tactile sensations. Environmental cues act as landmarks and may be used to guide multiple navigation strategies including beacon homing, piloting, and cognitive mapping (Gallistel 1990). Environmental cue-based navigational strategies may be reliable and flexible, but they require learning the association between cues and the location of a goal, which is reliant upon previous exposure to the environment. To be effective, it is not necessary to monitor environmental cues continuously, but rather they may be referred to episodically. In contrast, self-movement cues are generated internal to the organism as a consequence of its movement through the environment and include information from vestibular, proprioceptive, motor efference, and optic flow systems—often referred to as idiothetic cues (see Navratilova and McNaughton 2014). Path integration is the process of monitoring self-movement cues and integrating them over time to compute the amount of displacement the animal has moved in terms of distance and direction from a known starting point. This information may then be used to return directly to a previous location or to update one's location on a map. This process can be done independent of environmental cues and is not experience dependent, but it must be conducted continuously without interruption for it to be accurate. Self-movement cue processing can be inaccurate over time due to conflict between various self-movement cues, mnemonic constraints, inaccurate monitoring, or attentional interruptions, which results in a gradual accumulation of error, and environmental cues may then be used to periodically correct or reset the orientation system. Similarly, self-movement cues may aid in environmental cue-based navigation strategies by providing a reliable framework for calibrating space in a novel environment. Given the necessity of accurate navigation for survival, it is likely that environmental and self-movement cues are processed concurrently, with self-movement cues providing a foundation for spatial processing that is built upon by environmental cues.

Over the past half century, electrophysiological research has provided valuable insights into how the brain processes and represents spatial information. The first spatially tuned cells discovered in the brain that used an allocentric (world-based) reference frame were place cells (O'Keefe and Dostrovsky 1971; O'Keefe 1976). Place cells were first found in the hippocampus but have also been identified in the subiculum (Sharp and Green 1994) and entorhinal cortex (EC) (Quirk et al. 1992; Frank et al. 2000); however, place cells have not been reported in the EC since the discovery of grid cells, suggesting these findings may actually have been grid cells with large node spacing rather than place cells. Place cell activation is dependent

upon the location of the animal in the environment and can be controlled by environmental cues. The discovery of place cells, along with behavioral findings from hippocampal lesioned animals, led to the development of the theory that the hippocampus served as a kind of *cognitive map* for the organism, with place cells being the neural representation of the map (O'Keefe and Nadal 1978). Although place cells have been extensively investigated, the mechanism through which their firing patterns are generated is still unclear (Barry and Burgess 2007; Moser et al. 2008; Jeffery 2011; Burgess and O'Keefe 2011). In order to maintain an accurate representation of location one must monitor changes in linear and angular displacements over time. The hippocampus receives input from structures that contain spatially tuned cells that are sensitive to the animal's linear and angular displacement. First, grid cells have been identified in the EC (Fyhn et al. 2004; Hafting et al. 2005; Sargolini et al. 2006) and pre- and parasubiculum (PaS) (Boccara et al. 2010). Grid cells activate in multiple discrete locations in a triangular, grid-like pattern throughout an environment (see Derdikman and Moser 2014). This pattern of activity has been posited to provide a spatial metric for estimating distance during locomotion (Moser and Moser 2008). Second, head direction (HD) cells were first discovered in the postsubiculum (PoS), which is equivalent to the dorsal portion of the presubiculum (Taube et al. 1990a, b), but have since been found in multiple interconnected brain regions. HD cells are activated when the animal's head is pointing in a particular direction, independent of its location within the environment. Different HD cells are tuned to different directions, and it is hypothesized that the entire cell population represents all possible directions. Thus, HD cell activity is thought to provide the instantaneous perceived directional heading of the animal, similar to a compass. Together, distance estimates processed by grid cells and directional heading estimates processed by HD cells may provide the information necessary to maintain an accurate representation of the animal's location in the environment, which is represented by hippocampal place cells. This chapter will focus on HD cells and their relationship to the hippocampus. We will review several aspects of HD cells (1) fundamental properties, (2) anatomy and connectivity, (3) self-movement cue contributions to the generation and control of the signal, (4) environmental cue control, (5) their functional role, and (6) their interaction with place and grid cells.

4.2 HD Cell Properties

Since the discovery of HD cells by James Ranck in 1984, there has been extensive research on their properties [Ranck (1984), for reviews see Wiener and Taube (2005), Taube (2007)]. HD cells have been reported in multiple brain regions, most of which are interconnected to form a circuit. The firing characteristics of HD cells are very similar across all the regions they have been recorded. There are several parameters that may be used to characterize an HD cell, with the most common being the preferred firing direction (hereafter referred to as the preferred direction), directional firing range (tuning width), and peak firing rate (Taube

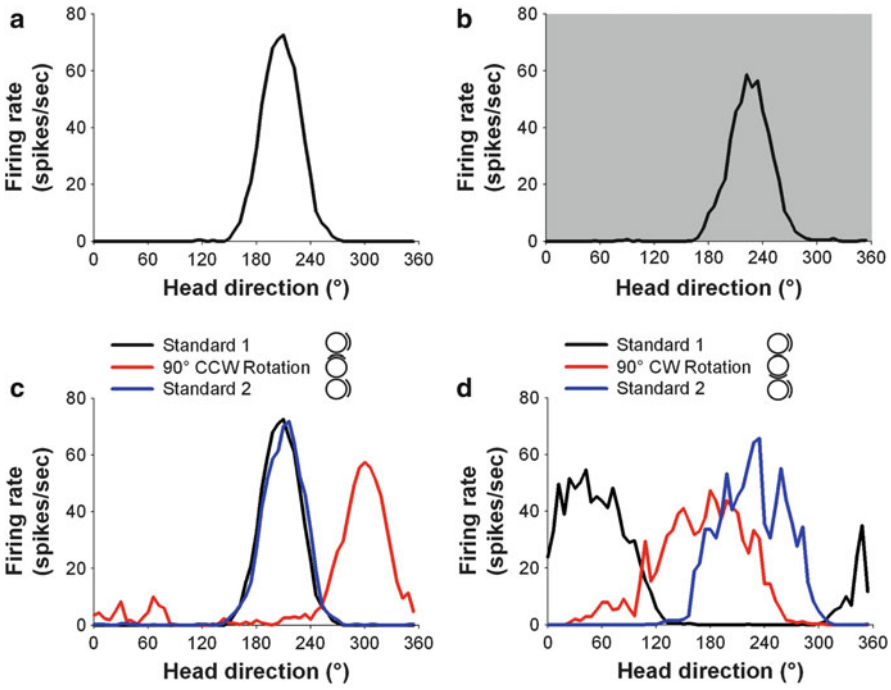

Fig. 4.1 Firing characteristics of a traditional HD cell recorded from the ADN and plotted as firing rate versus head direction. (**a**) An HD cell recorded in the standard cylinder under light conditions. (**b**) The same HD cell recorded in the standard cylinder with the cue removed under dark conditions (indicated by *gray shading*). (**c**) The same HD cell recorded with a 90° CCW rotation of the single prominent cue. The cell's original preferred direction (*black line*) shifted an equivalent 90° CCW (*red line*) with the rotation of the white cue and returned to its original preferred direction (*blue line*) when the cue was returned. (**d**) An HD cell recorded from LMN following lesions of the PoS with a 90° CW rotation of the single prominent cue. The cell's original preferred direction in the Standard 1 session (*black line*) shifted approximately 126° CCW (*red line*) following rotation of the cue. Note that this shift is in the opposite direction to the shift of the visual cue. When the cue was returned to its original position (Standard 2) the cell's preferred direction shifted another 48° CCW (*blue line*), which was not aligned to its original orientation in Standard 1. Thus, PoS lesions disrupt the ability of the HD signal to accurately be controlled by environmental cues. Note that the tuning curve for LMN cells has a higher directional firing range with more variability than the ADN depicted in *c*. This difference is common in the initial stages of the HD circuit. HD cells tuning curves become smoother and have smaller directional firing ranges further downstream in the HD circuit

et al. 1990a, b). Although the firing rate versus HD relationship is often plotted using a polar coordinate graph, it is easier to derive the above properties when firing rate is plotted versus HD using an *x*–*y* axes plot. The preferred direction is the heading orientation of the animal with respect to the environment when the cell fires maximally (Fig. 4.1a). When oriented outside of the preferred direction, the HD cell's firing rate in a well-isolated cell is usually at or near zero (referred to as the background firing rate). With the animal's head initially facing the cell's preferred

direction, there is a similar monotonic decrease in the firing rate as the animal turns its head in a clockwise or counterclockwise direction. The directional firing range is the range of directional headings in which the cell's firing rate is above the background firing rate. A typical HD cell has a directional firing range of ~90°; however, HD cells have been observed to exhibit firing ranges between 60° and 150°. The peak firing rate is the maximally observed firing rate, which usually occurs at or near the cell's preferred direction. There is considerable variability in peak firing rates across HD cells with rates observed from 5 to 120 Hz. Although peak firing rates vary considerably across cells, each individual cell's peak firing rate remains relatively constant, both across recording sessions and during varying task demands. The functional implication of different peak firing rates across the cell population remains unknown.

4.3 Anatomy and Connectivity of the HD Circuit

HD cells were first discovered in the PoS (Taube et al. 1990a, b) but have since been found in multiple interconnected regions. The regions that comprise the HD circuit include the dorsal tegmental nucleus (DTN) (Sharp et al. 2001), lateral mammillary nucleus (LMN) (Stackman and Taube 1998; Blair et al. 1998), anterodorsal (ADN) and anteroventral (AVN) thalamic nuclei (Taube 1995; Tsanov et al. 2011), retrosplenial cortex (RSC) (Chen et al. 1994a, b; Cho and Sharp 2001), PoS (Taube et al. 1990a, b), PaS (Boccara et al. 2010), and EC (Sargolini et al. 2006). The middle of Fig. 4.2 illustrates the anatomical connectivity within the HD circuit. In general, there is a hierarchical flow of information originating subcortically in the DTN that projects rostrally to the EC and is then conveyed to the hippocampus. The DTN has reciprocal connections with the LMN, which is thought to provide feedback to the DTN in order to generate the HD signal (Hayakawa and Zyo 1984). The LMN sends projections to the ADN via the mammillothalamic tract (Seki and Zyo 1984). The ADN has reciprocal connections with the RSC and projects to the PoS and PaS (van Groen and Wyss 1995; Shibata 1993). In addition to its connections with the ADN, the RSC sends projections to the PoS and PaS (van Groen and Wyss 1990b, 1992). The PoS and PaS are reciprocally connected but have distinct connectivity to the circuit (van Groen and Wyss 1990b). The PoS projects to the EC and sends feedback to the ADN, AVN, and LMN (van Groen and Wyss 1990a; Allen and Hopkins 1989), whereas the PaS has reciprocal connections with the EC and hippocampus and sends feedback to the ADN and medial, but not lateral, mammillary nuclei (van Groen and Wyss 1990b). Information is generally thought to flow in a unidirectional manner through this circuit in order to convey the HD signal to the hippocampal region. There are multiple sources of feedback into earlier regions in the hierarchy, such as projections from LMN to DTN, which are thought to provide necessary feedback for signal generation. Further, connections from the PoS to the ADN and LMN are thought to provide landmark control but are not necessary for the persistence of HD cells in the subcortical areas (Yoder et al. 2011b).

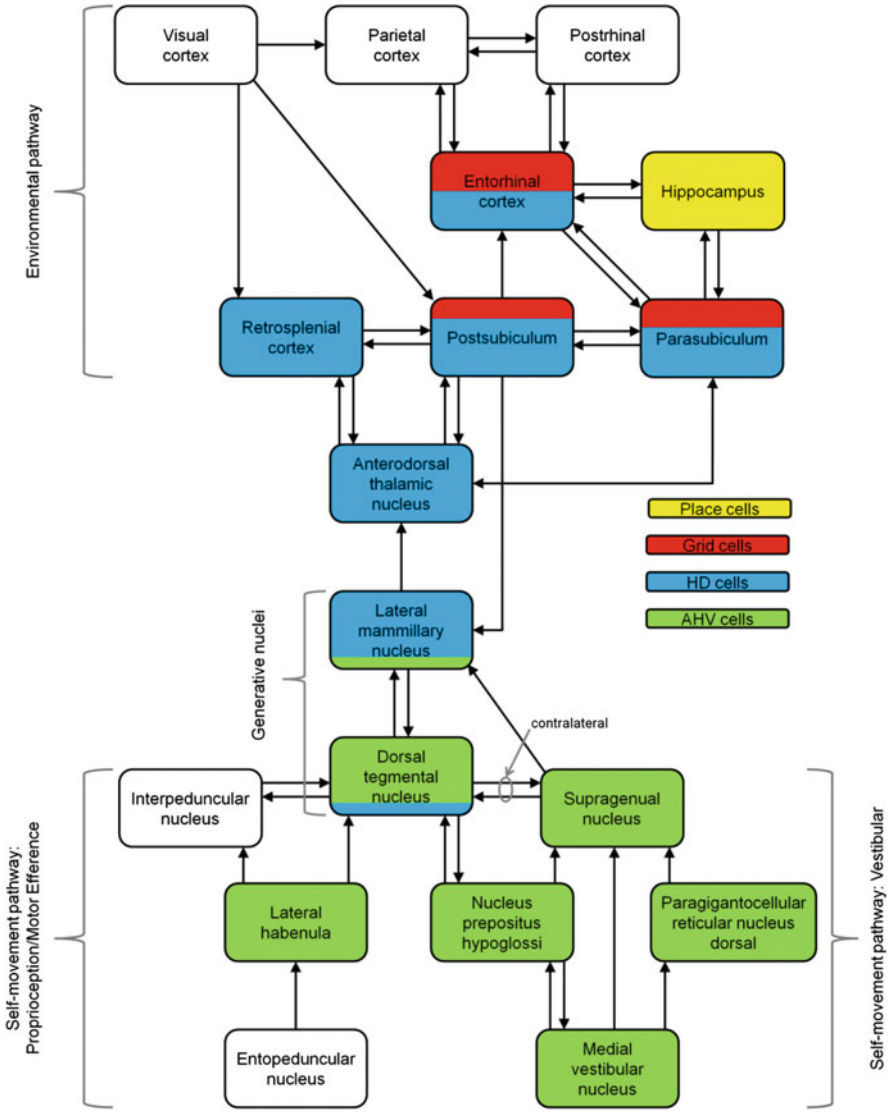

Fig. 4.2 Anatomy of the key regions involved in the HD circuit. *Green regions* contain AHV cells that are necessary for the generation and maintenance of the HD signal, and these regions can be divided between vestibular (*right side*) and proprioception/motor efference (*left side*) pathways. *Blue regions* contain HD cells. LMN and DTN communication is thought to underlie the generation of the HD signal as both regions contain AHV and HD cells but the distribution of cell types varies across them. HD regions downstream from the LMN are thought to be involved in associating the self-movement cue derived HD signal with environmental cues. *Yellow regions* contain place cells. *Red regions* contain grid cells. Note the PoS, PaS, and EC contain grid, HD, and grid × HD cells

The combination of lesion and recording studies has illustrated the functional relationship and unidirectional flow of information processing within the HD circuit. Lesions of the DTN or LMN disrupt the direction-specific activity in downstream structures such as the ADN (Blair et al. 1999; Stackman et al. 2002; Bassett et al. 2007). Lesions of the ADN (Goodridge and Taube 1997) or LMN (Sharp and Koester 2008) disrupt HD cell firing downstream within the PoS. In contrast, HD cell firing was maintained upstream in the ADN following lesions of the PoS, although the directional firing range increased indicating a less accurate directional signal (Goodridge and Taube 1997). Therefore, lesions early in the processing hierarchy disrupt HD firing in downstream regions, and lesions later in the processing hierarchy do not eliminate, but rather influence, HD cell firing in earlier regions. The influence of PoS lesions on subcortical HD cell areas is likely the result of disruption in the feedback the PoS sends to the ADN and LMN. Taken together, these studies provide evidence that the generation and maintenance of the HD signal is propagated through this series of brain regions in a unidirectional manner beginning with the DTN and terminating in the EC.

In addition to the circuit outlined above, there are other areas that contain HD cells whose functional relationship remains unknown. These regions include the lateral dorsal thalamus (Mizumori and Williams 1993; Yoganarasimha et al. 2006), dorsal striatum (Wiener 1993; Mizumori et al. 2000), medial precentral cortex (also referred to as the medial agranular cortex or FR2) (Mizumori et al. 2005), medial prestriate cortex (Chen et al. 1994b), and hippocampus (Leutgeb et al. 2000). Given the anatomical relationship between these regions and the HD circuit, these other areas are likely to be intermediate processing or output regions, rather than responsible for the generation of the HD signal, as lesions of these areas do not disrupt the HD signal within the hierarchical circuit (e.g., Golob and Taube 1997; Golob et al. 1998; Clark et al. 2010; Winter et al. 2012).

4.4 Self-Movement Cue Contributions to the Generation and Control of HD Cells

Vestibular cues appear to be necessary for the generation of the HD signal. HD cells are largely dependent upon angular head movements in the horizontal plane, although HD cell activity is maintained even when the animal is not moving or turning its head. The vestibular system is a key structure involved in monitoring both linear and angular head movements in all dimensions. The horizontal semicircular canals within the vestibular system are responsible for monitoring angular head movement in the horizontal plane (Goldberg and Farnandez 1975). Through lesion studies it has been shown that the vestibular system is the primary source of information used to generate the HD signal, as manipulations of the vestibular labyrinth eliminate the HD signal in the ADN and PoS (Stackman and Taube 1997; Stackman et al. 2002; Muir et al. 2009). More recent studies have dissociated the vestibular component contributions to the HD signal. Otolith-deficient mice maintain HD cells, but they contain a fewer percentage of cells with lower directional

tuning (Yoder and Taube 2009). In contrast, horizontal semicircular canal-deficient mice contain no directionally tuned cells (Taube and Valerio 2012). These findings indicate that vestibular signals, especially from the horizontal semicircular canals, must be conveying information about angular head displacement critical to the generation of the HD signal. Because vestibular efferents convey information about angular head velocity, these signals must be transformed before reaching the HD circuit to yield information concerning the amount of angular head displacement. The displacement signal can then be integrated with the animal's previous HD to generate their new directional heading.

The primary output of the vestibular end organs is the vestibular nuclei in the brainstem. In particular, the medial vestibular nucleus (MVN) responds to stimulation of the horizontal semicircular canals (Uchino et al. 2005). The exact route by which vestibular information within the MVN is conveyed to the DTN and contributes to the HD signal is still under investigation. Early anatomical work identified a direct projection from the MVN to DTN (Liu et al. 1984), but subsequent work has not confirmed these connections and has even questioned their existence (Hayakawa and Zyo 1985; Biazoli et al. 2006). In contrast, the MVN projects to the nucleus prepositus hypoglossi (NPH), supragenual nucleus (SGN), and paragigantocellular reticular nucleus dorsal (PGRNd) (McCrea and Baker 1985; Iwasaki et al. 1999; Biazoli et al. 2006). Of these three nuclei, only the NPH and SGN project into the HD cell network, and Fig. 4.2 (bottom) highlights their relevant connections. The NPH sends projections to the SGN and DTN, while the SGN projects to the LMN (a major projection site of the DTN) and the contralateral DTN. The PGRNd projects to the SGN. Direct investigation of each nucleus has implicated their role in processing angular head displacement and a large number of cells in each nucleus are sensitive to the animal's angular head velocity (AHV).

The MVN contains predominantly AHV cells, which fire as a function of the animal's angular head velocity (Leigh and Zee 1999). Four classes of AHV cells have been described: type I cells increase their firing with ipsiversive head turns (head turns to the same side in which the cell is recorded) and decrease with contraversive head turns (head turns to the opposite side in which the cell is recorded); type II cells have the opposite pattern; type III cells increase their firing with rotation in both directions; and type IV cells decrease their firing with rotation in both directions. AHV cells have also been reported within the DTN (Bassett and Taube 2001; Sharp et al. 2001) and are similar to those found in the MVN but thus far have been classified in two ways. Symmetrical AHV cells are the same as vestibular type III and IV neurons and respond by increasing or decreasing their firing rate when the head turns in either direction. Asymmetrical AHV cells have a differential response to turns in each direction. For example, some asymmetrical AHV cells are the same as vestibular type I and II neurons, while others may respond to turns in one direction and have no change in firing during turns in the other direction. Figure 4.3 illustrates examples of various types of AHV cells. The asymmetrical AHV cells that lack a response to turns in only one direction have not been described in the MVN. Many computational models have been developed in

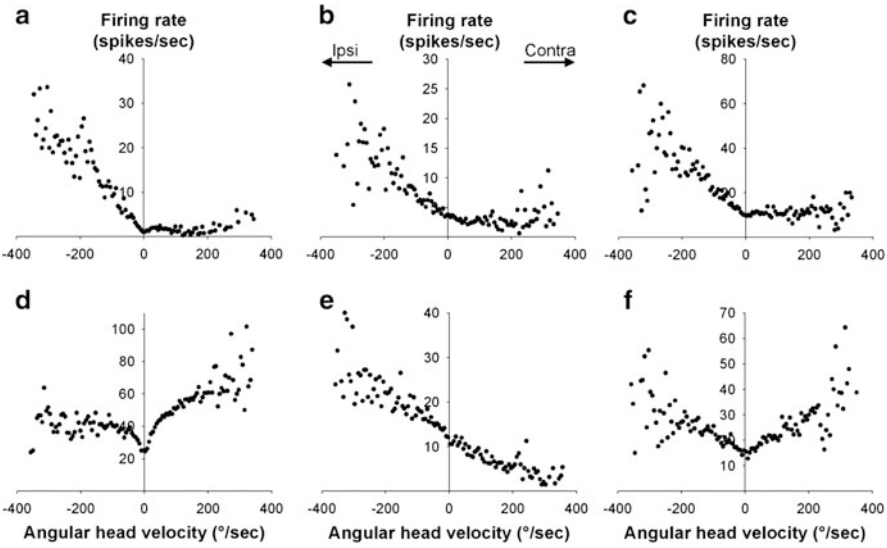

Fig. 4.3 Firing characteristics of various types of AHV cells plotted as firing rate versus angular head velocity. Asymmetrical AHV cells from the SGN (**a**), NPH (**b**), and PGRNd (**c**, **d**). Note that each of these AHV cells responds to turns in one direction, but do not change with turns in the other direction, similar to asymmetrical AHV cells within the DTN. (**e**) An asymmetrical AHV cell from the PGRNd that is similar to a vestibular type I cell. (**f**) A symmetrical/type III AHV cell from the PGRNd. Similar symmetrical AHV cells have also been observed in the SGN and NPH

an attempt to explain how HD cell activity is dependent upon AHV cells (Skaggs et al. 1995; Zhang 1996; Redish et al. 1996; Song and Wang 2005). These models assume HD cells are organized in a continuous attractor network, where HD cells are interconnected with one another, such that one cell excites neighboring cells with similar preferred directions and inhibits non-neighboring cells with dissimilar preferred direction. In most models AHV cells are used to shift the balance of activity in the attractor (often referred to as the activity hill) to indicate the perceived heading orientation. If AHV signals from the MVN are necessary for generating the HD signal in the DTN, then similar signals should be found in the intermediate nuclei of the NPH, SGN, and PGRNd.

AHV cells have been reported in the NPH (Baker and Berthoz 1975; Blanks et al. 1977; Lannou et al. 1984). Preliminary work from our laboratory in freely behaving rats in an open field environment has also confirmed the presence of AHV cells in the NPH, and we have also found them in the SGN and PGRNd (SS Winter and JS Taube, unpublished observations, see Fig. 4.3). All three regions contain symmetrical AHV cells. Interestingly, the NPH and SGN predominately contain asymmetrical AHV cells that only respond to turns in one direction and do not respond to turns in the opposite direction, similar to those reported within the DTN, whereas the PGRNd contains an even distribution of each type of asymmetrical AHV cells. Individual lesion studies of the SGN and NPH support the importance of

AHV signals from these nuclei for generating the HD signal. Lesions of the SGN reduce the number of HD cells found downstream in the ADN, and the HD cells that were present displayed large shifts in their preferred direction during locomotion in a dark environment, suggesting that the processing of self-movement information was impaired (Clark et al. 2012). Preliminary data from our lab has also found that NPH lesions similarly disrupt HD cell function in the ADN (Butler and Taube 2012). To date, no work has been done with lesions of the PGRNd. In sum, these findings indicate that at least two of the three intermediate subcortical nuclei between the MVN and DTN are involved in processing and conveying AHV information to the HD circuit.

One important unresolved issue is the type of information that is integrated with the vestibular AHV signals. For example, the NPH is assumed to be processing vestibular input from the MVN to generate AHV cells, but AHV cells in the NPH can be driven independently by optic flow from rotation of the surrounding environment (Lannou et al. 1984). In addition, proprioceptive and motor efferent signals may be projected to the DTN. Anatomically, the entopeduncular nucleus, a major motor output pathway of the basal ganglia, projects to the habenula, which in turn projects to the interpeduncular nucleus (IPN) and DTN (van der Kooy and Carter 1981; Contestabile and Flumerfelt 1981; Liu et al. 1984; Hayakawa and Zyo 1985; Groenewegen et al. 1986). The IPN is strongly reciprocally connected with the DTN (Contestabile and Flumerfelt 1981; Liu et al. 1984; Hayakawa and Zyo 1985; Groenewegen et al. 1986). The bottom portion of Fig. 4.2 depicts the anatomical connectivity of the motor output regions to the AHV and HD circuitry. Recording studies from these nuclei have found that the habenula contains asymmetrical AHV cells, but no AHV cells were reported in the IPN; however, both regions have cells that correlate with the rat's running speed (Sharp et al. 2006). In addition, lesions of the IPN did not eliminate HD cell activity in the ADN, but they did decrease the cells' peak firing rates and increase their directional firing ranges (Clark et al. 2009). Similar to SGN lesions, IPN lesions result in large shifts of the preferred direction during locomotion in a dark environment, indicating that self-movement cue processing may be impaired. These results provide evidence that all forms of self-movement cues significantly contribute to the maintenance of HD cell firing, but proprioceptive and motor efference cues are not necessary for the generation of the signal per se.

Self-movement cues are not only involved in the generation of HD cells, but they also play a role in accurate maintenance of the signal. When placed in a darkened environment, HD cells still maintain their accuracy without any familiar visual cues (see Fig. 4.1b) (Taube et al. 1990b; Goodridge et al. 1998). When traveling into a novel environment with no prominent extramaze cues, self-movement cues are sufficient for maintaining the accuracy of the cells' preferred directions (Taube and Burton 1995). Because these experiments were conducted within the same room, it was necessary to rule out the possibility that some unintended environmental cue may have been influencing the stability of the preferred direction. Therefore, Yoder et al. (2011a) required rats to travel through an enclosed pathway to a novel environment in another room that the rat had never visited previously. In this

case self-movement cues were sufficient to maintain the recorded cell's preferred direction in relatively the same orientation. There was, however, a small increase in the variability of the preferred direction when traveling between rooms versus the same task conducted in a single room. Either the increased distance traveled going between rooms increased the error accumulated when relying upon self-movement cues or some unknown environmental cues maintained influence over HD cell preferred direction accuracy, although this possibility seems unlikely since all cues in the room were novel. A second set of experiments was conducted in the novel room task where the rat had to travel between rooms under darkened conditions. This condition led to a further increase in the variability of the preferred direction, suggesting that the loss of optic flow under dark conditions increased the self-movement cue error. Manipulation of other self-movement cues has demonstrated their contribution to the HD signal. Eliminating a subset of self-movement cues (proprioception and motor efference) through passive rotation was initially shown to disrupt HD cell activity in the ADN (Knierim et al. 1995; Taube 1995). In these studies rats were passively rotated through their preferred direction while wrapped in a towel and held firmly. A subsequent study that used more controlled methods of habituating the rats to restraint and fixing their heads within a passive rotation apparatus found no loss or change in HD cell characteristics during passive rotation (Shinder and Taube 2011). The discrepancy between these studies may be the result of loose restraint that allows the rat to struggle and move its neck. These efferent motor commands and proprioceptive signals may be in conflict with the vestibular signals resulting in a decrement in the HD signal. Overall these results provide evidence that self-movement cues contribute to the generation and control of HD cells.

4.5 Environmental Cue Control of HD Cells

Screening and testing HD cells is often conducted in a relatively uniform environment with minimal environmental cues to allow the experimenter to more easily control cue manipulations. For this reason rats are tested in a gray cylindrical environment with a single white cue card attached to the inside cylinder wall that spans about 110°. The cylinder is surrounded entirely by a black curtain to prevent the use of distal visual cues. The single proximal cue allows for a salient landmark that can quickly be perceived by the rat. When testing in this environment, the preferred direction and peak firing rate of an HD cell can remain stable across several weeks with reports up to 23 days (Taube et al. 1990a; Taube 1995). Rotation of the proximal cue results in an equivalent shift of the HD cell's preferred direction (see Fig. 4.1c) (Taube et al. 1990b). When multiple HD cells are recorded simultaneously, the preferred directions of all cells rotate in register, indicating that the cells within a region act together, which is consistent with how attractor networks work (see Navratilova and McNaughton 2014). The dominant control of visual landmarks over HD cell preferred directions is established quickly. Insertion of a novel cue within the apparatus takes less than 1 min to gain rotational control over

the cell's preferred direction (Goodridge et al. 1998). This process seems sensible as an animal would want to align its internal spatial representation with the environment to aid in learning associations between landmarks in order to increase navigational accuracy. Subsequent research has investigated the types of landmarks that HD cells prefer for aligning with their internal representation. Zugaro et al. (2001) used a standard cylinder apparatus surrounded by a black curtain but placed three objects within the cylinder to act as salient visual cues. When the walls of the apparatus were present, rotation of these objects resulted in an equivalent shift of the cells' preferred directions, but when the walls were removed, the cells' preferred directions no longer shifted with the objects. Instead, the cells maintained their firing patterns relative to the surrounding black curtain. The authors noted that the curtain had random folds and thus was unlikely to be used for orientation, but the illustration of the apparatus indicates that the curtain was rectangular rather than circular (see Fig. 1B in Zugaro et al. 2001). The geometry of the curtain may have been sufficient to maintain orientation within the larger context of the room, resulting in alignment of the HD cells' preferred directions with the distal curtain, rather than the proximal objects. Behavioral studies have shown that rats are capable of using the geometry of their environment to guide navigation (Cheng 1986); thus, the geometric shape of the curtains may be used to align internal spatial representations with the environment. Further, the geometry of the environment is sufficient to produce rotational control of place cell firing fields (Jeffery et al. 1997). A follow-up study that provided distinct proximal and distal cue sets confirmed that HD cells predominantly align and rotate with distal over proximal cues (Yoganarasimha et al. 2006). Other experiments have explored the time it takes for a visual cue to influence HD cell firing, once a mismatch between orientation and landmark layout is perceived. In one study rats were trained to drink from a reservoir while facing the preferred direction of the currently recorded HD cell (Zugaro et al. 2003). While immobile and facing the cell's preferred direction, the lights were turned off, the visual cue was rotated 90°, and the lights were then turned back on. It took an average of 80 ms for the HD cells to cease firing once the lights were turned back on. Then, while still immobile, the lights were turned off and the cue was returned to its original orientation. This procedure restored the original orientation with the cue and reinstated HD cell firing. The authors estimated that the HD cells took ~80 ms to realign their preferred direction with the visual cue. It is noteworthy that for most visual cue rotation experiments, the cue rotation occurs with the rat out of view in order to remove any conflict between self-movement and environmental cues. However, rotation of a visual cue in the presence of a rat still maintains the ability of the cells to shift their preferred directions with the landmark, but the amount the preferred direction shifts relative to the amount the cue was rotated is usually less accurate than if the rotations occur with the rat out of view (Taube et al. 1990b).

Landmark control of HD cells from visual cues is processed in cortical regions of the HD circuit that are downstream from the subcortical regions involved in the HD signal's generation (for review see Yoder et al. 2011b). The processing of visual landmark information originates in the visual cortex and this information is then

projected directly to the PoS (Vogt and Miller 1983). Areas within the visual cortex also interconnect with the HD circuit via projections to the rhinal cortices (perirhinal and postrhinal which project to the EC) and RSC (van Groen and Wyss 1990a; Vogt and Miller 1983). The EC does not project heavily upstream to the HD circuit and as a result EC lesions spare landmark control of HD cells within the ADN (Clark and Taube 2011). Although the RSC is well connected with the HD circuit, having reciprocal connections with the PoS, ADN, AVN, and lateral dorsal thalamic nuclei—all areas that contain HD cells (Shibata 1993; van Groen and Wyss 1992)—RSC lesions produce only modest deficits in visual cue control of ADN HD cells (Clark et al. 2010). For rodents, it has been hypothesized that the PoS serves as the primary entry point for landmark information into the HD circuit and more generally into the limbic system. Lesions of the PoS result in severe disruption in the ability of landmarks to control HD cells within the ADN and the LMN (see Fig. 4.1d) (Goodridge and Taube 1997; Yoder and Taube 2008), as well as place cells in the hippocampus (Calton et al. 2003). The PoS not only conveys feedback information to the ADN, AVN, LMN, and RSC, but it provides a massive feedforward input to the EC. Thus, the PoS is centrally located to provide the ability to rapidly update the relationship between HD cells and environmental landmark information. This evidence indicates that the PoS is critical for integrating and aligning the HD circuit with visual landmarks. It is currently not known whether the PoS also integrates other non-visual environmental cues, such as auditory and tactile information, with the HD circuit.

Most environmental cue manipulations have been done with visual cues, but some studies have assessed both olfactory and auditory cues (Goodridge et al. 1998). Olfactory cue manipulations were conducted by using cotton-tipped applicators dipped in peppermint extract and taped to the wall of the cylinder above the reach of the rat. To reduce the influence of the applicator as a visual cue, four applicators were taped evenly spaced around the cylinder, but only one applicator was scented. Rat HD cells were monitored in the presence of the applicators; then the rats were taken out of the apparatus and disoriented while all four applicators were rotated by 90°. Olfactory rotation produced a significant shift in the HD cell preferred directions in the direction of the olfactory cue. Olfactory rotations usually resulted in under-rotations of the cells' preferred directions ($<90°$) and were not as accurate as manipulations with a visual cue. This error may be due to a lack of spatial resolution of the olfactory versus visual cue, especially when using a strong saturating odor such as peppermint extract. Auditory cue manipulations were conducted by using four evenly spaced speakers around the periphery of the cylinder about 0.2 m above the floor. HD cells were monitored in the dark to facilitate the use of auditory cues. Rats were exposed to the cylinder with one speaker emitting a 1 Hz audible click. They were then removed, disoriented, and placed back into the cylinder with an adjacent speaker (i.e., 90° rotation) emitting the click. This manipulation resulted in a mean shift of ~38° in the cells' preferred directions, but the shifts often did not follow the rotation of the auditory cue. The observed shifts were significantly different from a chance distribution, but could not be accounted for by the manipulation, since they did not have a tendency to shift in

the direction of the auditory rotation. These results indicate that non-visual environmental cues have the ability to influence HD cell activity. However, the precision of their influence is much less than the influence of visual cues.

4.6 Functional Role of HD Cells

Precisely how HD cells influence and guide an animal's spatial behavior is still unclear. As reviewed above, the generation of the HD signal is dependent upon self-movement cues produced by the vestibular system. In addition to eliminating the HD signal, lesions of the vestibular system produce significant impairments in self-movement cue processing (Wallace et al. 2002; Zheng et al. 2006, 2009). Disruption in the use of self-movement cues for spatial updating has been observed following lesions of all regions of the HD circuit, including the DTN and ADN (Frohardt et al. 2006); mammillothalamic tract, which is the major efferent of the mammillary bodies (Winter et al. 2011); RSC (Whishaw et al. 2001); and EC (Parron and Save 2004; Winter et al. 2013). The only exception is a recent study that found no impairments in path integration following lesions of the PoS in a food-hoarding task (Bett et al. 2012). It should be noted, however, that presurgical performance on this task indicated that rats returned to the correct refuge or the adjacent two refuge locations combined only 68 % of the time, suggesting rats were unable to accurately perform the task or were insufficiently trained. Also, on any given testing day, performance was never much above 50 % correct for eight trials. Thus, performance on the task appears to be poor before any experimental manipulations that could mask any potential effect of the lesion or indicate that the task is not an appropriate path integration task. In addition, the average lesion size was only 66 %, suggesting the possibility that there may have been insufficient damage or sparing of areas that contain large numbers of HD cells. Overall, these studies suggest that the HD circuit plays a critical role in processing self-movement cues used to guide navigation.

There are two possible ways in which HD cells may be used to guide navigation. First, HD cells may be a learned association between performance and orientation that develops during acquisition of a task. If this were the case, during learning HD cells would increase in directional specificity as performance accuracy increased. One study has shown that HD cell directional specificity increased with behavioral accuracy during training on a radial arm maze (Mizumori and Williams 1993). However, behavioral errors increased when these rats were tested under complete dark conditions, but importantly, there was no change in HD cell directional specificity. Performance under dark conditions, along with methodological concerns, suggests that increased directional specificity during training does not reflect learning within the HD cells to guide behavior. Second, the HD signal may be utilized as a continuous directional signal that an animal must learn to use to guide behavior. There are multiple lines of evidence to support this interpretation of HD cell function. Direction-specific firing in HD cells is established within seconds of entering a novel environment, and directional specificity remains constant across

testing sessions (Taube et al. 1990a, b; Taube and Burton 1995). In addition, HD cells maintain consistent firing during training on a spatial task. For example, Muir and Taube (2004) trained rats in a starburst maze where they had to run a circuitous route to obtain a reward. Once the task was learned they were given a probe trial where the learned route was blocked, but multiple novel routes were made accessible with one route forming a direct line to the reward location. During probe trials the preferred direction of HD cells maintained consistency with training. Other studies have found that the shifts of HD cell preferred directions during navigation correlate with the performance of the rat. In one study Dudchenko and Taube (1997) trained rats to run down one arm in a radial arm maze to obtain a water reward. The maze was surrounded by a black curtain, which had a white cloth sheet draped over one portion of it that served as a prominent visual cue. During trials where the white sheet and water reward were rotated, if the cell's preferred direction shifted to remain in alignment with the white sheet, then the rat's choice of arms also shifted to the correct arm. However, if HD cell's preferred direction did not shift, then the rat's choice did not shift and they made an error. Similarly, van der Meer et al. (2010) trained rats in a food-hoarding task with a central platform that could be rotated independent of the surrounding refuge locations. When the central platform was left stationary, HD cells' preferred directions remain consistent and rats made accurate returns to their home-based refuge. If the central platform was rotated 90° while the rat was on it, then the HD cells' preferred directions shifted an equivalent amount and the rat made a corresponding error in its refuge choice. Valerio and Taube (2012) built upon these findings with the food-hoarding paradigm using blindfolded rats that had to use their path integration system to accurately return to their refuge. They observed that rats occasionally made behavioral errors when returning to the refuge while blindfolded. During error trials the degree of behavioral error corresponded to the shift observed in the cell's preferred direction just prior to its return, which is similar to the findings of van der Meer et al. (2010) who induced the rat's behavioral error through their spatial paradigm. Following small behavioral errors ($<50°$), HD cells reset their preferred direction to the last accurate trial's orientation when the rat returned to the refuge between trials. Following large behavioral errors ($>50°$), the cells remap their orientation for subsequent trials such that there is no change in the cell's preferred direction while the rat is in the refuge. Thus, the cell maintains the error trial's shifted preferred direction in the next trial. Not only is there a correspondence between the return behavioral trajectory and the HD cell's preferred direction, but there is a predictable change in the preferred direction that corresponds to the degree of error in the return trajectory. These results provide evidence that HD cells provide a continuous directional signal that an animal must learn to use, rather than a signal that develops with learning.

4.7 HD Cell Interactions with Place Cells and Grid Cells

Multiple spatially tuned cells have been discovered in the rodent brain, including HD, place, and grid cells. How these cells interact with one another to guide behavior remains unclear. Simultaneous recording across multiple brain regions has begun to address the relationship of HD cells with these other spatially tuned cells. The firing characteristics of HD, grid, and place cells are controlled by manipulation of prominent environmental cues, and when tested, the three cell types are strongly aligned together (Knierim et al. 1995, 1998; Yoganarasimha et al. 2006; Hafting et al. 2005). Under normal recording procedures in the cylinder with a single proximal cue, the rat is taken out of the apparatus and disoriented while the cue is rotated, and then the rat is returned to the apparatus. The disorientation procedure is conducted in order to eliminate the potential use of self-movement cues across testing sessions and increase the reliance upon visual cues. In one study that recorded HD and place cells simultaneously, Knierim et al. (1995) trained rats in the food foraging task, where half of the rats were disoriented each day before training and the other half were not, but all rats were disoriented during cue rotation sessions. They found that the HD cell preferred directions and the place cell fields in non-disoriented rats would shift with the visual cue as had been reported previously. However, the visual cue had much weaker control over both HD and place cells in the group that was disoriented during training. During sessions when HD cell firing was not controlled by visual cues, place cells often remained in alignment with the HD cells, but there were a number of times that the place cells remapped. In a follow-up study Knierim et al. (1998) rotated the entire apparatus with the rat inside while recording HD cells and place cells. They found that during small rotations of the visual cue (~45°), both HD cell preferred directions and place cell fields shifted with the visual cue. During large rotations (~180°), both the preferred directions and the place fields remained in alignment with the visual cue when it was rotated slowly, but when it was rotated rapidly, HD cell preferred directions would not align with the visual cue and place cells remapped. These studies demonstrate two important findings. First, HD cells and place cells remained closely aligned with one another throughout all the manipulations regardless of their relationship to the visual cue. Second, on occasions when the visual cue did not control the firing of HD cells, the place cells would occasionally remap their firing fields. These results indicate that place cell stability may be related to the stability of HD cells or their ability to maintain their orientation relative to the environment and suggest that place cells are in some part dependent upon HD cells.

Other studies that have recorded HD cells and place cells simultaneously have assessed the strength of distal versus proximal cues in controlling the cells. These studies have shown that HD cells are more strongly coupled to distal cues than to proximal cues (Zugaro et al. 2001; Yoganarasimha et al. 2006), but place cells exhibit more of a split response where some cells follow distal cues and other cells follow proximal cues (Shapiro et al. 1997; Tanila et al. 1997). For example, during cue conflict rotations HD cells were strongly aligned to distal cues and followed

their rotation 94 % of the time, and all simultaneously recorded HD cells responded in register (Yoganarasimha et al. 2006). In contrast, place cells exhibited multiple responses, where only 25 % of the sessions showed simultaneously recorded place cells responding in register. The other 75 % of sessions resulted in different responses, with some place cells following distal cues, some place cells following proximal cues, some place cells showing split place fields, and other place cells remapping completely. When HD cells and place cells were recorded simultaneously, the place cells' most common responses were either to align their place fields in register with the HD cell signal or to remap. On a few occasions the place fields rotated in the opposite direction to the shift in the HD cells' preferred directions and did not remap. This result is important because it is the first observation of a place cell's field shifting out of alignment with the HD cell signal without remapping and provides evidence that hippocampal place cells are not entirely dependent upon alignment with the HD cell system. In general, HD cell and place cell activity tends to be aligned, but during cue conflict situations, the percentage of place cells that maintain alignment with HD cells decreases. Place cell remapping is the most common response when they do not maintain alignment, but there are occasions when place cell fields misalign with the HD cell signal, indicating that HD cell inputs are not solely responsible for controlling place cell activity.

The medial EC is an important structure for spatial processing as it receives projections from the HD circuit, has reciprocal connections with the hippocampus, and contains several cell types that are spatially tuned including HD cells, grid cells, and conjunctive grid $\times$ HD cells (Fyhn et al. 2004; Hafting et al. 2005; Sargolini et al. 2006). Simultaneous recordings of HD cells and grid cells have found that their spatial representations both shift together in alignment with rotation of a prominent visual cue (Solstad et al. 2008). However, when tested in similar apparati across two different rooms, the spatial representations of HD cells and grid cells remained aligned, but the vertices between the nodes of the grid (i.e., spatial phase) changed in grid cells. These results suggest that HD cell information may contribute to the alignment of grids, but the spatial phase is generated independently in grid cells. In contrast, when rats were tested in unique environments, HD cell preferred directions and grid cell firing patterns can become misaligned (Whitlock and Derdikman 2012). In this study rats were first trained to explore an open square box. Next, nine opaque walls were inserted into the box, which turned it into a series of alleys connected at the end by a 180° turn, referred to as the hairpin maze. Rats were monitored in the open box, allowed to run the hairpin maze, and returned to the open box. HD cells and grid cells recorded across the two open box sessions were consistent and in alignment with one another. When tested in the hairpin maze, HD cell preferred directions maintained their alignment with extramaze cues, but grid cells lost their grid characteristics; however, some of these grid cells that lost their gridness still appear grid-like in the hairpin maze where the grid pattern now appears more elliptical than hexagonal (see Fig. 3f in Whitlock and Derdikman 2012). The authors argue that there was no grid that spanned the entire apparatus, but grid cells reset at the beginning of each alley. If grid cells reset in this manner,

then they should fire at the same distance along every alley independent of the direction the rat ran. Instead, firing was dependent upon the direction the rats were running down each alley and the distance they traveled down that alley. Processing distance has been the proposed function for grid cells (Moser and Moser 2008), and in the hairpin maze they appear to continue to convey distance-related information. Although the signal no longer looks grid-like or can be analyzed using the normal grid score method, the firing of the cell still conveyed meaningful information about distance traveled. Overall HD and grid cells appear to remain in alignment during landmark rotations and across multiple testing environments, but they can be independently influenced by substantial changes in the environment.

Individual representations for HD and grid cells are not the only significant finding related to spatial processing within the medial EC. There are also conjunctive cells whose firing combines the characteristics of grid cells and HD cells concurrently (Sargolini et al. 2006). These conjunctive cells are thought to be integrating distance information from grid cells with direction information from HD cells. The grid and HD signal components of the conjunctive cells can be independently influenced by manipulating medial EC afferents. The medial septal area projects to the EC, exhibits theta rhythm, and generates EC theta rhythm, which is involved in the generation of grid cells (Mitchell and Ranck 1980; Mitchell et al. 1982; McKinney et al. 1983; Woolf et al. 1984; Alonso and Garcia-Austt 1987). Disruption of medial septal area activity inhibits theta in the medial EC and eliminates the presence of grid cells (Brandon et al. 2011; Koenig et al. 2011). In addition, conjunctive cells lose their grid characteristics while maintaining their direction-specific characteristics. Taken together, these results provide evidence that theta rhythm plays a critical role in generating the grid cell signal and that conjunctive spatial representations are integrating two independent spatial signals (theta rhythm and HD cells). The function of this conjunctive cell type appears to be integrating distance and direction, presumably for the process of path integration. Lesions of the EC have been shown to produce impairments in the processing of self-movement cues (Parron and Save 2004). In depth behavioral analysis following lesions of the EC has found that the impairments in processing self-movement cues were selective to the rats' ability to estimate distance while sparing direction (Winter et al. 2013). The primary function of the medial EC grid cell system may be to process distance, even though HD cells are co-localized and conjunctively represented in the EC. One possible explanation is that accurate distance estimation through the mechanism of a grid cell may in part be dependent upon direction. This possibility explains why EC lesions selectively impair distance estimation but spare direction estimation. The HD cells found within the medial EC may be providing a bearing for generating a grid cell signal. Evidence supporting this interpretation comes from preliminary data in our lab showing that lesions of the ADN eliminate both the HD and grid cell signals in the medial EC (Clark et al. 2011). These results indicate that grid cells are dependent upon HD cell information and are consistent with both attractor network and oscillatory interference models of grid cell generation (Burgess et al. 2007; Hasselmo and Brandon 2008, 2012; Burak and Fiete 2009). Grid cells are dependent upon theta and HD signals in order to generate an

accurate distance estimate. A distance estimation system dependent upon directional orientation is both attractive and plausible, given that real world navigation is often a circuitous route made up of nonlinear paths, punctuated by stops, and contains detours (Eilam and Golani 1989; Wallace et al. 2006; Souman et al. 2009).

Conclusion

We reviewed the fundamental properties of HD cells, which fire as a function of an animal's HD within the environment independently of the animal's location or behavior. The HD signal provides an animal with a continuous signal of their orientation with respect to the horizontal (yaw) plane—much like a compass, and they learn to use this signal to guide their navigational behavior. HD cells are found within many interconnected brain regions that are organized within a hierarchal fashion beginning in the brain stem and terminating in the EC and hippocampus. Embedded within the hierarchical framework are both parallel and feedback loops. AHV signals generated primarily from the vestibular system, but also involving motor and proprioceptive feedback, are critically involved in the generation of the HD signal. Higher-order cortical regions are involved in associating the internal representation of HD with environmental cues that can be used to reset and control the alignment of HD cells. These higher-order regions occur later in the hierarchy and interact with other spatially tuned cells. The preferred directions of HD cells remain in register with the spatial representations of place and grid cells during manipulations that influence their firing. The HD signal is believed to be the neural substrate for an animal's perceived sense of direction.

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Spatial Maps in the Entorhinal Cortex and Adjacent Structures

5

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Abstract

This chapter presents an introductory overview on grid cells and other cell types in the entorhinal cortex and adjacent regions, which are believed to be part of the brain's representation of space. Grid cells, which have been discovered only recently, are thought to be part of a class of cells in the mammalian hippocampal and parahippocampal cortices which are involved in the cognitive mapping of the spatial environment. These cells include also place cells, head-direction cells, and border cells. In this chapter, we shall portray the phenomenological characteristics of the recently discovered grid cells and compare them to the other types of mapping-related cells in hippocampal and parahippocampal regions.

5.1 Early Recordings in the Entorhinal Cortex and Associated Structures

One of the questions following the discovery of place cells in the 1970s in the hippocampus was how the place cell signal is generated. A variety of suggestions were made regarding the types of input that led to the formation of a place field (Best et al. 2001), but it was clear that such proposals could benefit from a better understanding of the anatomical circuitry of the hippocampus and its surrounding regions. Lesions of the intrinsic excitatory pathways of the hippocampus showed

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that place cells could be generated in CA1, the output stage of the hippocampus, without the rest of the hippocampus, suggesting that spatial signals might originate outside the hippocampus (Mcnaughton et al. 1989; Brun et al. 2002). Since the days of Ramon y Cajal, it has been known that the entorhinal cortex is the main structure sending input into the hippocampus from the neocortex (Witter and Amaral 2004). Based on this knowledge, researchers started recording in the entorhinal cortex in order to determine the origin of the place signal. The earliest recordings showed that neural activity is spatially modulated not only in the hippocampus but also in the entorhinal cortex (Barnes et al. 1990; Quirk et al. 1992; Frank et al. 2001; Fyhn et al. 2004). For example, Quirk et al. (1992) showed that, in rats that foraged in open fields, entorhinal cells fired consistently more in some places than others, and in the work of Frank et al. (2001), some entorhinal cells were shown to fire in confined places along a W-shaped or U-shaped track (Fig. 5.5a).

5.2 The Discovery of Grid Cells

Anatomically, the entorhinal cortex contains several subdivisions. The main division is between the medial and lateral entorhinal cortices (Witter and Amaral 2004). The medial entorhinal cortex (MEC) shows a dorsal-to-ventral organization in which the most dorsal parts project exclusively to the dorsal hippocampus and the most ventral parts only to the ventral hippocampus (Witter et al. 1989; Dolorfo and Amaral 1998). Similarly, the lateral entorhinal cortex (LEC) shows a medial-to-lateral organization of projections to the hippocampus (see Fig. 6.1). Before 2004, all recordings from spatial cells in the entorhinal cortex had been made in the ventral or intermediate parts of the entorhinal cortices, partly in medial and partly in lateral entorhinal cortex. These ventral regions project primarily to the ventral hippocampus, where place fields are large, and exhibit minimal spatial variation in small environments (Jung et al. 1994; Kjelstrup et al. 2008). No cells had yet been recorded in the most dorsal parts of entorhinal cortex, which provide the connections to the dorsal hippocampus where place cells were discovered. In 2004, the first recordings were made in the dorsal part of the entorhinal cortex (Fyhn et al. 2004). These studies showed cells with highly distinct firing fields but each cell had multiple fields. It was noticed in these recordings that the fields followed a regular organization with fields being spaced at an optimally close distance to each other. To better understand the spatial organization of the firing fields, the cells were subsequently recorded in larger environments, including boxes with surface areas that were more than three times larger than those of previous studies. When recording the cells in such environments, a pattern emerged: the firing fields took the form of tessellating hexagonal grids, where the repeating unit was an equilateral triangle (Hafting et al. 2005) (Fig. 5.1a). Cells with such periodic firing fields were referred to as grid cells. The finding has inspired a great deal of excitement, as the tessellating pattern resembled similar patterns appearing in nature, such as the beehive or oranges packed compactly into a box (Fig 5.1b).

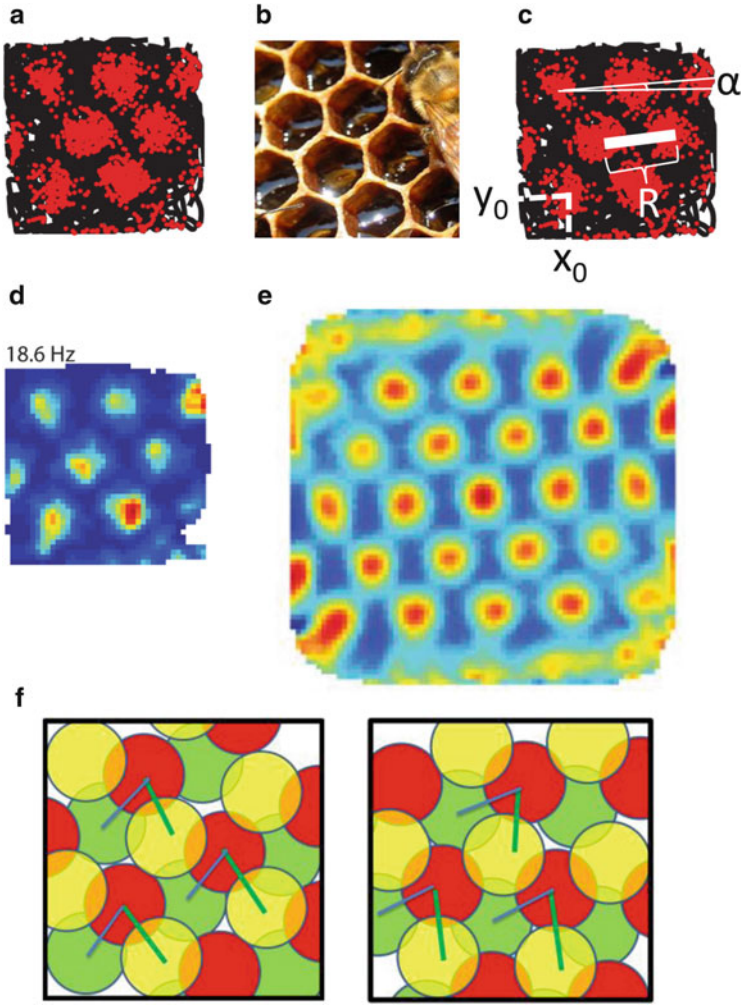

Fig. 5.1 Grid cells and their properties (**a**) An example of a grid cell. Trajectory of rat in box is shown in *black*, and positions of grid cell firing are marked with *red dots*. Note the repeating pattern of fields, forming equilateral triangles. Cell taken from Bonnevie et al. (2013). (**b**) Other *hexagonal patterns* in nature suggest that grid cells obey an optimality principle. (**c**) Grid cell definitions: spacing (R), phase (x_0,y_0), and orientation (α). (**d**) An example of a rate map generated from the grid cell in **a**. Color scale ranges from *blue* (no firing) to *red* (maximal firing rate). (**e**) A spatial autocorrelation map derived from the rate map in **d**. *Blue*, minimum correlation; *red*, maximal correlation. Note that the center of the figure represents a spatial autocorrelation distance of 0 and equals 1 by definition (the correlation of the rate map with itself is 1). (**f**) Grid cells of similar scale preserve phase differences in different environments. For example, in the *left* environment, three grid cells are represented by three colors (*yellow, red*, and *green*) and have a specific phase relationship (*blue* and *green* segments). In a new environment (*right*) the three grids may have a different phase and orientation, but they preserve their intrinsic phase and orientation relationships

5.3 Grid Cells and Their Properties

How do different grid cells differ from each other? The main parameters in which grid cells differ are spacing, phase, and orientation (Hafting et al. 2005).

Mathematically, we can write the following formula to describe the normalized firing rate $F(x,y)$ of an ideal hexagonal grid cell, built from three identical planar waves propagating at 60° to each other:

$$F(x,y) = \sum_{l=1}^{3} \cos\left[\frac{2\pi}{R}(x - x_0)\sin\left(\frac{l\pi}{3} + \alpha\right) + \frac{2\pi}{R}(y - y_0)\cos\left(\frac{l\pi}{3} + \alpha\right)\right] \quad (5.1)$$

where R defines the *spacing* of the grid, the points (x_0,y_0) define the *phase* of the grid, and α is the *orientation* of the grid, in radians. Below are explanations of each parameter:

5.3.1 Spacing

Spacing [R in (5.1)] is defined by the typical minimal distance between the centers of two consecutive grid fields (Fig. 5.1c). While it is possible to measure grid spacing on the spatial rate map of a grid cell (Fig. 5.1d), the spacing of the grid pattern can be measured with a much better signal-to-noise ratio in two-dimensional autocorrelograms of the spatial rate distribution (Hafting et al. 2005) (Fig. 5.1e). It was noticed from the outset that the spacing between grid cells is a function of the recording depth, or the dorsoventral position, within the entorhinal cortex (Fyhn et al. 2004; Hafting et al. 2005). Grid field spacing expanded along the dorsoventral axis of the medial entorhinal cortex. Cells that were recorded dorsally typically had a minimal grid spacing of about 30 cm in the rat, while in cells recorded more ventrally the spacing would typically grow up to at least twice that size. In a later study in which rats were running along a linear track, it was shown that the spacing between consecutive grid fields could increase to 3 m or more (Brun et al. 2008). Thus, it was speculated that grid cells encode spatial extent at different resolutions, such that grid cells in the dorsal end of the medial entorhinal cortex encode smaller spaces at a fine resolution, while grid cells in the ventral end of the medial entorhinal cortex encode larger spaces at a coarser resolution.

5.3.2 Phase

The phase of a grid can be defined by the position of a single peak [x_0 and y_0 in (5.1); see Fig. 5.1c]. Unlike grid spacing, which seemed to follow an anatomical gradient, the phase difference between two grid cells (Fig. 5.1c) did not have any apparent anatomical correlate (Hafting et al. 2005). Grid cells with similar spacing but different spatial phases could be recorded at the same location within the medial entorhinal cortex. Moreover, there was no apparent distance rule: two grid cells with

a large phase difference could be recorded in a single anatomical position (position "A") within the entorhinal cortex, while a simultaneously recorded cell at a different anatomical position ("B") could have a very small phase difference with one of the cells recorded in position "A" (but not with the other). Phase differences are known to translate between environments: two grid cells of a similar scale with a small phase difference between them in one environment will preserve a small phase difference when the rat is translocated to a second environment, while two grid cells with a large phase difference in one environment will preserve the large phase difference in the second environment (Fig. 5.1f) (Fyhn et al. 2007). The invariance of phase differences across environments has been researched in depth in Yoon et al. (2013).

5.3.3 Orientation

The third parameter defining a grid is its orientation [α in (5.1); Fig. 5.1c]. Grid cells of similar spacing tended to have almost identical grid orientations within the same environment. Grid cells with different spacing often differed also in grid orientation (Stensola et al. 2012) and grid cells with different values of grid spacing tended to preserve their orientation difference when the rat was translocated from one environment to another environment (Hafting et al. 2005; Fyhn et al. 2007). A recent study indicates that grid cell orientation is dictated mostly by the geometry of the behavioral boxes, and is relatively invariant between rats (Stensola et al. 2013).

Apart from these three classical measures of a grid, we should discuss two additional parameters which could dictate grid shape:

5.3.4 Field Size

The spacing between different grid field centers does not necessarily dictate the size of a single grid field. Thus, in theory there could be grid cells of large spacing with small fields and grid cells of smaller spacing with larger fields. In practice, there seems to be a relation between grid size and field size, such that larger grid spacing dictates a larger field size (Hafting et al. 2005; Giocomo et al. 2011), although to date there has not been a systematic study that checked this question thoroughly.

5.3.5 Ellipticity

Recently a "Keplerian twist" has been added to the description of grid cells: apparently grid cells may have an anisotropic spacing along its three axes of orientation, creating a situation in which grid patterns become slightly "elliptic" in shape (Fig. 5.2a) (Stensola et al. 2012). The eccentricity of the fitting ellipse (the ratio between the major axis of the ellipse and the minor axis of the ellipse) can change from 1 (totally isotropic grid) to more anisotropic values. Grids are usually almost isotropic; however, the slight anisotropy could be used to define grid cells as

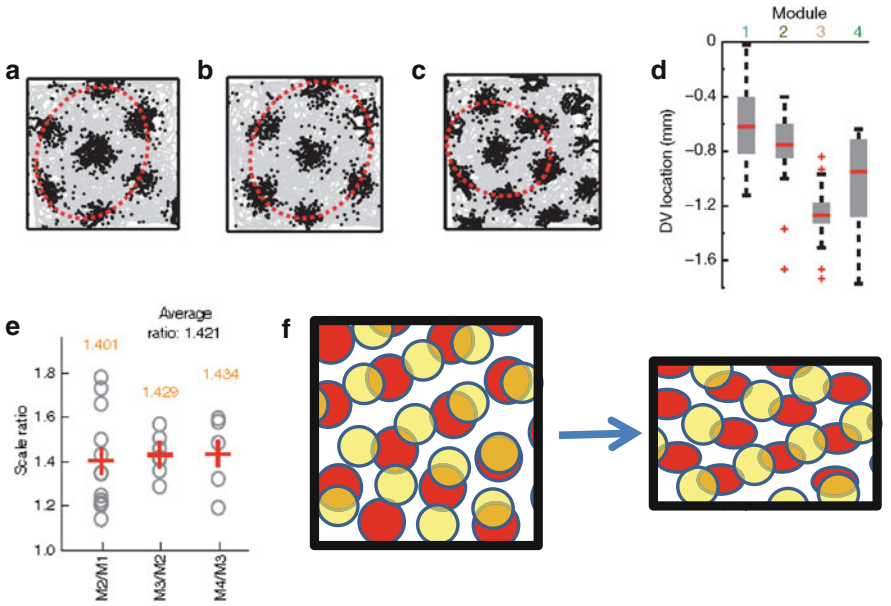

Fig. 5.2 Grid cell modules (**a**) Grid-cell anisotropy—an example of an "elliptic" grid cell. Rat's trajectory is shown in *gray*, spikes are shown in *black*, and ellipse through grid points is defined by *red dotted curve*. (**b**) A grid cell from the same module will tend to have a similar *ellipse* shape. (**c**) A grid cell from a different module may have a very different *ellipse* shape. (**d**) The anatomical extent (as a function of distance along the dorsoventral axis of the MEC) of each of four modules in one example rat demonstrates overlap between the modules. There is a great deal of anatomical overlap between cells belonging to different modules, although modules with large spacing (spacing increases from module 1–4) tend to be more ventral. (**e**) The size of grid modules tends to grow in multiples of $\sqrt{2}$: the figure plots the ratio between the scales of consecutive modules (from module M1 to M4), showing that on average the ratio between scales of consecutive modules is 1.421, which is very close to $\sqrt{2}$. Panels **a–e** adapted from Stensola et al. (2012). (**f**) Grid cells from different modules may scale independently when the rat changes its position from one environment to another. In this schematic typical example, when the environment is reduced in one dimension, the "*yellow*" grid, belonging to the module with the smaller grid spacing, conserves its scale, while the "*red*" grid, belonging to the other module, contracts in scale (it is yet unknown whether the individual fields contract in shape or rather conserve their round appearance)

belonging to different modules: we say that two grid cells which have been recorded simultaneously belong to the same "module" if the ellipse defining the two grid cells has the same dimensions and orientation (Fig. 5.2b).

5.3.6 Modular Organization

Recent work has shown that within a single animal, grid cells can be clustered into 4 or 5 modules, such that grid scale increases in a discrete fashion between one

module and the consecutive one in the same rat (Barry et al. 2007; Stensola et al. 2012) (Fig. 5.2c). Grid cells belonging to modules with large spacing tend to reside more ventrally than grid cells belonging to modules with small spacing; however, there is some anatomical overlap between the modules (Fig. 5.2d), such that grid cells from two modules with different spacing can in principle be recorded simultaneously in the same anatomical location. Interestingly, the grid spacing in modules of consecutive scales, as defined by the dimensions of the fitted ellipse, tends to grow in leaps of $\sim\sqrt{2}$, such that the area surrounded by the ellipse defining the grid tends to grow by multiples of 2 (Fig 5.2e). The geometric progression defined by this constant scale factor has been suggested to be optimal for representing environments at high spatial resolution (Mathis et al. 2012).

Recent work has shown that different grid modules may exhibit different degrees of grid expansion and grid contraction (Stensola et al. 2012). When an environment was stretched, grid cells of some modules did not stretch with the box at all, while grid cells of other modules stretched to acquire the new dimensions of the box (Fig. 5.2f). This suggests a picture in which different grid modules realign independently of each other—while all the cells of one module expand or contract together, the cells belonging to a different module are not necessarily affected directly by this process.

5.4 Grid × Head-Direction Conjunctive Cells

In rats, head direction cells are abundant in the entorhinal cortex, mostly in layers III and V, and are hardly existent in layer II (Sargolini et al. 2006). As such, they seem to be part of the heterogeneous population of cells in this region.

In some cases grid cells have head-directional properties too. The distribution of such cells in the entorhinal cortex is layer dependent. While the grid cells in layer II are mostly head-direction invariant, the grid cells found in deeper layers usually have head-direction selectivity. Furthermore, in the deeper layers of the entorhinal cortex, there are also pure head-direction cells. The proportion of directionally modulated cells in deeper layers has been estimated at approximately 70 % (Sargolini et al. 2006). Recent work has suggested that head-direction cells at the entorhinal-parasubicular border exist in patches which are connected to the entorhinal cortex through highly organized parallel projections (Burgalossi et al. 2011).

5.5 Border Cells

In addition to grid cells and head-direction cells, there is a third population of cells in the entorhinal cortex which responds when the rat is near the border of the environment. Such cells are known to exist in small percentages (~10 %) in the medial entorhinal cortex, both in deep and superficial layers (Savelli et al. 2008; Solstad et al. 2008). Cells with similar functional properties have also been found in the subiculum, where they have been termed “boundary vector cells” (Lever

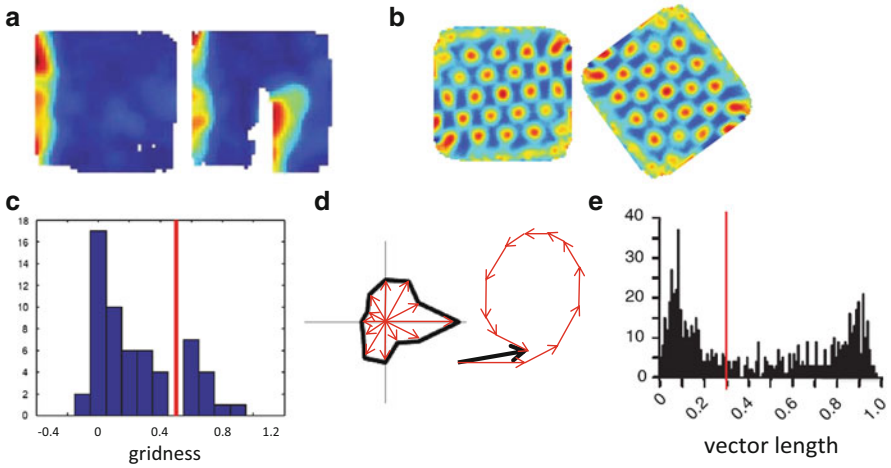

Fig. 5.3 Classifying mapping-related cells (**a**) Border cells continue to fire near a border regardless of the shape of the environment. In this example, the cell fires near a *left* border, both in a regular open field (*left*) or in an arena in which a flap has been inserted (*right*). (**b**) Calculation of the gridness score—in a *hexagonal* grid, the spatial autocorrelation pattern (*left*) is very similar to itself rotated by 60° (*right*). The gridness score uses this fact by adding the correlation of the autocorrelation pattern to its 60° and 120° rotated versions and also subtracting the correlation with the 30°, 90°, and 150° rotated versions (which are expected to be anticorrelated). (**c**) Typical distribution of gridness values, showing a bimodal distribution in a population of neurons from the medial entorhinal cortex. Figure taken from Whitlock and Derdikman (2012). *Red line* describes threshold of 0.5 used to define grid cells in this case. (**d**) Calculation of Rayleigh vector length from a polar head-direction histogram. The value for this example is 0.169, where value is obtained by comparing the length of the black arrow (which is the vector sum of the *red arrows*) to the sum of the lengths of the *red arrows*. (**e**) Example of a Rayleigh vector length bimodal distribution of cells recorded in the dorsal presubiculum. *Red line* demonstrates threshold for determining head-direction cells in this case (0.3). Figure adapted from Boccara et al. (2010)

et al. 2009), reflecting the suggestion that firing fields may be expressed at different distances from specific environmental boundaries (Barry et al. 2006). It is debatable whether border cells and boundary cells are actually a single type or are really separable (Derdikman 2009). On first glance border/boundary cells may be considered as place cells because they respond in a specific position within the environment. To actually discern that these cells are really border cells and not place cells, one needs to check how the cells transform between multiple environments. Border cells, unlike place cells, continue to fire near a border regardless of the shape of the environment (Fig. 5.3a) (Solstad et al. 2008).

An interesting theory about the formation of border cells originates from the idea of boundary vector cells, which are cells that fire at a certain distance from a border of the environment. It has been suggested that there exist "boundary receptive fields," such that the cells fire when a wall or boundary enters into the receptive field of the cell, where the receptive field is defined in space relative to the rat's egocentric position (O'Keefe and Burgess 1996; Hartley et al. 2000; Barry et al. 2006). Such boundary cells have been hypothesized to be part of the input to place cells (Lever et al. 2009). We note though that in medial entorhinal cortex,

the number of border cells with firing fields not touching one of the walls is very small (Solstad et al. 2008). This does not, however, preclude a contribution for border cells in the formation of place fields in the hippocampus.

5.6 Methods of Classifying Mapping-Related Cells

When recording from a population of mapping-related cells, it is sometimes hard to classify to what cell types they belong. In some cases, there is no doubt as to the classification. However, there are other cases in which the classification is not trivial due to noise in the brain or in the electrophysiological recording or due to highly conjunctive properties. For these reasons, a quantitative characterization of the various cell types is useful.

5.6.1 Grid Cell Classifiers

The most popular score used to classify a grid cell is the **rotational symmetry score** (Sargolini et al. 2006). The basic idea is that when looking at a spatial autocorrelation pattern of a grid cell, it will tend to have a 60° rotational symmetry. Furthermore, the grid pattern will tend to be anticorrelated with itself when rotated by 30° (Fig. 5.3b). Thus, a score has been devised in which the spatial autocorrelation of the grid pattern is correlated with its rotated versions at 60° and 120°, while subtracting the correlation with the rotated versions at 30°, 90°, and 150°. Such a score has been successfully used in several works, with small variations (Sargolini et al. 2006; Solstad et al. 2008; Boccara et al. 2010; Langston et al. 2010; Wills et al. 2010). In order to assess the significance of the score, a shuffling procedure is usually used, and values for grid cells are typically above 0.3–0.4 (on a scale from −1 to 1). Alternative measures for gridness also exist, for example, fitting the grid cell spatial autocorrelation pattern to a perfect grid generated from combination of sine and cosine waves (5.1) (Derdikman et al. 2009). An example of a distribution of gridness scores for a typical population of entorhinal cortex cells is given in Fig. 5.3c.

5.6.2 Head-Direction Cell Classifiers

It is common to classify head-direction cells using the *Rayleigh vector length*, which can be calculated easily from the polar head-direction histogram (Langston et al. 2010; Wills et al. 2010) (Fig. 5.3d). Similar to gridness scores, directional modulation can be assessed by using shuffling procedures. Typical values of significant head-direction cells display a Rayleigh vector length of at least ~0.25 (on a scale from 0 to 1). Approximately 50 % of the cells in the medial entorhinal cortex pass this criterion, suggesting the presence of a rich population of head-direction cells within the entorhinal cortex (Boccara et al. 2010), although the

degree of directional tuning is often weaker than in pre- and parasubiculum. Additional scores, not dealt with here, use information-theoretic measures (Taube et al. 1990; Sargolini et al. 2006).

5.6.3 Border Cell Classifiers

It is hard to find an adequate measure for "borderness." A measure that was used was that of comparing the average distance of a field from the wall to the length of the wall, and dividing by the sum of these values, with scores ranging from −1 to 1 (Solstad et al. 2008). Similar to classifiers for gridness and head directionality, this score was assessed using a shuffling procedure. Typical values for significant border scores (using shuffling procedures) were above ~0.5–0.6 (on a scale from −1 to 1). This lead to the conclusion that only ~10 % of the population of cells in the medial entorhinal cortex were border cells (Solstad et al. 2008).

5.7 Cell Types and Layer Divisions in the Pre- and Parasubiculum

Grid cells, head-direction cells, and border cells can be found also outside the medial entorhinal cortex in the adjacent regions of the presubiculum and parasubiculum. Approximately 13 % of the cells in the presubiculum, ~20 % in the parasubiculum, and ~35 % in the medial entorhinal cortex were classified as grid cells, showing that grid cells span multiple subregions of the parahippocampal cortex (Boccara et al. 2010).

5.8 Grid Cells vs. Place Cells: Similarities and Differences

One intriguing question is why there are two parallel representations of position within the hippocampal formation, one in the hippocampus and another in the entorhinal cortex. On one hand, the place cells in the hippocampus represent position. At each position of the rat, only a small subset of the place cells in the hippocampus is active. The ensemble of place cells can in principle be used to reconstruct the position of the rat in the environment (Fig. 5.4a) (Wilson and McNaughton 1993; Jezek et al. 2011). On the other hand, also the grid cells in the entorhinal cortex represent position. Similar to place cells, at each position of the rat, only a subset of the grid cells is active. With sufficient variation in the spacing and orientation of grid cells, the ensemble of grid cells can in principle be used to reconstruct the position of the rat in the environment (Fyhn et al. 2004) (Fig. 5.4b). Why then should there be two such parallel systems?

A key to answering this question derives from noting the differences between grid cells and place cells. The difference is most clear in experiments where hippocampal cells exhibit remapping. First, there are certain cases in which place

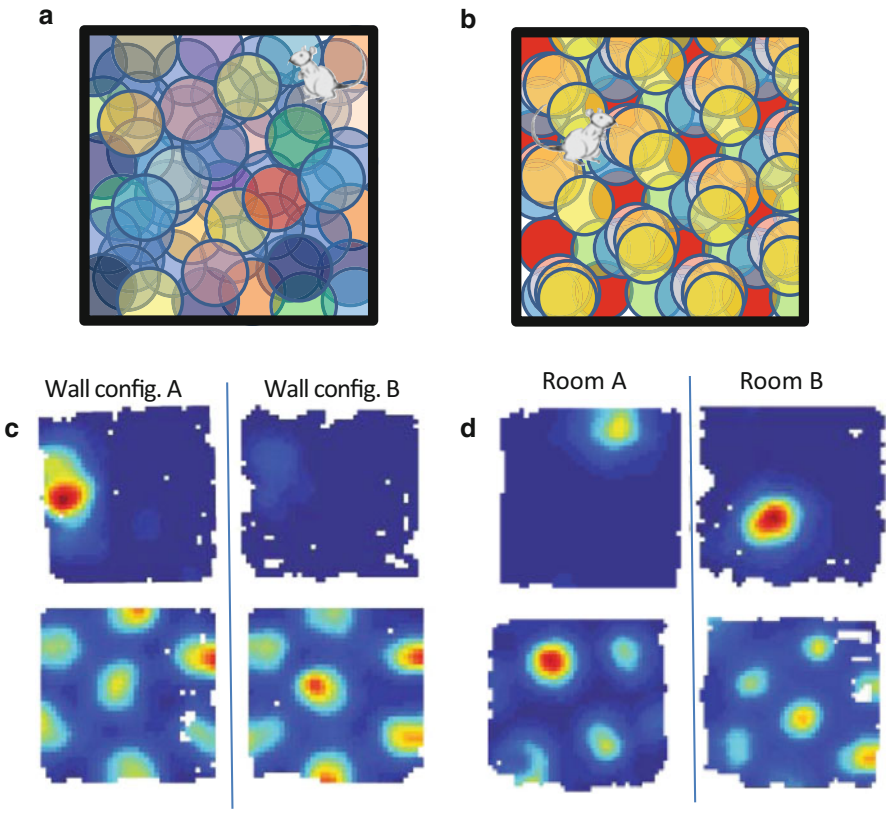

Fig. 5.4 Comparison of grid cells and place cells (**a**) The ensemble of place cells can be used as a basis for a cognitive map of the environment. Here, each place cell's firing fields are represented schematically within the box, as colored circles. When the rat is at a given position within the box, only a subset of the cells is active, making it possible to deduce the position of the rat from the place cell firing pattern. (**b**) Similar to place cells, the firing pattern of the population of grid cells can be used to deduce the position of the rat within the environment. Here, each grid cell is represented schematically as a set of *circles* of a single *color*. When the grid cells differ in grid spacing and the box is not too large, the combined pattern of activity will be unique at every location in the environment. (**c**) Rate remapping in this case is achieved by running the rat in the same box, but with a change of the wall colors. During rate remapping, the firing rate of place cell has changed, while the grid cell did not change its properties between the two conditions. *Top row*: example place cell; *Bottom row*: example grid cell; *Left column*: box with one set of walls; *Right column*: same box with a different set of walls. (**d**) Global remapping is characterized by a replacement of the population of active cells when moving from one environment to another, with a shift in the relative firing locations of the small subset of place cells that are active in both environments and in a simultaneous change in the phase or orientation of grid cells. *Top row*: example place cell; *Bottom row*: example grid cell. *Left column*: environment "A." *Right column*: environment "B." Panels **c** and **d** adapted from Fyhn et al. (2007)

cells change their firing rate systematically, in which grid cells do not show reliable changes in firing rate (Fig. 5.4c). In such cases, the position of the place field does not change, and the change in firing rate of the place cell is termed *rate remapping*. In other cases, the place cells change the position of their firing fields, and this is termed *global remapping* (Leutgeb et al. 2005). In cases of global remapping, grid cells belonging to a similar module may change grid phase and grid orientation (Fig. 5.4d), but their relative phases remain constant (Fig. 5.1f) (Fyhn et al. 2007; Stensola et al. 2012). During global remapping, two adjacent place cells in one environment do not necessarily remain adjacent in another environment, while two grid cells with a small phase difference preserve the small phase difference in the second environment. We deduce that grid cells belonging to the same module preserve relative-distance information, while place cells do not. It follows that while grid cells could be used to define the continuity of a space, place cells cannot. This is because a sequence of grid cell firing implies continuity in space, while a similar sequence of place cell firing does not: place cells are environment-specific, such that spatial continuity in one environment does not imply such continuity in another environment.

An interesting question regards the functional connectivity between grid cells and place cells. Early theories suggested that place cells are formed as combinations of multiple grid cells, in a manner resembling a Fourier transform (McNaughton et al. 2006; Solstad et al. 2006; Monaco and Abbott 2011). The recent findings demonstrating the modularity of grid cells may seem a confound to this idea because it is perhaps hard to conceive how grid cells of only 2–3 modules representing only 2–3 different spatial scales could account for the dramatic remapping seen in place cells, although the number of phase and orientation shifts between these modules is, in principle, unlimited (Stensola et al. 2012). A recent model has demonstrated that recurrent inhibition could potentially allow remapping to occur in place cells based on input from only a small amount of different grid cell scales (Monaco and Abbott 2011). Another potential solution uses Hebbian learning to map grid cells to place cells. In the Savelli and Knierim (2010) model, place cell remapping occurs due to small changes in the initial conditions as an animal explores a new environment. Furthermore, we should note that place cells may receive input from other cell types in the entorhinal cortex as well, such as border cells (Zhang et al. 2013). See Widloski and Fiete (2014) for a theoretical discussion on the formation of place cells from grid cells.

One way to check the interdependence between the two representations in the entorhinal cortex and in the hippocampus is to inactivate one region while recording from the other. Following this reasoning, inactivating grid cells in medial entorhinal cortex should cause place cells to disappear in the hippocampus. However, lesions of the medial entorhinal cortex do not conclusively cause the disappearance of place cells. Rather, they seem to cause a change of place cell field size and stability (Van Cauter et al. 2008). The remaining spatial firing may reflect inputs from spared parts of the medial entorhinal cortex or inputs from the lateral entorhinal cortex, where cells also have spatial firing properties, although much weaker than in the medial subdivision (Hargreaves et al. 2005; Neunuebel

et al. 2013) (see Deshmukh (2014) for a thorough discussion of spatial coding in the LEC). In the other direction, inactivation of the hippocampus causes a gradual disappearance of grid cells, while head-direction cells become predominant (Bonnevie et al. 2013). The dependence of grid cells on input from the hippocampus may result from the fact that the connections between layer II grid cells are mostly through inhibitory interneurons, such that without the excitatory drive of the hippocampus, the cells cease firing (Bonnevie et al. 2013; Couey et al. 2013). Excitatory drive from other brain regions may have a similar role in maintaining grid cell firing (Brandon et al. 2011; Koenig et al. 2011).

The fact that place-specific firing can be generated in the hippocampus without input from grid cells is further reinforced by findings on grid cell and place cell development. When recording from head-direction cells, place cells, and grid cells in very young rats, it seems that head-direction cells are already functional around the time of eye opening, at postnatal day 15 (P15), while place cells are the next to mature, and grid cells seem to form a nice and stable hexagonal pattern only several days later (Langston et al. 2010; Wills et al. 2010), at the time when inhibitory connections reach adult-like levels (Langston et al 2010; Couey et al 2013). These observations suggest that while place cells may receive much of their input from grid cells, border cells and other cells may provide sufficient spatial input to generate place cell firing in the hippocampus. The presence of direct hippocampal projections from border cells and other cells is consistent with this idea (Zhang et al. 2013).

5.9 Grid Cells in Complex Environments

While the results above describe the basic properties of grid cells in simple square environments, an important question is what happens when environments become more complex. First, how does the rat handle a multi-compartment environment? What happens when it moves from one compartment to another? Frank and colleagues have investigated grid cells along W-shaped and U-shaped linear tracks (Frank et al. 2001). They found similar patterns of firing fields on different legs of an M-shaped maze, suggesting that spatial firing followed the nature of the trajectory rather than the actual location of the animal (Fig. 5.5a). This question was revisited after the discovery of grid cells, when we tested rats in a hairpin maze, consisting of connected corridors, which form a zigzag pattern in which the rat has to run from one end to the other (Derdikman et al. 2009). In such a case the grid pattern broke up, resulting in a different grid pattern in every corridor. As the rats ran from one corridor to the next, a resetting process occurred and the same sequence of firing fields was repeated (Fig 5.5b). Such a breaking up of the grid was dependent on the geometry of the environment, and did not occur when the rat performed a zigzag behavior in the open field without walls, suggesting that behavior alone was not enough to cause resetting and realignment (Fig 5.5c). Interestingly, unlike grid cells, head-direction cells did not break up in the hairpin

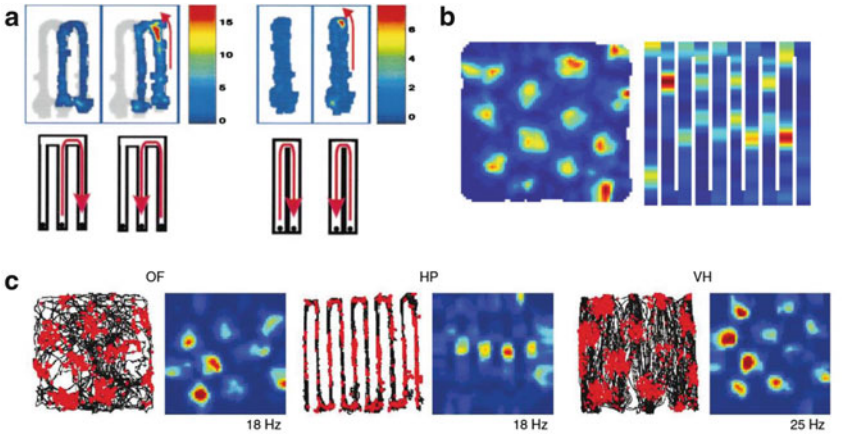

Fig. 5.5 Complex environments (**a**) The phenomenon of path equivalence—a putative grid cell fires in a similar manner when the rat is running in a U-shaped linear track (*right*) and when the rat is running on a M-shaped linear track (*left*), using a similar path (the cell fires on the anti-clockwise turn but not on the clockwise turn). Figure adapted with permission from Frank et al. (2000). (**b**) The grid pattern seen in the open field (*left*) breaks up in a multi-compartment environment (*the hairpin maze; right*), forming multiple maps, with resetting occurring when the rat is running from one corridor to the next one inside the maze. (**c**) When the walls were taken out of the environment, behavior in a *zigzag pattern*, similar to the behavior in the hairpin maze, did not result in a breaking up of the grid pattern. *Left*: grid cell in open field. *Center*: grid cell hexagonal pattern breaks up in hairpin maze. *Right*: in a zigzag behavior with no walls ("virtual hairpin"), the grid does not break up. **b** and **c** Adapted from Derdikman et al. (2009)

maze, suggesting that head-direction cells are computed upstream to grid cells (Whitlock and Derdikman 2012).

5.10 Relation of Space-Responsive Cells to Theta Waves

When recording brain waves in the entorhinal cortex of the hippocampus, very prominent theta oscillations are seen (Vanderwolf et al. 1977). These oscillations, in the frequency range of 5–12 Hz, are surprisingly strong in the rat, whose local-field potential signal in these regions sometimes seems like an almost perfect sine wave. Additional information about these oscillations can be found in Lever et al. (2014) and Las and Ulanovsky (2014) and also in various reviews (Buzsaki 2002; Buzsáki and Moser 2013). The oscillations are stronger when the rat is in transit and are relatively weak when the rat is at rest (Vanderwolf 1969). The oscillations are believed to be related to synchronized membrane fluctuations of the population of cells in the entorhinal cortex and adjacent regions. It is interesting to note that there is a relationship between grid cells at different layers in the entorhinal cortex and the theta oscillations recorded in those same layers. It has been known for a long time that place cells in the hippocampus fire at a specific phase of

the theta cycle when the rat enters the place field of the place cell, and this phase *precesses* backwards, such that the cell fires at an earlier phase of the theta cycle when the rat exits the place field. This phenomenon is called *phase precession* (O'Keefe and Recce 1993; Skaggs et al. 1996). This phase precession phenomenon exists also in grid cells in layer II of the entorhinal cortex. In contrast, most grid cells in layers III and V are rather phase locked and do not exhibit phase precession (Hafting et al. 2008). An interesting finding is that grid cells disappear when the medial septum is inactivated, suggesting, at first glance, that theta oscillations are necessary for the formation of grid cells (Brandon et al. 2011; Koenig et al. 2011). However, the loss of grid structure in these studies was also accompanied by a reduction in firing rate. When firing rates drop below a certain level, after removal of excitatory drive from the hippocampus, grid cells lose their spatially periodic firing pattern (Bonnevie et al. 2013). The loss of grid structure after medial septal inactivation may thus reflect the accompanying reduction in firing rate rather than the disappearance of theta oscillations. This interpretation is consistent with the observation that in the bat, grid cells can exist in the absence of theta oscillations (Yartsev et al. 2011). See more about these matters in Las and Ulanovsky (2014), Lever et al. (2014), and Navratilova and McNaughton (2014).

5.11 Cells with Spatial Firing Correlates: Anatomical-Functional Overview

There is a clear difference in the characteristics of cell firing and brain oscillations in different layers of the entorhinal cortex, which is related to the different connectivity patterns of the different layers. Layer II, whose cells project to the DG and CA3, contains stellate cells which have characteristics of grid cells (Burgalossi et al. 2011). Similar to the cells in the hippocampus, the cells in this region show phase precession (Hafting et al. 2008). It is also known that the cells in this region are not laterally connected to each other by excitatory connections. Rather, horizontal connections within this layer seem to be prominently mediated by inhibitory interneurons (Bonnevie et al. 2013; Couey et al. 2013). In addition, in the rat, head-direction cells seem to be quite rare in layer II of the medial entorhinal cortex (Solstad et al. 2008; Boccara et al. 2010). The story seems to be very different in deeper layers—head-direction cells and border cells are abundant in addition to grid cells, and most cells seem to be phase locked to the local theta oscillation (Hafting et al. 2008; Solstad et al. 2008; Boccara et al. 2010). Thus, we note that although layer V mostly receives feedback from the hippocampus and layer III mostly provides output to the hippocampus, they seem to share similar proportions of the various types of mapping-related cells (Solstad et al. 2008; Boccara et al. 2010). It is yet unknown what is the role of this difference between the layers; however, there is a clear distinction between layer II and the deeper layers, both in the distribution of mapping-related cells and in their relation to the theta oscillations, which will have to be accounted for in any future theory of this system.

5.12 The Hippocampal Formation as a Cognitive Map

O'Keefe and Nadel suggested that the hippocampus may be considered the locus of Tolman's cognitive map of space (Tolman 1948; O'Keefe and Nadel 1978). Following the discovery of grid cells, it seems that this suggestion needs revisiting. While primary cells in the hippocampus are indeed responsive mostly to place, changing the conditions of the experiment, e.g., by introducing new odors or new temporal patterns, may change the overall firing distribution within the hippocampal cell population (Wood et al. 1999; Wood et al. 2004; Pastalkova et al. 2008), as will be described in Eichenbaum et al. (2014). Thus, we suggest that the spatial aspect of the input to the hippocampus is generated in the medial entorhinal cortex, where the grid cells and border cells reside, while other aspects of place cell response are received through input from other regions, such as the lateral entorhinal cortex (see Deshmukh 2014). This conforms well with recent experiments in which it has been shown that directed lesions to the medial entorhinal cortex caused rats to lose their ability to recognize a change in the position of a familiar object, while lesions to the lateral entorhinal cortex had a different effect of causing the rats not to recognize the existence of a novel object (Van Cauter et al. 2012). Consistent with this, lesions in the lateral entorhinal cortex have been shown to reduce the magnitude of rate remapping in the hippocampus (Lu et al. 2013).

In this chapter we have portrayed some of the phenomenological aspects of spatially modulated cells in MEC and hippocampus, which are believed to be part of the cognitive map of space in the brain. There are many open questions yet to be answered. First, there is an ongoing debate about how these cells are generated, and many theories have been proposed. For a glimpse into this heated discussion, see Widloski and Fiete (2014); Navratilova and McNaughton (2014); Lever et al. (2014), and Las and Ulanovsky (2014). Second, the readout of these cells is still unclear. Who reads information from them, and for what purpose? Third, the relations between these cells and memory functions in the brain are yet to be revealed. All in all, the special and surprising phenomenology of these cells has spurred much interest, and we believe that the coming years will sprout many new discoveries and insights in this growing scientific field.

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Spatial and Nonspatial Representations in the Lateral Entorhinal Cortex

6

Sachin S. Deshmukh

Abstract

The hippocampus is thought to function as a "cognitive map," which stores nonspatial information such as items and events in a spatial framework. In order to understand the computations involved in creating such conjunctive nonspatial + spatial representations, it is essential to understand the function of hippocampal inputs. Medial entorhinal cortex (MEC) is known to convey spatial information to the hippocampus. In this chapter, we discuss recent evidence showing that lateral entorhinal cortex (LEC) conveys both spatial and nonspatial information to the hippocampus, in the presence of objects. Perirhinal cortex (PRC), a major cortical input to LEC, encodes nonspatial, object-related information, but does not encode spatial information in the presence of objects. Thus, the landmark-derived spatial information arises *de novo* in LEC. The classical dual-pathway model, in which LEC encodes nonspatial information while MEC encodes spatial information, cannot account for LEC spatial representation in the presence of objects. We propose that the functional difference between LEC and MEC is better understood in terms of the different inputs they use to create their representations: LEC generates spatial as well as nonspatial representations by processing *external sensory inputs* in contrast to MEC, which generates spatial representations by processing *internally based path integration information*.

6.1 Introduction

Episodic memory in humans and "episodic-like" memory in animals entail remembering *what* happened, *where* it happened, and *when* it happened. The hippocampus, together with its medial temporal lobe (MTL) inputs, plays a critical

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role in episodic and episodic-like memories (Scoville and Milner 1957; Vargha-Khadem et al. 1997; Squire et al. 2004; Clayton and Dickinson 1998; Eichenbaum and Fortin 2005). A detailed knowledge of anatomical connections between the hippocampus and related MTL structures, as well as the information encoded in these structures, is critical for understanding hippocampal contributions to episodic memory.

The hippocampus represents space using an ensemble of "place cells," with each place cell firing at its preferred spatial location. O'Keefe and Nadel (1978) proposed that this hippocampal spatial representation acts as a scaffold within which items and events of experience are organized and stored in memory, creating a "cognitive map." Cortical inputs to the hippocampus are channeled through the lateral entorhinal cortex (LEC) and the medial entorhinal cortex (MEC). Spatial input to the hippocampus arising from MEC has been studied extensively (see Derdikman and Moser (2014); in contrast, based on anatomical connectivity, LEC is thought to represent nonspatial information. In this chapter, we will address this purported spatial versus nonspatial dichotomy in the entorhinal cortex (EC). We will start with describing the parallel information streams in to the hippocampus, with an emphasis on differences in anatomy and physiology of LEC and MEC. Then we will discuss LEC behavioral physiology in the context of spatial versus nonspatial information processing and propose a conceptual model of a functional dissociation between LEC and MEC.

6.2 Parallel Input Streams into the Hippocampus

In primates, visual information is segregated between the ventral "what" stream that processes object identity and the dorsal "where" stream that processes location (Ungerleider and Mishkin 1982). This information enters the hippocampus via the perirhinal cortex (PRC)-LEC and the parahippocampal cortex-MEC pathways (Suzuki and Amaral 1994a, b). Similarly, in rats, LEC receives major input from the PRC, while MEC receives major input from postrhinal cortex (the rat homolog of parahippocampal cortex). In addition, MEC also receives major inputs from the presubiculum, postsubiculum, and retrosplenial cortex (Fig. 6.1; Burwell 2000; Witter and Amaral 2004), while LEC receives major input from the amygdala (Canto et al. 2008).

The regions projecting to LEC and MEC are functionally distinct. As a part of the ventral "what" pathway, PRC is involved in object recognition, although there is a controversy about whether PRC is primarily a mnemonic structure involved in object recognition (Aggleton and Brown 1999) or if it is a higher order perceptual region that provides representations of complex stimuli required for subsequent memory of those stimuli (Murray et al. 2007). The amygdala is involved in processing emotion (see Blair and Fanselow 2014) and thus provides another type of nonspatial information to LEC (Kerr et al. 2007); in contrast, postrhinal cortex is thought to be involved in processing information about context (Eichenbaum et al. 2007) (see Ho and Burwell 2014), and the presubiculum, postsubiculum,

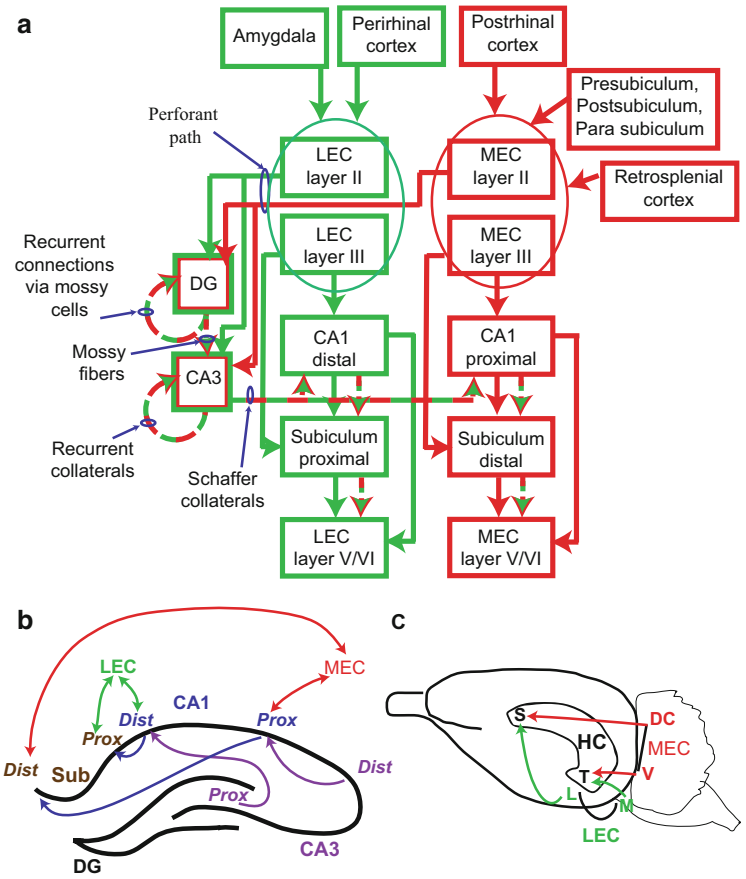

Fig. 6.1 Anatomical organization of entorhinal cortex input to the hippocampus. (**a**) Nonspatial information is thought to enter the hippocampal formation via LEC, while spatial information is thought to enter the hippocampal formation via MEC. (**a**, **b**) CA1 and subiculum show segregation of inputs from LEC and MEC layer III along the proximodistal axis, whereas DG and CA3 show convergent inputs from LEC and MEC layer II. Projections from LEC and MEC to DG and CA3 are omitted in (**b**) for simplicity. (**c**) Septotemporal gradient in EC projection to the hippocampal formation. The septal region of hippocampus (HC) receives inputs from the lateral (L) part of LEC and the dorsocaudal (DC) part of MEC, while the temporal region of hippocampus (HC) receives inputs from the medial (M) part of LEC and the ventral (V) part of MEC. Reproduced, with minor modifications, from Deshmukh and Knierim (2012)

and retrosplenial cortex show stronger spatial tuning than PRC and postrhinal cortex (Knierim 2006). This anatomical segregation of information entering the hippocampus into dorsal and ventral parallel processing streams has led a number of investigators to propose that the hippocampus derives spatial information from the MEC input and nonspatial information from the LEC input (Suzuki et al. 1997; Burwell 2000; Witter and Amaral 2004; Knierim et al. 2006; Manns and Eichenbaum 2006).

We shall limit the further anatomical descriptions in this chapter primarily to rat EC and hippocampus, since the hippocampal formation including EC has been studied most extensively in the rat [see Las and Ulanovsky (2014), for a comparative discussion of hippocampal neurophysiology across species].

6.2.1 Organization of Connections in the Hippocampal Formation

Figure 6.1 shows a schematic representation of major anatomical pathways in the hippocampal formation. EC has six well-defined layers. Feedforward connections from EC to the hippocampus originate primarily in layers II and III, while feedback connections from the hippocampus to EC terminate primarily in layers V and VI. Neurons from layer II of LEC and MEC project to the dentate gyrus (DG) and area CA3 of the hippocampus, converging on the same anatomical regions in these areas. The principal neurons in DG, called granule cells, send projections to CA3 as well as creating a local recurrent network within DG together with mossy cells of the hilus. CA3 pyramidal cells show extensive recurrent connectivity, as well as projecting to area CA1. Major inputs from LEC and MEC to CA1 originate in layer III and are segregated along the proximodistal axis of CA1. MEC layer III neurons preferentially project to proximal CA1, while LEC layer III neurons preferentially project to distal CA1 (Steward and Scoville 1976; Naber et al. 2001). Since LEC and MEC are thought to represent fundamentally different types of information, the segregation of projections from LEC and MEC along the proximodistal axis of CA1 indicates a possibility of functional segregation along the proximodistal axis of CA1 (Henriksen et al. 2010; Nakamura et al. 2013).

Entorhinal projections to the subiculum also show similar segregation along the proximodistal axis. LEC layer III neurons project preferentially to proximal subiculum, while MEC layer III neurons project preferentially to distal subiculum. Feedback connections from CA1 and subiculum to EC maintain this segregation, with proximal CA1 and distal subiculum projecting to layers V and VI of MEC and distal CA1 and proximal subiculum projecting to layers V and VI of LEC (Naber et al. 2001). Thus, while the MEC and LEC processing streams converge in DG and CA3, they remain segregated in the direct, bidirectional connections between EC, CA1, and subiculum. This anatomy suggests a functional segregation within the hippocampal formation. The EC-CA1-subiculum network might keep the spatial information from MEC segregated from object and landmark information from LEC, while DG and CA3 may combine LEC and MEC input streams to create a coherent memory representation. However, the anatomical data can also be interpreted as indicating that the functional segregation in the EC-CA1-subiculum pathway is not absolute, as the convergent LEC + MEC derived information from CA3 is passed onto all subregions of CA1. In addition, LEC and MEC are reciprocally connected (Dolorfo and Amaral 1998a), further supporting interactions between these pathways (Furtak et al. 2012; Hunsaker et al. 2013).

The hippocampus also shows functional segregation along the septotemporal axis (Moser and Moser 1998; Fanselow and Dong 2010). Entorhinal projections to the hippocampus show a topographical gradient that matches this functional segregation. Neurons in the lateral portion of LEC and dorsocaudal portion of MEC project to septal levels of the hippocampus, while neurons in the medial portion of LEC and rostroventral portion of MEC project to temporal levels of the hippocampus (Naber et al. 2001; Dolorfo and Amaral 1998b). This pattern of mapping from the lateromedial axis in LEC and from the dorsoventral axis in MEC to the septotemporal axis in hippocampus is echoed in intrinsic connection patterns in EC as well as in inputs to the subregions within EC. Dolorfo and Amaral (1998b) divided LEC and MEC into three projection bands: the lateral projection band comprising lateral LEC and dorsocaudal MEC projecting to the septal half of DG, the intermediate band projecting to the third quarter of DG and the medial projection band comprising medial LEC, and rostroventral MEC projecting to the temporal quarter of DG. The intrinsic projections within these bands are stronger than the connections across bands (Dolorfo and Amaral 1998a). The medial band of LEC receives lesser input from piriform cortex, and stronger input from insular cortex, compared to the lateral and intermediate bands of LEC. The strongest outputs from LEC to piriform, insular, and frontal cortical regions originate in the lateral band while the weakest originate in the intermediate band. Lateral and intermediate bands of LEC send strong projections to the basal ganglia. Occipital cortex and parietal cortex send the strongest projections to the lateral band of MEC. Lateral and intermediate bands of MEC receive very weak input from the piriform cortex, while the medial band of MEC receives strong input from the piriform cortex (Burwell and Amaral 1998; Kerr et al. 2007). These differences in anatomical connectivity imply functional segregation along the lateromedial axis in LEC and along the dorsoventral axis in MEC, which need to be experimentally verified.

6.2.1.1 Neuropharmacological Differences Between the Inputs from LEC and MEC to the Hippocampus

Both LEC and MEC inputs to the hippocampus are glutamatergic. In addition to glutamate, two different classes of neuropeptides are associated with EC projections to the hippocampus. Opioids are associated with the lateral perforant path (LPP; LEC projection to the hippocampus), while cholecystokinins are associated with the medial perforant path (MPP; MEC projection to the hippocampus) (Fredens et al. 1984; Gall et al. 1981; Witter et al. 1989). Bramham and colleagues (Bramham et al. 1988, 1991b) used opioid receptor antagonists to test the role of opioids in induction of long-term potentiation (LTP) in the medial and the lateral perforant path in anesthetized rats. Amplitudes of the excitatory postsynaptic potential (EPSP) and population spikes evoked in DG by electrically stimulating either LPP or MPP were used as a measure of strength of LPP-DG and MPP-DG synapses. LTP was induced using high-frequency electrical stimulation (400 Hz) in LPP-DG or MPP-DG synapses. Opioid receptor antagonists blocked LTP at LPP-DG synapses, but had no effect on MPP-DG synapses (Bramham et al. 1988, 1991b). In contrast, MPP-DG synapses exhibit NMDA

receptor-dependent LTP (Bramham et al. 1991a). A selective NMDA receptor antagonist, AP5, almost completely blocks EPSP as well as population spike LTP at MPP-DG synapses. AP5 has no effect on EPSP LTP on LPP-DG synapses, but it blocks population spike LTP at these synapses. Similarly, LPP-CA3 synapses exhibit opioid receptor-dependent/NMDA receptor-independent plasticity, while MPP-CA3 synapses exhibit opioid receptor-independent/NMDA receptor-dependent plasticity (Do et al. 2002). Thus, LPP and MPP synapses in the hippocampal formation show differences in mechanisms of plasticity correlated with the proposed differences in the nature of information encoded in the two regions.

When LPP and MPP are costimulated, they display associative LTP. Associative LTP refers to potentiation of a weakly stimulated pathway when stimulated simultaneously with a strongly stimulated pathway. When LPP was the weakly stimulated pathway, NMDA receptor antagonist CPP, but not opioid receptor antagonists CTOP and naloxone, blocked associative LTP in the LPP-CA3 synapses. In contrast, when LPP was the strongly stimulated pathway, opioid receptor antagonists prevented associative LTP in the MPP-CA3 pathway, although CPP also blocked LTP in this pathway. These data suggest that LTP induction is regulated by molecular mechanisms in the strongly stimulated pathway and that synapses from LPP and MPP to CA3 neurons share common downstream mechanisms of plasticity (Martinez et al. 2011). Associative LTP may underlie creation of the cognitive map in the hippocampus using the proposed nonspatial input from LEC and spatial input from MEC.

6.3 LEC Behavioral Physiology

This section reviews the behavioral correlates of LEC activity with a special emphasis on correlates that distinguish LEC activity from MEC activity. These findings show that LEC and MEC are indeed involved in distinct computations, but the difference between these cannot be explained simply in terms of the proposed "what" versus "where" dichotomy.

6.3.1 LEC Does Not Provide Spatial Information to the Hippocampus Under Standard Experimental Conditions

Hargreaves et al. (2005) were the first to perform an explicit comparison of the behavioral correlates of LEC and MEC activity. As superficial layers (layers II/III) of LEC and MEC are the feed-forward layers that project to the hippocampus, they recorded single neurons in superficial layers of LEC and MEC as the rats foraged in a square gray box (67 $\times$ 67 cm) with a single white cue card on one wall. While many MEC neurons showed spatially selective activity, LEC neurons did not (Fig. 6.2a). Spatial information score is used as a measure of spatial selectivity of a neuron. It quantifies the number of bits of information about a rat's position carried by a single spike of the neuron (Skaggs et al. 1996). Spatial information

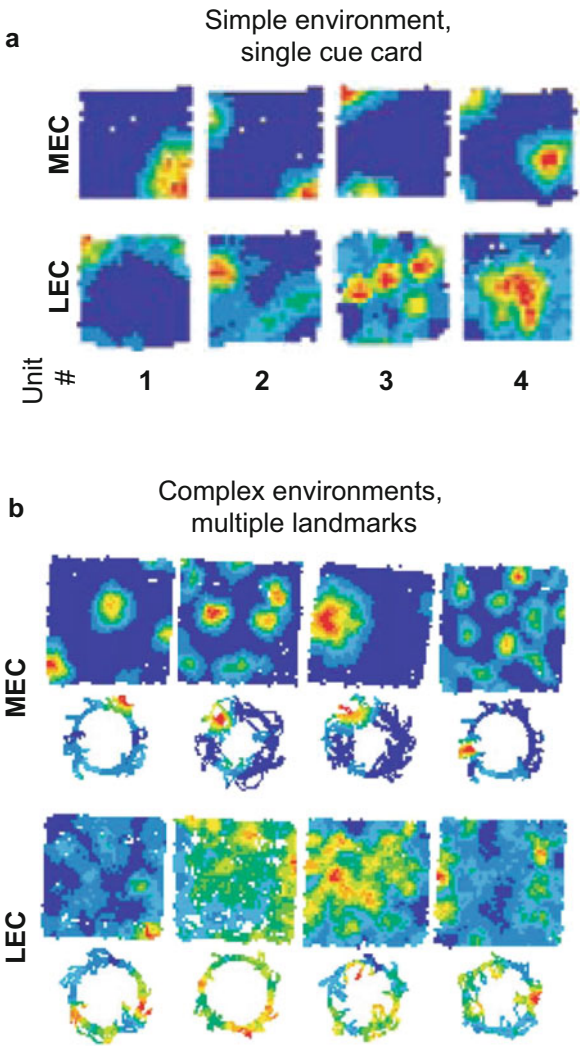

Fig. 6.2 Representation of space in the entorhinal cortex. Both in simple (**a**) and complex (**b**) environments, MEC had neurons with spatially selective firing while LEC did not. *Dark blue* in each firing rate map corresponds to no firing, while warmer colors correspond to increasing firing rates, with *red* corresponding to the peak firing rate for that neuron. (**a**) When rats foraged in a gray box (67 × 67 cm) with a single white cue card on the wall, MEC neurons fired in a spatially selective manner. In contrast, LEC neurons did not show much spatial selectivity (Hargreaves et al. 2005). (**b**) Even in complex environments with multiple landmarks, LEC neurons did not show spatial selectivity in the large box (135 × 135 cm) or circular track (56 cm inner diameter, 76 cm outer diameter). In contrast, MEC neurons showed spatial selectivity (Yoganarasimha et al. 2011). Notice the multiple peaks in the three MEC neurons are nonrandomly distributed, forming tessellating arrays of equilateral triangles. These are the "grid cells" (Hafting et al. 2005)

scores in LEC were significantly lower than spatial information scores in MEC, consistent with the proposed role of MEC, but not LEC, in spatial information processing. LEC neuron 4 in Fig. 6.2 seems to fire more in the central part of the environment, though it is a substantially large part of the environment. Could this weak selectivity for a spatial location really encode spatial information—albeit weakly—or does it arise from nonspatial factors, such as random bursts of activity or inhomogeneous sampling? If the neurons truly encode space, however weakly, their firing rate maps should be stable over time (i.e., they should show the neuron firing at the same part of the environment). The stability of firing rate maps over time can be estimated by measuring correlations of the firing rate maps of the same neuron across consecutive sessions or correlations of the firing rate maps of the same neuron recorded in first and second half of the same session. Hargreaves et al. (2005) ran one rat each with LEC and MEC recording electrodes in two consecutive sessions in the same environment. Firing rate maps of MEC neurons showed stronger correlations across sessions than those of LEC neurons, indicating that spatially selective MEC activity was more stable than the weakly spatially limited firing in LEC. Similarly, across all rats, spatial firing patterns in MEC in the first and second halves of a session were significantly more correlated than those in LEC. This difference in stability of spatial maps in MEC and LEC confirmed that MEC reliably encoded information about space, while LEC did not. PRC—a major cortical input to LEC—showed similarly weak spatial selectivity. Thus, the PRC-LEC pathway was not involved in spatial information processing under these experimental conditions.

This experiment was performed in a cue-poor environment. MEC is proposed to be a part of the path integration system, which can compute spatial location of the animal based on information about the animal's self-motion (Hafting et al. 2005; Fuhs and Touretzky 2006; McNaughton et al. 2006; O'Keefe and Burgess 2005) (see Navratilova and McNaughton 2014). In contrast, LEC receives inputs from sensory areas and hence may be postulated to infer spatial location from external sensory cues. Hence, the lack of spatial selectivity in LEC in this experiment could be interpreted as a consequence of a difference in the mechanisms by which spatial information is computed, instead of whether or not LEC is capable of encoding space. Could LEC use external sensory cues to create a representation of space in a cue-rich environment? Yoganarasimha et al. (2011) addressed this question by recording from superficial LEC and MEC neurons in two different cue-rich environments. The first environment was a curtained circular area with a circular track (56 cm inner diameter, 76 cm outer diameter) at its center. The track had four distinct textures, and there were six prominent, large visual cues located along the periphery of the curtain. The rats ran 15 laps in the clockwise direction on the circular track in a recording session. The other environment was a cluttered laboratory environment with clearly visible recording system, lab furniture, doors, etc. In this environment the rats foraged in first a small box (58 $\times$ 58 cm) and then a large box (135 $\times$ 135 cm). In both of these environments, LEC neurons continued showing very low, if any, spatial selectivity (Fig. 6.2b). MEC neurons had significantly higher spatial information scores than LEC neurons in both

environments. MEC neurons also showed significantly higher correlations in their spatial firing patterns between the first and second halves of the session than the LEC neurons. Taken together, the Hargreaves et al. (2005) and Yoganarasimha et al. (2011) studies show that in a variety of simple and complex environments commonly used for studying spatial information processing in the hippocampus, MEC is the reliable source of spatial information to the hippocampus while LEC is not (but see Neunuebel et al. 2013). Thus, the "where" component of the proposed "what/where" dichotomy in LEC and MEC was confirmed to be encoded in MEC but not in LEC under these conditions.

6.3.2 LEC Does Not Show Strong Theta Modulation

Correlated with the difference in spatial selectivity of LEC and MEC neurons, these regions also show a difference in theta modulation (Deshmukh et al. 2010) under the experimental conditions used in Yoganarasimha et al. (2011). Theta modulation is thought to be involved in temporal coding in the hippocampal system (O'Keefe and Recce 1993), which organizes the spikes of neurons with overlapping place fields in subtheta timescales. These timescales are within the operating time window of physiological mechanisms of synaptic plasticity (Bi and Poo 1998). Local field potentials in MEC show theta oscillations (Alonso and Garcia-Austt 1987a; Mitchell and Ranck 1980) and MEC neurons are modulated by theta oscillations (Ranck 1973; Alonso and Garcia-Austt 1987b; Stewart et al. 1992; Brun et al. 2008; Hafting et al. 2008) (see Lever et al. 2014). In contrast, LEC shows weak, if any, theta oscillations in local field potentials (Deshmukh et al. 2010; Fig. 6.3a). The theta power in LEC was significantly less than the theta power in MEC both on circular track and in large box. This difference in theta oscillations in LEC and MEC is clearly visible across cortical layers I through VI and across the dorsolateral to ventromedial projection bands. Furthermore, LEC neurons show significantly weaker theta modulation compared to MEC neurons (Fig. 6.3b). This difference in theta modulation in LEC and MEC might differentially affect the ability of these regions to influence the rate and temporal codes in the hippocampus.

Inhibitory interneurons are thought to be important contributors to theta oscillations in the hippocampus (Buzsaki 2002). In the extracellular recordings, the interneurons appear as high firing rate, narrow spike width neurons (Ranck 1973; Fox and Ranck 1981). Correlated with theta modulation of MEC neurons, MEC also has high firing rate (>10 Hz), narrow spike width interneurons (Frank et al. 2001; Hargreaves et al. 2005; Deshmukh et al. 2012). In contrast, LEC lacks theta modulation (Deshmukh et al. 2010), and correspondingly, LEC and PRC do not show high firing rate interneurons during foraging (Deshmukh et al. 2012; but see Burke et al. 2012). This absence of high firing rate interneurons in the PRC-LEC pathway indicates that fundamentally different network level computations are involved in information processing in PRC and LEC, compared to those involved in path integration computations in MEC and hippocampus.

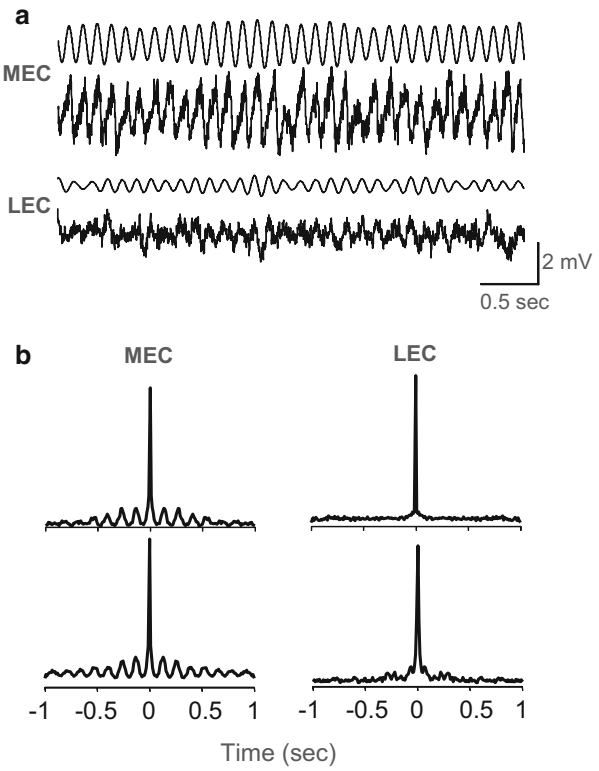

Fig. 6.3 Theta oscillations in the entorhinal cortex. (**a**) Local field potentials [raw (*bottom trace*) and filtered between 6 and 10 Hz (*top trace*)] in MEC and LEC. The MEC example shows theta oscillations typically seen in MEC whereas the LEC example shows the largest theta oscillations seen in LEC. (**b**) Many MEC neurons show theta modulation in autocorrelograms, similar to the two examples here. LEC neurons, on the other hand, do not show theta modulation in the autocorrelograms. The bottom LEC neuron is the LEC neuron that showed the strongest theta modulation of the autocorrelogram for any LEC neuron in the study. Reproduced from Deshmukh et al. (2010)

6.3.3 Object-Dependent Activity in LEC

The last two subsections described what LEC does not do: under a range of standard behavioral conditions used for studying hippocampal spatial information, LEC does not show spatial selectivity or theta modulation, while MEC does. Now we turn to testing the other half of the proposed LEC versus MEC dichotomy: showing that LEC, but not MEC, is the source of nonspatial information to the hippocampus. The earliest evidence for object-related activity in LEC comes from object-recognition memory studies. These studies showed that LEC responds to views of 3D objects (Zhu et al. 1995a, b), pictures of objects (Wan et al. 1999), and odors (Young et al. 1997). Since these studies were aimed at studying the role of parahippocampal regions in object recognition, they employed conditions different from those typically used for studying hippocampal place cells. Furthermore, these studies did not compare LEC and MEC neurons with each other, thus limiting our ability to compare spatial and nonspatial information the hippocampus receives from LEC and MEC.

In order to explicitly test the hypothesis that LEC, but not MEC, is the source of nonspatial information to the hippocampus, we allowed the rats to forage in a large box (120 × 150 cm) in the presence of objects while recording single neuron

activity from superficial layers of LEC and MEC (Deshmukh and Knierim 2011). On a typical day, the rats foraged for 15 min each in six consecutive sessions. Four of these sessions had four objects in a familiar, standard configuration; two manipulation sessions in which a subset of the objects (one or two) were moved to a new location or a novel object was introduced into the box were interleaved with the standard sessions. This protocol afforded us an opportunity to explicitly compare representations of both spatial as well as nonspatial information in LEC and MEC within the same session.

The distribution of spatial information scores of LEC neurons was statistically indistinguishable from the distribution of spatial information scores of MEC neurons under these conditions. This result is in stark contrast to the previous studies showing significantly lower spatial information scores in LEC as compared to that in MEC in the absence of objects, both in simple (Hargreaves et al. 2005) as well as in complex (Yoganarasimha et al. 2011) environments. As the spatial information score is sensitive to differences between studies in the size of the apparatus and in the size of the occupancy bins of the rate maps, these scores cannot be quantitatively compared across the experiments. However, the shape of the distribution of LEC spatial information scores was different from the previous studies, with a skew toward high values not seen in the previous studies, while the shape of the distribution of MEC spatial information scores was similar to the previous studies. It is possible that uncontrolled differences between the experiments, such as the individual animals, the exact locations of recording electrodes, or subtle differences in behavioral training by different experimenters, could account for the observed difference in the distribution spatial information scores in LEC. To control for this possibility, two rats were allowed to forage in an additional session without objects, in a different room. LEC neurons showed significantly higher spatial information in the presence of objects than in the absence of objects, in agreement with prior reports that spatial information is low for LEC in the absence of objects. Furthermore, LEC firing rate maps were as stable as MEC firing rate maps across consecutive standard sessions, unlike the previous studies. Thus, in the presence of objects, LEC activity is stably correlated with spatial location in the environment. In the following three subsections, we take a closer look at the causes of this apparent increase in spatial selectivity in LEC.

6.3.3.1 LEC Has Neurons with Object-Related Activity

In this experimental paradigm, objects remained at a fixed location throughout a session. Thus, neurons signaling the object-related information are likely to fire selectively at locations at or near the object, and consequently they show high apparent spatial information scores. Figure 6.4 shows an example of such an object-responsive neuron (Unit 1). This neuron fired at all four objects in all standard sessions (sessions 1, 2, 4, and 6) and also fired at novel (session 3) and misplaced (session 5) objects. LEC showed a significantly larger proportion of object-responsive neurons than MEC (e.g., session 1; LEC: 11/41; MEC: 1/28, $p = 0.0148$). Similarly, LEC had a significantly larger number of neurons responding to novel objects than MEC (LEC: 5/29; MEC: 0/29; $p = 0.03$). The

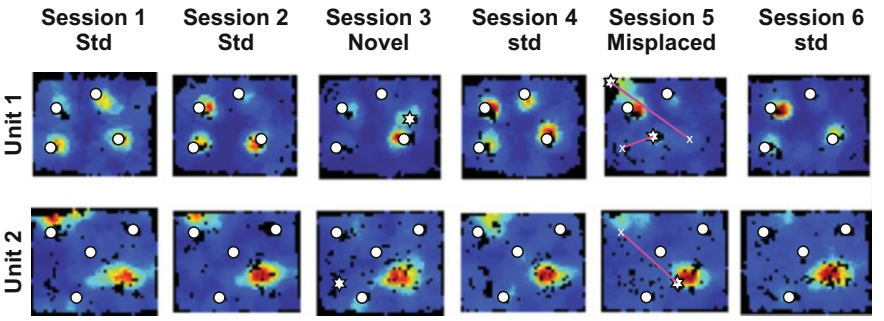

Fig. 6.4 Nonspatial and spatial representation in LEC in the presence of objects. The standard locations of familiar objects are marked by *white circles*, the locations of novel objects and the misplaced locations of misplaced objects are marked by *stars*, and the standard locations of misplaced objects are marked by *crosses*, connected to their misplaced locations with a *magenta line*. Unit 1 fired at all four familiar objects over multiple sessions. It also fired at novel and misplaced objects. Unit 2, in contrast, fired at a spatial location away from objects. It did so reliably over six consecutive sessions, including a session in which a familiar object was moved close to its place field. Reproduced from Deshmukh and Knierim (2011)

number of neurons responding to misplaced objects showed a similar trend, although this difference was not significant, perhaps due to small number of neurons tested (LEC: 6/30; MEC 1/27; $p = 0.069$).

Over all types of object-related activity, a much larger proportion of LEC neurons responded to objects (26/61 or 43 %) in at least one session compared to MEC neurons (6/44 or 14 %; $p = 0.0017$), consistent with the proposed role of LEC, but not MEC, in nonspatial information processing. However, this high proportion of object-responsive neurons in LEC cannot be taken as evidence for representation of object identity or novelty by individual LEC neurons. All five neurons responding to novel objects also responded to standard objects in at least one session with the standard object configuration, indicating that these neurons did not code exclusively for novelty. Furthermore, a number of LEC neurons, like neuron 1 in Fig. 6.4, fired at multiple objects in multiple sessions, suggesting that they are encoding object location or perhaps attention to objects. Attention gating might explain why many LEC cells did not fire consistently at the same object over multiple sessions, as the animal's attention to the given object is likely to have varied within and across sessions. This interpretation suggests a role for LEC in gating the flow of sensory input from PRC to hippocampus, allowing only the information about behaviorally relevant/salient or attended stimuli to reach hippocampus. The salience signal could arise from a subcortical structure. For example, PRC stimulation is insufficient to activate LEC on its own in slices; when coupled with amygdala stimulation, however, PRC stimulation drives LEC neurons sufficiently to generate responses both in LEC as well as the dentate gyrus (Kajiwara et al. 2003; de Curtis and Pare 2004). Such gating of sensory information reaching the hippocampus is consistent with the suggestion that the hippocampus automatically records only "attended" experience (Morris and Frey 1997).

The foregoing discussion does not completely discount the possibility that LEC has a distributed code for object identity, such that a vector of firing rates across the population encodes object identity, rather than activity of a single neuron. Consistent with this possibility, a few LEC neurons show some selectivity for a subset of objects across consecutive sessions. When rats foraged in conditions similar to this study, in the presence of objects without explicit behavioral significance, the hippocampus showed similarly weak representation of object identity (Lenck-Santini et al. 2005; Manns and Eichenbaum 2009; Deshmukh and Knierim 2013). In contrast, when the identity of individual items was critical for performing a behavioral task, hippocampal cells showed greater selectivity for the items (Wood et al. 1999; Komorowski et al. 2009). LEC may show similar improvement in selectivity under similar behavioral conditions requiring object discrimination. Such task-dependent enhancement in LEC object responsiveness is consistent with the idea that LEC may gate the flow of sensory information to the hippocampus, allowing only relevant/salient information to pass. Thus, while it is clear that there is a strong dissociation between LEC and MEC in terms of object-related activity, further experiments are needed to determine the precise nature of object-related information represented in LEC.

6.3.3.2 LEC Represents Space in the Presence of Objects

In addition to the object-responsive neurons, we unexpectedly found spatially selective neurons in LEC (Fig. 6.4, Unit 2). A number of LEC neurons consistently fired at spatial locations away from objects over multiple sessions. Six superficial LEC neurons (Deshmukh and Knierim 2011) and three deep LEC neurons (Deshmukh et al. 2012) met conservative criteria for putative place cell-like activity, which included thresholds for spatial information scores, session-to-session rate map correlations, and low likelihood of the neuron being object responsive. Together, these criteria selected for neurons that had very well-defined place fields away from objects in consecutive sessions. Indeed, these neurons showed more robust and stable firing across sessions than any of the object-selective neurons, and their spatial rate maps were indistinguishable from standard hippocampal place fields. The proportion of place-selective neurons obtained using these criteria is likely to be an underestimate of the actual proportion of spatially selective neurons in LEC. For example, two LEC neurons that fired at a single object across multiple sessions continued firing at the original location of the object even after the object was moved to a new location. These cells, thus, are either spatially selective neurons that happen to fire at the standard location of objects, or are object-responsive neurons with a memory for standard location of the object. In both these formulations, these neurons have to encode spatial information.

Memory of object locations cannot account for place-related activity of the majority of LEC neurons, since most of the neurons did not have a field at a location where an object had been placed previously (only one deep LEC neuron meeting the criteria for place-related activity fired at a location where a misplaced object had been placed 4 days before; Deshmukh et al. 2012). While it is possible that "unidentified objects" such as odors and specific walls drive the apparent spatial

selectivity, we think this is unlikely for multiple reasons. First, if "unidentified objects" were responsible for the place-related activity, the session-to-session variability should have been comparable to object-responsive neurons. As stated above, the place-related neurons showed lower session-to-session variability than object-responsive neurons. Second, in the rare sessions that the rat produced strong olfactory stimuli by urinating or defecating, the urine or feces were removed and the area wiped to spread the odor over a large area. This would make it highly unlikely that a strong sensory stimulus with a very small spatial distribution remained in the box from session to session. Last, textures on the circular track used by Yoganarasimha et al. (2011), from which it is impossible to eliminate odors, and the walls of the boxes used by Hargreaves et al. (2005) and Yoganarasimha et al. (2011), should have given rise to "unidentified objects" and thus apparent place-related activity. Putative place-related activity was not seen in LEC under these experimental conditions, further indicating that "unidentified objects" are unlikely to cause the observed place-related activity.

There are three possible mechanisms that may generate spatial selectivity observed in LEC. First, LEC may inherit spatial selectivity from PRC. We will describe experimental evidence disproving this possibility below. A second possibility is that LEC derives its spatial selectivity from either feedback from the hippocampus or lateral connections from MEC. However, this mechanism cannot easily explain the lack of place cell-like activity in LEC in the absence of objects (Hargreaves et al. 2005; Yoganarasimha et al. 2011). An alternative mechanism that involves creation of *landmark-derived* spatial information *de novo* in LEC, in addition to inheriting object representations from PRC, needs to be considered in order to account for the observed spatial selectivity in LEC.

If LEC derives its spatial representation from landmarks, why were no place cells reported in the Yoganarasimha et al. (2011) study, which employed multiple distal landmarks? A fundamental difference in the local, three-dimensional objects used in Deshmukh and Knierim (2011) and the distal landmarks used in the previous study may underlie the difference in spatial representation in these studies. Without a priori expectation for how large the distal landmarks are, it might be difficult to extract information about distance from the landmarks, while the same landmarks would serve as excellent directional orienting cues. Under these conditions, path integration-derived spatial information anchored by the orienting distal cues might suffice to create a hippocampal spatial representation, but the distal landmarks might be inadequate to create an exclusively landmark-derived spatial representation. In contrast, rats interacted with the local objects as well as walked toward and away from the objects in the Deshmukh and Knierim (2011) study. This would allow the rats to measure the sizes of the objects. The size of the retinal image of the object from any given location can then be easily converted into an estimate of distance from the object. A spatial map can be derived in LEC from information about distances and directions from these local landmarks. The hippocampal spatial representation is likely to be richer under these circumstances, given the fact that both *landmark-derived* spatial representation from LEC and *path integration-derived* spatial representation from MEC converge in the hippocampus

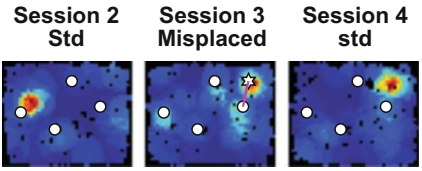

Fig. 6.5 Object + place conjunctive representation in LEC. In session 3, when one object was misplaced, this neuron fired the most at the misplaced location of that object. In addition, this neuron also fired at the location where this object used to be, as well as at standard locations of two other familiar objects. In session 4, the neuron continued firing at the location where the object had been in session 3, even after the object had been returned to its standard location. The firing in sessions 3 and 4 at locations where the object used to be is indicative of object location memory, which requires a conjunctive representation of object + place. Reproduced from Deshmukh and Knierim (2011)

in the presence of objects. The weak spatial tuning seen in LEC on the circular track (Yoganarasimha et al. 2011) rotates with the track when the track and the distal cues are rotated in opposite directions (Neunuebel et al. 2013). Consistent with the proposed role of LEC in sensory-derived information processing, this observation might indicate a rudimentary spatial representation derived from local textures and odors on the track.

6.3.3.3 LEC Shows Object + Place Conjunctive Representations

Since LEC has neurons with both nonspatial and spatial correlates when rats forage in the presence of objects, it is of interest to know whether LEC has neurons that combine spatial and nonspatial information. The total number of object-responsive neurons reported above included three LEC neurons that fired at an object only when it was moved to a new location and/or maintained the firing at the new location when the object was returned to its standard location (Fig. 6.5; Deshmukh and Knierim 2011). This is an object + place conjunctive response that encodes a specific combination of object and its spatial location, rather than encoding just the object or a spatial location at which the rat never encountered an object. Similar object + place conjunctive responses have previously been demonstrated in other regions of the brain. O'Keefe (1976) recorded misplace units in the hippocampus, which fired when the rat "failed to find something which was usually there." When an object is moved to a range of locations in consecutive sessions, providing an opportunity for the rat to remember multiple locations where the object has been, the hippocampus has neurons that fire at multiple locations where the object used to be (Deshmukh and Knierim 2013; Fig. 6.6). The anterior cingulate cortex, which projects to LEC, also shows neurons with similar correlates of memory for location where an object used to be (Weible et al. 2009). Consistent with the proposed role of anterior cingulate cortex in long-term memory, anterior cingulate cortex neurons retain such object location memory correlates even after 1 month (Weible et al. 2012). Similarly, the object + place conjunctive responses in LEC last over multiple days (Tsao et al. 2013). Thus, "what" and "where" information converges

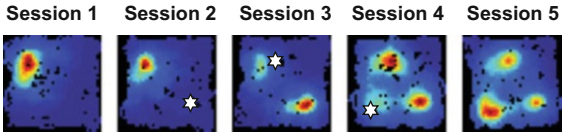

Fig. 6.6 Object location memory in the hippocampus. This neuron recorded from area CA3 of the hippocampus had a place field in the absence of objects in session 1. In session 2, when a novel object was introduced in the environment, this neuron continued firing at the same location and did not fire at the object. However, when this object was moved to a new location in session 3, the neuron fired more at the location where the object used to be in session 2 than at its normal place field. When the object was moved again in session 4, the neuron fired more at the two previous locations of the object, but it also fired at the current location of the object. When the object was removed from the box in session 5, the neuron fired at all three locations where the object had been in the previous three sessions. Reproduced from Deshmukh and Knierim (2013)

in single neurons at multiple stages of the hippocampal pathway, and this convergence may play a role in creating object location memory.

6.3.4 Lesion Studies Are Consistent with Partial Segregation of "What" and "Where" Processing in LEC and MEC

Place-related activity seen in LEC in the presence of objects is likely to be the mechanism underlying the involvement of LEC in contextual information processing reported in lesion studies. Before we look at the results of these experiments, a word of caution about interpreting lesion studies is in order. It is extremely difficult to make lesions that match between brain hemispheres and across animals. This often results in animals with lesions that cover only a part of a target region, while also extending into neighboring regions by variable amounts. Lesions that spare fibers of passage (e.g., excitotoxic lesions) are qualitatively different from lesions that do not (e.g., electrolytic lesions). Such differences in individual lesions across animals and across studies may be responsible for the apparent disagreements between different lesion studies. Another plausible source of the disagreements is subtle and not-so-subtle differences in behavioral protocols employed. Furthermore, the complexity of behaviors involved often makes it difficult to interpret the functional significance of the behaviors themselves. Despite these differences, a common thread is emerging across behavioral studies on lesioned animals, showing that LEC is involved in processing nonspatial as well as spatial information.

Many lesion studies of entorhinal contributions to spatial memory/navigation and hippocampal spatial representation often did not distinguish between LEC and MEC. These combined LEC + MEC lesions also often extended into the subicular complex. Given the privileged position of EC as the major conduit of neocortical information into the hippocampus, however, the observed spatial navigation deficits were often surprisingly small. For example, Miller and Best (1980) electrolytically lesioned EC and compared the performance of these rats with those of unlesioned

rats in an eight-arm maze. A food reward was placed at the end of all eight arms of the maze at the start of the day; subsequently, the arms were rewarded randomly. Control rats sampled the arms randomly in this protocol. In contrast, rats with EC lesion demonstrated perseverative behavior, in which they showed repeated patterns of 2 or 3 choices in succession. This behavioral difference can be interpreted as an indication of spatial deficit in the EC lesioned rats. Single neuron recordings from the hippocampus of lesioned and unlesioned animals showed differences in spatial encoding. In unlesioned rats, 24/24 hippocampal neurons recorded in the eight-arm maze were place cells; in contrast, in EC lesioned rats only 13/30 hippocampal neurons were place cells. Spatial selectivity of place cells was quantified as a percentage increase in firing rate inside the field as compared to overall firing rate. Hippocampal neurons in EC lesioned rats showed lower spatial selectivity than those in control rats. When the maze was rotated with respect to external landmarks, units in control rats followed the extramaze landmarks. In contrast, unit activity from lesioned animals followed local cues on the maze, rather than the extramaze landmarks. Similarly, Van Cauter et al. (2008) showed that single-unit activity in CA1 of rats with EC lesions represented space, but the spatial maps in CA1 of EC lesioned rats were less robust to cue rotation or removal, as compared to control rats. Other studies showed that EC lesions caused spatial learning and working memory deficits in Morris water maze (Glasier et al. 1995, 1999; Good and Honey 1997; But see Bannerman et al. 2001), although the rats with EC lesions clearly improved performance over the training period. Oswald et al. (Oswald et al. 2003) showed that rats with EC lesions learned to navigate using intramaze or extramaze cues, but failed to resolve conflicts between intramaze and extramaze cues. Thus EC, or its subregions, influence behavior in spatial tasks, but EC lesions do not completely disable the animal from solving spatial problems. Incomplete EC lesions, as well as the presence of extrahippocampal spatial representations that can be used for spatial memory/navigation, may account for these residual abilities.

Understanding the relative contributions of LEC and MEC to animal behavior and cognition require selective lesion/inactivation of these regions. Van Cauter et al. (2013) electrolytically lesioned either LEC or MEC and compared rats' performance on four different behavioral tasks. While rats with MEC lesions showed mild deficits in the Morris water maze, rats with LEC lesions did not. Similarly, rats with MEC lesions showed deficits in a path integration task, while rats with LEC lesions did not. In this task, the rats were trained to start from 1 out of 8 possible locations, search for a food reward in 17 possible locations, and on obtaining the reward, return to the starting location. Since the path taken by the rat from its starting location to the reward location meandered through a number of possible reward locations, a direct return from reward location to starting location was interpreted as path integration. Next, object exploration tasks tested if the rats recognized either that a familiar object had been moved to a different location or if a novel object had replaced a familiar object. While rats with LEC lesions showed deficits in both tasks, rats with MEC lesions showed deficits only in the task involving spatial change. In these tasks, rats had been exposed to familiar objects in their familiar positions in a number of consecutive sessions. A similar task

involving one trial recognition of a novel object or a novel location for a previously explored object showed that rats with MEC lesions as well as rats with LEC lesions showed deficits in the task involving the spatial change. Hunsaker et al. (2013) showed similar results in rats with excitotoxic lesions of MEC and LEC. Both groups of lesioned rats showed deficits in recognizing object novelty as well as a change in the context in which the objects were presented, compared to control rats. Rats with LEC lesions showed stronger deficits in object novelty detection than context change detection; in contrast, rats with MEC lesions showed stronger deficits in context change detection than object novelty detection. Furthermore, rats with LEC lesions showed stronger deficits in object novelty detection than rats with MEC lesions, while rats with MEC lesions showed stronger deficits in novel context detection than rats with LEC lesions. Wilson et al. (2013) used expression of an immediate early gene, *c-fos*, to measure the number of cells in LEC that were active during an object-context recognition task. A larger proportion of neurons in LEC were active in the object-context recognition task, as compared to tasks involving either objects in multiple contexts or objects in a single context. When LEC was excitotoxically lesioned, the rats showed deficits in the object-context recognition task. Lu et al. (2013) studied influence of LEC lesion on hippocampal activity. Changing the shape or the color of the behavioral apparatus leads to changes in firing rate, but not preferred spatial location ("rate remapping") of place cells in area CA3 of the hippocampus. LEC lesions impaired rate remapping in CA3, indicating that LEC inputs are essential for modulation of firing rates of CA3 neurons by environmental inputs like the shape and the color of the environment. The results of these four sets of experiments are consistent with the role of LEC in nonspatial information processing, as well as its involvement in some tasks involving integration of nonspatial and spatial information. The presence of object-responsive neurons as well as object-dependent place cells in LEC (Deshmukh and Knierim 2011) could underlie these behavioral consequences of LEC lesions.

6.3.5 Representation of Objects, but Not Space in PRC

The demonstration of place-related activity in LEC in the presence but not in the absence of three-dimensional objects in the arena raises a question about whether LEC inherits this spatial activity from PRC or if LEC is the first stage along the so-called "what" pathway showing spatial representation. In addition, it is of interest to know if PRC shows object-related activity in a foraging task, like it does in object-recognition experiments (Zhu et al. 1995a, b). We compared the activity of PRC neurons with that of LEC neurons as rats foraged in a large box (120 $\times$ 150 cm) in the presence of objects (Deshmukh et al. 2012). The proportions of object-responsive neurons in PRC and LEC, across all layers, were comparable, consistent with the proposed function of PRC as the source of object-related information to LEC. However, under these conditions, PRC did not match the spatial responsiveness of LEC, as quantified using a range of measures. First, the firing of PRC neurons was not spatially reproducible within a session, when

measured using the probability of obtaining the observed spatial information by chance. Although PRC showed a trend toward lower spatial information than LEC, this difference was not significant. The spatial information was calculated from firing rate maps. This measure does not test for reproducibility of firing at a given location over multiple passes. Hence, a shuffling procedure is routinely used to estimate the probability of obtaining the observed spatial information by chance. This probability is a measure of spatial reproducibility of the firing of the neuron. A much smaller proportion of PRC neurons showed statistically significant spatial information scores, compared to LEC (proportion of neurons meeting the criterion of $p < 0.01$; PRC: 23/67; LEC: 102/127; $p = 5.5 \times 10^{-10}$), indicating that unlike the LEC neurons, the PRC neurons did not fire reproducibly at the same locations within a session. Second, firing rate maps of PRC neurons displayed significantly weaker session-to-session correlations compared to LEC neurons. Third, the putative place cells observed in LEC were absent in PRC (LEC: 9/102 neurons; PRC 0/58 neurons; $p = 0.048$). Thus, PRC seems to be involved in purely nonspatial computations, in contrast to LEC, which appears to be involved in spatial as well as nonspatial computations in the presence of objects. [See Ho and Burwell (2014), for further discussion of PRC.]

6.3.6 Influence of Local Objects on Hippocampal Representations

It is clear from the foregoing discussion that the nature of information encoded when rats forage in the presence of objects along the PRC-LEC-hippocampus pathway evolves at each stage of the pathway. A purely nonspatial representation in PRC (Deshmukh et al. 2012) turns into spatial and nonspatial representation in LEC (Deshmukh and Knierim 2011) and hippocampus (Deshmukh and Knierim 2013). Furthermore, both LEC and hippocampus show conjunctive object + place representations, demonstrating a confluence of spatial and nonspatial information in a single cell. In addition, the hippocampus shows a unique object (landmark)-derived spatial representation not seen in LEC (Deshmukh and Knierim 2013). When rats forage in the presence of objects, a substantial minority of CA1 neurons have two or more place fields in the environment. More often than expected by chance, multiple fields of a single CA1 neuron are located at spatial locations that share vector relationships with two or more objects, i.e., distance and direction of one field from one of the objects is nearly identical to that of at least one other field from another object. Thus, these cells can be said to be landmark vector cells, which encode spatial location as a vector relationship to local landmarks (Deshmukh and Knierim 2013; Fig. 6.7).

The landmark vector cells could underlie the ability of animals to use individual landmarks to navigate to specific locations, as seen from experiments in gerbils (Collett et al. 1986). Gerbils were trained to navigate to a buried food reward located equidistant from the two landmarks. When the two landmarks were moved away from each other, gerbils did not search at the original reward location. Instead, they searched at two locations, each defined as a vector relationship to the

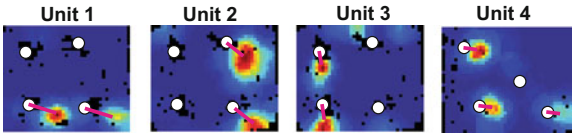

Fig. 6.7 Landmark vector cells in the hippocampus. The four CA1 neurons shown here had two to three fields, which fired at spatial locations that can be defined in terms of distance and direction from equal number of objects in the environment. Notice how the length and angle of the *magenta lines* are different for the four units, indicating the different landmark vectors encoded by these neurons. Reproduced from Deshmukh and Knierim (2013)

two landmarks, which matched the two original vectors connecting the reward location with the two landmarks. McNaughton et al. (1995) proposed a vector-encoding model to explain this behavior. This model hypothesized that individual place fields encoded a specific distance and allocentric orientation from a specific landmark. Such landmark vector representations are very useful in navigation. A simple operation of subtracting memory vector representing goal location with respect to a landmark from a perceptual vector representing current location of the animal with respect to the same landmark can be used to chart the route from current location to the goal location. The landmark vector cells we observe in the presence of objects may be a subset of the landmark vector-encoding cells proposed by McNaughton et al. (1995) which happen to encode more than one spatial location with respect to an equal number of landmarks (objects). Neurons with a single place field defined as a vector relationship to a single landmark cannot be identified using our landmark vector similarity analysis; hence, a much larger proportion of hippocampal place cells could be encoding landmark vectors than the proportion estimated using this analysis. Landmark vector encoding requires information about distance to an object as well as allocentric bearing of the object. While the head direction system (Taube et al. 1990; Yoganarasimha et al. 2006) (see Winter and Taube 2014) can set the allocentric bearing for the landmark vector cells, the information about distance from the landmark may originate in LEC.

6.4 A Conceptual Model for LEC Function

Recent neurophysiological and lesion data described above suggest that the proposed nonspatial versus spatial dual-pathway model for entorhinal inputs to the hippocampus needs to be modified. Consistent with the dual-pathway model, PRC shows a high proportion of neurons that fire at objects while rats forage in conditions typically used for studying spatial correlates of place cells. The presence of object-related activity and the absence of spatial selectivity in PRC are also in agreement with the hypothesized role of PRC in perception (Murray et al. 2007), object recognition, and familiarity (Aggleton and Brown 1999; Murray et al. 2007). However, the picture gets complicated in LEC. Consistent with the dual-pathway model, LEC has more neurons representing nonspatial information than MEC, but

it also has spatially selective neurons. The demonstration of spatial selectivity in LEC functionally dissociates it from PRC under these conditions. This spatial tuning also contradicts the proposed nonspatial versus spatial ("what" versus "where") functional dissociation between LEC and MEC. We propose a modification to the classical dual-pathway model to account for the observed data (Deshmukh and Knierim 2011; Deshmukh et al. 2012). We propose that the function of LEC is to generate spatial as well as nonspatial representations by processing *external sensory inputs* in contrast to MEC, whose function is to generate spatial representations by processing *internally based path integration information* (McNaughton et al. 2006; Burgess et al. 2007; Hasselmo et al. 2007). In this formulation, the PRC-LEC pathway uses sensory information to produce object-related representations such as object identity, novelty, and object + place conjunctions as well as object-dependent spatial representations. This distinction is similar to self versus nonself (or action versus cue) proposal of Lisman (2007). The external sensory information-derived spatial representation and path integration-derived spatial representation have multiple opportunities to interact with and influence each other. There are lateral connections between LEC and MEC; inputs from LEC and MEC converge in DG and CA3, and CA1 projects back to LEC and MEC (Dolorfo and Amaral 1998a; Burwell 2000; Naber et al. 2001; Canto et al. 2008). These interactions are likely to play a critical role in the formation as well as maintenance of these external sensory information-derived and path integration-derived spatial maps. While animals can keep track of their current location using path integration, a path integration system working on its own is prone to accumulate errors. These errors can be corrected intermittently by "taking a fix," i.e., by using external sensory information to estimate current location. On the flip side, path integration-derived information might play a critical role in the formation of spatial maps in the LEC by providing estimates of distances between landmarks. This is analogous to a cartographer measuring distances between landmarks to draw a map and a backpacker using self-motion cues for a real-time estimate of their current position, with intermittent stops to compare the visible landmarks with the map to take an accurate fix on their current location.

LEC may thus be viewed as an intermediary between the object perception/recognition/familiarity system in PRC and the cognitive map in the hippocampus, combining spatial as well as nonspatial information, and as such is well situated to function as the gatekeeper of experience to be stored in the cognitive map.

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Modulatory Influences on the Hippocampus and Entorhinal Cortex

7

Kishan Gupta and Michael E. Hasselmo

Abstract

The functional regulation of cortical circuits depends on neuromodulators such as acetylcholine, norepinephrine, serotonin, and dopamine to alter the information processing mediated by fast transmitters such as glutamate and GABA. The primary mechanisms shared by the neuromodulators include altering the dynamics of excitatory and inhibitory synaptic transmission, altering synaptic modification properties, and changing the resting membrane potential. Aside from synaptic modulation, the same neuromodulators can also affect spike frequency with prominent examples including pyramidal cell spike frequency adaptation. Though the cellular effects of neuromodulators may be similar, a diversity of upstream systems regulates the influence of competing neuromodulators both in the spatial distribution and temporal dynamics of release. The diversity of neuromodulator receptor subtypes also influences the nature of the cellular effects of neuromodulation. The purpose of this chapter is not to differentiate between competing neuromodulatory systems, but to survey evidence for how different neuromodulators affect change in information transmission in the hippocampal system. This chapter also highlights physiological examples of acetylcholine effects in active research areas of entorhinal persistent spiking, subthreshold properties of stellate cells, and theta modulation of hippocampal and entorhinal networks.

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7.1 Introduction

A number of neuromodulatory systems influence the functional properties of the hippocampus and entorhinal cortex (EC) and their role in memory function. Neuromodulators including acetylcholine, norepinephrine, serotonin, and dopamine alter the processing of information within these cortical circuits by altering the intrinsic properties of neurons, by causing presynaptic inhibition of glutamatergic and GABAergic synaptic transmission, by altering synaptic modification properties within these circuits, or by altering the spiking properties of cortical neurons. Physiological and behavioral data indicate that neuromodulators play an important functional role in these circuits.

For example, the encoding of episodic memory appears to depend upon the circuit dynamics induced by the neuromodulatory effects of acetylcholine. Patients administered scopolamine prior to encoding a word list perform worse in subsequent recall of those words compared to administration post-encoding (Ghoneim and Mewaldt 1975; Petersen 1977). This effect may be mitigated if test subjects are highly familiar with the task (Sarter et al. 2003) possibly because of a reduced need to attend to relevant cues. Memories for novel stimuli in recognition memory tasks are impaired in monkeys (Tang et al. 1997) and rats (Winters and Bussey 2005) with local infusion of scopolamine into the perirhinal cortex. Infusions of scopolamine into the hippocampus impair spatial encoding in the Morris water maze (Blokland et al. 1992) and in the Hebb-Williams maze (Rogers and Kesner 2003).

Based on the behavioral data described above and the circuit level effects of acetylcholine, extensive modeling shows that the effects of acetylcholine set appropriate dynamics for the encoding of new episodic memories (Hasselmo and Bower 1992, 1993; Hasselmo et al. 1996; Hasselmo and Wyble 1997; Hasselmo 2006). Acetylcholine may enhance encoding of memory by direct synaptic modulation and indirect modulation of theta encoding dynamics. As summarized in Fig. 7.1, acetylcholine can enhance encoding by enhancing the influence of feedforward afferent input to the cortex, making cortical circuits respond to sensory stimuli. At the same time, decreasing excitatory feedback reduces interference from retrieval and during consolidation. The muscarinic depolarization of pyramidal cells and the nicotinic enhancement of synaptic transmission clearly augment the influence of external afferent input, allowing more accurate encoding of multiple features of an event or item. The muscarinic enhancement of synaptic modification serves to increase the long-term maintenance of associations. The muscarinic presynaptic inhibition of feedback excitation reduces interference from previously encoded representations, whereas the release of this presynaptic inhibition during lower levels of acetylcholine can set appropriate dynamics for consolidation.

Acetylcholine can indirectly enhance encoding though its role in increasing theta rhythm oscillations within the hippocampal formation (Bland and Oddie 2001; Siok et al. 2006). Each cycle of theta rhythm could isolate separate phases for encoding and retrieval, as proposed in a recent model (Hasselmo et al. 2002). Encoding of sensory stimuli could occur at the trough and rising slope of theta rhythm measured

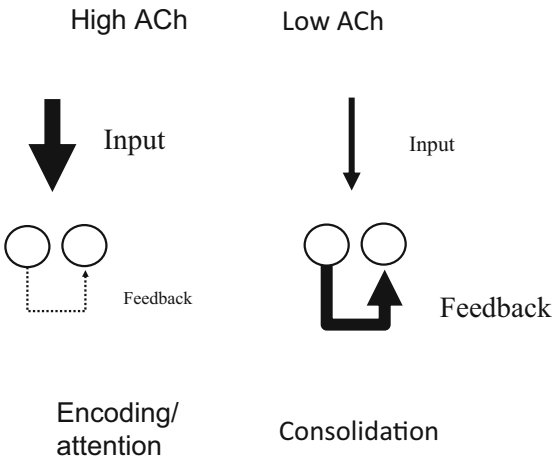

Fig. 7.1 Effect of acetylcholine on cortical dynamics. *Left*: High acetylcholine (ACh) levels enhance the magnitude of afferent input to cortex through action at nicotinic receptors and enhance the spiking response of cortical neurons through depolarization and suppression of spike frequency accommodation. High ACh also suppresses the magnitude of feedback excitation in cortex via presynaptic inhibition of glutamate release. *Right*: Low acetylcholine levels result in a weaker influence of afferent input on spiking activity relative to the strength of excitatory feedback, allowing a stronger influence of internal dynamics for consolidation

at the hippocampal fissure, when current sinks are strong in the stratum lacunosum-moleculare (SLM, where entorhinal input terminates) and weak in areas receiving CA3 input. Retrieval would occur on the peak and the falling slope of theta rhythm when current sinks are weak in the SLM and strong in layers receiving CA3 input. These theta phase dependencies of encoding and retrieval could be altered via cholinergic modulation. Both GABAergic and cholinergic septal outputs drive hippocampal theta (Yoder and Pang 2005). Interneurons also play an important role in local theta rhythm generation (Klausberger et al. 2003). Muscarinic receptors selectively depolarize oriens lacunosum-moleculare (OLM) and not non-OLM interneurons (Lawrence et al. 2006), providing possible rhythmic timing of dendritic and somatic inhibition. This mechanism could enhance separation of encoding and retrieval dynamics during theta rhythm oscillations (Hasselmo et al. 2002; Kunec et al. 2005).

Acetylcholine's direct and indirect mechanism of action on encoding and retrieval scheduling is just one of the potential functional roles of the cellular effects of neuromodulation. This chapter will begin with an overview of modulatory effects at the cellular level focusing on acetylcholine, norepinephrine, gamma-aminobutyric acid (GABA), dopamine, and serotonin. Specific examples of cellular cholinergic modulation will be looked at in more depth, followed by cognitive evidence of neuromodulation.

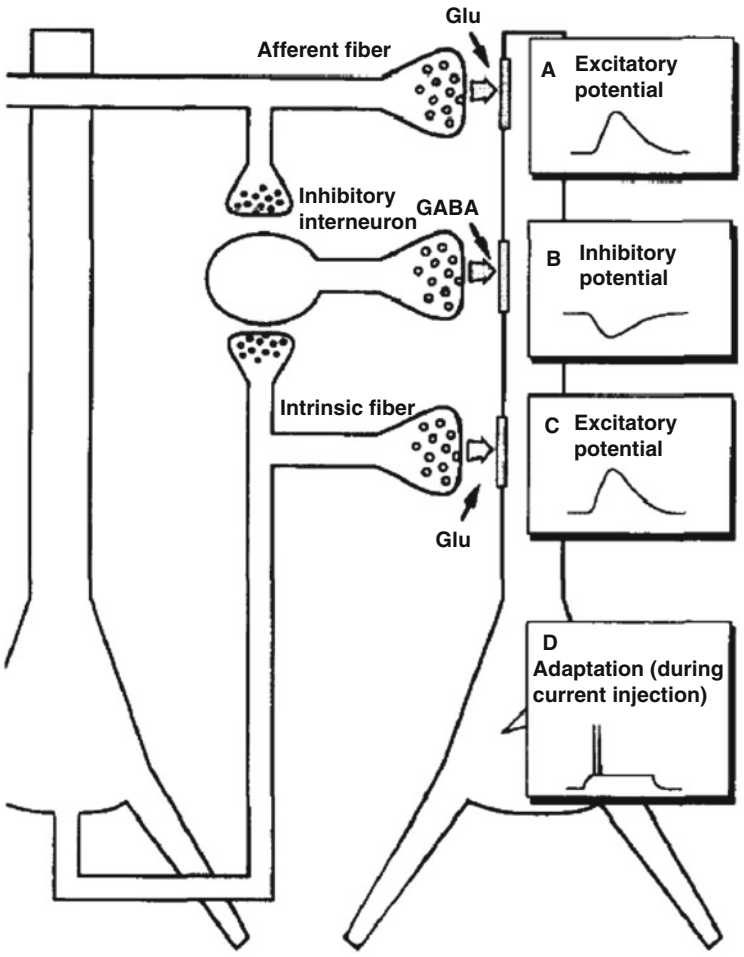

Fig. 7.2 Neurotransmission. Summary of neurotransmitter influences within the hippocampus. Afferent synapses from the entorhinal cortex and intrinsic synapses arising from other hippocampal pyramidal cells release glutamate, which causes fast excitatory postsynaptic potentials due to activation of AMPA and NMDA receptors by glutamate released from afferent synapses (A) or intrinsic synapses (C). Feedforward and feedback inhibitory interneurons activated by afferent or intrinsic fibers release GABA, which causes fast inhibitory potentials (B) mediated by $GABA_A$ receptors. Current injection to a single pyramidal cell elicits an initial high-frequency generation of action potentials which slows and often stops due to activation of calcium- and voltage-dependent potassium currents (D)

7.2 Mechanisms

An illustration of the respective role of neurotransmitters and neuromodulators in cortical activity is provided in Figs. 7.2 and 7.3. Many of these effects are general across hippocampus, entorhinal cortex, and other cortical areas. Sensory

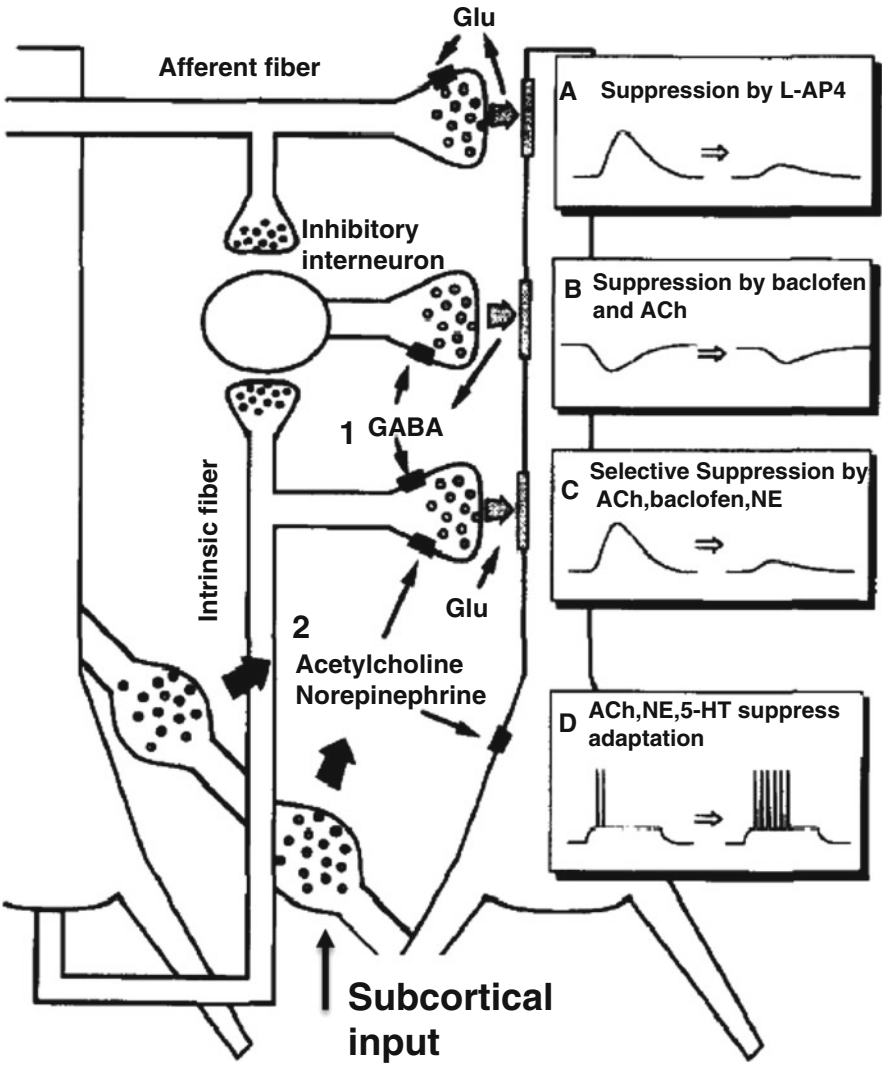

Fig. 7.3 Summary of some neuromodulatory influences. 1. Neurotransmitters released under local control can have neuromodulatory effects at metabotropic glutamate receptors and $GABA_B$ receptors. 2. Neuromodulatory innervation from subcortical structures may influence function via volume transmission (release from axonal varicosities without postsynaptic densities). This includes release of substances such as acetylcholine, norepinephrine, serotonin, and dopamine. A. Suppression of synaptic potentials at synapses from entorhinal cortex is caused by decreased release of glutamate due to activation of presynaptic metabotropic receptors (e.g., by L-AP4). Metabotropic glutamate presynaptic inhibition is much slower at Schaffer-collateral synapses. B. In the hippocampus, release of GABA appears to be blocked by activation of presynaptic $GABA_B$ (tested experimentally with agonists such as baclofen) and muscarinic receptors. C. Presynaptic inhibition of synaptic potentials at Schaffer-collateral synapses decreases release of glutamate due to activation of presynaptic muscarinic receptors, presynaptic $GABA_B$ receptors,

information arriving in the cortex from various peripheral structures commonly enters the cortex via fast glutamatergic synaptic transmission (see Haberly 1985 for review). Similarly, the rapid spread of activity within and between cortical structures (along intrinsic and associational fibers) is mediated by glutamatergic synaptic transmission. The glutamatergic neurons mediating this interaction between cortical regions are commonly pyramidal cells which display the property of neuronal adaptation. That is, they decrease in firing rate during sustained excitatory activation (Connors et al. 1982; Connors and Gutnick 1990). In contrast, inhibitory interneurons commonly do not show adaptation.

The dynamic properties of cortical function are also strongly influenced by feedforward and feedback inhibition, mediated by GABAergic interneurons (Connors et al. 1988; Tseng and Haberly 1988). In contrast to excitatory neurons, these interneurons commonly have much shorter axons, remaining within a local cortical region. Feedforward inhibition is here defined as inhibition activated by afferent input or input from other cortical regions. For example, the interneurons in stratum lacunosum-moleculare of region CA1 (Lacaille and Schwartzkroin 1988; Klausberger et al. 2003) mediate primarily feedforward inhibition. Feedback inhibition is defined as inhibition activated by the excitatory output of neurons within the cortical region. For example, the interneurons in stratum pyramidale and stratum oriens of hippocampal region CA1, including oriens lacunosum-moleculare cells (Klausberger et al. 2003; Kunec et al. 2005) mediate predominantly feedback inhibition. Both feedforward and feedback GABAergic interneurons activate inhibitory currents with two different time courses (Connors et al. 1988; Tseng and Haberly 1988). Activation of $GABA_A$ receptors elicits rapid, short-term chloride currents. Activation of $GABA_B$ receptors elicits slower, longer-term potassium currents (Satou et al. 1982). Throughout the chapter, the effects at $GABA_B$ receptors and metabotropic glutamate receptors will be discussed as falling in the realm of modulatory influences.

In cortical structures, endogenous substances such as acetylcholine, norepinephrine, serotonin, dopamine, and the peptides appear to have a primarily neuromodulatory influence. Though some of these substances have clear neurotransmitter effects in the periphery (acetylcholine and norepinephrine within the autonomic nervous system, for instance), they do not appear to be involved in the direct transfer of information in cortical structures. Rather, they appear to alter the processing characteristics of cortical structures through influences on physiological phenomena such as synaptic transmission and pyramidal cell adaptation. Though diverse neuromodulators exist, the synaptic receptor subtype density and

Fig. 7.3 (continued) and presynaptic noradrenergic receptors. Activation of these receptors has little effect on afferent fiber synaptic potentials. Increased frequency of inhibitory chloride ($GABA_A$) synaptic potentials is observed during perfusion of substances activating noradrenergic, serotonergic, dopaminergic, and cholinergic receptors. D. Increased spiking response to current injection is observed during perfusion of substances activating cholinergic and noradrenergic receptors, due to suppression of potassium currents underlying adaptation

the temporal characteristics of neuromodulator release define downstream influences.

Sometimes the same neurochemical may have rapid transmitter type effects, followed by longer modulatory influences, suggesting that neurotransmitter and neuromodulator effects may be most effectively classified at the receptor level. Activation of receptors on a protein structure directly incorporating an ion channel (an ionophore) will be defined as neurotransmission, while activation of receptors coupled indirectly to channels (e.g., via second messenger pathways) will be defined as neuromodulation. Thus, even effects of substances such as glutamate will be classified as neuromodulatory if they involve the dynamics of second messengers, as do effects at metabotropic glutamate receptors. Here we will discuss effects of neuromodulatory substances on (1) excitatory synaptic transmission, (2) inhibitory synaptic transmission, (3) pyramidal cell adaptation, (4) resting membrane potential, and (5) synaptic modification characteristics.

7.2.1 Modulation of Excitatory Synaptic Transmission

One of the clearest modulatory effects is the suppression of excitatory synaptic transmission in cortical structures. This effect has been most extensively analyzed in the hippocampus and piriform cortex, where the laminar segregation of fiber pathways and excitatory synapses allows isolation of synaptic field potentials and discrete stimulation of specific fiber pathways during intracellular and extracellular recording.

7.2.1.1 Acetylcholine (Muscarinic)

In early tangential slices of the dentate gyrus, Yamamoto and Kawai (1967) described presynaptic inhibition of synaptic potentials evoked in stratum moleculare during perfusion with carbachol. Presynaptic inhibition of synaptic transmission by acetylcholine was later described in stratum radiatum of region CA1 of the hippocampus (Hounsgaard 1978; Valentino and Dingledine 1981; Dutar and Nicoll 1988). Cholinergic suppression of field potentials has also been described in tangential slices of the piriform cortex (Williams et al. 1985; Williams and Constanti 1988) and in brain slice preparations of the prefrontal cortex (Vidal and Changeux 1993) and primary visual cortex (Brocher et al. 1992). During high levels of acetylcholine during active waking, this cholinergic presynaptic inhibition could prevent interference from previously encoded associations during encoding of new information (Hasselmo 1999), whereas the lower levels of acetylcholine during slow-wave sleep could allow excitatory feedback to drive the mechanisms of consolidation as shown in Fig. 7.1.

Cholinergic presynaptic inhibition of synaptic transmission demonstrates clear laminar selectivity in cortical structures (Kahle and Cotman 1989; Hasselmo and Bower 1991a, 1992; Hasselmo 1993), including the hippocampal formation (Hasselmo et al. 1995; Vogt and Regehr 2001; Kremin and Hasselmo 2007). Many of the earlier studies appeared to assume that the suppression of excitatory

synaptic transmission was uniform across all sets of synapses in cortical structures (Valentino and Dingledine 1981), though the functional value of such uniform suppression is unclear. However, even in tangential slices of the dentate gyrus, differences in the amount of suppression were noted depending upon the side of the slice being studied (Yamamoto and Kawai 1967). Later experiments in transverse slices revealed that cholinergic agonists have little effect in the outer molecular layer (receiving afferents from the lateral entorhinal cortex [LEC]) but more strongly suppress synaptic transmission in the middle molecular layer (receiving input from the medial entorhinal cortex [MEC]; Kahle and Cotman 1989). A similar pattern of laminar selectivity appears in the piriform cortex, where acetylcholine and cholinergic agonists strongly suppress synaptic transmission at intrinsic and associational fibers in layer Ib while having little effect on afferent fiber synaptic transmission in layer Ia (Hasselmo and Bower 1992, 1993). Laminar selectivity for presynaptic inhibition of synaptic transmission also appears in hippocampal region CA1, where cholinergic agonists more strongly suppress synaptic transmission in stratum radiatum compared to stratum lacunosum-moleculare (Hasselmo and Schnell 1994). Presynaptic inhibition at Schaffer-collateral synapses between regions CA3 and CA1 is mediated by G_q-linked muscarinic acetylcholine receptors (Gulledge and Kawaguchi 2007) with data suggesting a specific involvement of M4 receptors (Shirey et al. 2008; Dasari and Gulledge 2011) with some involvement of M1 receptors (Sheridan and Sutor 1990; Shinoe et al. 2005; Kremin et al. 2006; Leung and Péloquin 2010; Dasari and Gulledge 2011).

Muscarinic presynaptic inhibition in entorhinal cortex (EC) suppresses feedback connections from the subiculum that terminate in EC (Hamam et al. 2001, 2007) as well as synaptic connections within the EC (Richter et al. 1999). This common pattern of effects in different cortical regions suggests the selective suppression of synaptic transmission may represent a basic principle of cortical function. Presynaptic inhibition appears at feedback connections from region CA1 to the subiculum (Kunitake et al. 2004) but also affects input from the presubiculum. The effects are not just on feedback, as subiculum also shows selective presynaptic inhibition of MEC but not LEC input. Effects in neocortical structures are overall consistent with this same functional framework, as cholinergic modulation causes presynaptic inhibition of feedback synapses from higher order somatosensory cortex while having less effect on synaptic potentials elicited in layer IV (Hasselmo and Cekic 1996).

7.2.1.2 Norepinephrine (Alpha)

Norepinephrine has some effects similar to acetylcholine. It has been shown to suppress synaptic transmission in cultures of region CA3 of the rat hippocampus (Scanziani et al. 1993) and in neocortical slices (Dodt et al. 1991) through activation of alpha receptors. This noradrenergic suppression of synaptic transmission has laminar selectivity in brain slice preparations of the piriform cortex (Vanier and Bower 1992) and hippocampal region CA1 (Otmakhova et al. 2005). Both norepinephrine and dopamine show preferential suppression of inputs to region CA1 in rats from the LEC and MEC (Otmakhova and Lisman 1999; Otmakhova et al. 2005;

Ito and Schuman 2007) with preferential suppression of lateral entorhinal input to CA1 via reduced presynaptic release (Ito and Schuman 2012). In mice, direct input to CA1 from MEC is preferentially suppressed (Ito et al. 2010), and the opposing effects in different species may suggest that norepinephrine and dopamine are modality-dependent modulators of direct EC to CA1 transmission.

The possible selective presynaptic inhibition of synaptic transmission by norepinephrine might be enhanced by the apparent specificity of noradrenergic innervation for layers other than layer IV in the neocortex (Morrison et al. 1982). The presynaptic inhibition of synaptic transmission by norepinephrine is consistent with its capacity for decreasing spontaneous activity of hippocampal pyramidal neurons in vivo (Segal and Bloom 1974; Curet and de Montigny 1988a, 1988b), for suppressing seizure activity in the piriform cortex and hippocampus (Mueller and Dunwiddie 1983), and for decreasing population spikes in the hippocampus in vitro (Mynlieff and Dunwiddie 1988).

7.2.1.3 Dopamine and Serotonin

Dopamine and serotonin (5-HT) have been shown to strongly inhibit the perforant path providing excitatory input to region CA1 with little effect on Schaffer-collateral input (Otmakhova and Lisman 1999, 2000). Dopamine receptors are most concentrated in the stratum lacunosum-moleculare of region CA1(Goldsmith and Joyce 1994). Dopamine facilitates long-term potentiation (Frey et al. 1993; Otmakhova and Lisman 1996) and inhibits depotentiation of synapses from CA3 to CA1 (Otmakhova and Lisman 1998). In other structures, dopamine has been shown to enhance the NMDA component of synaptic potentials in the striatum (Arbuthnott et al. 2000) and to modulate gap junctions in the retina (Dowling 1991).

Serotonin, like norepinephrine, inhibits excitatory input via the perforant path to region CA1, possibly through 5-HT_7, 5-HT_2, and other receptors (Otmakhova et al. 2005), but other studies show a potentiation of perforant path input to CA1 by activation of $5HT_{1B}$ receptors (Cai et al. 2013). Depression of excitatory synaptic transmission within the EC is modulated by 5-HT_{1A} (Schmitz et al. 1998a, 1998b, 1999). Though earlier studies suggested 5-HT's depressant effect may be mediated by effects on postsynaptic glutamate receptors (Sizer et al. 1992), more evidence now indicates that 5-HT plays a bigger role via presynaptic modulation (Schmitz et al. 1995, 1998a, 1999; Grünschlag et al. 1997).

7.2.1.4 GABA ($GABA_B$)

The $GABA_B$ agonist baclofen has been shown to suppress excitatory synaptic transmission in the molecular layer of the dentate gyrus (Lanthorn and Cotman 1981), in hippocampal regions CA3 and CA1 (Ault and Nadler 1982; Kamiya 1991; Colbert and Levy 1992; Scanziani et al. 1992) and in the piriform cortex (Collins et al. 1982; Tang and Hasselmo 1994). This presynaptic inhibition of synaptic transmission has a laminar selectivity similar to that caused by cholinergic modulation, with much stronger presynaptic inhibition in stratum radiatum than in stratum lacunosum-moleculare (Ault and Nadler 1982; Colbert and Levy 1992) and stronger effects at intrinsic and associational synapses than at afferent synapses

in piriform cortex (Tang and Hasselmo 1994). This similarity of effect suggests that the cholinergic and GABAergic innervation arising from the basal forebrain may have similar modulatory influences.

7.2.1.5 Glutamate (Metabotropic)

Presynaptic inhibition of excitatory synaptic transmission has also been demonstrated with activation of metabotropic glutamate receptors. The glutamate analogue, L-AP4, was shown to suppress synaptic transmission in the molecular layer of the dentate gyrus (Koerner and Cotman 1982). That study demonstrates laminar specificity of the modulation of synaptic transmission, showing much stronger effects of L-AP4 in the outer molecular layer (note that this contrasts with the effect of cholinergic agonists). L-AP4 suppression of synaptic transmission has also been reported in region CA1 (Forsythe and Clements 1990), though AP4 effects in this region were previously attributed to postsynaptic antagonism (Koerner and Cotman 1982). L-AP4 has been demonstrated to have the same laminar specificity in the piriform cortex, more strongly suppressing afferent synaptic transmission in the superficial layer (layer Ia) (Hori et al. 1988; Hasselmo and Bower 1991b). This effect of L-AP4 contrasts with the laminar specificity of cholinergic and $GABA_B$ suppression of excitatory synaptic transmission at feedback synapses. Other studies have shown that different metabotropic glutamate receptors (mGluRs) influence different pathways within the hippocampus, with different time courses of modulation on these different pathways (Gereau and Conn 1995a, 1995b; Mannaioni et al. 2001; Giocomo and Hasselmo 2006; Ayala et al. 2008).

7.2.2 Modulation of Pyramidal Cell Adaptation

Extensive data demonstrate the influence of different neuromodulatory agents on the modulation of spike frequency adaptation or accommodation in cortical neurons. Pyramidal cells in the cortex respond to sustained current injection or excitatory synaptic input with an initial high firing rate which decreases over time (Connors et al. 1982; Madison and Nicoll 1982, 1984, 1986; ffrench-Mullen et al. 1983; McCormick et al. 1985; McCormick and Prince 1986; Schwindt et al. 1988, 1992; Coulter et al. 1989; Connors and Gutnick 1990; Barkai and Hasselmo 1994). This adaptation is so common that it is used as a defining feature of pyramidal cells that are referred to as "regular spiking" (McCormick et al. 1985). The decrease in spike frequency is termed adaptation or accommodation and appears to result from the activation of voltage- and calcium-dependent potassium currents (Madison and Nicoll 1984; Constanti and Sim 1987; Lancaster and Nicoll 1987; Schwindt et al. 1988, 1992; Barkai and Hasselmo 1994). The calcium-dependent potassium current also causes a long-lasting hyperpolarization of the membrane potential after calcium influx caused by action potentials, a phenomenon termed the slow afterhyperpolarization (sAHP). These properties of pyramidal cells contrast with the ability of inhibitory interneurons to respond with sustained firing

in response to current injection (Connors et al. 1982; McCormick et al. 1985; Connors and Gutnick 1990). A number of neuromodulatory agents influence the voltage- and calcium-dependent potassium currents underlying adaptation and afterhyperpolarization.

7.2.2.1 Acetylcholine

Early recordings from cortical structures in vivo demonstrated an increase in firing activity of cortical neurons during application of cholinergic agonists (Krnjevic and Phillis 1963; Krnjevic et al. 1971; Krnjevic 1984). This effect could be partly due to direct influences on pyramidal cell membrane potentials and partly due to modulation of adaptation. Cholinergic agonists have been shown to suppress the adaptation of pyramidal cells in brain slice preparations of region CA1 of the hippocampus (Madison and Nicoll 1984) of the cingulate cortex (McCormick and Prince 1986) and of the piriform cortex (Tseng and Haberly 1989; Barkai and Hasselmo 1994). This effect has also been demonstrated during in vivo intracellular recording from cat somatosensory cortex (Schwindt et al. 1992) and motor cortex (Woody and Gruen 1987). This suppression of adaptation appears due to decreases in the conductance of the voltage-dependent *M* current (Constanti and Galvan 1983; Madison et al. 1987) and calcium-dependent potassium currents (Constanti and Sim 1987; Madison et al. 1987).

7.2.2.2 Norepinephrine

The effects of norepinephrine on neuronal adaptation are very similar to acetylcholine. Acting at beta receptors, noradrenergic agonists appear to shut down the calcium-dependent potassium current, thereby decreasing adaptation in response to sustained current injection (Madison and Nicoll 1982, 1986). This appears to be an influence on the same channels influenced by cholinergic modulation, though mediated via a different second messenger pathway (see Nicoll 1988 for review). Coupled with the evidence for noradrenergic modulation of excitatory synaptic transmission, this suggests that acetylcholine and norepinephrine have very similar cellular influences on cortical dynamics, though the regulation of the timing and spatial distribution of these neuromodulators systems is very different. The beta-adrenergic suppression of neuronal adaptation, followed by the alpha-adrenergic suppression of synaptic transmission, could explain the initial increase followed by the decrease in population spikes during noradrenergic modulation (Mueller et al. 1981; Mynlieff and Dunwiddie 1988). In this way, conflicting effects of neuromodulation could be resolved in the temporal domain.

7.2.2.3 Dopamine

Dopamine has been reported to both enhance the afterhyperpolarization (Benardo and Prince 1982a, 1982b; Dinan et al. 1987; Berretta et al. 1990) and suppress the afterhyperpolarization potential in hippocampal pyramidal cells (Malenka and Nicoll 1986). The suppression of afterhyperpolarization with high doses of dopamine has been attributed to cross-reactivity of dopamine with β-noradrenergic receptors, since this effect can be blocked by propranolol (Malenka and Nicoll

1986). This latter study reported slight hyperpolarizations induced by dopamine, but did not see an increase in hyperpolarization at any concentration of dopamine. Despite the strong influence on the AHP current, no change in number of action potentials was reported in that study. One study suggested that activation of D1 receptors enhances and activation of D2 receptors suppresses the afterhyperpolarization currents (Berretta et al. 1990). Within the prefrontal cortex, dopamine acts through D1 and D5 receptors enhancing the NMDA component of excitatory synaptic inputs postsynaptically to layer V neurons (Seamans et al. 2001). Given a pulse train, dopamine acts to sustain inputs and equalize the size of postsynaptic potentials (Seamans et al. 2001).

7.2.2.4 Serotonin

Similar to acetylcholine and norepinephrine, serotonin has been shown to suppress the adaptation of cortical pyramidal cells, thereby increasing excitability. Serotonin decreases pyramidal cell adaptation in current-clamp recording (Colino and Halliwell 1987; Araneda and Andrade 1991; Sheldon and Aghajanian 1991), and voltage-clamp recording suggests that similar to acetylcholine and norepinephrine, this is due to suppression of the calcium-dependent potassium current underlying long-term afterhyperpolarization (Colino and Halliwell 1987; Sheldon and Aghajanian 1991). In contrast to acetylcholine and norepinephrine, however, serotonin simultaneously causes hyperpolarization through activation of a calcium-independent potassium current via 5HT1A receptors (Colino and Halliwell 1987; Araneda and Andrade 1991; Sheldon and Aghajanian 1991).

7.2.2.5 GABA ($GABA_B$)

The $GABA_B$ agonist baclofen does not influence adaptation characteristics of cortical pyramidal cells (Newberry and Nicoll 1984, 1985). This lack of effect also appears to be the case for metabotropic glutamate receptor agonists such as trans-ACPD.

7.2.3 Modulation of Inhibitory Synaptic Transmission and Inhibitory Interneuron Excitability

In addition to the regulation of excitatory synaptic transmission, neuromodulators appear to regulate inhibitory synaptic transmission and the spiking activity of inhibitory interneurons. Considerable evidence has been gathered showing modulatory effects on inhibitory interneurons.

7.2.3.1 Acetylcholine

Cholinergic agonists have been shown to suppress inhibitory synaptic potentials in the hippocampal formation. In whole-cell clamp recordings, the cholinergic agonist carbachol suppresses spontaneous $GABA_A$ inhibitory synaptic potentials, suggesting a direct suppression of the release of synaptic vesicles containing GABA (Pitler and Alger 1992). Surprisingly, carbachol also increases the number

of miniature synaptic potentials presumed to result from the spontaneous spiking of inhibitory interneurons (Pitler and Alger 1992). This coincides with other evidence suggesting a direct excitation of inhibitory interneurons by acetylcholine (McCormick and Prince 1986; Chapman and Lacaille 1999; McQuiston and Madison 1999a; Alkondon and Albuquerque 2001). In particular, Chapman and Lacaille (1999) recorded depolarizations of interneurons near the border of stratum radiatum (S-R) and stratum lacunosum-moleculare (SLM) as carbachol was added to the slice preparation in the presence of glutamate and $GABA_A$ antagonists. This effect was blocked by atropine, indicating muscarinic cholinergic control over interneuron depolarizations. Though CA1 interneurons are more likely to depolarize in the presence of muscarinic agonists (e.g., carbachol and muscarine), bath application can induce a diversity of responses including hyperpolarization, biphasic behavior (hyperpolarization followed by depolarization), and less-predominant oscillatory behavior and unresponsive cells (McQuiston and Madison 1999b; see also Widmer et al. 2006). Lawrence et al. (2006) elicited strong sustained afterdepolarizations in mouse hippocampal stratum oriens lacunosum-moleculare (OLM) interneurons. However, this response was not present in interneurons with different arborizations. Such anatomic organizational differences in OLM interneurons may contribute to the differential modulation of region CA3 and EC inputs to region CA1 while under cholinergic influence (Leão et al. 2012). Within the frontal cortex, application of cholinergic agonists to cholecystokinin (CCK) interneurons yields both a depolarization and biphasic response, whereas in somatostatin (SOM) or vasoactive intestinal polypeptide (VIP)-expressing interneurons, only a depolarizing response is visible, and parvalbumin-expressing interneurons are unresponsive (Kawaguchi 1997). Of note, direct cholinergic modulation amplifies the intrinsic oscillatory properties of CCK-interneurons in region CA1 (Cea-del Rio et al. 2011). The most prevalent interneuron type in the neocortex, fast-spiking cells, show marked decreases in GABA release after activation of muscarinic, serotonergic, adenosine, and $GABA_B$ receptors, an effect which suppresses feedforward inhibition (Kruglikov and Rudy 2008). Questions about the role of septal cholinergic modulation on inhibitory interneurons in EC remain and will be later discussed in further detail. Such behaviorally relevant cholinergic modulation may occur as a combination of properties based on muscarinic receptor subtype, interneuron subtype, and anatomical location (see Heys et al. 2012 for review).

7.2.3.2 Norepinephrine

Research on norepinephrine initially focused on the noradrenergic suppression of inhibition rather than noradrenergic suppression of excitatory synaptic transmission. Suppression of inhibition by NE was originally reported in the olfactory bulb (Jahr and Nicoll 1982) and appears to involve direct suppression of the release of GABA (Trombley and Shepherd 1991). Suppression of inhibition has also been reported in the hippocampus (Mody et al. 1983; Madison and Nicoll 1988) in the form of increased numbers of population spikes due to a suppression of excitatory synaptic transmission onto inhibitory interneurons (Doze et al. 1991). Similar to

muscarinic effects, the reduction of inhibitory synaptic transmission is paradoxically accompanied by an increase in interneuron spiking activity. The noradrenergic α1A- and α1B-adrenergic receptors (AR) have been fluorescently localized to GABAergic and NMDA receptor-containing neurons throughout neocortex and region CA1 of the hippocampus (Hillman et al. 2005, 2007; Papay et al. 2006). Activation of these noradrenergic receptors causes increased presynaptic spiking activity of inhibitory interneurons (Bergles et al. 1996; Hillman et al. 2009) and modulation of postsynaptic NMDA receptor responses (Scheiderer et al. 2004).

7.2.3.3 Dopamine and Serotonin

Both dopamine and serotonin appear to directly enhance the activity of inhibitory interneurons in the piriform cortex (Gellman and Aghajanian 1993), based on striking increases in spontaneous inhibitory potentials in the presence of these modulatory agents. Within the EC, 5-HT increases the frequency and amplitude of spontaneous inhibitory postsynaptic currents (IPSCs), but has no effect on mini-IPSCs in the presence of tetrodotoxin (Deng and Lei 2008). The lack of effect on mini-IPSCs suggests 5-HT has little effect on postsynaptic $GABA_A$ receptors, indicating any effect should be a presynaptic effect on interneuron spiking activity. Evoked IPSCs from extracellular stimulation show reduced amplitudes in the presence of 5-HT (Schmitz et al. 1998b; Deng and Lei 2008). 5-HT directly depolarizes and increases firing rate while blunting the amplitude of action potentials in presynaptic GABAergic interneurons. The direct influence of 5-HT on interneurons is further supported by confocal microscopy studies that colocalize $5\text{-}HT_{2A}$ receptors with GABA (Bombardi 2012).

7.2.3.4 GABA ($GABA_B$)

Similar to its suppression of excitatory synaptic transmission, the $GABA_B$ agonist baclofen suppresses inhibitory synaptic transmission in brain slice preparations of the hippocampus (Kamiya 1991) and neocortex (Howe et al. 1987). While the $GABA_B$-mediated suppression of inhibitory synaptic transmission could be interpreted as feedback regulation of inhibitory synaptic transmission, in the manner that metabotropic receptor effects on glutamatergic synaptic transmission have been interpreted, the influence of baclofen on excitatory synaptic transmission seems incompatible with this interpretation. Perhaps a more plausible explanation would be that inhibitory synaptic transmission must be modulated in a manner proportional to excitatory synaptic transmission.

7.2.4 Modulation of Resting Membrane Potential

Many neuromodulatory substances can influence the resting membrane potential of neurons, causing slow depolarizations or hyperpolarizations which are sometimes referred to as synaptic potentials, despite their much slower time constant in comparison to glutamatergic or $GABA_A$ synaptic potentials. Again, it may be more accurate to classify effects with regard to receptor subtypes, distinguishing

between ionotropic receptors and receptors coupled indirectly to ion channels. In this context, it is easy to distinguish between the more rapid effects of glutamate at AMPA and NMDA ionotropic receptors and the slower effects at metabotropic receptors, between the rapid effects of GABA at $GABA_A$ receptors and the slower effects at $GABA_B$ receptors, between the rapid effects of acetylcholine at nicotinic receptors and the slower effects at muscarinic receptors, and so on. Here we will describe only changes in resting membrane potential which appear to be due to metabotropic receptors (i.e., coupled indirectly to ion channels), with primary influences on potassium currents. These effects are usually smaller and longer-lasting than ionophore effects and may have a more modulatory influence on cortical dynamics.

7.2.4.1 Acetylcholine

Application of cholinergic agonists consistently causes a slow depolarization of the resting potential of cortical pyramidal cells (Benardo and Prince 1982c; Cole and Nicoll 1984; Madison and Nicoll 1984), after iontophoretic application or bath application in brain slice preparations. This effect appears to be due to suppression of a tonically active potassium current (Madison et al. 1987), thereby causing movement away from the reversal potential of potassium, which lies below resting potential for most cortical neurons. Phasic cholinergic changes in membrane potential in rat (Gulledge and Kawaguchi 2007) and mouse (Dasari and Gulledge 2011) are modulated primarily by M1 receptors. In mice with knockout of M1 receptors, hippocampal pyramidal neurons do not show the phasic and tonic changes in membrane potential caused by acetylcholine in wild-type animals (Dasari and Gulledge 2011).

7.2.4.2 Norepinephrine and Dopamine

Though norepinephrine suppresses adaptation currents in the same manner as acetylcholine, norepinephrine differs from acetylcholine in that it has commonly been reported to cause hyperpolarization of membrane potential (Madison and Nicoll 1986). Dopamine has been reported to occasionally cause a small hyperpolarization of membrane potential (Malenka and Nicoll 1986), but this has been attributed to action at noradrenergic or serotonergic receptors.

7.2.4.3 Serotonin

While its effect on adaptation and afterhyperpolarization is the same as acetylcholine and norepinephrine, serotonin differs from these modulators in that it has a clear hyperpolarizing effect on resting membrane potential due to activation of 5HT1A receptors (Andrade and Nicoll 1987; Colino and Halliwell 1987; Araneda and Andrade 1991; Sheldon and Aghajanian 1991), especially in EC layer II stellate neurons and layers II and III pyramidal neurons (Schmitz et al. 1995; Grünschlag et al. 1997; Deng et al. 2007; Ma et al. 2007). 5-HT activates a background K^+-channel resulting in a large amplitude hyperpolarization followed by a slow, but lasting, depolarization in layer II projections (Deng et al. 2007; Ma et al. 2007). The inward current associated with this latter depolarization is sensitive to ZD7288, a

blocker for the H-channel and I_H current (Ma et al. 2007). Activation of K^+-channels via 5-HT_{1A} receptors mediate the hyperpolarizing effect (Schmitz et al. 1995; Grünschlag et al. 1997; Deng et al. 2007), but the longer-lasting depolarization is independent of 5-HT_{1A} receptors (Ma et al. 2007). The K^+-current appears to be the same current activated by $GABA_B$ receptors (Andrade et al. 1986). Thus, during initial perfusion of serotonin in slice preparations, the response to low-current intensities is decreased due to hyperpolarization, while the response to high-current intensities is increased due to the suppression of adaptation (Andrade and Nicoll 1987).

7.2.4.4 $GABA_B$

The most familiar effect of $GABA_B$ receptor activation is the slow hyperpolarization of membrane potential due to activation of potassium currents. In addition to the suppression of excitatory and inhibitory synaptic transmission discussed above, the $GABA_B$ agonist baclofen causes hyperpolarization of pyramidal cell membrane potentials (Newberry and Nicoll 1984, 1985). This effect is most commonly observed after synaptic stimulation, when activation of $GABA_B$ receptors induces the slow, potassium-dependent component of the synaptic potential (Howe et al. 1987; Tseng and Haberly 1988; Patil and Hasselmo 1999).

7.2.5 Modulation of Synaptic Modification (Long-Term Potentiation)

Many neuromodulatory substances have been implicated in memory function. Because of this, considerable work has focused on how neuromodulatory substances influence synaptic modification, especially long-term potentiation (see Pawlak et al. 2010 for a review).

7.2.5.1 Acetylcholine

A number of studies have demonstrated that, at the same time as they suppress excitatory synaptic transmission, cholinergic agonists enhance the relative amplitude of long-term potentiation phenomena in the dentate gyrus (Burgard and Sarvey 1990), region CA1 of the hippocampal formation (Blitzer et al. 1990; Huerta and Lisman 1993), the piriform cortex (Barkai et al. 1993), and in neocortical structures (Lin and Phillis 1991; Brocher et al. 1992). In the hippocampus, this potentiation may be related to the induction of theta frequency oscillatory dynamics (Huerta and Lisman 1993). This cholinergic effect on synaptic modification may be due to a direct enhancement of the mechanisms involved in long-term potentiation, such as the enhancement of NMDA currents (Markram and Segal 1990a, b). It may also be due to indirect effects of the cholinergic modulation of activation dynamics, such as the suppression of neuronal adaptation (Barkai et al. 1993).

7.2.5.2 Norepinephrine

Considering its similarity with other effects of acetylcholine, it is perhaps not surprising that considerable evidence supports the notion that norepinephrine enhances long-term potentiation in hippocampal region CA1 (Hopkins and Johnston 1988) and in the neocortex (Brocher et al. 1992). More recent evidence suggests that norepinephrine does not significantly modify the plasticity of either lateral EC or medial EC layer III inputs to region CA1 with stimulation at 5–100 Hz (Ito and Schuman 2012).

7.2.5.3 Dopamine and Serotonin

Some reported effects of dopamine and serotonin on long-term potentiation have been attributed to interactions with other neuromodulators. Dopamine has been shown to potentiate inputs from the lateral EC to region CA1, with little effect on projections from medial EC to region CA1 (Ito and Schuman 2007, 2012).

7.2.5.4 $GABA_B$ Receptors

The $GABA_B$ agonist baclofen has been shown to enhance long-term potentiation in the hippocampal formation (Olpe and Karlsson 1990; Burgard and Sarvey 1991; Mott and Lewis 1991; Ballyk and Goth 1992), possibly through the disinhibitory influence of the suppression of inhibitory synaptic transmission (Ballyk and Goth 1992). This suppression of inhibition may in particular play a role in the greater capacity of theta frequency (3–10 Hz) stimulation for inducing long-term potentiation. Suppression of inhibition by baclofen aids in the induction of LTP with theta frequency stimulation (Mott and Lewis 1991).

7.3 Examples of Cholinergic Neuromodulation of Intrinsic Properties in Entorhinal Cortex

Work in the medial entorhinal cortex (MEC) has provided evidence of cholinergic neuromodulation of inputs to the hippocampus via persistent spiking, regulation of subthreshold properties, and theta rhythm, which are discussed below.

7.3.1 Persistent Spiking

Intracellular recording from in vitro slice preparations of rat MEC suggests a mechanism for long-lasting depolarizations modulated by acetylcholine (Klink and Alonso 1997; Egorov et al. 2002; Fransén et al. 2006; Tahvildari et al. 2007). Single neurons in MEC typically terminate their spiking response in an unsustained fashion after a single depolarizing current. However, bath application of cholinergic agonists like carbachol in the presence of a depolarizing current injection produces persistent spiking that continues after the termination of the depolarizing stimulus (Klink and Alonso 1997; Egorov et al. 2002; Yoshida et al. 2008). One possible cellular mechanism proposed for this persistent spiking is that activation of

muscarinic receptors activates a calcium-sensitive nonspecific cation current (I_{CAN}) on MEC neurons allowing further depolarization from calcium influx resulting in self-sustained persistent spiking (Klink and Alonso 1997; Egorov et al. 2002; Fransén et al. 2006; Tahvildari et al. 2007; Hasselmo and Sarter 2011). Cholinergic modulation of persistent spiking physiology has also been seen in the prefrontal cortex (Haj-Dahmane and Andrade 1996, 1997, 1998), postsubiculum (Yoshida and Hasselmo 2009), and perirhinal cortex (Leung et al. 2006; Navaroli et al. 2012). The ability for these regions to express a stimulus after it is no longer present has contributed to the idea that persistent spiking could be a mechanism for cued memory retrieval.

It is this particular feature of long-lasting stimulus representation that makes persistent spiking an attractive substrate for phenomena such as "time cells." Initially reported from hippocampal place cell assemblies, these cells fire throughout the duration of a cued, choice task as the animal runs in a running wheel prior to making a choice. Such cells not only organize spatial locations along a maze, but they can also organize temporal events. Recent work has also implicated similar temporal organizing roles in MEC grid cells that code for both distance and/or time (Pastalkova et al. 2008; MacDonald et al. 2011; Kraus et al. 2013). Either as input to the hippocampus or directly measured from the MEC, elevated firing rate representing time or distance could be served by persistent spiking cells.

Pyramidal neurons in layer II of MEC also show persistent spiking that tends to turn on and off over periods of many seconds under muscarinic modulation (Klink and Alonso 1997). Such cyclical persistent spiking could underlie the periodicity of grid cells. Grid cells are neurons found in MEC layers II, III, and V. As animals forage in a 2-D arena, these neurons fire action potentials when the rat visits spatially periodic locations in the environment that form the vertices of tessellating equilateral triangles (Fyhn et al. 2004; Hafting et al. 2005; see Derdikman and Moser 2014). Models representing grid cell periodicity have used persistent spiking cells that cycle on and off to generate grid cells (Hasselmo and Brandon 2008) or have used persistent spiking to generate interference of velocity-modulated theta frequency spiking (Hasselmo 2008) as in the broader class of "oscillatory interference" models (Burgess et al. 2005, 2007; Burgess 2008) discussed further in the next section (see also Lever et al. 2014).

7.3.2 Subthreshold Electrophysiology in MEC Stellate Cells

Below the spiking threshold of MEC stellate cells, the membrane potential demonstrates several intrinsic properties including sag (membrane potential response to hyperpolarization), resonance (preferred membrane potential for a given frequency of injected current), and membrane potential oscillations (MPOs) (Alonso and Klink 1993; White et al. 1998a; Dickson et al. 2000; Haas and White 2002; Erchova et al. 2004; Fransén et al. 2004; Nolan et al. 2007; Dudman and Nolan 2009). These three properties are thought to be driven by a hyperpolarization-activated current termed the h-current (I_h) which is reduced by

activation of muscarinic receptors (Heys and Hasselmo 2012). Additionally, it is thought that subthreshold MPO correlates with resonance frequency as suggested by several proposed models (White et al. 1998b; Dickson et al. 2000; Haas and White 2002; Erchova et al. 2004; Fransén et al. 2004; Nolan et al. 2007; Dudman and Nolan 2009). The overall hyperpolarizing shift in the activation curve and decrease in amplitude of I_h under muscarinic stimulation surprisingly do not change the time course of I_h (Heys and Hasselmo 2012) despite gene expression studies of muscarinic receptors and h-channels that would predict cholinergic delays in I_h activation (Pian et al. 2007). However, simple heterologous expression systems used in these predictions may not capture nuanced second messenger regulatory effects (see Zolles et al. 2009) on the HCN subunits of the h-channel. Slice preparations of stellate cells after carbachol application demonstrate that subthreshold MPO (Klink and Alonso 1997) and resonance (Heys et al. 2010) frequencies decrease. The latter resonance study also excluded the candidate M-current, potentially responsible for subthreshold oscillations via Kv7 potassium channels (Yoshida and Alonso 2007), by showing they are not expressed in entorhinal neurons.

Unit recordings from MEC layer II in wild-type and specific HCN-1 knockout awake-behaving mice have demonstrated that the properties of grid cell firing are influenced by the h-current (Giocomo et al. 2011). The periodicity of grid firing fields is eliminated with reduction of cholinergic and GABAergic input to the entorhinal cortex by pharmacological inhibition of the medial septum (Brandon et al. 2011; Koenig et al. 2011). The results of these studies place particular importance on theta rhythm for spatial periodicity of grid cells. However, neurons with selectivity to the direction the animal faces, including head direction cells (Taube et al. 1990a, b) and conjunctive grid-by-head direction cells (Sargolini et al. 2006), retain their tuning functions for head direction even during epochs of reduced theta power. Many models of grid cells have used phase differences of interfering velocity-modulated theta oscillations to generate grid firing fields (Burgess et al. 2005, 2007 see Lever et al. 2014). All variants of these oscillatory interference models depend on theta frequency modulation with the animal's running speed, specifically incorporating an experimentally derived parameter B describing the relationship of theta oscillation frequency and velocity (Giocomo and Hasselmo 2008a), which accounts for the size of and spacing between grid fields. These two properties of grid fields increase as recordings in the MEC move ventrally along the dorsal-ventral axis (Hafting et al. 2005; Brun et al. 2008) paralleling decreases in subthreshold MPO frequency (Giocomo and Hasselmo 2009; Yoshida et al. 2011), intrinsic resonance frequency (Giocomo et al. 2007; Boehlen et al. 2010), and time constant of I_h (Giocomo and Hasselmo 2008b) seen in slice preparations from more ventral locations. Decreases in subthreshold MPO frequency and intrinsic resonance frequency can affect parameter B resulting in larger grid field spacings. HCN-1 knockout mice show larger grid fields and grid spacings (Giocomo et al. 2011), similar to the effects of novelty exploration on grid fields from rat studies (Barry et al. 2012). The novelty effects on grid cells may be mediated by elevated acetylcholine release in novel environments (Acquas

et al. 1996; Thiel et al. 1998), which can decrease the amplitude of I_h and the frequency of resonance in MEC stellate cells (Heys and Hasselmo 2012) providing a potential mechanism for increasing the spacing between grid cell firing fields.

Recent data also show a phenomenon called "theta cycle skipping" in grid cells and head direction cells (Deshmukh et al. 2010; Brandon et al. 2013). Instead of firing on each cycle of theta rhythm, these cells fire on alternate cycles suggesting phase coding for discrete, noncontiguous cycles of theta. Simulations can accommodate cycle skipping by utilizing cells with h-current resonance receiving oscillatory inhibitory input (Brandon et al. 2013). This would imply the degree of cycle skipping could be modulated by cholinergic modulation of I_h and resonance in these cells.

7.3.3 Neuromodulation of Inhibition and Theta Rhythm Oscillations

In vivo unit recordings from rodents measure voltage responses of single neurons and the local field potential (LFP) arising from summed activity of neuronal populations. Hippocampal and entorhinal LFP exhibit strong oscillations in the 6–12 Hz frequency band known as theta rhythm (Walter and Dovey 1944; Green and Arduini 1954; Buzsáki et al. 1983; Alonso and Garcia-Austt 1987a, b; Buzsaki 2002). This frequency band is readily observed during locomotion (Vanderwolf 1969), attentive states (Sainsbury et al. 1987), and REM sleep (Lerma and Garcia-Austt 1985). Eliminating theta oscillations impairs performance on a variety of spatial memory tasks (Kesner et al. 1989) and working memory tasks (Givens and Olton 1994). Theta rhythm is modulated by cholinergic and GABAergic inputs from the medial septum via the fornix (Stewart and Fox 1990; Vertes and Kocsis 1997; Buzsaki 2002), and increases in hippocampal acetylcholine are associated with theta oscillations (Monmaur et al. 1997; Zhang et al. 2010). As previously discussed, elimination of both septal cholinergic and GABAergic input to the MEC significantly reduces MEC theta power and results in a loss of grid cell spatial periodicity (Brandon et al. 2011; Koenig et al. 2011). Encoding in tasks such as trace conditioning is enhanced when stimuli are presented during periods of theta rhythmicity (Griffin et al. 2004). Theta rhythm is reduced by cholinergic lesions (Lee et al. 1994) and blocked by combined lesions of the cholinergic and GABAergic input from the medial septum (Yoder and Pang 2005). Cholinergic neurons show theta rhythmic firing, which could provide rhythmic modulation of neuronal function in the hippocampus (Brazhnik and Fox 1999).

Interneurons play an important role in theta rhythm (Klausberger et al. 2003). As described above, cholinergic modulation directly depolarizes many hippocampal interneurons (Chapman and Lacaille 1999; McQuiston and Madison 1999b; Alkondon and Albuquerque 2001), which could enhance their activity during theta rhythm. Muscarinic receptors also cause presynaptic inhibition of GABA release (Pitler and Alger 1992). The combination of depolarization and presynaptic inhibition appears paradoxical, but computational modeling demonstrates that these combined effects reduce background activity, while heightening the response to

suprathreshold sensory stimuli (Patil and Hasselmo 1999). Cholinergic modulation also increases the rhythmicity of some interneurons (Chapman and Lacaille 1999). In the hippocampus, muscarinic receptors selectively depolarize OLM interneurons, but not non-OLM cells (Lawrence et al. 2006). Cholinergic regulation of interneuron rhythmicity could contribute to regulating the encoding and retrieval dynamics of the hippocampus. This could provide separate rhythmic timing of dendritic and somatic inhibition that could enhance separation of encoding and retrieval dynamics during theta rhythm oscillations (Hasselmo et al. 2002; Kunec et al. 2005; Cutsuridis et al. 2010; Cutsuridis and Hasselmo 2012).

Hippocampal interneurons receive medial septal rhythmic inhibition which acts as a theta band pacemaker for the network during animal locomotion (Green et al. 1990). Destruction of septal cholinergic projections reduces but does not eliminate theta entirely (Lee et al. 1994). Hippocampal theta may depend on two separate frequency components, namely a cholinergic-independent, movement-related theta rhythm at 8–9 Hz (type 1) and a lower 6–7 Hz cholinergic-dependent component (type 2) (Kramis et al. 1975; Jeewajee et al. 2008). As animals forage in novel versus familiar settings, hippocampal peak theta frequency shifts lower (Givens and Olton 1995; Jeewajee et al. 2008) presumably from novelty-induced hippocampal acetylcholine release (Acquas et al. 1996). Other work has shown that beyond adjusting peak theta frequency, environmental novelty (Sambeth et al. 2009) and altering hippocampal cholinergic levels (Givens and Olton 1994; Markowska et al. 1995) increase overall theta power.

7.3.4 Direct Cholinergic Effects on Encoding and Retrieval

At the beginning of this chapter, we introduced a model of encoding and retrieval/consolidation modulated by acetylcholine. To reiterate in terms of hippocampal CA1 encoding, high cholinergic states reduce the flow of internal recurrent information (see Fig. 7.1), namely, from the neocortex. This allows for increased throughput of sensory stimuli from the entorhinal cortex and region CA3 without neocortical interference during encoding states. Acetylcholine levels tend to be low in two quiescent modes—quiet rest and slow-wave sleep. Memory consolidation occurs during sharp wave/ripple oscillations associated with these quiescent states (Sutherland and McNaughton 2000; O'Neill et al. 2010). Here, low acetylcholine levels allow learned associations in neocortical recurrent connections to prevail while causing reduced response to sensory input (Hasselmo and Schnell 1994; Hasselmo et al. 1996; Hasselmo 1999, 2006; Meeter et al. 2004).

These direct cholinergic effects have been visible in the parahippocampus in humans, primates, and rodents. Local infusions of scopolamine into the perirhinal cortex in rats were shown to slow the acquisition of a working memory-dependent (i.e., trace) fear-conditioning task (Bang and Brown 2009). Such impairments have been found to vary in a dose-dependent fashion with infusions of the muscarinic M1 receptor antagonist pirenzepine (Esclassan et al. 2009). Similar results have also been observed in humans following systemic injections of scopolamine in DMS

tasks (Robbins et al. 1997; Koller et al. 2003) and visuospatial tasks (Thomas et al. 2008). FMRI studies also show reduced correlations between delay period activity and subsequent memory after scopolamine administration (Schon et al. 2005). In a study comparing the effect of systemic injections of scopolamine and the nicotinic receptor antagonist mecamylamine, patients were impaired on an *n*-back memory test with scopolamine alone and were synergistically impaired with scopolamine and mecamylamine (Green et al. 2005). Muscarinic blockade, however, does not impair performance on short-term memory tasks such as digit span (Broks et al. 1988) suggesting the familiar stimuli used in these paradigms may have already sufficiently strengthened synaptic connections, thereby reducing the need for cholinergic input to modulate mechanisms of active maintenance. This suggests that the cholinergic modulation of working memory might be more important for novel than for familiar stimuli.

Most previous models of working memory focus on persistent spiking maintained by excitatory recurrent connections in the prefrontal cortex (Durstewitz et al. 2000). However, novel stimuli would not match the pattern of previously strengthened synapses and therefore cannot use this mechanism. As an alternative, working memory for novel stimuli might depend upon the intrinsic mechanisms for persistent spiking that are enhanced by acetylcholine (Hasselmo and Stern 2006). In vivo studies have shown elevations in entorhinal and hippocampal activity from rodents (Young et al. 1997), monkeys (Suzuki et al. 1997), and humans (Stern et al. 2001; Schon et al. 2004, 2005) which could represent persistent spiking selectively gated by acetylcholine to specific stimuli. Such selective gating is necessary to maintain information even in the presence of distractor stimuli (Suzuki et al. 1997). The capacity for novel environments (Acquas et al. 1996; Thiel et al. 1998) and novel objects (Degroot et al. 2005; Stanley et al. 2012) to increase rat hippocampal acetylcholine levels argues for cholinergic enhancement of afferent input for encoding of new information. In Atri et al. (2004), cholinergic blockade with scopolamine impaired encoding on a paired-associate task where cues could have multiple associations rather than when cues signaled a single association. A similar finding is seen with scopolamine in rats performing the Morris water maze task as the goal location is moved daily (Baxter et al. 1995). Lack of cholinergic modulation via deafferentation of the rat entorhinal cortex spares working memory for familiar odor stimuli but impairs working memory of novel stimuli in a DNMS task (McGaughy et al. 2005). Similar lesions also reduce rat exploration of novel objects (Winters and Bussey 2005) and impair formation of novel associations for location and contexts (Easton et al. 2010).

7.3.5 Indirect Cholinergic Modulation: Encoding and Retrieval Scheduling

The direct effects of cholinergic action (e.g., presynaptically) can have longer-lasting effects on the order of seconds. However, behavioral tasks reliant on rapid spike-timing-dependent plasticity (Bi and Poo 1998) require rapid encoding and

retrieval processing. Scheduling these events relative to theta oscillations has been proposed where encoding and retrieval occur on preferred phases of theta oscillations (Buzsaki 1989; Hasselmo et al. 2002). Given the effect cholinergic modulation has on theta rhythm, acetylcholine can indirectly modulate encoding and retrieval scheduling. The canonical hippocampal circuit consists of entorhinal cortex layer III (EC III) and region CA3 providing inputs to region CA1. Measuring theta oscillations from local field potential at the fissure, EC III inputs are strongest with theta phases associated with peak theta rhythm. During these epochs, CA3 input is weakest reducing interference on the direct encoding from EC III. Additionally, the short timing of coincident strong EC III and weak CA3 inputs on CA1 drives long-term potentiation (LTP) of Schaffer-collateral (SC) synapses. Conversely, at the theta phases associated with the trough of theta rhythm, EC III inputs are weak, whereas CA3 inputs to CA1 are strong driving long-term depression (LTD) of SC synapses (Hasselmo et al. 2002).

This encoding and retrieval schedule relative to theta phase has strong evidence from in vitro studies of direct stimulation of SC synapses inducing stronger LTP on the peak and LTD on the trough of local theta rhythm (Huerta and Lisman 1993, 1995, 1996; Holscher et al. 1997; Hyman et al. 2003). More recently, Mizuseki et al. (2009, 2011) used high-volume silicon probes to accurately assess the expected theta peak-locked spiking from EC III and trough-locked spiking from CA3 onto CA1, confirming these assumptions in Hasselmo et al. (2002). They also show that peak phase of CA1 spiking occurs after the theta trough, suggesting that CA1 activity could be a weighted sum of activity with a preferred theta phase intermediate to those of EC III and CA3 spiking. Lever et al. (2010) hypothesized that high-encoding states induced by environmental novelty, where cholinergic input is elevated, should shift the phase of CA1 spiking towards the preferred peak theta phase of EC III spiking. Here, animals in a novel environmental context had mean phases of CA1 spiking occurring at a later theta phase compared to those animals in a familiar environmental context. They subsequently have manipulated both novelty and acetylcholine levels demonstrating that in familiar environments with systemic injections of scopolamine, CA1 spiking moves towards earlier phases of theta, closer to the preferred trough-theta phase of CA3 III spiking (Douchamps et al. 2013) . Scopolamine in animals performing in novel environments mitigates any transition to later theta phases for CA1 spiking. The results suggest that acetylcholine titrates the system towards encoding states by pushing spiking towards the scheduled encoding theta phases. In the absence of cholinergic modulation, the system is biased towards scheduled retrieval theta phases. This finding has support from in vivo recordings from rats with lesions of septohippocampal cholinergic neurons, where CA1 place cells were recorded in novel and familiar contexts (Ikonen et al. 2002). Place cells of lesioned and non-lesioned animals recorded in the novel context showed higher initial remapping rates. Subsequent exposure to this context produced distinct stable spatial representations in non-lesioned animals compared to familiar contexts. Lesioned animals, however, produced spatial representations that converged on that seen in the familiar

contexts. Here, lack of cholinergic modulation appears to bias the memory system towards retrieval states.

7.4 Summary

The role of acetylcholine in the encoding of memory in the hippocampus and parahippocampal structures can be linked to the specific cellular effects of acetylcholine, including the enhanced response to afferent synaptic input, the suppression of interference from excitatory feedback, and the enhancement of persistent spiking and synaptic modification. This example of the link between behavioral function and physiological effects at the cellular level provides an inspiration for understanding the effects of other neuromodulatory agents on the functional properties of the hippocampus and parahippocampal structures.

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Models of Path Integration in the Hippocampal Complex

8

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Abstract

Path integration is the process of summing up information about direction and distance traveled, in order to keep track of one's relative position. Path integration is hypothesized to be the basis for the formation of the "place code" the hippocampus uses to encode spatial memories. In this chapter, we discuss models of how the hippocampal system may implement path integration. First, we explain the relationship of path integration to the hippocampal system, compare path integration to other navigation strategies, and discuss evidence for its use in creating the place cell code. Then, we examine path integration models for the creation and updating of a place cell map representation. We compare two major classes of such models and discuss experimental tests of their predictions to date. Finally, we briefly discuss the role of associations between place cell activity and sensory information in resetting the path integrator systems upon visits to familiar locations and how those associations can modify the structure of the hippocampal map with experience.

Forty years or more of animal behavioral and neurophysiological studies lead compellingly to the conclusion that hippocampus plays its crucial role in memory by creating and storing a "cognitive map" of the animal's world (O'Keefe and Nadel 1978). This "map" is stored in allocentric coordinates (coordinates centered on the environment, not moving with the animal). The map appears to be an internally generated, metric coordinate system that is at least partly hard-wired in early development. This coordinate system is anchored to the external world by appending to it information about sensory experiences (landmarks and/or events) and can also incorporate internally generated patterns (goals, drive states, retrieved memories, etc.), which occur at a given location. This chapter stems from the well-supported hypothesis that path integration, the process of adding up directions and

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distances as an animal moves, is the fundamental mechanism by which the internal coordinate is updated and is hence crucial in forming the hippocampal "place code" (McNaughton et al. 1996; O'Keefe 1976).

8.1 Path Integration by Rodents and Its Importance to the Hippocampal System

The continuous updating of position by monitoring translational and rotational information is called "path integration." The ability to path integrate is well documented in many species, including ants, and is well studied in rodents (Alyan 2010; Etienne 1992; e.g., Jander 1957; Mittelstaedt and Mittelstaedt 1980). The integration of self-motion information could potentially be used to calculate two different quantities: a "homing vector"—the direction and distance to travel to return to a start location—or the animal's current location on a map-like internal coordinate system (Fig. 8.1). Homing vector navigation has also been called "dead reckoning" (from "*ded*uced reckoning"), and map-based navigation has been called "piloting" (Etienne 1992). Homing vector updating would be useful for executing a fast return to a single location such as a nest, or another secure location, for example, when a predator is spotted during foraging, as the return path has already been computed. It could also potentially be used to return to the last rewarded location. It would not be practical, however, to update such a vector continually for all of the locations the animal may want to revisit in the environment. It is not clear if there is a well-defined brain system in mammals dedicated to homing vector updating, but the hippocampal system has been implicated in map-based navigation (O'Keefe and Nadel 1978).

It has been shown that not all forms of path integration require the hippocampus proper (Alyan and McNaughton 1999). For example, in one experiment, rats moved in an L-shaped trajectory to obtain a reward, but then were prevented from using the same track to return. To escape, the rats had to dig their way out of the reward location. Like controls, rats with hippocampal lesions chose a path directly toward the start location, even though they had never traveled this route before (Alyan and McNaughton 1999). It is possible that the success of hippocampal rats in such tasks signifies the use of homing vector updating using self-motion and vestibular information, to return to the last rewarded location. Another explanation, however, is that path integration is computed outside of the hippocampus and only integrated with landmark cues there (O'Keefe 1976; Touretzky and Redish 1996). When the animal is not removed from the environment prior to the navigation test, as in these experiments, path integration is sufficient to return to a previously rewarded location, using a completely novel path.

An intact hippocampus is required, however, for navigation in the Morris water maze task (Morris et al. 1982). This test involves a tank of opaque water, which contains a platform submerged just under the surface of the water (and thus not visible) in a specific location in the tank. The rat is placed in the tank and has to swim in search of the platform. Over several trials, during which the rat is placed in

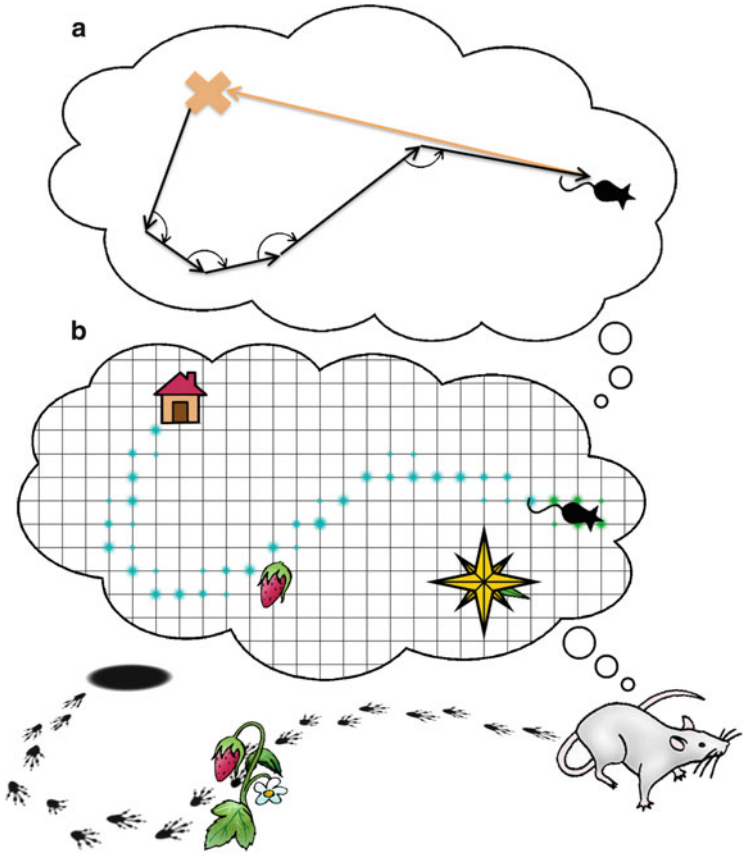

Fig. 8.1 Path integration in rodents. Rats can take a convoluted outward journey from "home" (e.g., footprints) and then return via a direct route, without vision or any other external cue (Mittelstaedt and Mittelstaedt 1980). To do this, they must keep track of changes in direction and distance traveled, which is called path integration or dead reckoning. Path integration refers to summing up distance vectors during travel (*black arrows*) and can be (and likely is) used for more than one purpose. (**a**) The rat may sum up travel vectors in order to keep track of a vector toward a single location, such as home (*orange arrow*). To do this, the animal does not need allocentric (world-centered) compass information, because the vector can be computed using only the egocentric changes in direction (*arcs*) and distance traveled. (**b**) Alternately, the rat may keep track of its position on a "cognitive map" (*green points*) and its allocentric heading direction (*green arrow on compass*) and store the locations of objects (e.g., home, *strawberry patch*) as coordinates on this map. Grid coordinates visited on this journey are marked with *blue spots*

the tank from different start locations, it learns the location of the platform and can eventually swim directly to it. Because the rat is removed from the tank in between trials and replaced in different locations, it has to use landmarks surrounding the maze to reorient itself, and self-motion cues are no longer sufficient. Variations of this procedure have been used to dissect the influence of different navigation methods on solving this task, and the brain regions required.

There are many different ways in which to solve the problem of localizing oneself in space. Given that navigation is highly important to the survival of mammals, it is likely that their brains contain multiple navigation systems. There are fairly simple methods of remembering how to approach a desired location: an animal can remember a cue that is present directly at the location, or follow a specific motor behavior plan, possibly including cue associations along the route (called "taxon systems" by O'Keefe and Nadel 1978). More complex navigation methods include triangulation based on distance and angle between two landmarks (O'Keefe 1990) and landmark vector navigation, in which the animal remembers a location based on the distance and compass (allocentric) direction away from a landmark (McNaughton et al. 1991).

Cue-based location finding is computationally the easiest method of navigation but also the most limited: it only works when a distinct cue reliably marks the desired location and only while that cue is visible from the start location. This method's simplicity, however, likely ensures that it is used whenever available to the animal. A more complex stimulus–response strategy can also be used to follow a learned path to the goal (e.g., when the rat is placed in the water maze in the same start location each time, an intact hippocampus is not required for rats to find the platform). Stimulus–response associations, such as these, require a functional dorsal striatum (McDonald and White 1994; Packard et al. 1989). In accordance with these behavioral data, the striatum has been shown to develop place-related responses when solving a navigation task (e.g., Wiener 1993). In addition to the striatum, the amygdala has been shown to participate in associations of stimuli to rewards or punishments (classical conditioning), which can also guide navigation by enhancing approach or avoidance behaviors. For example, the amygdala is required for conditioned cue preference which leads to more time spent in a location near the rewarded cue (McDonald and White 1993). When discrimination between nearby locations is required, however, neither the striatum nor the amygdala can guide correct navigation in the absence of the hippocampus (McDonald and White 1995). This is thought to be because the cues present at nearby locations overlap, and thus, no single cue can be used to discriminate those locations. A comparison of the relative distances to multiple cues, or a map, is required, and this necessitates the hippocampus (O'Keefe and Nadel 1978).

Navigation based on triangulation relies on the presence of two reliable landmarks visible from a goal location, the ability to see those two landmarks from a start location, and the ability to calculate the angles and distances to them. A model that would relate position to the location of all of the landmarks in the environment was proposed by O'Keefe (1990). In their comprehensive model of navigation, Touretzky and Redish (1996) included information about landmark relationships and suggested that this information would be used to reorient an animal when compass information is lost. Neural activity that would support the calculations required for triangulation in the absence of compass information has not yet been explicitly observed in the rat brain, and it is unclear where such a computation would take place. Candidates include the parietal cortex, which processes information about the locations of objects and movements in relation to

egocentric reference frames, and has been hypothesized to transform between various reference frames (reviewed in Andersen et al. 1997; modeled in Pouget and Sejnowski 1997), and retrosplenial and visual cortices, which aid in the resetting of compass information (reviewed in Taube 2007; also see Winter and Taube 2014). Collett et al. (1986) demonstrated that rodents can use the relationships between landmarks to orient themselves and locate a goal when necessary, but preferentially use bearings and distances from single landmarks, combining distance vectors from multiple landmarks as a "vote" to determine the most likely goal location. Navigation using compass information along with knowledge of the direction and distance of a single landmark to a goal is computationally fairly simple, requiring vector addition of the current distance and angle to the landmark and the goal's distance from that landmark (McNaughton et al. 1991). Rats are able to find a goal based on such information without an intact hippocampus (Pearce et al. 1998).

Map-based navigation is computationally the most complex navigational strategy but also the most flexible behaviorally (O'Keefe and Nadel 1978). Unlike the other methods, it does not require a priori knowledge of which locations should be remembered and which landmarks are reliable enough to use. An animal simply remembers all locations and all landmarks on a coordinate frame and can later calculate how to travel between any two locations. The storage of all landmark information requires a large memory capacity, but the information only increases linearly with each landmark, since for each, a simple coordinate on the map is required. The hippocampus is known to have a large number of quickly modifiable synapses, so is theoretically well suited for storing large amounts of information (e.g., Marr 1971). With the discovery of "grid cells" in one of the main areas that project to the hippocampus, the medial entorhinal cortex (MEC; Hafting et al. 2005; see Derdikman and Moser 2014), the existence of a coordinate map system in the rat brain was finally fully established. The current hypothesis is that the MEC provides the coordinate frame, and the hippocampus, through its connections from cortical structures, becomes coupled to information about the objects and events experienced in each location in such a manner that it can re-derive the correct coordinate from that information (e.g., McNaughton et al. 2006).

The existence of place and grid cells, however, does not mean that the complex problem of navigation in the brain is now fully understood. The hippocampal system is certainly not a perfect navigation device and there is in fact no evidence that actual computation of trajectories or routes takes place there. Information in addition to that carried by place cells is likely needed (McNaughton et al. 1995). Computational models of navigation often use vectors to represent distances between locations, or x and y coordinates to represent locations, which can easily be summed to calculate the distances and bearings between additional locations. Neither place cells nor grid cells, however, express this kind of information. Thus, it is not clear how, or if, place cells are used to compute trajectories between locations. Distances between nearby locations may be stored in the synaptic matrix between place cells or grid cells (Muller et al. 1996; Samsonovich and McNaughton 1997), but this does not result in the distances, and especially bearings, being easily

searchable (for a model of random search in this kind of synaptic matrix, see Hopfield 2010). The synapses between hippocampal and cortical neurons have been hypothesized to store information about which landmarks are visible from a location, and possibly even their bearing and distance from that location (e.g., Redish and Touretzky 1997). This kind of connectivity is useful for remembering which landmarks are present at the current location, or at which location a given landmark is located, but, again, calculation of distances or bearings between locations or landmarks is not easy with this storage method. From this complex "cognitive map," stored in the hippocampal complex, one can't simply draw a 2-D map of a city; this task stumped London taxi drivers (Maguire et al. 2006). The hippocampal place cell map is, instead, a very rich set of (directional) associations between objects and events (represented in cortex) and relative location (represented in hippocampus). What this map-like representation may accomplish is to facilitate recall items that "should" be present in the current and perhaps nearby locations, based on previous memory. So while it may serve as a natural novelty or incongruence detector, it does not appear to be a natural navigation calculator. O'Keefe and Nadel (1978) emphasized the hippocampus' role in detecting novelty and initiating exploration of novel environments. The use of the hippocampus for navigation is the subject of another chapter (Widloski and Fiete 2014). Here, we discuss possible mechanisms for the formation of the hippocampal place cell code.

It is likely that the hippocampus is connected to all of the other navigation systems and uses many types of information to generate place cell activity. Several models have been proposed for how place fields can be generated based on learning associations with sensory inputs related to landmarks (e.g., Burgess et al. 1994; O'Keefe 1991; Sharp 1991; Zipster 1985) or calculating distances to environmental boundaries (Hartley et al. 2000). Despite the success of these models in generating place fields solely from information about landmarks, experimental data shows fairly unambiguously that the integration of self-motion cues is crucial to at least the initial formation of place fields. Place cells fire in the location in which they form a place field during the very first traversal through that region ~75 % of the time (Frank et al. 2004, 76 %; Hill 1978, 78.5 %; data from Navratilova et al. 2012b, 73.5 %; Wilson and McNaughton 1993 (during first 10 min), 75 %). Long-term potentiation of synapses is not necessary for the formation of stable place fields, only for the recall of previously formed place fields in familiar environments (Barnes et al. 1997; Kentros et al. 1998). Both of these findings indicate that the initial formation of fields relies on pre-formed synaptic connections, and not on learning. Further, place field formation or stability does not require visible landmarks. Place fields form normally in the dark and remain stable when the lights are turned on while the rat is still in the environment (Markus et al. 1994; O'Keefe and Speakman 1987; Quirk et al. 1990). Finally, place cell firing completely distinguishes identical sensory environments that are located at different orientations (Fuhs et al. 2005) or in different rooms (Leutgeb et al. 2005) as well as the two halves of symmetrical environments (Sharp et al. 1990).

In contrast to sensory cues in novel environments, when self-motion cues are removed, the firing of place cells is affected dramatically. When a rat is restrained and thus prevented from movement, its place cells do not fire at all when the rat is placed inside the cell's firing field (Foster et al. 1989). When the rat is taught to move around a track by pushing a lever that moves the platform it is standing on, it is able to stop correctly at a rewarded location, but its place fields get dramatically bigger (Terrazas et al. 2005). In the latter study, the rat had no ambulatory motion signals, because it was not moving its limbs, but it did have optic flow and vestibular information to monitor movement. When vestibular information was removed as well (the lever moved the cues around the rat, but the rat remained stationary), the place fields got even bigger. Thus, it appears that the rat uses all three self-motion cues to integrate its movement in space and form place fields (McNaughton et al. 1996; Terrazas et al. 2005). If landmarks had been used to determine place field location in this experiment, the place fields would have remained in the same locations and of the same size as they had been when the rat was walking through the environment. Since path integration plays a major role in the determination of place cell firing, developing a model of how it is computed in the brain is crucial to understanding the hippocampal formation.

8.2 Attractor Models of Path Integration

One major class of path integration models has made use of neural attractor networks to compute position by integrating self-motion information. In this section, we will describe the principles behind this type of neural network, summarize some such models, and cite evidence for their manifestation in the hippocampus and medial entorhinal cortex.

An attractor is a stable state of a dynamical system. A system such as a neural network has potentially a large set of states—where state is defined as a list or vector of the relative activity of all the elements (neurons). An attractor is a specific state (or closed subset of states), toward which the system tends to evolve. Once the system reaches an attractor, it will stay within the attractor, either unchanging (a fixed attractor), or moving through a set of repeated states (cyclic attractor), or non-repeating but still bounded states (chaotic attractor). The classic analogy is a ball in a landscape. The ball randomly placed in the landscape will roll downhill, until it reaches a valley in which it will rest (fixed-point attractor). Neural networks with fixed points have been used to model memory systems based on Hebbian synaptic connectivity (e.g., Hopfield 1982). The point attractor is, for example, the pattern of neural activity that was previously learned by Hebbian synaptic modification. The set of initial states that will settle into a particular attractor is called the "basin of attraction." "Pattern completion" can be viewed as the process of a state within a basin of attraction evolving toward a point attractor. A neural network used for memory storage might have many attractor states, one for each stored memory. The boundaries between basins of attraction result in separate memories being recalled, determined by relative proximity (i.e., similarity) of the input state to

the stored memories (in other words, in which basin of attraction the input state exists). These dynamics of fixed-point attractors imply that memories will be recalled in an all-or-none fashion: any input pattern will recall one or another complete memory.

A "continuous" attractor network is another form of a fixed attractor system, in which the attractors are uniformly distributed over a manifold of N dimensions (where N is typically much lower than the number of neurons). For example, continuous attractors may span a line or a ring (Amit and Tsodyks 1991), a 2-D, or higher dimensional manifold (typically 1, 2, or 3 dimensions have been used in modeling spatial encoding systems). Any position on the manifold is equally stable, and the barriers between positions on the attractor manifold are low, enabling transitions between neighboring states under the influence of noise or by specific external inputs. This kind of attractor network can be used to perform the equivalent of summing up moment-to-moment changes in a variable over time, to indicate the variable's current value. Given an appropriate intermediate layer with asymmetries in connectivity to the attractor layer, external input to a continuous attractor can move activity over the manifold in a systematic fashion (McNaughton et al. 1991). In the absence of noise, when the input is removed, the network will stay in the last state. Another input can then move the network again. Thus, the network integrates its input and maintains the result in a stable activity state. Line attractors have been used to model integration of eye movements (reviewed in Robinson 1989), and ring attractors have been used to integrate head rotations (Skaggs et al. 1995; Zhang 1996).

The model of the ring attractor, which has been used to integrate and represent the one-dimensional variable of head direction, has been extended to design a torus-shaped continuous attractor, used to integrate directional velocity and thus to obtain a representation of two-dimensional relative position (Samsonovich and McNaughton 1997). In this model, cells were arranged in a 2-D sheet and recurrently connected to other cells as a decrementing (Gaussian) function of distance (see Fig. 8.2). This connectivity formed the continuous attractor for a 2-D manifold in neuronal state space, by making states in which multiple neighboring neurons are coactive relatively stable (because the neurons support the activity in each other) and any state in which non-neighboring neurons are coactive unstable. A stable state in this type of network is also called a "bump," based on the profile of the firing rates of the neurons when plotted on this sheet. Global inhibition limiting the total activity of the network allowed only a proportion of cells to be active simultaneously and ensured the formation with high probability of a single bump. Neurons themselves do not have to be arranged topographically in the brain, as long as the connections between them maintain such topography. Movement of the "bump" on the sheet of neurons was enacted by conjunctive, place-by-head direction cells. These neurons were posited to receive input from running speed-modulated head direction cells as well as certain place cells and project back to the place cell sheet, not to the same place cells but to a group offset in one direction. Thus, instead of stabilizing the bump, conjunctive neurons will move the bump in one direction: neurons that receive inputs from head direction cells active during

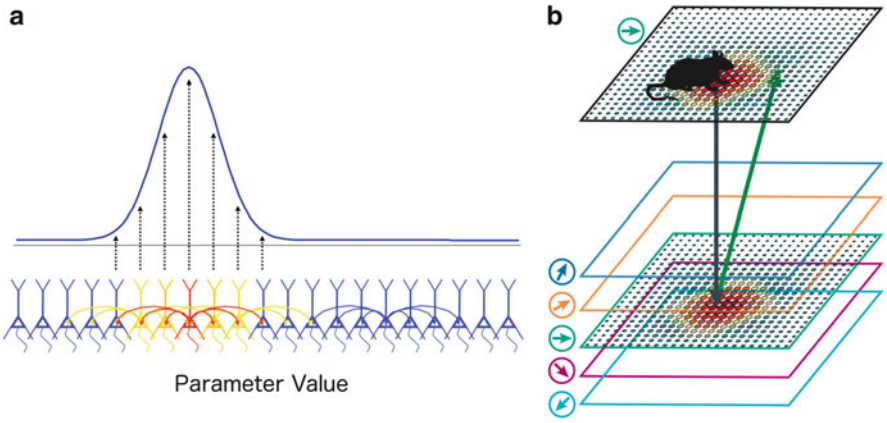

Fig. 8.2 "Continuous" attractor network. (**a**) A continuous attractor network is set up such that if neurons were arranged according to some parameter value, their connectivity would be to nearest neighbors. This connectivity, along with global inhibition, ensures that neurons representing similar parameter values are coactive, forming a "bump" of activity. (**b**) In a continuous attractor network for path integration, the parameter according to which neurons are arranged is the position in 2-D space that activates the neurons. Hidden layers, which contain neurons conjunctive for head direction and position, receive inputs from the attractor layer and project back to the layer with an offset, generating movement of the activity bump. Movement in the "eastward" direction is represented here, showing that the conjunctive layer that is activated by "east" head direction cells is active and projecting back to the attractor with an offset in the appropriate direction (Part B modified with permission from McNaughton et al. 2006)

"eastward" movement should move the bump in one direction; "westward" conjunctive neurons should move the bump in the opposite direction, and so on. In this way, conjunctive cells can transform information about speed and direction of movement of the animal in space into movement of the bump along the neural sheet. This formulation of the model predicted the existence of neurons conjunctive for place (or grid) and head direction tuning. Cells conjunctive for grid position and head direction were subsequently observed in the medial entorhinal cortex layers III–VI (Sargolini et al. 2006).

Samsonovich and McNaughton (1997) implemented their model as a closed, 2-D surface, a torus, in order to solve the problem of what would happen to the activity when the bump reached the boundary of the neural sheet encompassing the coordinate representation. The implication of the use of a toroidal attractor is that at some point the bump would move around the torus, returning to the same position in neural space, thus creating regularly repeating place fields. It was assumed that the reason this was not observed in hippocampus proper (i.e., CA3 or CA1) was either that the torus is large enough to represent large environments (experiments were actually performed to look for repetitions as rats moved along a long corridor) or that it was located in another brain region. The authors were actually agnostic to where in the system path integration was implemented and suggested the entorhinal cortex as one possibility:

In principle, the P–I path integrator loop of the MPI model could be based on other structures, such as presubiculum and parasubiculum or entorhinal cortex. One difficulty with this interpretation is that these structures appear not to express multiple charts (e.g. Quirk et al. 1992; Sharp 1997). The possibility remains, however, that dentate gyrus and CA3 may select an active chart that is expressed in these structures and in CA1, whereas a single, "universal" chart is implemented in the subicular complex and entorhinal cortex.

Redish and Touretzky (1997) similarly suggested that the path integrator might be based on "a loop including the hippocampus, the subiculum, the parasubiculum, and the superior layers of the entorhinal cortex," although they did not propose an explicit neural mechanism for path integration. The discovery of cells with regularly repeating place fields in the medial entorhinal cortex (Fyhn et al. 2004; Hafting et al. 2005) is consistent with the hypothesized toroidal synaptic matrix. If this is the case, however, biology seems to have implemented the torus as a wrapped-around rhomboidal sheet (McNaughton et al. 2006) or, equivalently, a square sheet wrapped with a 50 % twist in one dimension (Guanella et al. 2007), instead of the rectangle implemented by Samsonovich and McNaughton (1997).

An alternate solution to the problem of distortions at edges of a continuous attractor plane was provided by Fuhs and Touretzky (2006). They modeled a path integrator with grid firing properties by using a sheet of cells with center surround (Mexican hat)-type connectivity, which faded at the edges of the sheet. Each neuron connects to its neighbors forming a pattern of concentric circles of excitation and inhibition. Connections to neurons at the edges of the sheet are reduced, so that activity smoothly fades off. In addition to the symmetric connectivity, there is asymmetric connectivity, with adjacent neurons producing an offset in different directions, such that the asymmetry cancels out. Movement is generated by velocity and head direction input acting on neurons with specific offsets of asymmetric connections. Conjunctive activity becomes obscured in this model, because even though neurons are sensitive to head direction inputs, the attractor properties of the network prevent this response from manifesting in the firing rates. Multiple bumps form on the neural sheet, and because of the summing of the concentric circles of excitation and inhibition, these bumps arrange themselves in a hexagonal lattice (the tightest packing density of circles). However, Burak and Fiete (2006) pointed out that the network, as described, would not accurately path integrate because it produced a nonlinear response to velocity inputs, and the spatial pattern of bumps could rotate in addition to translating. Burak and Fiete (2009) conducted a thorough analysis of the requirements of a continuous attractor network that was capable of accurate path integration within the range of speeds at which rats travel. They found that both toroidal networks and networks with velocity inputs fading at the edges are capable of path integration, but networks without wrapped edges require more neurons and more restricted tuning to function properly and may rotate with noise.

A further complication to the realization of the continuous attractor model in hippocampus proper was the experimental finding that place cells often have fields in multiple environments, which appear to be randomly assigned, independently of the locations of fields of other cells. For example, when two place cells are active at

nearby locations in one environment, they are not likely to be active in nearby locations in another environment. This is a problem for any model in which hippocampal connectivity is assumed to be pre-formed, before any experience in the environment. Place fields generally appear immediately in a novel environment, and thus, these findings have to be accounted for. Samsonovich and McNaughton (1997) addressed this by showing that, in principle, multiple toroidal attractors, or "charts," can be embedded in the same synaptic matrix. Each chart is created by a 2-D random shuffle of cells, followed by creation of local (e.g., Gaussian) connectivity. When a position in a particular chart was activated, the recurrent connectivity of place cells on that chart would stabilize the bump in that chart, and the connections to neighbors on another chart would be randomly distributed and thus too diffuse to move the bump. Given sufficient connectivity, a large number of charts could coexist and be recalled without conflict between charts (see Battaglia and Treves 1998 for calculations on the capacity of such networks). This model was able to reproduce many known properties of place cells.

In the toroidal attractor model, the spatial scale of the place cell representation is set by the speed at which the bump moves in relation to movement of the animal in space. This will determine the apparent size of place fields. Field size varies along the dorsoventral (septal-temporal) axis of the hippocampus (Jung et al. 1994; Maurer et al. 2005), as well as medial entorhinal cortex (Brun et al. 2008). Thus, it was proposed that the running speed signal that moves the bump along the attractor manifold is reduced at more ventral locations in the hippocampal formation. Evidence for this is that theta power and neuronal firing rate increase much more steeply with running speed in dorsal hippocampus (Maurer et al. 2005). In addition, as described in more detail below, elimination of some self-motion cues causes a simultaneous expansion of place fields and a reduction of the slopes of the running speed versus firing rate and theta power functions (Terrazas et al. 2005).

Finally, a major component of the attractor-based path integration model is the resetting of position information by landmarks. Any integration system will accumulate errors over time and thus become unreliable. Therefore, an external input from environmental cues is needed to reset the network. McNaughton et al. (1996, e.g., 1991) hypothesized that during exploration, Hebbian learning between head direction and place cells and neurons responsive to stimuli experienced at particular locations would occur. The strength of the connections to particular stimuli would depend on how reliably those stimuli predicted the position of the animal. After some learning, the position of the bump could be corrected (moved along the attractor) or completely reset (caused to "jump") by these stimuli, depending on the level of mismatch of currently active cells and impinging stimuli. Such reset by external inputs was clearly demonstrated in experiments in which animals traversed a linear track from an open-ended start box containing food reward to a goal location about 2 m away. In some trials, the start box was shifted along the track while the animal was at the distant goal. On reentering the start box, the population activity reset such that cells normally associated with the box began to fire in the new box location. More importantly, when the animals left the box, cells continued to fire in relation to the animal's distance from the box for some distance along the

track and then shifted coherently to firing in the laboratory reference frame. In darkness, the coherent shift was typically delayed until the animal reached the goal site at the far end of the track (Gothard et al. 1996, 2001).

Attractor dynamics in the brain can be assessed by calculating how correlations of the activity of the whole population of recorded neurons change as the input is smoothly varied, for example, as the rat moves in space. In this case, the activity of each neuron can be calculated for each location bin, and the activity of all neurons in a particular bin combined in a "population vector." A gradual change in population vector correlation indicates gradual transitions, such as movement along a continuous attractor, or a lack of attractor dynamics. An abrupt change from high correlation to low correlation indicates a precipitous shift in neural activity, such as a jump between two discontinuous attractor states. In the above experiment, population vector correlations showed that both in light and dark conditions, smooth transitions between successive place cell activities occurred as the rat moved between positions when the track was in its initial configuration, but abrupt transitions between place cell firing from a laboratory reference frame to the box reference frame occurred as the rat approached the relocated box. Similarly, on leaving the box, cells fired in the box reference frame for some distance along the track before shifting coherently to the laboratory frame. Both CA1 and dentate gyrus place cells exhibited this abrupt transition. Since neither of these regions contain abundant recurrent excitatory connections, it appears that attractor dynamics in these two regions are inherited either from CA3 (there are a few feedback connections to the dentate) or more likely from the entorhinal inputs to the hippocampus (Gothard et al. 2001). Abrupt transitions between two separate activity patterns such as this have also been observed during experience of sensory cues that represent a gradual morph between two well-known, previously separate environments (Colgin et al. 2010; Wills et al. 2005). Similar transitions between alternate representations were shown to occur on a very fast time scale in a "teleportation" experiment, in which the cues were electronically switched (Jezek et al. 2011). Of particular interest in the interpretation of such phenomena is the study by Colgin et al. (2010), which demonstrated that, during smooth morphing between two environmental shapes, attractor-like abrupt transitions between place cell population firing patterns occurred only if the shapes had been learned in two distinct locations and the animal had had the opportunity to walk between them. In this case, the firing fields in the two end points were uncorrelated (i.e., both magnitude and position of firing changed unpredictably and independently across the population). This is called global remapping, which is the activation of a statistically independent set of place cells. When the rats were initially trained in the two box shapes at a single location, the place cells active in each shape were very similar; they fired in the same location in both shapes, but they expressed different firing rates in each shape. This is called rate remapping (Leutgeb et al. 2005; described in detail by Leutgeb and Leutgeb 2014). Morphing between the two shapes in this case was associated with continuous, smooth shifts in cell firing rates with little change in the firing location of individual cells. These results

imply that the attractor dynamics reflect changes in spatial location and not the completion of patterns representing the environmental input per se.

One complication in the interpretation of attractor dynamics in the hippocampal formation is the phenomenon of phase precession. The place field of a place cell is a derived construct based on averaging multiple traversals of the space. On a single traversal of the field, the firing is not a smoothly rate-modulated Poisson process, but consists of a series of brief bursts of spikes, with an inter-burst frequency slightly higher than the theta oscillation. This results in theta phase precession, such that, as the rat enters a place field, the spikes occur at the trough of the theta oscillation recorded extracellularly in the CA cell layer and then shift earlier and earlier in phase upon progression through the field, until the spikes have moved through 360°˜ (but never more), when the rat exits the field (O'Keefe and Recce 1993). Phase precession has also been observed in MEC layer II grid cells (Hafting et al. 2008). This precession results in different neurons being active at different times through the theta cycle, which means that the network doesn't settle on a single stable state. Rather, as the overall firing intensity waxes and wanes during the theta cycle, the network moves through a short series of states, which comprise the average (position weighted) place fields on either side of the average field which the animal is currently centered on. At the beginning of the theta cycle, there is weak firing from cells with fields centered behind the rat, followed by intense firing from the cells with fields centered on the rat and ending with weak firing from the cells with fields ahead of the rat. At the end of each theta cycle, there is a clear discontinuity (or "reset") in the order in which neurons fire (Tsodyks et al. 1996). This movement through states also cannot be described as cyclical, because as the rat moves forward in space, the sequence shifts forward in terms of mean field expression. So, although the attractor dynamics concept gives some insight into the network dynamics (e.g., they may predict the synaptic connectivity of the path integration network), it is clear that the full functioning of the network in vivo is more complex.

An explanation for phase precession, which is compatible with attractor-like synaptic connectivity, was proposed by Tsodyks et al. (1996) and by Jensen and Lisman (1996; see also Wallenstein and Hasselmo 1997). The foundation of these models is Hebb's (1949) idea of the "phase sequence," a series of cell assemblies linked together by asymmetric connections that result from repeated activation of a perceptual sequence, leading to Hebbian strengthening of connections in the forward direction. In this model, neurons responded at different locations along a one-dimensional track, as a consequence of differential synaptic inputs from information about external cues. During traversal of the track, cells responding earlier in the sequence activated cells responding later in the sequence. This was hypothesized to result from asymmetric LTP, such as might occur after repeated unidirectional traversals of the track. Phase precession was generated by gating the external input to activate place cells only at the beginning of each theta cycle. After the external input was gated off, the asymmetric intrinsic connections activated neurons coupled to locations ahead of the animal. This resulted in a "pre-play" or "look-ahead" of a short sequence of locations. At the end of each theta cycle,

accumulating inhibition interrupted this process, by which time the moving rat had advanced further in space, so that the next cycle began a little further into the sequence, triggered by the new external inputs.

The asymmetric connection model, as proposed, however, cannot account for omnidirectional phase precession (Burgess et al. 1994; Skaggs et al. 1996). Also, phase precession occurs during the first traversal of a field in any direction, and thus, the connectivity resulting in phase precession cannot be dependent on learning. Another problem with this model is that it is known that place fields can be updated solely by path integration (see above and McNaughton et al. 1996) which means that the reset mechanism at the beginning of each theta cycle cannot rely on external cues.

Navratilova et al. (2012a) developed a model for a possible mechanism of phase precession in grid cells. They applied the Tsodyks et al. (1996) framework to a toroidal attractor model of grid cells. Instead of asymmetry in the place cell connectivity, as required by the Tsodyks et al. model, the toroidal attractor model of grid cells had conjunctive (grid-by-head direction) cells providing asymmetric driving of movement of the "bump" of neural activity in all possible directions, depending on the rat's heading. Thus, precession could be observed in all possible directions of movement, as long as conjunctive cells directed the network "look-ahead," and a reset of the bump to a state consistent with the actual position of the rat occurred every cycle. The reset of the bump every cycle was not implemented by an external input but instead was controlled by intrinsic dynamics of the network. This was possible because, in the toroidal attractor, the relative distance between the firing nodes of different cells (spatial phase) is predetermined by their connectivity. The relative positions represented by MEC grid cells appear in fact to be predetermined, because each pair of grid cells with common spatial scale has grid nodes which are the same distance apart and have the same orientation (Fyhn et al. 2007).

In this phase precession model, the spatial scale of grids is set not only by the running speed inputs that set the speed of the bump during the "look-ahead" (implemented by changes in the amplitude of the firing rates of the head direction cells) but also by the size of the "jump-back" of the bump that occurs every theta cycle. This jump-back is caused by the H-current-mediated after-depolarization that occurs in the grid cells, as well as long-term synaptic currents (see Fig. 8.3a). The magnitude of the jump-back depends on the time constants and amplitudes of these currents. The time constant of the H-current (Giocomo and Hasselmo 2008) and the after-hyperpolarization (Navratilova et al. 2012a) has been shown to increase in more ventrally located stellate cells, and thus, this variation can account for the dorsoventral increase in grid spacing (Navratilova et al. 2012a) (Fig. 8.3).

In this section, we have described attractor networks and their use in models of path integration. We reviewed some evidence of attractor network dynamics in the hippocampus, concluding that this model can account for some aspects of hippocampal and entorhinal dynamics and that the most likely location of the continuous attractor for path integration, if it exists, is the medial entorhinal cortex. However, attractor dynamics alone do not describe the fine temporal firing patterns of hippocampal or entorhinal neurons. We summarized a model that accounts for

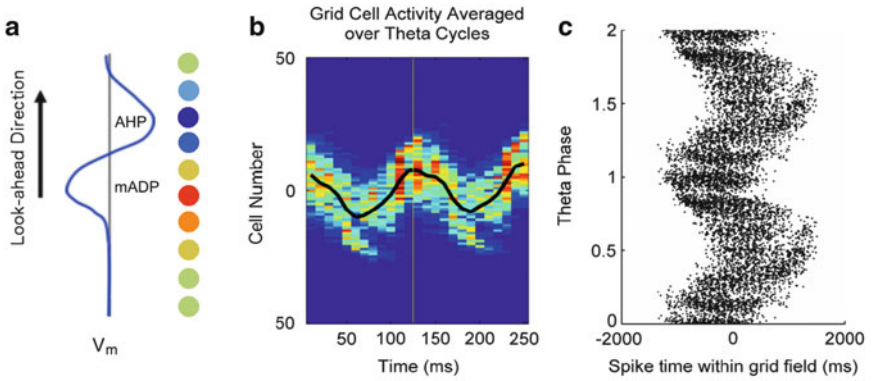

Fig. 8.3 Look-ahead and phase precession generated by Navratilova et al. (2012a) model. In this model, the same type of network that can use self-motion and head direction information as an input to update position and generate a grid code was used to generate "look-ahead" activity such as is observed during each theta cycle in MEC grid cells. (**a**) At the end of each theta cycle, conjunctive cell activity waned, and the membrane potential of grid cells was dominated by after-depolarization currents (related to the H-current) and long-lasting synaptic currents. These currents initiated a "jump-back" by activating not the neurons active in the immediate past (depicted in *blue*, experiencing after-hyperpolarization) but neurons that had been active ~100 ms before, in the previous theta cycle (depicted in *red*). (**b**) Following the jump-back, another advance of the bump, activating neurons representing positions ahead of the rat, is initiated. The look-ahead can be seen in the activity (averaged over several trials) of many model grid cells arranged in sequence according to the positions that they represent (*y*-axis) shown over two theta cycles. (**c**) This repeated "look-ahead" caused each cell to be active during multiple theta cycles, progressively earlier in the cycle, which is the phenomenon of phase precession (Parts **b** and **c** modified with permission from Navratilova et al. 2012a)

the temporal firing patterns of hippocampal neurons within a framework of synaptic connectivity resembling a toroidal continuous attractor network. An alternate model of path integration, the oscillatory interference model, can also account for many properties of medial entorhinal neurons, but originates from completely different mechanisms and produces some very different predictions. In the following section, we will compare the predictions of these two classes of model.

8.3 Comparison of Attractor-Based and Oscillatory Interference Models

When they first discovered phase precession, O'Keefe and Recce (1993) realized that this phenomenon could be the result of the interference of two waves. They proposed that hippocampal neurons intrinsically oscillate at a frequency slightly greater than theta and receive theta input. The summation of the two oscillations causes the neuron to fire within an envelope that represents the place field and on earlier and earlier phases of the slower oscillation (extracellular theta) as the rat moves through the field. If the frequency of at least one of these two oscillations is

modulated by the speed of the rat, then the firing rate and phase will depend on the location of the rat, rather than on time. Of course, the simple summation of two oscillations results in a repetition of envelopes at a frequency proportional to the difference between the two oscillations, suggesting that, unless the input to place cells is already place specific, place fields should repeat in a regular pattern. The discovery of the regularly repeating place fields of grid cells (Hafting et al. 2005) regenerated interest in this type of model. O'Keefe and Burgess (2005) and Burgess et al. (2007) proposed a model by which the product of three or more oscillators could cause the spatial firing pattern of grid cells in the MEC. They propose that the soma of MEC neurons oscillates at theta frequency and the dendrites oscillate at a frequency dependent on the speed of the rat in a particular direction. If there are at least two dendrites, all tuned to directions 60 or 120° apart, then the sum (or product) of the three (or more) oscillations creates spatial firing in a hexagonal pattern. Like the attractor models, this class of model integrates the rat's directional running speed, but by a very different mechanism, one in which (in its original formulation) grid cells fire completely independently of one another. The oscillatory models take advantage of the fact that an oscillator's phase is the time integral of its frequency. Thus, if the frequency is velocity modulated, then the phase will depend on position.

Both classes of path integration models, the toroidal attractor network and the oscillatory interference model, explained regularly repeating fields, but beyond that, the predictions of the two models are quite different. These predictions are summarized in Table 8.1 and described in detail below. A fundamental difference that leads to many of the differences in predictions is that one type of model relies on specific network connectivity to achieve path integration and the other relies on single cell dynamics such as membrane potential oscillations. The attractor network style model predicted the existence of grid-by-head direction conjunctive cells and has several other requirements related to the connectivity patterns of the attractor network. The running speed signal required for path integration is carried by an amplitude modulation of firing rates in this model. In the oscillatory interference model, on the other hand, the running speed of the rat has to modulate the frequency of one or more oscillations, providing very different predictions for cell classes. This model predicts that theta frequency oscillations are crucial for grid cell firing and has specific requirements for the directional and velocity tuning of these oscillations, as well as a high sensitivity to noise in the oscillations. In addition, two experimental tests of the membrane potential dynamics during passes through grid fields have been conducted to directly compare the two classes of model.

As discussed above, evidence of attractor dynamics can be observed in the hippocampus, although this may reflect dynamics inherited from upstream. Medial entorhinal grid cells show a random (but coherent) phase shift under the same conditions that place cells show global remapping (a change in physical location), but they do not show rate remapping in response to changes in sensory cues (discussed by Leutgeb and Leutgeb, this volume) as place cells do (Fyhn et al. 2007). These findings are consistent with the hypothesis that continuous attractor-like connectivity may exist in MEC. A criticism of the attractor model

Table 8.1 Predictions of continuous attractor and oscillatory interference models

Prediction	CANN	OIM	Experimental verification
Regularly repeating fields	✚	✚	Hafting et al. (2005)
Conjunctive cells	✚	O	Sargolini et al. (2006)
Attractor dynamics for space but not for cues	✚	O	Colgin et al. (2010)
Recurring connectivity in grid modules	✚	O	Couey et al. (2013)
Grid cells maintain their spatial relationships in different environments	✚	O	Fyhn et al. (2007)
Cells with adjacent fields should fire in precise order relative to each other	✚	O	Foster and Wilson (2007), Itskov et al. (2008)—in hippocampus
Grid scale quantization	✚	O	Barry et al. (2007), Stensola et al. (2012)
Velocity signal gain changes spatial scale	✚	✚	Terrazas et al. (2005)—in hippocampus
Oscillators are direction and velocity modulated	O	✚	Welday et al. (2011)
Theta rhythm necessary for grid field generation	O	✚	Koenig et al. (2011), Brandon et al. (2011), but not in bats, Yartsev et al. (2011)
Oscillators are tuned to directions exactly 60° apart	O	✚	Doeller et al. (2010), but not Welday et al. (2011)
Phase procession and linear relationship between phase and location	O	✚	No
Membrane potential ramping in fields	✚	O	Domnisoru et al. (2013), Schmidt-Hieber and Häusser (2013)

✚ predicts
O does not predict or explain

for path integration is that it requires a specific configuration of recurrent connectivity within the grid cell network. A model for how the toroidal 2-D continuous attractor network could be self-organized in early development was proposed by McNaughton et al. (2006); however, no model has yet been proposed for how the wiring between this layer and the conjunctive layer might be self-organized. Recurrent connectivity is more prominent in layer III of the entorhinal cortex (Dhillon and Jones 2000) but has also been observed between layer II cells (Kumar et al. 2007). Recent evidence indicates that stellate cells in layer II are interconnected almost exclusively through inhibitory interneurons (Couey et al. 2013). The apparent failure to find recurrent excitatory connectivity in layer II is a problem for the model as originally stated, but it should be kept in mind that the required overall connectivity is very sparse. Navratilova et al. (2012a) posited grid-cell-grid-cell connectivity on the order of only 3 %, which might be quite hard to detect, particularly in sliced tissue. Additionally, network architectures that differ from those initially proposed could also construct a "continuous" attractor network and result in path integration and similar grid cell properties. For example, the

majority of the recurrent connectivity could occur between grid cells and layer III conjunctive cells, or inhibitory connections could form the attractor (Couey et al. 2013). Couey et al. (2013) and Bonnevie et al. (2013) constructed models similar to Burak and Fiete (2009) with the exception that all connectivity was all-or-none and inhibitory and there was a uniform excitatory drive, assumed to be from the hippocampus. These models fit well with the data that the stellate cells in layer II of MEC are recurrently connected through inhibitory interneurons (Couey et al. 2013) and that in the absence of excitatory drive from the hippocampus, grid cells lose their grid patterns and begin to fire in response to head direction (Bonnevie et al. 2013). In the latter experiment, theta modulation of grid cells remained intact, even when grid patterns had disappeared, suggesting that oscillation generation mechanisms were still intact (Bonnevie et al. 2013).

Unlike the oscillatory interference models, attractor models predict that grid (and place) cells are coupled to one another and thus should fire in precise order relative to each other even given synaptic noise. Significant spike timing relationships between place cells exist, and the shuffling of spikes within the observed noise disrupts these relationships (Foster and Wilson 2007; Itskov et al. 2008). Additionally, the spatial relationships between grid cells with the same spacing are maintained during remapping between different environments (Fyhn et al. 2007), as predicted by the toroidal attractor model but not the oscillatory interference model. The attractor model also predicts that the spacing between grid fields of all the cells within an attractor module should be the same (even if the time constants of the currents in individual cells within the module differ; Navratilova et al. 2012a), and thus as grid spacing increases along the dorsoventral axis of the MEC, it should do so in abrupt jumps as one moves between attractor modules. Experiments have confirmed both that grid cells recorded on the same tetrode share the same spacing and orientation of their grids, suggesting that they belong to the same module (Fyhn et al. 2007), and that grid scale is quantized (Barry et al. 2007; Stensola et al. 2012) suggesting that different modules serve to represent space at different scales.

The velocity signal that is integrated in the attractor network model may be carried by amplitude modulation of the firing rates of head direction cells that input into the network (Navratilova et al. 2012a; Samsonovich and McNaughton 1997). Sargolini et al. (2006) showed that the firing rates of head direction, conjunctive, as well as grid cells are all modulated by the running speed of the rat. This velocity signal appears to be derived from ambulatory, optic flow, as well as vestibular signals (Terrazas et al. 2005). The removal of one or more of those signals reduces the input to the path integrator and causes an increase in place field size (Terrazas et al. 2005). This increase in field size is not accompanied by an increase in place field overlap, nor do the original fields expand about their centers. Rather, the distances between field centers increases. Thus, the scale at which space is represented in the whole system expands; each individual place field does not do so independently. This results in a change in the mapping between place fields and physical locations, which argues strongly against the primacy of external cues as fundamental determinants of where cells fire.

Initial versions of the oscillatory interference models, in contrast, involved the summation of oscillations within single independent neurons. It was shown, however, that maintaining oscillations of different frequencies in electrically connected dendrites is not biophysically plausible (Remme et al. 2009). Burgess et al. (2007) suggested that the role delegated to dendrites on the same neuron could instead be played by separate neurons. If there were only one oscillator tuned to velocity in one head direction interfering with an externally imposed "reference" theta signal, the neuron would fire in bands throughout the environment. Convincing evidence of such neurons has not been shown (but see Krupic et al. 2012). Blair et al. (2007) proposed instead that each *oscillator* exists as a single neuron. This neuron would have to fire over the entire environment at a frequency in the theta range, but the exact frequency would have to vary not only with velocity but also with the direction of motion. Welday et al. (2011) looked for such modulation in the frequency of "theta cells." Theta cells are putative interneurons that fire at high rates, bursting at the theta frequency, and do not typically have place fields. Three such oscillator neurons whose oscillation frequencies are modulated each in a different direction of motion (60 or 120° apart) will summate to create hexagonally spaced firing fields. Welday et al. (2011) discovered that the frequency of theta cells in the medial septum, anterior thalamus, as well as hippocampus is in fact modulated by heading direction in the way required by the models. The "theta cells" used in this analysis were extracellularly recorded neurons from those three brain regions that fired at high rates (>10 Hz at all times), and showed no spatial tuning (<0.1 spatial information bits per spike). A high proportion of all of such cells showed significant directional frequency tuning during at least one recording session (19 out of 21 cells, most of which were recorded for multiple sessions; 31 of 45 recording sessions met the criterion). It remains to be determined which specific types of cells show this kind of tuning. The authors show that the summation of spike trains similar to those generated by these theta cells could create the firing fields not only of grid cells but also of place and border cells.

A criticism of the early oscillatory interference models involved their sensitivity to noise. In order for the phases of the oscillations to correctly interfere with one another, they had to be pure sine waves of a single frequency and include no noise (Welinder et al. 2008). Such a pure signal is not likely to exist in the brain. In contrast, the benefit of a positive feedback integrator such as a continuous attractor is that it averages over high-frequency errors in the input signal (Robinson 1989). Initial solutions to this problem involved frequent resetting of the oscillator phases by connectivity either with place cells or other grid cells, via a connectivity resembling the toroidal attractor model (Burgess et al. 2007). This resetting was never modeled, but would likely have had to occur so often that the importance of the oscillators would be under question. Recent oscillatory interference models have solved the noise problem by enacting an integration step in the generation of the oscillation (Welday et al. 2011; Zilli and Hasselmo 2010). Welday et al. (2011) model the oscillators as a ring attractor identical to the one for head angular velocity integration (Skaggs et al. 1995; Zhang 1996), but with velocity in a particular heading direction providing the input, and a much faster, unidirectional movement

around the ring. The recurrent connectivity of the ring ensures that even though the spikes of a single neuron can be noisy, that noise will not disrupt the phase of the oscillation and the next cycle will recur on time. Thus, this model also suggests that path integration occurs through attractors, but in each direction separately. The authors hypothesize these ring attractors exist in the subcortical pathways (medial septum and anterior thalamus: in a pathway parallel to the head direction system; Vann and Aggleton 2004) and then the phase code for position in each direction is combined into a firing rate code in the MEC and hippocampus (Welday et al. 2011).

In order for a grid cell to have hexagonal grids formed from velocity-tuned oscillator inputs (e.g., band cells or Welday et al.'s theta cells), it needs to receive inputs from at least three oscillators, tuned to directions exactly 60 (or 120) degrees apart. Other architectures have been proposed (Burgess et al. 2007; Burgess 2008), but none of them can relax this requirement for precise tuning orientation, because other tunings result in different geometries of the grid. One solution to this requirement is if only band cells (or theta cells) tuned to directions 60° apart exist. In fact, head direction cells have been shown to be tuned only to directions that align with the six axes of the grid (Doeller et al. 2010), so it is possible that theta cells are too. Welday et al. (2011) show theta cells tuned to varied orientations, not necessarily 60° apart, however. They suggest that grid cells receive inputs from theta cells tuned to directions that are 120° apart, with other types of spatial firing resulting from inputs tuned to the other angles (e.g., single place fields result from multiple inputs tuned to various directions).

One problem with the oscillatory interference model has not been resolved, however. This model, though initially designed to account for phase precession, does not actually show omnidirectional phase precession in grid cells. Some ways of summing up the oscillators result in phase locking to the reference theta rhythm. Other architectures result in phase precession in one running direction (as the oscillators' frequencies are faster than the reference theta frequency in that direction), but phase *procession* in the other direction (because the oscillators' frequencies would have to be slower than the reference frequency in that direction; Burgess 2008; Welday et al. 2011). Burgess' (2008) solution to this problem, that six oscillators would be used to for the generation of each grid field, and all of them would be prevented from firing at slower than the reference theta frequency, adds complication to the model. Many conjunctive (grid-by-head direction) cells show theta phase locking, but most grid cells show phase precession, in both running directions on a track (Hafting et al. 2008). Place cells precess just as well in two-dimensional environments as on a one-dimensional track (Burgess et al. 1994; Huxter et al. 2008; Skaggs et al. 1996). An additional problem with a purely oscillator interference model is that the "look-ahead" observed in the activity of the grid and place cell population within a theta cycle (as well as the phase precession pattern of a single cell) would be strictly linear. In the attractor connectivity models, if the progression through states within a theta cycle is not linear (e.g., the look-ahead may get faster near the end of the theta cycle), then the relationship between phase and location is also not linear (phase precession progresses slower upon entry into the field than during exit from the field). In

experimental data, the look-ahead accelerates over the duration of a theta cycle (Maurer et al. 2012; Skaggs et al. 1996), as it did in Navratilova et al.'s (2012a) attractor-based model.

The oscillatory interference models predict that the theta signal is crucial to the formation of grid fields. It has been shown that in rats, removal of the theta signal by inactivating the septum does in fact degrade spatial firing by grid cells but not by head direction cells or place cells (Brandon et al. 2011; Koenig et al. 2011). However, theta has been shown to be very weak during locomotion in bats, even though grid cell firing resembles that in the rat (Yartsev et al. 2011; see Las and Ulanovsky 2014).

Stellate cells in rats also show intrinsic oscillations at theta frequency (Giocomo et al. 2007) that are due to H-currents (Giocomo and Hasselmo 2008) and create a strong resonance in the cell at a particular frequency determined by the time constant of the H-current. However, in vivo, the cells receive a lot of synaptic inputs that influence their ability to continuously oscillate (Fernandez and White 2008). The properties conferred on stellate cells by the H-current have been shown to be useful in attractor-like networks to generate phase precession (Navratilova et al. 2012a). In vivo recordings of grid cells are required to ascertain if the neurons continuously oscillate, resulting in interference with the extracellular theta signal or a synaptic input, or if their place specificity is generated by inputs, which unmask the membrane's resonance and cause the neuron to spike at a specific frequency. Two such experiments have been conducted recently, and both found that intracellular membrane potential of grid cells does not oscillate outside of grid fields and that entry into and exit from grid fields are accompanied by a ramping current such as that predicted by attractor models and not oscillator models (Domnisoru et al. 2013; Schmidt-Hieber and Häusser 2013). This slower ramping current is responsible for the spiking of grid cells, not the amplitude of theta oscillations (Domnisoru et al. 2013; Schmidt-Hieber and Häusser 2013). The intracellular theta oscillations determine spike timing (at the peaks of intracellular theta) and result in phase precession with respect to the extracellular theta oscillation (Domnisoru et al. 2013; Schmidt-Hieber and Häusser 2013). These findings are consistent with a continuous attractor model for the generation of place-specific grid cell firing and additional voltage-coupled oscillator inputs (Schmidt-Hieber and Häusser 2013) or intracellular currents (Navratilova et al. 2012a) for the generation of theta phase precession.

For these reasons, it is likely that an attractor-like connectivity of the grid cell network influences the activity of grid and place cells, possibly in addition to inputs from "theta cells." Each model provided a prediction that the other did not: the toroidal attractor model predicted the existence of neurons conjunctive for grid location and head direction, as well as grid scale quantization, and the oscillator model predicted the existence of theta cells with frequency modulated by running direction. Perhaps both an attractor network and theta cells provide the input that creates the envelope of grid (and possibly place) cell activity during navigation, and conjunctive cells provide the input that generates the look-ahead and influences grid and place cell activity during non-theta states, such as sharp waves.

8.4 The Influence of Sensory and Other Input

Landmarks and sensory cues are important in determining place cell firing in familiar environments. In path integration models, sensory cues can be used to reset the path integrator coordinates to correct for random drift or when an animal is reintroduced into a familiar environment or gets lost. Demonstrations of this "reset" caused by changes in sensory stimuli in experimental studies have already been described. For example, in Gothard et al. (1996), when the rat encountered the goal box moved to a new location, its place cell representation abruptly shifted from the coordinates of its location in the room reference frame to coordinates referenced to the box. In addition, other conditions than those modeled in most path integration models cause the rat's place cell network to rely on sensory cues, including conditions in which path integration and sensory cues are mismatched and when familiar environments are distorted in size (Bures et al. 1997; Fuhs et al. 2005; Muller and Kubie 1987). Bures and colleagues (1997; Zinyuk et al. 2000) created a mismatch between sensory cues and rats' own integration of self-motion (idiothetic cues) by testing their navigation ability and place cell firing on a rotating table. They discovered that place cell firing can be induced (by different training protocols) to follow either set of cues, but it is more likely to follow idiothetic cues. Further work showed that simultaneously recorded CA1 place cells follow one or the other set of cues at a given time, but can switch back and forth between the two reference frames, when both are important to the task being performed (Kelemen and Fenton 2010). The firing fields of grid cells were also shown to scale with changes in scale of the environment (Barry et al. 2007). However, these changes in scale were experience dependent, in that the rescaling occurred in the novel configuration of the environment, and not in the (now familiar) configuration that had been experienced first, regardless of whether the square or rectangle was experienced first. Additionally, the grids rescaled by about 50 % of the rescaling of the environment (as did place fields in the original finding; Muller and Kubie 1987), suggesting that they were not completely driven by the environment change; instead, the change in size may have represented a compromise between sensory and path integrator inputs (see Navratilova et al. 2012a and Samsonovich and McNaughton 1997 for a possible mechanism). Finally, sensory cues have influence over the in-field firing rates of place cells (Hetherington and Shapiro 1997; Leutgeb et al. 2005, 2006). Rate remapping is thought to be caused by inputs from the LEC to the hippocampus, because MEC grid cells do not show rate remapping (Fyhn et al. 2007).

In addition to sensory cues in the environment, aspects of the behavior that the animal is performing in the environment affect place cell firing. Many aspects of the behavior, such as the goal the animal is currently heading to, or the start location, only affect the firing rate of the place cells and not on the locations in which they fire [e.g., Wood et al. (2000); see Dudchenko and Wood, this volume]. These firing rate changes are smaller than other rate remapping effects (Leutgeb et al. 2005). The biggest differences in place cell firing occur between when a rat is randomly foraging in an environment and when it is following a specific trajectory

toward known reward locations in the same environment (Markus et al. 1995). Interestingly, the place cells fired in different locations when traversing the same path in opposite directions (Markus et al. 1995). This is consistent with the findings that place cell firing is not correlated in opposite running directions on a narrow track (McNaughton et al. 1983). This finding appears to conflict with the path integration model of place field generation.

Navratilova et al. (2012a), however, recently showed that the directional firing observed during traversal of specific paths develops with experience on the path. During the first traversals of a restricted route, place cell firing was multidirectional, just like during random foraging. Direction dependence of firing rates occurred gradually over the first 5–10 laps. Thus, it appears that place cell firing is at least initially generated by path integration, and the difference in firing between two running directions is a strong form of rate remapping. An experiment by Frank and colleagues (2004) showed similar results. During the initial day on the novel arm of an 8-arm maze, about 50 % of the recorded CA1 place cells expressed fields (Frank et al. 2004). The majority of all of the fields (85 %) were bidirectional. During early traversals of the track, the firing rates in 60 % of the fields increased, and 40 % of the fields decreased, some all the way to zero. In both the experiments by Frank et al. (2004) and by Navratilova et al. (2012a), some fields showed an increase or decrease in firing rates in both running directions, and some fields showed opposite firing rate changes in the two running directions. By the time the track became familiar, the percentage of recorded cells expressing fields on a single arm of the track decreased to somewhere between 30 and 40 % (Frank et al. 2004). This means that between 60 and 80 % of the initially expressed fields remained active by the time the track was familiar during the food retrieval task. If each running direction were considered separately, this percentage would be lower, as the majority of fields became unidirectional. It is interesting to note that the percentage of cells that begin to fire in a specific location, after that location has already been visited (15 %, as discussed above), is lower than the percentage of cells that stop firing after the track becomes familiar (20–40 %; Frank et al. 2004; Navratilova et al. 2012b). Thus, the gaining of familiarity with a track is associated with a net decrease in percentage of active place cells.

One proposed hypothesis for the directionality on running tracks is that different "spatial reference frames" are activated during runs in each direction (Touretzky and Redish 1996). This hypothesis was weakened by the finding that there is no abrupt change between place cell representations at the turnaround point on the maze (Redish et al. 2000), as there is during other transitions between spatial frames (Jezek et al. 2011). Evidence from the medial entorhinal cortex, however, suggests that there is an abrupt transition between the active grid cells during a 180-degree turn in a "hairpin" maze (Derdikman et al. 2009). Based on these results, Derdikman and Moser (2010) argued that space is actually broken up into smaller segments in the brain. Narrow passages or sharp turns around barriers would make the ideal places for such breaks to occur, because calculating the distances through barriers isn't very helpful. The fact that hippocampal cells do not show abrupt transitions at these points may be accounted for by two possible hypotheses. One is

that the hippocampus stitches these segments of space, or spatial frames together, to allow the continuity to be represented in the brain. This predicts that the "stitching" requires learning, and thus in a hairpin maze, initially the place cells should show abrupt transitions, and later gradual ones. The second possibility is that the hippocampus can generate sequences of place fields independently of the MEC and associates them to the path integration signal from the MEC during experience. Neither of these hypotheses, however, fully explains what happens on a narrow track. The hippocampus initially encodes both directions similarly, suggesting that they are not separate reference frames and that they are similarly encoded in the MEC. MEC recordings, however, also show that grid fields do not align in the two running directions after experience (Brun et al. 2008). Does this misalignment exist during initial passes along the track? If so, how does the hippocampus show similar place fields in both directions? If not, when and how does the separation into two separate spatial frames occur? These questions have yet to be answered by recordings in the MEC during novelty. The fact that the hippocampus gradually remaps the two running directions suggests that this is a learning process, and not an abrupt shift in spatial frames. Data from Navratilova et al. (2012a) show, additionally, that the remapping of the running directions doesn't occur until after behavior becomes stereotyped, suggesting an attention shift is involved in the learning of alternate representations for each running direction.

Rate remapping is suggested to create alternate representations of the same space not because the alternate sensory cues cause a movement of the "bump" of activity in an attractor landscape, but because the cues generate fine structure (i.e., fluctuations around the smooth Gaussian) in the bump, such that neurons show different firing rates, but the population is able to sustain activity within the same attractor (see Fig. 8.4a). This fine structure could be generated by connections from the LEC. DG and CA3 place cells each receive inputs from both MEC and LEC (Hjorth-Simonsen 1972; McNaughton and Barnes 1977; Steward 1976). The MEC inputs may create place fields from some kind of summation of grid fields (e.g., de Almeida et al. 2009; Solstad et al. 2006). According to the above theory of rate remapping, the LEC inputs have random strengths to each place cell, based on previous experience, that do not correspond with the new environment. As a result of many LEC connections with random weights, these weights do not contribute much to the spatial selectivity of place cells. During exploration of a new environment, these connections are adjusted upwards or downwards, based on which environment cues are coactive with which place cells, so that the LEC inputs can later induce recall of the correct place cell activity themselves. As the strength of these input connections changes, the firing rate of the place cells may change as well, but since only active neurons will undergo synaptic modification, the location of the place cells will not change. This would explain why the firing rates of CA3 cells can change with changes in the environmental cues. It may also account for firing rate changes between running directions during stereotyped tasks: since the animal preferentially experiences two separate spatial views, those two spatial views may become separately associated with the place cell firing and thus different firing rates in each direction result. Some support for this comes from the finding

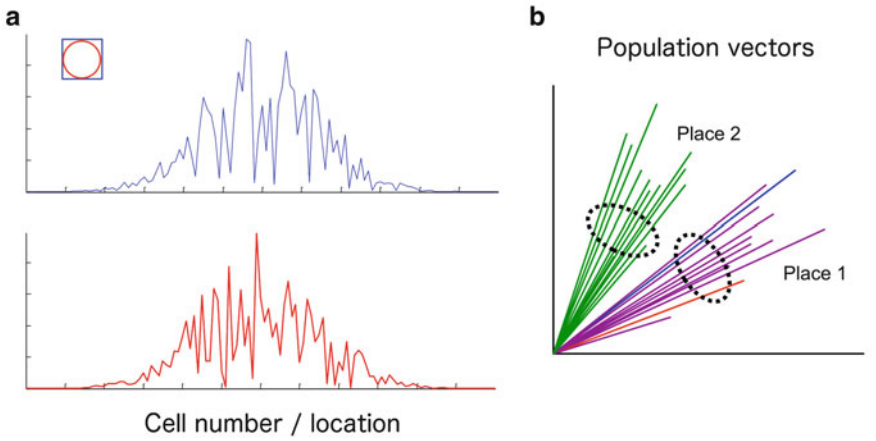

Fig. 8.4 Rate remapping and reference frames. (**a**) Fluctuations in the "activity bump" are not all noise but may reflect the influence of external cues on the cells encoding a given location. Rate remapping results in (possibly largely) different firing rates of individual cells, but the population activity remains centered on a single location in the attractor manifold. For example, a *square*-shaped enclosure might generate the place cell activity displayed in *blue*, while a circular enclosure viewed from the same location might generate the place cell activity depicted in *red*. (**b**) This results in population vectors of active neurons on two visits to the same place spanning statistically correlated subspaces, even if the cues are different. In contrast, the population vectors of active neurons in two different places span statistically independent subspaces, even if the cues are similar

that firing rates in each direction change independently: sometimes firing rates go up in both directions, sometimes down in both directions, and sometimes up in one direction and down in the other (Frank et al. 2004; Navratilova et al. 2012b). This hypothesis would also predict that if any small differences in firing rates as a result of LEC connections existed at the start, they would be amplified by the synapse modification procedure. The firing rate difference at the start of the novel environment exploration somewhat predicted the firing rate difference after the firing rates diverged (accounting for 8 % of the variability), but sometimes the preferred firing direction switched during the session (Navratilova et al. 2012b).

There may be a way to tie the rate learning and spatial reference frame hypotheses together: through synapse modification such as described above, the firing rates within each field change and some cells become "selected" to participate in one task-relevant spatial frame, others in another "task frame" (for the opposite running direction, in the case of these experiments), and some for neither. These task frames do not represent different space, as would two rooms separated by a hallway; instead, they are two alternate firing rate maps of the same space. In mathematical terms, if the full set of place cells defines a state space, a vector formed by the activities of all the cells defines the current location. The place cells that are (potentially) active at that location define a subspace within the full state space, and differences in firing rates of the cells (rate remapping, possibly including

some cells becoming silent) will form different vectors but remain within that subspace. The "task frame" is the specific vector within a location's subspace (see Fig. 8.4b). The firing rates may change significantly between the two tasks, making the two representations almost uncorrelated. A higher attention level during the learning of a task (accompanied by an increase in acetylcholine levels) might be what prompts the creation of separate task frames, by accelerating the learning processes and selecting the cues that the active place cells bind to. As the animal learns a task and begins chunking the aspects of the task into separate segments, the focus of attention will change during the performance of each segment and prompt the formation of a new task frame for that segment. Because each task frame is generated from the same active cells, the differences in the sensory experience during the association of place cells to the separate task frame will determine how different the task frames actually are. For example, the presence of local sensory cues may prompt many cells to be selected in both task frames. During attention shifts, different task frames become active, and associations between the task frames are learned in the CA3 recurrent synapses at locations where transitions commonly occur (the turn-around point in the maze). All task frames coexist in the synaptic matrix, and thus, the original path-integrated (nondirectional) representation of the environment can be recalled again when the task changes, such as during random foraging.

This hypothesis creates a few predictions. One prediction that differentiates it from the spatial reference frame hypothesis is that because each task frame is initialized from the same spatial representation, and because some cells decrease their firing rate to zero during rate remapping, during a specific running task, fewer cells should be active (in a given running direction or segment of the task) than in the same area during a nondirectional exploration task. In fact, as discussed above, there is a net decrease in the percentage of cells active on a track between novel running on the track and following several trials of a running task (Frank et al. 2004; Navratilova et al. 2012b). Additionally, according to this hypothesis, learning is required for the development of alternate representations of the same environment. Thus, blocking LTP should block rate remapping and the development of directionality on running tracks. Another possible prediction is that the presence of a larger number of explored sensory cues (but not more complex distal sensory cues; Markus et al. 1995; Yoganarasimha et al. 2011) may cause more place cells to be active in a given task frame, because more LEC inputs are active, and thus more connections are strengthened. This should not, however, be the case during random foraging, when the place cell activity is still mainly driven by path integration. These predictions also depend on the type of learning that results in the selection of the task frame. If LTD or inhibition limits the number of strengthened connections, there may be no change in number of active cells with changes in cues. Additionally, the type of input that is available to activate place cells should determine how the place cells are selected to participate in a task frame. All CA3 cells receive inputs from both MEC and LEC neurons, and thus should be able to become selected for a task frame based on a variety of cues. CA1 cells, on the other hand, each receive inputs only from MEC or LEC cells (in addition to the strong

projection from CA3). Thus, proximal CA1 cells, which receive inputs only from the MEC, should only show rate remapping when MEC remaps or in response to changes in boundaries (from border cell inputs), while distal CA1 cells, which receive inputs only from the LEC, should show more rate remapping in response to changes in local sensory cues. These predictions are partially supported by an experiment that shows that distal CA1 cells show a larger number of fields when objects are present on a track than when there are no objects on the track (Burke et al. 2011). This study failed to identify rate remapping between object conditions, but the authors did not calculate firing rates within individual place fields, and so the effect may have been washed out by the summation of firing rates, because many cells expressed multiple fields. Additionally, the rate remapping may have been so high that many fields disappeared completely when objects were removed. Additional studies are needed to examine rate remapping with changes in local objects and differences between proximal and distal CA1 cells.

The task frame hypothesis suggests a way in which attention to different aspects of a task can alter place cell activity, while preserving information about position. Shifts in attention have been proposed to alter place cell activity (Fenton et al. 2010). Different inputs may be active during different attentional states, resulting in the learning of different associations. It is important to note that inputs, as well as learning rates, may change with timescales on the order of theta cycles (or fractions of theta cycles). Colgin et al. (2009) showed that gamma frequency coherence between CA1 and MEC areas (in the local field potential) occurs on different theta cycles than coherence between CA1 and CA3 cells. This coherence also occurs at different frequencies: fast gamma in CA1 is coherent with gamma in MEC, and slow gamma in CA1 is coherent with gamma in CA3. The gamma bursts during which this coherence occurs also occur at different phases of the theta cycle. This finding suggests one way to test how the source of inputs to CA1 influences the firing of CA1 cells: maybe different task frames are represented when different inputs are active, and thus, place cells may fire at different rates during theta cycles dominated by each frequency. Additionally, a different source of input may dominate during novelty or during different attentional states. This may result in a different gamma frequency, and different task frame, dominating during novelty.

8.5 Summary

The implementation of models that can perform path integration aids in the understanding of both the temporal and spatial activity of grid cells and place cells. In this chapter, we discussed path integration, how important it is within the context of other navigation strategies, and evidence that it is used in the hippocampus to generate the place code. A consistent finding in the literature is that the initial formation of place fields is mainly determined by allocentric position in the environment. Then, we discussed one class of models of path integration: the attractor-based models. These models describe many features of entorhinal and hippocampal activity, including repeating fields of grid cells, the head-direction-by-grid-location

coding of conjunctive cells, and the presence of attractor dynamics. Ultimately, attractor dynamics are too simplistic to describe some aspects of hippocampal activity, including the temporal firing patterns, and rate remapping in place cells. However, the temporal firing patterns can be explained by combining a network with attractor-like connections and additional intracellular properties of neurons or additional oscillatory inputs into the attractor network. Next, we compared attractor models of path integration with another class of model, oscillator interference models, concluding that both models predict some aspects of grid cell firing, but attractor models explain more of the experimental findings, and at least some form of recurrent connectivity is necessary to account for noisy integration in the brain. Finally, we noted other inputs that affect place cell firing and presented a hypothesis for how those inputs could be integrated with MEC inputs to generate rate remapping. Some studies suggest that when alternate place cell representations of the same environment are generated, they are formed by gradual learning. This learning may "select" which place cells, from the group initially activated at a specific position, are active in a given behavioral context or in relation to a particular sensory cue.

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Part II

Hippocampal Processing

Remapping to Discriminate Contexts with Hippocampal Population Codes

9

Stefan Leutgeb and Jill K. Leutgeb

Abstract

Changes in the environment and in the internal state of an organism result in differences in hippocampal population activity, which is referred to as remapping. Studies of remapping have not only revealed the existence of a combinatorial code for space, objects, and time in hippocampus, but have also provided substantial insight into intrahippocampal computations that facilitate the acquisition, storage, and retrieval of memory. Hippocampal representations of remembered events consist of neuronal activity in place fields, which represent the location of the event, and of particular firing rates within each place field, which can reflect the current configuration of sensory inputs encountered at the current location. Perhaps not surprisingly, there is no fixed transfer function between sensory stimuli and hippocampal representations, but the firing patterns of place cells are flexibly configured and can be flexibly reconfigured. For example, the earlier processing stages in the hippocampal circuit, dentate gyrus, and CA3 generate neuronal activity patterns that distinguish new experiences from those that are already stored in memory. The new hippocampal representations can be more distinct than expected from the similarity of the current sensory input pattern compared to similar remembered patterns ("pattern separation"). Pattern separation may be particularly important for episodic memories because many novel experiences consist of new components that are added to otherwise familiar situations. Conversely, if parts of an event are

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recognized as familiar, the activation of hippocampal representations can be refined to retrieve full memories and to precisely resemble patterns that were stored earlier ("pattern completion"). In addition, a gradual drift of activity in hippocampal cell populations over time can be used for estimating the recency of a memory. Each hippocampal map can thus simultaneously represent the "where," "what," and "when" aspects of distinct experiences and code for the similarity between experiences.

9.1 Population Coding with Hippocampal Place Cells

Neurons in all hippocampal subregions of rodents fire at well-defined spatial locations during random foraging in two-dimensional environments. Principal cells in hippocampus are thus frequently referred to as place cells (O'Keefe and Dostrovsky 1971; O'Keefe and Nadel 1978). In many instances, described in other chapters in this book, the same cells show nonspatial firing patterns [e.g., odor cells, time cells (Wood et al. 1999; Pastalkova et al. 2008; MacDonald et al. 2011; see Eichenbaum et al. 2014; Ho and Burwell 2014; Deshmukh 2014)]. Nonetheless, even when the firing patterns of hippocampal cells are predominantly spatial, the hippocampal cell populations can represent nonspatial features of the environment, internal state of the animal, and information that is relevant to memory performance (Ferbinteanu and Shapiro 2003; Leutgeb et al. 2005b; Kennedy and Shapiro 2009; Allen et al. 2012). The representation of different aspects of an experience by changing the firing rates of the active subset and/or by activating different subsets of place cells is referred to as remapping (Muller and Kubie 1987). The term implies that multiple configurations of place cells (i.e., "maps") are used for a single environment, such that the hippocampus does not only code for places, but also for other aspects of the environment. Such conjunctive coding has been the basis for describing the hippocampus as a cognitive map (O'Keefe and Nadel 1978).

Before considering maps and representations at the population level and the manifestations of remapping in detail, it is important to point out that individual hippocampal and entorhinal cells show a considerable range of spatial firing properties. The size of the firing fields of hippocampal place cells can vary over at least an order of magnitude. In the most dorsal pole of the hippocampus, typical fields have an approximate size of 30 cm, while in the ventral hippocampus, fields have sizes of up to several meters (Jung et al. 1994; Kjelstrup et al. 2008). A similar gradient is also apparent in the entorhinal cortex, which provides input to the hippocampus and receives output from the hippocampus. Grid cells in the medial entorhinal cortex have the smallest spacing at the most dorsal border, adjacent to the postrhinal cortex, and have increasingly larger spacing towards more ventral locations (Hafting et al. 2005; Stensola et al. 2012). For grid cells in individual rats, the increase in spacing is not continuous, but rather occurs in discrete steps such that grid cells with similar spacing are organized into discrete (although partially

overlapping) modules along the dorsoventral axis (Barry et al. 2007; Stensola et al. 2012). Therefore, the size of the firing fields of grid cells and place cells along the dorsoventral axis is consistent with the topography of the connections of the dorsal medial entorhinal cortex with the dorsal hippocampus and of the ventral medial entorhinal cortex with the ventral hippocampus (Witter and Moser 2006).

The number of firing fields that are observed for a grid cell within a two-dimensional environment is determined by the cell's grid spacing and by the number of vertices that fit within the environment. For place cells, the number of fields for a given principal neuron varies depending on the hippocampal subregion and on the size of the environment. Typically, it is found that 25–40 % of the principal cells in CA1 and 5–15 % of principal cells in CA3 have at least one firing field in a 1 m by 1 m box (Barnes et al. 1990; Guzowski et al. 1999; Leutgeb et al. 2004). Furthermore, CA1 cells are more likely than CA3 cells to have more than one field (Muller et al. 1987; Fenton et al. 2008; Park et al. 2011). Dentate cells have a probability of only 2–4 % to show markers for neuronal activity after random foraging in a box (Chawla et al. 2005). If active, a subpopulation of dentate cells tends to fire at multiple locations. The multiple firing peaks of dentate cells do not show any regularity in the arrangement of firing locations, which is distinct from grid cells in the medial entorhinal cortex (Leutgeb et al. 2007; Neunuebel and Knierim 2012).

Considerations of the probability of activation and of the field size have important implications for inferring the firing statistics of hippocampal cell populations, for determining how individual cells are recruited to become part of a hippocampal map, and for predicting how maps change within and across environments. The partial activation of hippocampal cell populations in each environment allows for the coding of each environment with a different set of active place cells and even for the coding of the same environment on separate occasions with different sets of active neurons (Mankin et al. 2012; Ziv et al. 2013). Our knowledge of how the hippocampus flexibly represents sensory information contributes substantially to our understanding of how hippocampal computations support memory acquisition, storage, and retrieval.

9.2 Remapping Generates Multiple Maps for the Same Space

The term "remapping" emerged from studies that investigated the stability of hippocampal maps within a fixed environment and then proceeded to determine how place fields change with manipulations of the environment. When introducing a barrier into an enclosure, Muller and Kubie (1987) found that cells close to the barrier changed their firing patterns, while more distant ones remained unaffected. To indicate that the same space is encoded with a different pattern of neuronal activity, they thought of different place fields and the altered distance between them as different maps for the same space and referred to the process as remapping. In the same series of experiments, they found a more complete reorganization of place field firing when a circular enclosure was replaced by a rectangular one at the same

location. In response to the manipulation, cells either turned on or off or changed their firing rate. In follow-up studies Bostock et al. (1991) replaced a white cue card with a black cue card, which resulted in similar changes in network activity as described for manipulations of enclosure shape. To distinguish the major change for different box shapes and for different cue card colors from the more localized change at a barrier, they introduced the concept of "complex remapping" as opposed to "partial remapping." Although "partial" was initially meant to indicate that a new map was formed for a subsection of the recording arena, the term was widely adopted to describe incomplete changes in place fields in response to manipulations of enclosures and tasks. In many cases, remapping would not be restricted to a particular spatial location, but rather be restricted to a subset of the recorded place cells irrespective of their location within the recording arena. It has thus been suggested to use the term "local remapping" to refer to changes that are restricted in space and the term "partial remapping" for describing an incomplete or discordant response of a population of place cells to experimental manipulations (Knierim 2003). Moreover, "global remapping" is used for the reorganization of place field firing at all locations within the apparatus, such that two maps are only as similar as expected by chance (Guzowski et al. 2004; Leutgeb et al. 2004, 2005b).

Although remapping in response to a manipulation of the environment is the expected response, an opposite neuronal response can also occur. Hippocampal firing patterns can be remarkably consistent across varying experimental conditions. For example, a striking stability of place fields is seen when removing a subset of sensory cues. Along with the stability of the fields, the animals' behavioral responses can continue with accuracy despite the difference in sensory cues (O'Keefe and Speakman 1987; Nakazawa et al. 2002). A consistent neuronal firing pattern in conditions when the input to a neuronal network is incomplete or partially different is referred to as "pattern completion." This process can retrieve missing pieces of information from long-term memory and can be implemented in recurrent network architectures. It has thus been proposed to be performed by the intrinsic connectivity of the CA3 subregion (Marr 1971; McNaughton and Morris 1987; Treves and Rolls 1994; Nakazawa et al. 2002).

9.2.1 Partial Remapping Differs from Rate Remapping

When remapping occurs, it can occur along a continuum from minor changes in neuronal activity to the activation of completely nonoverlapping cell populations. Because neuronal activity in the hippocampus is organized into place fields, it is possible to not only observe quantitative differences in the degree of remapping, but to also observe qualitative differences in the type of remapping. First, each place cell can modify its intensity of firing at a particular location ("rate remapping") (Fig. 9.1a). Changes in firing rate within fields correspond to rate changes in classical receptive fields in sensory physiology where a preferred stimulus elicits the maximum firing rate and where nonpreferred stimuli or stimuli that are presented outside of the field elicit lesser or no firing. A second type of remapping

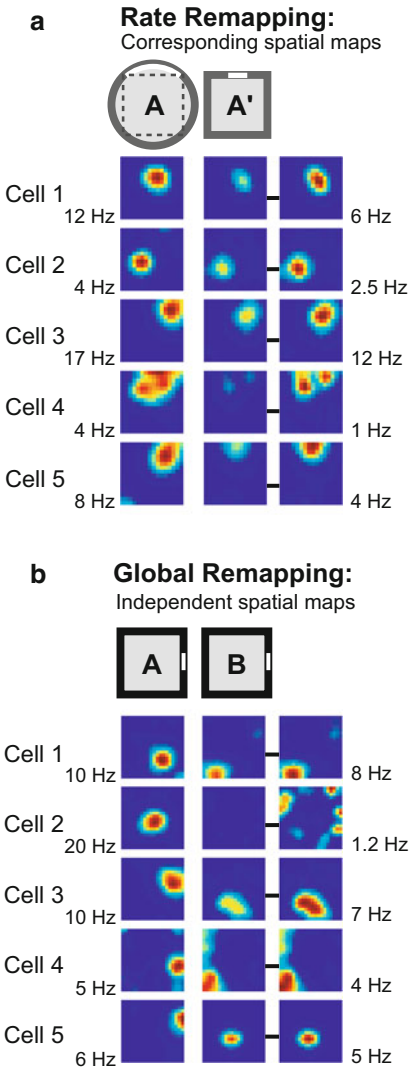

Fig. 9.1 Firing patterns of hippocampal place cells change in response to experimental manipulations. (**a**) Rate remapping describes changes in hippocampal firing patterns that occur within the same hippocampal spatial map. In this case, two different enclosure shapes (*circle* and *square*) are presented at different times at the same location. The place cells change their firing rate at a stable place field location. Firing in the two different box shapes (A and A') is shown next to each other (although they have been presented at the same place within the room during the experiment). Color-coded rate maps are shown for cells recorded in two enclosure shapes. Rate is coded on a color scale from *blue* (silent) to *red* (maximum rate). The *left column* shows data from the shape with the maximal firing. The *middle column* is from the other shape, but plotted at the same firing-rate scale. The right column contains the same data as the *middle column*, but scaled to the peak firing rate for that shape. For the circular enclosure, only the pixels that match the *square* enclosure are shown. In the example, all cells have their maximum rate in the *circular* enclosure, but in a larger sample of cells, an approximately equal number have maximum firing rates in one or the other shape. (**b**) In "global remapping" place cells respond to an experimental manipulation by

is a shift in the cells' preferred firing locations. This is referred to as "global remapping" when different place field locations are observed for all cells in the population (Fig. 9.1b). The firing of place cells in response to a stimulus at a different location does not have a direct correspondence to neural signaling in sensory pathways. In topographical maps of sensory pathways, the mapping of an external coordinate system to brain maps is typically constrained by the anatomical wiring diagram, such that neighboring coordinates in the external world correspond to neighboring cells in a cell layer. A major difference in the organization of hippocampal place cells is that adjacent locations in two-dimensional external space are not mapped to adjacent cells in hippocampal cell layers. Without an organization of the cell bodies of neurons according to nearest-neighbor relations, distances in the external world must be stored in the connection matrix between neurons (Wilson and McNaughton 1993; Samsonovich and McNaughton 1997; Redish et al. 2001; Dombeck et al. 2010). Through synaptic connectivity, anatomically distant place cells with overlapping or adjacent place fields can have strong functional connections with each other, while cells with distant fields may be only weakly connected even when their cell bodies are adjacent. Connection strength is thus not related to the relative distance between two neurons and can be flexibly changed without being constrained by any nearest-neighbor relations between the cells. A new, arbitrary mapping between external space and the neuronal activity patterns in the hippocampus can thus be quickly generated. It is important to note though that the connectivity matrix does not necessarily need to be implemented in local synaptic connections within a brain region. For example, CA1 cells do not have substantial projections to other CA1 cells, but CA1 cells with overlapping fields can nonetheless be co-activated by receiving common input from cells that themselves have strong functional connectivity.

Before further considering the process of generating and activating different maps, we will first consider the case when the neuronal activity corresponds to a stable map for the current two-dimensional environment (Fig. 9.2a). The organization of place cells into a two-dimensional array has been referred to as a "chart" (Samsonovich and McNaughton 1997). For illustrative purposes, cells with strong connections can be drawn next to each other (even though this does not correspond to their physical location in the cell layer), and the activation of place cells is depicted as an activity bump in which connected cells are co-activated and sustain each other's activity. In this framework, the activity bump can be continuously shifted by directional and velocity inputs that correspond to the path of the rat (Fig. 9.2b, c). These network dynamics correspond to those of a continuous attractor in which path integration is the predominant influence on updating the place cell firing (Knierim et al. 1995; Gothard et al. 1996a; McNaughton et al. 1996;

Fig. 9.1 (continued) switching between two independent spatial maps, which is the expected response to moving between two spatial locations (i.e., room A and B). The organization of the maps is as in (A), but now comparing the two rooms rather than the square and the circular enclosure. Modified with permission from Leutgeb et al. (2005b)

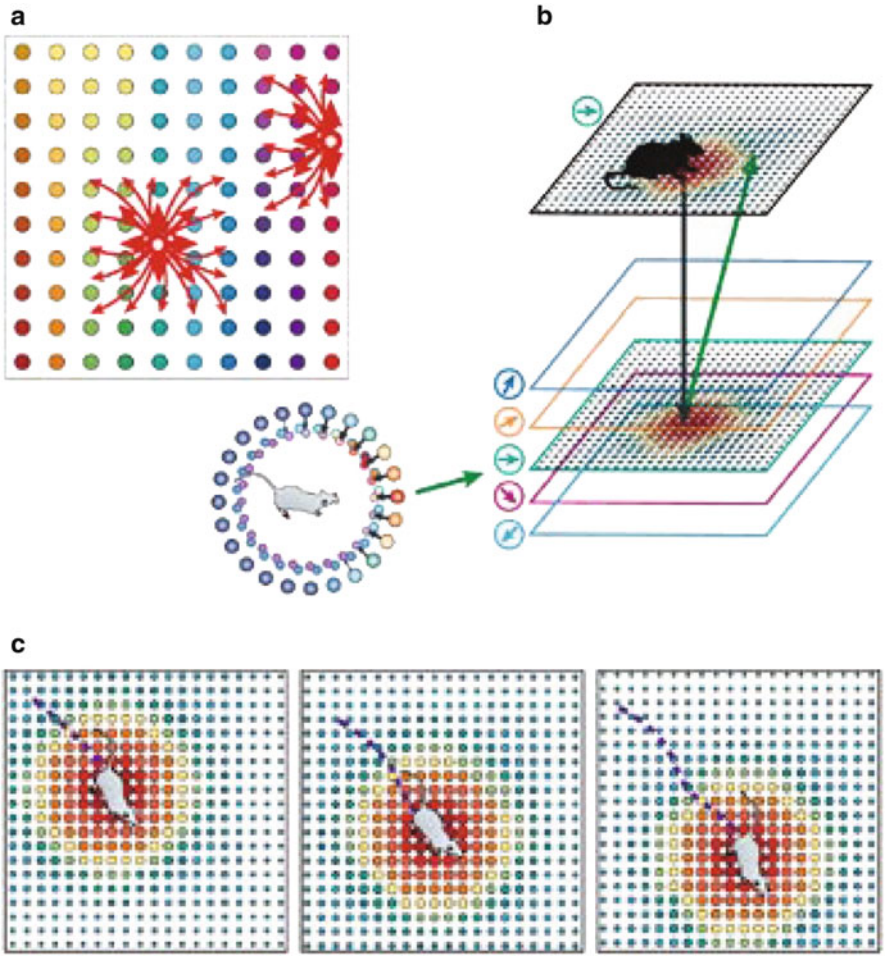

Fig. 9.2 Attractor network model of hippocampal spatial maps. (**a**) Spatial coordinates in the external world do not correspond to a topographical organization in the hippocampal cell layers, but neurons (*colored circles*) are redrawn such that neighboring neurons on the plane are those with stronger synaptic connections. The activation of place cells by external inputs forms an activity bump within the neural matrix (*red arrows*). (**b**) The bump can be moved by input from layers of neurons that compute head direction and linear speed signals. (**c**) The activity bump generated in the hippocampal attractor map moves between cells in response to head direction and running speed inputs, thus tracking the position of the rat in space. Modified with permission from McNaughton et al. (2006)

Samsonovich and McNaughton 1997). Without the accumulation of errors in the network, the velocity and direction signals return the neuronal activity to the same bump in the chart during each time when the animal returns to the same location (see Navratilova and McNaughton 2014).

9.2.2 Switching Between Two Randomly Selected Cell Populations During Global Remapping

According to the coding scheme in a continuous attractor, the same pattern of neuronal activity is reinstated when returning to the same location, but conversely, a completely different set of place cells is activated when moving to a distant location. The process of gradually turning off currently active cells while activating those that have place fields at neighboring locations in space results in a different population of active cells each time an animal has moved about half the radius of an average place field. Because place fields are of a different size in the dorsal and ventral hippocampus, the selection of a different set of place cells occurs sooner in dorsal hippocampus than in the ventral hippocampus (Maurer et al. 2005). The most intuitive example of selecting a different active cell population ("global remapping") is thus the generation of two different sets of active cells at two distant locations (Leutgeb et al. 2005b). However, the activation of a completely different set of place cells can even occur for a recording arena that remains at fixed world-based coordinates such that the recording arena is represented as if it was an environment at a different location (Muller and Kubie 1987; Lever et al. 2002; Fyhn et al. 2007). In the continuous attractor framework, remapping of the same location to a different set of active cells could occur when there is a discontinuity in the path integrator and when the network is abruptly reset to a new origin. By starting from a different coordinate within the brain's continuous map for space, each point in physical space would then coincide with a different set of active cells.

The manifestation of such a sudden transition was explicitly tested in experiments in which animals were first trained to run back and forth on a linear track and in which place cells were then recorded after shortening the track by moving the start box (Fig. 9.3) (Gothard et al. 1996a, 2001). When exiting the start box, the place cell system initially used the start box behind the animal as a reference point irrespective of its location on the track. While running towards the end of the track, the place cells abruptly reset their firing patterns to correspond to those before shortening the track. The transient anchoring of place field firing to an invisible reference point behind the animal (i.e., the start box) indicates that the animals' map keeps track of distance by path integration until the path integrator is reset to room-centered coordinates by visual cues. Similar resetting to a prominent landmark has also been observed for grid cells. In hairpin environments, in which the beginning or the end of each alley can be used as a landmark, periodic resetting results in grid firing at a particular distance from the end points and thus in a striped rather than in a grid firing pattern across adjacent alleyways in the maze (Derdikman et al. 2009; Derdikman and Moser 2014).

These experiments reveal that either path integration or external landmarks can align a map within an environment. The relative contribution of path integration as opposed to visual cues was tested by measuring place cell firing in two visually identical boxes that were placed next to each other and connected with an alleyway (Skaggs and McNaughton 1998). It was found that the boxes were partially distinguished, which suggests that the visual cues and the path integrator each partially

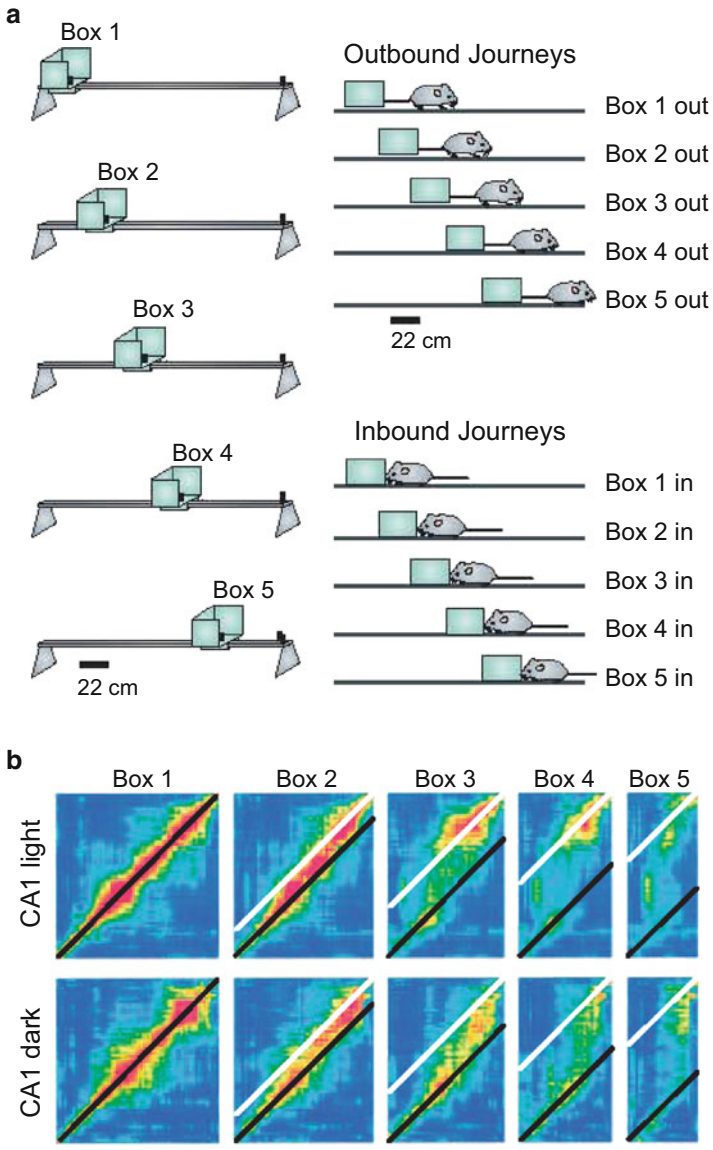

Fig. 9.3 Influence of the path integrator and of external reference cues on setting the hippocampal spatial reference frame. (**a**) Rats were trained to run on a linear track in which the start box was shifted during the rat's journey. (**b**) Correlation matrices for hippocampal neural firing patterns are shown comparing the population activity on the full track (*y*-axis) to locations on the full track (*x*-axis, Box 1) and locations on the shortened track (*x*-axis, Box2–5). Hot colors indicate higher correlations. The *white line* indicates a reference frame anchored to the room and the *black line* a reference frame anchored to the box. Experiments were conducted in the *light* (*top*) and in the *dark* (*bottom*). Linear path integration is sufficient to update the spatial coordinate system in hippocampal spatial maps. However, when there is mismatch between the path integrator and the surrounding room cues, the system can suddenly reset to the room cues. Modified with permission from McNaughton et al. (2006)

control place field firing. A possible interpretation of the observation that partial remapping occurs in adjacent, visually identical boxes is that the path integrator controls place field firing in the same way as other sensory modalities and thus exerts influence over a subset of the place fields at each position in space. However, studies that recorded from CA3 cells (Tanila 1999; Leutgeb et al. 2004) rather than CA1 cells (Skaggs and McNaughton 1998) showed that a path-integration-based mechanism could completely govern the firing patterns of place fields even when some of the visual cues were corresponding between two environments.

The differences between CA1 and CA3 could emerge from a mechanism in which CA1 cells are more prominently activated by box features, while CA3 cells are more exclusively activated by keeping track of the current location of the animal. The more pronounced binding of CA1 cells to external cues would result in similarities in the activation of CA1 cells across environments as long as the two recording arenas share some common elements. Accordingly, CA1 cells were shown to only have related activity patterns when enclosures shared common features, but not when enclosures were entirely distinct (Leutgeb et al. 2004; Vazdarjanova and Guzowski 2004). The possible binding of CA1 cells to discrete sensory cues within each environment therefore suggests that CA1 place cells are not exclusively organized by a single underlying spatial map, but can flexibly code for spatial and nonspatial information (Eichenbaum et al. 1999). Such an interpretation is further supported by the finding that CA1 fields cannot only be bound to sensory stimuli within one modality (i.e., visual), but also in a combinatorial way to stimuli of several different modalities. In this coding scheme, each modality can have a variable and experience-dependent weight in controlling each place field (Bostock et al. 1991; Knierim et al. 1995; Gothard et al. 1996b; Shapiro et al. 1997; Jeffery 1998; Wood et al. 1999; Lever et al. 2002; Anderson and Jeffery 2003; Deshmukh and Knierim 2013). The rather diverse responses of CA1 cells to contextual manipulations are in contrast to the more coherent responses of CA3 cells to follow one set of cues (Shapiro et al. 1997; Lee et al. 2004; Leutgeb et al. 2004; Vazdarjanova and Guzowski 2004). Unlike the memory space in CA1 (Eichenbaum et al. 1999), the CA3 network is therefore more constrained to a single map (Fyhn et al. 2007; Leutgeb and Leutgeb 2007; Mankin et al. 2012).

9.2.3 Rate Remapping Occurs While Place Field Locations Remain Stable

In the previous section, we described a mechanism in which the place fields that are stable across environments are those that are bound to particular sensory cues. However, a complementary mechanism could also result in partial remapping. In the second case, the spatial coordinates define the cells' place field locations, and manipulations of cues surrounding the environment (e.g., the wall color, wall geometry, distant cues) result in differences in the sensory information that is perceived at each place field location. In these paradigms, place fields retain their firing location, but the sensory differences result in rate changes within the fields

("rate remapping") (O'Keefe and Speakman 1987; Hayman et al. 2003; Leutgeb et al. 2005a, b; Allen et al. 2012). In support of a neural network mechanism that retains the spatial coordinates during hippocampal rate remapping, it was observed that medial entorhinal grid cells show firing patterns that are indistinguishable between two conditions in which the firing rates within hippocampal place fields substantially change (Fyhn et al. 2007; Leutgeb and Leutgeb 2007).

Although rate remapping is sometimes a less pronounced form of remapping (Lever et al. 2002; Hayman et al. 2003), the expression of rate coding is particularly robust in CA3 where rate changes reach more than tenfold differences in peak firing rates within the place field. For example, rate remapping can suppress the firing in the nonpreferred enclosure to such an extent that firing fields reach peak rates below 1 Hz, with few spikes occurring within the field that is otherwise well defined in the preferred enclosure (Leutgeb et al. 2005b). Such pronounced forms of rate remapping can result in firing differences within the hippocampal population code that reach approximately the same degree of dissimilarity as observed with global remapping (O'Keefe and Speakman 1987; Hayman et al. 2003; Leutgeb et al. 2005b). If rate remapping is pronounced, an apparent shift in the location of place fields is not necessarily indicative of the type of remapping. A substantially decreased firing rate in one field along with an increased firing rate in the other could appear as a shift in the firing location. Because CA1 cells are more likely to have two or more potential firing fields in an environment (e.g., Leutgeb et al. 2004), this is more likely to occur in CA1, and it is therefore more difficult to distinguish rate and global remapping in this subfield.

9.2.4 Morphing Sensory Inputs as a Test to Distinguish Between Rate and Global Remapping

Compared to experiments that contrast two conditions (e.g., black versus white, square versus circle), experiments that test intermediate ("morphed") enclosure configurations can unambiguously identify rate remapping. For rate remapping a strikingly linear activation of firing within the field becomes apparent (Fig. 9.4a). The gradual modulation of the firing rate within the place field according to the similarity of the current compared to the preferred cue configuration parallels what is observed for receptive fields in sensory systems. The preferred stimulus results in maximal activation, while less optimal stimuli that are presented within the receptive field result in lesser activation.

The remarkably linear changes in firing rate within each cell's firing field (Fig. 9.4a) are different from the sudden transition in the experiments in which animals were running along a linear track (see Fig. 9.3). A possible explanation for the difference is that rate remapping and global remapping depend on different network mechanisms, which would further support the notion that they are not merely quantitatively, but rather qualitatively, different forms of remapping. To illustrate the differences, an analogy to cartographical maps may be useful. For example, it would be next to impossible to use a map of one city to navigate in a

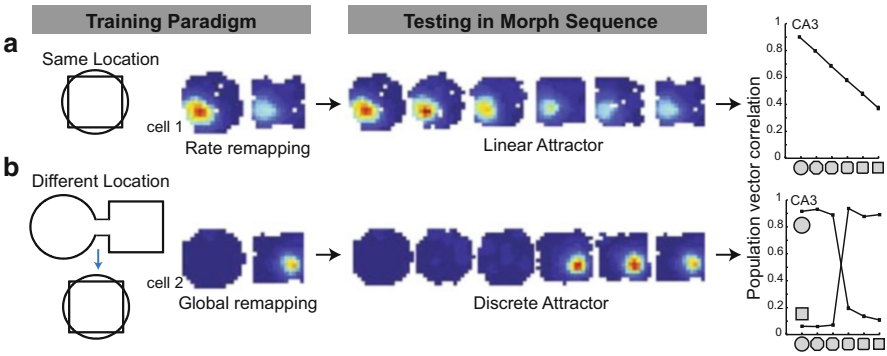

Fig. 9.4 Experimental tests of attractor dynamics in the hippocampal neural network. The nature of the network dynamics during a morph experiment depends on how the stored representations are initially encoded. Rodents are trained in an enclosure with flexible walls that are changed from a circle to a square configuration. After rodents are equally familiar with the box in the circle and in the square configuration, the enclosure is morphed from the *circle* shape through four novel intermediate morph shapes to the *square* shape. (**a**) If the *square* and *circular* box configurations are represented by rate changes within a single spatial map ("rate remapping"; induced by training in the same spatial location), then the incremental change in box shape during the morph experiment will be encoded as gradual changes in firing rates of single neurons such that hippocampal cell ensembles represent the similarity of intermediate morph shapes by a gradual change in the population activity (shown to the right by calculating the population vector correlations). (**b**) If the *square* and *circle* are represented by different spatial maps ("global remapping"; induced by initially learning the shapes in different spatial locations), then the hippocampal network will switch between discrete attractor states during the morph experiment. In this case, intermediate shapes are not encoded, but are represented as either the *circle* or the *square*. The switch from between the circle and square representations is sudden (shown to the right by calculating the population vector correlations with either the *square* or the *circle* representation). The figure illustrates data from Leutgeb et al. (2005a) and Colgin et al. (2010)

different city (even if the layout of both cities has some similarities), but one might be somewhat successful in finding a route when using a topographical map that has not been updated for decades (and we may even mentally update the map during route finding). The key difference between the two situations in which an ill-fitting map is used for route finding is that the one for a different city is based on using different global coordinates, while the old one for the same city merely uses incorrect signposts within an otherwise correct layout. The nature of hippocampal representations for situations that correspond to these two possibilities was tested with an experimental design that trained animals in two different ways (Fig. 9.4a, b) (Colgin et al. 2010). First, animals were trained in two enclosures that were placed next to each other and connected with an alleyway such that maps for separate locations could emerge (Fig. 9.4b). To make it possible that the two room coordinates could not only be identified based on their location relative to each other but also based on local sensory cues, two different shapes (i.e., square and circular) were used for the two connected enclosures. As expected for two different locations in space, separate populations of hippocampal place cells were found to

be active in each of the two enclosures. Because the separate map coordinates were also made distinguishable by enclosure shape, it could then be tested how hippocampal place cells would respond if one box shape was morphed into the other. Recordings in intermediate morph shapes (now at a central location) revealed that transitional maps were not generated, but rather that the map for either one or the other initial box location became activated. Second, a morph experiment was also performed in a separate set of animals in which the box shapes, box sizes, and sequence of box presentations during the morph phase of the experiment were exactly matched. However, the animals had previously been trained by placing each enclosure shape in only the center of the room rather than at different locations within the room (Fig. 9.4a). In this case, a linear response was seen during subsequent testing in the morph sequence (Colgin et al. 2010). The hippocampal activity patterns during the transition from one environment to another did thus not depend on the sensory features that were presented, but rather on how the different maps had been acquired. When rats learned that the maps correspond to different locations, global remapping was observed. When rats learned that the maps correspond to one location, rate remapping was observed. For enclosure shapes that are perceived as belonging to the same spatial map, neuronal activity patterns therefore code incrementally for stimulus differences. Conversely, for enclosure shapes that are perceived as identifying one or the other location in space, an all-or-none neuronal response switches between maps (Wills et al. 2005; Colgin et al. 2010), and the switching can occur on a sub-second timescale (Kelemen and Fenton 2010; Jezek et al. 2011).

The importance of distinguishing between different modes of remapping that normally occur either at a constant location or at two different locations has previously been recognized for recordings from aged animals (Barnes et al. 1997; Tanila et al. 1997b; Rapp 1998). When returning to a familiar room where the same spatial coordinates should be used, aged animals occasionally use a completely unrelated map (Barnes et al. 1997). In contrast, when tested in two different rooms, the older animals showed instances of reusing a previously learned map (Wilson et al. 2004). Such a propensity to inappropriately apply a preformed map to a different context is particularly pronounced in CA3, while CA1 cells respond to altered sensory cues to approximately the same extent as young animals (Wilson et al. 2005). These findings therefore suggest that the binding of the CA1 cells to sensory cues is relatively normal in the aged hippocampus, but that the mechanism for retrieving the appropriate CA3 map for each enclosure is impaired.

The finding that place fields can remain predominantly bound to a single spatial coordinate system also extends to experiments in which the shifting of box walls results in either smaller or larger rectangular and square boxes (O'Keefe and Burgess 1996). Here it is found that CA1 place fields can either split to be controlled by each of two displaced walls (hence by the visual landmarks) or that they can stretch to approximately the same extent as the increase in the distance between the walls. Although it was at first unclear how such geometrical changes in hippocampal place fields could go along with the constant spacing of grid cells in the medial entorhinal cortex in similar experimental paradigms (Hafting et al. 2005), it was

later found that the size invariance in spacing depended on the familiarity with the environment. Box resizing can result in shrinking or stretching of the grid spacing when animals have not yet been well familiarized with the manipulation (Barry et al. 2007; Stensola et al. 2012) (see Derdikman and Moser 2014). Geometric transformations of grid cells can therefore follow largely the same rules as those that were previously identified for hippocampal place cells. The only apparent difference between grid cells and place cells is that place cells respond with much more pronounced rate differences to the manipulations (O'Keefe and Burgess 1996; Barry et al. 2007), thus confirming the observation that intrahippocampal rate changes are the predominant form of encoding cue configurations when the spatial coordinate system remains in place (Leutgeb et al. 2005b).

9.3 Remapping Can Also Code for Elapsed Time on a Timescale of Minutes to Weeks

One of the key findings about hippocampal maps has been the observation that they remain stable during repetitions of the same experience, as would be expected for neuronal activity in a brain region that is essential for storing long-term memories. If the environment remains unchanged, the firing of place cells can persist at consistent locations for as long as place cell recordings with extracellular electrodes are feasible (Muller et al. 1987; Thompson and Best 1990). In recordings from a large set of identical hippocampal cells over extended time intervals, it has been confirmed that the firing of CA3 cells remains exquisitely stable over periods of at least several days (Mankin et al. 2012). This is consistent with the function of CA3 in generating complete and accurate patterns of neuronal activity over time periods when fluctuations in synaptic strength and in modulatory inputs can be expected in the hippocampal network. In contrast to CA3, neuronal activity in CA1 cell populations has been found to incrementally change with elapsed time (Manns et al. 2007; Mankin et al. 2012; Ziv et al. 2013). Despite this drift in activity patterns, the CA1 network can maintain a stable population code for spatial and contextual components of environments (Mankin et al. 2012), but nonetheless a code that shows a higher degree of similarity with itself over short rather than long intervals. This finding is consistent with theoretical considerations that the comparison between a time-varying and a stable firing pattern can be used to estimate elapsed time (Estes 1955; Howard and Kahana 2002). The finding of gradual changes during repeated exposures to identical environments thus suggests that hippocampal remapping does not only represent "where" and "what" information but also information about elapsed time, as would be expected from a brain region that is essential for episodic memories (Eichenbaum et al. 2014).

9.4 Complex Patterns of Remapping Emerge with Conflicting Cues

In experiments that only include manipulations in which cues are partially removed without adding new or conflicting cues, relatively minor changes in place field firing occur. Hippocampal firing patterns may even compensate ("pattern complete") and show the same response pattern that is elicited with the full set of cues. Another situation that only results in a minor degree of conflicting information is when all sensory cues within the room are rotated (O'Keefe and Conway 1978; Muller and Kubie 1987; Bostock et al. 1991). Because there are inevitably some cues within the room that cannot be moved during a rotation experiment, these manipulations generate a set of static background cues. Given that these static cues are not prominent, it is usually only a small fraction of the place fields that remains aligned with the background. Most place cells as well as all grid cells, head direction cells, and conjunctive cells rotate their firing positions along with the displacement of the rotating cues around the recording arena (Knierim et al. 1995; Sargolini et al. 2006).

In contrast to the coherent rotation of cues and place cells in paradigms in which the conflicting information is minor, much more complex hippocampal firing patterns emerge when two sets of sensory cues are explicitly rotated into opposite directions. The firing fields of the cells rotate with either one or the other set of cues, or they disappear completely. In addition, fields of previously silent cells can emerge rapidly (Bostock et al. 1991; Shapiro et al. 1997; Tanila et al. 1997a; Knierim et al. 1998; Fenton et al. 2000; Knierim 2002). Of the rotating CA1 fields, more than half remain aligned with the rotation of the head-direction system, and the head-direction system has been shown to always stay coherent with the more distal set of cues (Yoganarasimha et al. 2006). Furthermore, grid cells remain bound to the head-direction system (Sargolini et al. 2006; Hargreaves et al. 2007). CA3 cells also show a larger degree of coherence in the same experimental paradigm, but in contrast to most other cell types, they have been found to preferentially follow the local cues (Lee et al. 2004). Although CA3 cell ensembles and the head-direction/grid cell ensembles each remains strongly bound to a single map-like representation, a large degree of incoherence is thus possible when these strongly discordant cues converge in CA1 (Lee et al. 2004; Yoganarasimha et al. 2006; Fyhn et al. 2007; Leutgeb et al. 2007).

9.5 Place Cell Maps Do Not Require Input from Grid Cells

As described in the previous sections, the different cell types in the entorhinal cortex and in the hippocampus have been found to predominantly show matching responses within an experimental paradigm (Fyhn et al. 2007; Hargreaves et al. 2007; Leutgeb and Leutgeb 2007). Because each cell type in the entorhinal cortex provides input to the hippocampus (Zhang et al. 2013), this suggests that the spatial and directional firing patterns in the entorhinal cortex might determine the

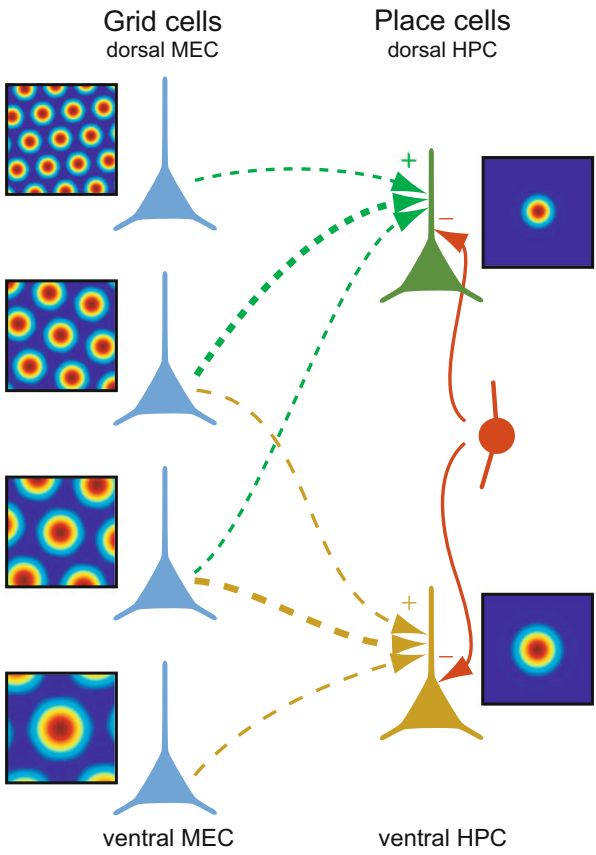

Fig. 9.5 The spacing between the firing fields of grid cells increases along the dorsal to ventral axis of the medial entorhinal cortex (MEC), with the smallest spacing at the dorsal pole. The convergence of grid cell input at different spatial scales is thought to result in nonrecurring place fields in the hippocampus. However, experimental tests of this model suggest that the flow of information to the hippocampus is also from other cell types in the entorhinal cortex and might also be in the opposite direction (Langston et al. 2010; Wills et al. 2010; Koenig et al. 2011; Bonnevie et al. 2013; Zhang et al. 2013). Modified with permission from Solstad et al. (2006)

firing patterns of hippocampal place cells. Moreover, the majority of spatially selective cells in the superficial layers of entorhinal cortex are grid cells (Boccara et al. 2010), and grid cells might thus have a particularly prominent role in providing spatial inputs to the hippocampus. In particular, the activation of a subset of place cells at each location could be obtained from the summation of grids with different spatial frequencies, as commonly proposed in theoretical models (Fig. 9.5) (Hafting et al. 2005; O'Keefe and Burgess 2005; Fuhs and Touretzky 2006; McNaughton et al. 2006; Rolls et al. 2006; Solstad et al. 2006; Gaussier et al. 2007; Hayman and Jeffery 2008; Molter and Yamaguchi 2008; Si and Treves 2009; Savelli and Knierim 2010; Monaco and Abbott 2011; de Almeida et al. 2012).

Several lines of evidence nonetheless suggest that it is premature to conclude that the flow of spatial information within the entorhino-hippocampal circuit is predominantly from grid cells to place cells. (1) The considerable diversity of place cell firing in double rotation experiments compared to the much more coherent response of grid cells and head direction cells suggests that place cells are not

exclusively activated by grid cells (Hargreaves et al. 2007). (2) During postnatal development, the emergence of place cells seems to precede the emergence of completely regular grid cells (Langston et al. 2010; Wills et al. 2010). The finding that grid cells do not show a fully matured periodicity during the period when place cells first appear raises the possibility that the spatial firing rather than the regularity of grid cells might be a prerequisite for place cell firing. (3) Grid cells can be abolished by inactivating the medial septal area (Fig. 9.6a, b) (Koenig et al. 2011), but the firing locations of hippocampal place cells are retained in the same experimental paradigm (Brandon et al. 2011; Koenig et al. 2011). Because head-direction cells and border cells in the entorhinal cortex are preserved during the septal inactivations, these findings support the notion that broad spatial firing in entorhinal cortex rather than grid regularity is sufficient for retaining hippocampal spatial selectivity. (4) It has been shown that grid cells are abolished after hippocampal inactivation (Fig. 9.6c, d) (Bonnevie et al. 2013). Spatial information processing in the entorhino-hippocampal loop may thus be predominant from place cells to grid cells rather than vice versa. Alternatively, it is possible that the effects of hippocampal inactivation on grid firing in entorhinal cortex are mediated by a third structure which, in turn, has effects on grid cells. For example, hippocampal inactivation resulted in a substantial reduction of the theta amplitude in the entorhinal cortex (Bonnevie et al. 2013). If the reduced entorhinal theta oscillations are caused by reduced neuronal activity in the medial septal area after the hippocampal inactivation, it would be expected, based on previous findings with the more direct manipulations of the septal region (Brandon et al. 2011; Koenig et al. 2011), that grid firing is diminished.

9.6 The Implications of Remapping for Learning and Memory

The occurrence of multiple maps across environments or even within environments implies that new, distinct maps need to be generated and/or activated when animals first move to novel environments (Muller and Kubie 1987; Dragoi and Tonegawa 2011). Maps may also be updated during ongoing experience. Because the firing patterns of grid cells are highly regular, their firing fields merely need to be aligned to a new set of environmental boundaries. Accordingly, the firing patterns in the medial entorhinal cortex can emerge instantaneously in novel environments (Hafting et al. 2005). Similar to what is observed for grid cells, the location-selective firing in CA1 also emerges rapidly, and new location-selective firing patterns in CA1 are stable within minutes after a rat is introduced to a novel environment (Muller and Kubie 1987; Wilson and McNaughton 1993; Kentros et al. 1998; Anderson and Jeffery 2003; Frank et al. 2004; Leutgeb et al. 2004; Wills et al. 2005).

Along with new CA1 firing after an animal begins to explore an arena, many CA3 cells also begin to immediately fire with spatial selectivity. In contrast to the stable firing locations in CA1, some of the emerging CA3 place fields continue to change for approximately 10–20 min. During this period, some fields completely

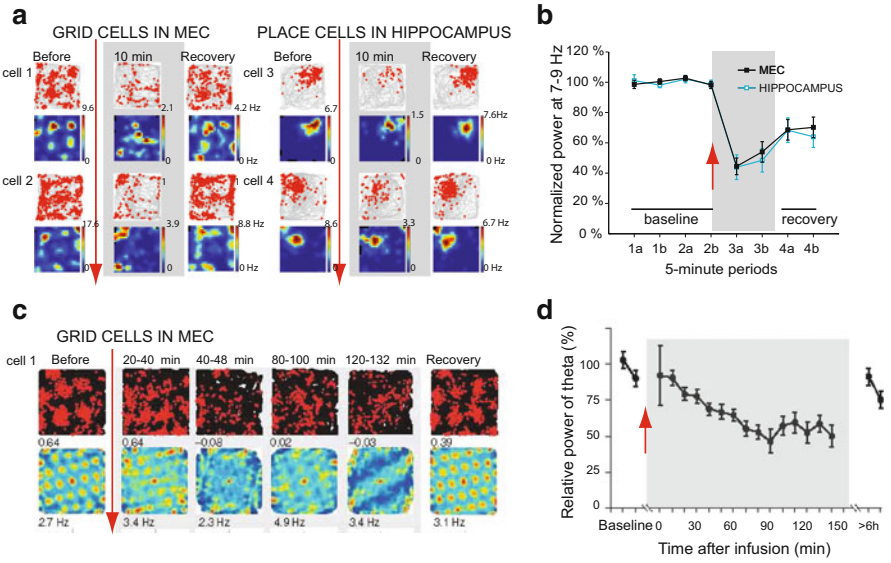

Fig. 9.6 Place cells in the hippocampus persist without input from grid cells in the medial entorhinal cortex (MEC). (**a**) The periodic firing pattern of grid cells is abolished following inactivation of the medial septal inputs to the hippocampus and entorhinal cortex (*left*). *Red arrow* indicates the onset of inactivation, and the *gray box* indicates the time during which the septal input remains inactive. During the period when grid cells lose all spatial periodicity in their firing patterns, the spatial firing patterns of hippocampal place cells remain unchanged (*right*). Trajectories (*gray*) with superimposed spike locations (*red dots*) are shown for two hippocampal principal neurons and two grid cells from MEC. The corresponding color-coded rate maps are shown below. (**b**) Inactivation of the medial septum by the infusion of lidocaine is accompanied by a significant reduction in theta oscillations of the local field potential (LFP) for both hippocampus and entorhinal cortex, as shown by the percent change in the power of LFP oscillations between 7 and 9 Hz compared to baseline. During the period of theta reduction, place fields in the hippocampus can retain spatial information in the absence of the precise spatial firing patterns from grid cell input (shown in **a**), which suggests that local theta oscillations and/or excitatory septal inputs are required to support the periodic firing of grid cells. (**c**) The periodic firing of grid cells is abolished by inactivation of the hippocampus (*red arrow*: muscimol delivery to hippocampus, *gray box*: the duration of inactivation). Spike trajectories from one grid cell are shown for time intervals after inactivation, with the corresponding spatial autocorrelation maps below. Hippocampal inactivation results in a reduction in grid periodicity. Grid firing may thus require excitatory drive from the hippocampus, although the decrease in excitation may also be mediated by the medial septal area, as indicated by a decrease in theta amplitude (**d**). Modified with permission from Koenig et al. (2011) and Bonnevie et al. (2013)

disappear, while others newly emerge. Despite the slow formation of CA3 fields at a new spatial location, CA3 cells can nonetheless show rapid rate changes in response to changes in sensory cues during this phase (Leutgeb et al. 2006). In contrast, CA1 cells generally show a lesser initial rate discrimination between detailed differences, such as for changes in the shape or color of new environments (Bostock et al. 1991; Lever et al. 2002; Leutgeb et al. 2006). The differences in the responses

of CA3 and CA1 cell populations to these manipulations indicate that the neural mechanisms that rapidly generate new place field locations may be separate from the mechanisms that encode more detailed information about distinct features of the new places. However, the rather slow time-course of developing distinct representations for similar environments in CA1 can be overcome when the differences are of significance to the animals during context fear conditioning (Moita et al. 2004).

The hippocampus does therefore not only generate new, distinct representations, but also incorporates these representations into memories (Frankland et al. 1998). For example, an environment can be readily associated with a foot shock during context fear conditioning once the exposure time to the new environment has exceeded approximately 1 min (Fanselow 2000). Different "contexts" in fear-conditioning studies generally correspond to the types of enclosures that are used in recording studies. Insights from hippocampal remapping studies should thus make predictions about the neuronal representations of contexts in fear-conditioning paradigms, and these predictions can be tested by artificially activating neuronal activity patterns that correspond to a particular context.

Several recent studies tested whether an artificially evoked neuronal firing pattern identifies a context to the extent that it is sufficient to generate and/or evoke fear memories (Garner et al. 2012; Liu et al. 2012; Ramirez et al. 2013). The first such study tagged neurons in many cortical areas and in all hippocampal subregions that were activated in one context (context A) (Garner et al. 2012). Fear conditioning was then performed in a second, distinct context (context B) while simultaneously activating a phenocopy of the activity in context A. The joint activation of the two context representations during acquisition obscured a later fear response to only context B, while the fear response to the joint pattern was at control levels. From a population-coding perspective, it can be inferred that the neuronal activity during context conditioning was a sum between the two contexts, and such additive activation was confirmed by counting the number of activated cells in CA3 and CA1. With many additional cells active, the sum of the two activity patterns resulted in a representation that is distinct from context A as well as distinct from context B. Accordingly, the joint activation (artificial A pattern added to the physiological B pattern) acted as if it was a completely distinct context during memory acquisition and retrieval (Garner et al. 2012).

In a second set of studies, fear conditioning was performed in an animal model in which only dentate cells that are active in a particular context were tagged, and a different outcome was obtained (Liu et al. 2012; Ramirez et al. 2013). Here, the dentate granule cell population that represented context A was activated either during fear conditioning in a different context or during retrieval testing in a different context. The artificial activation of context A resulted in a behavioral response as if the animal actually was in context A rather than in a joint context or in the context in which the testing was performed. Activation of context-selective neural activity in the early processing stages of the hippocampal circuit (i.e., the dentate gyrus and CA3) may tap into network mechanisms that are designed to perform pattern separation and to resolve conflicting information. Even though the

test context can be assumed to result in its own physiological activation pattern, the artificial activation of dentate cells may provide competing activation such that intrahippocampal processing can generate a rather complete pattern for context A (see Fig. 9.4b). Whether the synthetic activation of a memory trace generates a competing or a matching representation therefore depends on the way in which the added neuronal activity taps into hippocampal mechanisms for remapping, pattern separation, and pattern completion.

9.7 Summary

Hippocampal remapping has been discovered and predominantly studied with manipulations of sensory cue configurations. These controlled conditions have resulted in important insights into hippocampal network mechanisms that have been applied to experimental designs that explicitly test the nature of the memory trace. Recent advances allow for the selective manipulation of neuronal firing patterns in the hippocampus and entorhinal cortex, and the capability to activate select neuron populations will result in further mechanistic insight into network computations and how they contribute to memory acquisition and retrieval. Of particular importance in future studies is perhaps a distinct activation of neural networks for either path integration or memory processing. The separate activation of these two functions could be possible if they are allocated to different cell populations. For example, it is possible that key components for attractor-based path integration exist in the entorhinal cortex (Hafting et al. 2005; McNaughton et al. 2006), while the hippocampus may contribute more directly to spatial memory, for example, by joining discontinuities (Wallenstein et al. 1998) and by storing associations between different spatial maps (Witter and Moser 2006).

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Splitter Cells: Hippocampal Place Cells Whose Firing Is Modulated by Where the Animal Is Going or Where It Has Been

10

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Abstract

When a rat runs through a given location on its way to or from different destinations, place fields encoding this location often fire at a higher rate for one of the two (or more) journey types, compared to the others. This unequal "splitting" of a place field suggests that the hippocampus differentiates between common segments of routes leading to or from different places. In the current chapter, we review the initial demonstrations of this pattern of place cell firing and consider the contribution of different task demands and discriminative cues. We conclude by considering the development of splitters and what is known about their essential circuitry.

In the traditional view of hippocampal place cells, the location in an environment to which a specific cell is tuned—its place field—represents the animal's instantaneous (or slightly anticipated) location (O'Keefe and Conway 1978; Muller and Kubie 1989). Even in early accounts of hippocampal cell firing, however, there was evidence that place cells respond not just to the animal's location in the environment but also to the approach to reward (Rank 1973) or to the encounter of an unexpected stimulus (O'Keefe 1976). Subsequent work suggested that place cells encode different features of operant tasks (Eichenbaum et al. 1987; Hampson et al. 1993) and that place fields are anchored to different reference frames within an environment (Gothard et al. 1996; Redish et al. 2000). The current chapter focuses on a modulation of place fields that occurs when a rat runs repeatedly through a location as part of a goal-directed spatial task. This takes the form of a

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high firing rate when the rat runs through a given place cell's field on its way to or from some locations, but not others. In the laboratory we have referred to cells that show this pattern of firing as "splitters", as the strong modulation of their place fields is evident when traversals of the field are split into different journeys (see also Ji and Wilson 2008). The purpose of this review is to summarise what is known about splitters and to offer views about their potential function.

10.1 Initial Demonstrations

Splitters were first described by Wood et al. (2000) and Frank et al. (2000) and characterised further by Ferbinteanu and Shapiro (2003). In the Wood et al. (2000) study, CA1 place cells were recorded as rats performed an alternation task on a continuous T-maze, as shown in Fig. 10.1. The task was similar to a traditional T-maze alternation task, with rats running up a central stem and then taking a left or right turn at a T junction at the end of the stem. At the end of the choice arm, the rat received a sugar-water reward. In the modification of the traditional T-maze task, the rat then continued to the base of the stem via a connecting arm and traversed the stem again before entering the left or right choice arm. The rat was reinforced only if it chose the arm not chosen on the previous run. The rat would then continue back to the stem of the maze and continue alternating in this figure-of-eight manner.

The specific interest of Wood and colleagues was the place fields on the central stem of this maze. Did they encode the instantaneous location of the rat, or was their firing modulated by the specific journey that the rat was executing (left to right or right to left)? What the authors found when they separated the data for left and right journeys was that, for approximately 2/3 of the cells with fields on the central stem, firing rates differed depending on the journey. The remaining 1/3 of the cells fired at a similar rate and in the same location on left and right journeys. The differences observed in the 2/3 of cells that differentiated between the journeys were not the result of differences in the head direction, speed, or positions occupied as the rat ran through the central stem on the different journey types. Thus, in the same location and with the rat facing the same direction, some place cells fired at a high rate when the animals ran through the cell's field on a right-to-left journey and showed very few spikes on the opposite journey (Fig. 10.1). Others showed the opposite pattern, and the remainder fired similarly on both journeys. This suggests that, at any given location, a subset of CA1 cells were reliably signalling the current location of the animal, whereas those with differential activity were providing additional information about the current trial. Whether this differential firing reflected an encoding of where the rat was heading or reflected where it had just come from could not be determined in this study, as rats rarely made errors.

In an independent study, Frank et al. (2000) recorded CA1 place cells and entorhinal cortex (EC) cells (from deep and superficial layers) on an m-shaped maze and observed the same phenomenon. In their maze, the rats were trained on an alternation task in which they ran from the centre of the m and then down the left arm, then back to the centre arm, and then down the right arm and back to the

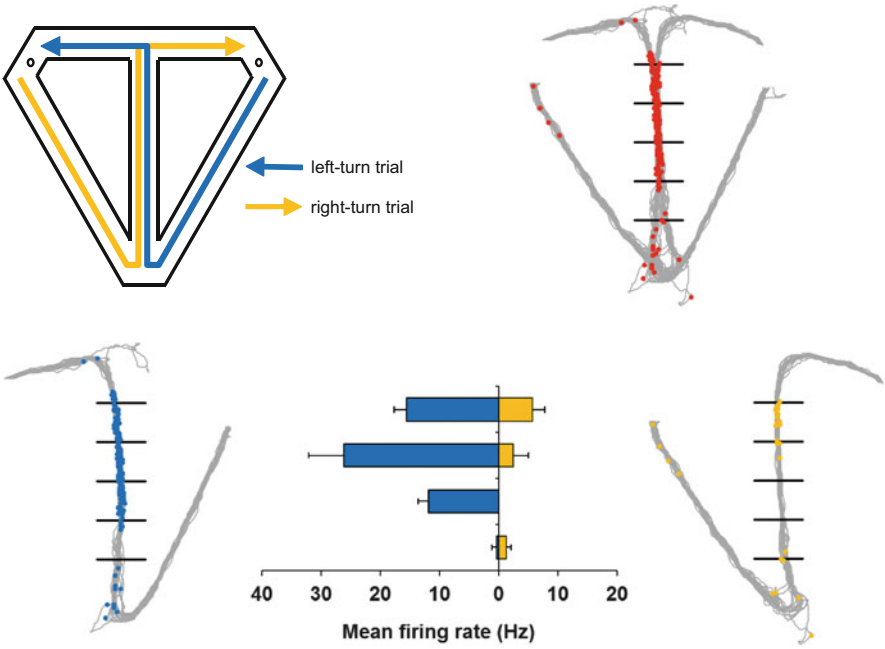

Fig. 10.1 An example of a splitter place cell. *Upper plots*: rats were trained to run a figure-of-eight pattern on a T-maze with return arms. An example of a place cell (*red dots* indicate spikes) recorded on the maze (*grey lines* indicate the path of a rat in a recording session; the reward location are omitted). *Lower plots*: on left-turn trials, this cell fired at a high rate on the central stem of the maze, while on right-turn trials, substantially fewer spikes were observed. Based on Wood et al. 2000

centre, and so on. Thus, the rats repeatedly travelled up and down the common centre arm, either on their way to the left or right arm, or on their return from these arms. Frank and colleagues observed that a subset of the cells recorded in CA1 and the EC showed firing differences in the central stem of the maze when the animal was in the same location and facing the same direction, but either heading to different maze arms or returning from different arms. As the animals were travelling to different arms on their outbound trajectories from the centre arm of the m maze, but returning to this arm from both arms on their inbound trajectories, it was possible to specify whether the activity of cells on the central stem predicted where the animal was going on outbound journeys or reflected where it had been on inbound journeys. Both types of splitters, prospective and retrospective, were observed, though prospective activity was relatively rare in CA1 and superficial EC and more prevalent in deep layers of EC, whereas retrospective activity was prevalent in all three regions. We will return to the potential significance of the entorhinal cortex splitters later.

Prospective and retrospective splitter activity in CA1 was further characterised by Ferbinteanu and Shapiro (2003). They tested rats on a plus-maze task in which a

given maze arm (e.g. the east arm) was reinforced for a block of trials, and the animal travelled to that arm from one of two different locations (the north or south arm) on different trials. After the animal chose the correct arm on 9/10 trials, the reward was shifted to the opposite arm (i.e. the west arm), and another block of trials was run, for a total of 4–6 blocks. As in the studies described above, Ferbinteanu and Shapiro found place fields with differential prospective and retrospective firing on the parts of maze where overlapping journeys were observed, as well as traditional, non-differential place fields. Specifically, of the cells that had place fields in the north or south start arms, a significant proportion (35–58 % depending on the type of analysis used) fired differently depending on whether the animal was executing an east-bound or west-bound journey, indicating prospective coding of the destination of the journey. Similarly, of cells that had place fields in a goal arm, 56–69 % fired differently depending on the origin of the journey (north or south arm), indicating retrospective coding of origin of the journey. The remaining cells had similar place fields in the goal or start arms on both journey types. In contrast with the Frank et al. (2000) study, in which only 4 % of CA1 cells showed prospective firing, prospective activity was quite prevalent in this task, suggesting that specific task demands may influence the extent to which these patterns of activity occur. For example, in the Ferbinteanu and Shapiro study, the change in reward locations across blocks of trials may have yielded a rate remapping in start arm place fields.

10.2 The Incidence of Splitter Activity Differs Depending on Task Demands

Since the initial demonstrations of splitter activity described above, splitter activity in CA1 has been reported by several groups. These studies suggest that the incidence of splitters, and the precise nature of this activity, is strongly influenced by task demands.

Two early studies failed to find significant splitter activity on continuous tasks similar to those on which splitter activity had previously been reported. In the first of these, Lenck-Santini et al. (2001) observed little journey-specific place cell firing on a continuous Y-maze task. This task appears similar to the m-maze task on which splitters were reported by Frank et al. (2000), the differences being the shape of the maze (m vs. Y) and the locations at which rewards were provided (in all three arms of the m-maze and in just the middle arm of the Y-maze). In the second study, Hölscher et al. (2004) found that only 4 of 45 cells with place fields on the middle section of a square, figure-of-eight maze were “turn sensitive”. This task appears similar to the continuous T-maze task in which splitters were described by Wood et al. (2000), the main differences being the shape of the maze and subtleties of the training protocol. An elegant study by Bower et al. (2005) provided potential explanations for these conflicting results. Bower and colleagues trained rats to run to a sequence of lights on the periphery of an open-field, circular apparatus. The sequence of paths that the rats took to these lights had overlapping elements,

where the animals ran the same path, either coming from or going to different locations. On this task, during which the animal received a reward when it reached each light, no splitters were observed (see also Berke et al. 2009). Next, the authors trained the rats on a different sequence, using barriers during initial training, (as had been done by Wood et al. (2000), but not by Hölscher et al. (2004)) to encourage the animals to take the correct route. On this task, splitters were observed. Finally, on a third sequence (the "skipped reward" task), reward was not provided at the beginning or end of the overlapping section of the paths but at other locations on the two paths. In this task again, differences in place fields were observed on the overlapping paths.

These findings suggest that whether a place cell shows differential firing likely depends in part upon whether reward is provided at the start or end of overlapping routes or whether the animal's goal choices are restricted with a barrier during training. Each of these manipulations could affect how an animal solves the alternation task, and this in turn could influence the incidence of splitter activity in the hippocampus. For example, Hölscher et al. (2004) have argued that the use of a barrier to direct an animal's choices early in training may increase the likelihood that they adopt a motor strategy consisting of a series of turns to get from the left reward site to right and back to the left to solve the alternation task. Such a strategy could be supported by the striatum rather than the hippocampus (McDonald and White 1994; Packard and Knowlton 2002) and would remain effective even after the barriers are removed. In contrast, if no barriers are present, and animals must make a free choice of goal arm during training, Hölscher et al. (2004) suggest that animals may require a hippocampus-dependent memory strategy to keep track of previous goal choices. Following this logic, they argue that the splitter activity observed by Wood et al. (2000) in CA1 may reflect the use of a motor strategy and may represent a conjunction of place information with egocentric motor information (trajectory encoding or turn sequence).

A study by Ainge et al. (2007b) provides partial support for these ideas. They showed that when rats were trained on the continuous T-maze task without barriers, a smaller proportion of splitter cells were observed on the central stem than in the original Wood et al. (2000) study (44 % compared to 66 %), consistent with an effect of barriers on the incidence of splitters. However, in contrast with Hölscher et al. (2004), a significant proportion of cells with activity on the central stem showed splitter activity under these conditions. A second important finding of this study was that rats with complete bilateral lesions of the hippocampus showed no impairment in acquisition or performance of the continuous alternation T-maze task. Thus, even when no barriers were used during training, it appears that rats can utilise a hippocampus-independent (motor) strategy to learn and perform the continuous alternation T-maze task. It is possible, therefore, that the splitter activity observed in the continuous T-maze alternation task does reflect the use of a hippocampus-independent motor strategy, as proposed by Hölscher et al. (2004), and that it represents a conjunction of allocentric place information and egocentric motor information.

10.3 The Nature of Splitter Activity Differs Depending on Task Demands: Delayed vs. Continuous Alternation Tasks

The preceding discussion focussed on splitter activity in continuous alternation tasks that may be solved by hippocampus-independent (possibly motor) strategies. However, robust splitter activity is also observed in tasks that require the hippocampus. For example, acquisition or performance on the m-maze task (Frank et al. 2000; Kim and Frank 2009) and the plus-maze task (Ferbinteanu and Shapiro 2003; Ferbinteanu et al. 2011) is significantly impaired by damage to the hippocampus or the fornix. Thus, splitter activity in CA1 is not associated in all tasks with the use of a hippocampus-independent motor strategy. In this section we explore the nature of splitter activity in both hippocampus-independent and hippocampus-dependent tasks.

A study by Ji and Wilson (2008) has provided further information about the nature of splitter activity in the continuous alternation tasks. They trained rats to alternate on a figure-of-eight maze and then altered the task such that reward was only available for running a loop on one or the other side of the maze. They found clear examples of splitters on the middle section of the maze in the alternation task and, when coupled with the single-side task, were able to show that the majority of these splitters were retrospective—encoding where the rat had come from and not where it was going. By extension, in the continuous T-maze, task splitters may reflect retrospective rather than prospective information.

Ainge et al. (2007b) recorded from CA1 cells in the rats trained on one of two versions of the continuous T-maze task. In the first version, the task was run as in the Wood et al. (2000) study, with the rats stopping at the ends of the choice arms for reward but otherwise running continuously on the maze. As discussed earlier, the hippocampus is not required to perform this task. In the second version, the rats were confined at the base of the stem of the T-maze on each trial for a 10 s delay period. Rats with hippocampal lesions were significantly impaired on this version of the task. Splitters were observed in both versions of the task, but whereas in the no-delay version of the task they were observed throughout the central stem of the maze, in the delay version they occurred predominantly at the base of the stem, where the animals were confined during the delay period. Thus, the location of splitters on the maze appeared to be dependent on the task demands and behaviour of the animal.

In a recent study using a similar delayed alternation task on the continuous T-maze, Robitsek et al. (2013) observed splitters on the central stem even when there was a delay at the start of the stem. As noted by the authors, Ainge et al. (2007b) recorded from animals that had not experienced the continuous (no delay) condition, whereas rats in the Robitsek et al. (2013) study were tested with both the continuous version of the T-maze *and* the delayed version in the same session. Thus, one possibility is that the splitter activity observed on the stem of the maze in the delay condition in the Robitsek et al. (2013) study may have developed during the continuous (no delay) task and then continued during delay trials. A second interesting finding in this study was that the majority of both traditional

place fields and splitters showed different firing rates on correct trials compared to error trials on the delay version of the task.

A study by Pastalkova et al. (2008) supports the idea that splitter activity is more prominent during the delay period than on the central stem in a delayed alternation task and also suggests that the splitter activity observed during the delay period tend be prospective rather than retrospective. They recorded from CA1 cells as rats performed a delay version of a figure-of-eight alternation task in which rats ran on a running wheel at the base of the central stem for 10 or 20 s on each trial. The main novel finding of this paper was that different place cells fired reliably at different times during the running wheel delay, indicating temporal coding by hippocampal place cells (see Eichenbaum et al. 2014). However, of relevance to the present discussion, they found that a significant number of the cells that fired during the running wheel delay period showed differential firing depending on the animal's future arm choice on the maze. Some of these cells fired exclusively during wheel running before either a left or right arm choice, whereas others showed differential firing rates and/or fired at different times after the beginning of wheel running depending on the subsequent arm choice. These splitter cells predicted not only where the animal would go on correct trials but also on error trials, indicating strong prospective coding in this version of the task. Interestingly, the largest proportion of neurons exhibiting prospective activity was at the beginning of wheel running, and the proportion decreased as a function of time during the delay and as animals ran in the stem of the maze. Therefore, as in the Ainge et al. (2007b) delayed alternation task, splitter activity was more prominent during the delay period than when animals were running on the central stem of the maze.

Taken together, observations from continuous T-maze and figure-of-eight tasks indicate important differences between the splitters observed in no-delay and delay conditions. In the hippocampus-independent no-delay condition, splitter activity typically occurs as the animals run up the central stem towards the location at which paths diverge and tends to be retrospective. As suggested, this may reflect aspects of the motor behaviour of the animal. In the hippocampus-dependent delay condition, more splitter activity is observed during the delay period than as rats run up the central stem, and, at least in the study of Pastalkova et al. (2008), this delay activity is predominantly prospective.

Adding a delay in the alternation task alters it in two important ways. First, it increases the memory load. Second, it breaks up the continuous trajectory from one reward arm to the other. This interrupts a motor pattern that is initiated at the reward site, which may force the animals to rely on a hippocampus-dependent spatial memory strategy. Thus, both retrospective and prospective splitter activity could contribute to task performance in hippocampus-dependent alternation. However, the emergence of prospective activity during the delay period raises the possibility that prospective splitter activity may be more important than retrospective activity in task performance.

10.4 The Nature of Splitter Activity Differs Depending on Task Demands: Going Beyond Spatial Alternation Tasks

Splitter activity is observed not only in spatial alternation tasks but also in the match-to-sample task with serial reversals on a plus maze (Ferbinteanu and Shapiro 2003) described earlier. In this hippocampus-dependent task, rats not only must keep track of which goal arm is rewarded during the ongoing block of trials but also must be able to switch to a new goal location. As described earlier, robust prospective and retrospective activities are observed as rats traverse the start and goal arms of this maze, respectively. An interesting finding in this study was that differential firing was maintained in 49 % of the retrospective cells in the goal arms even when the rat initially headed into an incorrect arm, before entering the correct arm. Thus, the retrospective firing of these cells appeared to reflect the rat's journey from a particular start point, as opposed to its specific trajectory. This suggests that it does not reflect the execution of a specific motor sequence but rather memory for the origin of the journey. The remaining 51 % of cells with retrospective firing lost selectivity for a specific journey on error trials, firing similarly regardless of the origin of the trial. This effect was more pronounced for prospective cells, with 72 % becoming journey independent on error trials. The decrease in splitter activity on error trials suggests that splitter activity may contribute to accurate task performance. Ferbinteanu and Shapiro (2003) argue that, as prospective activity is observed prior to the behavioural discrimination between goal arms in this task, it is likely to contribute more directly to accurate goal arm choices than retrospective activity, which may reflect memory of the recently executed journey. This is supported by the observation that on error trials, prospective firing is more affected than retrospective firing. Interestingly it was not the case that the activity of prospective cells predicted the arm that would be chosen on error trials, suggesting that it was not directly mediating response selection. Rather, activity became journey independent on error trials, suggesting that the journey-dependent prospective activity may signal the expectation of finding reward in a particular goal arm on correct trials (Ferbinteanu and Shapiro 2003).

Splitters have also been observed in a serial reversal task with more than one choice point. Ainge et al. (2007a) trained rats on a double Y-maze to run from a start box through two choice points to one of four goal boxes (Fig. 10.2). Only one of the four boxes was rewarded, and after ten trials, the reward was moved to a different goal box. Ainge et al. found a disproportionate number of CA1 place fields in the start box and the initial runway of the maze. When the firing of these fields was split between the journeys to each of the four goal boxes, 44 % showed a high rate of firing for one specific goal box, and little firing for the remaining three. As the animals always started the maze from the same location—the start box at the base of the maze—this firing likely encoded the animals intended destination. One interesting feature of this prospective splitter activity was that it did not differentiate between the two paths that could be taken at the first choice point on the maze but rather differentiated between all four possible trajectories. Therefore, it was associated not just with the immediate arm choice the animal would make (as had

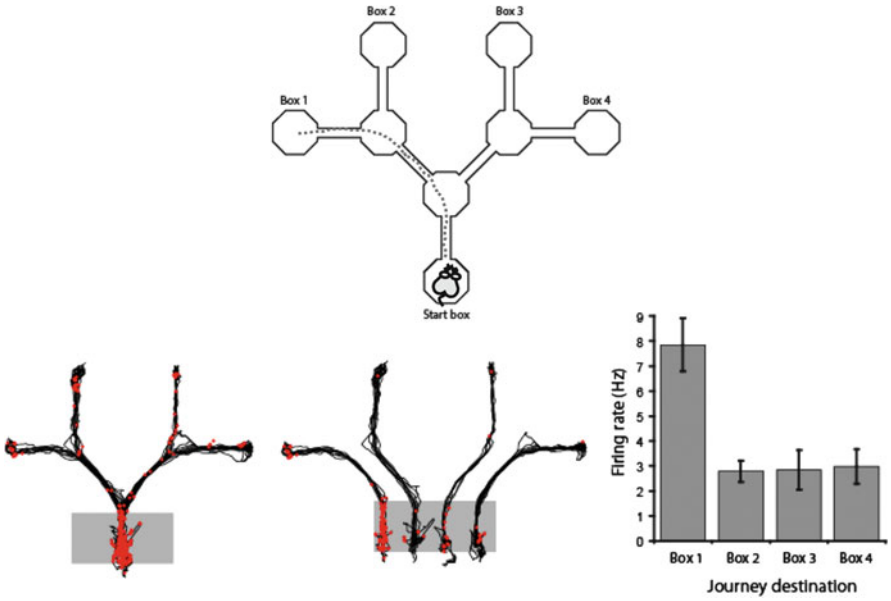

Fig. 10.2 A prospective splitter cell. *Upper plot*: rats were trained to run from a start box to a goal box, only two of which contained reward on a given trial. The rat was then picked up by the experimenter and placed back in the start box for another trial. After ten trials with reward in the same location, the reward was shifted to another location for the next ten trials, and this pattern was repeated until all four goal boxes had served as reward locations. *Bottom plots*: an example of a place cell recorded near the start box during performance of this task. *Red dots* indicate spikes; *black lines* indicate the rat's path. When the trials were separated according to the goal box selected, the firing of this cell was significantly higher for trips to goal box 1, as opposed to the other three goal boxes. Example based on Ainge et al. 2007a

been observed previously in the T-maze, plus-maze and m-maze tasks described earlier) but a more complex prospective coding, either of a series of turns or of the ultimate goal destination. As acquisition (Stevenson 2011) and performance (Ainge et al. 2007a) of this task is impaired by hippocampal lesions, the prospective activity observed in the initial segments of the double Y-maze may play a role in accurate performance.

10.5 Interim Summary

In hippocampus-independent tasks, splitter activity may be predominantly retrospective. Such retrospective activity may provide a readout of the most recent sequence of turns or the origin of the journey combined with place information. While this retrospective splitter activity signals salient differences between trial types or journeys, it is not required for solving the ongoing task. In contrast, in the delay versions of the task T-maze and figure-of-eight mazes, and serial reversal

tasks on the plus maze and double Y-maze (all of which require an intact hippocampus for accurate performance), prospective (as well as retrospective) activity is observed. This prospective activity may play an essential role in guiding choice behaviour in these tasks.

10.6 Splitter Activity May Reflect More than Prospective and Retrospective Encoding: Encoding Behavioural Contexts?

Smith and Mizumori (2006) recorded CA1 cells from rats performing a variant of the plus-maze task used by Ferbinteanu and Shapiro (2003—described above), in which reward was available in the east arm for the first block of trials each day and the west arm for the second block. In their version of the task, animals started each trial from any one of the three unrewarded arms. Smith and Mizumori (2006) reported what they termed "context-specific" firing, where the context was defined by the location of the reward during a block of trials. In some cases, this context-specific firing was similar to the retrospective and prospective firing observed by Ferbinteanu and Shapiro (2003), in that cells in a given start arm would fire at a high rate only when animals were going to a specific goal arm (prospective firing) or in a given goal arm only when they had started their journey in a particular start arm (retrospective firing). However, other cells fired in different locations on the maze depending on the reward location, indicating additional contextual modulation of the place fields.

Smith and Mizumori (2006) also recorded during the delay between trials, when animals were placed on a platform to the side of the maze. Context-specific firing was also observed during this delay period, such that a given cell might fire on the platform during one block of trials but not the other. This delay activity is reminiscent of the splitter activity observed during the delay period (Ainge et al. 2007b) or during wheel running (Pastalkova et al. 2008) in the delayed T-maze alternation task. Moreover, Gill et al. (2011) have recently reported context-dependent sequential activity during the delay period of this task, with different cells firing in a context-dependent fashion at different times during the delay, as in the Pastalkova et al. (2008) study.

Another form of context-specific encoding by place cells was reported by Griffin et al. (2007). They trained animals on a discrete trial nonmatching-to-place task on a T-maze similar to that used by Wood et al. (2000, Fig. 10.1). In this task, each trial had two phases. In the sample phase, one choice arm of the T-maze was blocked. The rat entered the base of the stem of the maze from a holding area beside the maze and ran up the stem into the unblocked arm, where it received a reward. After consuming the reward, the rat ran to the base of the stem via the return arm, where it was blocked for 10 s before being given access to the stem of the T-maze for the choice phase. On the choice phase, both goal arms were available, and the rat was rewarded for entering the arm not experienced during the sample phase. The trial ended with the rat running back down the return arm and from there to the holding

area for a 10–20 s ITI before the next trial. In this task, only 17 % of CA1 cells with activity on the central stem fired differentially depending which arm the animals subsequently entered. However, 70 % of CA1 cells with activity on the central stem fired selectively on either sample phase or choice phase of the task. Thus, in addition to prospective and retrospective activity related to the origin and goal destinations, Griffin et al. propose that different populations of CA1 cells may be selectively active during encoding and retrieval phases of a memory task.

Together, these studies indicate that hippocampal place cells code not only current location and retrospective and prospective journey-related information but also "contextual" information about the ongoing task.

10.7 Splitter Activity in Cue-Response Tasks and Spatial Tasks Guided by Discriminative Cues

The discussion so far has focussed on splitters recorded in tasks in which goal choices are made using spatial alternation or spatial matching-to-place rules. Splitter activity has also been examined in a number of tasks involving overlapping journeys through the same space to different goals in which behaviour is guided by cues available at the goal (cue-response tasks) or discriminative cues at or prior to the choice points. As for the spatial tasks described above, splitter cells related to specific trajectories or journeys are typically observed in these tasks, but in addition, the cells are often modulated by the particular strategy being used or the discriminative cues available.

Ferbinteanu et al. (2011) tested rats on two tasks on the plus-maze apparatus. In both tasks, rats started from the north or south arms, and reward was available in the east or west arm. In the hippocampus-independent cue-response task, the location of reward was signalled with a white flag in the goal arm, and the goal location varied according to a pseudorandom sequence. In the hippocampus-dependent spatial task, the flag was not available, and rats performed the match-to-place task with serial reversals described earlier. This set up a situation in which rats exhibited the same behaviours (running from north and south arms to the east and west arms) in both tasks, but this behaviour was guided by different types of information (cue response vs. spatial memory). Rats were trained on both tasks to criterion, after which recordings were made as animals performed both tasks within a single recording session. Journey-dependent splitter activity was observed in both tasks, and the proportion of prospective and retrospective fields was similar in both tasks. However, prospective and retrospective activities were differentially modulated by memory strategy. Specifically, for cells that fired in a start arm, approximately half showed prospective journey-dependent activity in one task and journey-independent activity in the other, while the other half fired similarly (either in a journey-dependent or journey-independent fashion) in both tasks. This indicates that different overlapping populations of cells coded journey destination in the two tasks. In contrast, 84 % of the place fields that fired retrospectively on the goal arm in one task also fired retrospectively in the other task, indicating that

journey origin is coded by a similar population of cells in both tasks. These data also indicate that the firing rates of cells in the start arm were influenced strongly by both memory strategy and journey destination, whereas those in the goal arms were influenced more by the origin of the journey than the memory strategy used to get there. In this task, animals were required to discriminate between and select the appropriate memory strategy while in the start arm and use this to guide behaviour. However, once they reached the goal arm, the memory strategy used to get there became irrelevant. The finding that memory strategy modulates prospective coding more than retrospective coding is consistent with the idea that this prospective activity may play a role in strategy implementation and goal selection in these tasks.

A study by Ainge et al. (2012) looked at splitters in a task where the animal's knowledge of the reward location was manipulated. They tested rats on a T-maze task where the food reward was signalled by either a constant light at the choice point (signalling that food was available in the right arm of the T) or a flashing light (signalling that food availability at the left arm of the T). The onset of this discriminative stimulus was manipulated, such that on some trials the signal was available throughout the stem of the T, whereas on other trials, the stimulus was only presented when the animal reached the choice point of the T. Splitter activity was observed on the stem of the T-maze on this task, but this did not differ between trials when the discriminative cue was on as the rats traversed the stem and those when the cue was not available until later. Thus, the prospective firing of splitters on this task appeared to be related to where the animal was going, as opposed to the discriminative stimulus.

Allen et al. (2012) examined CA1 splitters on a continuous T-maze task in which one arm of the T was associated with a chocolate reward and the other arm with a sweet corn reward. At the base of the T stem, the rat was provided with one or the other reward, and this served as the discriminative cue as to which reward was available after the choice point. They found that a subset of place fields in the central stem fired differentially depending upon the reward cue. Other splitters were retrospective, firing differentially depending on whether the animal had come from the right or left return arm. There were also fields that encoded both the reward type and the previous location of the animal, referred to as conjunctive cells.

10.8 Rate Remapping or Global Remapping?

Theoretically, splitter activity could be mediated by rate remapping, in which cells fire at a high rate in their place fields during one journey or task and at a lower rate in the same location (or not at all) during the other journey or task condition (Leutgeb et al. 2005). Alternatively it could be mediated by global remapping, in which, for different journeys or tasks, different overlapping populations of place cells are active, and those active in both tasks tend to fire at different locations (Bostock et al. 1991). For most of the studies described in this chapter, splitter activity has been defined on the basis of firing rate changes in sections of a maze where different journeys overlap (e.g. Wood et al. 2000; Ainge et al. 2007a, b) or on

changes in the spatial distributions of firing rates (firing rate map correlations, e.g. Smith and Mizumori 2006) and in some cases both (e.g. Ferbinteanu and Shapiro 2003; Ferbinteanu et al. 2011; Bahar and Shapiro 2012). Both global and rate remapping would result in changes in firing rate of a particular cell at a particular location, so this measure does not differentiate between the two processes. A decrease in firing rate map correlation could reflect global remapping (i.e. a shift in the location of a place field), although rate remapping in which a cell is almost silent in one situation and has a high firing rate in another would also result in a decrease in the spatial correlations. Where rate and global remapping have been specifically assessed, a mixed picture arises.

Several studies have calculated the centre of mass (COM) of place fields and compared this between journey types or task demands (e.g. Ji and Wilson 2008; Lee et al. 2006; Griffin et al. 2007). In general these analyses have provided no clear evidence for shifts in the locations of fields between different journeys, or between tasks with different memory demands, but rather favour a rate remapping account of splitter activity. However, a curious phenomenon that has been reported in two studies is that the COM of place fields shifts towards goal locations over the course of a recording session (Lee et al. 2006; Griffin et al. 2007). Allen et al. (2012) recorded splitters in a no-delay continuous alternation task and in a cued spatial task on the continuous T-maze apparatus. Using a combination of firing rate analysis, correlations between firing rate maps and the ability to reconstruct the animal's location based on cell activity, they found that only the firing rate of the cells varied between conditions; they did not observe any shifts in the locations of fields.

In contrast, other studies have reported both rate remapping and global remapping. Takahashi (2013) recorded CA1 cells as rats performed three different tasks on a continuous T-maze with return arms: a cued response task, in which a light at the end of one goal arm signalled the availability of reward, a non-delayed alternation task, and a delayed alternation task. Takahashi compared place cell activity on the stem of the maze across journeys from left to right and from right-to-left goal arms across all three tasks using independent measures of spatial similarity (correlation between firing rate maps) and a firing rate similarity (a firing rate difference score) across a large population of CA1 neurons. Comparison of different journeys (i.e. left to right vs. right to left) within a task resulted in significantly lower scores of both spatial similarity and firing rate similarity than the same analysis performed on the same journeys within a task. In contrast, comparison of the same journey across the three tasks resulted in a significantly lower firing rate similarity score, but no significant decrease in spatial similarity. For the author, these findings indicate that differences in task demands are represented by rate remapping, whereas differences between journeys or trajectories are represented by global remapping (Takahashi 2013). However, as the spatial correlation measure is sensitive both to changes in firing rate and to changes in place field location, it is unclear whether any neurons fired in distinct locations on the stem of the maze for different journeys, which would be the strongest evidence of global remapping.

Ferbinteanu et al. (2011) came to a slightly different conclusion based on their analysis of place cells recorded on the plus maze as animals performed a

cue-response task and a spatial matching-to-place task (described earlier). They concluded that retrospective firing of journey origin (which was relatively unaffected by task demands) was signalled by a firing rate code, whereas different memory strategies were signalled by population coding, whereby different overlapping populations of cells showed prospective firing on the start arms. While this does not speak directly to rate vs. location remapping of individual neurons, it does suggest that global remapping at the population level is associated with changes in task demands as opposed to journey type per se. Similarly, the data of Smith and Mizumori (2006) indicates that population coding is used to differentiate between contexts in their plus-maze task (perhaps reflecting global remapping), whereas retrospective firing within a given context is mediated by changes in firing rate of individual neurons (rate remapping).

Overall, under many conditions splitter activity takes the form of rate remapping, while strong evidence for a shift in place field locations underlying prospective or retrospective coding within a task is lacking. However, under some conditions different populations of neurons may be active, depending on task demands, reflecting global remapping.

10.9 Development of Splitters

To explore the relationship between CA1 splitters and behaviour further, several groups have investigated the development of splitter activity and related it to the behaviour or performance of animals on the task.

In the continuous T-maze task, Lee et al. (2006) found differential firing of place cells (splitters) on the central stem of the maze on the first day of alternation training on the maze. In addition, there was no difference in the proportion of cells that were splitters across the first 4 days of training. This suggests that splitter activity develops and stabilises very quickly. This rapid development of splitter activity appears to be inconsistent with our proposal that splitter activity in this task may result from acquisition of a motor strategy, as typically motor learning takes place over many trials (Packard and Knowlton 2002). However, prior to the alternation training, animals in this study were pretrained over several days to run unidirectional laps on one side of the T-maze (with barriers to prevent access to the other side), and on the first day of alternation training, they ran two blocks of unidirectional laps (first on the pretrained side, then on the opposite side) before progressing to the alternation task. Thus, it is possible that a representation of each trajectory was established before the first day of alternation training.

In unpublished work (Stevenson 2011), we have examined the development of splitters from the first exposure of animals to a maze. Rats were tested as they learned the hippocampus-dependent match-to-place task with serial reversals on the double Y-maze developed by Ainge et al. (2007a) (Fig. 10.2). The rats performed poorly on the first day of training but improved substantially over the next 2 days, with most rats achieving >80 % correct performance on the third or fourth day. Over the first 3 days of training, the percentage of place fields that were splitters

increased from ~ 10 to ~ 50 %, stabilising at ~45 % thereafter. Thus, prospective splitter activity developed as animals learned the double Y-maze task, suggesting that this activity was associated with the acquisition of the win-stay/lose shift spatial strategy. In a separate group of rats, Stevenson (2011) showed that splitter activity did not develop in a version of the task where all arms of the maze were baited, indicating that it is acquisition of a specific spatial strategy rather than familiarity of the maze per se that is correlated with the development of splitter activity.

Gill et al. 2011 examined the development of splitter activity during the delay period of the context-dependent plus-maze task used by Smith and Mizumori (2006) described above. Rats were first trained for one session on a random reward task, in which the rats started each trial on a randomly designated arm and could retrieve a reward from a different randomly designated arm for two blocks of ten training trials separated by a period of darkness. They were then trained daily on the context-dependent spatial task in which reward was available on the east arm for the first block of 15 trials and the west arm for the second block of 15 trials. They found that different CA1 cells fired at specific time points during the delay even during the random reward task, although their temporal specificity increased during the first day of training on the context-dependent task. However, these cells did not show any context-specific splitter activity (differentiating between the two blocks of trials) during the delay until the first training session on the spatial task, and the splitter activity increased across training (27 % of cells on day 1, compared to 53 % on the middle training day) as animals learned the task.

Together, these data indicate that splitter activity does not develop simply as a result of animals repeating a series of overlapping paths in a maze, as occurs in the random and all arms baited conditions in the Gill et al. (2011) and Stevenson (2011) studies. However, when animals start to use a goal-directed spatial strategy on the maze splitters develop quickly. This parallel development of splitter activity and spatial behaviour is consistent with the idea that splitter activity is driving or contributing to the behaviour. However, further experiments will be required to determine whether this is the case or whether splitter activity simply reflects that a spatial strategy has been adopted.

10.10 Where Are Splitters Found, and What Circuitry Supports Splitter Activity?

Most of the studies discussed so far have described splitter activity in CA1 place cells, the only exception being the Frank et al. (2000) study in which splitter activity was observed in superficial and deep layers of the entorhinal cortex. This raises two important questions. Where in the hippocampal network is splitter activity observed? And how is splitter activity generated? Recent studies are beginning to address these important questions.

The observation of both prospective and retrospective splitter activity in EC by Frank et al. (2000) raises the possibility that inputs from EC cells that show splitter

activity drive the splitter activity in CA1. However, it is notable that splitter cells were as (if not more) prominent in deep layers of EC than superficial layers, which raises the alternative possibility that CA1 splitters may drive the EC splitters. Interestingly, while retrospective splitters were found in both deep and superficial layers of EC, most of the prospective splitters observed were in deep layers. Thus, one possibility is that prospective splitter activity may be fed forward from CA1 to EC, whereas retrospective splitter activity could arise in either structure or even elsewhere. As the Frank et al. study predated the discovery of grid, head direction, border, and conjunctive cells in MEC (see Derdikman and Moser 2014), it is not known what cell types were being recorded from, although they report that superficial recordings were predominantly from layer III rather than LII cells. Moreover, the majority of recordings were taken from the ventral two thirds of MEC (Loren Frank, pers. comm.) so it is not known whether splitter activity is observed in the more spatially selective dorsocaudal region of MEC where grid cells with high spatial resolution are found (Hafting et al. 2005).

To investigate splitter activity in EC further, and specifically to determine whether it occurs in the superficial layers (II and III) of dorsocaudal MEC that project to the hippocampus, Lipton et al. (2007) recorded from CA1 and from the dorsocaudal MEC on the continuous T-maze alternation (Fig. 10.1). Of the 33 MEC cells recorded from layers II and III with activity on the central stem, 54 % showed statistically significantly different firing rates on left and right journeys. A slightly higher proportion of splitters were found in MEC cells recorded from layers V and VI, although very few cells were recorded from deep layers, precluding a comparison between deep and superficial MEC. Interestingly, Lipton et al. found that MEC cells exhibited a stronger and more reliable discrimination between the journeys than observed for CA1 place cells in their study. This, together with the clear evidence of splitters in Layers II and III of MEC, led the authors to conclude that disambiguation of the overlapping sequences (i.e. splitter activity) occurs before the hippocampus. While suggestive, other possibilities cannot be ruled out. For example, splitter activity may be generated in the hippocampus and fed forward to deep layers and from there to superficial layers of MEC. Moreover, as retrospective and prospective activity were not differentiated in the Lipton et al. study, this leaves open the possibility that different types of splitter activity (retrospective vs. prospective) may be generated by different mechanisms and in different locations.

Within the hippocampus itself, splitters have recently been reported in CA3 (Bahar and Shapiro 2012). CA1 and CA3 cells were recorded as rats performed the matching-to-place task with serial reversals on the plus maze used by Ferbinteanu and Shapiro (2003). Splitter activity (termed "journey coding") was prominent in both CA1 and CA3, with 30 % of cells in each region showing significant retrospective activity, and 20 % and 22 %, respectively, showing significant prospective activity. Individual cells in both regions showed stable journey coding across sessions. On the basis of this finding, it might be proposed that CA1 splitter activity is driven by CA3 splitter activity. However, additional observations of Bahar and Shapiro cast doubt on this scenario. After recording from rats on the standard

matching-to-place task, Bahar and Shapiro then tested animals on two variants of the task. They found a dramatic decline in the proportion of CA3 neurons exhibiting place fields in an altered environment task compared to the standard task, while a similar proportion of CA1 neurons exhibited place fields and a similar proportion showed journey-dependent firing in each task. From this observation they suggested that journey selective activity in CA1 does not depend on CA3 inputs.

Preliminary findings from Ito et al. (2011), implicate a direct input from the nucleus reuniens (RN) in the generation of splitter activity in CA1. They observed trajectory-dependent firing in RN as rats ran a continuous figure-of-eight task for alternating rewards and found that lesions of the RN substantially decreased the number of CA1 fields that were splitters on this task. As RN projects to CA1 but not to CA3 (Vertes 2006), this is consistent with the proposal that CA1 splitter activity does not depend on input from CA3 neurons but rather that CA1 splitters may result from converging spatial (place) information directly from MEC and trajectory information from RN. As RN receives a powerful excitatory projection from prefrontal cortex (PFC, Vertes 2006), it has been suggested that information regarding memory strategy and task rules from medial PFC, as well as current goal information from orbitofrontal cortex (OFC) may be instrumental in mediating prospective splitter activity in CA1 (Bahar and Shapiro 2012; see Shapiro et al. 2014). It will be interesting to determine how lesions of RN affect performance and prospective splitter activity in hippocampus-dependent task.

Several questions regarding the generation of splitter activity are still outstanding. First, are prospective, retrospective, and "contextual" or task-related splitter activity in CA1 generated by the same mechanisms and do they require the same inputs? For example, to the extent that retrospective splitter activity reflects motor sequences, it is possible that interactions with striatum are required (discussed in Ainge et al. 2007b). Alternatively, it has been proposed that retrospective activity in CA1 may depend on direct inputs from cells with retrospective splitter activity in layer 3 of MEC (Ji and Wilson 2008). Is prospective and task-modulated splitter activity dependent on interactions with PFC, as suggested by Bahar and Shapiro (2012)? Finally, related questions include whether splitters in different regions (CA3, CA1, superficial and deep layers of EC) signal the same information and whether they are generated by the same or different mechanisms.

Conclusion

In this chapter, we have summarised the work done thus far on place cells which exhibit differential firing in the same location under different behavioural conditions. These cells, which we refer to as splitters, can encode upcoming locations (prospective firing) or past locations (retrospective firing), specific mnemonic demands, or other "contextual" demands of an ongoing task. Their function has not been definitively established, but they may provide a means of differentiating episodes occurring in the same location (Wood et al. 2000), differentiating behavioural contexts (Smith and Mizumori 2006), encoding sequences of behaviours (Pastalkova et al. 2008), or linking current events with established memories to inform goal-directed learning (Bahar and Shapiro

2012). Another view is that they map well-learned, overlapping trajectories in space (Ito et al. 2011; Grieves et al. 2013). Further investigation into the circuitry that mediates splitter activity and properties of splitter activity in different hippocampal regions and in different behavioural situations will be instrumental in understanding how splitter activity is generated and what it signals. Crucially, we do not yet know whether and how splitter activity of different types is *causally* related to behaviour.

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Time and the Hippocampus

11

Howard Eichenbaum, Christopher J. MacDonald, and Benjamin J. Kraus

Abstract

Episodic memory is defined by the temporal organization of events in specific experiences. The hippocampus plays an essential role in episodic memory, suggesting that studies on temporal processing by the hippocampus might offer insights in the mechanisms of episodic memory. Here, we review reports on the effects of hippocampal damage in humans and animals and physiological studies using brain imaging in humans and single neuron recordings in animals. These studies provide converging and compelling evidence that the hippocampus is critical for the temporal organization of memories in humans and animals, including when spatial cues are irrelevant. Furthermore, the hippocampus in engaged in humans associated with temporal processing of memories, and hippocampal neuronal networks in animals and humans represent the temporal organization of experiences and disambiguate overlapping temporally extended experiences. In particular, hippocampal "time cells" fire at particular moments during temporally structured experiences, much as hippocampal place cells fire associated with particular locations in spatially organized experiences. Comparisons of firing properties of hippocampal neurons across species and behavioral situations suggest that the hippocampus provides a temporal and spatial "scaffolding" that organizes events to compose episodic memories.

In introducing his proposal for a distinction between episodic and semantic memory, Tulving (1972) emphasized that "Each experienced event always occurs at a particular spatial location and in a particular temporal relation to other events that have already occurred, events occurring simultaneously with it, or events that have not yet occurred" (p. 388). Later, Tulving (1984) elaborated on the information contained in episodic and semantic systems: "Organization of knowledge in the episodic system is temporal," whereas, "The organization of knowledge in the

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semantic system, on the other hand, is defined by many relations that could be classified as 'conceptual'" (p. 225). Although several accounts following on Tulving's characterizations of these memory systems argued that the hippocampus plays a specific role in episodic memory (see Eichenbaum and Cohen 2001), a strong linkage came with the report by Vargha-Khadem et al. (1997) that damage early in life isolated to the hippocampus results in a selective loss of episodic memory with intact semantic memory. Combining Tulving's characterization of the organization of episodic memory as temporal and the observation of an essential function served by the hippocampus in episodic memory, one might expect that the hippocampus plays a key role in the temporal organization of memories.

Consistent with this expectation, an early computational model of hippocampal function emphasized its role in temporally organized memories (Levy 1989; Levy et al. 1995). Also many early studies on the effects of hippocampal damage in animals revealed deficits in behavioral tasks that emphasize a temporal discontiguity, including a variety of "working memory" tasks (Olton et al. 1979), tasks that require timing [e.g., differential reinforcement for low rates of responding; DRL; Sinden et al. (1986)], and trace conditioning (Solomon et al. 1986). These observations led to the proposal by Rawlins (1985) that the fundamental role of the hippocampus in memory is to bridge temporal gaps. However, there are also deficits following hippocampal damage in memory tasks in which bridging a temporal gap is not required, e.g., the standard water maze (Morris et al. 1982) and other spatial "reference memory" tasks (O'Keefe and Conway 1980), and minimal or no deficit following selective hippocampal damage in some tasks that emphasize delays, e.g., delayed nonmatching to sample (see Mumby 2002). Based on these mixed findings, the idea that the hippocampus plays a fully selective role in bridging temporal discontiguities fell out of favor in the animal literature, especially in contrast to the more pervasive role of the hippocampus in spatial memory, although there are also exceptions wherein animals with hippocampal damage exhibit intact spatial memory (e.g., Eichenbaum et al. 1990).

Here, we will consider the nature of the hippocampal contribution to the temporal organization of memory, updating studies on the effects of hippocampal damage and reviewing physiological studies on hippocampal activation during temporal processing. At the outset of this review, we highlight two general issues that will be discussed. First, it is important to distinguish ways in which episodic memories are defined in time. We commonly characterize our memories by their occurrence on a particular date or period in life, e.g., "yesterday," "in high school," and "at my wedding." These characterizations likely do not involve representing time directly, but rather describe situations or contexts for which we use temporal labels. In contrast, Tulving (1972, 1984), as well as virtually all of the models of episodic memory, focus at a much briefer time scale that characterizes the order of events within an episode, and there has been considerable emphasis on how the hippocampus disambiguates memory for sequences of events that overlap in their elements. We will discuss the role of the hippocampus both in "dating" memories and in the sequential organization of events within memories. Second, there are different views about the neural and cognitive mechanisms that underlie the

temporal organization of events within episodes. By one view, temporal organization is constituted as a serial concatenation of events, whereas an alternative idea is that temporal organization involves as a gradually changing temporal context representation onto which event representations are bound at the appropriate moments. We will discuss the evidence for these two mechanisms that hippocampal circuits might employ in supporting the temporal organization of memories and consider how the role of the hippocampus in temporal processing relates to its better known role in spatial processing.

11.1 Memory for When Episodes Occurred

There is a wealth of evidence that the hippocampus is activated during the retrieval of temporally dated memories that involve personal events (Rekkas et al. 2005; see Maguire 2001 for review). In particular, one study directly compared temporal specificity and personal relevance in autobiographical memories and showed that hippocampal activation was strongly influenced by both factors, most strikingly when time-specific memories were also personally relevant (Maguire and Mummery 1999). Conversely, following loss of neurons in hippocampal area CA1, memory for the temporal and spatial context of autobiographical information is impaired (Bartsch et al. 2011). Patients with hippocampal damage are also impaired when asked in which of two lists specific items had previously been studied (Mayes et al. 2001; Downes et al. 2002). Correspondingly, in normal individuals, accuracy in this test is predicted by activation of the hippocampus (Fig. 11.1a; Jenkins and Ranaganath 2010).

In a popular assay of temporal dating in rats, animals are presented with different object stimuli in experiences separated by an hour, after which their relative exploration of the two objects is assessed during simultaneous presentation of both objects. Rats and mice spontaneously investigate the earlier experienced object more so than the later experienced object, thus reflecting their memory for the order of widely separated events. Hippocampal lesions impair memory for the order of stimulus presentations, even as the same animals show normal memory for previously experienced objects as compared to novel objects (DeVito and Eichenbaum 2011; Barker and Warburton 2011).

How might hippocampal neuronal networks distinguish memories that are widely separated in time? A study that recorded from hippocampal neurons as rats performed many trials of a memory task described a slow drift of the neural ensemble firing pattern over an hour or more, which could reflect an evolving temporal context representation (Fig. 11.1a; Manns et al. 2007). Extending further, Mankin et al. (2012) reported that CA1 neurons shift spatial firing patterns when rats explore the same environment repetitively across 30 h, and Ziv et al. (2013) reported gradual changes in the hippocampal population representation over many days. These findings show that, in both humans and animals, the hippocampus supports memory for when experiences occurred, and dating of memories may be

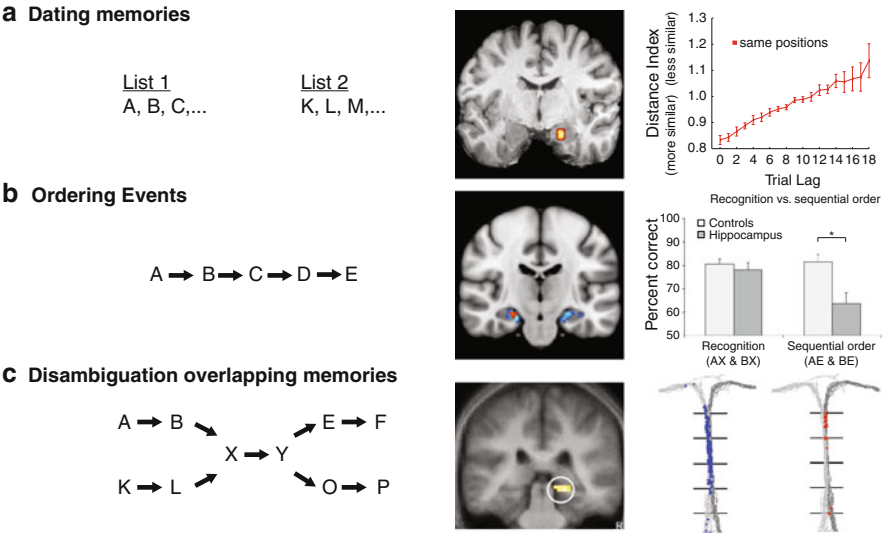

Fig. 11.1 Involvement of the hippocampus in the temporal organization of memory in humans and rats. (**a**) *Left*: memory for when an episode occurred, specifically in this example, memory for which list contained particular items. *Middle*: activation of the hippocampus in the task shown on the *left* (Jenkins and Ranaganath 2010). *Right*: amount of change in CA1 ensemble representation across trials in rats performing a sequence memory task (Manns et al. 2007). (**b**) *Left*: memory for serial order in lists. *Middle*: activation of the hippocampus in humans remembering the order of scenes in a movie (Lehn et al. 2009). *Right*: performance of normal rats and rats with selective hippocampal damage on memory for the order of odors vs. recognition of odors from a list ($p = 0.009$; Fortin et al. 2002). (**c**) *Left*: disambiguation of overlapping sequences. *Middle*: activation of the hippocampus during learning of overlapping face sequences (Kumaran and Maguire 2006b). *Right*: firing patterns of a hippocampal neuron as a rat traverses the stem of a T maze on left-turn (*blue dots* represent spikes) and right-turn (*red dots*) trials. *Gray lines* are paths through the maze on both types of trials (Wood et al. 2000)

supported by a gradually changing temporal context signal that is represented in hippocampal neuronal activity.

11.2 Memory for the Sequential Order of Events Within Episodes

Neuropsychological studies in both humans and animals have shown that the hippocampus plays an essential role in remembering the order of events within episodes, and physiological studies have identified activation of the hippocampus during encoding and retrieval of the order of items in memories.

11.2.1 Studies on Humans with Hippocampal Damage

Early neuropsychological studies showed that amnesic patients of various etiologies were impaired in reproducing the ordering of words on a list, although the deficit was attributed to possible disconnection of prefrontal pathways (Shimamura 1990). Subsequently, studies on individuals with selective hippocampal damage identified impairments in recalling or recognizing the order of words presented in lists or as word pairs, thus implicating the hippocampus itself in memory for order (Mayes et al. 2001). The same patients were intact in recognizing familiar words and word pairings, indicating the deficit was in temporal organization rather than in memory for the items. Similarly, in a study where subjects were asked to remember the order of objects obtained while driving through a virtual reality town, patients with selective hippocampal damage were impaired, even though they could recognize the familiar objects (Spiers et al. 2001).

11.2.2 Functional Imaging in Normal Human Subjects

The hippocampus is activated during the encoding of ordered events, and this activation predicts subsequent memory for the temporal order of those events. Tubridy and Davachi (2011) reported that hippocampal activation during the encoding of word triplets predicted subsequent accuracy of memory for word order. Importantly, the amount of hippocampal activation during encoding was equivalent for word triplets that were subsequently remembered out of order and for those that were forgotten, indicating that hippocampal activation during encoding signaled memory for the temporal organization, not memory for the words themselves. In another study, Staresina and Davachi (2006) showed that the level of encoding activation increased with greater demand to bridge a temporal (as well as spatial) gap between color and object pairings, independent of memory success. Thus, the level of hippocampal activity reflected the degree of temporal integration more so than memory for the pairings.

In addition to activation during encoding, the hippocampus is also activated during retrieval of the order of objects in human subjects. For example, hippocampal activation was observed when humans accurately remembered the order of places visited while playing a virtual reality driving game (Ekstrom and Bookheimer 2007). Another study showed strikingly selective activation of the hippocampus when humans reconstruct the correct ordering of scenes previously viewed in a movie clip as compared to when they infer a logical order of related scenes from the same movie (Fig. 11.1b; Lehn et al. 2009). In addition, exploiting the well-known observation of enhanced BOLD responses to novel stimuli, Kumaran and Maguire (2006a) observed enhanced hippocampal activation when subjects were presented with items out of order late in a familiar series. In contrast, activation was not observed in the hippocampus when an entirely novel ordering of familiar pictures was presented, although activation was observed in the entorhinal/perirhinal cortex for completely novel sequences. Thus, the hippocampal activation

signaled a mismatch of expectation in temporal order, not merely a novel sequence of pictures. These combined findings indicate a strong engagement of the hippocampus during encoding and retrieval of the temporal organization of memories in humans. Furthermore, the combined studies on amnesic patients and functional imaging studies provide strong evidence that hippocampal participation in remembering the temporal organization of event sequences is distinct from remembering the events themselves.

11.2.3 Studies on Animals with Hippocampal Damage

Initial studies on animals focused on whether rats can remember the order of once-experienced sequences of events and whether the hippocampus is involved in temporal order memory in animals. In an early study, Fortin et al. (2002; see also Kesner et al. 2002) examined whether rats could remember unique sequences of odors and compared their ability to remember temporal order with recognition of the odor stimuli that had appeared within the list. On both the order and recognition tests, rats initially were rewarded for sampling each of a list of five odors. Five minutes later, on the order test, they were presented two nonadjacent odors from the list and were required to choose the less recently experienced odor to obtain another reward. On the recognition test, the rats were presented with one odor from the list and another odor not on the list, and the rats were required to choose the odor not on the list. Rats performed well above chance on temporal order memory and better when the lag between previously presented items was larger. Rats with selective hippocampal damage were impaired at all lags, and performance was above chance only for the largest lag. By contrast, on the recognition test, rats with hippocampal damage performed as well as normal rats; and the selective impairment in order memory compared to intact item memory was striking even when overall accuracy in normal animals was matched between tasks (Fig. 11.1b). In another study that explored the contributions of memory for a list of odors and the locations where they were experienced, Ergorul and Eichenbaum (2004) found that normal rats used a combination of odor and location information to remember the order of odors experienced in trial-unique lists and that rats with hippocampal damage were impaired in temporal order memory, whereas probe tests showed spared memory for the odors and for the locations alone. These studies contrast intact memory for items on lists following hippocampal damage, but impaired memory for the temporal organization of items.

There is substantial evidence that memory for order in these tests is not based on different strengths of memories for items experienced more recently and those experienced more remotely. Thus, in the Fortin et al. (2002) study, rats with hippocampal damage showed the same superior performance on more recently experienced items in the recognition task (i.e., a recency effect), indicating intact item familiarity following hippocampal damage and suggesting that the performance of normal rats in temporal order memory was not based solely on differences in the relative recency of the odors. Also, using a similar training procedure in

monkeys, Templer and Hampton (2012) showed definitively that memory for order is not based on differences in the strengths of earlier and later experienced items, or by list position, and they confirmed that accuracy in order judgments was improved by greater separation of items within a list. In addition, DeVito and Eichenbaum (2011) presented mice repeatedly with lists of serially presented odors and observed that, in subsequent probe tests where pairs of nonadjacent odors were re-presented, the mice preferential explored earlier over later presented odors. This form of temporal order memory, but not memory for the odors themselves, was dependent on the hippocampus. The same normal mice did not show a preference for an odor experienced much less recently between lists that were widely separated in time, showing that their memory for order within lists was not based on recency, but rather on serial order within a list.

Two additional studies showed that the hippocampus is essential in memory for the ordering of stimulus pairings. Honey et al. (1998) trained rats on two stimulus sequences, each composed of a distinct tone followed by distinct light cue. Both normal animals and rats with hippocampal lesions oriented to the visual targets when they were novel and these responses habituated. Subsequently, in test trials, the specific tone-light assignments were switched and this caused normal rats to re-orient to the novel sequences, whereas rats with hippocampal damage failed to re-orient. Thus, the hippocampus plays a critical role in the temporal organization of their representation of audiovisual sequences. In another study, Farovik et al. (2010) presented rats with 10 two-odor sequences, where the items within each pair were separated by either 3 or 10 s and the interval between pairs was 15 s. Then, following a 10 min delay, the animals were tested for memory of the ordering of the items within pairs by differentially reinforcing choices of the same vs. reversed pairings. Normal rats performed well (80 % correct) in remembering the order of items within pairs. Rats with selective neurotoxic lesions of CA1 performed well when the interstimulus interval was 3 s, but performance fell to chance at the 10 s interval. Rats with selective neurotoxic lesions of CA3 failed at both interstimulus intervals. These findings indicate that both hippocampal subdivisions are critical to stimulus associations involving ordered stimuli, but CA1 plays an especially important role in bridging a substantial temporal gap between key events.

Taken together, a broad range of studies on animals and humans, using different stimulus modalities and procedures, indicates an essential role for the hippocampus in remembering the order of a sequence of stimuli, even though memory for the stimuli themselves can be supported by other brain areas.

11.2.4 The Hippocampus and Memory for Action Sequences

Another line of studies has examined the role of the hippocampus in learning sequences of behavioral actions in humans and animals. In one test called "deferred imitation of action sequences," human subjects watch an experimenter produce a sequence of actions with objects and then imitate the action sequence either

immediately or after a delay (deferred). McDonough et al. (1995) observed that amnesic subjects were impaired in deferred imitation of action sequences, and a more recent study on patients with selective hippocampal damage were similarly impaired, albeit with less severity (Adlam et al. 2005).

In addition, several studies have examined performance on the serial reaction time test, a task in which subjects gradually become faster in tapping keys as they are lit in repeated sequential order on a keyboard. These studies have shown that humans can use either explicit recall of the sequences or implicit habit learning to facilitate performance of the repeated action sequences. Schendan et al. (2003) showed that the hippocampus is activated during learning, and this activation is observed independent of conscious awareness of the sequence, suggesting hippocampal involvement in temporal representation per se rather than the experience of conscious recall for the sequences.

In studies on rats, Ergorul and Eichenbaum (2006) trained animals to nose-poke at sequentially illuminated ports and found that selective hippocampal damage impairs anticipatory approaches to successive ports in repeated sequences. Similarly, DeCoteau and Kesner (2000) trained rats to approach doors that were subsequently opened to allow entry into arms in a radial maze, and the sequence of arms was repeated such that intact rats learned to orient to each successive door in anticipation of its opening. They found that hippocampal damage impaired these anticipatory ("declarative") actions, although there were unimpaired in a continuous running of sequences if unimpeded by the doors ("procedural"). Also, Fouquet et al. (2010) trained rats to make a sequence of body turns in a star pattern maze and found that hippocampal damage impaired the flexible expression of novel body turn sequences that took animals efficiently to a goal arm when animals began runs from different starting locations. These studies show that the role of the hippocampus in temporal order memory extends to action sequences in humans and animals. Thus, combined with the earlier described studies on stimulus sequences, the full set of findings suggest a fundamental role for the hippocampus in temporal organization across a broad range of sequence memories.

11.3 Disambiguation of Overlapping Sequences of Events

Many of our memories for sequences of events involve common elements. For example, we often walk through the same streets on the way to different locations, and we often visit with the same people to have diverse discussions. Yet, we usually are able to recall each ordered experience distinctly. The disambiguation of overlapping sequence memories is another aspect of temporal organization that can provide insights into the nature of temporal organization of memories. Indeed, Levy (1996) proposed that the ability to disambiguate sequence memories is a key feature of their temporal organization.

11.3.1 The Hippocampus and Sequence Disambiguation in Animals

The role of the hippocampus in disambiguating overlapping stimulus sequences has been studied in rats trained on odor sequences that overlap (A–B–**X**–**Y**–E–F and L–M–**X**–**Y**–P–Q), implemented as a series of choices between two odors (A vs. L, then B vs. M, etc.) for which the first correct choice indicates each of the remaining correct choices (Agster et al. 2002; Fig. 11.1c). Importantly, some of the odors (**X** and **Y**) were common to both sequences (each of these involved a consistent choice against a different foil, e.g., X vs. Q), so subjects were required to remember the ongoing sequence through the overlapping elements in order to make the final choices. Rats with hippocampal damage were impaired at the critical choice just after the overlapping elements only when a delay was imposed between those choices. These findings indicate that other brain systems can support reproduction of overlapping continuous sequences, but the hippocampus is required when the sequence production is halted and then must be remembered to continue [compare to the findings of DeCoteau and Kesner (2000) described above].

11.3.2 The Hippocampus and Sequence Disambiguation in Humans

Kumaran and Maguire (2006b; Fig. 11.1c) used fMRI to examine hippocampal activation during the learning of sequences of images of faces and observed strong hippocampal activation during the encoding of overlapping, but not nonoverlapping, sequences and this activation predicted accurate sequence retrieval. The hippocampus is also activated during retrieval of overlapping (as well as nonoverlapping) face sequences (Ross et al. 2009) and overlapping routes through a virtual maze (Brown et al. 2010). The combination of these studies show that, in both humans and animals, the hippocampus plays a central role in temporal organization that distinguishes overlapping nonspatial and spatial memories.

11.3.3 Hippocampal Neuronal Representations in Sequence Disambiguation

In animals, neural representations of sequence disambiguation has been studied using variants of spatial alternation tasks in which rats traverse the "stem" of a T-maze then alternately choose between left and right turn arms. On each trial the rat must remember its last choice and maintain this information as it traverses the stem that is common to both left and right turn paths that follow. Several studies have observed that hippocampal place cells fire differentially as the rat passes through successive locations on the maze stem, depending on either the previous choice or the succeeding choice [Fig. 11.1c, Wood et al. (2000), Frank et al. (2000), Ferbinteanu and Shapiro (2003), Ainge et al. (2007), Pastalkova et al. (2008), see Shapiro et al. (2006), and Chap. 10 for reviews]. Similarly, in the nonspatial domain, as rats disambiguate sequences of odors, hippocampal principal neurons

fire differentially in anticipation of or during presentation of the ambiguous odors depending on the ongoing sequence (Ginther et al. 2011).

11.4 How Do Hippocampal Neurons Encode Temporally Organized Memories?

Eichenbaum (2004) proposed that a key aspect of neural activity in the hippocampus is the coding of sequences of events in a distinct experience. There are multiple lines of evidence from recordings of single neuron activity in animals and humans showing that hippocampal neuronal ensembles encode and retrieve memories of sequential events.

11.4.1 Hippocampal "Replay" of Spatial and Nonspatial Sequences in Animals and Humans

There is substantial evidence that hippocampal neuronal ensembles encode the order of events in sequence memories as revealed in studies showing that hippocampal neural ensembles "replay" sequences of activations that occurred during previous experiences. The earliest studies on replay by hippocampal neural ensembles reported that place cells that fired in order during behavior tended to also fire in the same order when animals subsequently slept (Skaggs and McNaughton 1996). Since then, numerous studies have reported forward and reverse replay of place cell sequences, both when animals are asleep and during periods of quiet wakefulness (see Karlsson and Frank 2009; Jadhav and Frank 2014). Furthermore, when rats are engaged in vicarious trial and error of maze choices, hippocampal neurons replay firing sequences that reflect possible paths of response choices (Johnson and Redish 2007). Conversely, interfering with hippocampal replays retards learning of critical choices in spatial memories, but not the general skills of performance in the maze (Jadhav et al. 2012). In addition, hippocampal replays are synchronized with cortical replays consistent with the view that sequence replays reflect a temporal organization involved in remembering and memory consolidation (Ji and Wilson 2007).

In addition to memories for routes through mazes, neurons throughout the hippocampal region replay firing sequences as human subjects recall scenes from previously viewed movies (Gelbard-Sagiv et al. 2008). Moreover, selectively within the hippocampus, neuronal ensembles develop reliable firing sequences as subjects gradually learn a sequence of scenes in a film (Paz et al. 2010). These findings provide strong evidence that hippocampal neuronal ensembles can encode and retrieve the temporal structure of sequential events.

11.4.2 Hippocampal "Time Cells" Represent the Flow of Time Within Distinct Experiences

There is also growing evidence that hippocampal neuronal ensembles compose a gradually changing representation of the flow of time, independent of explicitly identifiable locations or events that might directly drive sequential neural activations. The initial evidence of gradually changing temporal context representations in the hippocampus came in a study in which ensembles of CA1 neurons were recorded as rats performed the above-described task wherein rats encode and remember unique sequences of odors (Fortin et al. 2002). The firing patterns of CA1 ensembles gradually evolved over entire recording sessions. Moreover, within those sessions, CA1 ensemble representations gradually changed even over a few minutes in which individual sequences were encoded, and the extent of ensemble change during the sequence of odor sampling events predicted subsequent success in remembering the order of odors experienced on each trial (Manns et al. 2007).

Because this task involved unique memories on each trial, it could not be determined whether distinct evolving temporal context representations are generated for specific memories. However, Pastalkova et al. (2008) recorded the activity of hippocampal (CA1) neurons as rats ran in a running wheel in between trials in spatial alternation and found that different hippocampal ensemble sequences were associated with different subsequent memory choices and, when the animals made errors, these sequences were disrupted. Although Pastalkova et al. (2008) referred to these neurons as "episode cells," we prefer to call them "time cells" because, just as place cells encode locations in a specific space, time cells encode moments in a specific period of experience. The populations of time cells observed in Pastalkova's study likely reflect the repetition of ensemble firing patterns that gradually changed in the Manns et al. (2007) study.

11.4.3 Time Cells in Nonspatial Memory Performance

The phenomenon of time cells was further examined using a nonspatial task developed by Kesner and colleagues (2005) that identified the hippocampal CA1 region as necessary for rats to learn distinct sequences in which an object and an odor were separated by a 10 s temporal gap (Fig. 11.2a). In this task, each trial began with the presentation of one of two objects that the rat investigated for a short period. Then the rat was confined in a small area for 10 s, after which it was presented with one of two odors mixed into common playground sand. Each odor was paired with one of the objects, such that if the odor followed the correctly paired object then the rat could dig in the sand for a buried reward. Conversely, the rat obtained no reward for digging when the odor followed the object with which it was not paired. Critically, the object-odor sequences were presented repeatedly during each testing session so that the rats had to remember across the delay the object that had started the trial in order to respond appropriately to the odor at the

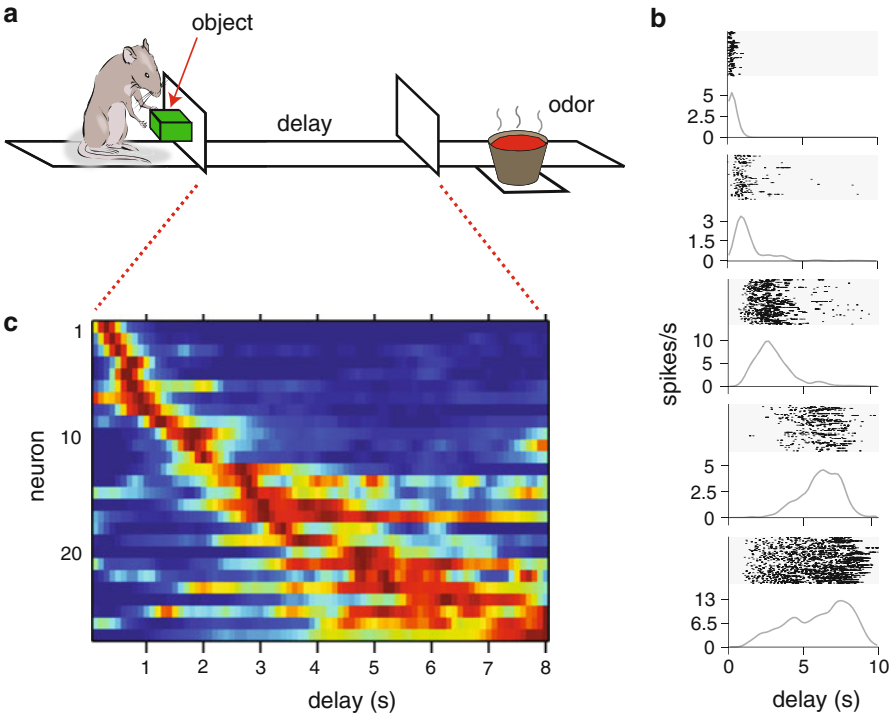

Fig. 11.2 (**a**) The trial structure for object-delay-odor sequences. (**b**) Each panel shows a raster plot and peri-event time histogram illustrating neural activity of a time cell during the delay period. (**c**) Normalized firing rates of 26 neurons recorded simultaneously during the delay period. Each *row* represents the activity pattern of a single neuron

end of the trial. Rats with lesions of the CA1 region show no evidence of learning these object-odor sequences (Kesner et al. 2005). Conversely, rats with CA3 lesions learn the sequences with a time course that is comparable to control rats. These results extended upon an earlier study from the same group that showed hippocampal lesions spare learning when there is no intervening temporal gap separating object and odor presentation (Gilbert and Kesner 2002). Taken together, these results are consistent with a selective role for the CA1 in representing a temporally extended sequence of events to compose a distinct experience.

To explore the nature of the hippocampal representation supporting performance in this task, MacDonald et al. (2011) adapted the task and examined activity from large ensembles of hippocampal CA1 neurons monitored simultaneously. Many neurons activated during presentation of the object or odor and often fired differently depending on the object that started the trial, indicating that the hippocampus distinguished the key events composing each object-odor sequence. Most striking, nearly half of the cells that were recorded activated during the delay period, and the period of activity of each cell was typically selective for a specific moment (Fig. 11.2b). To better illustrate the temporal signature of these cells, Fig. 11.2c

plots normalized firing patterns from an ensemble of cells recorded simultaneously during the delay. It is readily apparent that the cells activated in sequence and the overlap among their firing fields bridged the delay. Most importantly, time cells distinguished the object starting the trial, which is consistent with a function in integrating the object with its paired odor across the delay. These results confirmed a robust temporally organized representation for a sequence of events in the hippocampus, highlighted by cells that bridged the delay and composed the flow of time in a distinct memory.

Could temporal signals reflected in the activity of time cells be confounded to representation of a sequence of locations occupied or a reliable sequence of behaviors? A detailed statistical analysis of the firing patterns of neurons recorded by MacDonald et al. (2011) revealed that while many of these cells also represented the spatial location and ongoing behavior during the delay, these factors did not account for the timing signal reflected in the activity of these cells. While the temporal signal encoded by time cells was independent of the rat's location and movements, many of these cells did incorporate information about spatial and behavioral events into their representation.

11.4.4 Time or Path Integration?

In the MacDonald et al. (2011) and the Pastalkova et al. (2008) studies, as well as another study that observed time cells during the delay periods in a delayed spatial task (Gill et al. 2011), the rats were in motion the entirety of the key delay periods. Therefore, the distance moved and time elapsed were entirely confounded during the periods when time cells were observed, and other studies have reported that hippocampal neurons can signal the accumulated linear distance that a rat has moved from a reference point (Gothard et al. 1996; Redish et al. 2000). Thus, it was unclear whether hippocampal neurons can signal the flow of time independent of self-generated cues that may support path integration (McNaughton et al. 2006). To address this issue, an experiment was conducted to eliminate movement-related variables altogether (MacDonald et al. 2013). A head-fixed preparation was developed for rats to record hippocampal CA1 activity while their memory was tested using an odor delayed matching to sample task. Each trial began with the presentation of a sample odor, followed by a fixed 2–5 s delay period, then presentation of a test odor. The restrained rats were rewarded with water for licking at a lick spout if the test odor matched the sample odor, but were not rewarded for licking when a nonmatching test odor was presented. This task was similar to the object-odor sequence memory task in that there were a small number of highly repeated sequences that composed each combination of sample and test odors, and on each trial the rat had to remember the sample odor across the delay period to identify a target odor sequence.

Over one third of the hippocampal neurons activated at brief moments in sequence during the delay period. Therefore, even in head-fixed rats, hippocampal CA1 neurons segmented the delay period into discrete temporal units that reflected

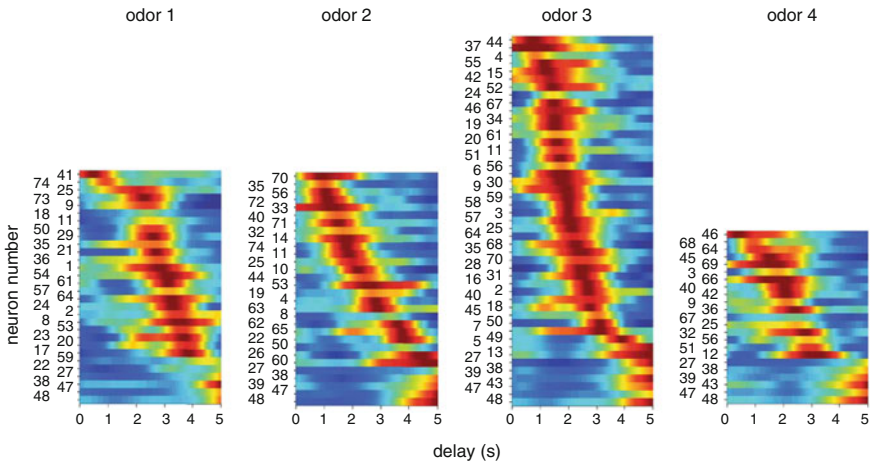

Fig. 11.3 Odor memory representations during the delay following each sample odor involved largely distinct, temporally organized neural ensembles. Each *column* provides normalized firing rate plots for a neural ensemble over the delay period following one of the four sample odors

the flow of time within the trial. Moreover, many time cells were temporally modulated during the delay specifically following presentation of a particular odor that started the trial. Figure 11.3 shows four normalized ensemble activity patterns depicting trial-averaged activity during the delay for a population of 74 time cells, with ensemble patterns plotted separately for activity following one of the four sample odors. A time cell is included only if its activity was temporally modulated during the delay after the sample odor. By comparing each cell's identifying number across the plots (indicated at the left), it is clear that some time cells contributed to a representation of only one odor memory while others contributed to more than one odor memory representation, though rarely to all four. In the latter case, some of these cells fired around the same time during delay following different odors, typically at different rates. Other cells had distinct temporal firing patterns after different sample odor presentations. Thus, each sample odor was represented during the delay by a largely distinct temporally organized ensemble of time cells. Largely distinct neural ensembles activate in sequence over extended intervals to compose the flow of time in different odor memories. Moreover, the overlap among the different odor memories, embodied in cells that fire at the same or different rate at comparable moments during the delay, is consistent with the crucial role of the hippocampus in linking together different experiences in support of a relational memory network (Eichenbaum et al. 1999; Eichenbaum 2004).

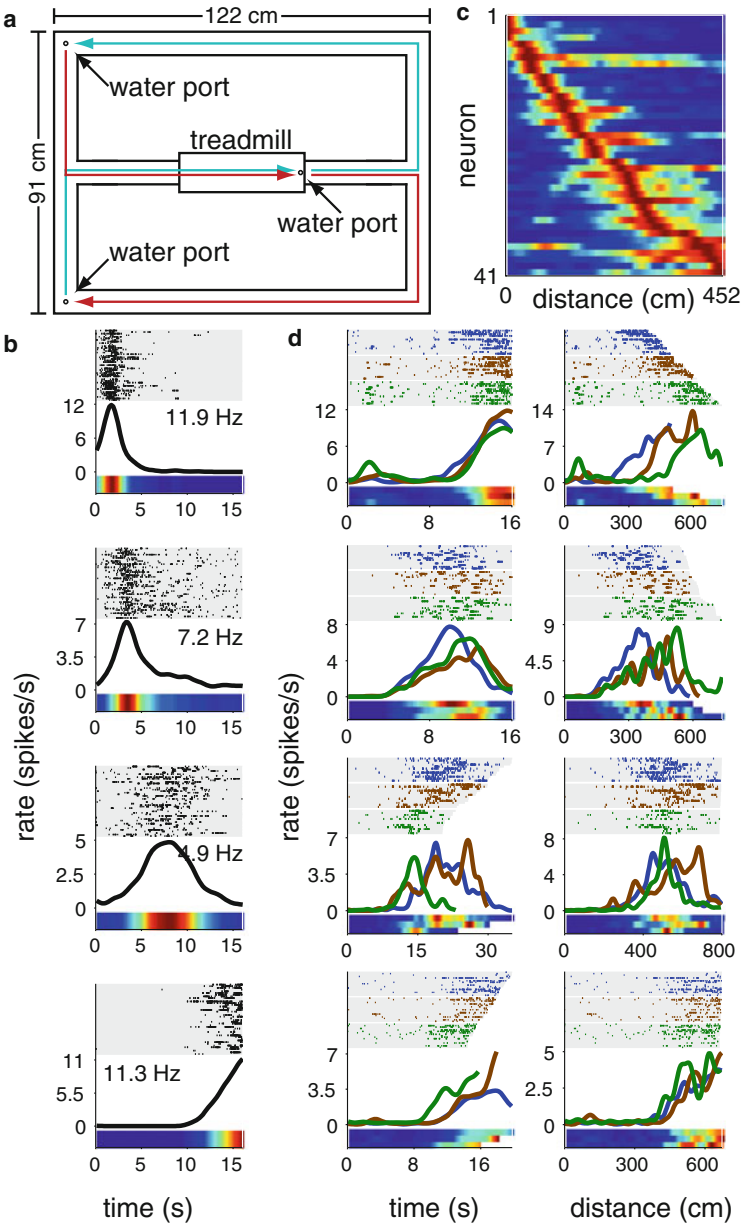

Fig. 11.4 Hippocampal activity during stationary treadmill running: temporal integration vs. path integration. (**a**) Diagram of the figure-eight maze indicating the dimensions and location of the water ports and treadmill. *Cyan line* indicates *right*-to-*left* alternation; *red line* indicates *left*-to-*right* alternation. (**b**) Firing patterns of four different example neurons active during stationary

11.4.5 Temporal Integration Vs. Path Integration

While the just described study revealed a temporal signal under conditions where place was fixed and movement prevented, time cell firing patterns during movement could reflect path integration rather than elapsed time. To address this possibility, Kraus et al. (2013) recorded from multiple hippocampal neurons as rats ran continuously in place at different speeds on a treadmill placed in the stem of a figure-eight maze (Fig. 11.4a). On each trial, the rats entered the central stem of the maze from one of two directions (left or right), and then walked onto the treadmill where they received a small water reward. After a short delay, the treadmill accelerated to a speed randomly chosen from within a predetermined range, and the rats ran in place until the treadmill stopped automatically and another small water reward was delivered. Subsequently, the animals finished the trial by turning in the direction opposite from their entry into the stem (spatial alternation) to arrive at a water port at the end of a goal arm. To distinguish behavior, location, time, and distance as factors influencing neuronal activity, behavior and the location of the animal on the maze were "clamped" and the treadmill speed was varied to decouple the distance the rat traveled from its elapsed time on the treadmill.

As with previous experiments that examined hippocampal activity during task delays (Pastalkova et al. 2008; Gill et al. 2011; MacDonald et al. 2011), at each point during treadmill running a subset of hippocampal neurons fired, and the subset of neurons activated in a regular sequence that repeated during every treadmill run (Fig. 11.4b, c). In addition, the speed of running was systematically varied to allow for the separation of the influences of time and distance on firing patterns and to measure the extent to which each variable influenced firing. These analyses revealed both "distance cells," that is, cells that more reliably encoded the distance the rat has run on the treadmill, and "time cells," cells that more reliably encoded the time the rat has spent on the treadmill (Fig. 11.4d). The observation of "distance cells" in this task indicates that hippocampal neurons can integrate the length of a path even in the absence of visual flow usually associated with movement through space. Also, the presence of "distance cells" in this task indicates that these neurons

Fig. 11.4 (Continued) treadmill running, aligned to the time the treadmill started. *Black lines* and *color bars* represent firing rate averaged over all runs. *Number* indicates peak firing rate in spikes per second (Hz). (**c**) Ensemble firing rate map showing all neurons active on the treadmill during a single session. Each *row* represents the normalized firing rate of one neuron sorted by the peak firing time. In each row, *blue* represents no firing (zero spikes per second) and *red* represents peak firing for that particular neuron. (**d**) Examples shown in each *row* represents the activity from one neuron plotted both as a function of time since the treadmill started (*left column*) and distance traveled on the treadmill (*right column*). *Blue*, *brown*, and *green ticks* (and *tuning curves*) represent the slowest 1/3 of runs, middle 1/3 of runs, and fastest 1/3 of runs, respectively. The *rows* in the raster plots in panels **b** and **d** are sorted with the slowest treadmill speed on top and fastest speed on the bottom. Note better alignment of the neural activity to time in the top two examples (time cells) and better alignment of neural activity to distance in the bottom two examples (distance cells)

are not driven entirely by network dynamics without the influence of either idiothetic or allothetic cues, as suggested by Pastalkova et al. (2008) (see also Itskov et al. 2011a), as the neurons must be responding to the treadmill speed, or self-motion cues influenced by the speed of the treadmill, in order to encode distance. In addition, the observation of "time cells" indicates that these neurons are also not exclusively driven path integration but also by elapsed time (McNaughton et al. 1996, 2006; Etienne and Jeffery 2004). Thus, Kraus et al. (2013) showed that, when both of these dimensions are prominent, the hippocampus represents both the distance traveled and time elapsed. Furthermore, a large fraction of hippocampal neurons combine information about these dimensions to varying extents, such that different neurons largely reflected distance or time, and others equivalently reflected the combination of these dimensions. It is noteworthy that, while the number of neurons that represented time without a significant contribution of distance was modest, so it was also the case that the number of neurons that represented distance alone was smaller, and no cells represented only place. Thus, the overall population coded a broad range of combinations of time and distance with some degree of place coding as well.

During treadmill running, when behavior and location were held relatively constant, time and distance predominated in their influence over the firing patterns of hippocampal neurons. However, other neurons, and many of the same neurons that were active on the treadmill, had place fields elsewhere on the maze, indicating that during other components of the task, where locations on the maze were important to task success, space was a strong influence over firing patterns of even the same neurons. These observations support the view that hippocampal neuronal activity reflects both the temporal and spatial regularities, along with other salient features of experience, all of which are reflected in our capacity for episodic memory.

11.4.6 What Is the Source of Temporal Signals for Time Cells in the Hippocampus?

Since the discovery of time cells in the hippocampus (Pastalkova et al. 2008), and the demonstration that time cells have many of the same properties as hippocampal place cells (MacDonald et al. 2011), the next question was whether this activity is originating in the hippocampus, or if the hippocampus is responding to time cell activity it is receiving from an upstream source. As the medial entorhinal cortex (MEC) is a dominant source of input into the hippocampus (Amaral and Witter 1989; Witter and Amaral 1991), and many models hypothesize that the outputs from MEC grid cells, neurons that have periodically spaced place fields (Hafting et al. 2005; see Chap. 5), are used by the hippocampus to generate place cells, it was a natural location to check for the presence of time cells. Compared to the activity of hippocampal neurons during open-field foraging, which tend to have one well-defined place field, medial entorhinal cortical (MEC) neurons have a wider variety of spatially tuned firing patterns. Many MEC neurons have spatially tuned

responses that are not clear firing fields, but when MEC neurons do have "place fields," a single neuron often has multiple or larger place fields, including "grid fields" (Fyhn et al. 2004; Hafting et al. 2005).

To explore temporal coding in MEC neurons, rats were trained to perform spatial alternation on a figure-eight maze that included a motorized treadmill in the center stem, the same as in Kraus et al. (2013) described above. To determine the spatial firing properties of the same neurons, their activity was also recorded as the rats foraged for food pellets in an open field, allowing each neuron to be classified as either a grid cell, conjunctive grid-by-head-direction cell, head-direction cell, or spatially modulated cell.

The results showed that many MEC neurons exhibited temporally modulated firing patterns (i.e., "time cells") during treadmill running that were very similar to those seen in hippocampal CA1 during either wheel running (Pastalkova et al. 2008) or treadmill running (Kraus et al. 2013; Fig. 11.5), each with a single well-defined temporal firing field. These firing fields expanded to fill the entire duration on the treadmill, so that at any one point during treadmill running, a subset of both hippocampal and MEC time cells were firing. Unlike hippocampal time cells, many neurons also fired with multiple distinct firing fields. Still, other neurons exhibited temporally periodic firing on the treadmill. These results suggest that a parallel comparison can be made between hippocampal time cells and MEC time cells as can be made between hippocampal place cells and spatially modulated cells in the MEC (including grid cells).

Using methods similar to those used in Kraus et al. (2013), it was shown that time cell activity in the MEC could not be explained by movements through space or changes in head direction. For each neuron, the firing activity was modeled using either a spatial firing rate map or a polar (head-direction) rate map, and then these models were tested to see how well they predicted the actual temporal firing. If time cells were an artifact of stereotyped changes in spatial location or head direction, then the models should be able to accurately predict the temporal firing properties of each cell. However, this was not the case: neither spatial position nor head direction were able to account for the temporal modulation of MEC time cell firing.

The firing activity of MEC neurons during treadmill running was correlated with the firing activity of those same neurons during open-field foraging. Although it might be expected that temporally periodic MEC time cells would also have grid cells responses during open-field foraging, this did not turn out to be the case. Rather, periodically firing MEC time cells tended to have spatially modulated responses that were not clearly grid-like (Fig. 11.5), suggesting that temporal periodicity may be driven by a different mechanism than spatial periodicity. However, neurons with either one or two distinct, well-defined temporal firing fields often turned out to be grid cells during open-field foraging, and the majority of neurons that were grid cells during open-field foraging had either one or two temporal firing fields during treadmill running. Notably, the spatial information of MEC neurons on the open field was correlated with temporal information on the treadmill.

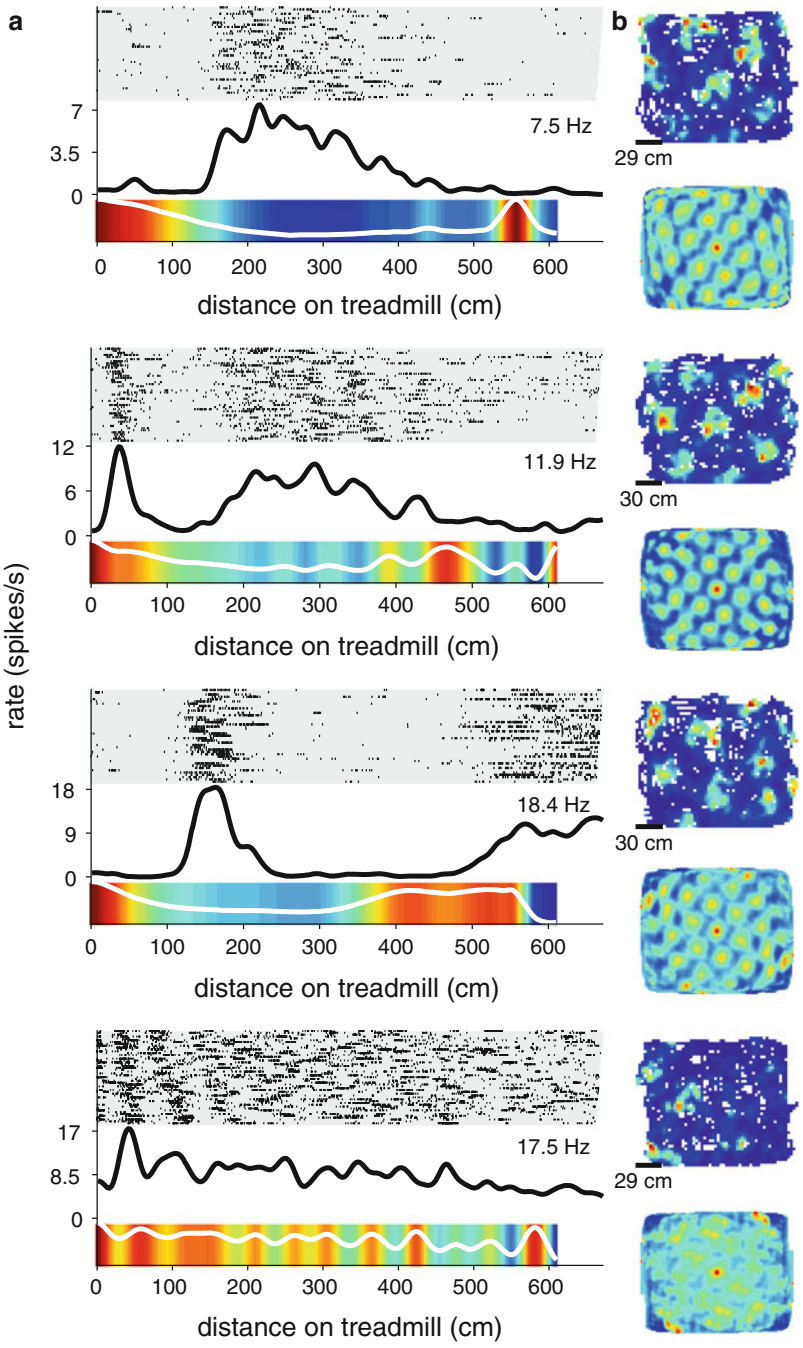

Fig. 11.5 MEC time cells. (**a**) Activity during treadmill running of four neurons recorded from the medial entorhinal cortex (MEC), plotted as in Figure 11.4b, except the *colored bar* under each raster represents the 1D autocorrelation of the average firing rate. (**b**) Spatial rate maps and 2D

These findings, showing both key similarities as well as key differences between temporal modulation in the hippocampus and temporal modulation in the MEC, suggest a role for the MEC in providing temporal information to the hippocampus to drive time cell firing in much the same way that it provides a spatial signal driving place cells.

11.5 What Is the Mechanism for Hippocampal Organization of Events Over Time?

What is the underlying mechanism for the representation of temporal structure by neuronal ensembles in the hippocampus? There are two major categories of explanation on this issue: neuronal ensembles might represent temporal order via a chaining of enhanced direct connections between neurons that represent temporally adjacent events or they might represent a gradually evolving temporal context to which memories are bound at appropriate moments of experience. Consistent with the chaining model, Lisman (1999; also Jensen and Lisman 2005) proposed that serial events are linked via long-term potentiation (LTP), and sequence representations are sequenced within repeatedly updated cycles of the theta rhythm. Supporting such models, Mehta et al. (1997, 2000) observed that, when rats run repeatedly through a sequence of locations, the place fields of hippocampal neurons representing those locations expand backward from their centers. They interpreted the backward expansion of the place fields as reflecting each place cell being driven through LTP-mediated enhanced connectivity by an earlier firing place cell, and this claim was supported by showing NMDA receptor dependency of the expansion (Ekstrom et al. 2001). Also in support of this view, Dragoi and Buzsaki (2006) reported that the correlated firing of hippocampal neurons with overlapping spatial fields is greater than that expected if place cells fire independently driven by an external pacemaker. While a chain of neurons can most straightforwardly explain sequence representation, sequence disambiguation is more difficult to explain using chaining models. To the extent that the same neurons would be expected to represent the events that are common, overlapping elements of a sequence, it is difficult to imagine how simple neuronal chains can lead to divergent outcomes.

Temporal context models offer mechanisms that can readily order sequential events and disambiguate overlapping sequences. Olton (1986) may have been the first to suggest that the hippocampus plays a fundamental and essential role in

Fig. 11.5 (Continued) spatial autocorrelation of the firing rate maps showing the firing patterns of the same four neurons shown in panel A during a period of open-field foraging that immediately followed the treadmill running session. Note strong temporal modulation with one (*top* examples) or more (*middle two* examples) of the cells that have grid fields in the open field and a cell with periodic firing and poor spatial firing (*bottom* example)

representing the temporal context of memories. On a mechanistic level, Levy and colleagues (1995; Levy 1996) and Wallenstein et al. (1998; see also Rolls 2010) offered temporal context models that proposed the existence of hippocampal "context" neurons that fire for periods that bridge between sequential events, thus constituting the temporal context signal to which specific events are associated at appropriate moments. Howard et al. (2005) postulated that ensembles of hippocampal context cells might arise as leaky integrators that incorporate events that occur prior to, including, and following each sequential event, together composing a representation of experiences surrounding each sequential event. While events contribute to the temporal context signal, the signal may also reflect a preexisting temporal framework. Thus, a recent intriguing finding is that hippocampal ensembles tend to "pre-play" sequences that will subsequently reflect serial place cell firings in a new environment, suggesting that preexisting ensemble structure contributes to sequence coding (Dragoi and Tonegawa 2011).

Within temporal context models, the disambiguation of memories is accomplished by the use of different populations of neurons that carry different temporal context representations for each of the overlapping memories. These models predict distinct ensemble firing patterns during multiple sequence representations, even when the overt behaviors, places, and times in the sequence are identical. In support of this model, there is substantial evidence of hippocampal context neurons that distinctly represent the same overt events that are common to different memories by differential activity depending on preceding and succeeding events. The findings on studies of firing patterns of hippocampal neurons in animals remembering overlapping spatial routes (reviewed in Shapiro et al. 2006; see Chap. 10) and odor sequences (Ginther et al. 2011) indicate that hippocampal networks develop unique representations that distinguish the context of different memories, even when those memories contain identical events and occur in common places (also see Markus et al. 1995; Skaggs and McNaughton 1998; Fig. 11.1c).

The observations on time cells described above also support the view that sequence memories in the hippocampus are supported by different temporal context representations rather that a chained representation. In the object-odor association paradigm, when the standard 10 s delay between the object and odor presentations was elongated to 20 s, the sequence of cell firings that represent the original early component of the delay was not preserved and extended with additional neuronal activations, as might be expected in a firing chain (MacDonald et al. 2011). Instead, after the delay was elongated, even though some neurons continued to fire at the same time, the majority of the neurons that fired in the original sequence "retimed," that is, either turned off or fired at a different moment, and new neurons joined the sequence representation, consistent with the view that the elongated delay required a reformulated temporal context representation. These findings indicate that time cells fire independently and not as elements of a tightly bound chain. In addition, in the delayed matching to sample task used to examine time cells in head-fixed rats (MacDonald et al. 2013) and in other paradigms (Pastalkova et al. 2008; Gill et al. 2011), the different time cell sequences that represent distinct memories involve combinations of neurons that fire at the same time and others that

fire at moments unique to a particular memory. The partial re-timing observed across all these studies is consistent with a temporal context signal that contains common elements that encode the common temporal structure and distinct elements that encode the differences in memories.

In another study Naya and Suzuki (2011) recorded from neurons in the cortex and hippocampus in monkeys performing a visual paired associate task where the stimuli were separated in time and explored neural activity related to the visual cues and elapsed time during the interstimulus interval. They found that neurons in higher-order visual areas (inferotemporal and perirhinal cortex) encoded the visual cues but had little temporal signaling and that entorhinal neurons encoded both the visual cues and time. Strikingly, hippocampal neuronal ensembles signaled only the temporal organization without specificity for the items held in memory. Thus, in this study, the hippocampus contained no information about specific sequences, but rather represented the reliable temporal structure that occurred on all trials. It is not clear why the studies on rats observed memory-specific time cell sequences whereas Naya and Suzuki observed the same time cell sequence for all memories, but a major distinction between the protocols is that the tasks used for rats involved a small number of repetitive sequences whereas the monkeys performed a task that involved a large number of sequences. Possibly, after many repeated exposures, repetitive stimulus sequences are embodied in the regularities of the temporal structure, whereas when diverse stimulus sequences seldom repeat, only the reliable temporal structure of the task is represented by the hippocampus. These findings strongly support the idea that hippocampal time cells represent temporal context rather than sequences of specific events.

11.6 Conclusions

The studies reviewed here provide compelling evidence that the hippocampus is involved in the temporal organization of memories. There is a wealth of evidence, from diverse experimental approaches in humans and animals, that the hippocampus plays a central role in the temporal organization of memories, both in dating episodic memories and in the sequential organization of events within each memory. Furthermore, the hippocampus encodes the temporal organization of sequential events in a manner that supports the disambiguation of overlapping episodes. Ensembles of hippocampal time cells may represent a gradually changing temporal context signal that bridges between and integrates information across events and thereby both separates distinct episodes and defines the temporal structure within each unique episode. The evolving hippocampal temporal context representation may incorporate particular events at specific times itself, or the hippocampus may contain only the temporal structure for unique experiences, which guides the timing of event representations in cortical areas to which the hippocampus is connected.

Importantly, the study of temporal representation by the hippocampus, especially at the level of neuronal coding, is just the beginning. There remain many unanswered questions—here we will conclude by considering four of these questions:

11.6.1 What Is the Source of Temporal Information to the Hippocampal Region?

A more complete understanding of the mechanisms by which the temporal representation supports episodic memory will depend on future studies aimed to identify the source of temporal information to the hippocampus, the mechanisms by which temporal representations distinguish memories that overlap, and how specific events are incorporated into the temporally organized representation. The origin of temporal signals to the medial temporal lobe have not been identified. There are, however, several studies that have examined the functional and neural mechanisms of timing in humans and animals, and these studies point to several brain areas, including the striatum, cerebellum, and multiple cortical areas, that support our ability to time (Mauk and Buonomano 2004; Buhusi and Meck 2005; Yin and Troger 2011; Wearden 2013).

11.6.2 What Is the Relationship Between Place Cells and Time Cells?

Many studies have provided considerable evidence that the activity of hippocampal place cells signal an animal's location within an environment [e.g., O'Keefe and Nadel (1978), McNaughton et al. (1996, 2006), and several chapters in this volume] and there is strong evidence of spatial representation by hippocampal neurons in humans as well (Ekstrom et al. 2003; Maguire et al. 1997). How do we reconcile the observations on temporal representation by the hippocampus with its well-known role in spatial representation? There are many properties of hippocampal place cells that parallel the findings on time cells described above. Place cells encode spatial context by parsing environments into representations of specific places (place fields), much as time cells parse temporally defined periods into representations of specific moments ("time fields"). Ensembles of place cells distinguish different environmental contexts, much as ensembles of time cells distinguish temporal contexts. Both place cells and time cells encode specific events within their spatial and temporal frameworks, respectively. Indeed, merging these parallel observations, time cells typically incorporate spatial information (MacDonald et al. 2011) just as place cells incorporate information about past and future events (Shapiro et al. 2006). The observation of predominant spatial or temporal coding in particular reports is likely more a reflection of the experimental design in a specific study than a fundamental distinction between time cells and place cells. A synthesis of our emerging knowledge about time cells and place cells suggests that the same population of hippocampal neurons encode both the spatial and temporal regularities of experience, creating a framework that organizes the spatial and temporal context of experiences and puts each event into its time and place.

11.6.3 Is Time Just Another Nonspatial Signal Processed by the Hippocampus in Addition to Its Predominant Role in Spatial Representation?

There are numerous reports of hippocampal neurons that encode nonspatial stimuli and events, in addition to the prevalence of place cells. Thus, across a variety of learning paradigms, many recent studies have described hippocampal neurons that encode objects (Manns and Eichenbaum 2009); local visual cues (Leutgeb et al. 2005); olfactory (Komorowski et al. 2009; Muzzio et al. 2009), auditory (Moita et al. 2003; Itskov et al. 2012), and somatosensory cues (Itskov et al. 2011b); behavioral responses (Lenck-Santini et al. 2008); motivational state (Kennedy and Shapiro 2009); and other features relevant to task demands [Allen et al. (2012), also see Eichenbaum (2004), for review of earlier papers]. These responses to nonspatial stimuli and events are predominantly (although not always) overlaid on top of spatial firing patterns, such that they are commonly characterized primarily as responses to particular stimuli or events at a particular location. So, it bears asking, is the representation of elapsed time just another nonspatial cue encoded in hippocampal neural activity? There is good reason to argue that this is not the case. The studies on time cells reviewed here suggest that hippocampal neurons can represent continuous dimensions of time and space independently or in combination (Kraus et al. 2013) and encode specific stimuli at particular times just as they encode specific stimuli at particular places. Therefore, the discovery of time cells suggests a dimension of representation that is parallel to that of space, rather than a representation of another type of nonspatial event. The discoveries about the essential role of the hippocampus in temporal organization and about temporal information processing by hippocampal neurons challenge the prevalent view that the hippocampus is a dedicated spatial processing device. Rather, the findings on time cells suggest that, at a minimum, we need to move towards thinking that hippocampal networks encode events within spatiotemporal frameworks and not just in spatial frames (Eichenbaum 2004).

11.6.4 Did the Hippocampus First Evolve to Represent Space and Support Navigation, and Its Circuitry Later Was Co-opted to Represent Time and Memories?

It has been suggested that the hippocampus evolved initially to support navigation, and only later its information processing was co-opted for temporal processing in episodic memory (O'Keefe and Nadel 1978; Buzsaki and Moser 2013). This conjecture has no basis in scientific evidence and seems unfounded in evolutionary logic. The adaptive value of episodic memory is at least as great as that of navigation at the earliest stages of evolution. Indeed, it seems that the adaptive value of memory necessarily precedes that for navigation. In an old joke, we ask "why did the chicken cross the road?" Surely the answer is not just because it knew how to navigate to the other side, but rather primarily because it remembered what happens on the other side.

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The Function of Oscillations in the Hippocampal Formation

12

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Abstract

Some of the strongest experimental and computational links between oscillations and cognition concern the oscillations in the hippocampal formation supporting spatial and mnemonic processing. We review experimental and theoretical work concerning well-established hippocampal oscillations such as theta, gamma, and high-frequency ripples and how they relate to spatial, mnemonic, and anxiety-related representation and behaviour. We specifically consider the following computational roles for oscillations: organising processing into discrete chunks, as seen in encoding versus retrieval scheduling; ordinal and metric coding by oscillatory phase; temporal integration by oscillatory phase; and interregional communication. The literature on oscillations has typically been concerned with changes in band-specific power. Here, focusing on the theta oscillation, we summarise how key variables are linked not only to power but also to frequency and to coherence. We conclude that the hippocampal formation provides an invaluable model system for understanding the functional roles of neuronal oscillations and the interaction between oscillations.

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12.1 Different Types of Hippocampal Oscillations

12.1.1 Characteristic Oscillations in the Rodent Hippocampus

It is perhaps worth stating at the outset that the characteristic oscillatory bands historically defined by human scalp EEG are of only limited relevance to those identified by invasive electrophysiological studies of the rodent hippocampus. At the lower-frequency end, researchers of the rodent hippocampus do not consider there to be a distinct 'alpha' (8–12 Hz) oscillation. Rather, it seems that the theta oscillation extends into 'alpha' territory, and theta is typically assigned a range of around 4–12 Hz. Indeed, the upper limit of rodent hippocampal theta seems higher than that typically found in intracranial and magnetoencephalographic (MEG) studies of the human hippocampal formation, an issue we briefly discuss in Sect. 12.1.3. At the higher-frequency end, there is a lot of important hippocampal activity beyond 100 Hz: most notably, the high band (90–150 Hz) of gamma oscillations (30–150 Hz; Bragin et al. 1995; Csicsvari et al. 2003; Scheffer-Teixeira et al. 2011; Belluscio et al. 2012) and ripple oscillations (140–200 Hz, O'Keefe and Nadel 1978, pp. 150–153; Bragin et al. 1999;). For excellent general reviews of hippocampal oscillations, see Buzsaki (2006) and O'Keefe (2007).

The most prominent distinction in the hippocampal EEG of awake behaving rodents is that between 'large irregular activity' (LIA), typically present during stationary behaviours such as eating and grooming, and theta, which is very prominent during behaviours which involve spatial translation of the head (Vanderwolf 1969; O'Keefe and Nadel 1978) or arousal and anxiety (e.g. Green and Arduini 1954; Sainsbury 1998; Seidenbecher et al. 2003). In the next section, we discuss the idea of two types or components of theta. The typical observation is that LIA and theta are exclusive and dominant hippocampal EEG states. That is to say, either LIA occurs or theta occurs, and higher-frequency oscillations accompany LIA or theta. 'Small irregular activity' has also been described (Vanderwolf 1969; Jarosiewicz et al. 2002; Jarosiewicz and Skaggs 2004a, b), which may be an intermediate state between LIA and theta, occurring during sleep and during transitions to alertness. During sleep, the characteristic EEG states are LIA, SIA, theta during REM sleep, and a more recently described slow oscillation which may be linked to neocortical input (Wolansky et al. 2006).

Oscillations intermediate between theta and gamma have generally received comparatively little attention. As noted above, a hippocampal 'alpha' is not really recognised. An oscillation termed 'flutter' has been reported, occurring at around 10–12 Hz, which does not show phase reversal across the CA1 pyramidal layer, and is most prominent when an environment is familiar rather than novel (Nerad and Bilkey 2005). Berke et al. (2008) reported transient beta oscillations in CA3 and CA1 fields in the 23–30 Hz ('beta2') range which were highly modulated by environmental novelty. These beta oscillations were most prominent on the second and third laps of continuous linear tracks and were greatly attenuated when an environment was familiar. Grossberg (2009) has interpreted this oscillation within the framework of adaptive resonance theory and has suggested that it reflects a

learning-eliciting signal of the mismatch between bottom-up sensory-based and top-down expectation-based mechanisms. Vanderwolf (2001) noted a set of specifically olfactory stimuli which elicits ~20 Hz beta waves in the dentate hilus, but not the Cornu Ammonis fields (CA1 and CA3), of the hippocampal formation. Various stimuli in other sensory modalities do not elicit these beta waves. Importantly, these odours do not provoke sniffing but rather behavioural withdrawal. Vanderwolf (2001) interpreted these stimuli as signalling the possible presence of predators. (The idea that the hippocampus is sensitive to both environmental novelty and anxiety-eliciting stimuli is one that we return to in Sect. 12.3.4.) The similarity of the novelty beta waves in CA fields and the 'predator' beta waves in the dentate, apart from their frequency, is not clear.

Flutter and the novelty-related beta oscillations co-occur with theta (Nerad and Bilkey 2005; Berke et al. 2008); their potential co-occurrence with other EEG states is currently unclear. Hippocampal gamma oscillations (Bragin et al. 1995; Csicsvari et al. 2003) have been much more studied and can be found throughout the hippocampal formation. Like flutter and beta oscillations, gamma oscillations can be coincident with theta oscillations, but it is clear that gamma can also occur in sharp wave/ripple states (e.g. Sullivan et al. 2011). The modulation of gamma by theta is an important theme according to the usual rule whereby the lower-frequency oscillation (theta) appears to modulate the higher-frequency oscillation (gamma). Theta-gamma interactions are a recurring theme in the study of theta and gamma. In Sect. 12.1.4, we consider gamma oscillations in more detail, focusing on subtypes of gamma and theta-gamma coupling in CA1. In Sect. 12.2.2, we consider a theoretical model of working memory relying on gamma oscillations nested within theta (Lisman and Idiart 1995). Senior et al. (2008) identified two broad classes of CA1 pyramidal cells according to their relationship to theta, one class firing on theta phases associated with highest gamma power and another firing at all stages of theta phase precession. These authors suggested that only the latter class could support the mechanism required by Lisman and Idiart (1995). In Sect. 12.3 (passim), we review evidence suggesting functional roles for theta-gamma interactions.

The oscillatory band above (high) gamma is the highest-frequency oscillation seen in the normal hippocampus and is known as the ~200 Hz 'ripple' oscillation (O'Keefe and Nadel 1978), spanning a frequency band of around 140–220 Hz as characterised by Buzsaki and colleagues (Sullivan et al. 2011). The ripple oscillation has attracted a great deal of interest over the last 20 years. In Marr's (1971) influential model of hippocampal function, information is transferred from the hippocampus to the neocortex during sleep. It is now well established that during slow-wave sleep and LIA, high-amplitude sharp waves and ripples coincident with the sharp waves frequently occur; if the electrodes are in the pyramidal layer, it is very striking that many pyramidal cells fire simultaneously with the ripples. Ripples have maximal amplitude in the pyramidal layer. The idea that the sharp-wave burst/ripple activity might represent the Marr-esque information transfer phase in which hippocampal information is passed onto neocortex was first proposed in the 1980s by McNaughton (1983) and in particular by Buzsaki (1989). The suggestion was

that theta represents the online learning state and the sharp-wave burst/ripple activity the offline consolidation state. These suggestions proved to be prescient (Wilson and McNaughton 1994; Skaggs and McNaughton 1996) and have led to a considerable body of interesting work advancing our understanding of memory consolidation processes in intrahippocampal and hippocampo-neocortical networks during sleep and rest. We refer the reader to the excellent reviews on sharp-wave burst/ripple activity and memory consolidation, including in this volume (Sutherland and McNaughton 2000; O'Neill et al. 2010; Jadhav and Frank 2014). LIA may have other memory-related roles than consolidation. It is increasingly thought that sharp-wave burst/ripple activity may reflect prospective aspects of spatial processing (Pfeiffer and Foster 2013). Finally, perhaps some periods of LIA represent offline 'housekeeping' processes: O'Keefe (2007) has suggested that synaptic renormalisation and overall gain control processes may occur during LIA.

In summary, the available evidence from rodents supports the following picture of the hippocampal EEG. There are two dominant EEG states, the LIA state and the theta state. (SIA is an intermediate state between the two.) The two states LIA and theta are likely mutually exclusive. Sharp wave and ripple oscillations typically co-occur with LIA, while flutter and beta co-occur with theta, and gamma co-occurs with either the LIA or theta states. Theta may represent an online state supporting encoding and retrieval, while the sharp wave/ripple activity may represent an offline state supporting consolidation, 'what if' cognition, and synaptic reorganisation processes.

12.1.2 Two Components of Hippocampal Theta

Studies focusing on theta amplitude/power have long noted that hippocampal theta has an atropine-sensitive component and atropine-resistant component (Kramis et al. 1975). The general observation is that systemic injection of nonspecific muscarinic antagonists such as atropine and scopolamine eliminates the theta that is observed during alert immobility (aroused/anxious states) and certain anaesthetised states but fairly minimally affects the theta observed during locomotion (Kramis et al. 1975; Buzsaki 2002). Lesions to the septum eliminate both kinds of hippocampal theta. Thus the conception has emerged of two 'types' of theta, one atropine sensitive (type II), linked to arousal and anxiety, and one atropine resistant (type I), linked to spatial translation and movement. Since theta is essentially always present during locomotion, and several studies have shown that theta power and frequency positively correlate with running speed during naturalistic behaviour (reviewed, Lever et al. 2009; and see Hinman et al. 2011; Wells et al. 2013), there is little doubt that type I theta is linked to movement. There is less consensus as to the best characterisation of type II theta. For instance, Sainsbury (1998) views type II theta in sensory terms, while Bland and colleagues (Bland and Oddie 2001; Bland et al. 2007) view this 'sensory' type II theta as limited to the sensory signalling which cues preparation for locomotion. Buzsaki (2002) reviews evidence suggesting that the atropine-resistant theta is conveyed by

the entorhinal afferents onto dentate, CA3, and CA1 cells and partly involves NMDA-receptor activation; notably, for instance, entorhinal lesions render hippocampal theta atropine sensitive, while combined blockade of muscarinic and NMDA receptors abolishes hippocampal theta.

While conceptions of the two contributions to theta are typically not formalised, some researchers appear to implicitly conceive these types of theta as *alternative categories*; either the atropine-sensitive type II theta occurs during immobility-related behaviour (when one might otherwise expect to see LIA), or the atropine-insensitive type I theta occurs during locomotion-related behaviour. Concomitant with this is the identification of particular frequency bands with the two types of theta, lower for type II theta and higher for type I theta. Thus a representative view is 'Atropine-sensitive type 2 theta activity (4–8 Hz) has been shown to occur in the hippocampal formation during periods of immobility, whereas atropine-resistant type 1 theta (8–14 Hz) is observed during exploration' (Seidenbecher et al. 2003). We should note, however, that there are indications that type II theta can have a higher limit. For instance, Sainsbury (1998) reports that a guinea pig in the presence of a snake can show type II theta in the 10–12 Hz range. An additional confusion comes from the developmental aspect of movement-related theta frequency increasing from 4–5 Hz when exploration begins in rat pups at age 16 days to 8–9 Hz seen in the adult (Wills et al. 2010). This may help to explain the relative low frequencies seen in models of theta in slice preparations: slices are typically taken from young animals (up to around 20 days old).

In contrast to characterisation of two mutually exclusive types of theta, in the models of Bland (Bland and Oddie 2001; Bland et al. 2007) and Burgess (2008), both type I and type II mechanisms simultaneously contribute to theta during locomotion-related behaviour. In the Burgess (2008) model, these contributions are complementary. It has long been noted that theta frequency increases, broadly linearly, with running speed (see references above). The (Burgess 2008) model links the type I and type II theta mechanisms to dissociable components of the relationship of theta frequency ($f_\theta(t)$) to running speed ($s(t)$):

$$f_\theta(t) = f_0 + < \beta > s(t),$$

where the rate of increase with running speed ($<\beta>$, 'slope') reflects the presence of 'velocity-controlled oscillators' in the septo-hippocampal system (Burgess 2008; Welday et al. 2011): neurons whose firing shows theta-band modulation whose frequency increases with running speed, as also seen in place (Geisler et al. 2007) and grid cells (Jeewajee et al. 2008a). This slope component is identified with type I mechanisms in being movement related and entorhinal cortex dependent; the second component (f_0, 'intercept') is identified with type II theta mechanisms, in being independent of both movement and entorhinal cortex (Burgess 2008, pp. 1168–9). Thus, the model predicts a dissociation between the factors affecting the intercept and slope of the relationship of theta frequency to running speed, with the intercept component linked to arousal/anxiety and the slope, more obviously, to spatial representation mechanisms updated by translational movement.

In Sects. 12.3.3 and 12.3.4, we discuss new evidence in support of this model showing that the intercept is related to anxiety/anxiolytic drugs and the slope to spatial representation and spatial novelty.

12.1.3 Hippocampal Theta Across Species

In the freely moving rat, theta is the dominant oscillation in the hippocampus (Vanderwolf 1969), and amplitudes of one millivolt are not unusual. By contrast, finding hippocampal theta oscillations in humans has proven elusive until recently. Other than a relatively small number of intracranial EEG recordings in humans (iEEG, Halgren et al. 1978; Arnolds et al. 1980) with unclear behavioural correlates, there was very little evidence relating the hippocampal theta rhythm measured in the rodent to electrophysiological activity elicited by human mnemonic function. Furthermore, human and monkey hippocampal theta oscillations (4–8 Hz) appear to be much more transient in duration than the rodent hippocampal theta rhythm measured during exploration (Jacobs and Kahana 2010). This is only further confounded by differences in frequency, where often the LFP is not dominated by the centre of the theta band like with rodents, but by either lower 1–4 Hz delta frequencies or higher frequencies in the 8–12 Hz alpha band (Lega et al. 2012; Jacobs and Kahana 2010; Buzsaki et al. 2013).

One problem for across-species comparisons is that the historical scalp-EEG-derived frequency boundaries used in human research are somewhat arbitrary, and the frequency of characteristic oscillations (e.g. eyes-closed alpha) may vary considerably even in aged-matched subjects, such that a priori fixed-band analyses may mask real effects (Klimesch 1999). A key challenge for reconciling animal-human data is that theta-behaviour links have mostly been characterised in freely moving rodents, while no recordings exist of theta during human locomotion, where virtual reality video games are more commonly used. One feasible possibility for species-matching is to record theta from ambulating mammals including humans in virtual reality setups where the subject's ambulation updates the visual scene (Harvey et al. 2009; Chen et al. 2013). Further evidence of the utility of VR systems for measuring theta comes from targeted electrode recordings in rodents showing the presence of movement-related hippocampal theta during ambulation in a virtual reality system and even when experiencing virtual visual motion without physically moving (Chen et al. 2013).

Still, it is uncertain whether human hippocampal delta oscillations during virtual exploration (Ekstrom et al. 2005; Watrous et al. 2011) are more analogous to theta in rodents or whether the 8 Hz amplitude increases seen during some components of goal-directed virtual navigation (Ekstrom et al. 2005; Kaplan et al. 2012) and purely mnemonic tasks (Fell et al. 2011; Lega et al. 2012) are more comparable to rodent theta (Watrous et al. in press). Notably some ~8 Hz oscillatory activity extends well into the 8–12 Hz alpha band (Fell et al. 2011; Lega et al. 2012), which is interesting given hypotheses that posit that alpha inhibition in the neocortex makes neural representations more sparse during memory formation

(Axmacher et al. 2006). Further, the proposed cognitive mechanism of transient hippocampal theta triggering top-down alpha inhibition in the neocortex (Axmacher et al. 2006) may relate to early ideas on the hippocampal theta rhythm and behavioural inhibition (Douglas 1969).

12.1.4 Gamma Oscillations and Theta-Gamma Coupling

Much has been learned about gamma oscillations and theta-gamma interactions by recording from silicon probes in the behaving rat (Bragin et al. 1995; Csicsvari et al. 2003). The well-established finding that hippocampal gamma power is appreciably higher during theta states than non-theta states (e.g. Bragin et al. 1995; Csicsvari et al. 2003) has long suggested the possibility that theta modulates gamma. Notably, for instance, the amplitude of gamma varies as a function of the theta cycle, and the frequency of theta and gamma is positively correlated (Bragin et al. 1995; Belluscio et al. 2012). Recently, hippocampal gamma has increasingly been subdivided into different frequency bands, with a view to better understanding the physiological basis of theta-gamma coupling and the neuroanatomy of gamma in the hippocampal formation. As we shall see, subdividing gamma also helps to clarify theta's role in encoding versus retrieval scheduling, discussed in Sect. 3.2.

A clear consensus has not yet fully emerged, but three gamma bands have been identified in hippocampal region CA1, here called low, middle, and high gamma (Scheffer-Teixeira et al. 2011; Belluscio et al. 2012). Belluscio et al. (2012) assign ranges of 30–50, 50–90, and 90–150 Hz to these three bands. Scheffer-Teixeira et al. (2011) identified two separate gamma bands in the high range, centred at around 80 Hz and 140 Hz, respectively. An influential study of theta-gamma coupling by Colgin et al. (2009) identified the slow band (~25–50 Hz) but did not subdivide the broad fast band (~65–140 Hz). Whether this could be related to the location of the recording electrodes with respect to CA1 layers is currently unclear. The absolute values of the characteristic peaks of these bands will likely vary with individual differences, similarly to alpha (Klimesch 1999), and with behaviour. For example, gamma frequency increases with running speed (Ahmed and Mehta 2012). (This may reflect theta-gamma frequency coupling; as mentioned above, theta frequency reliably increases with running speed.)

Scheffer-Teixeira et al. (2011) examined phase-amplitude coupling between theta phase and the amplitude of different gamma bands in CA1. Phase-amplitude coupling refers to the amplitude modulation of a higher-frequency oscillation by a lower-frequency oscillation. These authors found that activity in the two gamma ranges (one peaking at ~80 Hz, 'middle gamma'; one at ~140 Hz, 'high gamma') was controlled by theta phase. Using electrodes located at different depths in CA1, Scheffer-Teixeira and colleagues showed that the strength of the theta-middle-gamma coupling appeared to peak in the lacunosum-moleculare layer, which is the layer where entorhinal axonal terminals synapse onto CA1 dendrites. In other words,

theta-middle-gamma coupling probably reflects a state of enhanced communication between entorhinal-CA1 projection neurons and their CA1 targets.

Belluscio et al. (2012) used current source density analysis to identify the anatomical location of the different gamma bands. Consistent with Scheffer-Teixeira et al. (2011), Belluscio and colleagues locate middle gamma to the stratum lacunosum-moleculare, indicating that entorhinal afferents drive the middle gamma. Consistent with Colgin et al. (2009), Belluscio and colleagues show that slow gamma had the largest sink in the mid-stratum radiatum, indicating that CA3 afferents drive the slow gamma. Scheffer-Teixeira et al.'s theta-phase-gamma-amplitude coupling study was unable to detect significant theta phase modulation of low gamma activity, but the other studies found that this gamma was linked to the descending phase of pyramidal-layer theta (slow-gamma-to-theta coupling, Colgin et al. 2009; peak slow-gamma power, Belluscio et al. 2012).

In summary then, CA3–CA1 communication is preferentially mediated by slow gamma on the descending phase of CA1 pyramidal-layer theta, while entorhinal-CA1 communication, according to the Scheffer-Teixeira and Belluscio studies, is mediated by middle gamma at the peak of pyramidal-layer theta. The different theta phase preference of the coupling between entorhinal cortex and CA1, on the one hand, and CA3 and CA1, on the other, is a theme we return to (Sect. 12.3.2) in the discussion of encoding versus retrieval scheduling. If encoding is primarily entorhinal driven and preferentially occurs at one phase of theta, and retrieval is primarily CA3 driven and preferentially occurs at another phase of theta, then theta phase may be one of the mechanisms scheduling encoding and retrieval (Hasselmo et al. 2002; Manns et al. 2007; Lever et al. 2010; Douchamps et al. 2013). In Sect. 12.3.2, we discuss experimental work on place cells in support of this proposal.

12.1.5 Human Hippocampal Gamma and High-Frequency Activity

Similar to across-species differences in theta, discrepancies related to shorter duration and lower frequencies have been observed when investigating the human/non-human primate homologues of fast gamma (>100 Hz) and sharp wave/ripple activity. 80–150 Hz ripple activity typically lasting around 50 ms has been observed in both humans (Axmacher et al. 2008) and non-human primates (Skaggs et al. 2007; Logothetis et al. 2012), which is lower than the traditional 140–220 Hz activity in rodent recordings. Despite these differences, Axmacher et al. (2008) found that increased ripple events during a short nap after a memory encoding task predicted successful post-nap memory recall, which matched later findings in rodents also showing behavioural relevance for ripples (e.g. Girardeau et al. 2009; Ramadan et al. 2009; Jadhav et al. 2012). Furthermore, robust >200 Hz hippocampal activity has also been observed; however, it appears to directly relate to epilepsy pathology (Bragin et al. 1999; for review see Engel et al. 2009). Other non-pathological >100 Hz fast gamma activity in the parahippocampal gyrus was found during slow-wave sleep, but hippocampal gamma was mostly below 100 Hz

(Le Van Quyen et al. 2010). In Sect. 12.3, we discuss findings involving human and non-human primate hippocampal gamma (<100 Hz) and memory performance in further detail.

12.2 Computational Functions of Oscillations

In this section we attempt to define some of the potential functional roles of oscillatory brain activity, so as to provide a framework for discussion of the experimental data relating hippocampal oscillations to cognition and behaviour. Memory will be one focus for this discussion, given the undisputed role of the hippocampus in memory, following Scoville and Milner's seminal (1957) paper. The theta rhythm will be another focus, given the predominance of the theta rhythm in the hippocampal electrophysiology of behaving rodents (Vanderwolf 1969). A third phenomenon, relevant to several of the examples discussed, is the theta phase precession of place cell firing (O'Keefe and Recce 1993). This provides one of the most robust examples of a behavioural correlate of the temporal organisation of neuronal firing. We briefly describe this finding here, to be available for reference in many of the discussions below.

Place cells in the hippocampus fire whenever the animal moves through a specific portion of its environment (the cell's firing field; O'Keefe and Dostrovsky 1971). In parallel with this firing rate code for location, there is a temporal organisation to firing relative to the ongoing theta rhythm in the local field potential (LFP), such that the theta phase of firing systematically advances from later to earlier phases as the animal moves through the firing field (O'Keefe and Recce 1993) see Fig. 12.1. Since the finding of theta phase precession in hippocampal place cells, a similar phenomenon has been shown to exist in the grid cells found in layer II of medial entorhinal cortex (Hafting et al. 2008). These cells fire whenever the animal enters any one of an array of firing fields that are arranged across the environment at the vertices of a regular triangular grid (Hafting et al. 2005). The systematic advance of theta phase of firing from later phases to earlier phases is seen as the animal traverses any of the firing fields.

Below we discuss some of the potential functional roles of oscillatory brain activity, including organising processing into discrete chunks, representing the order of events by firing phase, representing metrical information such as distance by firing phase, using phase differences to perform temporal integration of variables encoded as frequency differences, and using phase coupling to route interregional communication.

12.2.1 Organisation of Processing into Discrete Chunks

An oscillation can be seen as dividing processing into cycles or parts of cycles. This can serve as an organisational principle in the same way as the processing cycles of the CPU of a computer: processing occurs within each theta cycle, so that the

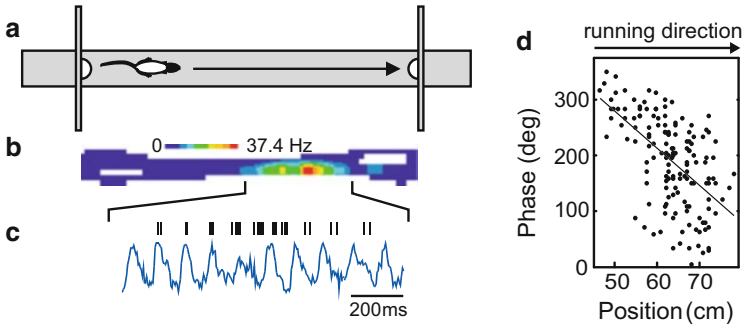

Fig. 12.1 Theta phase precession of place cell firing. (**a**) As a rat runs along a linear track, a place cell in the hippocampus fires as the animal moves through the firing field (**b**). The firing rate code for location is also a temporal code (**c**) spikes (*ticks*) are fired at successively earlier phases of the theta rhythm of the local field potential (*blue trace*), referred to as 'theta phase precession'. The theta phase of firing correlates with the distance travelled through the place field (**d**), even when pooled over runs that might be fast or slow. Adapted from (Huxter et al. 2003)

outputs of the process are discretised, one per cycle. These discrete outputs have some advantages over a seamlessly evolving process. For example, it becomes well defined to compare one output to the next so as to detect change. This type of organisational role is most often associated with lower frequencies, including hippocampal theta, with higher frequencies such as gamma often being considered part of the processing that is being organised. Indeed, this type of organisation may reflect a more general hierarchical organisation in which lower-frequency oscillations modulate higher-frequency oscillations (Lakatos et al. 2005) and in which lower frequencies provide organisation over larger spatial scales (von Stein and Sarnthein 2000; Buzsaki and Draguhn 2004).

The view of theta as parcellating computation into discrete chunks (see, e.g. O'Keefe and Nadel 1978) is nicely consistent with several experimental observations, briefly summarised below. Theta modulation of the overall activity of principal cells in the hippocampus produces preferred firing phases and non-preferred firing phases (Mitchell and Ranck 1980; Fox et al. 1986). Theta modulation of synaptic plasticity produces phases permissive of LTP or not (Pavlides et al. 1988) or distinguishing LTP from LTD (Huerta and Lisman 1995, 1996; Hyman et al. 2003). Theta modulation of higher-frequency oscillations such as gamma provides discrete periods of gamma power (Bragin et al. 1995; Canolty et al. 2006) or discrete periods of differential responsiveness to different sources and frequencies of gamma-modulated input (Chrobak and Buzsaki 1998; Colgin et al. 2009).

Several potential functional consequences of organising processing into discrete phases of an underlying oscillation have been suggested. In one early example, Gardner-Medwin (1976), following Marr (1971) in modelling CA3 as an auto-associative network, suggested that pattern completion was an incremental process that occurred across each theta cycle. Pattern completion is the process by which a

subset of cues from an event trigger reactivation of the full neural representation of that event. Starting with a high firing threshold (high inhibition), only the most strongly driven neurons would fire which would be those mostly likely to be consistent with the input pattern initiating retrieval. A gradual reduction in firing threshold allowed more neurons to be activated, via recurrent activity from those initially activated, eventually completing the stored pattern with very few erroneously active neurons. The next theta cycle then starts with high phasic inhibition, curtailing the activity of the previous cycle and allowing pattern completion of a new pattern, i.e. whichever stored pattern is most consistent with the pattern of input to CA3 on that cycle.

In a related, second example, Hasselmo et al. (2002) proposed a subdivision of the theta cycle in CA1 into phases associated with encoding into memory (permissive of LTP and driven by sensory input from entorhinal cortex) and phases associated with retrieval (resistant to LTP and driven by pattern-completed input from CA3). This proposal, and supporting evidence for it, is discussed in more detail below; see Sect. 12.3.2.

A third example concerns the gamma rhythm. If gamma oscillations are a natural consequence of local feedback inhibition (Whittington et al. 1995), then it is possible that populations of neurons representing distinct objects might compete in a winner-take-all fashion to dominate activity within a gamma cycle. As in the above example of pattern completion, phasic inhibition curtails that activity in the previous cycle, allowing a new competition for activity in the next cycle. In this manner, the neurons firing in the same gamma cycle might be thought to represent different aspects of the same object, i.e. object binding via firing synchrony (Singer and Gray 1995; Fries 2005). We discuss this type of mechanism further in the context of interregional phase coupling and the 'communication through coherence' hypothesis (Fries 2005); see Sect. 12.3.5.

12.2.2 Ordinal Coding by Oscillatory Phase

Extending the idea of winner-take-all competition between items within each gamma cycle (see above), Lisman and Idiart (1995) proposed a hierarchical theta-gamma organisation of sequence memory. In this model, sequences of items could be represented such that each item corresponded to activity in one gamma cycle, and the entire sequence was represented in the gamma cycles within one theta cycle. A process of after-depolarisation (ADP, following the usual after-hyperpolarisation, AHP) with a timescale of one theta period meant that the neurons representing each item reactivated at the same point in the next theta cycle, allowing the sequence to be maintained indefinitely. This cyclic process of competition, activation, and suppression parallels the process of 'competitive queuing' used in psychological models of memory for sequential order (Grossberg 1972; Houghton 1990; Burgess and Hitch 1992) and in patterns of neural firing in primates performing sequential tasks (Averbeck et al. 2002; Bullock 2004). The model provides predictions for how many items can be remembered in order

(the number of gamma cycles per theta cycle) and for patterns of theta and gamma oscillations in working memory tasks (which we return to in Sect. 12.3).

The example of theta phase precession of place cell firing is also relevant here. A population of place cells with spatially overlapping firing fields distributed along a linear track will fire in a sequential but temporally overlapping way as the animal runs along the track. However, as a consequence of the theta phase precession of individual cells, there will be temporal structure to the pattern of firing within each theta cycle: those place cells firing at later phases will have firing fields centred ahead of the animal, while those firing at earlier phases will have firing fields centred behind the animal. Thus, the spatial order of firing fields on the track will be present in the temporal order of firing within each theta cycle. While this effect is most clear on a linear track (O'Keefe and Recce 1993), the same pattern can also be seen in animals foraging in open environments (Burgess et al. 1994; Skaggs et al. 1996). This effect can also be thought of as the location represented by the population of place cells 'sweeping forwards' from behind the animal to in front of it during each theta cycle (Skaggs et al. 1996; Gupta et al. 2012).

If we consider the sequential activation of place cells as the animal runs along a linear track, the ordered firing of place cells within each theta cycle, combined with spike-time-dependent long-term potentiation, allows the formation of associations from a place cell firing earlier on the track to one firing later on the track. In principle this could explain theta phase precession in terms of a place cell's early phase firing being driven by environmental input to the place cell and firing nearer to the start of the track being driven by learned associations from place cells firing nearer to the start of the track, and occurring at later phases due to synaptic conduction delays (Tsodyks et al. 1996). The Lisman and Idiart (1995) model can be adapted to model this situation, predicting that a discrete number of place locations are represented in each gamma cycle within a theta cycle (Jensen and Lisman 1996), and the Tsodyks et al. (1996) model can be adapted to include theta phase precession in open environments by including similar neuronal AHP/ADP dynamics to the Lisman model (Navratilova et al. 2012).

12.2.3 Metrical Coding by Oscillatory Phase

A large-scale oscillation, such as that reflected in the local field potential, provides a clock against which the phases of the activity of different neurons can be used to represent continuous or metrical quantities. For example, Hopfield (1995) outlined a situation in which incoming sensory information encoded in firing rates could be represented as phase advances relative to a global subthreshold membrane potential oscillation (MPO): the greater the depolarising input to each neuron, the earlier it would take the MPO over the firing threshold, i.e. the earlier the phase of firing relative to the global oscillation. This scheme can implement scale-invariant pattern recognition in a natural way, if there is a logarithmic translation of depolarisation into phase advance.

The theta phase precession of place cell firing can also be seen as a metrical phase code. A key observation of O'Keefe and Recce (1993) was that the phase of firing codes the distance travelled through the firing field (and more so than the time spent in the firing field, even though the data include spikes fired during fast and slow runs through the firing field). Thus the theta phase of firing provides metrical information concerning distance travelled: providing a fine-scale code for position within-field to go with the firing rate code and providing additional spatial information to that in the firing rate alone (Jensen and Lisman 2000). In fact, the firing phase appears to code for distance travelled independently of the firing rate, which could vary to independently encode nonspatial variables (Huxter et al. 2003).

12.2.4 Temporal Integration by Oscillatory Phase

Temporal integration is a key component of all mnemonic processing that requires knowledge of what has happened in the recent past. A simple mechanism for this is provided by the phase of one oscillator (an 'active' oscillation) compared to another oscillator (a 'baseline' oscillation). If the active oscillation varies its frequency relative to the baseline oscillation, then its phase relative to the baseline oscillation will be the time integral of the frequency difference. Thus, by encoding information as a variation in frequency, the phase of the active oscillation automatically performs temporal integration of that information.

The phase precession effect can be seen in terms of temporal integration by phase coding. O'Keefe and Recce (1993) showed that place cell firing is temporally modulated at a frequency slightly higher than the LFP theta frequency. If the increase in frequency is proportional to running speed, then the theta phase of firing will represent distance travelled (i.e. the temporal integration of running speed; Lengyel et al. 2003). Populations of place cells can be considered as 'speed-controlled oscillators' in this way (Geisler et al. 2007). Because the firing rate of place cells is spatially modulated, the LFP will be consistent with the oscillation in overall population firing rate, even though each individual place cell has a higher frequency of oscillation (Burgess et al. 1993; Geisler et al. 2010).

The temporally repeating nature of phase codes, the spatially repeating nature of grid cell firing patterns, and the assumption that grid cells perform 'path integration' (i.e. represent translation by integrating movement) suggest that a similar phase-coding mechanism might underlie grid cell firing. To perform accurate path integration, and to produce coherent 2-dimensional firing patterns, requires that the animal's distance travelled is tracked along more than a single direction. To do this, several 'velocity-controlled oscillators' (VCOs) could vary their frequency relative to baseline proportional to the component of velocity along different 'preferred' directions. Then their phases relative to baseline will encode the distances travelled along their preferred directions, and grid cell firing could reflect constructive interference between inputs from VCOs with coincident phases (Burgess et al. 2005, 2007; Burgess 2008; Hasselmo 2008). Again, the baseline LFP

frequency is consistent with the mean frequency of all of the VCOs coding for different preferred directions (Burgess 2008).

Thus, type I 'movement-related' theta may represent a baseline oscillation frequency against which phase coding can perform temporal integration of movement speed (in the case of place cells) or the component of movement speed along preferred directions (in the case of the putative inputs to grid cells). A key observation here is that the scale of spatial coding is determined by the rate of change of frequency with running speed, while the absolute value of the baseline frequency itself is irrelevant to spatial coding. This suggests that type I 'movement-related' mechanisms of theta generation are specifically reflected in the *slope* of the frequency-speed relationship, while type II mechanisms (e.g. associated with alert immobility and anxiety, Kramis et al. 1975; Sainsbury 1998) are specifically reflected in the *intercept* of the frequency-speed relationship (Burgess 2008). We consider evidence for this suggestion about two components of theta frequency in Sect. 12.3.4.

Of course place cell firing and grid cell firing will also reflect inputs carrying environmental information, such as boundary vector cells (Hartley et al. 2000; Lever et al. 2009), to provide spatial stability to any temporal integration of movement (e.g. Burgess and O'Keefe 2011; Cheung and Vickerstaff 2010), and this input need not be theta modulated. They may also reflect recurrent inputs from other place or grid cells, increasing stability (Burgess et al. 2007) and potentially supporting an alternative 'continuous attractor' mechanism for integration (Zhang 1996; Fuhs and Touretzky 2006; McNaughton et al. 2006; Burak and Fiete 2008).

12.2.5 Oscillations and Interregional Communication

Just as oscillations can provide potentially useful temporal organisation of processing within a region, they can also support efficient interregional processing. Thus, if processing is temporally organised into chunks (as discussed in Sect. 12.2.1), but is spread across two brain regions, then coherent temporal organisation is required across both regions. For example, if processing is organised such that information concerning different objects occurs in different cycles of gamma, and this information is spread across multiple brain regions, then local gamma rhythms must be coherent for the correct object bindings to be maintained. Equally, if neural activity in two regions each tend to oscillate (e.g. due to local feedback inhibition), coupling the activity in both regions via interregional synaptic transmission will tend to lead to coherence in the local oscillations. This view, of oscillatory coherence as diagnostic of functional interregional coupling, is elaborated in the 'communication through coherence' hypothesis (Fries 2005).

There are several other proposed functions for oscillations in interregional communication. For example, a hierarchical generative model of perception supposes alternating phases of 'bottom-up' inference and 'top-down' prediction involving projections between perceptual areas and higher areas representing hidden variables or causes (e.g. Mumford 1994; Dayan et al. 1995), with

implications for the hippocampus as supporting and maintaining the highest level representation (e.g. Kali and Dayan 2004). This type of temporal organisation of processing modes (like the separation into encoding and retrieval modes discussed in Sects. 12.2.1 and 12.3.2) would be well suited to oscillatory control of the entire processing stream from hippocampus down to sensory neocortex. Such an arrangement would require a coherent oscillation in all of these disparate areas, e.g. modulation of activity in sensory areas by hippocampal theta.

We note that the occurrence of sharp wave/ripples in the hippocampus (O'Keefe and Nadel 1978; Buzsaki et al. 1983) has been suggested to represent a processing mode in which information is communicated to neocortex (Buzsaki 1989). This interesting suggestion is discussed in detail in Jadhav and Frank (2014). More generally, electronic communications often increase the number of distinct information streams carried by a single channel by multiplexing: i.e. using each successive cycle of a high-frequency oscillation to carry a different stream, so that all streams are carried within one cycle of a lower-frequency oscillation. Such a role has been proposed for theta-gamma coupling (Nadasdy 2009, see 2010 for review; Lisman and Idiart 1995)

12.3 Experimental Findings Relating Oscillations to Cognition and Behaviour

12.3.1 Oscillatory Power and Performance

When processing is temporally organised, as discussed in Sect. 12.2, then normal operation of the process will likely produce an oscillatory modulation of activity. In this case, the presence of oscillations can be diagnostic of efficient processing. Here we review evidence consistent with this position: correlations between the presence of oscillatory power in the relevant frequency band and performance on the associated cognitive or behavioural task.

Before we do, we should comment on the nature of this evidence. Correlation-type evidence dominates in the analysis of the importance of oscillatory activity to brain function. Hippocampal-dependent spatial and mnemonic processing is no exception to this. Unlike the targeting of, say, specific genes and receptor subunits, one cannot act selectively on oscillations without disrupting the interacting components from which the oscillations emerge. Oscillations are an emergent property, and Buzsaki has written eloquently on the difficulty, indeed perhaps the 'logical absurdity in the quest of expunging oscillations selectively' (Buzsaki 2006, p. 359). Accordingly, observing the consequences of eliminating oscillatory activity selectively may be an elusive goal.

One point of leverage in analysing cause and effect relationships regarding septo-hippocampal theta has been to disrupt the function of the medial septum. Early studies in this vein using lesions (Winson 1978) suggested that septo-hippocampal theta was crucial to spatial learning. More recently, two studies (Koenig et al. 2011; Brandon et al. 2011) have inactivated medial septum (MS)

and shown an interesting dissociation in the representations underlying spatial cognition. MS inactivation strongly disrupts grid cell firing, while only minimally affecting head direction cell firing. Place cells are somewhat affected, but surprisingly mildly. Such evidence provides important clues to theta's role in spatial cognition and the memory dependent upon that cognition, but there is the obvious significant caveat; it cannot be ruled out that other effects of MS inactivation, such as the acute deprivation of acetylcholine, drive the disruption to grid cell signalling.

With the almost impossible quest of selectively expunging oscillations in mind, then, we turn to the correlations between oscillatory activity and performance.

12.3.1.1 Human Theta and Cognition

The introduction of virtual reality navigation tasks for epileptic patients that have hippocampal depth electrodes has given researchers the ability to use similar spatial memory tasks as ones used with rodents and investigate the same correlates in the human hippocampus (Burgess et al. 2002). Kahana et al. (1999) published the first study of movement-related theta oscillations from the human brain, including the medial temporal lobe, and follow-up studies recording from hippocampal neurons found neural firing that correlated with place, goal, and direction (Ekstrom et al. 2003; Jacobs et al. 2010) and also grid-like firing patterns (Jacobs et al. 2013).

Further research has attempted to classify the exact human analogue of type I hippocampal theta with iEEG (Ekstrom et al. 2005; Watrous et al. 2011) and MEG (de Araujo et al. 2002; Cornwell et al. 2008; Kaplan et al. 2012). Robust but transient increases in delta (1–4 Hz) oscillations have been observed (Ekstrom et al. 2005; Watrous et al. 2011) in addition to power increases at other frequencies (~8 Hz), depending on the specific task during virtual navigation (see Sect. 12.1.3 for further discussion of across-species differences). Similar to rodents, movement-related theta is highest in amplitude at movement initiation and is also accompanied by a reduction in theta power (not frequency like in rodents) in novel environments (Kaplan et al. 2012). Notably, Cornwell et al. (2008) observed an increase in hippocampal theta power during goal-directed virtual movement versus aimless virtual movement and also that hippocampal theta power correlated with performance in navigating a virtual reality water maze. Another study has found that movement-initiation-related theta power increases during encoding of object locations within a virtual environment correlate with subsequent memory for the object locations (Kaplan et al. 2012). This study may provide a link between human theta and the proposal that movement-related theta plays a role in exploratory behaviour in rodents (O'Keefe and Nadel 1978).

In humans, frontal midline theta is often viewed as a surrogate to the hippocampal theta usually observed in rodent recordings (Mitchell et al. 2008), and numerous studies have related human frontal midline theta oscillations to memory performance (see Klimesch et al. 2001; Addante et al. 2011 for examples). However with advances in intracranial recordings and non-invasive MEG source reconstruction, investigations into the theta rhythm of the human hippocampus and medial temporal lobe are becoming more prevalent. An emerging literature of MEG and iEEG studies has demonstrated correlations between theta power in the

hippocampus/medial temporal lobe and memory performance (Cornwell et al. 2008; Guderian et al. 2009; Fell et al. 2011; Poch et al. 2011; Kaplan et al. 2012; Lega et al. 2012; Guitart-Masip et al. 2013). Furthermore, recent findings have implicated the importance of single unit phase-locking to the hippocampal theta rhythm (Rutishauser et al. 2010). Rutishauser et al. (2010) found the precision of phase-locking of amygdala and hippocampal neurons to the LFP theta rhythm during memory encoding predicted whether an encoded item would be successfully remembered. This finding indicates that hippocampal phase concentration could serve as a diagnostic of system state. In addition to hippocampal theta, a distinct theta rhythm has been reported in the human entorhinal cortex (Mormann et al. 2008), preliminary evidence suggests that direct stimulation of entorhinal cortex resets hippocampal theta and improves performance on a spatial memory task (Suthana et al. 2012), and stimulation eliciting memories is associated with theta-band synchronisation of multiple areas (Barbeau et al. 2005).

Earlier studies have focused on using paradigms like the Sternberg working memory task to investigate working memory maintenance. Theta oscillatory activity during working memory has been reported in the human hippocampus using MEG (Tesche and Karhu 2000) and also iEEG (Raghavachari et al. 2001). A hippocampal source of theta during working memory has been supported by MEG studies of patients with bilateral hippocampal atrophy (Cashdollar et al. 2009), in which the patients were impaired at retaining associative information and showed reduced occipital-temporal theta synchrony compared to healthy control participants. There have also been studies looking at declarative memory rather than working memory. These studies have mainly focused on correlating theta activity during encoding with subsequent memory performance. One MEG study found that subsequent memory performance correlated with pre-stimulus MTL theta during memory encoding (Guderian et al. 2009), while another found that theta amplitude, including signal attributed to the MTL, was higher for recollection than recognition (Guderian and Duzel 2005). Parallel findings relating theta to subsequent memory have been made with intracranial hippocampal recordings (Sederberg et al. 2003, 2007) and with combined fMRI/EEG (Sato et al. 2010). These subsequent memory effects have also been observed with hippocampal gamma power (Sederberg et al. 2007). Finally, a transient increase in hippocampal theta for encoding of unpredictable compared to predictable events in an iEEG study has also been reported (Axmacher et al. 2010a).

12.3.1.2 Human Hippocampal Theta in Psychiatry and Anxiety

Attempts have been made to translate spatial navigation-related theta findings into clinical domains. For instance, virtual navigation tasks show potential to be applied to psychiatry, where research has shown reduced hippocampal theta in depressed patients compared to healthy controls during virtual navigation (Cornwell et al. 2010). While investigating threatening (unpredictable shocks) versus non-threatening (no threat of shocks) environments during navigation in a virtual Morris water maze, Cornwell et al. (2012) found that self-reported anxiety during navigation in threatening environments correlated with 2–6 Hz power in the left anterior

MTL. They also found that better individual spatial memory performance in threatening environments correlated with left posterior MTL 4–8 Hz power. Increasing use of MEG in cognitive neuroscience, potentially combined with simultaneous investigation using iEEG recordings from the hippocampus, may help to bridge some of the gaps between direct measurements from the hippocampus of oscillatory activity in patient populations and non-invasive but indirect measurements of oscillatory activity in healthy participants.

12.3.2 Theta Phase and Encoding Versus Retrieval Scheduling

In Sect. 12.2, we outlined different potential functions of oscillations and identified one of these as organising processing into discrete chunks (Sect. 12.2.1). Several potential functional consequences of organising processing into discrete phases of an underlying oscillation have been suggested. In this section, we consider the idea that theta organises the encoding and retrieval stages of hippocampal memory processing. It appears that there are several memory-modulating processes which are dominant at different phases of the theta oscillation. These include when feedforward and feedback-related input are dominant, when synaptic potentiation or depression is dominant, and when inhibition is dominant. The theta oscillation appears to organise these in such a way that one theta phase is propitious for encoding, while another theta phase is propitious for pattern completion-based retrieval.

12.3.2.1 Models of Encoding Versus Retrieval Scheduling

Memory systems need to encode novel information in the face of interference from previously encoded associations (proactive interference). That food was previously abundant in a specific location should not prevent us from learning that there is no food in that location now. That a prominent ex-girlfriend was called ‘Olivia’ should not prevent us from learning that the sister of a new girlfriend is also called by that name.

In counteracting proactive interference, a general solution is to separate encoding and retrieval processes and to propitiously co-align facilitatory processes (such as synaptic potentiation or depression) appropriate to each memory state. Two sets of models have been proposed for the hippocampus, one involving neuromodulators, notably acetylcholine (Hasselmo and Schnell 1994; Hasselmo et al. 1996; Meeter et al. 2004; see Gupta and Hasselmo 2014), and acting on longer timescales (seconds), and one involving the theta oscillation (Hasselmo et al. 2002; Kunec et al. 2005), and thus acting on subsecond timescales. In theta-based models, the phase of ongoing theta oscillations temporally separates encoding and retrieval and determines the different synaptic plasticity regimes that encoding and retrieval require. These models, originated by Hasselmo and colleagues, have been reviewed in detail very recently (Hasselmo 2012). Accordingly, after a short summary of the modelling approach, our presentation here focuses on new empirical support for

these models: two studies of rodent hippocampal place cell firing consistent with control of encoding and retrieval scheduling by theta phase (Douchamps et al. 2013; Jezek et al. 2011).

CA1 has two major inputs, one from the entorhinal cortex (perforant path), which might convey feedforward sensory information, and one from CA3 (Schaffer collaterals), which might convey retrieved information following recurrent-collateral-mediated pattern completion (Marr 1971; McNaughton and Morris 1987; Treves and Rolls 1994). A relatively high proportion of synaptic input onto CA3 pyramidal cells actually comes from other CA3 pyramidal cells ('recurrent collaterals'). Marr (1971) suggested that this anatomical feature meant that CA3 cells could subserve an evolving pattern completion process, whereby partial input (a subset of cues from an event) could trigger stages of mutual co-activation eventually activating the full set of cells originally associated with the complete inputs (i.e. recalling the whole event). As described in Sect. 12.2.1, Gardner-Medwin (1976) suggested a particular implementation of this idea, whereby the initial process of partial input pattern presentation, then mutual co-activation, and then pattern completion would take place within a single theta cycle.

In the (Hasselmo et al. 2002) model of CA1 encoding and retrieval, encoding takes place preferentially at the peak of theta as recorded from the CA1 pyramidal layer, when entorhinal cells are maximally active and CA3 cells are minimally active. At this phase, long-term potentiation of the excitatory CA3-CA3 recurrent connections, and the CA3-CA1 Schaffer collateral connections, should be maximal. In contrast, retrieval takes place preferentially around the trough of theta, when CA3 cells are maximally active and entorhinal cells are minimally active (though sufficient to cue retrieval). This allows the network to be driven mainly by activity at previously modified synapses. At this phase, there should be no long-term potentiation, to preserve the purity of the retrieved traces and the novel associations. In the Hasselmo et al. (2002) instantiation of the model, long-term depression occurs at this theta phase.

One of the empirical foundations of the theta-based Hasselmo et al. (2002) model is the strong relationship between theta phase and plasticity (Pavlides et al. 1988). In CA1, LTP at Schaffer collateral synapses (i.e. CA3 to CA1) is preferentially induced by stimulation at the peak of local theta, while stimulation at the trough does not induce LTP and can induce LTD or depotentiation (Hölscher et al. 1997; Huerta and Lisman 1993, 1995, 1996; Hyman et al. 2003). The model's assumption that entorhinal and CA3 input arrive at different phases of theta, based originally on Brankack et al. (1993), is supported by recent studies (Mizuseki et al. 2009). The current data are certainly consistent with the view that the entorhinal activity peak, and entorhinal-CA1 coupling peak, occurs at the peak of pyramidal-layer theta. Current indications are that the CA3 activity peak and the CA3–CA1 coupling peak occur on the descending, pre-trough phase of pyramidal-layer theta. (See Sect. 12.1.4 for discussion of the theta-gamma coupling data.) Determining the precise theta phase preference of entorhinal-driven and CA3-driven activity is complicated by recent findings that theta phase of firing depends on anatomical location, particularly along the long axis (Lubenov and

Siapas 2009; Patel et al. 2012). Thus, it will be important in future work to ensure that the electrodes are in those regions of entorhinal cortex and CA3 that project to the CA1 cells under study.

12.3.2.2 Place Cell Studies Support Theta-Based Encoding and Retrieval Scheduling

We recently conducted an experiment designed to test predictions from both the cholinergic-based and theta-based encoding versus retrieval scheduling models (Douchamps et al. 2013). In the cholinergic-based model, high levels of acetylcholine promote an encoding mode. Acetylcholine is released in novelty, enhances long-term potentiation, and suppresses input relating to CA3 recurrent activity (i.e. suppresses CA3–CA3 and CA3–CA1 synaptic activity). Thus levels of acetylcholine control the balance between encoding and retrieval.

We used both models to derive predictions about the theta phase of firing of CA1 pyramidal cells, under the assumption that encoding prevails in novelty and retrieval in familiarity. In a familiar environment, the mean theta phase of neural firing occurs just after the trough of LFP theta recorded from the pyramidal layer. Using spiking activity in this condition as a baseline, we made three predictions as follows. First, in a novel environment under saline (Novel + Saline), preferred theta phase should shift *later*, closer to the pyramidal-layer theta peak, reflecting increased levels of entorhinal-driven encoding. Second, in a novel environment under scopolamine (Novel + Scopolamine), this muscarinic cholinergic antagonist should antagonise ACh's presumed role in novelty-elicited suppression of CA3 excitatory input to CA1 and should disrupt the later-theta-phase-in-novelty effect. Third, in a familiar environment under scopolamine (Familiar + Scopolamine), this cholinergic antagonist should shift preferred phase *earlier*, closer to the theta trough, by removing baseline cholinergic suppression of the CA3 projections onto CA1.

As Fig. 12.2 shows, we found evidence in clear support for all three of these predictions. Figure 12.2 shows the theta phase distribution of ensemble spiking activity for two representative ensembles in the control condition (Familiar + Saline) and in the three experimental conditions referred to above (Novel + Saline, Novel + Scopolamine, Familiar + Scopolamine). Figure 12.2a depicts an example of a raw and theta-bandpass-filtered LFP trace from the pyramidal layer. Figure 12.2b shows two cycles from this trace for illustrative purposes as the theta reference for the spike phase distributions shown in Fig. 12.2c–j. Figure 12.2c, d shows that theta phase distribution was unchanged under saline in the familiar environment. Figure 12.2e, f shows that preferred theta phase shifted to a later phase in the novel environment, closer to that of the pyramidal-layer theta peak. They also show that the phase distribution of spikes upon reexposure to the familiar environment (grey lines) closely resembles that seen in the baseline trial (black lines). In a previous study (Lever et al. 2010), we had shown this later-phase-in-novelty effect, but due to differing theta references could not be certain that resulting phase was closer to the pyramidal-layer theta peak. Figure 12.2 g, h illustrates how scopolamine injection shifted the phase distribution of spike firing

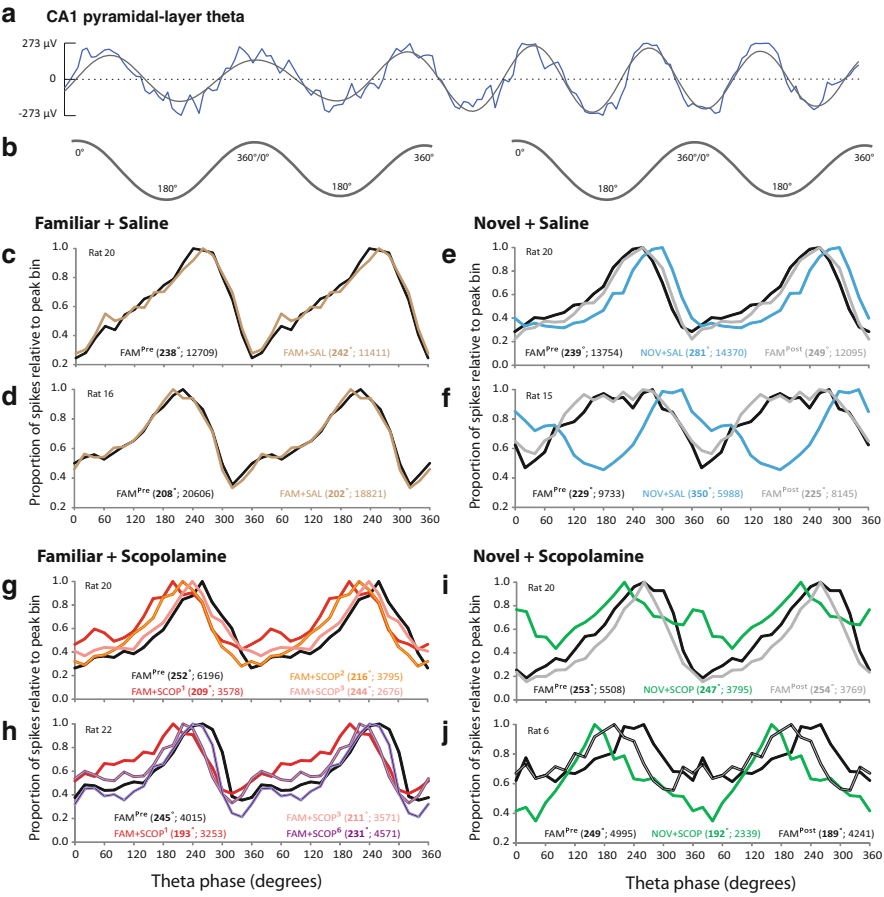

Fig. 12.2 Theta phase controls encoding and retrieval scheduling in the hippocampus. CA1 ensembles show later preferred firing phases in novelty, an effect disrupted by scopolamine, and show earlier firing phases under scopolamine in familiarity. Examples of the firing phase distributions of CA1 ensembles in individual rats. (**a**) Raw (*blue*) and filtered (6–12 Hz; *grey*) LFP trace recorded from CA1 pyramidal layer showing ~6 theta cycles. (**b**) Two theta cycles from trace in **a** are shown for illustrative purposes as the theta reference for the spike phase distributions below. (**c, d**) The preferred phase is very stable in the familiar environment before and after saline injection (FAM + SAL). (**e, f**) Novelty (NOV + SAL) elicits a later preferred phase compared to the baseline familiar trial T3 (FAM^{Pre}), but the distribution reverts to baseline on return to the familiar environment (FAM^{Post}). (**g, h**) Scopolamine elicits an earlier preferred phase in the familiar environment (FAM + SCOP); then the phase progressively approaches baseline phase as drug wears off over 3 (**g**) or 6 (**h**) sessions. (**i,j**) Scopolamine blocks the novelty-elicited coherent shift to a later firing phase characteristic of the undrugged state (NOV + SCOP). In C-J, preferred phase and total spike count of each ensemble shown in parentheses. Adapted from Douchamps et al. (2013)

in a familiar environment to an earlier phase, closer to the pyramidal-layer theta trough (red lines). Note that, in both rats, as the drug wore off, preferred phase gradually approached the phase seen in the baseline trial. Finally, Fig. 12.2i, j illustrates how scopolamine disrupts the shift towards the pyramidal-layer theta peak (c.f. Fig. 12.2e, f). There is some peak-related firing in the ensemble shown in Fig. 12.2i, which was also seen in another rat, but overall the results were clear: the novelty-elicited shift to a later preferred phase characteristic of the undrugged state was disrupted by scopolamine. In summary, all three predictions were confirmed.

We additionally tested a prediction based on the cholinergic model alone that scopolamine would disrupt 'remapping'. Remapping occurs when the hippocampus produces divergent representations (maps) of different environments (Muller and Kubie 1987). Greater difference in the environments, and more experience in the environments, elicits greater divergence in the maps (Lever et al. 2002; Leutgeb et al. 2004, 2005; Wills et al. 2005; Fyhn et al. 2007; McHugh et al. 2007; Nakashiba et al. 2012). Remapping is a well-established phenomenon and is related to encoding a representation of a new environment (Kentros et al. 1998; Nakazawa et al. 2003; Lever et al. 2002; Leutgeb et al. 2004, 2005; Wills et al. 2005; Sava and Markus 2008; Nakashiba et al. 2012). Accordingly, we reasoned that scopolamine should disrupt encoding and thus attenuate the distinctiveness of the map in the novel environment. This prediction was also confirmed: levels of remapping were reduced in the novel environment under scopolamine as compared to under saline (as broadly consistent with Ikonen et al. 2002). Taken together, the fact that all our predictions were confirmed offers strong support for both the cholinergic-based and theta-based models and suggests that the processes they model are complementary and should be integrated into a common framework (Hasselmo 2012; Easton et al. 2012; Barry et al. 2012).

The Douchamps et al. study was mostly focused on hippocampal encoding in response to novel environments, using place cell activity in a familiar environment as a baseline. We now turn to the study of Jezek et al. (2011), which investigated the process of retrieving pre-existing representations ('maps') of two highly experienced environments. These authors developed an elegant paradigm whereby they could instantaneously change the sensory cues (colour/lighting) triggering CA3 place cell maps of two very familiar environments. They asked what happened to CA3 place cell ensemble activity following the instantaneous cue change from the first to the second environment. Typically, ensemble activity flip-flopped between all-or-none representations of either the first or the second environment before settling on the second. Perhaps surprisingly, representations of the first environment were still occurring several seconds and occasionally tens of seconds after the instantaneous cue switch, broadly consistent with an earlier demonstration of slow-timescale place cell attractor dynamics in CA1 (Wills et al. 2005).

A key result in the Jezek et al. study was that the flip-flop transitions between maps occurred on a theta frequency timescale. Analysis showed that the best-performing period for separating the two maps was a theta cycle whose beginning was defined by the lowest point of CA3 pyramidal cell firing. Mixed ensemble activity, where both maps were co-active, was rare in a single theta cycle (~121 ms) and particularly so in the second half of the theta cycle.

In the first whole theta cycle after both first-to-second and second-to-first map transitions, representations were typically mature: they did not become more similar to the baseline representations over successive theta cycles. This implied that the fast-timescale attractor mechanism needed only one theta cycle for full pattern completion.

In summary, sharp transitions between CA3 spatial maps occurred preferentially at the theta phase of minimal pyramidal firing, and mixed maps were much rarer in the second half cycle, as expected if attractor dynamics dominate that half cycle. These findings are clearly consistent with the theta-based encoding versus retrieval scheduling models where hippocampal encoding and retrieval occur at theta frequency, and each cycle is alternately dominated by extrinsic sensory input and intrinsic recurrent/feedback input (Hasselmo et al. 2002; Kunec et al. 2005).

In conclusion, recent place cell studies provide good support of the idea that encoding and retrieval are scheduled by theta phase.

12.3.3 Theta Phase Coding of Metrical Spatial Information

Part of the interest in the theta phase precession of place cell firing comes from the observation that firing phase correlates better with distance travelled through the firing field than with other variables such as the time spent in the firing field (O'Keefe and Recce 1993). Thus, when pooling data over runs of variable speed, the intrinsic firing frequency of the place cell must adjust to exceed the LFP theta frequency by a greater amount during fast runs than slow runs, so that the correlation with distance is maintained. Even more intriguing is that simple explanations linking the firing phase to the overall depolarisation level of the neuron (Harris et al. 2002; Mehta et al. 2002) are inconsistent with the observation that variation run by run in firing phase is unrelated to variation in firing rate (Huxter et al. 2003) and that the theta phase of firing is unrelated to intracellular measures of depolarisation (Harvey et al. 2009).

The robust relationship between firing phase and location, in which firing phase adds spatial information beyond that contained in firing rate (Jensen and Lisman 2000), has led to the idea that theta phase precession plays a role in path integration. This idea is implemented by the 'dual oscillator' model of place cell firing, in which firing phase calculates distance travelled (O'Keefe and Recce 1993; Lengyel et al. 2003), and the oscillatory interference model of grid cell firing, in which 'velocity-controlled oscillators' encode the distances travelled along specific preferred directions which are combined in the grid cell firing pattern (Burgess et al. 2005; 2007; Burgess 2008; Blair et al. 2008; Hasselmo 2008) see Sect. 12.2.4.

The oscillatory interference model of grid cell firing (see Burgess 2008, and Sect. 12.2.4) makes specific predictions relating a grid cells' frequency of firing rate modulation ('intrinsic frequency' f_i) to the spatial scale of the grid (G), running speed (s), and the LFP theta frequency extrapolated to zero speed (f_0):

$$f_i(t) = f_0 + \frac{2(\pi + 1)}{\sqrt{3\pi G}} s(t).$$

When looking in grid cell data from Barry et al. (2007) and from the Moser laboratory, we found this relationship to be broadly verified (Jeewajee et al. 2008a). The baseline frequency (observable as LFP theta and equivalent to the mean frequency of all the VCOs with different preferred directions) should not vary with running direction; in fact the prediction for theta frequency (f_θ) as a function of running speed is

$$f_\theta(s(t)) = f_0 + < \beta > s(t),$$

where $< \beta >$ is a constant of proportionality which is inversely proportional to average grid scale.

The model also predicts that 'velocity-controlled oscillators' (VCOs) exist, whose frequency varies from the baseline frequency to encode the component of running speed along different preferred directions. The VCOs driving a grid cell could in principle be dendritic MPOs or input from other neurons (Burgess et al. 2005, 2007), but the former option is not biophysically plausible (Remme et al. 2010). Thus, VCOs should be neurons whose intrinsic frequency varies as a cosine function of running direction and a linear function of running speed. Welday et al. (2011) recorded from 'theta cells', i.e. presumed interneurons with strongly theta-modulated firing, along the septo-hippocampal circuit. They recorded for long enough to be able to make separate estimates of intrinsic frequency as a function of running direction and running speed, and found the predicted relationship. See Fig. 12.3 for a schematic summary of this oscillatory interference model of grid cell formation, in which a grid cell acts as a coincidence detector of multiple VCO inputs (Hasselmo 2008).

As well as supporting a specific novel prediction of the oscillatory interference model, the finding of Welday et al. (2011) potentially changes how we view theta cells. Not simply being involved in feedback inhibition and theta generation, they appear to be playing a key role in path integration by encoding the component of movement velocity along different preferred directions. Welday et al. (2011) point out that the firing of these VCOs provides a basis set from which any arbitrary spatial firing pattern could be constructed via oscillatory interference (including grid-like patterns as a subset). Thus oscillatory modulation of firing rates may have a very specific role in encoding information, beyond the more general functions usually ascribed to oscillatory firing, such as those outlined in Sect. 12.2.

The predicted link between theta rhythmicity and grid scale, and the observation that theta frequency reduces when the animal is put into a new environment (Jeewajee et al. 2008b) prompted us to examine the effect of environmental novelty on grid scale (Barry et al. 2012). Consistent with the model, we saw that grid scale expands under environmental novelty and slowly contracts as the new environment

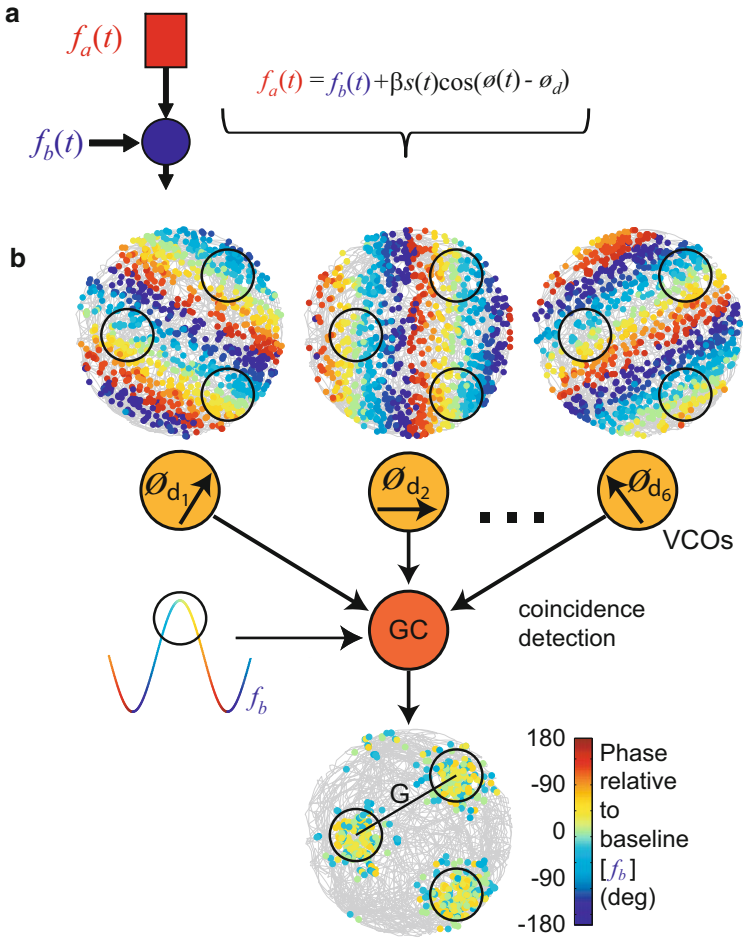

Fig. 12.3 The oscillatory interference model of grid cell firing. (**a**) A 'velocity-controlled oscillator' (VCO) is an active oscillation that has a frequency f_a which varies around the baseline frequency (f_b, identified with the local field potential) according to running speed $s(t)$ and running direction $\phi(t)$ relative to the VCO's preferred running direction ϕ_d. The dependency on running speed and direction causes the phase of the active oscillation relative to baseline to reflect displacement along the preferred direction (see mid *top panel* of **b**). (**b**) Multiple VCOs with different preferred directions combine with each other and the somatic baseline input to produce grid firing. Grid scale depends on the constant β as: $G = 2/\sqrt{3}\beta$. Adapted from (Burgess and O'Keefe 2011)

becomes familiar, while grid cells' intrinsic frequency reduces. The more specific prediction is that the reduction in theta frequency with novelty is due to a reduction of the slope of the relationship to running speed rather than a reduction in the intercept, as discussed in Sect. 12.3.4.

12.3.4 Dissociating Two Components in the Theta Frequency to Running Speed Relationship

The hippocampal formation is thought to play key roles in two very distinct sets of brain functioning: (1) spatial and context-dependent memory, linked to novelty detection, and (2) anxiety, linked to stress and depression. Each of these functions was the subject of highly influential books published over 30 years ago. O'Keefe and Nadel (1978) theorised on the hippocampal role in spatial cognition and episodic memory, while Gray (1982) set out the case that the hippocampus was involved in behavioural inhibition and anxiety. Interestingly, both O'Keefe and Nadel (1978) and Gray (1982) assumed that theta was crucial to the function they studied, with O'Keefe and Nadel (1978) suggesting that theta acted as a record of spatial translation and Gray (1982) noting that drugs which were effective as anxiolytic drugs in humans impaired septo-hippocampal theta in rodents.

Since, as we argue in this chapter, the temporal organisation of hippocampal online processing is dominated by the theta oscillation, it would be expected that hippocampal theta has increasingly been implicated in both the functional sets outlined above, and this is indeed the case. To give a quick pass through this literature in the last decade, many studies cited here have continued to implicate hippocampal theta in anxiety/anxiolytic drug action (e.g. Adhikari et al. 2010; Cornwell et al. 2012; Gordon et al. 2005; Gray and McNaughton 2000; Seidenbecher et al. 2003; Shin et al. 2009), memory-related novelty processing (e.g. Hasselmo et al. 2002; Lever et al. 2010; Rutishauser et al. 2010; Kaplan et al. 2012), and spatial cognition (e.g. Brandon et al. 2011; Buzsaki 2006; Giocomo et al. 2007; Huxter et al. 2003, 2008; Jezek et al. 2011; Jones and Wilson 2005; Koenig et al. 2011; Maurer et al. 2006; O'Keefe 2007; Skaggs et al. 1996).

By and large, however, there has been little attempt to understand how the hippocampal processing relating to spatial cognition (O'Keefe and Nadel 1978) and anxiety (Gray 1982) might be related to each other, despite their common substrate. One reasonable theoretical starting point is that the processing of one should not, of necessity, interfere with the processing of the other. In recent work, we have explored the potential independence of theta mechanisms relating to spatial cognition and anxiety (Wells et al. 2013).

In Sects. 12.1.2, 12.2.4, and 12.3.3 above, we suggested that theta frequency overall might result from the additive contribution of two components, one corresponding to the slope of the theta frequency to running speed relationship and one corresponding to the variable offset of this relationship, defined by its intercept on the speed axis at 0 cm/s (Burgess 2008). Importantly, in this model, the spatial translation and arousal/anxiety-related contributions to frequency are independent. The scale of spatial coding is determined by the rate of change of frequency with running speed, while the absolute value of the baseline frequency itself (the intercept) is irrelevant to spatial coding.

The idea that spatial scale increases in environmental novelty (Barry et al. 2012) was a prediction of the oscillatory interference models (Burgess et al. 2007; Burgess 2008), given that theta frequency is reduced in environmental novelty

(Jeewajee et al. 2008b). More specifically, the Burgess (2008) model predicts that the increase in spatial scale in novelty results from a decrease in the slope of the theta frequency to running speed relationship. Thus we made specific predictions regarding the 'spatial cognition' functional association of hippocampal theta: environmental novelty would reduce the *slope* of the theta frequency to running speed relationship, without any obligatory effect on intercept, and this would increase spatial scale, with the level of slope change predicting the level of scale change (e.g. place field size).

We also made a corresponding prediction regarding the 'anxiety' functional association of hippocampal theta. It has long been noted that all clinically effective anxiolytic drugs (i.e. those effective for generalised anxiety disorder) reduce the average frequency of hippocampal theta elicited by stimulation of the reticular formation under anaesthesia ('reticular-elicited theta'). This frequency-reduction effect of reticular-elicited theta is seen across a wide range of *anxiolytic* drugs, despite their substantial neurochemical dissimilarities (Gray and McNaughton 2000; McNaughton et al. 2007; Engin et al. 2008; Siok et al. 2009; Yeung et al. 2012), but is not seen with *antipsychotic* drugs (Gray and McNaughton 2000). In addition, 'immobility-related' type II theta occurs during predator-elicited arousal/anxiety (Sainsbury et al. 1987) and during 'anticipatory anxiety' (Gray and McNaughton 2000) following standard-footshock conditioning (Seidenbecher et al. 2003). Accordingly, since (a) arousal/anxiety is explicitly linked to type II theta, (b) anxiolytics reduce reticular-elicited theta frequency, and (c) the Burgess (2008) model links type II theta mechanisms to intercept, we used the model to predict that anxiolytics should reduce the *intercept* of the theta frequency to running speed relationship, without any obligatory effect on slope.

In summary, we predicted a double dissociation whereby anxiolytics would specifically reduce intercept, and environmental novelty would specifically reduce slope. This is what we observed (Wells et al. 2013). Figure 12.4a,b,c shows the effect of systemic injection of two well-established clinically effective anxiolytic drugs (4a, CDP, a benzodiazepine agonist; 4b, buspirone, a 5HT-1A agonist) and one putative anxiolytic (4c, O-2545, a CB1 agonist). All the anxiolytic drugs elicit a reduction in the intercept (without affecting slope). Figure 12.4d-f shows the effect of introducing the rat into novel environments (in the same geocentric location as a familiar baseline environment). In line with a central prediction of the oscillatory interference model (Burgess 2008), in all cases, the novelty elicits a reduction in the slope (without significantly affecting intercept). Place fields of CA1 place cells expanded in the novel environments, and a significant correlation was observed between the change in slope across the baseline and novel environments and the change in the spatial scale (i.e. average field size) of the place cells. This result is also predicted by the (Burgess 2008) model.

We also observed a dissociation between slope and intercept that was not predicted by the model. A few studies, perhaps too few, have investigated the positive relationship between temperature and theta frequency (e.g. Whishaw and Vanderwolf 1971). Our data show that, in the locomoting rat at least, temperature is positively correlated with the slope, but not the intercept, of the frequency-speed

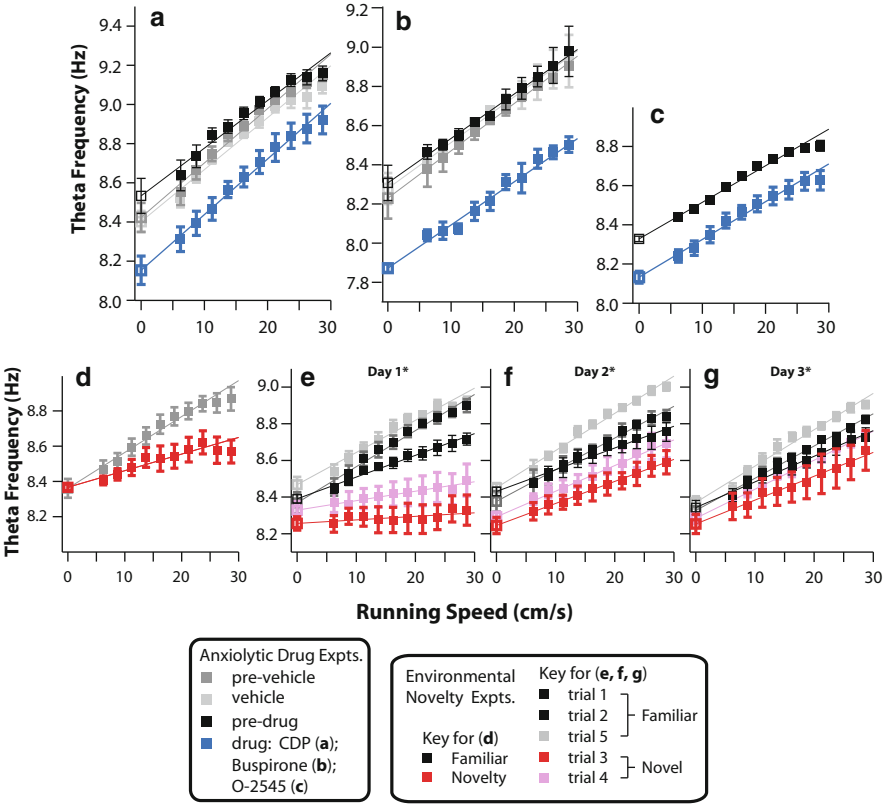

Fig. 12.4 Anxiolytic drugs reduce the intercept of the theta frequency to running speed relationship, while environmental novelty reduces its slope. Three neurochemically different anxiolytic drugs (all i.p. injections: (**a**) CDP, benzodiazepine agonist, 5 mg/kg; (**b**) buspirone, 5HT-1A agonist, 1 mg/kg; (**c**) O-2545, putative anxiolytic, CB1 agonist, 100 μg/ml, 0.5 ml/kg) have the common effect of reducing the 0 cm/s intercept of the theta frequency to running speed relationship. In contrast, exploration of a novel environment reduces the slope of this relationship (**d** and **e**), which then recovers as the novel environment itself becomes familiar (**e, f, g**). Parts **c** and **d** present data from the same rats (i.e. a within-subject's double dissociation of intercept and slope effects is observed). *Open squares* indicate *y*-intercept of regression lines. All recording sites CA1 except **e**, **f**, **g** = various hippocampal sites (dentate, CA1, subiculum). Adapted from Wells et al. (2013)

relationship. The dissociation may also prove useful in understanding mechanisms driving type I theta frequency. This finding also has implications for the study of theta phase precession and spatial cognition. For example, if slope is flatter on the first trials of the day, when the rat's brain is colder, phase precession may be weaker, given some noise, than when the brain is hot and slope is steeper.

Taken together, this set of findings provides good support for the additive two-component model of hippocampal theta in Burgess (2008). More generally,

the findings may lay the groundwork for a quantitative approach to hippocampal theta that unifies parallel streams of research on hippocampal cognitive and emotional processing.

12.3.5 Interregional Coherence and Communication

The idea that oscillatory synchronisation has behavioural relevance came from observations of visual cortex gamma phase synchronisation (Gray and Singer 1989; Gray et al. 1989; for review see Singer and Gray 1995) and work showing that this type of synchrony predicts performance on cognitive tasks (Womelsdorf et al. 2006). Related theoretical approaches have highlighted the importance of 'communication through coherence' and task-relevant communication between different regions through phase-locking within the same frequency (Malsburg 1995; Fries 2005, 2009). Concepts from 'communication through coherence' have been applied to the rodent hippocampus and to the investigation of how interactions between task-relevant regions might guide memory (Wang et al. 1990; Buzsaki 2006; Battaglia et al. 2011). In parallel, recent research investigating how local computations in neocortex could be facilitated by gamma oscillations, and potentially modulated by the phase of lower-frequency oscillations such as theta, has highlighted how synchrony or cross-frequency coupling might underlie interregional interactions (Schroeder and Lakatos 2009a, b; Buzsaki 2006).

Theta-gamma coupling is often hypothesised to function in a sort of master–slave relationship, implying that theta might function as an instrument of sensory selection (Lakatos et al. 2008; Buzsaki 2006). This has caused theta-gamma coupling to be the focus of several studies recording from the rodent hippocampus during spatial navigation. Informed by theoretical work hypothesising that the hippocampus serves as a comparator (Vinogradova 2001), Colgin et al. (2009) found that different gamma frequencies in the medial entorhinal cortex (~65–120 Hz) and CA3 (~25–50 Hz) couple with the ongoing theta rhythm in CA1 in awake behaving rodents (findings detailed in Sect. 12.1.4). Notably, these different gamma sources are usually phase-locked to different phases of the ongoing CA1 theta rhythm and tend to occur in different cycles. Previous studies had found a lower-frequency (25–50 Hz) gamma rhythm in CA3 than in medial entorhinal cortex (Bragin et al. 1995) and that (40–100 Hz) gamma phase coupling between CA3 and CA1 was higher during awake behaviour than REM sleep (Montgomery et al. 2008). Additionally, Montgomery et al. (2008) found that both theta and gamma phase coupling increased between CA3 and dentate during REM sleep. Furthermore, recent work has found that increased CA3–CA1 gamma synchrony predicted increased precision of place cell replay in the awake rodent (Carr et al. 2012). The capability of the CA1 theta rhythm to couple with different frequency oscillations is further supported by work from Belluscio et al. (2012) who found that CA1 theta phase coupled with the amplitude of slow (30–50 Hz), mid- (50–90 Hz), and fast

gamma (90–150 Hz) frequencies both during maze exploration and REM sleep. Cross-frequency coupling between the hippocampal formation and other regions has also been found. Tort et al. (2008) found striatal (~110–150 Hz) gamma amplitude was modulated by the ongoing hippocampal theta phase around the onset of T-maze trials. Furthermore, Sirota et al. (2008) found that neocortical gamma rhythms with different neocortical sources and different frequencies occurred at different phases of the ongoing hippocampal theta rhythm in the freely behaving rodent.

Another form of interregional oscillatory coupling comes from investigation of low-frequency (0.01–0.1 Hz) endogenous fluctuations in the blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal in humans. One of the primary endogenous brain networks, commonly referred to as the 'default mode network', centres on the hippocampus, parietal midline, and mPFC (Raichle et al. 2001; Buckner et al. 2008) and shows anatomical overlap with fMRI activity patterns observed during spatial and autobiographical memory tasks (Hassabis and Maguire 2007; Buckner and Carroll 2007). In parallel research with MEG, a study by Hipp et al. (2012) observed ongoing (5–7 Hz) theta synchronicity between the human MTL and other default mode network regions. Related to both electrophysiological and fMRI signals, Logothetis et al. (2012) used hippocampal electrode recordings simultaneously with fMRI to measure hippocampal ripple events in both awake and sleeping primates. The authors found that ripple events were phase-locked to the hippocampal delta rhythm and inhibited endogenous BOLD activity in neocortical areas, but increased activity in subcortical brain regions.

There is now an emerging literature investigating inter-areal coupling in humans using ECoG recordings (Watrous et al. 2013) and non-invasive MEG source connectivity techniques to explore phase interactions that could underlie mnemonic function. Interregional and cross-frequency coupling does not appear to be behaviourally specific and has been observed during spatial memory, evaluative, and anxiety-related behaviours in health and disease, so we will summarise the current literature based on specific field and animal model below.

12.3.5.1 Interregional Coherence and Communication: Integrating Spatial Knowledge and Decision-Making

Interregion coherence may be a general mechanism for task-led interregional communication (see Sect. 12.2.5). Here we summarise evidence for this hypothesis within spatial, mnemonic, and anxiety-related behaviour. [For related discussion of spatial tasks, see Shapiro et al. (2014); for related discussion of anxiety-related tasks, see Blair and Fanselow (2014).] We first describe work on interregional communication in the rodent, where there is more data at the level of ensembles of single neurons, and then turn to humans.

Jones and Wilson (2005) recorded from CA1 and medial prefrontal regions during a spatial working memory task. The task was designed such that they could investigate runs when a choice of direction was required, compared to when there was no choice. As expected, coherence between the local field potentials

in the theta range was significantly higher during choice-related behaviour. The phase-locking of medial prefrontal neuronal firing to CA1 theta, and the cross-correlation of CA1-prefrontal neuron spike trains, was also greater during choice-related behaviour. Other work has shown that mPFC firing rate changes during exploratory behaviour are entrained to hippocampal theta, and that mPFC cells can dynamically alternate between being entrained to the hippocampal theta rhythm and nonphasic firing (Hyman et al. 2005; Siapas et al. 2005).

Sigurdsson et al. (2010) used a similar paradigm to Jones and Wilson to investigate hippocampal-prefrontal coupling in a mouse model of schizophrenia. They contrasted the choice runs versus the sample runs in a discrete-trial, T-maze, working memory task. In wild-type mice, replicating the findings of Jones and Wilson (2005) in rats, they showed that both theta-band coherence of the two regions' LFPs and phase-locking of medial prefrontal neuronal firing to CA1 theta, was higher during choice runs. In the schizophrenia-model mice, however, this theta-band coupling was impaired.

In summary, both studies showed theta-band coherence at the cellular and LFP level between the hippocampus and the prefrontal cortex during choice-related behaviour in a spatial working memory task. The interpretation of these results is that increased theta coherence mediates the communication required to integrate spatial memory with decision-making.

In related findings, Benchenane et al. (2010) measured hippocampal and mPFC theta oscillations in rodents performing a Y-maze decision-making task, where rats learned two reward contingency rules (e.g. to receive a reward, the rat must go to the arm on the right and then go to the arm that lights up). The authors found that after learning a reward contingency and coming upon a choice point in subsequent trials, mPFC-hippocampus coherence increased. Furthermore, the authors also observed increased replay during sleep of mPFC cell firing that previously occurred during time periods with strong hippocampal-mPFC theta synchronisation (Benchenane et al. 2010). Recently, an MEG human decision-making study, without a specific spatial component, found similar theta-band phase-locking between these two structures (Guitart-Masip et al. 2013), suggesting a role for human hippocampal-mPFC theta phase-locking in decision-making and planning.

12.3.5.2 Interregional Coherence and Communication: Anxiety Behaviour

The hippocampus clearly plays a well-established role in spatial and other forms of memory. But it has also long been implicated in anxiety (Gray 1982; Gray and McNaughton 2000; Engin and Treit 2007; Oler et al. 2010), including unconditioned anxiety (Kjelstrup et al. 2002; Bannerman et al. 2004; Pentkowski et al. 2006). Thus, one might expect that the increased communication through coherence shown between the hippocampus and prefrontal cortex during spatial memory-guided choice behaviour (Jones and Wilson 2005; Sigurdsson et al. 2010) will also apply in anxiety behaviour.

The characterisation and delineation of anxiety and fear and the contribution of the hippocampus to these emotions are debated. For instance, the contribution of the

hippocampus to anxiety/fear could be attributed to its support of context-dependent memory. This is a reasonable interpretation of the report by Seidenbecher et al. (2003) which showed increased theta coherence between the dorsal hippocampus and the lateral amygdala during the retrieval of conditioned fear (what Gray and McNaughton (2000) would call 'anticipatory anxiety').

However, Adhikari et al. (2010) recorded theta from the hippocampus and medial prefrontal cortex while mice were exposed to two anxiety-provoking environments thought to model *unconditioned* anxiety (a bright open field and an elevated plus maze). Though subsequent learning occurs, initial anxiety in the anxiety-provoking environments is usually thought to reflect unconditioned anxiety. Thus the finding of increased CA1/medial prefrontal cortex theta coherence in these tasks is less obviously attributable to the hippocampal role in memory. In keeping with this, and supporting the linking of dorsal hippocampus to space and memory and ventral hippocampus to anxiety (Bannerman et al. 2004; Fanselow and Dong 2010), it was found that the region of CA1 that increased coherence with mPFC was the ventral hippocampus (Adhikari et al. 2010).

Even in the control environment, theta coherence between ventral CA1 and medial prefrontal cortex was much higher than between dorsal CA1 and medial prefrontal cortex. Exposure to the anxiety-provoking environments further increased ventral CA1/medial prefrontal cortex theta power correlations and increased the phase-locking of medial prefrontal cortex multiunit activity to ventral CA1. Anxiety-induced increased theta coherence likely reflected hippocampal-to-mPFC influence, rather than the reverse: (a) ventral CA1/medial prefrontal cortex theta power correlation was maximal when the medial prefrontal cortex EEG signal was shifted backwards by 8 ms; (b) theta frequency increased in anxiety in medial prefrontal cortex, approaching the frequency seen in ventral CA1; (c) phase-locking of mPFC multiunit activity to ventral CA1 theta was maximal when mPFC spikes were shifted backwards by 32 ms. These results are in line with anatomical tracing data showing that direct CA1-mPFC projections come from the ventral, not dorsal, CA1, while prefrontal influence on CA1 is multisynaptic. [Importantly, future work needs to resolve the apparent contradiction between the description of theta as a travelling wave (Lubenov and Siapas 2009; Patel et al. 2012) and the finding of reduced frequency in the ventral, relative to the dorsal, hippocampus (Adhikari et al. 2010)].

In summary, the studies of theta-band coherence between the hippocampus and its efferent regions such as the prefrontal cortex suggest that the increased coherence-communication mechanism may apply to both spatial memory-guided and anxiety behaviours and to both the dorsal and the ventral hippocampus.

12.3.5.3 Interregional Coherence and Communication: Human Memory

Results showing that gamma band synchronisation during encoding precedes successful memory formation, in both non-human primates (Jutras and Buffalo 2010) and humans (Fell et al. 2001), raise the possibility that interregional coherence might underlie memory formation. Fell et al. (2001) measured ~40 Hz oscillatory activity

from the LFP of intracranial electrodes in the hippocampus and rhinal cortex (entorhinal and perirhinal cortices), finding that oscillatory synchronisation preceded successful declarative memory formation. This study indicates that gamma oscillations help interregional coordination during memory encoding. Another study, in non-human primates, found that hippocampal gamma synchronisation during encoding predicted subsequent memory performance in a visual recognition memory task (Jutras and Buffalo 2009). Other work by Fell and colleagues showed that 1–19 Hz rhinal-hippocampal intrafrequency phase-locking also occurred during continuous word recognition, and phase-locking at encoding predicted subsequent memory formation (Fell et al. 2003, 2008). Theta phase-locking between hippocampus, amygdala, and neocortex has also been observed with auditory memory in intracranial patients (Babiloni et al. 2009), but so far task-relevant interactions between 4 and 8 Hz human hippocampal theta oscillations and the neocortex have been missing. Recordings from the surface of prefrontal and parahippocampal cortices in humans suggest that low-frequency (1–10 Hz) phase-locking between the MTL and the PFC is predictive of successful memory recall (Watrous et al. 2013). Two Hz phase-locking between PFC and MTL predicted recall of spatial locations, while 8 Hz phase-locking between PFC and MTL predicted successful recall of serial order. Notably, other ECoG studies with similar frontotemporal electrode placements have found that synchronisation in theta and surrounding frequency bands was higher for recall than baseline (Anderson et al. 2010). In sum, there is growing evidence that interregional synchronisation is important for successful memory formation and retrieval, but there is a dearth of evidence implicating specific tasks or frequency bands.

12.3.6 Cross-Frequency Coupling

A potential mechanism for organising distributed representations, particularly relevant in mnemonic function, is cross-frequency coupling. In the context of memory tasks, cross-frequency coupling usually entails the phase of a low-frequency oscillation, like the hippocampal theta rhythm, showing phase consistency with the amplitude of a higher-frequency oscillation, like gamma (see Sects. 12.2.1, 12.2.2, 12.3.1 for the theoretical implications of cross-frequency coupling). This phase-amplitude coupling could work in the service of memory formation and retrieval by providing a mechanism to organise learned sequences (Jensen and Colgin 2007). Researchers have examined cross-frequency coupling during working memory maintenance in humans to support this hypothesis. In a MEG study, Fuentemilla et al. (2010) applied pattern classifiers to theta and gamma activity elicited during encoding for individual stimuli and subsequently decoded their replay during working memory maintenance. Replay of different stimuli categories (e.g. whether participants were maintaining a picture of an indoor or an outdoor scene) was decoded during maintenance, and the reactivation of maintained items was usually locked to a particular phase of theta, and the consistency of decoded items with theta phase correlated with memory performance.

Follow-up analyses determined that the timing of item reactivations during working memory maintenance was locked to the ongoing theta phase in the hippocampus and dorsolateral prefrontal cortex (dlPFC) (Poch et al. 2011). Further evidence of the importance of cross-frequency coupling during working memory maintenance comes from a paper by Axmacher and colleagues, who observed theta-gamma coupling during working memory maintenance in patients with hippocampal depth electrodes (2010b). The authors also demonstrated that the consistency of hippocampal theta-gamma coupling predicted memory performance, extending the behavioural relevance of cross-frequency coupling further (Axmacher et al. 2010b).

12.4 Summary and Conclusions

In this section, we offer an integrative view of the whole chapter, not necessarily in the order of presentation and without the detailed referencing given above.

12.4.1 Hippocampal EEG States and Their Correlates

Two mutually exclusive states dominate the hippocampal local field potential in awake rodents: LIA and theta. LIA is observed when the animal is idling, theta (around 4–12 Hz) whenever the animal is moving, but also sometimes during immobility such as in the presence of predators. The characteristic frequency band of theta may be somewhat lower in humans than in rodents, but it has not been definitively established if this reflects genuine species differences. Ripple oscillations (140–200 Hz) occur during LIA which may represent memory consolidation and 'what if' cognition mechanisms.

While gamma (30–150 Hz) can be present during LIA, gamma appears to be strongly controlled by theta. The presence and phase of theta modulates the amplitude of gamma, and the frequencies of theta and gamma are often positively correlated. A prominent model of sequence memory proposes that item sequences correspond to a sequence of gamma cycles within one theta cycle, with each item corresponding to one gamma cycle's activity, at a particular phase of theta. The model began as a model of working memory but has been adapted to model theta phase precession of place cell firing. The number of items that can be remembered in order will be constant across varying theta cycle durations so long as theta and gamma frequency are correlated. In summary, in this scenario oscillatory phase (theta) and gamma nesting within theta implement ordinal coding.

12.4.2 Encoding Versus Retrieval Scheduling in CA1: Theta Phase and Theta-Gamma Coupling

Coupling of specific gamma bands to different theta phases could reflect switching between different input channels. Thus, in CA1, entorhinal-CA1 communication

may be preferentially mediated by middle gamma (50–90 Hz) timed to the peak of CA1 pyramidal-layer theta, while CA3–CA1 communication may be preferentially mediated by slow gamma (30–50 Hz) timed to the descending phase of CA1 pyramidal-layer theta. Such theta phase-based theta-gamma coupling appears consistent with theoretical suggestions (old and new) that theta schedules encoding versus retrieval states. The theta-based encoding versus retrieval scheduling models are also consistent with empirical evidence relating theta phase to the strength and direction (potentiation, depression) of long-term synaptic plasticity. In CA1, entorhinal-driven encoding may preferentially occur near the peak of CA1 pyramidal-layer theta, while CA3-driven retrieval may preferentially occur nearer the trough, with each memory state associated with different levels of inhibition and different synaptic plasticity regimes. We reviewed two recent place cell studies which provide good evidence for theta phase correlating with the propensity for encoding versus retrieval. In the study of CA3 place cells, apparent attractor-based retrieval was dominant in one half of the theta cycle. (This was the second half of the cycle, whose start was defined as the phase of lowest CA3 spiking.) In the study of CA1 place cells, an encoding-enhancing manipulation (novelty) elicited a later phase of preferred spiking closer to the pyramidal-layer theta peak, while a retrieval-enhancing manipulation (scopolamine in a familiar environment) elicited an earlier phase of preferred spiking close to the pyramidal-layer theta trough. These results closely match the predictions of encoding versus retrieval scheduling models based on theta phase.

12.4.3 Theta and Memory Performance

While some of the relationships between oscillations and memory are harder to observe in human memory studies, the research summarised in the two paragraphs above strongly suggests a role for theta in the efficiency of memory operations. Consistent with this, an emerging literature of MEG and iEEG studies is increasingly demonstrating correlations between theta power in the hippocampus/medial temporal lobe and memory performance in humans. For instance, a MEG study showed that hippocampal theta power when setting out on a route correlates with performance in navigating a virtual reality water maze. Another study found that increases in movement-initiation-related theta power during exploration/encoding of object locations within a virtual environment correlate with subsequent memory for those object locations.

Furthermore, invasive electrophysiological recording studies in humans have implicated the importance of single unit phase-locking to the hippocampal theta rhythm; the precision of phase-locking of amygdala and hippocampal neurons to the LFP theta rhythm during memory encoding predicted whether an encoded item would be successfully remembered. This suggests that hippocampal theta phase concentration, as well as power, could serve as a diagnostic of system state. Intriguingly, preliminary evidence indicates that directly stimulating the entorhinal cortex resets hippocampal theta phase and improves performance on a spatial

memory task. Thus, the improved performance could derive from the way in which theta phase determines synaptic plasticity and is consistent with theta-based encoding versus retrieval scheduling models.

12.4.4 Spatial Memory and Anxiety: Communication Through Coherence

What is the function of the hippocampus? Two broad sets of functions have been proposed: (1) spatial and episodic memory, linked to novelty detection, and (2) anxiety, linked to stress and depression. Research on both humans and rodents across a variety of behaviours provides good support for the 'communication through coherence' hypothesis whereby two regions show a transient increase in coherence when a particular task requires communication between those two regions. This phenomenon is observed in tasks tapping both of the two broad functions ascribed to the hippocampus: spatial coding and anxiety. In these tasks, the hippocampus communicates with a hippocampus-efferent region such as the medial prefrontal cortex or the amygdala, and theta coherence between the two regions increases. For instance, increased hippocampus-prefrontal theta coherence is observed in tasks which require decision-making based on spatial memory and in tasks including environment-elicited anxiogenesis. This between-region coherence is seen between both the local field potentials and between the firing of cells in the efferent region (medial prefrontal cortex or the amygdala) and the hippocampal LFP theta.

12.4.5 Spatial Memory and Anxiety: Two Components of Theta

Grid cells, and indeed place cells, may subserve path integration. One set of models of grid cells is based on the oscillatory interference of multiple inputs with somewhat different theta-band frequencies. Computational modelling and unit recording studies suggest that at least some theta cells (i.e. theta-modulated interneurons) may play a key role in path integration by encoding the component of movement velocity along different preferred directions. Each such VCO cell will have a different preferred direction. This encoding is not by rate but by frequency (i.e. inter-burst frequency in the theta band) and the resultant patterns of synchrony between cells. Thus oscillatory modulation of firing may have a very specific role in encoding information, beyond the more general functions usually ascribed to oscillatory firing.

We tested a model which suggested that theta frequency overall might result from the additive contribution of two components, one corresponding to the slope of the theta frequency to running speed relationship and one corresponding to the intercept of this relationship on the speed axis at 0 cm/s. The first component (the slope) is posited to reflect type I theta mechanisms, relating to spatial translation, and the second (the intercept) is posited to reflect type II theta mechanisms, relating to arousal/anxiety. In agreement with predictions derived from the model, we

showed that (1) environmental novelty reduces the frequency-speed slope in CA1 LFP theta and increases spatial scale in CA1 place cells and that there is a correlation between these variables and (2) anxiolytic drugs reduce the intercept of the frequency-speed slope in CA1 LFP theta. In summary, we show two contributions to theta frequency within a unifying, quantitative framework potentially linking the two rather different functions ascribed to the hippocampus.

12.4.6 Conclusions

A range of specific computational functions have been proposed to be supported by oscillatory processes and by the interactions between oscillations, such as integration, representations of order, providing quantised processing cycles, and facilitating communication between regions. Many of the most robust phenomena and most well-instantiated computational models concern the oscillations found in and around the hippocampal formation and their relationship to spatial and mnemonic processing. Here we have attempted to review some of the experimental and theoretical work in this rapidly growing field, in the hopes that it provides an instructive model system for wider application to neural processing in the brain and in support of other aspects of cognition.

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Memory Replay in the Hippocampus

13

Shantanu P. Jadhav and Loren M. Frank

Abstract

The hippocampus is required for the encoding, consolidation, and retrieval of episodic memories, but the neural mechanisms underlying these processes are still not well understood. Apart from place field activity, hippocampal neurons exhibit replay of past experience during sharp-wave ripples (SWRs), which involve sequential reactivation of hippocampal place cells representing previously experienced behavioral trajectories on a fast timescale. Replay during SWRs occurs both during slow-wave sleep and in the awake state, especially during periods of relative immobility. Repetition of stored memory patterns on a compressed timescale during replay is ideally suited to promote memory consolidation in distributed hippocampal–neocortical circuits. Further, since memory replay during SWRs has the capacity to recreate patterns of activity associated with past experience in hippocampal–neocortical circuits, it is also well suited to support memory retrieval. Thus, a common physiological mechanism, memory replay during SWRs, may underlie the consolidation and retrieval functions of the hippocampus.

13.1 Introduction

A key feature of memory is the ability to store and recapitulate our experiences in a flexible manner. We can store memories for long-term use, bind together and integrate spatially and temporally remote experiences, instantly recall long-lasting experiences, and use our memories to mentally infer novel and abstract episodes that have not been directly experienced. These psychological phenomena indicate the presence of a neural mechanism that supports a flexible memory representation,

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which allows accessing and replaying representations of our memories on a fast timescale.

The hippocampus and associated areas of the medial temporal lobe form the central component of a declarative memory system that allows us to store memories of daily experiences and retrieve those memories as needed to guide our day-to-day behavior (Squire and Zola-Morgan 1991; Scoville and Milner 1957; Squire 1982; Cohen and Eichenbaum 1993; Rudy and Sutherland 1995). Declarative memories are explicit memories that are consciously accessible, including episodic memories (memory of specific events) and semantic memories (memory for general knowledge) (Squire and Zola 1996; Tulving 1987; Eichenbaum and Cohen 2001). The role of the hippocampus in episodic memories is established (Tulving and Markowitsch 1998; Squire and Zola-Morgan 1991; Eichenbaum and Cohen 2001), although the physiological mechanisms underlying its role in memory processes are not yet well understood. Much of the description of hippocampal physiological patterns underlying learning and memory comes from rodent studies, and in particular the observation of place cells, where individual cells in the hippocampus encode restricted regions of an environment and ensembles of place cells provide a unique spatial representation of a given environment (O'Keefe and Nadel 1978; Best et al. 2001; Muller and Kubie 1987; Leutgeb et al. 2007; Karlsson and Frank 2008; Wilson and McNaughton 1993). While place cells have been proposed to underlie spatial navigation and the encoding of spatial contextual memories (O'Keefe and Dostrovsky 1971; O'Keefe and Nadel 1978), it is not clear how different memory processes and some of the key features of episodic memories outlined above can be explained using place cells. Here we argue that the replay of sequences of place cells seen during sharp-wave ripple (SWR) oscillations in the hippocampus (Pavlides and Winson 1989; Wilson and McNaughton 1994; Lee and Wilson 2002; Foster and Wilson 2006; Diba and Buzsaki 2007; Karlsson and Frank 2009; Johnson and Redish 2007) is a neural mechanism that underlies some of the key psychological features of memory, and in particular memory consolidation and retrieval processes.

Memory consolidation is a time-dependent memory stabilization process in which memories make the transition from a labile, unstable shorter-term memory to a stable, long-term memory. Such a time-dependent, slow stabilization process is a prominent model for multiple types of memory formation (Glickman 1961; McGaugh 1966). For declarative memories, the hippocampus is thought to interact with the rest of the brain during this consolidation process to engrain stable, long-lasting representations in hippocampal–neocortical circuits (Squire and Zola-Morgan 1991; Kim and Fanselow 1992; Buzsaki 1996; Dudai 2004). While there is still debate about how long this consolidation process lasts and whether memories ever become truly independent of the hippocampus (Jarrard 2001; Nadel and Moscovitch 2001; Zola-Morgan and Squire 1990; Haist et al. 2001), it is clear that the hippocampus plays an essential role in the initial encoding and subsequent stabilization of long-term memories. The consolidation process is thought to require that the hippocampus repeatedly reactivate previously encoded associations in the absence of experience, thereby engraining those associations into the

less-plastic neocortex (Eichenbaum and Cohen 2001; Alvarez et al. 1994; Diekelmann and Born 2010; McClelland et al. 1995).

After initial learning, we are able to retrieve stored associations about past experiences to guide ongoing behavior. Inactivation of the hippocampus in both humans and rodents leads to severe deficits in the retrieval of recently stored associations, suggesting that the hippocampus plays a fundamental role in memory retrieval for at least a period of time after the experience (Kim and Fanselow 1992; Squire et al. 2001; Fortin et al. 2004; Riedel et al. 1999). For recently stored memories, current theories suggest that the hippocampus acts to reactivate distributed neocortical patterns associated with the memory (Eichenbaum and Cohen 2001; Eldridge et al. 2000). Thus, just as for memory formation, hippocampal output during memory retrieval should have the capacity to recreate patterns of activity associated with past experience in other brain regions (de Hoz and Wood 2006).

As we have argued previously (Carr et al. 2011), physiological mechanisms underlying a consolidation process would need to have several properties. First, putative patterns of hippocampal activity supporting consolidation should repeatedly reactivate mnemonic representations in the absence of behavioral repetition. Further, as consolidation refers to the progressive stabilization of a memory trace over time, processes that support consolidation would need to persist for some time period following the experience. Finally, consolidation processes would need to promote plasticity in broadly distributed neocortical circuits, allowing memories that initially depend on the hippocampus to become encoded in more distributed networks.

We can make a parallel argument about the patterns of hippocampal activity that are likely to support retrieval (Carr et al. 2011). First, retrieval events must necessarily occur after the experience they represent and recapitulate the internal representation of an experience in the absence of behavioral repetition. This could support the "mental time travel" associated with episodic memory recall (Tulving and Markowitsch 1998). Furthermore, for a recalled trace to influence memory-guided decisions, retrieval would need to occur during the awake state at times when memory-guided decisions are made. Second, we can recollect a memory on a faster timescale than the behavioral experience, suggesting that retrieval of stored representations can be compressed in time. Third, current sensory input should be able to influence which stored representations are retrieved, as in the case of cued memory recall. Finally, in order to retrieve a memory that was stored in distributed hippocampal–neocortical circuits, a retrieved hippocampal trace would need to either initiate or be part of a broader neocortical retrieval event that could be used to make memory-guided decisions (Eldridge et al. 2000; Eichenbaum and Cohen 2001; de Hoz and Wood 2006).

The replay of stored hippocampal representations during sharp-wave ripples (SWRs), seen during sleep and in the awake state, is a physiological pattern of activity that exhibits all of these properties. This has led us to propose that hippocampal memory replay during SWRs could be a common neural mechanism for both consolidation and retrieval (Carr et al. 2011). Further, the process of replay

lends itself quite well to the psychological phenomenon where spatially and temporally disparate episodes can be recalled and linked together. A key feature of our memories is their dynamic nature, and it is thought that even consolidated memories are rendered labile during the process of retrieval, which could theoretically support the integration of new experiences in previously stored memories (Nader and Hardt 2009; McKenzie and Eichenbaum 2011; Sara 2000), and these retrieved memories therefore have to undergo a process of reconsolidation to be stabilized again. This phenomenon of "reconsolidation" also suggests an intimate link between the consolidation and retrieval process and lends support to the hypothesis that memory replay processes in the hippocampus could support both processes. We discuss below SWR replay processes in the hippocampus, the evidence supporting a relation between sleep replay and consolidation, and recent results showing awake replay could support consolidation and retrieval processes.

13.2 Hippocampal Memory Replay in the CA3–CA1 Network

The replay of previously stored patterns of activity in the hippocampus occurs frequently during transient bursts of high-frequency activity seen during SWRs in the local field potential (LFP, or EEG) signal (Fig. 13.1) in the hippocampus (Buzsaki 1996). Sharp-wave ripples originate within the hippocampus and are generally triggered by synchronized activation of CA3 pyramidal excitatory cells, leading to characteristic negative potentials (called "sharp waves") in the CA1 stratum radiatum layer, where CA3 projections synapse onto CA1 pyramidal cells (Buzsaki 1986; Csicsvari et al. 2000). This synchronized activation of CA3 pyramidal cells can be measured as a 100–150 Hz oscillation in the LFP in area CA3 (Csicsvari et al. 1999). The population burst in the CA3 region recruits CA1 pyramidal cells as well as inhibitory interneurons (basket and chandelier cells), leading to a transient, high-frequency "ripple" oscillation (150–250 Hz) in the CA1 pyramidal cell layer (Ylinen et al. 1995). SWRs are prominent during sleep as well as in the awake state during immobility, slow-speed movement, consummatory behavior, and grooming (Buzsaki 1986) and also can occur during running (O'Neill et al. 2006; Cheng and Frank 2008). Activity during SWRs propagates from CA3 to CA1, one of the major output areas of the hippocampus, and also out to neocortical areas during sleep (Chrobak and Buzsaki 1996; Siapas and Wilson 1998; Wierzynski et al. 2009).

Based primarily on the extensive excitatory recurrent connections among CA3 pyramidal cells (Amaral et al. 1990), it has been postulated that CA3 acts as an auto-associative pattern completion network (Marr 1971; McNaughton and Morris 1987). The idea is that the activation of even a small subset of CA3 neurons initiates a cascade of excitation across previously modified synapses. When coupled with balanced inhibitory feedback, this pattern of activation would push the CA3 network into an attractor state corresponding to a previously stored memory. Reinstatement of stored representations in CA3 would then reinstate the corresponding representations in CA1 through feedforward excitation.

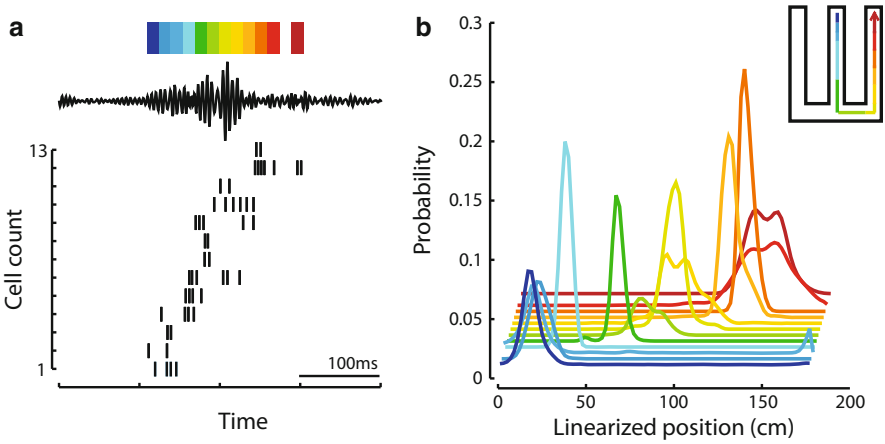

Fig. 13.1 Replay of stored patterns of activity in the hippocampus representing spatial sequences occurs during SWRs. (**a**) Sequential spiking of place cells during SWRs. The black LFP trace on *top* (filtered, 150–250 Hz) shows a SWR detected in CA1 during performance on a W-track maze. *Bottom*, spike rasters for all neurons with place fields on the W-track during the SWR. Thirteen cells recorded in both the CA3 and CA1 region of the hippocampus show sequential spiking on a compressed timescale during the SWR. *Color bar on top* shows the *colors* associated with each 15 ms decoding bin used for decoding replayed trajectory based on place cell spiking. (**b**) Probability distributions of decoded locations (using a Bayesian decoding method) for each 15 ms bin shown in (**a**). *Colors* correspond to the *color bar* shown at the *top* in (**a**). *Inset* shows a schematic of the replayed trajectory on the W-track based on the decoded trajectory. Reproduced from Carr et al. (2012)

Hippocampal memory replay during SWRs is thought to reflect this type of auto-associative pattern completion in CA3 followed by feedforward recruitment of pyramidal cells and interneurons in CA1.

Sequential pattern completion may underlie replay, which is marked by the ordered reactivation of ensembles of hippocampal neurons reflecting previous behavioral experiences. In rodents, place field activity across multiple neurons implies a unique firing pattern associated with each location and unique sequences of patterns that represent sequentially experienced places. Many studies have documented replay during SWRs where sets of hippocampal place cells that fired together during exploration are more likely to fire together afterwards during sleep or rest (Pavlides and Winson 1989; Wilson and McNaughton 1994; O'Neill et al. 2008). In pair-wise measures, replay is detected by comparing the coactivity of neurons during awake SWRs with the degree of co-firing during behavior (co-firing within 100 ms time bins (Jackson et al. 2006; O'Neill et al. 2008) or co-firing as measured by place field overlap (O'Neill et al. 2006; Cheng and Frank 2008; Singer and Frank 2009)), thus indicating how likely two cells will fire together during a SWR as a function of their coactivity during behavior. Entire sequences of place cells associated with specific trajectories have also been reported to be replayed at high speed during SWRs (Lee and Wilson 2002; Ji and

Wilson 2007; Nadasdy et al. 1999; Csicsvari et al. 2007; Foster and Wilson 2006; Diba and Buzsaki 2007; Karlsson and Frank 2009; Davidson et al. 2009). Thus, sequences that are experienced by the animal on the timescale of seconds are replayed at a compressed timescale of milliseconds during awake SWRs (Fig. 13.1).

Replay-like phenomena have also been reported in CA3 at times associated with low levels of power in the 150–250 Hz ripple band, but high levels of theta and gamma power (Johnson and Redish 2007). These "vicarious trial-and-error" (VTE) events occurred at the decision point in a multiple T-maze and suggested an internal exploration of future possibilities. These events transiently encode locations on paths ahead of the animal to either the left or the right of the animal's current location when the animal must make a choice between left or right trajectories. The relationship between these events and replay seen during SWRs remains unclear, but a recent observation of transient increases in CA3 and CA1 gamma power as well as CA3–CA1 gamma coherence during SWRs (Carr and Frank 2012) raises the possibility that VTE and SWR replay events share common mechanisms. For the purposes of this review, we include VTE events as part of the general class of replay events and explore their possible roles in memory processes.

13.3 Memory Replay in the Hippocampus During Sleep

13.3.1 Sleep and Learning

One of the primary roles of sleep has been suggested to be the establishment of memories (Marr 1971; Buzsaki 1989, 1996; Stickgold 2005; Walker and Stickgold 2004; Maquet 2001; Born et al. 2006; Diekelmann and Born 2010). The loss of behavioral control and consciousness is incompatible with the normal stimulus processing in the brain that occurs during waking, and sleep is thought to promote the consolidation of memory (Diekelmann and Born 2010; Walker and Stickgold 2004), although it may also function to renormalize synaptic strength (Tononi and Cirelli 2006). A number of studies have shown that sleep periods after learning lead to improved memory formation, supporting the notion that sleep promotes consolidation and reorganization of memories (Gais et al. 2006; Ellenbogen et al. 2006; Gais and Born 2004; Walker et al. 2003; Ambrosini et al. 1993). Correlations between sleep and memory have been demonstrated for both declarative and procedural memories (Diekelmann and Born 2010; Walker and Stickgold 2004), and it has been proposed that sleep-dependent consolidation is particularly important for explicit memories (Diekelmann and Born 2010). Both REM and SWS stages of sleep are thought to support memory processes, but the exact role that these stages play in consolidation and the neural processes that support these functions is still a matter of debate (Diekelmann and Born 2010; Walker and Stickgold 2004). However, it is widely accepted that this involves replay of stored patterns of brain activity elicited during behavior and learning coupled with synaptic plasticity processes. The reactivation of memories in the context of a

hippocampal–neocortical dialogue is thought to occur primarily during non-REM or slow-wave sleep (SWS). This is particularly true for declarative memories, where it is hypothesized that hippocampal reactivation stimulates the redistribution of memory representations to neocortical networks (Marshall and Born 2007; Walker and Stickgold 2004; Diekelmann and Born 2010).

13.3.2 Memory Replay During Sleep

In humans, reactivation of brain activity related to a previous experience has also been observed in the hippocampus during sleep (Peigneux et al. 2004). In rodents, hippocampal memory replay during sleep has been primarily observed as fast timescale reactivation during sharp-wave ripples in slow-wave sleep (SWS), although persistent, reverberation-like activity that recapitulates activity during behavior has also been described during SWS (Ribeiro et al. 2004), as well as REM (Louie and Wilson 2001). During SWS, hippocampal activity shows prominent SWRs, accompanying neocortical slow oscillations and thalamocortical spindles (Sirota et al. 2003; Peyrache et al. 2011; Siapas and Wilson 1998; Phillips et al. 2012). Since SWRs provide a high-frequency burst of activity on a short timescale which is conducive to promoting synaptic plasticity, it was suggested that memory replay could occur during SWRs, thereby strengthening stored representations associated with a memory (Buzsaki 1986). In support of this hypothesis, reactivation of cells and cell pairs following an experience was first reported during sleep (Pavlides and Winson 1989; Wilson and McNaughton 1994). These results and a series of subsequent studies (Skaggs and McNaughton 1996; O'Neill et al. 2008; Nadasdy et al. 1999) which demonstrated reactivation of pairs of neurons during SWRs in sleep lent support to the hypothesis that reactivation associated with the consolidation process occurs during sleep. High-speed replay of entire sequences of place cells that represent experienced trajectories has also been shown to occur during SWS (Lee and Wilson 2002; Ji and Wilson 2007; Nadasdy et al. 1999; Csicsvari et al. 2007).

Further, replay is most prevalent immediately following an experience and decays with time; however, replay persists at above chance levels even 18–24 h after an experience in rodents (Kudrimoti et al. 1999; Karlsson and Frank 2009), and possible even longer, which aligns with the timescale suggested for a putative systems consolidation process (Diekelmann and Born 2010). Thus, the presence of hippocampal memory replay during SWRs in sleep has provided strong support to a two-stage memory formation model, in which memories are initially rapidly encoded in the hippocampal circuit during experience and then subsequently replayed during sleep for strengthening the distributed hippocampal–neocortical patterns associated with the memory (Buzsaki 1996; McClelland et al. 1995; Sutherland and McNaughton 2000).

13.3.3 Linking Sleep Replay and Memory Consolidation

The replay hypothesis for consolidation requires that, during memory replay in the hippocampus during SWRs, activity in other brain regions should also show signs of reactivation aligned to hippocampal replay. As predicted by this hypothesis, it has been demonstrated that communication between the hippocampus and prefrontal cortex, one of the major sites of consolidation, occurs specifically during SWRs in SWS (Wierzynski et al. 2009) and there is very little coactivity in the two structures during REM sleep periods. Similarly, activity during SWRs propagates out from hippocampus to entorhinal cortex (Chrobak and Buzsaki 1994, 1996). Further, memory replay has also been demonstrated to occur in prefrontal cortex (Euston et al. 2007; Peyrache et al. 2009), visual cortex (Ji and Wilson 2007), and striatum (Lansink et al. 2008, 2009; Hoffman and McNaughton 2002), and cortical reactivation is present preferentially during hippocampal SWRs (Peyrache et al. 2009; Ji and Wilson 2007).

A recent study in primates also showed that, during the period of hippocampal SWRs, there is a global increase in activity in neocortical areas and a widespread decline in subcortical areas (Logothetis et al. 2012), supporting the notion that neocortex is "primed" to be receptive to hippocampal replay events during SWRs by shutting off subcortical inputs. It has been suggested that coordinated interactions of hippocampal SWRs and cortical rhythms during SWS should support a transfer of memory-related information between the brain regions. Indeed, hippocampal SWRs are correlated with delta waves (1–4 Hz) and spindles (8–12 Hz oscillations) in neocortex (Sirota et al. 2003; Peyrache et al. 2011; Siapas and Wilson 1998; Phillips et al. 2012). Further supporting this notion, it has been shown that slow-wave oscillations play a leading role organizing hippocampal-to-neocortical information transfer by providing temporal frames for organizing the other rhythms. The upstates of slow oscillations are associated with increase in thalamocortical spindles and hippocampal SWRs, thereby purportedly providing a period of depolarization during which hippocampal memory replay during SWRs can instruct activity in neocortex and mnemonic patterns can be engrained in cortical circuits (Diekelmann and Born 2010).

An alternative approach for investigating the function of replay is to attempt to enhance memory consolidation by manipulating which encoded memories are replayed in the hippocampus. Several recent studies in human subjects have paired sensory cues with a hippocampus-dependent memory task and have observed learning improvements when these sensory cues are presented during SWS between sessions (Rasch et al. 2007; Rudoy et al. 2009; Diekelmann et al. 2011). For example, presentation of odor cues during sleep that were associated with a learning process leads to better subsequent performance, pointing to an enhanced consolidation process triggered by the sensory cues in sleep (Rasch et al. 2007). In support of the hypothesis that this is due to enhanced hippocampal reactivation, it was shown that in rodents, presenting an auditory cue associated with learning during slow-wave sleep biased reactivation events towards replaying the previous

experience associated with the cue, although this study did not examine if this leads to improved performance (Bendor and Wilson 2012).

Thus, there is a large body of evidence that strongly suggests that memory replay during hippocampal SWRs contributes to a consolidation processes during sleep. Memory replay has the potential to meet all of the criteria for a mechanism that could support memory consolidation, since it is associated with a repeated reactivation of patterns associated with past experience on a timescale consistent with the induction of synaptic plasticity in the absence of behavioral repetition. Indeed, a number of links between replay and memory consolidation have been demonstrated. These include results showing that the intensity of SWRs following an experience is correlated with subsequent improvements in performance (Eschenko et al. 2006, 2008; Molle et al. 2009). Similarly, enhanced reactivation is associated with improved memory performance (Dupret et al. 2010). Conversely, genetically mediated suppression of CA3 output reduces correlated firing in CA1 and impairs consolidation (Nakashiba et al. 2009). Finally, other recent studies have provided evidence of a direct, causal link between SWR-related replay in sleep and memory processes. These studies used real-time disruption of SWRs during sleep to demonstrate that SWR disruption following each day of training impairs the acquisition of a spatial task, measured as performance on the following day (Girardeau et al. 2009; Ego-Stengel and Wilson 2010). Taken together, these results lend strong support to the notion that hippocampal memory replay during SWRs in sleep is part of a memory consolidation process that is required for forming stable, long-term memory representations.

13.4 Memory Replay in the Hippocampus During Awake Behavior

13.4.1 Hippocampal Reactivation During Awake SWRs

Although it was known that in addition to slow-wave sleep, hippocampal SWRs also occurred in the awake state, especially during consummatory behaviors and immobility (Buzsaki 1986), the initial focus on hippocampal memory replay was on sleep SWRs. Recent studies have demonstrated that this memory replay process is not exclusive to sleep, but also occurs during SWRs that occur during waking behavior, especially during brief periods of slow movement or immobility (Kudrimoti et al. 1999; Foster and Wilson 2006; Diba and Buzsaki 2007; Karlsson and Frank 2009; Davidson et al. 2009; Gupta et al. 2010; Jackson et al. 2006). In the first demonstration of SWR-associated replay of entire behavioral sequences during awake behavior (Foster and Wilson 2006), it was found that, when animals stopped and consumed reward following traversal of a linear track, sequences of place cells representing trajectories on the track were replayed during SWRs. These awake replay events originated at the animal's current position and often reactivated place cells in the reverse order as had been experienced behaviorally. Reverse replay was seen immediately after the very first traversal of the track, indicating that the

hippocampus can replay sequences that are experienced briefly. Other studies subsequently reported awake replay of sequences in either the same (forward replay) or the opposite (reverse replay) direction as observed during behavioral traversal (Diba and Buzsaki 2007; Karlsson and Frank 2009; Davidson et al. 2009; Gupta et al. 2010). The directions of replay has been reported to be related to the animal's behavior (Diba and Buzsaki 2007), such that reverse replay occurs preferentially at the end of runs when the animal reaches the reward location, potentially linking behavioral trajectories to their outcomes, and forward replay occurred preferentially at the beginning of runs, perhaps providing information relevant for evaluating future trajectories (Diba and Buzsaki 2007). Importantly, reverse replay is seen even when animal's experienced a trajectory only in the forward direction (Gupta et al. 2010), and activity consistent with forward and reverse replay has also been observed in an open-field maze where animals do not traverse paths in a stereotyped fashion (Csicsvari et al. 2007). Furthermore, forward and reverse replay events of extended sequences spanning long distances in large environments have been shown to span across multiple SWRs, indicating that the timescale of a single SWR event does not limit the extent of memory reactivation (Davidson et al. 2009). Replay events can also represent sequences of locations distant from the animals' current position (Karlsson and Frank 2009; Davidson et al. 2009; Gupta et al. 2010) and depict future paths to remembered goals (Pfeiffer and Foster 2013).

These results suggest that, rather than simply recapitulating recent experiences, awake replay reflects trajectories through a "cognitive map" that represents the relationships between locations or episodes (O'Keefe and Nadel 1978). These events therefore resemble the psychological phenomenon of mental spatial exploration or mental time travel. This hypothesis is consistent with the observation that replay events can occasionally represent "shortcut" sequences made up of joined forward and backward sequences that were never experienced together (Gupta et al. 2010). Even brief experiences therefore seem to establish a functionally bidirectional network in the hippocampus that can reinstate both experienced (forward replay) and non-experienced (reverse replay and shortcut sequences) trajectories through the cognitive map. Due to the reinstatement of previously stored patterns of activity related to behavioral experience of the current environment, awake replay of the local environment could be important for memory consolidation and retrieval, action planning, and decision making.

13.4.2 Factors Affecting Awake Replay

Awake replay reinstates behaviorally relevant sequences experienced not only in the current local environment but also in remote environments (Karlsson and Frank 2009; Carr et al. 2011), indicating that it might be related to a consolidation process. By decoding the activity of awake SWRs in two separate environments, it was shown that entire sequences of neurons representing trajectories through a previously explored environment were replayed long after that experience (Karlsson and Frank 2009). The reactivation of a memory for experience in one environment

during learning in another environment raises the intriguing possibility that awake replay of the remote experience, in conjunction with input from the current experience, could contribute to the formation of associations between past and current events. Awake remote replay, like sleep replay, is ideally suited to contribute to memory consolidation as it reinstates hippocampal representations in the absence of behavioral repetition or relevant sensory cues. Indeed, awake replay is a higher fidelity recapitulation of past experiences than replay seen during quiescent, sleep-like states, suggesting that awake replay could play a crucial role in memory consolidation (Karlsson and Frank 2009). The presence of remote awake replay suggests that animals do not have to sleep to consolidate memories of previous experiences and that the consolidation process begins as soon as new memories are encoded in the hippocampus. Moreover, the intermingling of remote and local replay suggests a mechanism by which spatially and temporally distinct experiences may be associated.

It has also been shown that awake replay is enhanced by the saliency of experiences, such as novelty (Cheng and Frank 2008) and reward (Singer and Frank 2009). Indeed, we form strong long-lasting memories of salient experiences, suggesting that these experiences enhance memory consolidation processes. Memory formation is especially important when new information needs to be learned, as in a novel environment, and awake replay has been seen to be more prevalent in novel environments than in familiar ones (Foster and Wilson 2006). Further, reactivation is also more temporally precise in a novel environment, and the precision of awake reactivation decreases with familiarity (Cheng and Frank 2008). This enhanced precision may serve to drive synaptic plasticity in a more efficient manner and thus may be important for consolidation processes (Hebb 1949; Bi and Poo 1998). Novelty has also been shown to increase the reactivation of neurons associated with new experiences during subsequent sleep (O'Neill et al. 2008), and thus novel experiences might lead to enhanced memory consolidation due to increases in both awake and sleep replay. The occurrence of reward after an experience has also been shown to lead to an increase in reactivation of that experience, perhaps facilitating the learning of associations and their outcomes (Singer and Frank 2009). These changes in replay processes by salience could occur in part due to associated changes in neuromodulatory influences, such as dopaminergic (Schultz 1998), noradrenergic (Bouret and Sara 2005), and cholinergic input (Giovannini et al. 2001) and thereby contribute to consolidation by supporting the stabilization of representations.

Current sensory input can also bias the initiation of awake replay events, which is a key requirement if awake replay does support a memory retrieval process. Awake replay often begins at the animal's current location and progressively moves away from the animal in either the forward or reverse direction (Foster and Wilson 2006; Diba and Buzsaki 2007; Karlsson and Frank 2009; Davidson et al. 2009). At the onset of an awake SWR, place cells with field centers near the animal's current location have a higher probability and show a shorter latency to spiking. We and others have suggested that cells active in the current location may influence the initiation of awake replay by acting as "initiator cells" (Buzsaki 1989; Carr

et al. 2011) that trigger the reactivation of previously stored sequence. This is similar to a cued memory retrieval process in which current sensory input triggers retrieval of relevant episodic sequences. Thus, awake replay appears well suited to also support a cue-triggered memory retrieval processes. This retrieval process may have a role in action planning and supporting ongoing memory-guided decision making.

13.4.3 Awake Replay and Memory Processes

Similar to sleep replay, awake replay repeatedly reactivates stored patterns of activity on a timescale suitable for the induction of synaptic plasticity and hence is ideally suited to support memory consolidation. In support of such a role, the degree of awake reactivation has been seen to be correlated to ongoing learning (Dupret et al. 2010). This study found that the intensity of reactivation occurring during brief pauses in exploration was related to subsequent performance.

We have also shown that awake replay supports retrieval processes. We selectively disrupted hippocampal activity during awake SWRs while monitoring hippocampal activity during learning on a continuous alternation task in a W-shaped maze (Fig. 13.2, Jadhav et al. 2012). This disruption led to a specific deficit in learning on one component of the task that requires linking experiences across time ("outbound trials" from the center arm of the maze). Also, animals continued to have impaired performance as compared to control animals even after learning the task during repeated training. Further, a small but significant decrease was seen in the performance of control animals that had learned the task when awake SWRs were disrupted following task acquisition. In sharp contrast, learning of another task component ("inbound trials" from the outer arms to the center arm) was intact. Further, place field activity and reactivation processes were also unaffected. As hippocampal lesions impair learning on both inbound and outbound trials (Kim and Frank 2009), these results indicate that awake SWRs support more complex memory retrieval processes, while place field activity may be sufficient to support simple location–action associations.

Similar findings of an important role of activity at the time of SWRs were obtained in a hippocampal-dependent trace conditioning paradigm (Nokia et al. 2012). A bright light was triggered by SWR detection, which presumably disrupted cortical processing of hippocampal output during SWRs. This resulted in a learning deficit and suggests that processing of SWR activity outside the hippocampus is important for learning and memory.

But how would replay during SWRs inform choice behavior? A very recent result provides strong support for the idea that replay events can support an internal evaluation of possible options. Singer et al. (2013) examined reactivation during SWRs during learning on the same outbound trials where SWR disruption impaired performance. They found that the intensity of pair-wise neural activity preceding each trial predicted whether that trial would be correct or incorrect. Stronger activity preceded correct trials, while weaker activity preceded incorrect trials.

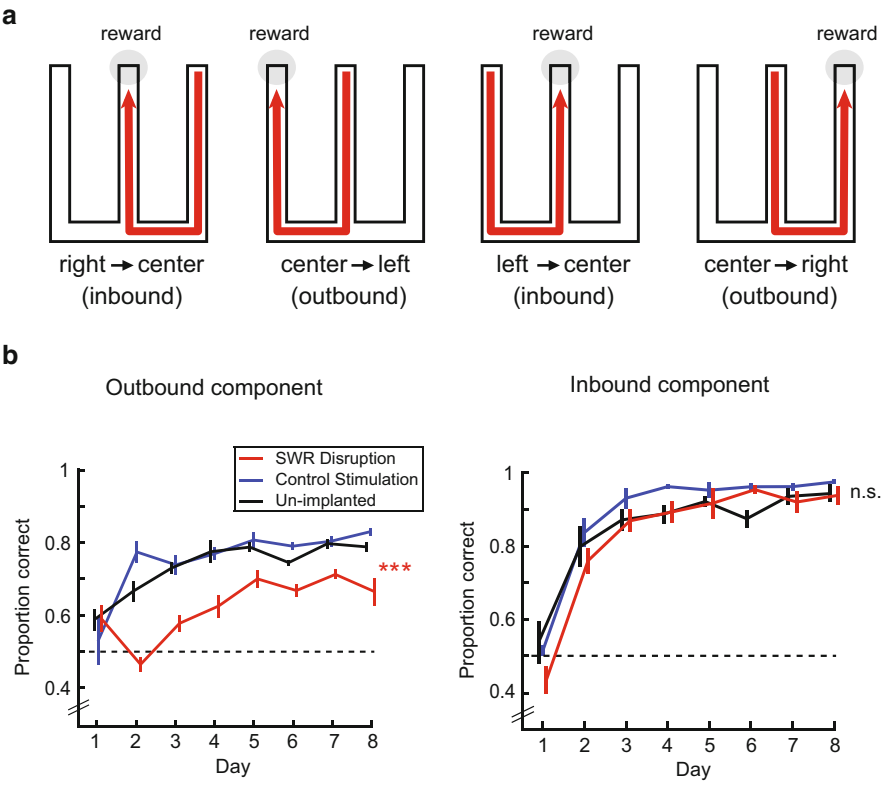

Fig. 13.2 Causal role of awake SWRs in spatial memory. (**a**) Schematic illustrating the W-track spatial alternation task. Rats had to learn to alternate between left and right outbound trajectories (Panels 2 and 4). After each outbound trajectory, the animals returned to the center arm (Panels 1 and 3). During the outbound trajectories, when the rats leave the center arm, they must choose the side arm that was not visited on the previous trial in order to get a reward. During the inbound trajectory, the rats always had to return to the center arm from the side arm to get a reward. Thus, the rats need to remember the previous trial in order to choose the correct outbound trajectory, which requires working memory. The inbound trajectory does not have a working memory requirement. (**b**) Awake SWR disruption causes a specific impairment in the outbound spatial working memory component of the task. (*Left*) Animals in which awake SWRs were disrupted using stimulation on the track (*red*) were impaired in learning the outbound component as compared to stimulated controls (*blue*) and un-implanted controls (*black*). In contrast (*right*), there was no detectable difference in the groups in learning the inbound component. Reproduced from Jadhav et al. (2012)

This effect was seen specifically as animals began to master the task and was no longer detectable once animals reached asymptotic behavioral performance. Interestingly, the content of the reactivation events, that is, which of the two choices available to the animal was represented in each event, did not predict subsequent behavior. Instead, the hippocampus tended to replay activity consistent with possible options before correct trials. These data suggest that, during learning, the

hippocampus provides information about possible choices to other brain regions that would then weight those options in the context of associated reward values and knowledge of task constraints. In another study (Pfeiffer and Foster 2013), it was shown that replay sequences can be biased to depict future paths to remembered goals. In an open arena with multiple reward locations, replay sequences encoded spatial trajectories that were strongly biased from the current location to a known goal location, which changed during each learning session. Interestingly, these sequences predicted the immediate future trajectory of the animal from the current reward location to the known goal location. We therefore suggest that awake replay likely reinstates previously stored representations in distributed circuits and reflects a process in which memory sequences reactivated in the hippocampus are communicated to other regions for action planning and decision making.

13.5 Sleep Vs. Awake Replay

Does memory replay seen during SWRs in slow-wave sleep and during awake behavior reflect the same process, or are there differences in the two phenomena? Given the significant differences in global state of the brain during slow-wave sleep and awake states, it is unlikely that these two processes are exactly the same. During SWS, there is a significant decrease in cholinergic tone and cortisol levels as compared to awake states (Diekelmann and Born 2010). Although there might be fast timescale, dynamic changes in neuromodulatory tone depending on the behavioral state of the animal during awake behavior, it is unlikely to be the same during awake SWRs as compared to sleep SWRs. Indeed, only forward replay has been reported during sleep (Lee and Wilson 2002), whereas both forward and reverse replay are prevalent during the awake state (Diba and Buzsaki 2007; Karlsson and Frank 2009; Davidson et al. 2009; Gupta et al. 2010). How memory replay during sleep and awake states might differ can partly be answered by looking at the effect on downstream structures. During slow-wave sleep, hippocampal SWRs are accompanied by thalamocortical spindles, and delta waves and slow oscillations in neocortex (Sirota et al. 2003; Peyrache et al. 2011; Siapas and Wilson 1998; Phillips et al. 2012). There seems to be a tight coordination between these neocortical rhythms and hippocampal SWRs during sleep, which has been proposed to be essential for transfer of memory-related information required for consolidation (Diekelmann and Born 2010). It remains to be seen whether distinct neocortical states can be identified that accompany awake SWRs.

One additional clue about the differences in awake and sleep replay comes from studies of memory reactivation in humans. Reconsolidation models have proposed that that reactivation during wakefulness transiently destabilizes memories, requiring them to again undergo a process of consolidation (reconsolidation) in order to persist (Nader and Hardt 2009; McKenzie and Eichenbaum 2011; Sara 2000). This suggests a strong link between retrieval and consolidation processes. On the other hand, reactivation of memories during sleep is thought to stabilize memories during consolidation. In support of this idea, reactivating memories in humans by

presenting associated odor cues during sleep strengthened memories, increasing their resistance to interference. However, reactivating memories during wakefulness rendered memories labile, making them more prone to interference (Rasch et al. 2007; Diekelmann et al. 2011). Reactivations during the awake state may serve to update memories with respect to current perceptual input, whereas reactivation during sleep may allow gradual stabilization and integration of memories in a broader framework of existing memories. Contrasting effects of awake and sleep replay in distributed circuits across the brain may explain these effects.

13.6 Summary and Future Directions

Memory replay processes underlie a central component of the mechanisms underlying hippocampal-dependent memory. Both consolidation and retrieval are thought to depend on the reactivation of previously stored patterns of neural activity, and memory replay during SWRs possesses all the attributes necessary to contribute to these processes. Considerable evidence points to a role of sleep and awake replay in memory consolidation and memory retrieval. However, a number of questions still need to be addressed.

First, while slow, progressive changes in representations outside the hippocampus have been documented (Takehara-Nishiuchi and McNaughton 2008), there is currently no established link between replay and the reorganization of neocortical representations. Although it seems unlikely, it remains possible that SWR activity during sleep only serves to alter representations within the hippocampus, perhaps by de-potentiating strengthened synapses (Lubenov and Siapas 2008) to ready the system for new learning.

We also need to understand the nature of activity patterns during replay in all the subregions of the hippocampal system, and not just areas CA3 and CA1 where the focus principally has been. Further, the role of replay in memory processes is contingent upon the assumption that replay reinstates previously learned associations in distributed hippocampal–neocortical circuits. This has to be directly tested, by examining mnemonic patterns of activity in neocortex during both sleep and awake SWRs, which should be coherent with the content of memory replay in the hippocampus. The differences between sleep and awake replay especially with respect to effect on target structures and the role of accompanying neocortical patterns need to be elucidated. Related to this point, the difference between forward and reverse replay also needs to be examined. It is possible that forward and reverse replay may be triggered at different times to support different types of memory processes and may affect neocortical regions in distinct ways. At the same time, it is important to note that place fields tend to be active in both directions of motion in novel linear environments (Frank et al. 2004; Navratilova et al. 2012). As a result, it is not clear that one can meaningfully separate forward and reverse events in novel environments, and it may be that other brain regions are only affected by the order of the place field activation, not by its reverse or forward direction based on the directional firing bias that develops as the environment becomes more familiar.

Finally, it will also be necessary to extend the investigation of replay beyond spatial sequences during spatial memory behaviors by using multimodal behavioral tasks, since the hippocampus is known to be involved in transfer of rules and schemas related to behavior (Tse et al. 2007).

If awake replay indeed does play a role in memory retrieval, action planning, and decision making, then the content of replay should be related to immediate past experiences or be able to predict future choice behavior of animals. Alternatively, hippocampal memory replay should be able to trigger patterns predictive of future behavior in target structures. One particularly interesting possibility is that replay events that begin at the animal's current location provide information about possible upcoming trajectories to target brain structures such as the prefrontal cortex and nucleus accumbens. These downstream structures could then assess the value of different trajectories and make an informed choice about future actions. Thus, awake replay should reinstate previously stored associations that are relevant for ongoing behavior. It also remains to be tested whether the relatively short bursts of activity seen during single SWRs can trigger longer-lasting processes in neural circuits across brain regions that correspond to the perceived timescale of memory retrieval processes.

Another important question that needs to be addressed is to understand the mechanisms that trigger replay. Although it is known that SWRs are internally triggered in the CA3 region of the hippocampus, the mechanisms that generate these events and determine the content of replay events remain poorly understood. For example, is there a role of external contextual input that biases the content of replay events, and what is the mechanism for such a biasing? This is especially important in the context of awake replay events and memory retrieval, where the content of memory replay should be influenced by current contextual input. Further, it is unclear how sequences experienced in only one direction can be stored in such a way as to allow both forward and reverse replay.

With the advent of better causal manipulation techniques, it should be possible to test if memory replay manifests a fundamental mechanism for communication between hippocampus and other structures and to probe the specific role it plays in memory processes. Specific disruption of sleep and/or awake replay during the course of learning will allow an evaluation of whether this impairs formation of memory representations in distributed neocortical locations, as predicted by models of consolidation. To demonstrate a causal link between awake replay and memory retrieval, it will be essential to specifically disrupt awake SWRs at times when a memory-guided decision must be made. The advent of optogenetic techniques might also permit manipulation of specific replay patterns to look at the resulting effect on downstream representations and behavior. Optogenetic methods will also permit manipulation of activity patterns in specific circuits in distributed regions of the brain during memory replay in the hippocampus to investigate their role in specific memory processes during behavior.

Thus, many questions need to be answered to conclusively determine the role of memory replay in the hippocampus, and a thorough understanding of this phenomenon is vital for elucidating the role of the hippocampus in memory.

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How Does the Brain Solve the Computational Problems of Spatial Navigation?

14

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Abstract

Flexible navigation in the real world involves the ability to maintain an ongoing estimate of one's location in the environment, to use landmarks to help navigate, and to construct shortcuts and paths between locations. In mammals, these functions are believed to be performed by a circuit that includes the hippocampus and associated cortical areas. The physiological characterization of the neural substrates for navigation has progressed rapidly in the last four decades, together with plausible mechanistic models for the generation of such activity. However, questions about how the various components of the circuit interact to perform the overall computations that account for the navigational ability of mammals remain largely unsolved. We review physiological and anatomical data as well as models of hippocampal map building and self-localization to establish what is understood about the brain's navigational circuits from a computational perspective. We discuss major areas where our understanding is incomplete.

14.1 Introduction

Many animals, from insects to mammals, exhibit complex collections of spatial behaviors for survival, including foraging for food, remembering where home is, remembering safe routes between home and various known food sources, improvising new routes back home after an exploratory outbound path to a previously unvisited location, learning maps of new environments, and setting goal locations. To be successful, these spatial behaviors must be robust and able to deal with obstacles that hamper straight paths and occlude views, with novel environments, and with dynamically changing cues within familiar environments.

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Navigation involves localizing oneself in space, modeling or mapping the external environment, setting goals, and selecting routes. Self-localization and mapping have a chicken-and-egg relationship. If a "map" of the environment is available (i.e., the spatial coordinates for all landmarks are known), then localization is not difficult, through reference to a sufficiently dense set of landmarks. Conversely, if self-motion estimates are precisely integrated to determine location, then building a map of the environment involves simply visiting and attaching a coordinate to each landmark. Typically, however, neither is known reliably, and the problem is to simultaneously localize oneself within an environment while acquiring a map of it, a computationally challenging problem in sequential probabilistic inference. Goal selection brings into play decision-theoretic questions involving exploration–exploitation trade-offs (Dayan and Daw 2008). Finding routes home involves not only knowing where one is and where home is but also the conversion of those coordinates into the vector pointing to home, as well as deciding when to follow landmarks and when to follow beeline paths based on internal estimates of location.

In this chapter, we focus on a small subset of questions related to animal navigation. We discuss how animals estimate their locations within environments while building internal models of these environments. In other words, our central aim here is to describe potential neural substrates for localization and mapping and to discuss computational efforts to understand the mechanisms underlying how the brain solves these problems. Other important aspects of goal-directed spatial behavior, such as selecting spatial goals and routes, are not directly addressed here (however, such behaviors will depend on the animal's ability to solve the problems of localization and mapping, which we discuss here). In what follows, when we refer to the entorhinal–hippocampal circuit for spatial navigation, we intend to convey the spatial functions subserved by this circuit without implying that this is the sole function of the circuit.

We begin with a historical perspective on advances in the field, then summarize the current state of electrophysiological findings on activity in different parts of the circuit, briefly describing progress in modeling the mechanisms underlying such responses, and finally highlight several models of the overall entorhinal–hippocampal spatial navigation circuit that show how the various subcomponents might contribute to simultaneous self-localization and mapping in the presence of noisy and ambiguous sensory cues.

14.2 Early Ideas on Animal Navigation: Stimulus-Response Learning Vs. Map-Based Learning

Experimental work on spatial navigation in the animal literature began in the early twentieth century. This work was largely confined to observing how rats learned spatial mazes. Behaviorists believed that spatial learning, like other types of learning, could only be based on the association of actions and stimuli with rewards. For spatial learning, this implied that only locations and location-relations

associated with rewards could be learned. In this view, chaining stimulus-reward associations could subserve more sophisticated behaviors like navigation along a route.

Tolman and some of his contemporaries (Tolman 1948; Hebb 1949) observed that there was much more to spatial learning. A notable study that challenged the behaviorist point of view was the sunburst maze experiment. In this task, after preliminary training in a spatially restricted, roughly L-shaped enclosure, rats were given the choice of many novel radial arms, the sunburst, to move directly to the end point (Tolman et al. 1946). Interestingly, some rats were observed to take the shortest radial route corresponding to the beeline path between the starting and end points. This suggested that rats could improvise paths and shortcuts through regions they had not previously traversed and thus which had no reward associations. Tolman reasoned that animals are capable of constructing mental representations of spatial locations in the environment and relations between them, independent of reward. He called these representations "cognitive maps." By construction, cognitive maps could hypothetically provide route information between any two points in the environment and thus be used to navigate the sunburst maze.

Tolman's conception of cognitive maps (Tolman 1948) was perceptive, but the lack of any known neurophysiological basis for such hypothesized computations contributed to a decline in popularity of the cognitive map hypothesis in the decades after its proposal (O'Keefe and Nadal 1978). It was not until the 1970s that the cognitive map theory was dusted off and elaborated upon (O'Keefe and Nadal 1978), in light of the exciting experimental discovery of place cells (O'Keefe and Dostrovsky 1971).

14.3 Map-Based Navigation Theory Spurred by Discovery of the Place Cell

Place cells, discovered by O'Keefe and Dostrovsky in the early 1970s (O'Keefe and Dostrovsky 1971), are neurons in the hippocampus that fire if and only if the animal is in the immediate neighborhood of a particular location (the place field) in an environment. Many place cells possess place fields within any given environment. Because the recording environments (typically 0.5–1 m per dimension) tended to be covered by different place fields, place cells were hypothesized to form the basis for spatial mapping. This pointed to the hippocampus as the locus of the cognitive map for space.

The groundbreaking discovery of place cells prompted the renewal and further development of the cognitive map hypothesis. O'Keefe and Nadel extensively reviewed the psychological, behavioral, anatomical, and physiological evidence for the existence of abstract spatial maps in the brain in their comprehensive and prescient book on the topic (O'Keefe and Nadal 1978). O'Keefe and Nadel provided a clear definition of a spatial map as an abstract representation of locations in an environment, the relationships between them, and the sensory inputs related to the locations. An important contribution to the cognitive map theory by O'Keefe

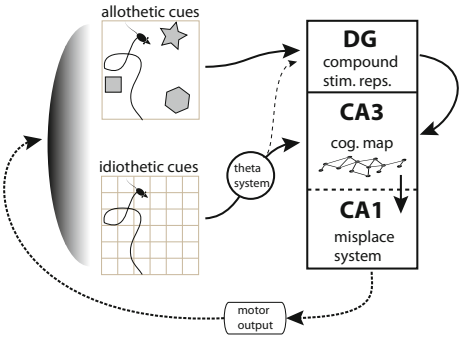

Fig. 14.1 High-level schematic of cognitive map hypothesis of O'Keefe and Nadel. Place cells in the CA1/CA3 region can be activated by two independent means: through external sensory (allothetic) cues, which are preprocessed in the DG, and through movement-related (idiothetic) cues. Mismatches in the two inputs propel the animal toward further exploration

and Nadel (1978) was to elaborate on the problem of ongoing location identification. Reasoning that it was sufficiently difficult to estimate location purely from the observation of shifting angles of visible landmarks relative to the animal, they hypothesized that another system, sensitive to the movements of the animal, would be required, Fig. 14.1. This second system was hypothesized to follow the self-motion of the animal through space, shifting the hippocampal place representation accordingly. The self-motion drive was suggested to supplement purely external sensory inputs, which provided cues originating from viewing the world from different locations and angles. The "internal" system was seen as providing predictions about what to expect at a particular place that were compared with the actual sensory input provided by the "external" system. Discrepancies between expectation and actual input might be conveyed via *misplace units* (O'Keefe 1976), whose hypothesized role was to signal mismatches between the two systems, Fig. 14.1. In the theory, active misplace units would trigger further exploration of the environment until enough information was acquired to fix the incongruities between the two inputs and silence the misplace units. Thus, in a way, each system was seen as providing partially accurate representations of the animal's location within the environment, with the interplay between the two suggested as leading to the formation of a consistent map.

O'Keefe and Nadel (1978) stimulated the rediscovery of the cognitive map theory by the rest of the scientific community and, at the same time, developed it into a far more complete framework for understanding the neural substrates of navigation. However, two key elements were lacking. First, although place cells offered the first glimpse of the neural substrates for high-level cognitive representations, all other critical components of the spatial navigation circuit remained poorly characterized at the time. Second, there were no computational models of how the appropriate navigational operations could be performed in the hippocampal circuit. In the next two sections, we describe how empirical work and theoretical and computational studies have begun to fill in these elements.

14.4 Neural Substrates for Navigation

A series of discoveries of cells beautifully tuned to specific spatial and navigation-specific variables followed the discovery of place cells, laying a more solid neurophysiological foundation for our understanding of a cognitive map in the brain. In parallel, computational and theoretical studies have helped provide mechanistic explanations for how such neurophysiological responses might arise in the brain.

14.4.1 Head-Direction Cells

In 1983, Ranck discovered head direction (HD) cells (Ranck 1984). HD cells fire when the animal's head points in a particular direction, independent of the actual location of the animal within the environment, Fig. 14.2a. HD cells were found in many regions of the brain, including the postsubiculum and thalamus (Taube et al. 1990a, b; Taube 1995). The HD signal is carried to the entorhinal cortex (EC) through the postsubiculum (van Groen and Wyss 1990; Caballero-Bleda and Witter 1994; Taube 2007). The specific set of HD cells firing along one direction in an environment is not fixed by magnetic or compass cues but by a local orienting stimulus: a white stripe or cue-card placed on an otherwise featureless cylindrical wall provides a reference angle for the HD cells. If the cue is rotated clockwise, the preferred firing orientation of all the HD cells rotates clockwise, robustly and coherently, by a very similar amount (Dudchenko and Taube 1997). HD cells continue to fire if the lights are switched off, spiking at the appropriate orientations as the animal moves about the room for an extended period of time (several seconds) (Mizumori and Williams 1993). Moreover, HD cells can become decoupled from external cues, while maintaining their tuning curve shapes and relationships, highlighting the influence of idiothetic cues on HD activity (Knierim et al. 1995; Yoganarasimha and Knierim 2005). These observations, together with lesion studies on the vestibular inputs to HD cells (Stackman and Taube 1997), suggest that HD cells integrate the animal's head's angular velocity as signaled by the vestibular system to arrive at updated estimates of the animal's head direction. Head direction estimation is a critical element of any navigational circuit; however, it is important to note that instantaneous head direction need not directly correspond to the instantaneous direction of movement of the animal through space (termed "heading direction"), because the animal can turn its head relative to the forward direction, to smell, view, or touch peripheral objects.

The remarkable HD cells, when discovered, constituted the best evidence available then that the brain might compute using continuous attractor dynamics (Skaggs et al. 1995; Zhang 1996; Seung 1996; Redish et al. 1996): a continuum of stable—or attracting—neural activity states that can be used, because of their stability, to store short-term memories of continuous variables and integrate these variables over time based on motion input (integration is the operation of summing external inputs, and in the absence of changes in the external input, holding the state obtained from summing past inputs; therefore, integration requires memory).

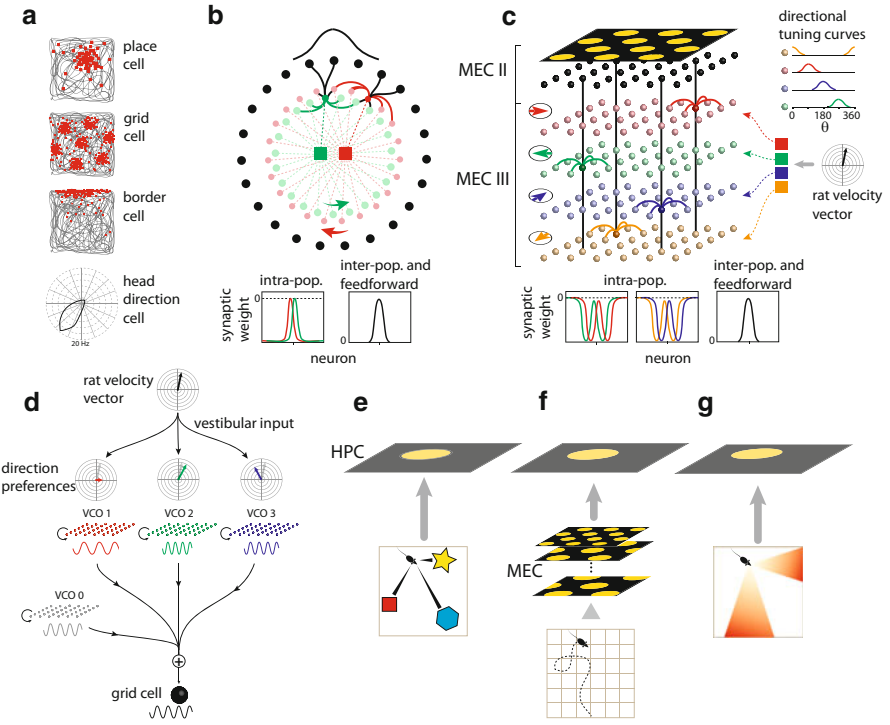

Fig. 14.2 Neural models of grid cells, HD cells, and place cells. (**a**) Schematic of spatial responses of four basic cell types of the hippocampal navigation circuit: Place cell (*top*), grid cell (*second panel*), border cell (*third panel*), and HD cell (*bottom*). The place, grid, and border cell panels show the animal's trajectory (*gray trace*) as it explores a box environment. *Red dots* represent locations at which the cell emitted a spike. The last panel is a polar plot of the firing rate of an HD cell as a function of the animal's heading direction. (**b**) 1D continuous attractor model of head direction cells: Two populations of conjunctive HD cells (*red* and *green circles*), arranged according to their head direction preferences. Red (*green*) cells receive vestibular inputs (*red* or *green boxes*) coding for clockwise (counterclockwise) angular head velocity. The conjunctive HD populations project to a population of pure HD cells (*black circles*). Weights between and across layers are described in boxes below: *Curves* represent the weights of one neuron to its postsynaptic targets. Conjunctive layers receive uniform excitatory input (not shown), causing formation of stable bump in conjunctive (not shown) and pure HD layers (*black curve*). The bump state can be moved around the network by biasing input into the conjunctive layer. (**c**) 2D continuous attractor model of grid cells: Four populations of conjunctive grid cells (*colored balls*), arranged according to the preferred phases of their grid fields, receive input from speed-modulated HD cells (*colored boxes*) that encode animal velocity and project to a population of pure grid cells (*black balls*). The conjunctive grid cells inherit these directional preferences, as indicated by the colored tuning curves (as a function of animal's heading direction, Θ) in *upper right*. Weights between and across layers are shown in the *boxes* below [same as in (**b**), only 1d projections are shown]. If the conjunctive layers are supplied with a uniform excitatory drive, a stable, multimodal pattern of activity arises (*black surface with yellow spots*, shown only for the pure GC layer). The activity pattern can be translated in any direction by biasing input into the conjunctive layers (*encircled colored arrows* indicate direction the activity pattern moves if that conjunctive layer receives biased input). (**d**) OI model of grid cells: Three velocity-coupled

Because single-neuron activity states are transient, typically decaying within a membrane time constant of about 100 ms, models of continuous attractor dynamics in the brain involve strong recurrent connections that may be excitatory or inhibitory, whose function is to provide a net positive feedback drive that cancels the tendency of individual neural activities to decay over time (Skaggs et al. 1995; Ben-Yishai et al. 1995; Zhang 1996; Seung 1996).

The HD system is well modeled by a specific continuous attractor network, with neurons arranged (conceptually, not necessarily anatomically) along a ring, that excite or disinhibit each other locally and inhibit each other globally (Ben-Yishai et al. 1995; Zhang 1996). If the connectivity is the same across the ring, a bump-like activity state and all translations of the bump are stable states, Fig. 14.2b (Skaggs et al. 1995; Ben-Yishai et al. 1995; Zhang 1996; Stringer et al. 2002; Boucheny et al. 2005). Each bump location along the ring represents a specific head orientation. The network is further hypothesized to possess asymmetrical recurrent connectivity and feedforward inputs signaling angular head velocity, in such a way that the inputs drive the bump along the ring, with speed and direction proportional to the angular head velocity. In this way, these bump states can be used to maintain a representation of the animal's current heading direction. A specific hallmark of the continuous attractor network theory is that the preferred orientations of pairs of neurons should maintain a fixed angular separation relative to each other, even when the overall orientation preferences rotate or are otherwise changed due to mismatched angular cues from the external world (Yoganarasimha et al. 2006). Experiments involving inconsistently rotated external cues cause rotations in the preferred directions of HD cells, but as predicted by attractor models, their relative preferred directions remain fixed (Taube et al. 1990b; Yoganarasimha et al. 2006).

14.4.2 The Entorhinal Cortex as Gateway to the Hippocampus

In addition to the hippocampus and the distributed regions where HD cells are found (Taube 2007), the EC is a key brain area involved in spatial navigation. Lesion studies have implicated the EC in spatial computation (Ferbinteanu

Fig. 14.2 (Continued) oscillators (*red*, *green*, and *blue*; the VCOs could be networks as pictured here, or single neurons, or dendrites of a single neuron) receive vestibular input whose amplitude is given by the projection of the animal's velocity vector onto a specific preferred direction (*red*, *green*, *blue arrows*). These inputs modulate the oscillation frequency of the VCOs: this is the actual path integration stage in the OI model. The oscillatory signals are summed, along with a fourth, velocity-insensitive baseline oscillatory signal (*gray*), within a single grid cell (*black circle*). (**e**) Place fields driven by sensitivity to distance, direction, and/or angle subtended by landmarks in the environment (*yellow blob* represents the active ensemble of place cells, topographically arranged according to place preference). (**f**) Place fields formed by summation of multiple grid cells (*black sheets* in the MEC indicate different grid cell modules; *yellow blobs* indicate active neurons in each module). (**g**) Place fields formed by summation of BVC inputs, which convey information about distance and direction to geometric boundaries

et al. 1999; Parron and Save 2004a, b; Steffenach et al. 2005; Van Cauter et al. 2012). The EC is the cortical gateway of inputs to the hippocampus: the medial and lateral portions of EC (MEC and LEC, respectively) project to the proximal and distal portions of CA1, respectively, but have overlapping projections at the dentate gyrus (DG) and CA3 (Witter and Amaral 2004; Witter et al. 2006; McNaughton and Barnes 1977). Electrophysiological studies in the EC of the freely moving rat reveal a dissociation in the nature of the LEC and MEC representations (Deshmukh and Knierim 2011): LEC cells tend to respond to objects in the animal's immediate environment (Zhu et al. 1995; Young et al. 1997; Wan et al. 1999; Deshmukh and Knierim 2011), while cells in MEC ignore object locations and instead fire at multiple locations in the open field (Barnes et al. 1990; Quirk et al. 1992; Frank et al. 2000; Fyhn et al. 2004; Wills et al. 2005). Thus, the LEC and MEC might form the two parallel streams postulated in the cognitive map hypothesis, carrying external sensory and internal motion-based cues, respectively, to be synthesized in the hippocampus.

14.4.3 Grid Cells

Less than a decade ago, the MEC was found to contain a class of cells—grid cells—with astonishing spatial firing characteristics (Hafting et al. 2005): each cell fires at multiple locations in an environment, and the locations are arranged on the vertices of an essentially equilateral triangular lattice, Fig. 14.2a. The period of the lattice is typically determined intrinsically by the cell network and not by the size and shape of the enclosure (Hafting et al. 2005) [but see Barry et al. (2007)]. Nearby cells share common grid periods and orientation, and there are a range of distinct periods, hypothesized to be discretely spaced (Fuhs and Touretzky 2006; McNaughton et al. 2006; Fiete et al. 2008; Burak and Fiete 2009) and later shown to be so in Stensola et al. (2012). Grid cells are most commonly found in layer II of MEC. The postsubiculum, a major source of input to the MEC, terminates in the deep layers (van Groen and Wyss 1990). Thus, layers III–V of the MEC contain cells responsive to the animal's head direction, either in the form of pure head direction tuning or combined head direction and grid-like tuning (the latter are known as "conjunctive" grid cells) (Sargolini et al. 2006). In contrast, grid cells in layer II of the MEC tend to be insensitive to heading and head direction ("pure" or "non-conjunctive" grid cells) (Sargolini et al. 2006).

The spatial fields of MEC grid cells can rotate when salient external cues are rotated (Hafting et al. 2005), and periods of their spatial tuning can resize in response to a rescaling of a familiar environment (Barry et al. 2007), but other than firing-rate modulations (Savelli et al. 2008), the spatial locations of grid cell firing are relatively insensitive to the particulars of the environment. This is in contrast to the spatial responses in LEC and the hippocampus, which exhibit more detailed and complex changes to environmental manipulation (Zhu et al. 1995; Young et al. 1997; Wan et al. 1999; Deshmukh and Knierim 2011; Muller and Kubie 1987; Leutgeb et al. 2004; Wills et al. 2005; Leutgeb and Leutgeb 2007;

Colgin et al. 2008). The relative insensitivity of grid cells to external cues and the stability of their fields in cue-poor environments and darkness (Hafting et al. 2005) suggest that self-motion is the primary determinant of grid cell firing. For these reasons, it is widely hypothesized that the grid cell system computes, or at least is responsive to, a path integrated estimate of the animal's position (see Chap. 8). However, direct evidence of the role of grid cells in path integration is lacking.

Most grid cell models rely on the conversion of motion inputs into spatial representations (Welinder et al. 2008; Giocomo et al. 2011; Zilli 2012). On the one hand, continuous attractor models of grid cells (Fuhs and Touretzky 2006; Burak and Fiete 2006, 2009; Guanella et al. 2007; McNaughton et al. 2006), Fig. 14.2c, posit that strong local recurrent connectivity destabilizes the uniform activity state in the population and stabilizes a state which displays regular triangular lattice patterning within the population. The recurrent connections may be purely inhibitory, as first proposed in Burak and Fiete (2009) and supported by Pastoll et al. (2013) and Couey et al. (2013), or excitatory with a local inhibitory surround (McNaughton et al. 2006; Guanella et al. 2007; Burak and Fiete 2009). Translation invariance of such connectivity stabilizes all translations of this pattern through the population, and an asymmetric component of the connectivity allows external inputs signaling animal velocity to drive the pattern in direct proportion to the direction and speed of the animal's movements. These models are straightforward 2D extensions of the 1D continuous attractor models for HD cells (Welinder et al. 2008; Zilli 2012).

All cells in the continuous attractor network model share the same grid period and orientation, because their responses are generated by translations of the same pattern, and all spatial phases are exactly uniformly distributed, consistent with the data. Disjoint network copies (modules) are required to produce different grid periods and, because each network is large (consisting of 4,000–40,000 neurons), leads to the prediction of a few, discrete grid periods within each animal (Fuhs and Touretzky 2006; McNaughton et al. 2006; Burak and Fiete 2009). This prediction was recently experimentally verified in Stensola et al. (2012). The fundamental prediction of continuous attractor models is that the differences in preferred spatial activation phase between pairs of grid cells will remain stable over time, regardless of environmental manipulations that induce sizeable distortions in the grid fields, if the network architecture remains unchanged. Recent analysis of simultaneously recorded grid cells with similar period and orientation across experiments involving grid cell distortion (including the environmental stretching experiments of Barry et al. (2007)) establishes the stability of these predicted relationships and shows that the grid cell population responses within a single grid network (module) are confined to a 2D manifold within the high-dimensional state space (Yoon et al. 2013).

On the other hand are oscillatory interference (OI) models in which interfering temporal oscillations produce periodically amplitude-modulated activity outputs (O'Keefe and Burgess 2005; Burgess et al. 2007; Hasselmo et al. 2007; Hasselmo 2008; Blair et al. 2008; Zilli et al. 2009) (see Chap. 12). These amplitude modulations can be mapped to spatial grid patterns that are invariant to animal

speed if the frequency of the temporal oscillations is based on animal speed, Fig. 14.2d. The elementary oscillators are called velocity-coupled oscillators (VCOs). Whereas in the continuous attractor models, the grid cell network integrates animal velocity by shifting the phase of the periodic population-level grid pattern (made possible by asymmetric recurrent connections), integration in the OI models is performed by the VCOs, because the velocity inputs change their frequency and thus also increment their phase.

To account for the systematic variation in grid period along the dorsoventral axis of MEC (Hafting et al. 2005), OI models predict a gradient in the baseline oscillation frequencies of the VCOs. Empirical study (Giocomo et al. 2007) shows that, intriguingly, the intrinsic resonance frequency and subthreshold membrane oscillations of stellate cells in MEC decreases systematically toward the ventral end along the dorsoventral axis, qualitatively matching the prediction, if the hypothesized VCOs correspond to subthreshold oscillations in the membrane potential. However, there are biophysical arguments against identifying membrane potential oscillations with VCOs (Remme et al. 2010; Fiete 2010). Identifying the local field potential (LFP) oscillation at theta frequency with the baseline (not velocity-modulated) oscillator also has some problems, including a mismatch between the phase fidelity of spatial patterning in grid cells across multiple periods vs. the tendency of the LFP oscillation to decohere or lose all phase information after five to six cycles (Welinder et al. 2008). The theta frequency is not linearly related to grid period across modules (Stensola et al. 2012), as would be predicted by OI models if baseline oscillations were reflected in the LFP. Bats, which exhibit grid cell activity, do not display sustained theta oscillations, suggesting a dissociation between the grid-like spatial tuning and theta oscillations or at least between the hypothesized VCOs and theta oscillations (Yartsev et al. 2011). Together, these studies suggest that the LFP theta is not related to VCOs or that the OI models require revision. Studies showing that grid fields degrade when theta oscillations are abolished (via lesion to the medial septum) (Brandon et al. 2011; Koenig et al. 2011) are more consistent with a possible role for the LFP in grid formation. However, these results are also consistent with continuous attractor models in which the recurrent circuitry amongst grid cells is predominantly inhibitory (Burak and Fiete 2009; Couey et al. 2013) and grid patterning requires a spatially nonspecific excitatory input to drive cells above threshold (Burak and Fiete 2009; Pastoll et al. 2013; Bonnevie et al. 2013).

Recent intracellular recordings of grid cells (Schmidt-Hieber and Hausser 2013; Domnisoru et al. 2013) show that grid cell firing fields are clearly correlated with slow depolarizing voltage ramps that last the duration of the field and that the firing fields are better predicted by the voltage ramps than by the smaller superimposed oscillations that are also present during the field. These findings suggest either a feedforward or feedback synaptic contribution to the spatial patterning of grid cells. Synaptic contributions to the grid cell response are consistent with continuous attractor models of grid cells (Fuhs and Touretzky 2006; Burak and Fiete 2006, 2009; McNaughton et al. 2006; Guanella et al. 2007; Welday et al. 2011; Zilli 2012) as well as other models that involve cell–cell coupling (Kropff and Treves 2008;

Mhatre et al. 2010) and may also be consistent with versions of OI models that incorporate lateral network connections (Zilli and Hasselmo 2010; Yoon et al. 2013). More specifically, a recent analysis of simultaneously recorded neurons shows that grid cells with similar spatial period and orientation (i.e., from a single network or module) exhibit key signatures of two dimensional continuous attractor dynamics, as predicted by the continuous attractor models (Fuhs and Touretzky 2006; Burak and Fiete 2006, 2009; McNaughton et al. 2006; Guanella et al. 2007). Thus, all models of a grid cell population should, to be consistent with the data, display continuous attractor dynamics across the population.

At the same time, the intracellular studies of grid cells show that individual spike timings within one firing field are strongly correlated with theta oscillation peaks in the intracellular voltage. Thus, while network mechanisms determine the spatial locations of firing fields, the OI mechanisms might be responsible for a more fine-grained temporal code of spike timing within field (Schmidt-Hieber and Hausser 2013; Domnisoru et al. 2013), including the phenomenon of phase precession (O'Keefe and Recce 1993; O'Keefe and Burgess 2005; Kamondi et al. 1998; Magee 2001; Lengyel et al. 2003). Finally, at present both classes of grid cell models (Welday et al. 2011; O'Keefe and Burgess 2005; Burgess et al. 2007; Hasselmo et al. 2007; Fuhs and Touretzky 2006; Burak and Fiete 2006, 2009; Guanella et al. 2007; McNaughton et al. 2006) are subject to the criticism of complexity in the wiring required to generate grid fields and to the question of how these architectures may form during development or through experience-dependent synaptic plasticity, although some progress has recently been made in understanding how the continuous attractor networks capable of generating grid cell activity may arise from relatively simple plasticity rules (Widloski and Fiete, unpublished observations).

There are a number of questions one may ask about grid cells and their downstream readouts in the brain. Are homing vectors computed from the grid cell representation, and if so, where and how is this done? Animals can compute and execute beeline paths home with the help of visual beacons or landmarks after executing tortuous outgoing trajectories, a behavior known as homing. There are some studies that this sort of behavior is EC-dependent (Parron and Save 2004a; Steffenach et al. 2005). However, while the grid cell output contains the information necessary for specifying vector displacement relative to a starting point (e.g., home) (Fiete et al. 2008; Sreenivasan and Fiete 2011), it is not coded in a straightforward or linearly decodable way: the grid cell activity patterns for nearby locations are nearly maximally distinct from each other, while the activity patterns for remote locations can be very similar (Fiete et al. 2008; Sreenivasan and Fiete 2011). This fact implies the need for separate nonlinear computations to recover the metric distance and direction information from the grid code, but it is not clear which downstream readouts of the MEC might perform these computations. It is possible that the subiculum, with its relatively uncharacterized role in the spatial circuit (Sharp 2006), may play a role.

Second, why, if grid cells are producing a path-integrated estimate of location, do they represent it in a single 2D network response, rather than in two 1D activity

patterns that increment like a cartesian basis for 2D space. The number of neurons required to represent a 2D space in a combined representation scales like N^2, whereas the number required in two independent 1D representations scales only as $2N$ (Fiete et al. 2008). One problem with representing 2D space with a pair of 1D representations, each conveying information about one cartesian coordinate, is that one coordinate and thus one representation remains unchanged for all movements parallel to the corresponding coordinate axis (Fiete et al. 2008). Thus, the representation is not "whitened" or decorrelated across locations. A single 2D representation allows for a more whitened representation of different locations, without inducing correlations along two specific coordinate axes (Fiete et al. 2008). Whether this gain is enough to offset the neuron number costs of constructing a single 2D representation depends on the importance of achieving such decorrelation, another question that remains to be answered.

Closely related is the question of how the grid cell system represents 1D environments. Often during real-world navigation, the animal might run along a wire or along the wall of a hallway and perceive these trajectory segments as navigating in an inherently 1D environment, even though they are merely 1D paths embedded in a higher-dimensional world. Intriguing grid cell recordings from 1D environments (narrow elevated tracks) appear to show irregular, or at least non-periodic, responses (Brun et al. 2008; Derdikman et al. 2009; Domnisoru et al. 2013) that in some circumstances appear to be more closely tied to external cues than are the 2D responses (Brun et al. 2008; Derdikman et al. 2009). Moreover, the spatial periodicity of 1D responses appears to be much larger than the periods seen in 2D. These observations raise the question of whether the 1D response is generated under the same dynamical mechanisms as the 2D response (e.g., whether the 1D response is simply a 1D slice through a regular 2D grid (Yoganarasimha et al. (2011); Domnisoru et al. (2013) and unpublished observations by KJ Yoon, S Lewallen, A Kinkhabwalla, DW Tank, and IR Fiete), or whether 1D dynamics, and by extension, the grid cell code in 1D environments, is in a distinct dynamical regime and follows very different rules).

14.4.4 Place Cells

Layers II and III of the EC (both the LEC and the MEC where grid cells and conjunctive grid cells reside) project to the hippocampus and to areas DG/CA3 and CA1, respectively (Anderson et al. 2007). All of these target areas contain cells with place-like fields. Place cells, unlike grid cells, are sensitive to many aspects of the external environment, including features that animals are known to use for navigation [see Redish (1999) for a review]. This includes sensitivity to proximal and distal landmarks (Siegel et al. 2008; Yoganarasimha et al. 2006; Renaudineau et al. 2007), contextual cues (including nonspatial ones like color and lighting) (Muller and Kubie 1987; Hampson et al. 1999; Wood et al. 1999, 2000; Hayman et al. 2003; Komorowski et al. 2009; Manns and Eichenbaum 2009), geometric boundaries (Lever et al. 2002), and reward associations (Wikenheiser and Redish

2011). Place cells continue to fire in the absence of visual cues, suggesting that their activities can be updated through idiothetic cues (Fuhs et al. 2005; Gothard et al. 1996; Knierim et al. 1996; Taube et al. 1996; Jeffery et al. 1997; Quirk et al. 1990). These results support the hypothesis by O'Keefe and Nadel that the hippocampus contains the brain's spatial map and that this map derives from both idiothetic and allothetic cues.

Early models of place cells hypothesized that they were driven primarily by visuo-spatial cues (Zipser 1985; Sharp 1991; Schmajuk 1990; Schmajuk and Blair 1993; Burgess et al. 1994; Benhamou et al. 1995; Prescott 1996). For instance, each cell might be particularly sensitive to the constellation of cues as seen from some particular location in the environment and would fire whenever that constellation was in view, Fig. 14.2e. In accordance with these models, external cues do seem to play a role in driving place cell activity: some place cells seem to fire based on landmark location (Deshmukh and Knierim 2013) and are sensitive to external sensory cues in general, as described above. These external sensory cues might arrive at the hippocampus through the LEC, given the presence of object/landmark related cell types found there (Zhu et al. 1995; Young et al. 1997; Wan et al. 1999), or possibly through the MEC itself.

To account for the continued expression of place fields in darkness and for the omnidirectionality of place cells in two-dimensional environments, which fire when the animal approaches a location from diverse angles with diverse views, a number of models (described in more detail in the following section) invoked the possibility that place cell activity was at least partially based on path integrated estimates of location (Touretzky and Redish 1996; Samsonovich and McNaughton 1997; Balakrishnan et al. 1999; Arleo and Gerstner 2000). Several models placed the locus of path integration within the CA1/CA3 network itself, suggesting how the hippocampus might integrate velocity inputs, for example, through the use of sinusoidal arrays (Touretzky et al. 1993) or continuous attractor networks (Tsodyks and Sejnowski 1995; Samsonovich and McNaughton 1997). However, lesion studies (Wan et al. 1993; Van Cauter et al. 2012), the discovery of grid cells (Hafting et al. 2005), theoretical considerations about the limited spatial range and resolution of the hippocampal code (Fiete et al. 2008), and models of path integration by grid cells (Fuhs and Touretzky 2006; Guanella et al. 2007; Burak and Fiete 2009; Burgess et al. 2007; Hasselmo 2008), point instead to the MEC as the locus of path integration, leaving to the hippocampus the still-formidable function of synthesizing information from multiple sensory streams and constructing associations between them.

Models of place cells that have followed the discovery of grid cells suggest that place fields are formed by summing and then thresholding the activity of multiple grid cells with different spacings and orientations, Fig. 14.2f (O'Keefe and Burgess 2005; Rolls et al. 2006; Solstad et al. 2006; Franzius et al. 2007; Hayman and Jeffery 2008; Savelli and Knierim 2010; Monaco et al. 2011). These models swing in the opposite direction, seeming to suggest that the primary input to and determinant of place cell firing is based on feedforward idiothetically derived grid cell activity, rather than external sensory cues or structured lateral connectivity. The

reality of place cells is likely somewhere in between, if indeed place cells are the basis of the brain's cognitive map of space. Thus, they must derive their activity by combining idiothetic and allothetic cues, as in the more comprehensive, functionally motivated models of place cell activity, summarized in the next section.

14.4.5 Other Cells with Strong Spatial Correlates

The spatial circuit contains several other cell types that respond selectively to external spatial cues. Some cells in the subiculum fire at a fixed perpendicular distance from environmental borders, even when the environment is resized (Lever et al. 2009). These cells were predicted to exist by the boundary vector cell (BVC) model of place cell firing, Fig. 14.2g (O'Keefe and Burgess 1996; Burgess et al. 2000; Hartley et al. 2000; Barry et al. 2006). According to the BVC model, place cells are formed by summing multiple BVCs with intersecting firing fields; BVC activation is clearly related to external features in the environment, and these cells are hypothesized to be largely driven by external sensory cues. However, it remains unclear whether in the hippocampus the BVC cells drive place cells or if place cells dominated by external inputs sum to drive BVCs (Derdikman 2009) (in a way similar to the Hubel–Wiesel model for V1 orientation tuning from selective feedforward summation of LGN neurons). Similar to BVCs, the MEC contains border cells (Solstad et al. 2008; Savelli et al. 2008), which respond by firing whenever the animal is directly at an environmental boundary. In contrast to BVCs, these cells do not tend to fire at a finite perpendicular distance away from the boundary, Fig. 14.2a.

14.4.6 The Responses of Spatial Cells to Changes in the Environment

The descriptions of neural representations of space described above involved the static representation of familiar, unchanging environments. How do these representations change when the environment changes? Real-world navigation involves representation of novel environments and modified familiar environments. Thus, it is critical to understand spatial representation under changing conditions.

When an environment is rotated, grid cells (Hafting et al. 2005) and HD cells (Taube et al. 1990b) continue to be active and coherently rotate their field centers as a group. Across different familiar environments, the firing fields of grid cells may additionally display coherent shifts in spatial phase while maintaining regular periodic tuning (Hafting et al. 2005; Fyhn et al. 2007; Yoon et al. 2013). These findings suggest that HD and grid cells track angular displacements relative to a starting angle or linear displacements relative to a starting location, respectively, roughly independent of context or specific location within the environment. Under mismatched cue rotations, HD cells rotate coherently (Yoganarasimha et al. 2006), suggesting that they represent a single best estimate of the external orientation of

the world. Across diverse *familiar* environments, grid cells maintain the specific periodicity of their spatial responses, which suggests that they use a fixed internal scale to measure displacement.

Place cells, on the other hand, can display a response known as global remapping (Muller and Kubie 1987; Leutgeb et al. 2004; Wills et al. 2005; Leutgeb and Leutgeb 2007; Colgin et al. 2008) across environments: when an animal is moved to a clearly different environment, or the contextual cues in the environment are made sufficiently different (e.g., change in both the wall color and boundary shape or both boundary shape and texture), the ensemble of active place cells changes, and the relationships between their firing fields also changes (see Chap. 9). For example, one of two cells with overlapping fields might stop firing in the new environment, while the other continues to fire. In this way, place cells generate largely independent representations across sufficiently different environments. Place cells can alternatively display a less dramatic change in their representation, through rate remapping, in which the relative field amplitudes are differentially modulated by as much as a factor of 10 in the peak firing rates in response to more subtle contextual changes (Leutgeb et al. 2005). In rate remapping, the centers of place fields and their spatial relationships do not change.

What are the mechanisms underlying global and rate remapping? Global remapping is accompanied by shifts and rotations in the activity patterns of grid cells in EC neurons (Fyhn et al. 2007), but under rate remapping such changes are undetectable (Fyhn et al. 2007; Leutgeb et al. 2007). Theoretical (Fiete et al. 2008) and modeling studies (Monaco et al. 2011) suggest that if shifts or rotations (either shifts or rotations are sufficient) of grid cell responses are *different* across the *different* grid networks or modules, then the spatial representation undergoes discontinuous changes, and a procedure for constructing place cells from grid cells by summing the activities of grid cells from different grid networks will result in globally remapped place cell responses. This suggests that the orthogonalization of CA3 representations across environments can be attributed to changes at the level of the MEC (Leutgeb and Leutgeb 2007). What remains to be tested is whether global remapping can be observed in CA3 in the absence of such global remapping in the MEC, which would suggest that perhaps LEC, or perhaps DG, participate in hippocampal global remapping.

Rate remapping, then, might involve a separate, non grid-cell source, since consistent shifts or zero shifts in the grid input will produce no differential modulation of place fields under the model where place fields are driven only by grid cells. There are two likely candidate sources for rate remapping: the DG and the LEC. The DG is sensitive to subtle changes in environmental context, as revealed by the morph-box paradigm (Leutgeb et al. 2007), and several studies have shown that animals with DG lesions are impaired when making place discriminations (Gilbert et al. 2001; Goodrich-Hunsaker et al. 2008; Morris et al. 2012; Kesner 2013) and context discriminations (Lee et al. 2004b; McHugh et al. 2007; Tronel et al. 2012; Kheirbek et al. 2012; Nakashiba et al. 2012). For example, in a fear conditioning paradigm, animals with DG lesions failed to distinguish between ambiguous environments (one box in which they were fear conditioned and a second similar

but unfamiliar box that differs from the first only in some nonspatial cue, like color) (McHugh et al. 2007). At the same time, the DG is not required for distinguishing between unambiguously different environments (McHugh et al. 2007) and in some circumstances does not appear to participate in global remapping (Leutgeb et al. 2007). These findings point to a role for DG in discriminating between subtle differences in environment context based on external sensory cues, through some form of pattern separation, and support the idea that DG might provide the drive for rate remapping in response to environmental changes that do not invoke global remapping (Treves et al. 2008). The LEC is also likely involved in rate remapping, as a recent study has shown that lesioning the LEC impairs the expression of rate remapping in CA3, even though spatial tuning remains intact (Lu et al. 2013).

To summarize, it is possible that parahippocampal remapping (grid field shifts and rotations and head direction rotations) elicits the near-orthogonal global remappings in hippocampus, whereas rate remapping is due to an altogether different mechanism. This mechanism could be intra-hippocampal (and DG-dependent) in origin (Leutgeb et al. 2006; Leutgeb and Leutgeb 2007), or alternatively, might depend on external sensory cues arriving via the LEC (Deshmukh and Knierim 2011).

What is the computational role of these different types of remapping? Clearly, if the brain uses cognitive maps of space to navigate, a new or sufficiently different environment calls for the construction of a new map. On the other hand, a given map should be capable of modification by smaller or incremental changes to a familiar environment, without losing the information already built into the present map or being rewritten by an entirely new map for the environment. Rate and global remapping may be the hippocampal solutions for these two scenarios, respectively. Important unanswered questions involve learning what determines the threshold of similarity before rate remapping gives way to global remapping, how flexible or adaptable are such thresholds as a function of animal experience in stable and unstable worlds, which computations and areas are responsible for setting the threshold, and what are the mechanisms by which global and rate remapping trigger map plasticity and learning.

14.4.7 Differential Roles of the Hippocampal Subfields in Localization and Mapping

The data recounted thus far indicate that the hippocampus receives both allothetic and idiothetic cues and is in a position to encode associations between the two to generate a map-like representation. These data support the cognitive map hypothesis of O'Keefe and Nadel (1978). But what differentiates the different hippocampal subfields, and where might the spatial map reside?

It has long been proposed that the DG performs pattern separation to allow, as discussed above, the disambiguation of relatively similar environments based on subtle differences (McNaughton and Morris 1987; Treves and Rolls 1992; O'Reilly and McClelland 1994; Kesner 2007). This hypothesis is supported by

electrophysiological work (Leutgeb et al. 2007; Marrone et al. 2011; Satvat et al. 2011) and behavioral studies (McHugh et al. 2007; Tronel et al. 2012; Kheirbek et al. 2012; Nakashiba et al. 2012; Gilbert et al. 2001; Creer et al. 2010; Clelland et al. 2009; Sahay et al. 2011; Goodrich-Hunsaker et al. 2008; Morris et al. 2012; Kesner 2013; Tronel et al. 2012; Lee et al. 2004b). A number of developmental, physiological, and anatomical factors, including neurogenesis (Nakashiba et al. 2012; Piatti et al. 2013), sparse firing (Barnes et al. 1990; Jung and McNaughton 1993; Chawla et al. 2005; Neunuebel and Knierim 2012), large efficacious mossy terminals (McNaughton and Morris 1987; Henze et al. 2002), and the anatomical divergence of inputs from EC onto DG (Amaral et al. 2007), are likely to play a mechanistic role in the pattern separation functionality of this layer, possibly for the formation of independent (if not completely separated) representations of relatively similar places and environments [see recent review articles Aimone et al. (2011), Yassa and Stark (2011), Schmidt et al. (2012), Piatti et al. (2013), Kesner (2013)].

The functional advantage of such pattern separation is that downstream areas, in particular CA3, can easily recognize these places as distinct in forming a map and in forming episodic memories involving these places. Thus, DG may be viewed as a preprocessor of external sensory inputs that are used downstream in map building.

Computational models of the spatial circuit (some of which are described in the following section) suggest that the overall spatial map resides in either CA3, CA1, or both.

According to a number of studies that involve simultaneous recordings in both areas (Lee et al. 2004a; Leutgeb et al. 2004, 2006), CA3 can respond rapidly to environmental changes by exhibiting immediate (global and rate) remapping, in contrast to CA1, whose responses tend to often remain, at least initially, relatively stable and independent of such contextual changes. These findings are consistent with earlier studies that showed a lagging response in CA1 to environmental changes (Bostock et al. 1991; Lever et al. 2002), as well as behavioral studies showing that NMDARs in CA3, and not CA1, are necessary for rapid memory acquisition (Lee and Kesner 2002; Nakazawa et al. 2003). In addition to these differences in the time course of their responses to environmental change, CA3 and CA1 exhibit differences in their spatial representations: representations across environments in CA3 are more orthogonalized than those in CA1 (Vazdarjanova and Guzowski 2004; Leutgeb et al. 2004; Colgin et al. 2010). Moreover, CA3 representations tend to shift coherently when proximal and distal cues are put into conflict, in contrast to CA1, which shows more variable changes (Lee et al. 2004b).

CA3 and CA1 also differ in their internal anatomy and anatomical inputs: CA3 receives overlapping projections from LEC and MEC, while in CA1 these projections are well separated (Witter et al. 2006). Since LEC and MEC are believed to code for complementary aspects of the world [object vs. place; external sensory information vs. internal sensory information; non-self vs. self (Knierim et al. (2006), Lisman (2007)], this suggests an associative role for CA3, in this case binding together different kinds of cues to build episodic or conjunctive representations of place, context, reward contingency, etc. This is consistent with

the primate literature on the role of hippocampus in forming associative and episodic memories (Eichenbaum and Lipton 2008; Buzsáki and Moser 2013). As variously noted, this associative role is consistent with the extensive recurrent excitatory collaterals in CA3 (Marr 1971; Hopfield 1982; Lansner 2009). A map of an environment is commonly understood to mean a representation that encodes relationships between pairs of locations and the relationships between landmarks in the environment and their locations. By this definition and based on the associational role of CA3, it's likely that some version of a map of space resides in CA3. The map could in principle either encode detailed metric (distance) and geometric (angle) information relating different locations or encoding more qualitative topological information that preserves relative distances and other topological features (Muller et al. 1996; Balakrishnan et al. 1999). Recent mathematical analysis of the CA3 code suggests the latter, that the CA3 map appears to be more topological than geometric and metric (Dabaghian et al. 2012).

A large fraction of the lateral connections in CA3 are directed rather than reciprocal (Muller et al. 1996; Buzsáki 2006), suggesting the possibility that CA3 is further involved in the associative learning of location sequences between place cells. These place cell sequences would correspond to routes or trajectories between locations in the external environment. Indeed, studies report the existence of various sequence-playback events, including replay and preplay of place field sequences when animals are quiescent, sleeping, or about to start running down a path (Foster and Wilson 2006; Johnson and Redish 2007; Diba and Buzsáki 2007; Davidson et al. 2009; Karlsson and Frank 2009; Dragoi and Tonegawa 2011). The function of such playback events may be related to route memorization, recall, and planning (Hasselmo 2012).

O'Keefe and Nadel hypothesized that CA1 functions as a mismatch detector, or comparator, comparing predictions derived from the map with direct observations (O'Keefe and Nadal 1978). Mismatch detection is a form of novelty detection, and there is some empirical support for this hypothesis. CA1, but not CA3 or DG, showed marked increases in expression of the immediate early gene Fos, a marker for recent neural activity and plasticity, after animals were exposed to environmental novelty (VanElzakker et al. 2008). In addition, CA1 cells appear to primarily respond to combinations of input from CA3 and EC, not separately: only when inputs from CA3 and EC arrive concurrently at the proximal and distal portions of a CA1 pyramidal cell dendrite, respectively, does a dendritic plateau potential, necessary for burst firing and plasticity, triggered (Takahashi and Magee 2009). In the comparator view, CA1 is comparing the learned associations or predictions from CA3 with the sensory cue-driven outputs of EC to decide whether to fire. On the other hand, with inputs from MEC and LEC terminating on different cells of CA1 (Witter et al. 2006), it is unclear whether and how the MEC and LEC inputs may be combined and integrated within CA1.

Thus, spatial computation within the hippocampus might function as follows: In a familiar environment, sensory sensory cues, through the perforant path, retrieve a learned topological map in CA3 that contains relative spatial information about different locations, together with "handles" to other variables like context, salience,

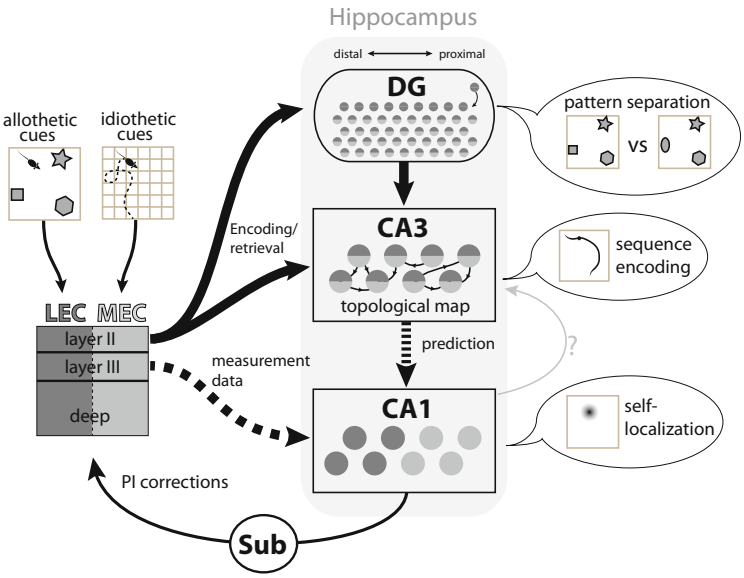

Fig. 14.3 Self-localization and mapping in the hippocampal circuit. Spatial representations and computations in the hippocampal circuit: External sensory information and idiothetic cues are relayed to the hippocampus through the LEC and MEC, respectively. These areas convey information about location given the sensory data. The perforant path, via layer II of the EC, projects to both DG and CA3, where allothetic and idiothetic cues from LEC and MEC, respectively, are mixed (indicated by the *shading* of the cells) and used, together with the internal recurrent connectivity of CA3, which encodes a topological map of the environment, to generate a prediction of the animal's current location. For self-localization, the prediction from CA3 is compared in CA1 against the direct sensory input conveyed from EC. Output from CA1 may be used to correct the PI in the MEC via the subiculum (Sub) or to alter the map in CA3 (*gray arrow with question-mark*, where the question mark highlights the lack of a direct connection from CA1 back to CA3), possibly through EC

and reward contingencies. This map may be compressed in the sense that it lacks geometric and metric information about the environment (angles and distance between locations and landmarks) (Dabaghian et al. 2012). This retrieved map generates predictions about location based on learned knowledge of commonly taken past routes and relative locations, which may then be compared, may then be compared in CA1 against the sensory-based inputs arriving from the EC (Hasselmo and Wyble 1997), to perform self-localization and possibly influence, via feedback, the map in CA3 (Sik et al. 1994), Fig. 14.3. The role of CA1 in this view is as a user of the spatial map to perform localization during navigation. Finally, the more mysterious of the hippocampal subfields, the subiculum, contains cells of diverse spatial tuning, including place cells (Barnes et al. 1990; Sharp and Green 1994), with some cells whose field locations appear to be invariant to environmental context (Sharp 2006; Kim et al. 2012). From a computational point of view, many important functions, including the computation and incorporation of metric

information into navigation calculations (for instance as needed in homing and map building), have yet to be assigned neural loci, some of which may be performed by the subiculum.

In the following sections, we explore computational models that seek to explain how the different areas combine into an entorhinal–hippocampal circuit that is capable of solving the navigational tasks of localization and mapping.

14.5 Computational Models of the Cortical-Hippocampal Circuit for Spatial Navigation

Empirical findings do not yet provide a complete answer for how the components of the brain's spatial navigation circuit work together to perform the computations necessary for localization and mapping. In this section we review three computational models from amongst a number of such models that incorporate, to greater or lesser extent, the neurophysiological findings on codes for space in the brain to obtain a functioning circuit for localization and mapping. These models help drive a better understanding of how the circuit might work, while highlighting the gaps in our knowledge.

A notable early model that incorporated both allothetic and idiothetic cues, and identified the brain areas likely to be involved in map building and self-localization, was presented in Redish and Touretzky (1998). Redish and Touretzky reasoned that the path integrator (PI) resides outside the hippocampus (Touretzky and Redish 1996). In Redish and Touretzky (1998), which forms one of a series of models involving both allothetic and idiothetic drive to place cells (Wan et al. 1993; Touretzky and Redish 1996; Redish and Touretzky 1997), a spatial map is constructed in a composite CA1/CA3 network. Local view and PI inputs are associated at the level of the EC layer, which then projects to CA1/CA3, Fig. 14.4a (see caption for details of model). The CA1/CA3 network is endowed with recurrent connectivity and learns a topological representation of the environment through the formation, by associative plasticity, of lateral connections between pairs of place cells with nearby field centers. Learning takes place under idealized circumstances, in which there is no ambiguity in the visual input, and the PI is error-free. After map formation, the system is capable of self-localization with noisy cues (including noise in the PI): the topological map arrives at a single estimate of location from ambiguous and possibly conflicting sensory cues (both PI cues and visual cues) through winner-take-all (WTA) dynamics in the CA1/CA3 network. The field center of the winner place cells represents a guess of the animal's location, which can be used to reset the PI. The neural dynamics of this model are relatively realistic, incorporating rate-based neurons with biophysical time constants that support attractor dynamics in the PI, the local view network, and CA1/CA3. Associations between the allothetic and idiothetic (PI) inputs are formed in a high-level sensory area that is distinct from the CA1/CA3 network, but it is not entirely clear if performance would be hurt by shifting these associations to the CA1/CA3 network, as would seem more consistent with a modern understanding of

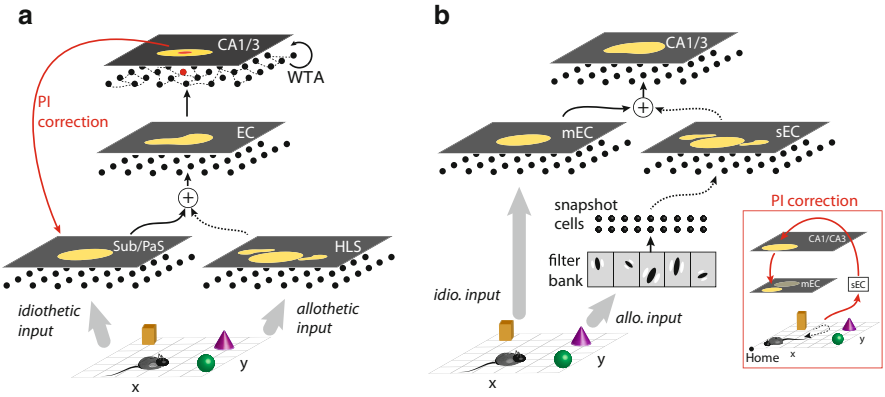

Fig. 14.4 Hippocampal circuit models. (**a**) Model of (Redish and Touretzky 1998): Sub/PaS (subiculum/parasubiculum) and HLS (high-level sensory areas), respectively, represent path integration-based (unimodal bump on *gray sheet*; in this and other panels, neurons are arranged topographically according to place preference) and local view-based location estimates (the view-based estimate may be unimodal or multimodal, depending on the ambiguity of the visual cues). These regions project to EC. Sub/PaS projections to EC are fixed (*solid line*), whereas HLS projections to EC are learned (*dotted line*). This enables a mapping of the HLS representation into PI coordinates so that inputs from the HLS and PI representation match. EC projects one-to-one to CA1/CA3. During exploration, coactive CA1/CA3 cells become recurrently coupled through Hebbian plasticity (*dotted lines*). The learned weights in CA1/CA3 are excitatory and, coupled with global inhibition, facilitate winner-take-all (WTA) dynamics (*red cell* is winning cell), which can be used to reset the PI (*red arrow*) through one-to-one projections back to Sub/PaS. (**b**) Model of (Arleo and Gerstner 2000): Allothetic input drives a collection of snapshot cells, each connected to a random assortment of visual filters. Snapshot cells project to superficial EC cells (sEC) through plastic synapses (*dotted line*), creating a sparse representation of visual location signatures in sEC. Idiothetic cues drive a unimodal bump in the medial EC (mEC). Together, mEC and sEC drive CA1/CA3. During learning, when too few CA1/CA3 cells are active at a location, a new cell is added to the sEC and CA1/CA3 layers, with random initial weights to and from the EC layers. The weights between the CA1/CA3 and EC layers undergo Hebbian plasticity. *Inset*, when the path integration error exceeds a certain threshold, the animal moves toward familiar territory (e.g., toward home) to recalibrate the PI. Once the territory is sufficiently familiar, the position estimate in CA1/CA3 resets the PI

the circuit. It is also unclear how the system would perform if the inputs during map learning were noisy and unreliable, as is the case in the real world. Indeed, the problems of localization and mapping become particularly difficult when both must be solved simultaneously in a noisy world: map development without accurate location coordinates and localization without an accurate map.

Arleo and Gerstner proposed a multilayer model (Arleo and Gerstner 2000), similar to that of Redish and Touretzky (Touretzky and Redish 1996), with a focus on how maps might be built over the course of exploration from noisy and ambiguous multimodal (allothetic and idiothetic) sensory cues. Here, the PI (a set of neurons with Gaussian tuning curves, whose firing is determined based on an integrated estimate of animal location, without a neural network model of the integration process; this area is referred to by the authors as mEC) is subject to

error accumulation. The visually derived (allothetic) input to the system is nonmetric, meaning that it does not directly encode animal position in allocentric coordinates, Fig. 14.4b. This allothetic sensory input is computed [in a network referred to as the superficial EC (sEC)] from snapshot cells, which encode ego-centric pictures of the world. Snapshot cell firing rates are determined by the sum of the projections of the visual input scene onto a select group of visual filters. Unlike previous models, this model does away with the need for assuming explicit landmark identification from visual inputs, because the snapshot cells use simple linear filters to generate visual input-determined fingerprints for different locations.

A downstream layer, the CA1/CA3 network, receives input from sEC and mEC and constructs a map of the environment in the form of place cells that are activated by the combination of the external sensory cues (from sEC) and the corresponding PI inputs (from mEC), for each location. This is achieved by updating the sEC and mEC input strengths to active cells in the CA1/CA3 layer through Hebbian learning. New place cells are added when a location is sufficiently unfamiliar (i.e., when an insufficient number of the existing CA1/CA3 cells are activated). At any given time, the preferred locations of the active ensemble of CA1/CA3 cells, as driven by the mEC and sEC, are averaged to represent the animal's location in the environment. The PI, which accumulates error over time by design, passes its inconsistencies to the map being learned, if uncorrected. The model mitigates the likelihood of any resulting discontinues in the map by assuming that the trajectory during map learning in unfamiliar environments consists of short exploratory excursions that loop back quickly to a familiar location, a hypothesis supported by behavioral evidence (Eilam and Golani 1989; Golani et al. 1993; Tchernichovski et al. 1998; Whishaw et al. 2006; Wallace et al. 2006). At familiar locations (determined by the number of active CA1/CA3 cells), the PI coordinates are reset, Fig. 14.4b, resulting in a PI whose error is effectively bounded.

A further development of this line of models, triggered by the discovery of grid cells (Hafting et al. 2005; Fiete et al. 2008), was provided by Sreenivasan and Fiete 2011. Theoretical considerations show that the grid cell code makes possible corrections of noise-driven errors resulting from the neural path integration process, even without the help of external landmarks (Sreenivasan and Fiete 2011). The readout layer for error-correction, equated with CA1, receives feedforward path-integrated inputs from the multiple-scaled grid cell networks and performs WTA dynamics. The winner place cell represents the estimated location, and the estimate thus formed is approximately a maximum-likelihood estimate of location given the noisy PI inputs of all spatial periods. The specific multi-period grid cell code ensures that the accuracy of this estimate of location is high, compared to if the PI inputs were coded simply as unimodal or more place cell-like representation [this is because of the specific, very perturbation-sensitive representation of different locations by the collective grid cell code; see Sreenivasan and Fiete (2011) for details]. Return projections from CA1 to grid cells (via intervening areas) would then reset the PI. The same return projections can correct the PI if the CA1 WTA dynamics were run based on visual or other allothetic inputs instead of grid cell inputs. A notable feature of the model is its separation of the roles of CA1 and CA3:

CA3 inputs are hypothesized to provide internal guesses or predictions to CA1 that constrain the set of possible locations from which CA1 selects the winner for the current time-step. CA3 predictions are based on the last estimate of location, combined with learned knowledge about physical boundaries in the environment, about commonly taken past routes in the environment, and about physical constraints of the world, such as the impossibility of spontaneously tunneling between remote locations. CA3's constraints on CA1 are enforced by a coincidence rule, so that EC feedforward input can only allow a CA1 place cell to win in the WTA dynamics if the cell also simultaneously receives a CA3 input signifying that the cell represents a possible location for the present time-step. Thus, CA3 inputs are "enablers" of CA1 firing. External sensory cues, when present, are assumed to enter CA3, thus contributing to the prediction of possible locations.

The three models described above have several features in common; a notable shared element is that they all view location estimation as a process of computing at each time a single best guess, then updating that single guess in the next time-step. A contrasting approach, as widely used in robotic SLAM (Simultaneous Localization and Mapping) systems (Meyer and Filliat 2003; Durrant-Whyte and Bailey 2006), is to always represent a probability distribution over possible locations and then update that distribution over time (Balakrishnan et al. 1999). The representation and updating of probabilities can allow for far more robust and accurate location estimation in a noisy world, than possible by updating and storing only a single best guess.

The models covered here represent a small sample of the dozens of hippocampal spatial models introduced over the last 3 decades. A notable omission from the computational perspective in this review are ratSLAM algorithms (Milford and Wyeth 2010), which meld insights from robotic SLAM with the physiology of the hippocampus. These algorithms achieve impressive performance in localization and mapping, but many complex computational steps are performed without plausible biological implementation. We have highlighted a particular set of models because they illustrate some of the problems involved in mapping and self-localization in a transparent way. What conclusions do we draw from these models, and what gaps remain?

One important insight from these models is that combining information from multiple sources—external landmark-based sensory cues, self-motion-based cues, and information about previously visited locations—can greatly enhance one's ability to self-localize, both in adding precision to one's estimate as well as functioning in a compensatory fashion when a subset of cues are absent. Simultaneously, the models highlight the incompleteness of our knowledge in how the spatial circuit performs this information fusion: they lack the rich dynamics that the hippocampus expresses across environments and under different behaviors and at best provide caricatures of the different components of the circuit and their roles in navigation.

Conclusions

Our knowledge of how the brain performs localization and mapping is rapidly growing, thanks in large part to the discovery of various cell types that represent different pieces of spatial information in decipherable ways. In concert, our understanding on a mechanistic level of the underlying neural circuits for each of these cell types is also rapidly expanding, and the evidence of this is the agreement between computational predictions about neural activity from circuit models of cells (e.g., HD cells and grid cells) and the data. However, there are at least three major areas that deserve more attention from the communities of theorists and experimentalists: one is to determine the role and mechanisms of cell types whose codes are not easy to decipher but which make up a large or possibly even majority fraction of principal cells in areas like the MEC (Zhang et al. 2013; Sargolini et al. 2006; Boccara et al. 2010; Mizuseki et al. 2009). Some of these cells have firing patterns that correlate with spatial location and associated spatial variables, and others do not. The second is to resolve the mechanisms through which temporal oscillation dynamics in the theta and gamma bands obtain and represent spatial information. It is clear that neural firing rates convey spatial information through the tuning curves of grid cells, HD cells, and place cells; it is also clear that oscillations strongly influence spike timing and convey spatial information (Brown et al. 1998; Mizuseki et al. 2009; Domnisoru et al. 2013; Schmidt-Hieber and Hausser 2013; Royer et al. 2012; Jadhav et al. 2012; Reifenstein et al. 2012). However, are these spike time representations fundamental to the spatial circuit, in the sense that computations within the circuit are based on detailed spike timing and coincidences, or are the spike time outputs merely readouts, translated into a phase code, of the rate-based dynamics of the network? The third is the question of how the different cell types and areas of the spatial circuit work together to combine incomplete data and predictions about spatial location in order to arrive at the high-quality spatial inference that is a hallmark of navigating animals. Related to this third question, we will in a separate review discuss spatial navigation in the robotics field of SLAM (Durrant-Whyte and Bailey 2006) as it may relate to the problems faced by the brain in solving the same challenges. We seek to understand how the brain solves the sequential probabilistic inference problems of navigation that have been identified as computationally difficult in robotic SLAM. In this way, we may gain insight into some of the more mysterious aspects of neural representation in the spatial circuit.

In this chapter we have focused on exploring how the brain's navigational circuit solves the problems of map building and self-localization in novel and familiar environments. Despite this focus, it bears emphasizing that the hippocampus does not likely exist solely or even primarily to serve this function. Even in seeking to learn the role of the hippocampal circuit in navigation, it might be profitable to take the bigger view of the hippocampus' general computational role (Buzsáki and Moser 2013), because its spatial role may be understood as a special case of the general functions it performs. Given its intrinsic organization

and anatomical relationship with the cortex, the hippocampus appears to organize, index, and enable access to the brain's contents for fast, efficient retrieval (Teyler and DiScenna 1986; McNaughton et al. 1996; Leutgeb and Leutgeb 2007; Teyler and Rudy 2007). In this view, the role of the hippocampus in the brain is akin to the role of a librarian (Buzsáki 2006): given vague or partial information about a book (or an event or thing), the librarian (hippocampus) can retrieve the full record and return a pointer to the book (or the full memory of the event or thing). This is consistent with the autoassociative pattern-completion role usually ascribed to CA3 (Grossberg 1969, 1971; Hopfield 1982; Amit 1994; McClelland and Rumelhart 1985; McNaughton and Morris 1987; Treves and Rolls 1992). To understand the elevation of the spatial variable, we might build on the analogy. The full record kept by the librarian includes a title, author names, a summary, a publication date, a publisher, number of copies in the library, and importantly, a call number. The call number is a privileged indexing variable: one author can have multiple books and multiple books may share a title, etc., but each book has a unique call number, and this number further specifies where on the shelves to find the book. On the shelves, books placed near each other address related topics, and thus the call number conveys semantic meaning that goes beyond simply providing a unique identifier. Similarly, whereas the full record of an episode consists of a place, a time, context, valence, reward contingency, and landmarks, the place or location index is privileged. It is an efficient locator of a memory, and, in general, records with similar spatial labels will tend to have important relationships to each other because of the spatiotemporal continuity of the world.

The spatial roles of the hippocampus in mapping and self-localization are perfectly consistent with the view of hippocampus as a general indexing machine for episodic memory (Teyler and DiScenna 1986): mapping, which involves the acquisition of information about external sensory landmarks and contexts and their association with internal sensory inputs at specific locations and with each other, is a spatial form of memory storage. Self-localization, which involves the recall of spatial associations and memories when some semblance of the sensory inputs is reencountered in noisy or ambiguous form, is a spatial form of retrieval.

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Adult Neurogenesis in the Dentate Gyrus 15

James B. Aimone, Wei Deng, and Fred H. Gage

Abstract

Adult neurogenesis is a unique form of structural plasticity in the brain. Localized specifically to the dentate gyrus region, new granule cells continue to integrate into the functioning circuit throughout life. Over the last 2 decades, neurogenesis has gone from a controversial side note within the hippocampal community to a process believed to potentially impact many aspects of learning and memory. Here, we will provide a basic overview of the neurogenesis process, both in terms of its anatomical and physiological development and its tight coupling to physical and cognitive behavior. We will then summarize the current hypotheses explaining how new neurons could affect dentate gyrus and hippocampal function, touching both on theoretical and computational studies. From this perspective, we will review results from behavioral studies in animal knockdowns of neurogenesis and the observations of new neuron behavior during behavioral tasks.

15.1 Introduction and Background

The dentate gyrus (DG) has long been an area of considerable interest to those investigating the hippocampus. Notably, while the DG has been a site of historic, classic observations—it was the site of the first observation of in vivo long-term potentiation (LTP) by Lomo and Bliss in the early 1970s (Bliss and Lomo 1973)—its function has long been shrouded in mystery (Treves et al. 2008). This latter

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comment is partly due to the fact that it is harder to record place fields in the DG compared to downstream CA3 and CA1 regions (Leutgeb et al. 2007; Neunuebel and Knierim 2012). However, a possibly more fundamental reason for the uncertainty surrounding the function of the DG is that it is one of the two sites of considerable neurogenesis in the adult mammalian brain, a fact that eluded the majority of neuroscientists until only recently.

In fact, the earliest observations of ongoing neurogenesis in the DG occurred not long after Lorente de No's comprehensive description of hippocampal anatomy. In the 1960s, Altman and colleagues extensively characterized the ongoing birth of new cells in the DG region post-development using tritiated thymidine, a radioactive tracer that selectively incorporates in mitotic cells (Altman 1962). However, because these early studies predated methods for identification of neuronal identity, the observation was not widely realized by the community. Neurogenesis progressed from ignored to controversial in the late 1970s and 1980s, when Michael Kaplan claimed that electron microscopy (EM) proved that the H^3-thymidine-labeled cells in the adult DG were indeed neurons. This claim met with substantial criticism in high-profile debates. Again, while EM was sufficient to identify cells as neurons, it was not well suited for co-labeling neuronal identity with the proliferation marker (Kaplan 2001).

In the 1990s, three aspects of neurogenesis brought it to the forefront. The first was the observation that proliferation levels of the early progenitor cells were regulated. Gould and McEwen demonstrated that stress levels negatively affected the numbers of proliferating cells in the DG (Gould et al. 1992). Subsequently, researchers showed that neurogenesis could be substantially increased by running (van Praag et al. 1999), enrichment (Kempermann et al. 1997), learning (Dobrossy et al. 2003; Gould et al. 1997), antidepressants (Malberg et al. 2000), and other behaviors. Likewise, neurogenesis could be decreased by aging (Kuhn et al. 1996), alcohol (Nixon and Crews 2002), and other interventions. At the same time, advances in immunohistological techniques for labeling dividing cells [namely bromodeoxyuridine (BrdU)] and neurons, such as NeuN, allowed the simultaneous co-labeling of neurons and proliferating cells, convincingly demonstrating that the dividing cells in the DG indeed became neurons (Kuhn et al. 1996). Finally, in 1998, Erikson, Gage, and colleagues identified new neurons in terminal cancer patients who were given BrdU for diagnostic purposes (Eriksson et al. 1998). This conclusive demonstration of neurogenesis in humans along with its regulation by behavior highlighted its relevance to the community and helped motivate research in the wider regenerative potential of neural stem cells.

15.2 Development of New Neurons

New neurons born in the DG undergo a maturation process that takes several months before they are essentially equivalent to mature neurons. Arising from a local stem cell population (Gage 2000), adult-born neurons initially are not directly connected at all to local circuitry. Nonetheless, they are apparently responsive to local neurotransmitters, likely through spillover from nearby synapses in the

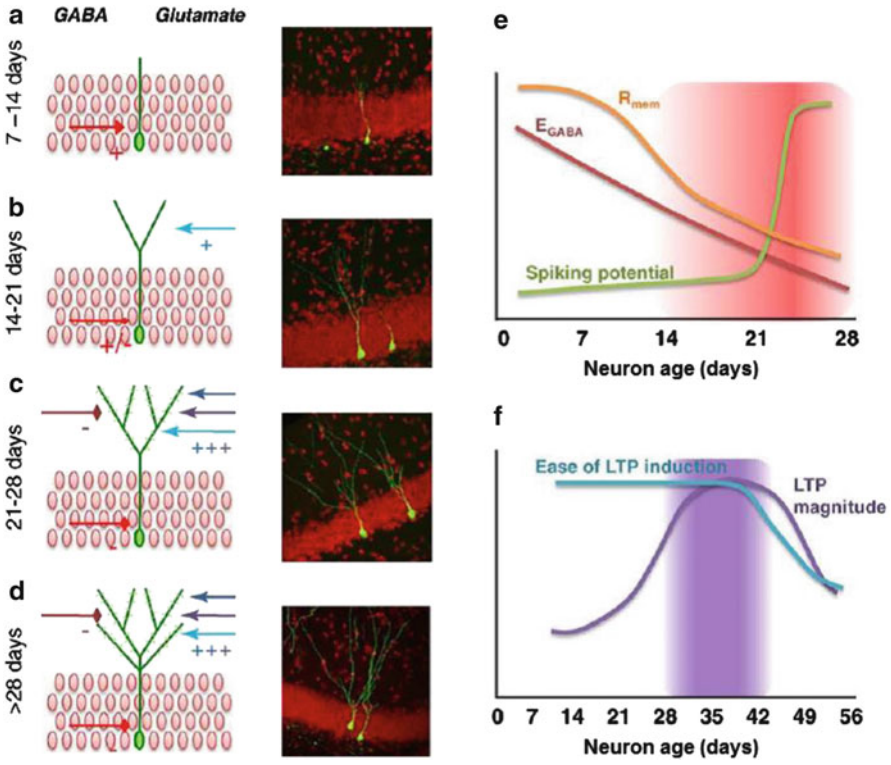

Fig. 15.1 Overview of new GC maturation. Young neurons progress from an initial progenitor state with minimal responsiveness to external inputs to fully connected granule cells (GCs) over the course of about 2 months. Over this time, the neurons progressively receive increasing inhibitory and excitatory synaptic inputs and exhibit a more robust dendritic arborization (**a**–**d**). Maturation is also accompanied by a distinct electrophysiology profile, with young neurons being more "excitable" at about 2–4 weeks of age (**e**), and a distinct plasticity profile, with young neurons being more easily driven to long-term potentiation (LTP) and exhibiting stronger LTP at different ages (**f**) [Adapted with permission from Aimone et al. (2010a)]

subgranular zone (SGZ). Parvalbumin basket cells, which release substantial GABA in the granule cell layer, are the local neuron population that is most likely to influence these early progenitors (Song et al. 2012). Initially, this indirect GABA response is important for directing stem cells towards a neuronal fate and early maturation. Several days post-fate commitment, these very young granule cells (GCs) begin to polarize their projections, sending their future dendrites towards the molecular layer and axons towards the hilus.

There are two major features of neuronal differentiation and maturation that must occur: the intrinsic development of neuronal physiology and the extrinsic development of synaptic connections (Fig. 15.1) (Aimone et al. 2010a). Importantly, in maturing adult-born GCs, these two processes take place simultaneously. The intrinsic physiology of progenitors is substantially different than their ultimate

neuron state. Maturing neurons progress from a very high-resistance, glia-like non-spiking physiology to an essentially normal GC in about 2 months. While spikes can be observed even within a few days after the last cell division (Esposito et al. 2005), the most pronounced development of the spiking capacity of young neurons occurs around 3 weeks of age, with new GCs becoming capable of firing more than one spike at 24 or 25 days of age (Mongiat et al. 2009). Some properties of young neurons, such as an increased resistance and lower capacitance, continue to drift towards mature levels gradually for several weeks after that.

This slow change in intrinsic activity is accompanied by the neurons' wiring into the network. Once neurons are a couple of weeks old, dendritic maturation begins in earnest, with spine formation first observed around 16 days of age and progressing fairly rapidly until approximately 28 days and older (Zhao et al. 2006). Over this time period, young neurons go from zero glutamatergic synaptic inputs to the more than 4,000 that are common on mature neurons. This process appears to include a competitive mechanism with existing synapses, though it is not clear how many new synapses arise de novo, or from existing synapses splitting, or through a truly competitive process (Toni et al. 2007). Not surprisingly, this rapid increase in synaptic growth is accompanied by increased synaptic plasticity, with young neurons being both easier to induce to long-term potentiation (LTP) and exhibiting higher levels of LTP (Schmidt-Hieber et al. 2004; Ge et al. 2007).

Notably, the formation of GABA inputs proceeds at a roughly similar rate (Laplagne et al. 2007; Li et al. 2012; Marin-Burgin et al. 2012; Overstreet Wadiche et al. 2005). While young neurons do experience GABA signaling through non-synaptic mechanisms, the first direct interneuron inputs appear at roughly 2–3 weeks of age (Li et al. 2012; Esposito et al. 2005), a time comparable to glutamatergic inputs. Several different local DG interneuron populations have been shown to affect young neurons, both through dendritic and somatic targeting (Markwardt et al. 2009, 2011). Of note, the mechanism by which these synapses form has not been well explored from a structural level. Indeed, the physical processes underlying GABAergic synapse formation may be quite different, as many of these synapses are not on spines but rather on the neurons' dendrites themselves, suggesting that a different form of synaptogenesis may be in play.

The axonal efferents of maturing GCs have proven more challenging to study than dendritic afferents, in part due to the need to not only look at the new neuron but at its target as well. GCs have substantially fewer axonal targets than inputs, making isolation of new neuron–new neuron downstream target pairs particularly challenging. Nonetheless, several studies have indicated that downstream synaptogenesis progresses similarly to that observed for new neuron dendrites. EM studies have indicated that new mossy terminals formed onto CA3 targets are likely relying on a competitive mechanism similar to that observed at the dendrites (Toni et al. 2008). Recent work using optogenetic techniques in which young neurons are photostimulated has likewise shown that the timing of the new neurons' influence on the CA3 is comparable to dendritic maturation (Gu et al. 2012). This similarity extends to plasticity as well, with young mossy terminals exhibiting stronger LTP than mature mossy terminals.

There are still important aspects of this process that remain unknown. In addition to the aforementioned mechanisms underlying the development of inhibitory inputs onto young neurons, it is unclear how other populations of GC targets are affected as these neurons mature. Mossy fibers are a unique type of projection, forming at least three distinct types of synapses on downstream targets. In addition to the mossy terminals on CA3 pyramidal cells and mossy cells, they form numerous smaller, en passant connections onto interneurons in both the hilus and CA3. Understanding how these less-characterized synapses form while neurons mature could be critical to determining the influence of young neurons on the broader hippocampal circuit, as they are likely critical for both feed-forward (to the CA3) and feedback (to the DG) inhibition.

15.3 The Context: The DG and the Hippocampus

It is likely not coincidental that neurogenesis occurs at the entry layer of the hippocampus. Although we now recognize that the hippocampus circuitry is considerably more complex than the classic "tri-synaptic loop" concept, the DG does generally lie upstream of the more heavily studied CA3 and CA1 regions. Due to its position at the forefront of the hippocampus, several functions have been proposed for the DG region. The first function is *conjunctive encoding* (O'Reilly and McClelland 1994). Conjunctive encoding is essentially the combination of multimodal inputs arising from different cortical sources. In some sense, conjunctive encoding is an anatomical inevitability; the same DG neurons receive inputs from lateral and medial entorhinal cortex (LEC and MEC, respectively). The LED predominantly receives inputs from the perirhinal cortex and, above that, the olfactory and temporal "object" visual streams; as a result, it is believed to represent the "what" information in the cortical inputs of the hippocampus (Hargreaves et al. 2005; Deshmukh and Knierim 2011) (see Deshmukh 2014). Complementing this process, the MEC receives inputs from the postrhinal cortex and the parietal "spatial" visual streams, representing the "where" information to the hippocampus in the form of grid cells (Hafting et al. 2005) (see Derdikman and Moser 2014). Individual GCs in the DG receive inputs from thousands of LEC and MEC neurons, suggesting that they are capable of representing a highly complex combination of spatial and object features simultaneously. Several studies have suggested that the DG's encoding can be thought of in this fashion (O'Reilly and McClelland 1994; Morris et al. 2013; Rolls and Kesner 2006).

The second proposed function of the DG, which has attracted considerable attention in recent years, is *pattern separation*. Pattern separation, as related to the DG, can be described as recoding cortical input information into a sparse, essentially orthogonal, representation (Treves and Rolls 1992; McNaughton and Morris 1987). This separation process enables highly similar cortical representations (i.e., very similar events) to be encoded in downstream regions of the hippocampus with little representational overlap, ultimately minimizing interference between memories. This function is based not only on the anatomy—there

are many more GCs than either upstream EC or downstream CA3 neurons—but also on the observed physiology of GCs. GCs in vivo are very quiet and are likely tonically inhibited by the substantial DG interneuron population (Jung and McNaughton 1993; Marin-Burgin et al. 2012; Li et al. 2013). Furthermore, the outputs of GCs, the mossy fibers, are quite sparse and very large. A single GC, if bursting, is capable of sufficiently depolarizing a downstream CA3 pyramidal neuron to spike threshold (Henze et al. 2002).

Behaviors consistent with both of these functions have been observed in rat DG lesion studies (Gilbert et al. 2001; Kesner 2007; Lee and Kesner 2004). Further, spatial pattern separation has been described in vivo (Leutgeb et al. 2007). It is possible for these two functions to be consistent with one another; the DG forms distinct sparse codes that represent both spatial and context features. However, it is also important to note that these two functions are at one level something most neural network layers do: recode combinations of different input neurons in distinct ways. How this separation is achieved related to the computation that is taking place and the nature of the DG's separation remains controversial (Treves et al. 2008). As mentioned above, the anatomy of the DG and slice physiology of GCs suggest an orthogonal population coding scheme. However, in vivo results indicate that different contexts are discriminated using rate coding (see Leutgeb and Leutgeb 2014). This distinction is further complicated by the presence of new neurons, as neither proposed function (conjunctive encoding or pattern separation) necessarily explains the presence of neurogenesis.

15.4 Theoretical Functions of Neurogenesis

As with other hippocampal processes, computational and theoretical studies have been conducted to explain the function of the ongoing addition of neurons to the DG. These proposed neurogenesis models have ranged from abstract to biologically detailed (Aimone and Gage 2011). Despite this variation in approach, the studies' conclusions have been remarkably consistent, particularly when addressing the role of new neurons in pattern separation. Although an effect of neurogenesis on separation has been demonstrated in different ways by the various models, the studies agree on the overall benefit of new neurons, with a few subtle, but potentially important, distinctions.

15.4.1 Pattern Separation in Models

The first models to study neurogenesis were simple feed-forward neural networks, with replacement of units after a period of learning. These studies were quite abstract and distinct from the DG biology; for instance, several relied on learning rules such as back-propagation (Deisseroth et al. 2004; Chambers and Conroy 2007; Chambers et al. 2004). However, the general observation of these studies was consistent: in well-trained, feed-forward systems, the replacement of highly

trained units with naïve units greatly facilitated the learning of novel information, albeit occasionally at the expense of already learned information. Wiskott and colleagues expanded on these studies by showing how neuronal addition in such a network could avoid the catastrophic interference that some networks experience due to overtraining (Appleby et al. 2011; Appleby and Wiskott 2009; Wiskott et al. 2006). Essentially, in these simple networks, new neurons would allow the network not to get stuck in a highly trained state, essentially allowing the learning of future information to be separated from past information.

Using a somewhat different approach, Becker and colleagues (Becker 2005; Becker et al. 2009) and Weisz and Argibay (2009, 2012) modeled neurogenesis in models of the full hippocampal loop (EC → DG → CA3 → CA1 → EC). This more anatomically constrained approach allowed the effects of neurogenesis on overall hippocampal memory function to be examined. Notably, as with the abstract studies, these models demonstrated that the replacement (Becker 2005) or addition (Weisz and Argibay 2009) of new neurons facilitated overall hippocampal performance by reducing the interference of old memories on the encoding of new memories.

15.4.2 Temporal Coding by New Neurons

Possibly the largest deviation from a simple "new neurons improve pattern separation" story is the potential impact of time. As described above, young neurons appear to have a substantially different physiology than mature neurons. The implications of the effects of the distinct behavior of immature neurons on DG function were first discussed in a couple of theoretical papers in which the potential function of temporal encoding was first described (Aimone et al. 2006; Becker and Wojtowicz 2007). Their basic hypothesis was that the encoding of events by the DG would utilize both young and mature neurons. Even if the mature neurons were manifesting pattern separation (essentially forming an orthogonal code), immature neurons, by virtue of their increased activity, would counter that by adding overlap, decreasing pattern separation. Importantly, this increased overlap would only exist if two events were encountered close in time. If events occurred far apart in time, the young neurons from the first event would have matured, and new young neurons would have taken their place. Because each event would activate different populations of young neurons, the representations of such events would be even more separated.

Subsequently, Aimone and colleagues modeled neurogenesis in substantially more detail than previous studies (Aimone et al. 2009). This model, which took into account the addition of new neurons into the DG gradually over a long period of time (notably, all GCs in the model were "born" naïve and matured to a series of changing contexts), was well suited to illustrate how the ever-changing population of young neurons would result in a limited set GCs available to encode novel information at proximal times (yielding overlapping representations) and distinct sets of GCs used to encode information at distinct times (yielding separated

representations). As a result, neurogenesis was capable of providing a temporal dimension to the pattern separation function of the DG.

While other studies have not directly modeled a continuous neurogenesis process over time, and thus could not explicitly investigate a temporal coding function, several other models have shown behaviors consistent with this function. Wiskott observed that the naïve new units added to his model caused learning to be preferentially directed to young neurons, a finding that would be consistent with the added similarity between multiple events encoded at that time (Wiskott et al. 2006). Similarly, Weisz and Argibay (2009) observed that young neurons preferentially were utilized in learning novel information in their full hippocampal model, noting that this effect would be consistent with the temporal coding hypothesis as well.

15.4.3 Memory Resolution and Other Theories

Although much of the work on neurogenesis function (both in terms of modeling and behavior) has focused on different aspects of the pattern separation hypothesis, it is nonetheless likely that young neurons are contributing something more substantial to the circuit (Fig. 15.2). The aforementioned role of the DG in conjunctive encoding has not been well explored in neurogenesis modeling studies, although to some extent conjunctive encoding is appealing given that new neurons could easily be responsible for increasing coding capacity. Along these lines, we have introduced a theory that suggests that mature neurons are capable of encoding familiar features whereas young neurons are best suited for ensuring that novel features can be encoded (Aimone et al. 2011). Specifically, the broad tuning of young neurons due to their reduced inhibition and more excitable physiology permits them to be activated by novel inputs, whereas the strong inhibition onto mature cells limits their activity solely to aspects of experiences on which they have been trained. Over time, the young neurons become less responsive, and the novel events they respond to will become the familiar events to which they are selective. This process allows the DG to continuously shape itself to be both optimized for encoding previously experienced events, while still being responsive to the unknown.

There are other perspectives that have been considered. The observation that maturing cells become less responsive has led to the hypothesis that they "retire" from the circuit (Alme et al. 2010), which could have several potential implications on the broader computational role of the DG (Aimone et al. 2010b; Lisman 2011). Another line of research proposes that neurogenesis provides the network a source of flexibility for synaptic dynamics (Butz et al. 2006). Finally, we have recently introduced a hypothesis regarding the possible interaction between neurogenesis and temporal oscillations of the neuronal population. Specifically, we predict that young neurons fire at different phases of theta than mature neurons, which could drastically affect how young neurons influence the rest of the hippocampus (Rangel et al. 2013).

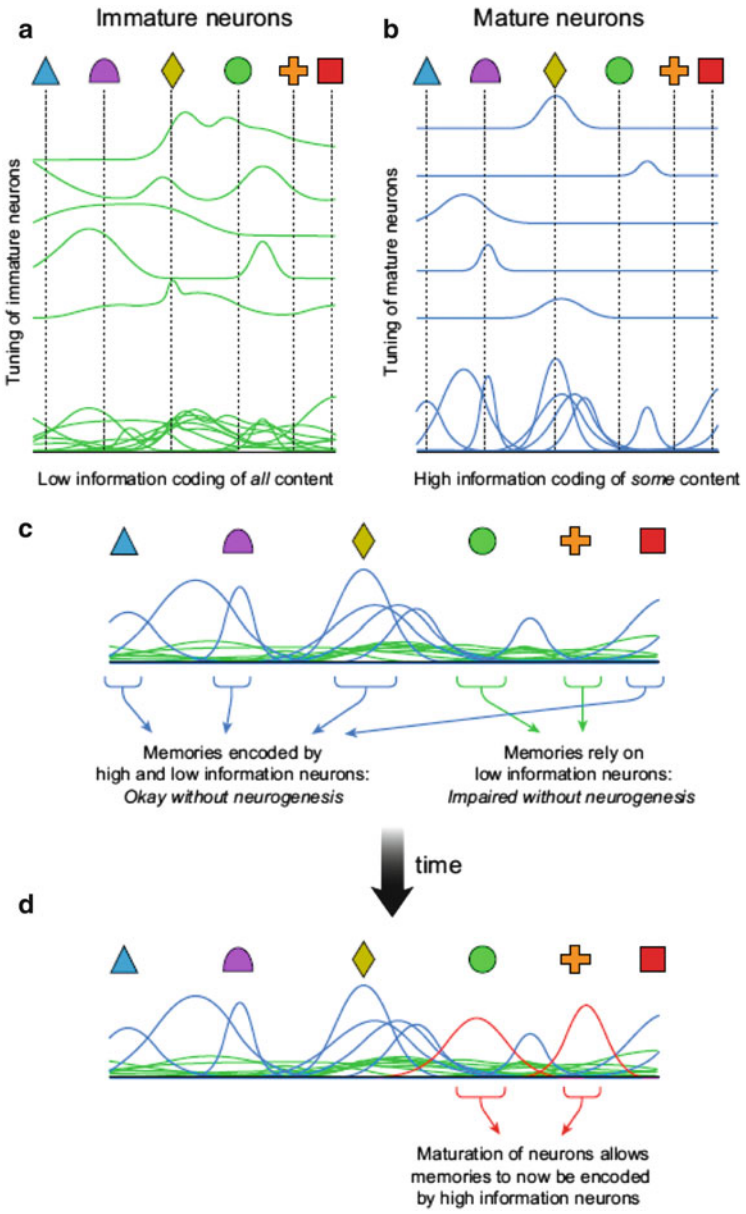

Fig. 15.2 Memory resolution hypothesis for neurogenesis function. One hypothesis for neurogenesis function is that young neurons provide a complementary coding scheme to mature neurons. (**a**) Young neurons respond to many features, both novel and familiar, forming a distributed code that ensures that all events get encoded into memory. As a result, individually young neurons have very low information content (i.e., explanatory power) on their own; however, as a population, they are

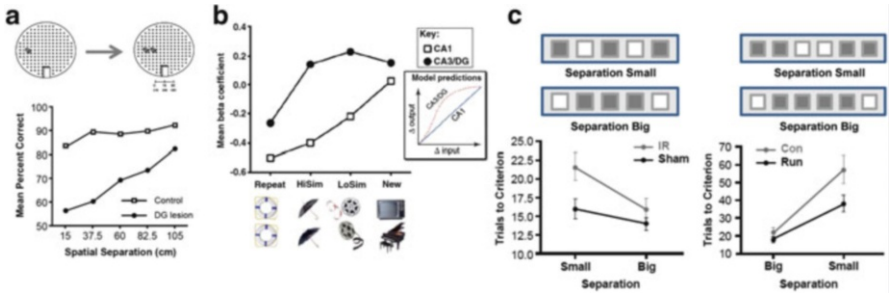

Fig. 15.3 Experimental studies of the dentate gyrus and neurogenesis in pattern separation. (**a**) The classical cheeseboard maze task revealed a role of DG in spatial discrimination [Adapted from Gilbert et al. (2001)]. (**b**) fMRI studies demonstrating that activities in DG/CA3 are particularly sensitive to small changes in stimuli [Adapted from Yassa and Stark (2011)]. (**c**) Touch screen tasks for pattern separation demonstrating the role of neurogenesis in spatial discrimination. *Left panel*: knockdown of neurogenesis results in impaired performance for distinguishing proximal spatial locations [Adapted from Clelland et al. (2009)]. *Right panel*: voluntary running, which increases neurogenesis and improves performance when spatial locations are close to each other [Adapted from Creer et al. (2010)]

15.5 Experimental Studies of the DG and Its Role in Pattern Separation

As mentioned above, a comprehensive understanding of the function of hippocampal neurogenesis can only be achieved in the context of its effect on overall DG function, such as pattern separation. To test the pattern separation function of the DG experimentally, a straightforward approach is to manipulate the DG and look for the behavioral consequences in a learning and memory task. Obtaining a behavioral readout for pattern separation can be very difficult, because the pattern separation process, which is modeled computationally at a sub-second time scale, can be confounded by many other neurological processes in behavioral tasks that occur at a much longer time scale, including those that can be in direct competition with pattern separation, such as pattern completion, a process of retrieving the complete representation from partial cues. A task for pattern separation should involve both interference and mnemonic components. A common strategy is to have the subject learn an event and subsequently test for the ability to distinguish this learned event from an interfering foil or lure. In an ideal task, the degree of interference induced by lures should be parametrically manipulated, and the

Fig. 15.2 (Continued) quite informative. (**b**) Mature neurons in turn are more tightly tuned with very high individual information content—responding specifically to familiar features, forming the sparse, nearly orthogonal, code classically associated with the DG and pattern separation. (**c–d**) Over time, the young neurons will mature into tight-tuning neurons themselves, specializing in those features they responded to when young [Adapted with permission from Aimone et al. (2011)]

subject's response across the extent of interference would be measured within the same individual. Such a design ensures that altered behavior can be attributed to pattern separation specifically but not to other processes in learning and memory.

15.5.1 Pattern Separation Tasks in Rodents

A pioneer study by Kesner and colleagues (Gilbert et al. 2001) provided the first experimental evidence for the pattern separation function of DG in a task that depends on working memory and involved systematical manipulated interference (Fig. 15.3a). In this task involving a cheeseboard maze, rats needed to distinguish a learned location from a foil location, both of which were marked by copies of the same object, in order to receive a reward. To modulate the interference systematically, five different distances between the target and foiled location were chosen, ranging from 15 to 105 cm. Gilbert et al. found that the behavioral measures in the DG-lesioned animals decreased as a function of the distance between the target and lure, with the most severe impairment detected when the lure was placed closest to the target. Several follow-up studies demonstrated that the dorsal DG was critical for separating spatial information or information related to the spatial attribute, whereas the ventral DG was involved in odor pattern separation (Goodrich-Hunsaker et al. 2008; Hunsaker and Kesner 2008; Kesner et al. 2011; Morris et al. 2012). More recently, it was found that DG-specific deletion of NR1, the essential subunit of the NMDA receptor, led to impaired performance in a contextual fear discrimination task, where mice were trained to distinguish two contexts over repeated trials with a foot shock delivered in one predetermined context. This finding implied that NMDA-mediated plasticity may also contribute to pattern separation (McHugh et al. 2007).

15.5.2 Physiological and Molecular Studies of Pattern Separation

Pattern separation is also studied by examining how GCs respond to changes in environmental inputs using either physiological or molecular and cellular techniques. In vivo physiological recording revealed that GCs were more sensitive to subtle environmental changes than CA3 neurons (Leutgeb et al. 2007). For example, small changes in the enclosure shape were sufficient to trigger an alteration in the firing patterns of GCs, especially in terms of their firing rates and place fields. However, the same ensemble of GCs responded in different environments, regardless of the extent of changes in inputs. It is proposed that the recorded GCs are those newborn GCs with enhanced excitability (Alme et al. 2010; Neunuebel and Knierim 2012).

GC activities in response to input changes have also been studied using the expressions of immediate early genes (IEGs) as markers for neuronal activities.

In situ hybridization shows that the transcription of IEGs is first detected in the nucleus within a few minutes after an environmental exposure and then can be found in both the nucleus and the cytoplasm, after about 30 min (Guzowski et al. 1999, 2005). Based on these observations, Barnes and colleagues (Chawla et al. 2005) exposed rats sequentially to two environments (either different or the same) with a 30-min interval. Analysis of the expression and cellular localization of Arc mRNA revealed that the GC populations active in response to the two exposures had less overlap if the two environments were different. Modeling the data with a computational model led to the postulation that distinct populations of GCs were selected to represent different inputs. More evidence for this hypothesis was provided by our recent work using TetTag mice to explicitly label GC populations in response to two sequential events that were separated by days. We revealed that memory recall did not preferentially reactivate the GC population involved in the encoding of the same memory. Furthermore, the GC ensemble that responded to the first event was suppressed to be reactivated in response to a subsequent different event, even if the latter event was only slightly different from the former one (Deng et al. 2013). As seen with different environmental inputs, different behavioral strategies also recruit different populations of GCs to solve the same task (Satvat et al. 2011).

15.5.3 Pattern Separation Studies in Humans

In humans, high-resolution fMRI is used to monitor brain activities during incidental memory encoding by presenting the subjects with pictures of novel items, repeated items, and similar items (i.e., lure) (Bakker et al. 2008). Activities consistent with a bias towards pattern separation were only observed in CA3/DG, where the response to lures is similar to that to novel items and is substantially higher than the response to repeat items (Fig. 15.3b) (Yassa and Stark 2011). Such a bias towards pattern separation in CA3/DG can be triggered by small changes in inputs when the lure is highly similar to the original item (Lacy et al. 2011). Aged individuals and patients with amnestic mild cognitive impairment (aMCI) have difficulty identifying the lures as "similar" and also have increased activity in CA3/DG, suggesting that elevated activity in these regions may impair pattern separation (Bakker et al. 2012; Stark et al. 2013; Yassa et al. 2011).

15.6 Functional Studies of Adult Hippocampal Neurogenesis

Early studies regarding the function of adult hippocampal neurogenesis demonstrated a correlation between neurogenesis and behavioral performance in hippocampus-dependent tasks (reviewed in Zhao et al. 2008). Conditions that increase neurogenesis, such as voluntary running and enriched environmental exposure, improve hippocampus-dependent learning, whereas learning and memory are impaired by factors that decrease neurogenesis, such as stress and aging.

More recently, a causal relationship has been established between neurogenesis and hippocampus-dependent learning through behavioral evaluations of rodents in which neurogenesis was ablated physically, chemically, or genetically (reviewed in Deng et al. 2010). However, how adult-born GCs contribute to the specific processes during learning and memory is less well understood. Recent research has begun to address this question in light of the theoretical predictions arising from computational studies.

15.6.1 Adult Hippocampal Neurogenesis and Pattern Separation

Because of the role of DG in pattern separation and the exclusive differentiation of newborn neurons in the hippocampus to GCs, one obvious hypothesis is that adult-born GCs play a critical role in pattern separation. To test this hypothesis, Bussey, Gage, and colleagues developed two behavioral tasks to test the animals' ability to discriminate two spatial locations in either an eight-arm maze or a touch screen apparatus (Clelland et al. 2009) (Fig. 15.3c). The mice with reduced levels of hippocampal neurogenesis had difficulty discriminating between two proximately located positions but performed as well as controls in distinguishing between two distally positioned locations. Conversely, mice that underwent voluntary running had increased hippocampal neurogenesis and displayed improved performance on the touch screen task only when the locations for discrimination were close to each other (Creer et al. 2010) (Fig. 15.3c). An increase in neurogenesis can also be achieved by blocking the apoptosis of newborn neurons, because considerable numbers of the newborn GCs undergo apoptosis before they integrate into the hippocampal circuits (reviewed by Ming and Song 2011). Genetic blockage of the apoptotic pathway in neural progenitors not only resulted in increased neurogenesis but also improved performance in the contextual fear discrimination task, suggesting the involvement of neurogenesis in separating contextual information (Sahay et al. 2011). The role of hippocampal neurogenesis in pattern separation is more obviously demonstrated in the experimental setting for retrograde effects. When DTR, a human receptor for diphtheria toxin (DT), is ectopically expressed in adult-born GCs, the DTR-expressing GCs can be ablated by DT administration (Saito et al. 2001; Arruda-Carvalho et al. 2011). After contextual fear conditioning training, ablation of neurogenesis by DT injections impaired discrimination of the training context from a similar context (Arruda-Carvalho et al. 2011). Similarly, post-training ablation of neurogenesis impaired the selected search of the target zone in a probe test after acquisition of the water maze task. All this experimental evidence points to a role for adult hippocampal neurogenesis in pattern separation.

The dynamic nature of neurogenesis makes it an ideal substrate for separating events across temporal domains. Using in vivo physiological recording, Rangel and colleagues have recently shown that global remapping occurs to a greater extent with regard to temporally separated events compared to events that happen at the same time and reduced neurogenesis results in less global remapping for the

temporally separated events (Rangel et al. 2014). These data provide experimental evidence for the temporal coding theory of neurogenesis.

15.6.2 Adult Neurogenesis in Memory Retrieval and Systems Consolidation

The role of adult hippocampal neurogenesis has also been examined in other memory processes, such as memory retrieval and systems consolidation. Ectopic expression of halo-rhodopsin in adult-born GCs causes these neurons to be silenced by photostimulation. Post-training photostimulation disrupts memory recall of both spatial information in a water maze task and contextual information in a contextual fear conditioning task, implying a role for adult-born GCs in memory retrieval (Gu et al. 2012). In humans, hippocampal damage only affects the recall of recent memories, not remote ones, suggesting that the hippocampus-dependent memory can be consolidated into neocortical structures over time (Bayley et al. 2003). This type of system consolidation has also been observed in contextual fear memory in rodents, where the hippocampus becomes dispensable for memory recall several weeks after initial memory acquisition (Anagnostaras et al. 1999). Reduction of hippocampal neurogenesis results in a prolonged dependency of contextual fear memory on the hippocampus; conversely, voluntary running shortens the hippocampal dependency of the memory (Kitamura et al. 2009). Because the dendritic spines of newborn GCs preferentially synapse on the existing perforant pathway synapses by forming multiple-synapse boutons (Toni et al. 2007), it is therefore postulated that newborn GCs, with their enhanced plasticity, compete with mature GCs to "drive" the system consolidation of memory traces.

15.6.3 Mature Vs. Immature Adult-Born GCs

Although the adult-born GCs compete with the existing mature GCs for synapse formation (Toni et al. 2007, 2008), it is not clear that the newly born GCs and their mature counterparts carry out the same function during learning and memory. In a recent study, Tonegawa and colleagues suggested that the adult-born young GCs are responsible for pattern separation whereas the old GCs are involved in pattern completion (Nakashiba et al. 2012). This conclusion is based on the theoretical assumption that pattern separation and pattern completion are the two ends of a unitary process in information processing and on two experimental findings: (1) - pre-learning blocking of the output from mature GCs facilitates the discrimination of two very similar contexts in the contextual fear discrimination task, and (2) post-learning blocking of the output from mature GCs impairs performance of quick memory recall with incomplete sets of cues. Regarding the latter observation, it is noticed that there was a long delay between the learning and recall phases in the design of the study. During this delay, the newborn GCs that were young at learning became mature, and their output was blocked at recall, making it impossible to

attribute the recall deficit solely to the mature GCs at learning. In fact, recent studies of the Ge and Frankland groups suggested that young GCs played a critical role in memory retrieval (Arruda-Carvalho et al. 2011; Gu et al. 2012).

It is worth restating that during the processes of maturation and integration, newborn GCs have special physiological properties, such as enhanced excitability and plasticity, compared to either the developmentally born or the fully matured adult-born counterparts (Ge et al. 2006; Esposito et al. 2005; Marin-Burgin et al. 2012; Li et al. 2012). These unique properties of the immature adult-born GCs raise the possibility of distinct functions for these newborn neurons in learning and memory. Using a genetic approach to transiently reduce the proliferation of the neural progenitors, the role of adult-born GCs at different maturation stages during hippocampus-dependent learning was studied by varying the time interval between proliferation reduction and behavioral testing (Deng et al. 2009). Mice with a reduction in the population of immature adult-born GCs displayed impaired performance in long-term memory retention and inhibitory learning, whereas those with a reduction in the mature adult-born GC population showed no behavioral effect (Deng et al. 2009). Furthermore, specifically silencing the adult-born GCs at 4 weeks of age, but not their 2-week- or 8-week-old counterparts, by halorhodopsin after task acquisition resulted in impaired memory recall (Gu et al. 2012). In addition, blocking the outputs from developmentally born and old adult-born (>6 week old) GCs did not affect the performance in contextual or spatial discrimination tasks, suggesting that immature adult-born GCs are sufficient for pattern separation (Nakashiba et al. 2012). Therefore, instead of replenishing/replacing damaged neurons in the DG to function as single coding units, the newborn GCs at their immature stages have distinct functions that cannot be replicated by their mature counterparts.

15.6.4 Modulation of Hippocampal Network Activities by Adult-Born GCs

Inhibitory inputs from local networks on GCs are thought to be critical for maintaining sparse activity in the DG. Local interneurons and mossy cells in the molecular layers and the hilus innervate GCs and can exert inhibition of GCs through both feed-forward and feedback mechanisms. Therefore, adult-born GCs may play a role in the maintenance of sparse activity of the DG by regulating the local inhibitory network. By ensuring the sparseness of the DG, the immature adult-born GCs indirectly affect pattern separation mediated by mature GCs. This hypothesis for the network function of adult-born GCs not only explains how a small population of newborn neurons can have a relatively large impact on DG function but is also supported by several lines of evidence from recent studies. First, long-term suppression of neurogenesis results in reduction of inhibitory tone in the DG, as indicated by decreased expression of vesicular GABA transporter (a molecule involved in mediating accumulation of GABA to synaptic vesicles) in the inner molecular layer and a reduced frequency of miniature inhibitory

postsynaptic currents (mIPSCs) in the DG (Singer et al. 2011). In vivo recording also reveals that ablation of neurogenesis leads to elevated spontaneous network activity and increased firing synchronization in the GCs (Lacefield et al. 2012). Along the same lines, hilar mossy cells can inhibit DG activity indirectly through local interneurons, in addition to the direct excitatory effect on GCs. Specific ablation of mossy cells induces GC hyperexcitability acutely and impairs performance in contextual discrimination tasks (Jinde et al. 2012). We have recently found that a reduction in the immature GC population leads to increased DG activity in response to perforant path stimulation (Deng et al., unpublished data). Finally, in humans, aMCI patients with a disability in pattern separation display excess activity in the DG/CA3 region, and treatment with levetiracetam, an antiepileptic medicine, not only reduced DG/CA3 activity but also improved behavioral performance in patients (Bakker et al. 2012).

15.7 Future Outlook

Although we have learned a considerable amount about neurogenesis over the past decade, there is still considerable uncertainty about the role of new neurons and the DG itself. From a functional perspective, there are several key areas where we expect new experimental approaches to impact our understanding. First, we need to be able to see what is going on in the functioning circuit. In vivo physiology of the DG is challenging in general, yet identifying young neurons in blind recordings is a daunting, but necessary, requirement. Optogenetic techniques, perhaps coupled with the transgenic approaches described above, represent a possible approach, but these are not without their limitations. Second, new behavioral tasks that more directly examine neurogenesis function in a hypothesis-driven manner, for use in both rodent knockdown studies and in neurogenesis-sensitive human populations, need to be designed. Finally, and perhaps most importantly, more effort needs to be placed on integrating the insights about neurogenesis into the broader understanding of hippocampal function. Not surprisingly, most of the studies described above focus on neurogenesis and the DG in relative isolation. However, as we learn more about what new neurons are doing and as our understanding of the DG becomes more sophisticated, it is going to be necessary to relate these observations to the well-studied processes in the rest of the hippocampus, and vice versa. This task will represent a challenge not just for the neurogenesis community but for the hippocampus community as a whole.

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Hippocampal Neurophysiology Across Species

16

Liora Las and Nachum Ulanovsky

Abstract

Comparative research in neuroscience can contribute to the understanding of general principles underlying brain function; it can also provide testable hypotheses that direct future research. This chapter provides a comparative review of the neurophysiology of the hippocampal formation across mammals. Over the last 40 years, the vast majority of findings on hippocampal electrophysiology were based on research from a single animal model—the rat. Yet, while rat hippocampal studies provided one of the richest datasets in systems neuroscience, the paradigms generated based on rat data were, until recently, largely untested in other mammals—and at least some of the ideas have been questioned by the few studies that were conducted in other species. Here we will summarize the data available from different mammalian species regarding hippocampal neurophysiology, focusing on similarities and differences across species—including functional implications. We will limit our discussion to two aspects: spatial cell types in the hippocampal formation and hippocampal oscillations. We will conclude by highlighting some of the major gaps in the available comparative data and by raising a "call to arms" to conduct further comparative research on the hippocampal formation.

16.1 Introduction

Different animal species have very different lifestyles, behaviors, and phylogenetic histories, and hence we may expect some differences in brain function. Yet, those brain functions that are core to all mammals should be conserved. Therefore, comparative studies could help identify the core properties of a given brain system. While sensory systems are indeed typically studied in many species, this is not the

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case in hippocampal research. Why is it that neurophysiological data on the hippocampus, collected over the last 40 years, were recorded almost exclusively in rats? In the 1960s, this was not the case: at that time, many species were used as animal models for hippocampal studies—including rabbits, dogs, cats, rats, and monkeys (Green and Arduini 1954; Winson 1972; O'Keefe and Nadel 1978; Robinson 1980). The shift to rats as the one central model occurred in the 1970s and 1980s, following the major finding of place cells by O'Keefe and Dostrovsky (1971)—and henceforth, most hippocampal research in animals focused on spatial cognition and spatial memory in the rat (O'Keefe 2007). Only in the 1990s, when the power of transgenic mice became available, some researchers started using the mouse. As we will review below, these studies demonstrated major similarities between rats and mice, but also some differences. Concurrently, research of hippocampal neurophysiology in monkeys has gradually increased in volume, including studies of place cells and additional types of cells such as "spatial-view cells" (Georges-François et al. 1999), which are not found in rats—indicating the need for further comparative research. In 2007, we introduced a new mammalian species to hippocampal research, the bat, which revealed many similarities but also substantial differences to the rat (Ulanovsky and Moss 2007)—leading to new functional insights, as we will argue below. Additional interspecies comparisons are needed, in order to help identify hippocampal functional properties that generalize across species, versus those that do not. Here we will compare hippocampal-formation neurophysiology across different mammalian species, including rats, mice, bats, and primates. We will concentrate on two aspects: the spatial cell types of the hippocampal formation (place cells, head-direction cells, grid cells, and border cells) and hippocampal oscillations (focusing on high-frequency ripples and on theta oscillations). Finally, we will suggest some future experiments to enhance our understanding of hippocampal function across species.

16.2 Functional Properties of Spatial Neurons in the Hippocampal Formation

16.2.1 Place Cells

Place cells, neurons that are activated when the animal passes through a specific region of the environment, were first discovered in the rat hippocampus by O'Keefe and Dostrovsky in 1971 (see example in Fig. 16.1a). Place cells were found in other species only >20 years later: in 1993 in monkeys (Ono et al. 1993—although this is controversial: see below), then in 1996 in mice (McHugh et al. 1996), in 2003 in humans (Ekstrom et al. 2003), in 2007 in bats (Ulanovsky and Moss 2007), and in 2009 in another rodent species—chinchillas (Muir et al. 2009; basic properties of place cells in chinchillas seem quite similar to rats, so we will not discuss them further below). There was also a preliminary report of place cells in rabbits (O'Keefe 1979), but this awaits further confirmation.

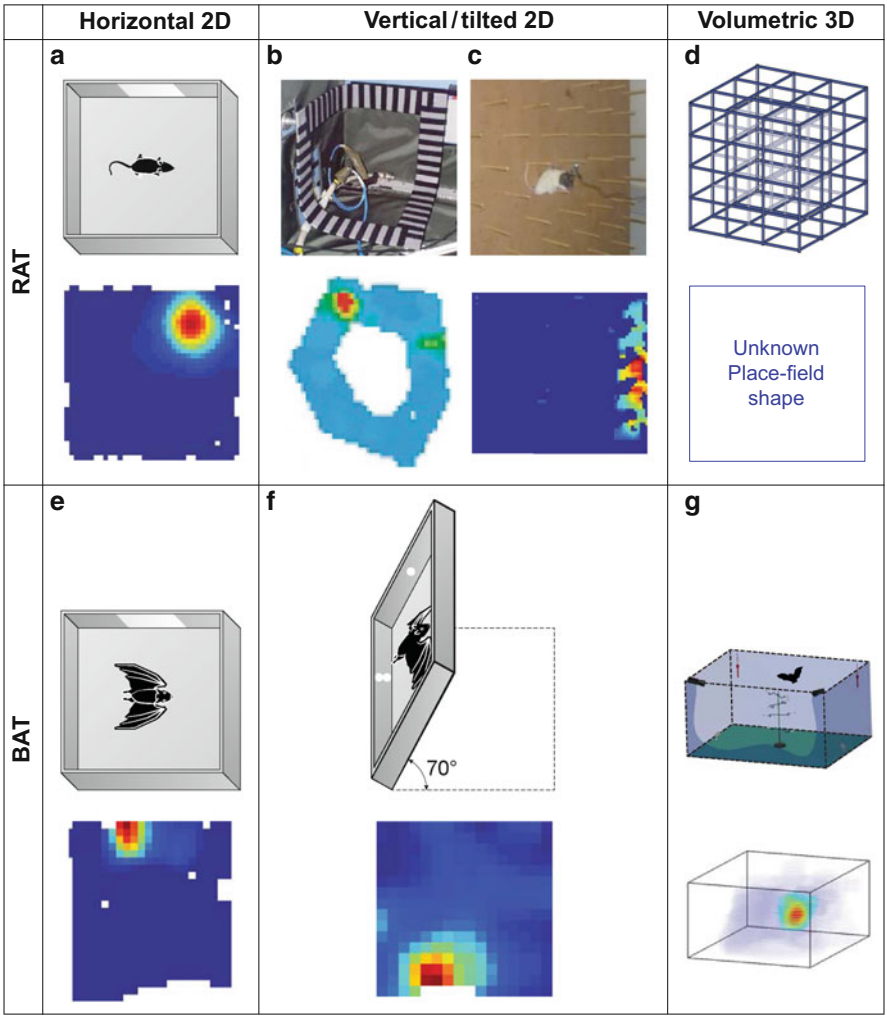

Fig. 16.1 Hippocampal place cells in rats and bats in 2D and 3D. (**a**–**d**) Rats. (**e**–**g**) Bats. In each case, the *top panel* shows the behavioral setup, and the *bottom panel* the place fields. (**a**) Rat running in a horizontal 2D arena [adapted with permission from Whitlock et al. (2008)]. (**b**, **c**) Rats climbing on vertical surfaces aboard a NASA space shuttle (**b**) or on a 90°-tilted pegboard platform (**c**) [adapted with permission from Knierim et al. (2000), and Hayman et al. (2011), respectively]. (**d**) Volumetric 3D place fields were not measured to date in rats (shape of 3D place fields in rats is unknown). (**e**) Bat crawling on a horizontal arena [from Yartsev et al. (2011)]. (**f**) Bat crawling on a nearly vertical arena, which was tilted by 70° [from Ulanovsky and Moss (2007)]. Note the isotropic shape of the place field. (**g**) Volumetric 3D place field from a freely flying bat, showing a nearly isotropic (spherical) place field [from Yartsev and Ulanovsky (2013)]. Peak firing rates in panels **a**, **b**, **c**, **e**, **f**, and **g** were 40, 2, 3.7, 4.7, 1.8, and 15 Hz, respectively

We will start by listing the similarities and will then discuss some of the major differences in place-cell properties across species. Table 16.1 compares the basic characteristics of place cells (as well as of other spatial cell types: see below) in the

Table 16.1 Functional properties of spatial cells in the hippocampal formation: cross-species comparison

Cell type	Property	Rats	Mice	Bats	Primates
Place cells	Existence	Yes[1]	Yes[2]	Yes[3]	Yes[4, 5] (but see text for controversy regarding place cells versus spatial-view cells)
					We will separate below three types of setups: • Place cells in freely moving monkeys • Place cells in humans and monkeys in virtual reality (VR) • Spatial-view cells in monkeys
	Brain areas where these cells were found to date	Hippocampus (CA1, CA3, DG, Subiculum)[6]	Hippocampus (CA1, CA3, DG, Subiculum)[2, 7–9]	Hippocampus (CA1, Subiculum)[3, 10–12]	Hippocampal formation[4, 5, 13]
	Complex-spike/regular firing	Complex-spike[1, 14]	Complex-spike[2, 15]	Complex-spike[3, 10, 11]	Complex-spike[13, 16]
	Fraction from all recorded complex-spike cells (CA1)	30–45 %[17]	~50 %[2]	30–40 %[3, 10, 11]	Place cells in free movement: ~33 %[4, 13]
					Place cells in VR: 32 % in monkeys[18] and 24 % in humans[5]
					Spatial-view cells: ~10 % in both monkeys[19, 20] and humans[5]

Peak firing rates	Range 0.2–35 Hz[21–23]	Range ~1–30 Hz[2, 24–26]	Crawling bats: range 0.2–16 Hz[3, 10, 11]	Place cells in free movement: range ~1.5–43 Hz[13]
			Flying bats: range 0.3–28 Hz[11]	Place cells in VR: *unclear*
				Spatial-view cells: ~3–44 Hz[19, 20]
Increase of firing rate with velocity	Yes[27]	*Unknown*	Yes[11]	*Unknown*
Typical number of fields for each neuron in 2D (open field ~1 m^2 arenas)	1–2[17, 21]	1–2[2, 25]	1–2[3, 10, 28]	Place cells in free movement: 1–3[4, 13, 29]
				Place cells in VR: *unclear*
				Spatial-view cells: 1–2[20]
Increase of place-field size and of the number of fields in larger 2D environments	Yes [30–32]	*Unknown*	Yes[11]	*Unknown*
Directionality of firing in 1D	Yes[27]	Yes[2]	Yes[12]	Place cells in free movement: *unknown*
				Place cells in VR: yes (Humans in VR[33])
				Spatial-view cells: *unknown*
Stability (correlation of firing-rate map across sessions, during open-field random foraging)	Range: $r = 0.6$–0.8[21–23, 34]	Range: $r = 0.1$–0.35 [25, 35, 36]	Average: $r = 0.74$ (big brown bat)[3]	*Unknown*
3D tuning	Some studies show elongated fields in the vertical z-dimension[37], while others seem to show more circular fields on a vertical wall[38]	*Unknown*	Nearly isotropic (spherical) 3D place fields in flying bats[11]; isotropic (circular) tuning on a tilted surface[3]	Variety of place-field shapes on vertical wall[13]: generally *not* elongated in the vertical dimension

(continued)

Table 16.1 (continued)

Cell type	Property	Rats	Mice	Bats	Primates
Head-direction cells	Existence	Yes[39]	Yes[40, 41]	Yes[10, 42]	Yes[43]
	Brain areas where these cells were found to date	Presubiculum[44–46]	Medial entorhinal cortex[40, 41]	Presubiculum[42]	Presubiculum[43]
		Medial entorhinal cortex[47]	Anterodorsal thalamus[52]	Medial entorhinal cortex[10]	
		Lateral mammillary nucleus[48]			
		Retrosplenial cortex[49]			
		Anterodorsal thalamus[50]			
		Lateral dorsal thalamus[51]			
		Additional areas[39]			
	Fraction from all recorded cells that exhibit directional firing	Presubiculum: 25–50 %[45, 53]	MEC: ~10 %[41]	Presubiculum: 30 %[42]	Presubiculum: 33 %[43]
		MEC: ~50 %[47, 53]		MEC: 10 %[10]	
	Peak firing rates	Presubiculum: peak rates are typically < 20 Hz[45, 53], though a few cells go up to ~100 Hz[45]	*Unclear*	Presubiculum: peak rates in crawling bat are < 12 Hz[42]	Presubiculum: range of peak rates: ~2–30 Hz[43]
		MEC: peak rates are typically < 20 Hz[47, 53, 54], though a few cells go up to ~45 Hz[53]			
	Tuning width in the horizontal plane (width at half-height)	Presubiculum: ~55–60°[45, 53]	*Unknown*	Presubiculum: 79.0° ± 3.9°[42]	Presubiculum: ~75°[43]
		MEC: ~65–70°[53]			
	3D tuning	Tuning to azimuth, and possibly weak selectivity to elevation[48]. Roll was never tested	*Unknown*	Tuning to all 3 Euler angles of head direction: azimuth, elevation, and roll[42]	*Unknown*

Grid cells	Existences	Yes[55]	Yes[40]	Yes[10]	Yes • Grid cells in VR in Humans[56] • "Spatial-view grid cells" in Monkeys[57]
	Brain areas where these cells were found to date	MEC[55] Presubiculum[53] Parasubiculum[53] Subiculum[58]	MEC[40]	MEC[10]	Posterior EC[57]
	Complex-spike/regular firing	MEC principal cells (not necessarily grid cells) are mostly regular firing[59]	*Unclear*	Bat grid cells are mostly regular firing (ref. 10, their Supplementary Fig. 2)	*Unclear*
	Fraction from all recorded cells in MEC	20–80 % (depending on layer and on size of arena)[53, 55]	~50 % (in layers II and III)[40]	36 % (average across all layers)[10]	12 % (average across all layers)[57]
	Peak firing rates	Range of peak rates: ~1–50 Hz[22, 23, 47, 55]	Range of peak rates: ~1–40 Hz[40, 41]	In crawling: less than 2 Hz[10] In flight: *unknown*	Range of peak rates: ~1–20 Hz[57]
	Increase of firing rate with velocity	Yes[47]	Yes[40]	Yes[10]	*Unknown*
	Stability across sessions	Mean: r = ~0.4–0.75[22, 23, 47, 55, 60]	Mean: $r = 0.7$[40]	*Unknown* (just one session was recorded)	*Unknown* (just one session was recorded; stability between first and second half of the session was very low, median $r = 0.24$[57])
	Co-localized grid cells in superficial layers share similar orientation and spacing but have different phases	Yes[55]	Yes[40]	Yes[10]	*Unknown*
	Grid spacing increases along the dorsoventral axis of MEC	Yes[55, 61]	Yes[40, 41]	Yes[10]	Yes[57]
	Conjunctive grid × head-direction cells	Yes (only in layers III–VI, not in layer II[47, 53])	Yes (in all layers[40, 41])	Yes[10]	*Unknown*

(continued)

Table 16.1 (continued)

Cell type	Property	Rats	Mice	Bats	Primates
Border cells	Existence	Yes Border cells in free movement [54, 62, 63]	Probably (not tested with insertion of a new border)[41]	Probably (not tested with insertion of a new border)[10]	Probably (not tested with insertion of new border[57]). These were not measured in free movement, but are "spatial-view border cells"[57]
	Brain areas where these cells were found to date	MEC[54, 63] Subiculum[62]	MEC[41]	MEC[10]	Posterior EC[57]
	Fraction from all cells in MEC	~10 %[54]	~8 %[41]	< 10 %[10]	~9 %[57]

This table focuses on data from freely moving animals and does not discuss in detail results obtained in virtual-reality (VR, e.g., refs. [64–66]) setups—except VR in primates (both humans and monkeys), where free-movement versus virtual-reality setups are mentioned separately

When listing properties of place cells, we focus on data from hippocampal area CA1—for which there are the most extensive datasets to compare across species

When listing properties of head-direction (HD) cells, we focus mostly on data from presubiculum and medial entorhinal cortex (MEC)—where the most extensive datasets exist across species

1. O'Keefe and Dostrovsky (1971), 2. McHugh et al. (1996), 3. Ulanovsky and Moss (2007), 4. Ono et al. (1993), 5. Ekstrom et al. (2003), 6. Andersen et al. (2007), 7. Hussaini et al. (2011), 8. Lee et al. (2009), 9. Chang and Huerta (2012), 10. Yartsev et al. (2011), 11. Yartsev and Ulanovsky (2013), 12. Geva-Sagiv et al. (2013), 13. Ludvig et al. (2004), 14. Fox and Ranck (1981), 15. Muller (1996), 16. Skaggs et al. (2007), 17. Wilson and McNaughton (1993), 18. Hori et al. (2005), 19. Rolls et al. (1997), 20. Georges-François et al. (1999), 21. Fyhn et al. (2004), 22. Wills et al. (2010), 23. Langston et al. (2010), 24. Rotenberg et al. (2000), 25. Muzzio et al. (2009b), 26. Rotenberg et al. (1996), 27. McNaughton et al. (1983), 28. Ulanovsky and Moss (2011), 29. Matsumura et al. (1999), 30. O'Keefe and Burgess (1996), 31. Kjelstrup et al. (2008), 32. Fenton et al. (2008), 33. Jacobs et al. (2010), 34. Van Cauter et al. (2008), 35. Kentros et al. (2004), 36. Muzzio et al. (2009a), 37. Hayman et al. (2011), 38. Knierim et al. (2000), 39. Taube (2007), 40. Fyhn et al. (2008), 41. Giocomo et al. (2011), 42. Finkelstein et al. (2012), 43. Robertson et al. (1999), 44. Ranck (1985), 45. Taube et al. (1990a), 46. Taube et al. (1990b), 47. Sargolini et al. (2006), 48. Stackman and Taube (1998), 49. Cho and Sharp (2001), 50. Taube (1995), 51. Mizumori and Williams (1993), 52. Yoder and Taube (2009), 53. Boccara et al. (2010), 54. Solstad et al. (2008), 55. Hafting et al. (2005), 56. Jacobs et al. (2013), 57. Killian et al. (2012), 58. Lever (2013), 59. Frank et al. (2001), 60. Derdikman et al. (2009), 61. Stensola et al. (2012), 62. Lever et al. (2009), 63. Savelli et al. (2008), 64. Harvey et al. (2009), 65. Domnisoru et al. (2013), 66. Schmidt-Hieber and Häusser (2013)

rat, mouse, bat, and primate. Note that there is relatively little comparative information even for the very basic properties of place cells (e.g., firing rate, place-field size, stability, directionality, and other properties; see Table 16.1). This problem is most noticeable in monkeys, where detailed characterization is mostly lacking, but also in mice, where most studies focused on molecular or genetic manipulations, rather than on basic characterization of place cells. That said, many properties of place cells seem similar in all these species (Table 16.1). In rats, place cells have been found in multiple hippocampal areas: CA1, CA3, subiculum, and dentate gyrus. In the other species, the hippocampus was not studied nearly as intensively as in rats, and place cells were mainly studied in CA1 (Table 16.1). We will therefore restrict our functional comparisons to the CA1 area only. In all animal models, the firing patterns of place cells are characterized by prevalence of complex-spike bursts, suggesting that these are pyramidal cells (Harvey et al. 2009; Epsztein et al. 2010). In all species and in all tested environments, between 30 and 50 % of the pyramidal cells in CA1 were found to be active during exploratory behavior; the majority of those are place cells. Further, in all species, the peak firing rates of place cells were found to range from <1 to 20–30 Hz. In rats and bats, the peak firing rates were found to be correlated with movement velocity (McNaughton et al. 1983; Yartsev and Ulanovsky 2013; see Table 16.1); such correlation awaits to be tested in mice and primates. In bats, place cells tend to exhibit low firing rates during crawling, when the movement speed is on average 3 or 4 cm/s (peak firing rates 0.2–16 Hz; Table 16.1)—but the firing rates go up dramatically during flight, when movement speed can reach 3 m/s and peak firing rates go up to 28 Hz (Table 16.1; Yartsev and Ulanovsky 2013).

Additional properties of place cells that are similar across rats and bats include the increase in place-field size and number of place fields in larger environments (this was demonstrated in rats and bats but awaits testing in mice and primates) and the directionality of place cell firing in one-dimensional (1D) tracks (Table 16.1).

One domain where there seems to be a real difference between rats and bats on the one hand, and mice on the other hand, is place-field stability. As originally reported in rats, the spatial representation of a familiar environment is stable: when place cells are recorded over several hours in the same environment, the fields occur at the same location, as quantified by correlating the firing-rate maps between consecutive recording sessions (Muller and Kubie 1987). The same is true for bats (Table 16.1; Ulanovsky and Moss 2007; Yartsev and Ulanovsky 2013): in both rats and bats, place fields are stable with a correlation of $r \sim 0.6$–0.8 between sessions (Table 16.1). In contrast, place fields in mice are unstable, with correlation coefficients of $r \sim 0.1$–0.35 (Table 16.1; Kentros et al. 2004; Muzzio et al. 2009b). What factors could explain the low stability in mice? The answer to this question is still unclear. In the original study that showed place-field instability in mice (Kentros et al. 2004) and in subsequent studies (Muzzio et al. 2009b), place fields were stabilized by increased attentional demands. However, even under the highest attentional load, mouse place fields exhibit a stability of $r \sim 0.3$–0.45—much less stable than in rats or bats. We speculate that a possible explanation for this discrepancy may be the effect of other senses besides vision. Olfactory cues, in

particular, may play a key role in place-field formation. In rats, when lights are turned off and olfactory cues are wiped from the floor, place fields become unstable (Save et al. 2000); yet, if olfactory cues are maintained when turning off the lights, place cells fire stably (Quirk et al. 1990; Save et al. 2000). Further support for the role of olfaction in controlling place fields was provided by a recent experiment in rats, where the rotation of a set of stable olfactory cues (odor ports) led to a corresponding rotation of place fields (Ozdogan and Morris 2012; see also Goodridge et al. 1998). While olfactory cues are likely to play an important role in rats and in bats, we hypothesize that they should be of particular importance for mice. Indeed, laboratory mice have poorer visual acuity than hooded laboratory rats or Egyptian fruit bats (Pettigrew et al. 1988; Heffner et al. 1999; Prusky et al. 2000) but have a very developed olfactory sense. Further, various pheromone effects are found strongly in mice but weakly in rats (such as the Bruce effect—see Cheal and Sprott 1971; Marashi and Rulicke 2012). Likewise, a number of studies demonstrated that olfactory bulbectomy is devastating to mouse species-typical behaviors, but much less so for rats: sexual, aggressive, maternal, and other pheromone-related behaviors are all strongly reduced in bulbectomized mice but are less affected in bulbectomized rats (Schultz and Tapp 1973). If we assume that hippocampal maps are formed according to a sensory hierarchy—namely, the most dominant senses in each species (which may be task-specific) will control the place fields—then this may have implications for place cells. Some notable cross-species sensory differences are in visual acuity, which is better in rats than it is in mice (Prusky et al. 2000) and in olfaction, which is more dominant in mice than in rats (see above); further, Egyptian fruit bats have highly developed senses of vision and echolocation (Heffner et al. 1999; Holland et al. 2005; Yovel et al. 2010). Consequently, according to our hypothesis, rats are expected to develop more visually based maps (even in the presence of olfactory cues); Egyptian fruit bats would develop maps based on a combination of vision + echolocation; whereas mice would develop a more olfactory-based map. This could have implications for place-field stability, because open-field arenas used in place-cell experiments are not controlled for olfactory cues—and because self-deposited odors are continuously formed by the animal when it runs across the arena and are therefore unstable across time, the place fields in mice will be less stable—because according to our hypothesis, mice pay particular attention to the (unstable) olfactory cues. To test this hypothesis, one would need to manipulate the different sensory cues in the different species. For example, stable visual cues should be used while cleaning carefully all odors; or conversely, stable olfactory cues (odor ports) should be used in the dark. Consistent with this hypothesis is the observation that place-field stability in mice increases when the mouse attention is directed primarily to visual cues (in experiments where reward was visually guided: Muzzio et al. 2009b). The effects of these and similar sensory manipulations should be carefully tested in mice, rats, and bats.

Another domain in which there might be possible differences between place cells across species is the representation of three-dimensional (3D) space. There were a few attempts to characterize the tuning of place cells in a variety of 3D environments, in several species: rats, bats, and monkeys. Notably, in all rat studies

that employed tilted or vertical platforms, the animals were in fact constrained to move on a particular 1D or 2D surface that was embedded in 3D space (Fig. 16.1b, c); thus the rats were not navigating in a *volumetric* 3D space (Knierim et al. 2000; Knierim and McNaughton 2001; Jeffery et al. 2006; Hayman et al. 2011). On tilted surfaces, place fields in rats are generally circular (Jeffery et al. 2006)—similar to place fields in horizontal 2D arenas (Wilson and McNaughton 1993; Henriksen et al. 2010). For vertical 2D surfaces, the few studies that were published were not always consistent with each other. One study in rats moving on a 3D surface aboard a NASA space shuttle has found a variety of place-field shapes, with fields in the 3D corners being rather isotropic (circular), while fields on linear portions of the track were somewhat elongated along the running direction—similarly to place fields on standard 1D horizontal tracks (McNaughton et al. 1983); importantly, there was no systematic elongation in any one absolute direction in space (Fig. 16.1b; Knierim et al. 2000). Another study, using a vertically oriented pegboard, reported a somewhat different result, with place fields being systematically elongated (non-isotropic) along the vertical z-dimension (Fig. 16.1c; Hayman et al. 2011; Jeffery et al. 2013). Discussion of the underlying sources of difference between these two studies in rats is beyond the scope of the current chapter; a detailed discussion can be found in Ulanovsky (2011) and Taube and Shinder (2013). In monkeys climbing on vertical walls, a variety of place-field shapes were found (Ludvig et al. 2004), generally being rather isotropic and not elongated in the vertical dimension. In bats, isotropic fields were found in 2D horizontal arenas (Fig. 16.1e; Yartsev et al. 2011) and on 2D surfaces tilted by 70° (Fig. 16.1f; Ulanovsky and Moss 2007, 2011)—as well as in a recent study of 3D place fields in flying bats, where >90 % of the 3D place fields were statistically not different from a sphere (Fig. 16.1g; Yartsev and Ulanovsky 2013). In summary, in most studies in rats, monkeys, and bats, in both 2D and 3D environments, hippocampal place fields tended to have a rather isotropic shape: mostly circular fields in 2D and spherical fields in 3D (with the exception of one study in rats that reported a systematic vertical elongation of place fields on vertical apparatus: Hayman et al. 2011). It would be interesting to test rats or monkeys in a truly volumetric 3D apparatus (e.g., the one depicted in Fig. 16.1d, top)—such an experiment was not conducted so far—and to see if isotropic volumetric 3D place fields will be found in these species, or not.

Finally, there have been several reports of spatial responses that are very different from classical rodent-like place cells; these reports came from pigeons, as well as from monkeys and humans. In pigeon hippocampus, only neurons with multi-peaked and unstable firing-fields were found so far (Bingman et al. 2003; Hough and Bingman 2004; Kahn et al. 2008)—very different than the well-circumscribed place fields in rodents or bats (Fig. 16.1). This difference could indicate that the "correct" regions of the pigeon hippocampus were not yet recorded from—which calls for additional experiments in pigeons. Alternatively, it could be that birds truly do not have mammalian-like place cells, perhaps due to their different evolutionary history, or to the different anatomical structure of their hippocampus. For further discussion of possible functional differences and similarities between the hippocampus of mammals, birds and reptiles, see Treves et al. (2008).

In monkeys, some studies have demonstrated the existence of "spatial-view cells," neurons that respond when the monkey looks at a certain point in the room (a "spatial-view" field), regardless of the animal's location (Rolls and O'Mara 1995; Georges-François et al. 1999; Rolls 1999, 2002). It was even suggested that monkey hippocampus might contain only spatial-view cells, and that the reported place cells in monkeys are in fact spatial-view cells that exhibit an apparent spatial selectivity (Georges-François et al. 1999). According to this explanation, the monkey exhibits behavioral correlations such that it tends to look at a certain spatial view more often when it is located within a certain region of the environment—which will result in an observed place field, which is not real (Georges-François et al. 1999). There has been a fair amount of controversy over this suggestion, and it remains unclear how many of the reported place cells in monkey hippocampus are true place cells and how many are spatial-view cells. The reason why it has been difficult to dissociate these possibilities is that this requires recording neural activity while measuring the position and eye direction (gaze) of freely moving monkeys, a difficult task. Experiments so far were done either without measuring eye-gaze (Ludvig et al. 2004), or in monkeys that were not totally free to move (Rolls and O'Mara 1995; Georges-François et al. 1999), or both (Ono et al. 1993; Nishijo et al. 1997; Matsumura et al. 1999). The need to resolve this conundrum is yet another reason why it would be crucial to measure neural activity, position, and eye-gaze in monkeys that are freely moving in 2D environments or in 3D environments such as the one depicted in Fig. 16.1d.

In humans, there are only a handful of reports on single-cell neuronal activity related to navigation. Place cells in the human medial temporal lobe were first reported by Ekstrom et al. (2003) (see Table 16.1) and then by Jacobs et al. (2010) and Miller et al. (2012). In addition, Ekstrom et al. (2003) reported the presence of cells responding to views of landmarks; however, unlike spatial-view cells in monkeys, not all of the reported view cells in humans were location-independent. Additionally, unlike in the monkey experiments, where the animals faced a variety of directions, in these experiments in humans the subjects could only turn at 90-degrees angles; this 90° angular resolution in Ekstrom et al. (2003) made it difficult to verify that these were true spatial-view cells. Recently there were also reports of "path cells," neurons that encode the current direction of traveling: these were found both in a circular virtual environment (Jacobs et al. 2010) and in more complicated virtual environments (Miller et al. 2012); see Table 16.1. Further studies are needed to corroborate the finding of view cells and path cells in humans and their relation to place cells—and to assess the relative contribution of these cell types to navigation.

16.2.2 Head-Direction Cells

Head-direction (HD) cells are neurons that are activated when the animal's head is oriented towards a specific absolute direction. Unlike place cells, the activity of HD cells is largely independent of the animal's position and can be elicited even if the

animal is being moved passively (Taube 2007). In addition, while place fields seem to "mature" along the rat's ontogeny, adultlike HD cells were found in very young rat pups, as early as 16 days old (Langston et al. 2010; Wills et al. 2010). HD cells were first discovered in the dorsal presubiculum of rats in 1983 by James Ranck (Ranck 1985), and their basic properties were described in 1990 (Taube et al. 1990a, b). Later on they were found in other species: in 1999 in monkeys (Robertson et al. 1999), then in 2008 in mice (Fyhn et al. 2008), and in 2011 in bats (Yartsev et al. 2011) (see also Winter and Taube 2014).

Similar to place cells, HD cells were mainly studied in rats, where they were identified in multiple subcortical areas, including the lateral mammillary nucleus, the striatum and some thalamic nuclei (lateral dorsal and anterodorsal nucleus), and several other areas (reviewed in Taube 2007). HD cells were also found in several cortical structures, including the retrosplenial cortex and medial entorhinal cortex (MEC), in addition to the cortical area where they were first found, the dorsal presubiculum (also called postsubiculum; Taube 2007). In other species, HD cells were studied mainly in the cortical structures: in mice, HD cells were studied to date only in MEC (Fyhn et al. 2008; Giocomo et al. 2011); in bats, HD cells were found both in presubiculum and in MEC (Yartsev et al. 2011; Finkelstein et al. 2012); and in monkeys, they were found so far only in the presubiculum (Robertson et al. 1999). Accordingly, we will limit our cross-species comparison of HD cells to presubiculum and MEC.

In rats, bats, and monkeys, the fraction of HD cells out of all cells in presubiculum is rather similar—between 25 and 50 % (there are no presubicular recordings in mice, so far); in contrast, the fraction of HD cells in MEC seems to be more variable, ranging from 10 % in mice and bats to 50 % in rats (Table 16.1). These differences in reported fraction of HD cells in MEC could reflect a true species difference, or it could be due to differences in data-sampling across MEC layers. Peak firing rates are $<$20 Hz in most HD cells in rat presubiculum and MEC (Table 16.1; Taube et al. 1990a; Sargolini et al. 2006; Boccara et al. 2010), with a few cells going up to 100 Hz (Taube et al. 1990a). Similar firing rates are found in monkeys. We note that the available information on HD cells in monkeys is based on a very small cell sample (Robertson et al. 1999), so the fraction of HD cells and their firing rates should be taken with caution.

Tuning widths of HD cells are quite similar between rats, bats, and monkeys (Table 16.1; no quantification is available for mice): in all three species, the width of the tuning curve at half of the peak firing rate is typically between 55° and 80° (Table 16.1). This width refers to the HD curve in the horizontal plane (tuning to the azimuthal angle, or yaw). Indeed, the large majority of HD cell studies were done in the horizontal plane, while HD cell representation in the other two planes was much less studied. In rats, the neuronal representation for elevation appears to be less prominent than for azimuth, while the neuronal representation for roll was never tested systematically (Stackman and Taube 1998; Calton and Taube 2005). In bats, in contrast, we recently found a substantial neuronal representation also for elevation and roll, in the presubiculum (Finkelstein et al. 2012). This interesting difference between HD cells in rats and bats could result from differences in

experimental methodology or in recorded areas (no experiments to date have tried to measure 3D HD tuning in the presubiculum of rats), or it could reflect true species differences in tuning of 3D HD, perhaps arising from differences in 3D locomotion or in 3D sensory inputs during ontogeny.

Finally, we note that, overall, very little comparative work has been done on HD cells—even less than on place cells. For example, while the contribution of visual and vestibular inputs for controlling HD tuning was studied extensively in the rat (Taube 2007), virtually nothing is known about sensory determinants of HD cells in the mouse, bat, or primate. Likewise, we do not know whether, in species other than the rat, HD cells show remapping, in the sense that they rotate their preferred direction between different environments. If they do, then an important question would be whether, similarly to rats, this remapping (rotation) is coherent across neurons (Taube 2007). These and many other questions await experimental testing.

16.2.3 Grid Cells

Grid cells—neurons showing spatially periodic selectivity, firing at the vertices of a hexagonal (or triangular) grid spanning the entire environment—were first discovered in MEC of rats in 2004/2005 by Moser, Moser and colleagues (Fyhn et al. 2004; Hafting et al. 2005). Each grid is characterized by a particular combination of spacing (distance between fields), orientation (angle relative to an external reference axis), and phase (displacement of the grid relative to an external reference point) (see also Derdikman and Moser 2014).

Since their discovery in rats, grid cells were also found in the MEC of freely moving mice (Fyhn et al. 2008) and bats (Yartsev et al. 2011), and very recently also in humans navigating in virtual reality (Jacobs et al. 2013). A study in head-fixed, stationary monkeys engaged in a visual-search task has reported grid-like neurons in the monkey MEC, which fired in relation to the gaze of the monkey within the reference frame of the vertical screen (Killian et al. 2012). These neurons in monkey MEC could be thought of as "spatial-view grid cells," because—just like the spatial-view cells in the monkey hippocampus (Georges-François et al. 1999; and see above) – they are tied to where the animal is looking at, rather than to its physical position in space. However, because the properties of these "spatial-view grid cells" in monkeys are in many ways similar to standard grid cells in rats, mice, and bats, we will discuss them all together.

In rats, mice, and bats, grid vertices were shown to be separated by ~60° angles, on average (Hafting et al. 2005; Fyhn et al. 2008; Yartsev et al. 2011—though we note that grid cells can be also quite elongated and deviate from 60°: see Brandon et al. 2011; Yartsev et al. 2011; Stensola et al. 2012). Grid cells in rats, mice, bats, and monkeys are organized in functional columns, in the sense that co-localized grid cells share similar spacing and orientation (Hafting et al. 2005; Fyhn et al. 2008; Yartsev et al. 2011; Killian et al. 2012). Further, in all these species, grid cells exhibit a large-scale functional organization, forming a gradient of the grid spacing along the dorsoventral axis of MEC (whereby cells in dorsal

MEC, close to the postrhinal border, show smaller spacing than cells located more ventrally; Table 16.1). In contrast to grid spacing and orientation, the grid phases of co-localized neurons are randomly shifted, spanning all possible phases (this was shown only in mice, rats, and bats). Recently, grid cells in rats were shown to be organized in discrete, steplike modules, rather than in a smooth gradient along the dorsoventral axis (Barry et al. 2007; Stensola et al. 2012); this arrangement awaits testing in other animal species. Almost none of the above properties of grid cells were tested in humans (Jacobs et al. 2013).

Another characteristic that is similar across rats, mice, and bats is the positive correlation between movement velocity and the firing rate of grid cells (Table 16.1). As in the case of place cells, this correlation might explain the low firing rates of MEC neurons in crawling bats, because they crawl rather slowly (Yartsev et al. 2011). Accordingly, the peak firing rate of grid cells is expected to be much higher in flying bats, similar to the case for 3D place cells (see above); this prediction remains to be tested.

Grid cells in rats and mice were found to be relatively stable across sessions, with correlations r ranging between 0.5 and 0.7. In monkeys and bats this stability was not tested, because just a single session was recorded (the within-session stability of grid cells in monkeys, when comparing the first and second half of the session, was reported to be very low: median $r \sim 0.24$; see Killian et al. 2012).

The MEC of rats, mice, and bats includes a set of diverse spatial cell types, including pure grid cells, HD cells, conjunctive grid × HD cells, and border cells (the latter will be described in the next section)—which seem to have similar properties across species (Table 16.1; bats—Yartsev et al. 2011; mice—Fyhn et al. 2008; Giocomo et al. 2011). Yet the laminar arrangement of these cell types is slightly different in mice as compared to rats and bats: whereas MEC layer II of rats and bats contains mainly pure grid cells, layer II in mice contains a mixture of a high fraction of HD cells and conjunctive grid × HD cells, in addition to pure grid cells (Fyhn et al. 2008; Yartsev et al. 2011); though we note that a larger cell sample needs to be collected in bats to verify this. This difference may be related to the diffuse anatomical border between the superficial layers in mouse dorsal MEC (Fyhn et al. 2008)—and it is unknown whether this species difference has any functional significance. In monkeys, HD cells and conjunctive grid × HD cells still need to be found in MEC.

A major difference between grid cells in rats and mice, on one hand, and bats and monkeys, on the other hand, is that rodent grid cells exhibit very pronounced theta oscillations, while in bats and monkeys theta oscillations seem to be very weak and appear in intermittent bouts (Yartsev et al. 2011; Killian et al. 2012). This difference has major implications for models of grid cells and will be discussed further in the section on theta oscillations, below.

16.2.4 Border Cells

Border cells (or boundary cells) are neurons that are activated along one or several borders of the environment. They were first described in rats (Savelli et al. 2008;

Solstad et al. 2008; Lever et al. 2009) and later reported in mice (Giocomo et al. 2011) and bats (Yartsev et al. 2011) in an open-field environment. Recently, "spatial-view border cells" were found in monkeys that visually scanned a computer screen (Killian et al. 2012). In all species, border cells comprise a small percentage of the MEC population—about 10 %—and are intermingled with grid cells and HD cells. We note though that there is an important caveat in the demonstration of border cells in mice, bats, and monkeys. In rats, it was demonstrated that, after introducing a new parallel wall, the border cells started to fire also along the new, similarly oriented border (Solstad et al. 2008; Lever et al. 2009). These tests, however, were not conducted to date in mice, bats, or monkeys. Moreover, almost none of the basic properties of border cells were studied outside of the rat. Therefore, the definitive demonstration of border cells in mice, bats, or monkeys—as well as their detailed characterization in these species—awaits further experiments.

16.3 Oscillations in the Hippocampal Formation

Neural oscillations in the hippocampus were studied in detail as early as 1954 (Green and Arduini 1954; and in a preliminary study already in 1938: Jung and Kornmüller 1938), in a variety of species—including rabbits, cats, dogs, rodents, bats, and monkeys (Vanderwolf 1969; Winson 1972; Robinson 1980; Buzsáki 2006; Ulanovsky and Moss 2007; see also Lever et al. 2014). The most prominent oscillations found in hippocampal LFP are delta (1–4 Hz), theta (4–10 Hz), beta (12–25 Hz), gamma (30–100 Hz), and high-frequency ripple oscillations (100–250 Hz). We will focus below on ripples and theta oscillations, for which cross-species comparative data exist; much less is known across species about the other frequency bands, such as gamma. We note that although much of the research on theta oscillation until the early 1980s was done in non-rodent species (reviewed in detail in Winson 1972; Robinson 1980)—and in fact, the original discovery of hippocampal theta was done in rabbits and cats (Green and Arduini 1954)—we chose to focus below, for coherence purposes, mostly on the same model species which we discussed above when reviewing spatial cells, namely rats, mice, bats, and primates.

16.3.1 High-Frequency Ripples

Ripples are hippocampally generated high-frequency oscillations that are most prominent during slow-wave sleep or during quiet wakefulness (epochs of relative inactivity during the awake state). Ripples have short duration, lasting typically between 40 and 100 ms, and are accompanied by intense synchronous firing of a substantial fraction of the hippocampal neuronal population ("population burst"). These ripple events are thought to send information to neocortex for long-term memory storage (Siapas and Wilson 1998; Sirota et al. 2003; Battaglia et al. 2004)

and thus to be crucial for hippocampal-neocortical communication and memory consolidation (Buzsáki 2006; Jadhav et al. 2012).

The basic properties of ripple oscillations in CA1 are very similar between rats, mice, bats, and primates—see Table 16.2 (Chrobak and Buzsáki 1996; Buzsáki et al. 2003; Skaggs et al. 2007; Ulanovsky and Moss 2007; Yartsev et al. 2011). In all species, ripples are most prevalent during slow-wave sleep and calmness (see Fig. 16.2a, f for examples of ripples from rats and bats). In all species, high-frequency ripples have their maximal amplitude in the CA1 pyramidal layer (see for mice and bats: Fig. 16.2b, g) and are riding on top of sharpwaves that reverse their polarity in the CA1 pyramidal layer (Buzsáki et al. 2003; Ulanovsky and Moss 2007): see Table 16.2. Similar to rats and mice, CA1 neurons in bats increase their firing rate during sharpwave-ripple events (Fig. 16.2a, f), and their firing is phase locked to the ripple oscillation, with peak firing rate occurring at the trough of the ripple (Fig. 16.2c, h) (Ulanovsky and Moss 2007); thus, ripples in bats, rats, and mice are not only qualitatively similar but in fact quantitatively have the exact same numerical value for the phase of best locking (Csicsvari et al. 1999; Buzsáki et al. 2003; Ulanovsky and Moss 2007; Yartsev et al. 2011). In all species, ripples in CA1 often occur in doublets, i.e., there is a relatively higher prevalence of short inter-ripple intervals <200-ms, as compared to longer intervals (see distributions of inter-ripple intervals from mice and bats: Fig. 16.2d, i) (Buzsáki et al. 2003; Ulanovsky and Moss 2007). While the durations of ripples in CA1 are quite similar across species (Table 16.2), ripple frequencies seem to slightly differ between species, with typical frequencies of 120–200 Hz in rats, 120–170 Hz in mice, 120–160 Hz in bats, and 100–120 Hz in monkeys and humans (Fig. 16.2e, j and Table 16.2).

Ripples in MEC were studied to date only in rats and bats (Chrobak and Buzsáki 1996; Yartsev et al. 2011). As in CA1, properties of ripples in MEC appear to be very similar between rats and bats. In both species, MEC ripples often occur in doublets and are accompanied by an increase in neuronal firing rate that is phase locked to the ripples' oscillatory cycles (Chrobak and Buzsáki 1996; Yartsev et al. 2011). Ripples in MEC, in both rats and bats, have a similar frequency to ripples in CA1 (120–200 Hz in rats, 120–160 Hz in bats: Chrobak and Buzsáki 1996; Yartsev et al. 2011). Duration of ripples in MEC is similar between rats and bats (Yartsev et al. 2011), but in both rats and bats, this duration is shorter than that of CA1 ripples, and generally the MEC ripples tend to be more variable than CA1 ripples. We thus conclude that high-frequency ripples, in both CA1 and MEC, are very similar across species, including rats and bats.

While the basic properties of ripple oscillations are highly similar across species—which may suggest that they serve similar functions across mammals—there has been in fact very little comparative work on the functional significance of ripples. Thus, while in rats there is evidence for hippocampal-neocortical interactions via ripples (Siapas and Wilson 1998; Sirota et al. 2003; Battaglia et al. 2004), and a demonstrated role for ripples in spatial working memory (Jadhav et al. 2012), such experiments were not done so far in other species—with the exception of one study in monkeys which showed that around the time of ripples,

Table 16.2 Hippocampal oscillations: cross-species comparison

Oscillation	Property	Rats	Mice	Bats	Primates
Ripples	Frequency	120–200 Hz[1–3]	120–170 Hz[2, 4]	120–160 Hz[5, 6] (see also our Fig. 16.2j)	Monkey CA1: 100–120 Hz[7, 8] Human CA1: 80–160 Hz[9]
	Duration	Typically ~50 ms[3]	Mean ~65 ms[4]	Mean ~45–50 ms[5, 6]	Monkey CA1: ~40–50 ms[7, 8] Human CA1: ~50 ms[9]
	Tendency of ripples to occur in doublets, spaced ~100–200 ms	Yes	Yes[2]	Yes[5] (see also our Fig. 16.2i)	Monkeys: occasionally[7]
	Ripple amplitude is maximal in the CA1 pyramidal cell layer	Yes[10, 11]	Yes[2, 12]	Yes[5] (see also our Fig. 16.2g)	Monkeys: yes[7]
	Ripples in CA1 associated with sharpwaves; sharpwave polarity reverses in the CA1 pyramidal cell layer	Yes[10, 11]	Yes[2]	Yes[5, 6]	Monkeys: yes[7]
	Increase of neuronal firing-rate in CA1 during a sharpwave-ripple complex	Yes[10, 11]	Yes[2]	Yes[5, 6] (see also our Fig. 16.2f)	Monkeys: yes[7]
	Phase locking of CA1 neurons onto ripple phase	Yes. Spikes locked to ripple trough[10, 11]	Yes. Spikes locked to ripple trough[2]	Yes. Spikes locked to ripple trough[5, 6] (see also our Fig. 16.2h)	*Unclear*
Theta	Frequency	5–10 Hz[13]	5–10 Hz[2]	4–8 Hz[5, 6]	3–8 Hz[14, 15]
	Behavioral correlate	Exploration and locomotion[13]	Exploration and locomotion[2]	Active sensing: echolocation; no dependence on locomotion[5]	Active sensing: visual search using saccades
	Continuity	Continuous (during exploration and locomotion, and REM sleep)[13]	Continuous (during exploration and locomotion, and REM sleep)[2]	Intermittent bouts[5, 6]. Bout duration 1–2 s; bouts occur every 20–40 s	Intermittent bouts in monkeys[7, 16] and in humans[14]

(continued)

Table 16.2 (continued)

Oscillation	Property	Rats	Mice	Bats	Primates
	Locking of CA1 place-cell spikes onto theta phase (when theta is present)	Yes	Yes	Yes	Probably
		Peak discharge at ~30° after the trough of locally recorded theta[17]	Double-peak locking: first peak at ~30° after the trough of theta[2]	Place cells have their peak discharge at ~30° after the trough of theta, in both big brown bat and Egyptian fruit bat[5, 6]	Hippocampal neurons in humans do show phase locking to theta during theta bouts[15], but the neurons in that study were not necessarily place cells[15]
	Theta amplitude increases in size below the CA1 pyramidal cell layer, towards the hippocampal fissure	Yes[11]	Yes[2]	Yes[5]	*Unknown*

Note: because most of the available cross-species comparative information comes from studies of hippocampal area CA1, we limited this table to CA1 data (see main text for some additional comparisons, e.g., ripples in MEC versus CA1)

1. Chrobak and Buzsáki (1996), 2. Buzsáki et al. (2003), 3. Nguyen et al. (2009), 4. Maier et al. (2011), 5. Ulanovsky and Moss (2007), 6 Yartsev et al. (2011), 7. Skaggs et al. (2007), 8. Logothetis et al. (2012), 9. Bragin et al. (1999), 10. Buzsáki et al. (1992), 11. Ylinen et al. (1995), 12. Gordon et al. (2005), 13. Buzsáki (2002), 14. Ekstrom et al. (2005), 15. Rutishauser et al. (2010), 16. Stewart and Fox (1991), 17. Csicsvari et al. (1999)

the neocortex is excited while most subcortical regions are inhibited (Logothetis et al. 2012). Similarly, while a large literature exists on replay and preplay of place sequences by the population bursts that accompany the ripples (see Jadhav and Frank 2014), there were only two studies that showed ripple-associated replay in mice (Dragoi and Tonegawa 2011, 2013), and no such studies were done to date in bats or primates (one study in monkeys did show replay in neocortex (Hoffman and McNaughton 2002), but did not examine hippocampal data, nor the relation to ripples). Thus, it is crucial to conduct much more comparative work on ripples, in order to, first, establish if there are any differences between species and, second, can such differences teach us anything interesting about hippocampal processing. For example, if one would record from populations of spatial-view cells in the hippocampus of monkeys trained on a visual-search task, would there be replay of ripple-associated sequences of spatial views by these hippocampal ensembles? Would this depend on whether the monkey performs a random-search visual task, in which the eyes are saccading quite randomly, as opposed to visual smooth

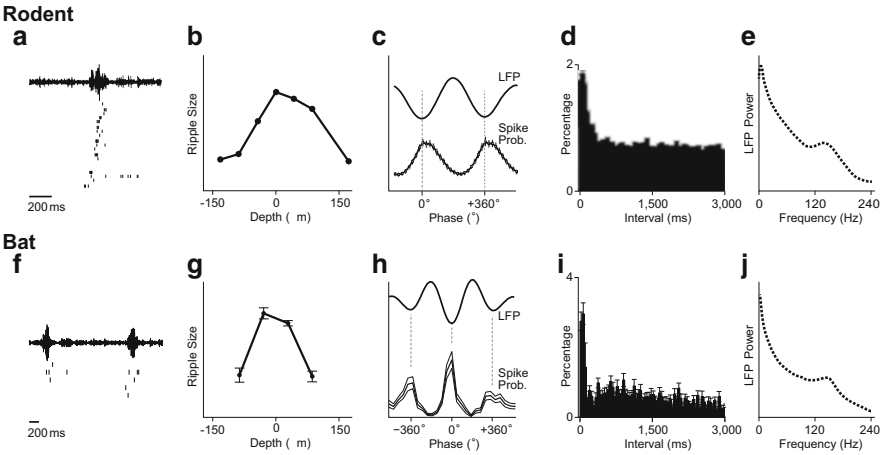

Fig. 16.2 High-frequency ripples oscillations are very similar in rodents and bats. (**a**–**e**) Rodents. (**f**–**j**) Bats. (**a**, **f**) Examples of high-frequency ripples (filtered in the ripple frequency range) and associated population burst across many neurons (raster), in rat (**a**) and big brown bat (**f**). (**b**, **g**) Ripple amplitude is maximal at the CA1 pyramidal cell layer; shown is ripple amplitude (y-axis) versus depth, with $x = 0$ indicating the layer, in mice (**b**) and big brown bats (**g**). (**c**, **h**) Very similar phase locking of spikes from CA1 pyramidal cells onto the phase of CA1 ripples; shown is the phase locking in mice (**c**) and big brown bats (**h**). (**d**, **i**) Ripples tend to occur often in doublets with <200-ms intervals; shown are examples of inter-ripple interval distributions in mice (**d**) and big brown bats (**i**). (**e**, **j**) Similar ripple frequencies for bats and mice; shown are power spectra of hippocampal LFP in CA1 during slow-wave sleep, in mice (**e**) and Egyptian fruit bats (**j**). Big brown bat data in (**f**–**i**) were replotted from Ulanovsky and Moss (2007); Egyptian fruit bat data in (**j**) replotted from Yartsev et al. (2011). Data in (**a**) reproduced with permission from Foster and Wilson (2006); data in (**b**) remeasured from Gordon et al. (2005); data in (**c**, **d**) reproduced with permission from Buzsáki et al. (2003); data in (**e**) remeasured from Gordon et al. (2005)

pursuit, where the eyes are moving smoothly through a sequence of views? Or, in bats, would one find replay of sequences that are associated with sonar behaviors? Would such replay correlate with subsequent memory performance? Any such findings will shed light on the function of ripples and the ripple-associated replay phenomenon, in hippocampal processing across species.

16.3.2 Theta Oscillations

Hippocampal theta oscillations have been studied extensively for 60 years, starting with the pioneering work of Green and Arduini (1954), and this massive neuroscientific effort has produced a staggering amount of experimental data and a plethora of theories (reviewed in Buzsáki 2006; Andersen et al. 2007). One of the most striking features that emerged over these 60 years or research is the cross-species *differences* in theta oscillations (Winson 1972; Robinson 1980). In rodents (rats and mice), the main behavioral correlate of theta is exploration and locomotion (Vanderwolf 1969), whereby theta is observed continuously while the animal is

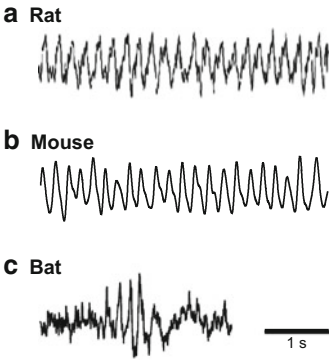

Fig. 16.3 Theta oscillations are continuous in rodents but occur in short intermittent bouts in bats. (**a**, **b**) Examples of continuous theta oscillation recorded in hippocampal dorsal CA1 area of rodents: Recordings from a rat (**a**) [reproduced with permission from Hollup et al. (2001)] and a mouse (**b**) [reproduced with permission from Wulff et al. (2009)]. (**c**) Example of a short, intermittent bout of theta recorded in hippocampal dorsal CA1 area of an Egyptian fruit bat [from Yartsev et al. (2011)]. LFP was filtered between 1 and 117 Hz in (**a**), 1–20 Hz in (**b**), and 1–475 Hz in (**c**)

running in the environment (Fig. 16.3a–b) (see also Lever et al. 2014). In cats, by contrast, theta is observed most strongly when the animal is in fact stationary and is visually tracking prey or other moving items with its eyes (Winson 1972; Robinson 1980). In rabbits, theta is observed most prominently upon presentation of a sensory stimulus, unrelated to the movement state of the animal (Winson 1972; Robinson 1980). In monkeys and humans it has been very difficult to observe hippocampal theta oscillations, and those few studies that did find them, during behavior, sleep, or anesthesia, reported that theta is weak and occurs in short intermittent bouts (Stewart and Fox 1991; Cantero et al. 2003; Ekstrom et al. 2005). A recent study in monkeys performing a visual-search task found theta bouts that were related to eye-saccading behaviors (Jutras and Buffalo 2009; Jutras et al. 2013). In bats, our own studies showed similar results to those from humans and monkeys: theta oscillations were difficult to detect in the bat and occurred in short intermittent bouts that lasted ~1 s and occurred every ~30 s on average (Fig. 16.3c; Ulanovsky and Moss 2007; Yartsev et al. 2011). In big brown bats, we found that theta bouts were more prominent in time-epochs when the bat explored the arena using echolocation (Ulanovsky and Moss 2007). Thus, the phenomenology of theta oscillations differs substantially across species—which is in striking contrast to the case of the other hippocampal oscillation discussed above, the high-frequency ripples, which seem to be very similar across species, including between rats and bats (see previous section and Table 16.2).

We note that one feature which may be common to all of these occurrences of theta, across species, is the relation to sensory inputs (Table 16.2). If we consider the hypothesis that theta is important for the processing of stimuli across time and in learning of temporal sequences (Skaggs et al. 1996; Wallenstein and Hasselmo

1997; Jensen and Lisman 2005), then maximal theta may be expected when sensory information arrives at high rates or changes rapidly. In rats, which rely mostly on their well-developed proximal senses, new olfactory and somatosensory information arrives most rapidly when the animal runs at high velocities, and hence we would expect theta amplitude to increase with running velocity, as is indeed the case. In bats, which rely on echolocation, we would expect theta amplitude to increase with the rate of echolocation calls, as we indeed found (Ulanovsky and Moss 2007). In monkeys performing a visual-search task, in which they rely on eye saccades, we would expect theta to be related to the occurrence of saccades, as was indeed reported (Jutras and Buffalo 2009; Jutras et al. 2013). In fact, what is common to olfaction and whisking in rats, echolocation in bats, and eye saccades in monkeys is that these are all active-sensing systems—in which the animal is engaged in actively scanning space and collecting sensory information from the environment (Nelson and MacIver 2006). Thus, it could be that the phenomenological differences in theta oscillations that were observed across species are in fact related to differences in active-sensing strategies—while the general principle still holds that hippocampal oscillations are related to processing of active-sensing inputs, across all species (see further discussion of this prediction in our paper: Ulanovsky and Moss 2007).

Theta rhythmicity of spike trains is another key characteristic of hippocampal and entorhinal neurons in rodents. Neurons in the rodent hippocampus and MEC exhibit robust and strong locking of single-unit and multiunit spikes onto the theta oscillation (Csicsvari et al. 1999; Buzsáki et al. 2003). In contrast, place cells and grid cells in bats show very weak locking to theta, and this weak locking is observed only during the short intermittent theta bouts (Ulanovsky and Moss 2007; Yartsev et al. 2011; Yartsev and Ulanovsky 2013). This has important implications for theories of hippocampal and entorhinal function, because a major class of models of grid formation—the "oscillatory interference models"—relies critically on the existence of continuous theta rhythmicity in the spike patterns of grid cells (Burgess and O'Keefe 2011). Our finding of grid cells without theta oscillations in the MEC of bats (Yartsev et al. 2011) argues strongly against these theta-based models of grid formation [although it was proposed that interference-based mechanisms might operate at non-theta frequencies in bats (Heys et al. 2013); for additional views and a detailed description of these models, see Lever et al. (2014), Navratilova and McNaughton (2014)].

Several additional recent studies, in mice and bats, have provided further evidence against the theta-based models. First, two recent studies have examined suprathreshold and subthreshold dynamics of MEC grid cells in mice navigating in virtual-reality environments (Domnisoru et al. 2013; Schmidt-Hieber and Häusser 2013). These studies found that when the mouse enters the grid field, the subthreshold membrane potential exhibits ramp depolarizations—which is consistent with predictions of continuous attractor network models; moreover, there is relatively little increase in theta power within the grid field, and sometimes theta is even decreased—which argues against the oscillatory interference theta-based models of grid formation (Domnisoru et al. 2013; Schmidt-Hieber and Häusser 2013).

Second, while MEC layer II stellate cells in rodents show prominent subthreshold theta oscillations and theta-frequency resonance (Giocomo et al. 2007), a recent slice study in bats depicted a different picture (Heys et al. 2013). This study reported the lack of theta-frequency subthreshold membrane potential oscillations and no theta-band intrinsic resonance in layer II stellate cells of bat MEC—in neither big brown bats nor Egyptian fruit bats (Heys et al. 2013). Some stellate cells in bats lacked any resonance whatsoever, in any frequency, while other neurons showed resonance at extremely low frequencies of ~1 or 1.5 Hz—although this resonance was very weak (Heys et al. 2013). This is reminiscent of the weak subthreshold oscillations found in MEC layer II of monkeys (Buckmaster et al. 2004). Thus, it seems that the biophysical resonance properties of MEC neurons in bats and monkeys do not support theta oscillations—which, again, argues against the oscillatory interference models of grid formation (at least not at the theta frequency range) but is consistent with continuous attractor network models of grid cells (Fuhs and Touretzky 2006; McNaughton et al. 2006; Burak and Fiete 2009; Couey et al. 2013), as well as with adaptation-based models (Kropff and Treves 2008).

We suggest that much more work needs to be done on theta oscillations across rodents, bats, primates, and additional species, in order to study in more detail the interplay between cellular and network mechanisms in the hippocampal formation, across mammals—and also to elucidate whether the interspecies differences in theta oscillations are indeed related to differences in active-sensing behaviors between the different species, as we proposed (Ulanovsky and Moss 2007).

Concluding Remarks: The Need for Further Comparative Studies

While much progress has been made in describing basic properties of spatial cell types and hippocampal oscillations across species, a lot more work needs to be done. There are clearly differences between species, even within rodents—such as the marked differences in place-field stability between rats and mice. The differences between rodents, bats, and primates are even more substantial—as illustrated by the example of the theta oscillations—but we note that in many other ways there are also striking similarities across mammalian species, such as in the properties of high-frequency ripple oscillations and in functional properties of place cells and grid cells. We propose that by contrasting and comparing hippocampal processing across species, we would unravel the *invariant* properties of hippocampal function—which are crucial for truly understanding hippocampal processing across mammals.

Moreover, there are many "known unknowns": hippocampal properties that were investigated to date only in rats and for which it is simply unknown whether and how they manifest in other species. For example, can we find remapping in non-rodent species? Which kinds of remapping? How do they depend on different sensory inputs or on the behavioral context?

Second, as we noted above, there were hardly any large-scale ensemble recordings of hippocampal populations in non-rodent species. Will one find evidence for prospective and retrospective coding in neural ensembles recorded from non-rodent species, as was found in rats? Or—if one would record from

populations of spatial-view cells in the hippocampus of monkeys trained at a visual-search task, would they exhibit replay of sequences of spatial views? And what about replay of sequences of remembered items in monkey hippocampus? Or sequences of auditory sonar targets in bat hippocampus? What would this teach us about hippocampus, space, time, and memory?

Third, over 40 years of hippocampal research have produced an amazing set of findings on the spatial cell types of the hippocampal formation, in laboratory-sized environments. But what if we could record place cells or grid cells in animals locomoting over kilometer-sized environments—would we find kilometer-sized place fields and huge grids? Or perhaps, as suggested by some theoretical studies, a radically different picture would emerge, for example, based on combinatorial grid coding (Sreenivasan and Fiete 2011; Mathis et al. 2012a, b). Similarly, would place cells exhibit a single well-circumscribed field, as in laboratory-sized arenas – or perhaps each cell will have dozens of fields in a kilometer-sized environment? It is crucial to answer these questions, if we are to understand hippocampal spatial representations and the neural basis of navigation under truly ethologically-relevant conditions.

And of course, there are many "unknown unknowns" that await us down the comparative road. The lack of theta oscillations in the hippocampus of bats was one such unexpected finding. The discovery of spatial-view cells and "spatial-view grid cells" in the hippocampal formation of monkeys was another. Many more surprises surely lie ahead. We are just starting to scratch the interesting facets of hippocampal neurophysiology across species.

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Part III

Hippocampal Readout

Fear and Memory: A View of the Hippocampus Through the Lens of the Amygdala

17

Hugh T. Blair and Michael S. Fanselow

Abstract

Studies of the brain's fear circuits have significantly advanced our neurobiological understanding of learning and memory systems. Fear and anxiety are often rooted in memories of past experiences and can be aroused by recognition of familiar stimuli that predict danger. In this chapter, we examine how the amygdala and hippocampus regulate interactions between fear and memory, with emphasis upon evidence derived from studies of Pavlovian fear conditioning. Convergent behavioral, pharmacological, anatomical, and neurophysiological findings indicate that amygdala circuits can rapidly and permanently store information about which environmental stimuli and events predict danger. These same amygdala circuits are interconnected with the ventral hippocampus (VH), and together, the amygdala and VH may be core components of an emotional memory system in the mammalian brain. The dorsal hippocampus (DH) is not directly connected with the amygdala, but it also makes important contributions to fear conditioning by supporting cognitive memory processes that are essential for recognizing cues and contexts that can predict threats. We discuss how neural representations stored in the amygdala and hippocampus support the mammalian brain's ability to map states of the world onto expectations of danger.

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17.1 Introduction

"Fear" is an emotional state that accompanies anticipation of danger and benefits survival by motivating defensive behaviors that protect against threats (Fanselow and Lester 1988; LeDoux 2000). Humans sometimes experience pathological fear, characterized by recurring anticipation of danger that is out of proportion with available evidence of threat, which is symptomatic of anxiety disorders such as post-traumatic stress and phobias (Craske 1999). Neural circuits that regulate fear and anxiety have become a major focus of research to advance the diagnosis and treatment of such disorders (LeDoux and Muller 1997; Cahill and McGaugh 1998; Garakani et al. 2006). This line of research has also deepened our understanding of learning and memory systems in the mammalian brain.

17.1.1 Learning to Anticipate Danger

Fear can be elicited by cues in the environment that signal the presence of danger. Some cues and events are programmed by natural selection to be innately threatening [such as encounters with natural predators, Lester and Fanselow (1985)], but other cues acquire the ability to predict danger through experience-dependent learning. Much of our current knowledge about the brain's fear circuitry has come from studies of *Pavlovian fear conditioning*, an associative learning task in which subjects are trained to fear a neutral conditional stimulus (CS) by pairing it with an aversive unconditional stimulus (US). After being paired with the US, the CS becomes a predictive cue that signals danger and thereby acquires the ability to elicit *conditional fear responses* (CFRs). One of the most widely studied CFRs in rodents is freezing, an innate defensive response characterized by suppression of musculoskeletal movements (Bolles 1970; Bolles and Riley 1973). In the wild, natural selection has favored freezing in rodents because it reduces the likelihood of being detected by predators. But freezing also reduces the probability of attack once the prey is detected, because movement is a releasing stimulus for attack by many predators (see Fanselow and Lester 1988 for a review). Other commonly measured CFRs include startle potentiation, vocalization, and autonomic changes in heart rate or blood pressure (Davis 1992). After subjects have been trained to fear a CS by pairing it with a US, they can subsequently be trained to suppress CFRs via extinction training, in which the CS is presented alone without the US it was previously paired with.

Like other forms of Pavlovian learning, fear conditioning is a process by which organisms learn to anticipate future events. But anticipating danger is a high-stakes enterprise, because failing to predict a threat may result in injury or death, a consequence considerably more severe than, say, a missed meal or lost mating opportunity. In accordance with the maxim that it is "better to be safe than sorry," fear conditioning is acquired more rapidly than most other forms of Pavlovian conditioning (a single CS-US pairing is sufficient) and is also more resistant to forgetting and extinction, so that fear memories are difficult to suppress once they

have been acquired. Fear conditioning places unique demands upon neural systems for learning, memory, and prediction, and the amygdala and hippocampus contain circuits that contribute to meeting these unique demands.

17.1.2 Contributions of Amygdala and Hippocampus to Conditional Fear

The amygdala is critical for recognizing and responding to danger in mammals (Phelps and LeDoux 2005), and evidence indicates that amygdala neurons can rapidly and permanently store memories of the CS-US association during fear conditioning tasks (see Sect. 17.2). By contrast, the hippocampus seems to play a time-limited role in fear conditioning and do so preferentially under certain circumstances (see Sect. 17.3). For example, the hippocampus is necessary for *contextual* fear conditioning, where the predictive stimulus is not a discrete cue but an environment or situation where US is encountered. Additionally, the hippocampus contributes to *trace conditioning*, in which the CS and US are separated by an interval of time during training. Extinction of fear conditioning also engages the hippocampus (Bouton and King 1983; Maren et al. 2013), because hippocampal circuits mediate the context specificity of extinction (see Sect. 17.3.2).

The ability of a Pavlovian CS to elicit expectation of a US can transfer to other stimuli that are similar, but not identical, to the trained CS. For example, a person who is bitten by a dog in the park may become conditioned to fear a predictive CS (the dog) by associating it with an aversive US (the bite). The bite victim may subsequently become afraid of all dogs (not just the dog that made the bite), but not necessarily all animals (for example, not cats). The victim might also become afraid of a contextual cue—the park—and subsequently feel afraid upon returning to any location within the park, not just to the specific location where the bite occurred. Such generalization of associative learning can occur in all forms of Pavlovian conditioning, but it is especially important in fear conditioning. An encounter with danger must not be interpreted too narrowly as evidence that only one specific cue is a signal of threat (because this could result in failure to anticipate a future threat), or too broadly as evidence that irrelevant stimuli are signals for threat (because this could result in "pathological" fear and anxiety). How can predictive stimulus categories be accurately inferred from the limited set of cues that are present during a single encounter with danger? Solving this problem may require specialized circuits for pattern classification or completion, and such circuits have been posited to reside in the hippocampus (see Chap. 9). Before discussing hippocampal contributions to fear learning in greater detail, it is helpful to first review evidence concerning the role of the amygdala in fear conditioning.

17.2 Role of the Amygdala in Fear Conditioning

The amygdala has been proposed to assign motivational valence to emotionally arousing stimuli (Weiskrantz 1956). By assigning aversive valence to stimuli that have co-occurred with danger in the past, the amygdala may allow the brain to map states of the world onto expectations of when danger will occur in the future (Seymour and Dolan 2008; McNally et al. 2011), which are then relayed to brain circuits that drive defensive behaviors to protect against anticipated threats (Davis 1992). Hence, *expecting* and *responding to* danger may be regarded as two distinct stages of fear processing. These sequential stages of fear processing are thought to be regulated by specific neural circuits in the amygdala.

17.2.1 Circuit Architecture of the Amygdala

Figure 17.1 illustrates how amygdala subregions that regulate fear conditioning are interconnected with one another and with other brain structures. The amygdala contains two primary anatomical subdivisions: the basolateral (BLA) and centromedial (CMA) amygdala. BLA contains excitatory (glutamatergic) projection neurons that resemble cortical pyramidal cells, whereas CMA contains inhibitory (GABAergic) projection neurons that resemble medium spiny cells of the striatum (Swanson and Petrovich 1998). BLA is partitioned into lateral (LA) and basal (B) subnuclei, both of which play important roles in emotion and motivation. CMA is partitioned into medial (MeA) and central (CeA) subregions, and CeA is especially involved in regulating fear-motivated defensive behaviors.

Principal neurons of the BLA receive convergent inputs from multiple brain regions that relay sensory, motivational, and mnemonic information into the amygdala (Aggleton 2000). Some of these inputs arrive at modifiable synapses on the dendrites of BLA neurons, which can undergo associative plasticity during fear conditioning (see Sect. 17.2.2). When BLA is activated by afferent inputs, the animal's defensive behavior system is activated (Bolles and Fanselow 1980). Consciously perceived aspects of this activation may lead to the subjective experience of fear [although the exact relationship between amygdala activity and emotive fear in humans is unclear; see Anderson and Phelps (2000)]. Evidence suggests that different defensive behaviors may be driven by distinct output pathways from BLA. Outputs from the B subnucleus to structures such as the prefrontal cortex, hippocampus, and ventral striatum can modulate ongoing instrumental behaviors (Killcross et al. 1997; Amorapanth et al. 2000) as occurs when food-reinforced lever presses are suppressed in the presence of a danger cue (Estes and Skinner 1941). Projections from the B nucleus may also mediate influences of emotion upon memory storage and consolidation (Cahill and McGaugh 1998). By contrast, a system of projections from BLA to CeA, and then from CeA to brainstem, midbrain, and hypothalamic regions, is thought to drive CFR behaviors such as freezing and startle potentiation (Nader et al. 2001; Goosens and Maren 2001; Campeau and Davis 1995). However, expression of some CFRs—including freezing—may also

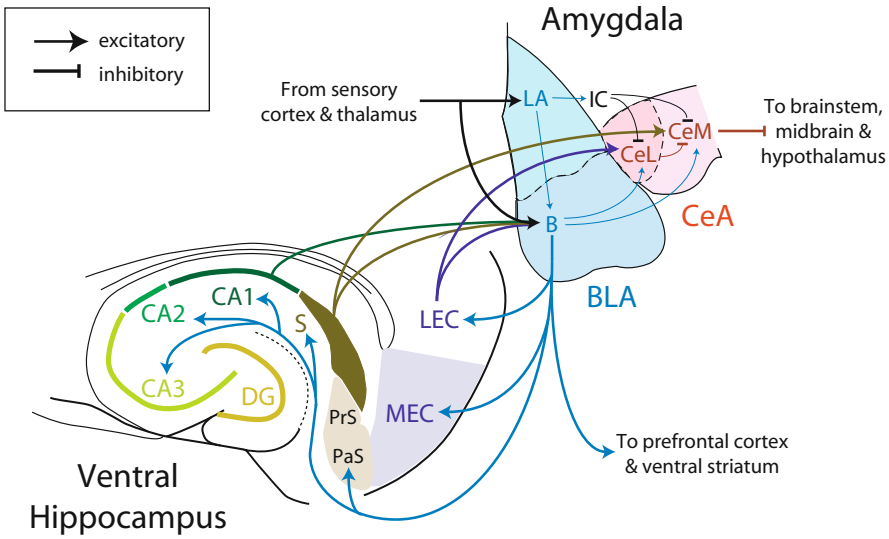

Fig. 17.1 Interconnectivity between amygdala and VH. Schematic shows circuit architecture of the amygdala and its connections with VH. *S* subiculum, *PrS* presubiculum, *PaS* parasubiculum (see main text for explanation of other abbreviations)

involve projections from amygdala to the prelimbic region of prefrontal cortex (Burgos-Robles et al. 2009; Sotres-Bayon and Quirk 2010).

CeA can be partitioned into the centromedial (CeM) nucleus, which contains most of the projection neurons that send output to brainstem and hypothalamic structures, and the centrolateral (CeL) nucleus, which contains mostly local circuit neurons that terminate within CeA. BLA sends excitatory projections to both CeM and CeL, as well as to a population of intervening inhibitory neurons called intercalated (IC) cells that send feedforward inhibition onto CeL and CeM (Paré et al. 2004). This rather complex circuit architecture allows BLA neurons to directly excite projection neurons in CeM, or alternatively, to indirectly excite or inhibit CeM projection neurons via polysynaptic pathways routed through CeL and IC (Haubensak et al. 2010; Ciocchi et al. 2010). Since CeM projection neurons are inhibitory, they may disinhibit (rather than excite) downstream defense circuits to generate fear-motivated responses.

17.2.2 Storage of Fear Memories in the Amygdala

Evidence suggests that during fear conditioning, memories of the CS-US association are stored by strengthening synapses that relay information about the CS to BLA neurons (see Fanselow and LeDoux 1999; Maren 2003). Associative plasticity in the amygdala has been widely investigated by studies in which an auditory CS (such as a tone or white noise) is paired with an aversive US (such as footshock). Findings

indicate that information about the auditory CS is relayed to the amygdala's LA subnucleus via afferent inputs from auditory thalamus and cortex. Before the CS has been paired with the US, these inputs are weighted by weak synapses onto LA pyramidal neurons, so that the CS cannot reliably elicit postsynaptic firing in BLA; however, weak CS input synapses are strengthened when the CS is paired with an aversive US, so that subsequently, the CS can elicit postsynaptic firing from BLA neurons. This synaptic strengthening appears to involve Hebbian long-term potentiation (LTP), which occurs when the CS activates presynaptic inputs to BLA neurons simultaneously with strong postsynaptic depolarization triggered by the US (for review, see Sah et al. 2008).

In addition to inputs from auditory thalamus and cortex, BLA also receives inputs from other structures that can participate in signaling danger, depending upon the nature and source of the threat. Primary sensory cues other than sounds (such as visual, tactile, or olfactory cues) are likely to be relayed from modality-specific sensory regions to synapses in BLA. Although these input synapses have not been clearly identified for all modalities, it is believed that most can undergo associative LTP if they are paired with an aversive US and can thereby acquire the ability to activate the amygdala. In addition to primary sensory cues, fear can also be elicited by complex spatial or temporal patterns of stimuli or by memories of past experiences. Arousal of fear by such complex cues may involve associative plasticity at inputs to the amygdala from multimodal regions of the hippocampus and cortex which, like sensory inputs, can become potentiated when they are paired with an aversive US and thereby acquire the ability to activate BLA and elicit fear (Maren and Fanselow 1995). Rather than directly activating the amygdala to elicit expectations of danger, some inputs to the amygdala—especially from areas such as prefrontal cortex and hippocampus—may instead exert modulatory influences that mediate "cognitive control" over emotional processing and defensive behaviors, by dynamically gating the flow of information through the amygdala (Quirk and Beer 2006; Maren et al. 2013). For example, animals can learn to suppress conditioned fear responses via extinction training when a fear-conditioned CS is presented alone without the US, and evidence suggests that this learned suppression of fear is mediated by prefrontal cortex projections to BLA, IC, and CeA interneurons that suppress activation of the amygdala by the CS (see Milad and Quirk 2012). The hippocampus plays a role in mediating the context specificity of fear inhibition after extinction (see Sect. 17.3.2).

17.2.3 Recall of Associative Fear Memories

Evidence reviewed above suggests that a primary function of the amygdala may be to solve a specific class of pattern recognition problems, namely, mapping states of the world that signal threats (encoded by patterns of input to the amygdala) onto expectations of danger (encoded by patterns of neural firing in the amygdala itself). Stored patterns of neural activity in the amygdala are sometimes referred to as "fear engrams" (Josselyn 2010). Experimental studies using modern techniques for

molecular imaging and manipulation of neural activity patterns have shown that similar subpopulations of amygdala neurons are activated during storage and recall of a conditioned fear memory (Han et al. 2007; Tayler et al. 2013; Garner et al. 2012), and such findings lend credence to the idea that acquisition of fear conditioning stores a "fear engram" of patterned activity in the amygdala, which is later reactivated when associative fear memories are recalled.

17.3 Hippocampal Contributions to Fear Conditioning

Unlike the amygdala, which appears to be a permanent and mandatory storage site for most associative fear memories (Gale et al. 2004), the hippocampus contributes to fear conditioning under more selective circumstances. Before considering how and when the hippocampus contributes to fear conditioning, it is helpful to review anatomical connections between hippocampus and amygdala.

17.3.1 Interconnections Between Hippocampus and Amygdala

In rodents, the hippocampus is often said to resemble two "bananas" joined by a midline "stalk" (the fimbria/fornix) located at the septal pole of the dorsal hippocampus (DH). Each "banana" descends from the common stalk into either hemisphere of the brain, where its bottom tip forms the temporal pole of the ventral hippocampus (VH). Figure 17.1 illustrates a horizontal cross section through the ventral hippocampus taken perpendicular to the septotemporal axis, which reveals the familiar stations of the "trisynaptic loop" circuit: perforant path inputs from the superficial layers of entorhinal cortex (EC) terminate in the dentate gyrus (DG), which sends mossy fiber projections to the CA3 subfield, which in turn sends Schaffer collaterals to the CA1 subfield. Parallel to the trisynaptic loop circuit is the temporoammonic pathway, consisting of direct projections from EC to subfields CA3–CA1. CA1 neurons send direct outputs to other brain regions, as well as indirect outputs relayed through the subiculum.

The structure of the canonical hippocampal circuit is largely preserved across the septotemporal axis, but there are significant variations in the circuit's sources of input and targets of output (Swanson and Cowan 1977; Fanselow and Dong 2010). These anatomical differences are corroborated by evidence from behavioral, physiological, and gene expression studies which indicate that the dorsal and VH are functionally distinct from one another (Moser and Moser 1998; Fanselow and Dong 2010). The transition between DH and VH occurs relatively abruptly within an intermediate zone (most caudal portion of the rodent hippocampus) that shares some features of the dorsal and ventral regions but also has its unique properties (Fanselow and Dong 2010). In contrast with DH, which seems to be mainly associated with "cognitive" functions and brain regions, VH appears to be more associated with "emotive" functions and brain regions. Accordingly, the

amygdala—a primary emotive center in the mammalian brain—is interconnected exclusively with VH but not DH (Pitkänen et al. 2000).

Hippocampal projections to the amygdala arise mainly from ventral CA1 and subiculum, and there are also significant projections from lateral entorhinal cortex (LEC), as well as the neighboring perirhinal and postrhinal cortices; many of these projections terminate mainly in the B subnucleus (Swanson and Cowan 1977; Canteras and Swanson 1992; Pitkänen et al. 2000). These hippocampal inputs may undergo associative plasticity during encounters with an aversive US and thereby support acquisition and expression of conditioned fear (Maren and Fanselow 1995). Amygdala sends projections back to the same hippocampal regions from which it receives inputs and additionally projects to ventral CA2, CA3, and parasubiculum as well (Pitkänen et al. 2000). These return projections may participate in mediating influences of emotion upon learning and memory (Cahill and McGaugh 1998).

17.3.2 Delay Fear Conditioning and Extinction

Cued fear conditioning occurs when a discrete CS (such as a tone or light) is paired with an aversive US. Two variants of cued fear conditioning are *delay conditioning*, where the CS and US are contiguously paired by presenting them simultaneously at overlapping moments in time, versus *trace conditioning*, where the CS and US are presented sequentially at nonoverlapping times. In both cases, testing of cued fear is usually conducted by presenting the CS in a chamber different from where it was paired with the US during training; this is important for dissociating expression of cued versus contextual fear (Jacobs et al. 2010).

Simple delay conditioning, such as auditory fear conditioning to a tone CS, does not normally require the hippocampus for acquisition of CFRs (Kim and Fanselow 1992; Phillips and LeDoux 1992). However, hippocampal deficits in the expression of delay fear conditioning can be observed, depending upon how CFRs are measured. In rodents, when a delay conditioned CS is presented during the test session, there is virtually no freezing prior to the CS; when the CS comes on, the animal rapidly begins to freeze. Freezing persists throughout the tone, and when the tone terminates, the freezing response declines very gradually. Rats with hippocampal lesions freeze normally during the tone, but unlike intact rats, they cease freezing immediately when the tone turns off (Quinn et al. 2008b). Another way in which hippocampal impairments are manifested in delay fear conditioning is in tests of stimulus generalization. Quinn et al. (2009) found that rats trained with a pure tone CS and tested with a white noise CS (or vice versa) showed almost complete generalization to the untrained stimulus. Hippocampal lesions had no effect on responding to the trained stimulus, but virtually abolished responding to the untrained stimulus. Responding to the untrained stimulus could not be explained as pseudoconditioning or sensitization, since unpaired training did not produce generalization. This auditory generalization effect might be driven by fear-conditioned auditory responses of hippocampal neurons (Moita et al. 2003;

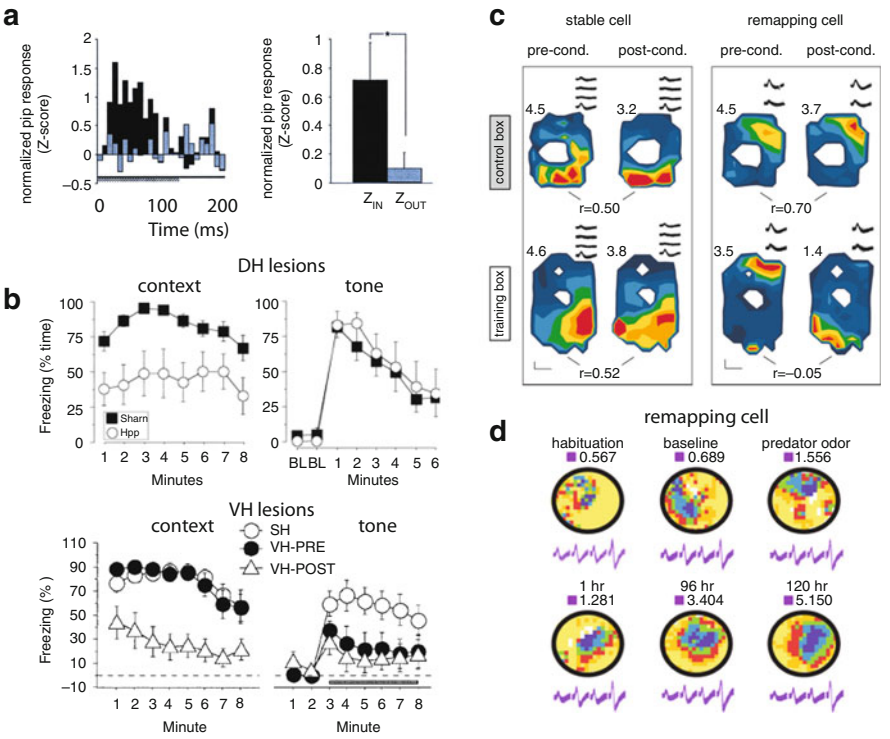

Fig. 17.2 Hippocampus in fear conditioning. (**a**) *Left graph*: population-averaged responses (bin size = 10 ms) of DH place cells to a fear-conditioned auditory CS (250 ms white noise pip, onset at time zero) when the rat is inside (*black bars*, $n = 19$ cells) versus outside (*gray bars*, $n = 20$ cells) of the cells' place fields. *Right graph*: population responses during the first 150 ms of the pip (from Moita et al. 2003). (**b**) *Top graphs*: post-training lesions of DH impair context but not tone fear (from Anagnostaras et al. 1999). *Bottom graphs*: pre- or post-training lesions of VH impair tone fear, but only post-training lesions impair context fear (from Maren and Holt 2004). (**c**) Two place cells recorded during auditory fear conditioning to a shock US. Remapping cell changes its place field in the conditioning box but not a neutral control box; stable cell retains the same field in both boxes (from Moita et al. 2004). (**d**) Place cell recorded during fear conditioning to a predator odor US remapped once during the odor, and then again 1 h later, with the second remapped field remaining stable over days (from Wang et al. 2012)

see Fig. 17.2a) and may depend especially upon DG, as such generalization is increased by a genetic mutation that selectively eliminates postnatal neurogenesis and reduces adult DG size to about 75 % of normal (Cushman et al. 2012).

Another way that the hippocampus contributes to delay fear conditioning is by regulating the context specificity of extinction. Fear of a delay conditioned CS can subsequently be extinguished by presenting the CS alone (without the US), but it is difficult to permanently extinguish conditioned fear. The hippocampus interacts with the amygdala and prefrontal cortex to mediate three major influences of context upon fear extinction (Ji and Maren 2007; Maren et al. 2013). First, fear

extinction is specific to the context where the unpaired CS is delivered; if an extinguished CS is presented in a different experimental chamber from where extinction training (CS alone presentations) occurred, then conditioned fear of the CS returns, a phenomenon referred to as *renewal* of extinguished fear (Bouton 1993). A second example of the contextual control of fear is *reinstatement*, where fear to an extinguished cue returns in a specific context because that context (but not the cue) has been paired with the US after extinction (Bouton and Bolles 1979). Hippocampal lesions and inactivations impair both renewal (Corcoran and Maren 2004; Ji and Maren 2005) and reinstatement (Wilson et al. 1995) of delay conditioning and do so in a manner that parallels its effects on contextual fear conditioning (Zelikowsky et al. 2012a). Third and finally, context representations may also modulate extinction during *spontaneous recovery*, whereby an extinguished CFR returns spontaneously after the passage of time (Bouton 1993; Quirk 2002). It has been proposed that spontaneous recovery might be similar to renewal, insofar as time may be an element of context, so passage of time may be a form of contextual shift (Spear 1981; Bouton 2004). Hippocampal representations of spatial contexts can change with the passage of time (Lever et al. 2002; Mankin et al. 2012; Ziv et al. 2013), so temporal instability of hippocampal context representations might induce spontaneous recovery (see Sects. 17.4.2 and 17.4.3).

17.3.3 Trace Fear Conditioning

In trace fear conditioning, the CS and US are presented sequentially at nonoverlapping times during training. Subjects can acquire conditioned responses during trace conditioning—even though the CS and US are separated in time by a trace interval—as long as the trace interval is short enough for the association to be learned. Limitations upon the length of the trace interval vary among different Pavlovian learning tasks. For example, in Pavlovian eyeblink conditioning (which is not a fear conditioning task and is mediated by neural plasticity in the cerebellum rather than the amygdala), the CS and US must be separated by a trace interval of less than 2 s for learning to occur (Christian and Thompson 2003). By contrast, during amygdala-dependent fear conditioning to an auditory CS, conditioned freezing responses can be acquired even when a footshock US is delivered tens of seconds after CS termination during training (McEchron et al. 1998; Quinn et al. 2002; Burman et al. 2006; Esclassan et al. 2009a; Czerniawski et al. 2012). Among Pavlovian learning tasks, fear conditioning and conditioned taste aversion (which also depends upon the amygdala) stand out for the ease with which CS-US associations can generalize liberally across time, in accordance with the "better safe than sorry" principles discussed above (see Sects. 17.1.1 and 17.1.2).

The fact that fear conditioning can occur across long trace intervals poses a challenge to the notion that memories of the CS-US association are stored by Hebbian LTP in BLA (see Sect. 17.2.2), because neurophysiology studies show that induction of LTP typically requires precise temporal coincidence—on a timescale of milliseconds—between presynaptic and postsynaptic activity (Bi and Poo 2001;

Markram et al. 2012). This implies that fear conditioning should require CS-evoked presynaptic activity to occur nearly simultaneously with US-evoked postsynaptic depolarization of BLA neurons. How can this coincidence occur when the CS and US are delivered many seconds apart? One hypothesis for resolving this discrepancy between timescales is that the brain generates a *temporal trace* of the CS; that is, a long-lasting memory representation that persistently encodes the CS even after it is no longer present (Desmond and Moore 1988; Grossberg and Schmajuk 1989). If such a memory trace remains active throughout the time interval between CS and US, then a neural representation of the trace—rather than the sensory representation of the CS—may enter into association with the US. The hippocampus has been proposed to participate in storing such memory traces of sensory stimuli, but this view does not easily account for why the timescale of hippocampal involvement varies widely across different forms of Pavlovian trace conditioning. For example, trace eyeblink conditioning depends upon the hippocampus when the interval between CS and US exceeds about 250 ms (Moyer et al. 1990; Thompson and Kim 1996), but a hippocampectomized animal has no trouble with fear conditioning at trace intervals as long as 10 s or more; only at trace intervals longer than about 15 s does a clear hippocampal deficit begin to emerge (Chowdhury et al. 2005; Guimarãis et al. 2011; Misane et al. 2005; Yoon and Otto 2007). From such evidence, it may be tempting to conclude that the hippocampus is needed to store "long" but not "short" memory traces, but this interpretation is challenged by other findings. In an experiment by Quinn et al. (2002), an unpaired "control" group was given backward US-CS pairings across a long trace interval; the US was followed 28 s later by the CS (the same trace interval used for forward CS-US pairings in a separate experimental group). Surprisingly, a tone CS trained in this manner provoked a freezing response when tested in a novel context, and this response was completely eliminated by post-training hippocampal lesions. Since the US preceded the CS, this "backward conditioning" phenomenon cannot be explained by a model in which the hippocampus stores a memory trace of the CS. Backward conditioning—and by implication forward trace conditioning as well—might be better understood in terms of the episodic memory functions of the hippocampus. In both cases, the CS is uniquely experienced within a specific temporal frame, the conditioning session (Quinn et al. 2002), which occurs in a specific place, the conditioning chamber. Thus, tone and shock share a set of common temporal and spatial boundaries that define the conditioning session. The tone may serve as a retrieval cue for the time and place of shock; the tone provokes fear because it causes the recall of the conditioning "episode." In humans, the type of memory most tightly linked to hippocampal function is episodic memory (Eldridge et al. 2000; Nadel and Moscovitch 1997; Viskontas et al. 2009). Thus, trace conditioning may be an example of a positive inference that spans events that have occurred within a common episodic frame. Instead of relying upon neurons that encode simple memory traces of the CS, trace fear conditioning might rely upon neurons that encode time in conjunction with context and other ongoing events (see MacDonald et al. 2011).

17.3.4 Contextual Fear Conditioning

In contextual fear conditioning, animals are typically trained to fear a spatial environment (or context) where an aversive US is encountered. Animals are first allowed to explore (and thus become familiar with) one or more experimental chambers that are distinct from each other along feature dimensions such as shape, size, odor, color, lighting, visual landmarks, surface textures, and so forth. An aversive US (such as footshock) is then presented in one of the chambers, and the animal subsequently expresses CFRs when it is returned to any location in the conditioned context, but not when it is placed in other contexts, indicating that only the trained context has become associated with the aversive US (e.g., Fanselow 1980). Hence, context fear spans a continuous region of space within a given context chamber, but does not cross discontinuous regions of space that span different context chambers.

Contextual fear conditioning does not occur if the US is delivered immediately after an animal enters a novel context that has never previously been explored, an effect referred to as the *immediate shock deficit* (Fanselow 1986). By contrast, if the US is delivered almost immediately after an animal enters a familiar (that is, previously explored) context, then there is no immediate shock deficit, and the animal exhibits CFRs (such as freezing) upon subsequent return to the context (Fanselow 1990). These results imply that animals must explore and thereby construct a memory representation of the context before it can become associated with an aversive US (McHugh and Tonegawa 2007). Abundant evidence suggests that storage and recall of such contextual memories normally depends upon the hippocampus. Most of this work has focused on DH. For example, damage to DH can selectively impair expression of context but not cued fear conditioning (Phillips and LeDoux 1992; Kim and Fanselow 1992). Pharmacological disruption of hippocampal plasticity during preexposure to a novel context (which may block the hippocampus from storing a cognitive map of the context) prevents such preexposure from rescuing the immediate shock deficit (Barrientos et al. 2002; Matus-Amat et al. 2004; Stote and Fanselow 2004).

After a context has become familiar, a stored memory representation of that context may become associated with an aversive US that is subsequently encountered there. Like memories for cue-US associations, memories for context-US associations appear to be stored by potentiating synaptic inputs to BLA, possibly those that arise from hippocampal regions where cognitive maps are stored (Maren and Fanselow 1995; Fendt and Fanselow 1999). This possibility is supported by several lines of evidence: contextual fear conditioning (like cued fear conditioning) is impaired by disruptions of synaptic plasticity in the amygdala (Fanselow and Kim 1994), stressful situations can potentiate synaptic inputs to BLA from the hippocampus (Adamec et al. 2005), contextual fear conditioning is accompanied by enhanced synchronization of theta-band oscillations between the amygdala and hippocampus (which might be indicative of enhanced synaptic coupling between the two regions after context conditioning) (Seidenbecher et al. 2003), and water deprivation increases hippocampal theta and selectively potentiates context

conditioning (Maren et al. 1994) (see Chap. 12 for discussion of hippocampal oscillations). While the majority of these studies targeted DH, contextual fear conditioning can also be impaired by disrupting areas of VH that project to the amygdala, indicating that VH may be necessary for normal acquisition or expression of context fear (Maren and Fanselow 1995; Zhang et al. 2001; Maren and Holt 2004). This suggests that context representations stored in DH may be communicated to the amygdala via the VH. Information from DH might be relayed to VH via successive iterations of the hippocampal-entorhinal loop (with outputs from dorsal hippocampus targeting areas of entorhinal cortex that project to progressively more ventral areas of the hippocampus) or by projections from DH to the medial septum and/or the supramammallary nucleus, both of which project back the entirety of the hippocampus (Fanselow and Dong 2010).

It is important to note that although DH and VH both contribute to contextual fear conditioning, there are clear and important differences in their functions. A primary test for a selective deficit in context fear (as opposed to a general deficit of fear and anxiety) is to show that when a subject shows impairment in context fear, it remains possible for fear to be elicited by non-contextual cues (such as an auditory tone) that are paired with the same US that normally trains context fear. Figure 17.2b shows that this is observed when the hippocampal lesions are confined to DH (Anagnostaras et al. 1999), but lesions of VH tend to produce deficits that affect multiple aspects of fear and anxiety, including cued as well as context fear (Esclassan et al. 2009a; Maren and Holt 2004; Hunsaker and Kesner 2008; Rogers et al. 2006; Bast et al. 2001). This supports the view that these regions should be considered as distinct, with DH serving contextual/spatial/cognitive function and VH serving emotion more generally (Fanselow and Dong 2010; Kjelstrup et al. 2002).

17.3.5 Consolidation of Conditioned Fear

The effects of hippocampal manipulations upon fear conditioning can vary, depending upon when they are performed. When post-training hippocampal lesions are made within a week of training, they cause a profound loss of context fear over a wide range of training and testing parameters (Kim and Fanselow 1992; Maren et al. 1997). However, pretraining effects are much smaller (Fig. 17.2b shows an example of this for VH lesions from Maren and Holt 2004), and they can be overcome with modest increases in training (Maren et al. 1997; Wiltgen et al. 2006). This difference between pre- and post-training lesions indicates that while the hippocampus is normally used for contextual conditioning, compensatory circuits and plasticity can take over when it is unavailable (Fanselow 2010). This compensation occurs in the medial prefrontal cortex (Zelikowsky et al. 2013). However, the compensation is only partial, as contextual fear learned without a hippocampus is retained for less than a month (Zelikowsky et al. 2012b).

Although synaptic plasticity at hippocampal inputs to the amygdala may be required to store memories of trace and context fear at the time they are acquired, the hippocampus appears to play a time-limited role in storing such memories.

If the hippocampus is lesioned within a few days after a familiar context has been paired with shock, then context-evoked freezing is severely impaired after the lesion, whereas if the hippocampus is not lesioned until several weeks after the context-US pairing, then context-evoked freezing persists after the lesion (e.g., Anagnostaras et al. 1999; Debiec et al. 2002; Kim and Fanselow 1992; Maren et al. 1997; Winocur et al. 2009). Additionally, pharmacological and genetic manipulations that target the hippocampus have greater effects upon recent as opposed to old contextual fear memories (Goshen et al. 2011; Wang et al. 2003; Kitamura et al. 2009). Moreover, if animals are preexposed to a context several weeks prior to context-shock pairings and the hippocampus is subsequently lesioned 1 day before or after presenting a shock in this previously preexposed context, then the lesion does not prevent conditional freezing to the context (Anagnostaras et al. 2001; Young et al. 1994). These findings indicate that the role of the hippocampus in storing context representations diminishes with the age of the context memory itself, so that the hippocampus is primarily needed for storing and retrieving fear associations with recently formed context representations, but not older representations. Trace fear conditioning exhibits a similar temporal gradient of hippocampal dependence (Quinn et al. 2008a; Beeman et al. 2013).

The time-limited role of the hippocampus in recalling trace and context-fear memory bears striking resemblance to the phenomenon of temporally graded retrograde amnesia for declarative and episodic memories in human patients that suffer from hippocampal damage (Scoville and Milner 1957). Such patients typically exhibit selective impairment for recent memories (those acquired shortly before the hippocampal damage occurred), while remote memories (those acquired long before the damage occurred) are spared. To account for retrograde gradients of amnesia in humans and animals, it has been hypothesized that memories which initially depend upon the hippocampus are gradually "consolidated" into a form that depends only upon other brain regions, such as the neocortex (Zola-Morgan and Squire 1990; McClelland et al. 1995; Knowlton and Fanselow 1998; Debiec et al. 2002; Wiltgen et al. 2004). According to this view, as time passes following the initial acquisition of a memory, neocortical regions may acquire the ability to support context memory on their own, without need for the hippocampus.

Several lines of research support the idea that as the hippocampus wanes in importance, the role of the medial prefrontal cortex increases in importance. Patterns of immediate early gene expression, dendritic spine formation, and inactivation show inverse relations for hippocampus and prefrontal cortex (e.g., Frankland et al. 2004; Restivo et al. 2009; Quinn et al. 2008a; Tayler et al. 2013). However, there have been some reports of remote memory impairment with lesions of the hippocampus (Broadbent and Clark 2013; Sparks et al. 2013). The reason for the discrepancies between these studies is currently unknown, but there are at least two factors that contribute to the hippocampus' role in remote memory. First, the test experience itself may be a time of new encoding that is hippocampus dependent. When memories are reactivated prior to a test of contextual fear, they seem to regain their dependence on the hippocampus (Debiec et al. 2002; Winocur et al. 2009). Additionally, as the contextual memory consolidates into the

hippocampus-independent and cortex-dependent form, it loses some specificity, and this results in increased generalization across contexts over time (Wiltgen and Silva 2007). Manipulations that cause the contextual memory to retain its specificity also cause it to retain its dependence upon the hippocampus (Winocur et al. 2009). Other factors are certainly at play. For example, Kitamura et al. (2009) found that reducing neurogenesis in the dentate gyrus prolongs the consolidation period during which hippocampal inactivation impairs context fear. There are methodological issues to consider as well. Goshen et al. (2011) compared the effect of optogenetic and pharmacological inactivation of CA1 upon expression of context fear. As expected, both types of inactivation blocked recently acquired context fear. Also as expected, pharmacological inactivation did not affect recall of a remote contextual fear memory, and optogenetic stimulation did not affect remote recall if the light stimulation began 30 min before and continued throughout the test session. However, if the light was turned on during the remote test session, it interfered with freezing. One explanation for this could be that sudden loss of the hippocampus was a novel event that acted like a "distractor" stimulus to disrupt fear expression; novel distractors can phasically disrupt acquisition and expression of conditioned fear (Fanselow 1984; Han et al. 2003).

If it is true that contextual memories are consolidated to the neocortex over time and also that the context-US association is initially stored by LTP at hippocampal inputs to BLA, then where is the association stored after the context representation has become consolidated and no longer depends upon the hippocampus? Expression of contextual fear remains dependent upon the amygdala throughout an animal's lifetime (Gale et al. 2004), suggesting that contextual fear memories are stored in the amygdala both before and after consolidation of the memory into a hippocampal-independent form, although not necessarily by exactly the same amygdala neurons and synapses. Experiments using activity-dependent cell labeling have found that when a contextual fear memory is recalled 2 days after it was acquired, memory recall activates the same subpopulations of neurons in amygdala, hippocampus, and neocortex that were previously activated during storage of the memory; by contrast, when the contextual fear memory is recalled several weeks after it was stored, only the cortex exhibits activity patterns similar to those observed during storage, whereas the amygdala and hippocampus show altered activity patterns (Tayler et al. 2013). This suggests that when the context-US association is initially formed, the context is represented not only in the hippocampus but also in the neocortical structures that will eventually become the permanent repository of the context representation after consolidation. Prior to consolidation, activation of the cortical context representation may depend upon the hippocampus, and both hippocampal and cortical inputs to BLA may undergo LTP to store contextual fear memories. After consolidation, activation of the cortical context representation may become independent of the hippocampus, and the hippocampal representation may become altered or no longer be activated at all, so that the contextual memory must subsequently be read out through cortico-amygdala rather than hippocampo-amygdala synapses.

17.4 Neural Representations of Cues and Contexts in the Hippocampus

As discussed above in Sect. 17.2, the amygdala stores associative fear memories that map patterns of input from other brain structures onto patterns of neural activity in the amygdala ("fear engrams") that encode anticipated threats. Some of the amygdala's inputs come from the hippocampus, and to understand how these hippocampal inputs might contribute to activating fear engrams, it is necessary to consider how cues and contexts that can predict danger are encoded by patterns of neural activity in hippocampal memory circuits.

17.4.1 Configural Representations

Patterns of multiple sensory cues (for example, a sound in combination with an odor) are sometimes more accurate predictors of future events than individual sensory cues alone. It has been posited that prior to forming associations with a US, such cue patterns might be compounded into distinct neural representations referred to as *hierarchical* (Nadel and Willner 1980), *configural* (Rudy and Sutherland 1995), or *conjunctive* stimuli (O'Reilly and McClelland 1994). When a US is predicted by such configural stimuli, Pavlovian conditioning may require subjects to first solve a pattern recognition problem—namely, identifying and activating a mental representation of the configural stimulus—before it is possible to store (or recall) an association between the configural stimulus and the US.

It has been argued that the hippocampus may be important for constructing neural representations of configural stimuli and that perhaps the role of the hippocampus in contextual fear conditioning might ultimately derive from its role in configural learning (see Nadel 2008; Rudy 2009). According to this line of reasoning, the hippocampus recognizes contexts by performing pattern recognition upon configurations of cues (such as odors, textures, and visuospatial landmarks) that distinguish different contexts from another. It is certainly possible that discrimination of configural cue patterns might be one mechanism by which animals distinguish among contexts, so that conditioned fear is expressed selectively in the training context. But at any given point in time, the animal can only be in one location within a context and can thus only experience a subset of a context's features (those perceivable from its current location). For context fear to be expressed at locations in the training environment other than that where the US was delivered, the animal must generate a positive inference that cues observed from these other locations are part of the original training context. But cue configurations at these other locations within the context may be quite different from cues observed at the US location, and if so, configural representations of cue patterns may not be the best coding scheme to support generalization of context fear throughout the spatial continuum of the training environment. Instead, it may be better to represent the context using a "cognitive map" that encodes the spatial geometry of the environment (O'Keefe and Nadel 1978).

17.4.2 Spatially Tuned Neurons

The CA3 and CA1 regions of DH contain spatially tuned neurons called "place cells" that encode the animal's position in space (O'Keefe and Dostrovsky 1971). Each place cell fires selectively when an animal visits a preferred location, referred to as the "place field" of the cell. Most contextual fear conditioning studies are carried out in relatively small experimental chambers, usually measuring <0.5 m along their widest dimension; in a chamber of this size, it is typical for about 30–40 % of the pyramidal cells in the CA1 layer (Wilson and McNaughton 1993; Guzowski et al. 1999) and about 15–20 % of cells in the CA3 layer (Vazdarjanova and Guzowski 2004) of DH to exhibit a place field somewhere in the chamber. Dorsal place cells commonly exhibit small firing fields measuring about 10–40 cm wide, and their field centers tend to be evenly distributed throughout the environment (Muller et al. 1987). It is thus reasonable to estimate that about 10 % of pyramidal neurons in DH (CA3 and CA1) would fire at any given location in a context. Since all of these cells are drawn from a subpopulation of cells that have place fields in that context, the place code in CA3 and CA1 could provide information not only about where the animal is located in a context but also which context it is in (see Chap. 9 for discussion of remapping between contexts).

Place cells are found not only in DH but also in VH. Firing fields in VH tend to be larger than those of DH place cells, measuring up to several meters wide (Kjelstrup et al. 2008). Less is known about what percentage of VH place cells might be active in each context or how their field centers are distributed. Depending upon how the field centers are distributed, it is theoretically possible for a population of place cells with large firing fields to support place discrimination at exactly the same spatial resolution as an equal-sized population of place cells with small firing fields (Zhang and Sejnowski 1999). Hence, at the population level, it is not necessarily the case that VH place cells with large firing fields encode space at a lower resolution than DH place cells with small firing fields, even though it might be intuitively tempting to assume this. Nonetheless, at the level of single neurons, the large firing fields of ventral place cells may make them better suited than dorsal place cells for supporting generalization of contextual fear associations across continuous regions of space (see Sect. 17.5).

Spatially tuned neurons are also found in DG, but they behave differently from place cells in CA3 and CA1. One type of "sparse firing" neuron in dorsal DG exhibits very low firing rates; on the rare occasions when such a cell fires a spike, it tends to do so within a small unitary place field (measuring 10–30 cm across) at a very specific position in the environment, and it is estimated that less than 5 % of these sparse firing DG cells exhibit place fields in a typical context chamber (Jung and McNaughton 1993; Chawla et al. 2005; Neunuebel and Knierim 2012). Thus, at any given location, <1 % of the population of sparse firing DG neurons is likely to be active. So in comparison with the representation of space stored by CA3/CA1 place cells, sparse firing DG cells appear to store a less distributed code, with the property that only a small number of neurons are active at any location the animal visits. However, a different population of "multi-punctate" DG neurons have been

reported to fire at multiple locations (rather than a single location) that are randomly distributed throughout the whole environment (Leutgeb et al. 2007). It is presently unknown whether these multi-punctate firing fields are generated by a subpopulation of DG neurons that is anatomically or morphologically distinct from cells that generate sparse fields. It is possible that one firing pattern might be generated by granule cells and the other by mossy cells, or alternatively one firing pattern may be generated by mature granule cells, the other by newly born granule cells (Alme et al. 2010; Neunuebel and Knierim 2012) (see Chap. 15). Further study is needed to investigate this issue.

It has been proposed that DG and CA3 may contain circuits that mediate opponent processes of pattern separation versus completion, respectively (Treves and Rolls 1994; Guzowski et al. 2004; Knierim et al. 2006; Leutgeb et al. 2007; Yassa and Stark 2011). According to this view, DG neurons may perform pattern separation by detecting changes in hippocampal input patterns that occur when the animal moves to a different place or context. Disruption of plasticity in DG throughout the dorsoventral axis of the hippocampus results in abnormal generalization of contextual fear to untrained contexts (McHugh et al. 2007), suggesting that DG plasticity may be needed to support pattern separation mechanisms that allow animals to discriminate one context from another and thereby constrain generalization of context fear to occur only across continuous but not discontinuous regions of space. It has recently been shown that optogenetic activation of context representations stored by a neural activity patterns in the dorsal DG is sufficient to trigger the recall of contextual fear memories (Liu et al. 2012; Ramirez et al. 2013). There is also evidence to suggest that mature versus newly born DG granule cells make differing contributions to pattern separation versus completion (Nakashiba et al. 2012). In contrast with DG, recurrent connections among CA3 neurons are thought to support pattern completion by filtering out small fluctuations in hippocampal input, so that the same subpopulation of CA3 neurons can remain stably active even when hippocampal input patterns are noisily fluctuating. This stability of CA3 activity is thought to be important for the ability to recognize familiar cues even when they are altered or perturbed in novel ways (Lee et al. 2004). Supporting this, disruption of neural plasticity in CA3 has been shown to impair spatial navigation by rodents in familiar environments where spatial cues have been altered, which animals are normally able to do when CA3 plasticity is unimpaired (Nakazawa et al. 2002) (see Chaps. 14 and 8).

Hippocampal circuits are believed to perform pattern classification upon their inputs, but where do these inputs come from? Major cortical and subcortical inputs to the hippocampus are routed through EC and the fornix/fimbria, respectively. The medial entorhinal cortex (MEC) contains “grid cells” that fire at multiple locations which form a hexagonal lattice that tiles the floor of the environment, and like place cells, grid cells exhibit a dorsoventral gradient of their field sizes and vertex spacings (Hafting et al. 2005). MEC also contains “border cells” that fire along specific environmental boundaries (Solstad et al. 2008; Savelli et al. 2008; Lever et al. 2009) (see Chap. 5). Neurons in the lateral entorhinal cortex (LEC) do not show pronounced spatial tuning, but their firing appears to be related to objects and

landmarks in the environment (Deshmukh and Knierim 2013), and inputs to hippocampus from LEC may modulate place cell firing rates to encode memories of episodes within a context (Lu et al. 2013) (see Chap. 6). Many studies have found that contextual fear is impaired by disruption of EC (Maren and Fanselow 1997; Ferbinteanu et al. 1999; Schenberg et al. 2005; Ji and Maren 2008; Majchrzak et al. 2006), but other studies have reported conflicting results (Phillips and LeDoux 1995; Good and Honey 1997; Hebert and Dash 2004). Trace conditioning can also be impaired by disruptions of entorhinal cortex (Esclassan et al. 2009b; Suh et al. 2011). Subcortical inputs to the hippocampus that arrive through the fornix are involved in theta synchronization of neural activity in the hippocampus (Pignatelli et al. 2012), and disruption of these inputs can impair contextual fear conditioning (Maren and Fanselow 1997; Bannerman et al. 2004).

17.4.3 Storing and Updating Context Memories

Spatially tuned neurons in the hippocampus and elsewhere may serve as elementary building blocks for constructing cognitive maps that store memories of familiar environments and events that have occurred there (O'Keefe and Nadel 1978; Leutgeb et al. 2005; Moser and Moser 2008). When an animal is first introduced to a novel environment, population coding of the animal's position by DH place cells becomes more accurate with increased exposure time (Wilson and McNaughton 1993), and inactive cells can acquire new place fields during the first few minutes of context exposure (Frank et al. 2004). Such refinement of place cell firing during initial exploration of a novel environment may reflect the formation of a stable cognitive map of the context. Supporting this, the amount of exploration time required for DH place cells to stabilize their activity patterns in a new environment is similar (tens of seconds to a few minutes) to the amount of preexposure time required to overcome the immediate shock deficit in contextual fear conditioning (Pevzner et al. 2012). Disruption of hippocampal plasticity in dorsal CA1 or CA3 prevents place cells from forming compact (McHugh et al. 1996; McHugh and Tonegawa 2009) or stable (Kentros et al. 1998) firing fields and also prevents context preexposure from rescuing the immediate shock deficit (Barrientos et al. 2002; Matus-Amat et al. 2004; Stote and Fanselow 2004). These findings suggest that hippocampal plasticity may be needed to form a representation of a novel context during early exploration, so that the context can subsequently serve as a predictive fear cue if an aversive stimulus is encountered there.

Once place cell firing fields have stabilized in a familiar environment, they tend to remain stable during future visits to that same environment. However, gradual changes in place fields over hours or days have been reported (Lever et al. 2002; Ziv et al. 2013), and CA3 place fields may be more stable across long time periods than those in CA1 (Mankin et al. 2012). As noted above (see Sect. 17.3.2), such instability of place fields might contribute to spontaneous recovery of fear to an extinguished CS after the passage of time. Nonetheless, it is generally believed that

if environmental cues do not change, then the preferred firing locations of many place cells will retain long-term stability with respect to the static coordinate frame of the environment and with respect to one another as well. These stable place cells are thus thought to implement a distributed population code that tracks the animal's current location as it navigates through a familiar environment. When an animal is transported from one familiar environment to another, the preferred firing locations of place cells (and their adjacency relationships to one another) become scrambled, a phenomenon referred to as "global remapping" of the place code (Leutgeb et al. 2005). After global remapping is induced by transport to a different context, a different subset of place cells will be active (presumably still comprising 30–40 % of all pyramidal neurons), so that firing rate vectors encoding positions in different contexts are drawn from distinct subpopulations of pyramidal neurons, which can partially overlap with one another, but may overlap less in CA3 than CA1 (Vazdarjanova and Guzowski 2004). Global remapping of place fields may thus be an important neural mechanism for discriminating different familiar contexts from one another (see Chap. 9).

When a rodent first explores a novel context, it frequently rears its head to sniff the air and visually observe the surroundings, as if taking careful measurements of the environment to store information about the cues it contains and their relationships with one another (Lever et al. 2006). Such rearing behavior diminishes as the context becomes familiar but returns if familiar cues in the environment are perturbed into novel configurations. Renewed rearing may be accompanied by shifts in the preferred firing locations of some place cells (Anderson et al. 2006), a phenomenon referred to as "partial remapping" of place fields, suggesting that altering a familiar context can alter its neural representation by place cells as well. Supporting this, place cells in DH have been shown to exhibit remapping of their firing fields when spatial cues in the environment are altered in various ways (Bostock et al. 1991; Lee et al. 2004; Leutgeb et al. 2006, 2007).

When place cells change their firing properties, it is not always easy to determine whether the changes are caused by global remapping (i.e., a reshuffling of the preferred locations at which place cells fire) or by what has been termed "rate mapping," defined as systematic modulation of the rate at which a place cell fires when the animal visits its firing field, while the firing field itself remains at a stable location (Leutgeb et al. 2005). It has been posited that global remapping may occur when an animal perceives a transition to a new spatial environment, whereas rate remapping may provide a mechanism for encoding memories of different episodes or circumstances that can occur within the space of a single environment (Leutgeb et al. 2005). Consistent with this idea, place cells have been reported to change their spatial firing properties in response to alterations in nonspatial factors such as odors (Anderson and Jeffery 2003), goals and motivational states (Kennedy and Shapiro 2004; Smith and Mizumori 2006; Lee et al. 2004; Kim et al. 2007), or future behavioral choices (Frank et al. 2000; Wood et al. 2000). Some of these reported changes are likely to result from rate rather than global remapping, and such rate remapping may provide a mechanism for integrating nonspatial information into the spatial code. In addition to encoding information about space, some

hippocampal neurons can also encode information about time (Manns et al. 2007; Pastalkova et al. 2008; MacDonald et al. 2011; Mankin et al. 2012; Kraus et al. 2013) or exhibit evoked responses to nonspatial stimuli such as odors (Wood et al. 1999) and sounds (Berger et al. 1976; Moita et al. 2003) (see Chap. 11). These nonspatial influences upon the firing of hippocampal neurons may support encoding of episodic memories for stimuli and events that occur in a specific time and place.

An encounter with an aversive US is one kind of salient "episode" that can occur in a spatial environment, and it is important for animals to store memories of such encounters so that they can learn to avoid danger in the future. Emotional memories encoding which cues predict aversive encounters may be stored in the amygdala (see Sect. 17.2.2), but episodic memories of where and when such encounters have occurred in the past are thought to be stored by the hippocampus (Bechara et al. 1995). Hence, if remapping of place cells is important for encoding memories of episodes that have occurred in a given context, then it might be expected that place cell remapping should be observed in a context where fear conditioning occurs. Supporting this prediction, Figure 17.2c shows that cued fear conditioning to an auditory tone was found to induce remapping of place fields in the conditioning context, but not in a neutral context (Moita et al. 2004). Place cells have also been reported to remap in a context where a predator odor is encountered and retain stable new firing fields after the encounter (Wang et al. 2012; see Fig. 17.2d). Hippocampal place cells and interneurons can also acquire cue-evoked responses to a fear-conditioned CS; for place cells, CS-evoked responses are expressed only within the cell's place field and not at other locations (Fig. 17.2a), and for interneurons, CS-evoked responses reset the phase of theta bursts (Moita et al. 2003). Taken together, these findings suggest that an aversive experience can alter representations of spatial contexts encoded by place cells, and these changes in place cell firing may reflect influences of emotion upon memory that are thought to be mediated by projections from amygdala to the hippocampus and entorhinal cortex (Cahill and McGaugh 1998; Majak and Pitkänen 2003).

17.5 Summary and Conclusions

Here we have surveyed evidence from studies of Pavlovian fear conditioning—as well as other anatomical and neurophysiological experiments—that elucidate how interactions between the amygdala and hippocampus regulate influences of memory upon fear. The amygdala is believed to store associative memories that map states of the world onto patterns of neural activity ("fear engrams") that encode expectations of danger (Sect. 17.2). To recall stored fear memories, the amygdala may compare its current pattern of inputs against patterns that have co-occurred with danger in the past. If the current input pattern is similar enough to a pattern that has previously been associated with a "fear engram," then the amygdala is activated and this can trigger expression of defensive behaviors. Conversely, if the current input pattern is different from stored patterns, then no fear engram is activated. VH

provides a source of inputs to the amygdala (especially the B nucleus) and exerts influence over storage and recall of fear memories by the amygdala. Hippocampal memory representations play an especially important role in certain forms of fear conditioning, such as trace and contextual fear conditioning, and in mediating the context specificity of fear extinction (see Sect. 17.3).

The ability of a Pavlovian CS to elicit expectation of the US can transfer to other stimuli that are similar, but not identical, to the trained CS. From the viewpoint of the amygdala, there are two mechanisms by which such generalization of conditioned fear might occur (which are not mutually exclusive). First, if different predictive stimuli are encoded by distinct patterns of input to the amygdala, then it may be possible for fear engrams to be activated by amygdala input patterns that are similar, but not identical, to the input pattern that was originally associated with the fear engram during CS–US pairing. If so, then amygdala circuits may have some capacity to perform pattern completion on their inputs and thereby reactivate a stored fear engram even when the current input pattern fails to exactly match a stored pattern. Alternatively (or in addition), the amygdala might rely upon the hippocampus to perform pattern completion functions. If so, then when the animal encounters a cue that is similar to a previously fear-conditioned CS, the hippocampus might first perform pattern completion upon its own inputs to recall an "exact" hippocampal representation of the CS and then feed this representation to the amygdala, providing it with an input pattern that closely matches the pattern that was originally associated with the fear engram. In this way, the hippocampus could relieve the amygdala from the burden of performing pattern completion on its own and thereby help it to recognize threatening stimuli.

Pattern separation and completion are posited to be primary computational functions of hippocampal circuits in DG and CA3, respectively (see Chap. 9), so the hippocampus may be involved in determining which broader categories of cues should inherit a fear association, and which should not. Supporting this, evidence reviewed above indicates that hippocampal manipulations can alter generalization of auditory fear conditioning (Sect. 17.3.2) and enhance generalization (or equivalently, impair discrimination) of contextual fear conditioning (Sect. 17.3.4). In normal animals, contextual fear conditioning generalizes within but not between contexts, suggesting that contexts are encoded in a representational space where different locations in the same environment are judged "similar" enough to share Pavlovian associations with one another. For Pavlovian fear association to generalize across spatial locations in this way, it may be necessary to encode contexts in a representational space where similarity between different locations in the context can be judged by their spatial distance from one another, rather than more subjective similarity measures such as the degree of overlap between cues perceived at different locations (since the sensory cues that are perceived at one location in an environment might differ considerably from those perceived at a another location). Spatially tuned neurons in the hippocampus and related structures (such as EC) may represent context memories as "cognitive maps" that facilitate these observed patterns of spatial generalization (Sect. 17.4).

Place cells with small firing fields are found in DH, but only VH (and not DH) is interconnected with the amygdala (Fig. 17.1). Despite this, DH still makes important contributions to contextual and other forms of fear conditioning (Sect. 17.4), suggesting that it may not be possible for VH circuits to relay cue and context representations to the amygdala without support from DH. VH contains place cells with larger firing fields than those in DH, so projections from VH projections to the amygdala may support storage of context-fear associations that generalize broadly over space. Perhaps DH place cells do not project to the amygdala because their small firing fields cannot support generalization of contextual fear across the entire spatial extent of an environment. It is not presently known whether transitions between different contexts can induce "global remapping" of place cells in VH (as appears to occur in DH), but if so, then this would probably be sufficient to prevent generalization of fear conditioning across different contexts. From the amygdala's perspective, contextual fear conditioning would then reduce to the problem of mapping specific patterns of firing among ventral hippocampal place cells (those that encode contexts where aversive encounters have previously occurred)—and possibility EC grid cells as well—onto patterns of activity in the amygdala ("fear engrams") that can drive appropriate defensive behaviors in those contexts. Further research is warranted to investigate the details of how VH neurons encode information about cues and contexts that become associated with danger during fear conditioning.

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Hippocampal Projections to the Ventral Striatum: From Spatial Memory to Motivated Behavior

18

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Abstract

Multiple regions of the hippocampal formation project to the ventral striatum, a central node in brain circuits that subserve aspects of motivation. These projections emphasize information flow from the ventral (temporal) pole of the hippocampus and interact with converging projections and neuromodulatory inputs upon arrival in the ventral striatum. Simultaneous neural recordings in the rat show that ventral striatal activity displays intricate timing relationships with the hippocampus, spanning multiple timescales and behavioral states, such as theta phase precession during reward approach and reactivation of place-reward associations during sleep. Disconnection of the hippocampus and ventral striatum results in impairments in the use of spatial information for place preference, as well as in location-appropriate responding to reward-predictive cues. Together, these findings indicate that spatial and contextual information from the hippocampus shapes reward-predictive activity in the ventral striatum, which in turn contributes to the learning and expression of place-reward associations.

Information processed by the hippocampus is dispersed to a number of structures. The anatomical properties of these projections form a basis for an exploration of how hippocampal processing ultimately contributes to behavior. In this chapter we discuss the anatomy and function of hippocampal projections to the ventral striatum, a heterogeneous brain structure that plays a central role in the motivational control of

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behavior (Berridge 2007; Nicola 2007; Humphries and Prescott 2010). The hippocampal input to the ventral striatum is therefore well placed to provide spatial and episodic information to aspects of motivation, such as learning from appetitive and aversive feedback and invigorating and directing ongoing behavior (Mogenson et al. 1980; Robbins and Everitt 1996; Pennartz et al. 2011; van der Meer and Redish 2011a).

To be consistent with other chapters in this volume and to facilitate connections between anatomy, physiology, and behavior, we focus exclusively on studies in the rat. Most of these studies that included behavior have used spatial tasks, providing a rich domain for the study of different hippocampal-dependent aspects of memory (this volume; see also Mizumori 2007). However, for a more human-centered view with a different emphasis, see Wimmer and Shohamy (2011). This chapter is intended to complement related reviews (Pennartz et al. 2011; Malhotra et al. 2012) by providing an accessible overview of hippocampus-striatum interactions.

18.1 Macrocircuitry: Anatomical Basis

Output pathways of the hippocampal formation[1] can be grouped anatomically into those with nearby targets—such as the entorhinal cortex and amygdala—and those with "long-distance" targets, primarily passing through the fimbria/fornix (Witter and Amaral 2004). The projection to the striatum is not reciprocal, and it is part of the so-called postcommissural bundle of the fornix, which also contains projections to the prefrontal cortex and the septum (Aggleton et al. 2010). In this section, we discuss the major features of this descending projection from the hippocampal formation to the striatum.

First, multiple hippocampal subregions project to the striatum, targeting the ventral regions specifically.[2] These hippocampal inputs originate predominantly from CA1 and the subiculum, but projections also arise from the entorhinal and perirhinal cortices, which, although not technically part of the hippocampal formation, are nevertheless strongly interconnected with it. The projections from CA1/subiculum on the one hand, and associated cortical areas on the other hand, follow somewhat different pathways—discussed separately below—but all target the ventral aspect of the striatum. In turn, multiple ventral striatal subregions, including not just the core and shell of the nucleus accumbens but to a lesser extent also the ventral caudate-putamen, receive inputs from the hippocampal formation and associated cortices. This is clear from both anatomical (Groenewegen et al. 1982, 1987; Kelley and Domesick 1982;

[1] Following convention, we take this term to include the dentate gyrus, the "CA" subfields of Ammon's horn, and the subiculum.

[2] Following Heimer et al. (1997) and others (Voorn et al. 2004; Haber 2009), we define the ventral striatum as the nucleus accumbens core, shell, and the striatal bridges of the olfactory tubercule, while recognizing that boundaries with the ventral caudate-putamen may not be sharp.

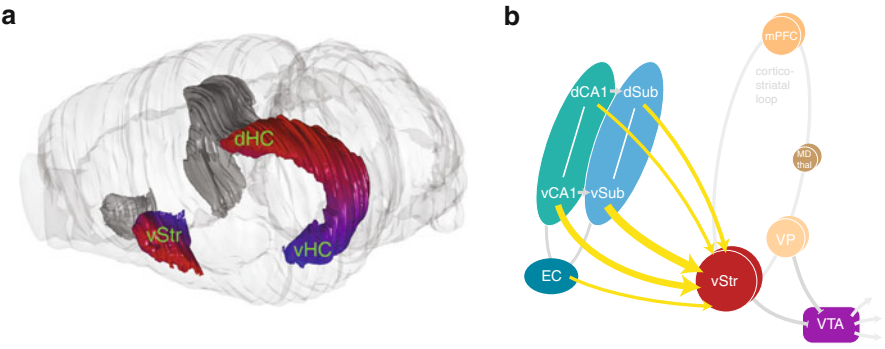

Fig. 18.1 (**a**) Perspective rendering of the hippocampal formation and the ventral striatum in the rat brain. The dorsal-to-ventral (septal-to-temporal) axis of the hippocampal formation (HC; CA1 and subiculum shown, colored *red*-to-*blue*) projects topographically onto the caudomedial-to-rostrolateral axis of the ventral striatum (vStr; nucleus accumbens core and shell shown), rendered in matched colors to illustrate this overall organization. Note, however, that this figure does not indicate the relative densities along this axis; ventral hippocampus sends a denser projection to the vStr compared to dorsal HC. Figure based on data from the freely available INCF Atlas3D suite (Hjornevik et al. 2007). (**b**) Reduced schematic of anatomical connections centered on the hippocampus and the ventral striatum. *Thickness of the yellow arrows* indicate the relative density of projections. Areas are not drawn to scale, nor are the relative positions meant to indicate any particular arrangement

Phillipson and Griffiths 1985; Brog et al. 1993) and electrophysiological studies (Finch 1996).

Second, for CA1 and subicular input, projection density increases along the dorsal-to-ventral (septal-to-temporal) axis of the hippocampal formation, with a relatively sparse distribution in the dorsal pole and a relatively dense projection pattern in the ventral pole. This result has been confirmed independently using a number of different techniques; anatomically, the clearest support has come from the Groenewegen et al. (1987) anterograde tracing study and the retrograde fluorogold tracing by Brog et al. (1993). This principle maps well onto electrophysiological and functional studies demonstrating dissociations along the dorsal-to-ventral axis (Bannerman et al. 2004; Bast 2007; Fanselow and Dong 2010; see also Sect. 18.2).

Third, the dorsal-to-ventral axis of the hippocampal formation maps topographically onto the ipsilateral rostrolateral-to-caudomedial axis of the ventral striatum (Kelley and Domesick 1982; Groenewegen et al. 1987; McGeorge and Faull 1989; Brog et al. 1993; Voorn et al. 2004; Sesack and Grace 2010; Fig. 18.1). Taken together with the previous point, this suggests that the caudomedial vStr, corresponding to the medial shell, tends to receive the strongest hippocampal input, with the rostrolateral vStr receiving relatively weaker inputs. In addition, the proximal subiculum has denser projections to the ventral striatum than does the distal subiculum (Groenewegen et al. 1987; Witter et al. 1990). This latter organization seems to be most prominent in the dorsal subiculum (Witter and Groenewegen 1990).

Finally, the projections from the entorhinal cortex to the ventral striatum, which like the projections from the hippocampus are almost exclusively ipsilateral, are also organized topographically. The lateral entorhinal cortex (see Deshmukh 2014) preferentially targets lateral aspects of the ventral striatum (along the entire rostrocaudal axis), and the medial entorhinal cortex (see Derdikman and Moser 2014) preferentially targets the medial ventral striatum (Phillipson and Griffiths 1985; Totterdell and Meredith 1997). Some further organization in projection density along the rostrocaudal axis of the entorhinal cortex and ventral striatum has also been noted (Totterdell and Meredith 1997).

18.2 Microcircuitry: Convergence and Interactions

In this section we highlight some features of the hippocampal-ventral striatal projection at the microcircuit level.

In the hippocampus, several studies have noted that CA1 cells projecting to the striatum are found predominantly in the "deep" pyramidal lamina and to a lesser extent in the stratum pyramidale (McGeorge and Faull 1989; Brog et al. 1993). A recent study found differences in the spike-field relationships of deep and superficial CA1 cells (Mizuseki et al. 2011). Of particular interest for understanding the information these cells may convey to the striatum is the observation that these deep pyramidal cells were more likely to have place fields. Entorhinal inputs to the ventral striatum seem to originate primarily from deep cell layers that contain hippocampally processed information (Finch 1996). This suggests that entorhinal inputs to the ventral striatum may be functionally related to those from the hippocampus.

In the striatum, HC inputs commonly converge upon vStr neurons with inputs from medial prefrontal cortex (mPFC) and the basolateral amygdala (Finch et al. 1995; O'Donnell and Grace 1995; Groenewegen et al. 1999; Floresco et al. 2001; French and Totterdell 2002, 2003), raising the question of how these inputs interact. The interaction of mPFC and HC inputs has received attention particularly in the in vivo anesthetized preparation, where vStr neurons (likely medium spiny neurons, "MSNs") display bistable membrane potentials. Under these conditions, vHC inputs appear to be particularly effective in eliciting "up" states and may function as a permissive "gate" for subsequent mPFC inputs (O'Donnell and Grace 1995; Goto and O'Donnell 2002). However, there is also evidence that with sufficient stimulation, mPFC inputs can effectively drive state transitions (Gruber et al. 2009; Britt et al. 2012), and the nature of these phenomena likely depends on dopamine levels, anesthesia, the precise location of stimulation, and other factors (Lodge and Grace 2011). Similar interactions have been reported for the interaction of HC and basolateral amygdala inputs (Mulder et al. 1998).

In sum, despite some caveats, inputs to vStr appear capable of richer interactions than simple additive effects, particularly when the effects of feedforward (afferent-triggered) inhibition are included (Pennartz and Kitai 1991). Additional nonlinearities between powerful, combined inputs likely arise because of recurrent

interactions between medium-sized spiny neurons (Tunstall et al. 2002; Taverna et al. 2004). An important area of research is to determine how these interactions play out in awake settings (Gruber et al. 2009; Wolf et al. 2009), an issue facilitated by the possibility of (in)activating specific neuron types with high temporal specificity (e.g., Szydlowski et al. 2013).

A further aspect of hippocampal inputs to the ventral striatum is their preferential association with D1-expressing MSNs. The mapping of D1/D2 receptor expression onto downstream anatomical direct/indirect pathways (Gerfen et al. 1990) is much less clear in the ventral compared to the dorsal striatum (Groenewegen et al. 1996). However, the vStr does contain MSNs that preferentially express D1 or D2 receptors (Nicola et al. 2000; Matamales et al. 2009), a distinction relevant to understanding hippocampal inputs. For instance, MacAskill et al. (2012) found that HC inputs to the core have significantly stronger effects on identified D1-expressing MSNs relative to D2-expressing MSNs—an asymmetry not present in mPFC or thalamic inputs. The preferential association of HC inputs with D1R-expressing MSNs has also been demonstrated pharmacologically. Goto and Grace (2005) found that D1 agonists infused into NAcc core transiently increased evoked responses to HC stimulation, while D2 agonists had no effect. How these distinctions relate to downstream projection targets is an active area of current research (Papp et al. 2012).

18.3 Function: Intervention Studies

There is a large body of work on lesions of the fornix, which carries the majority of hippocampal input fibers to the ventral striatum. However, because the fornix carries many other fibers as well, the results of these studies can rarely be cleanly attributed to HC-vStr interactions specifically. In particular, fornix lesions severely disrupt hippocampal processing in general due to loss of theta pacemaker inputs from the septum and directional input from head direction cells in the anterior thalamus, for instance. Nevertheless, these studies can be informative in that if a certain behavior is intact following fornix lesions, it is unlikely to require HC output to the vStr.

One approach to revealing the contribution of the HC-vStr connection to behavior is to exploit the fact that the projection between them is primarily ipsilateral: a so-called asymmetric "disconnection lesion" involving unilateral lesions of each structure in opposite hemispheres selectively removes communication between the two structures. Ito et al. (2008) used this technique to study the effects of the HC-vStr projection on a Y-maze conditioned place preference task (Fig. 18.2). The disruption of serial communication between the HC and shell subregion of the vStr induced a deficit in the ability of rats to express conditioned place preference (the preference for reward-associated place in extinction), as well as an impairment in using spatial information to guide a discriminative approach response to a reward-associated cue (Fig. 18.2).

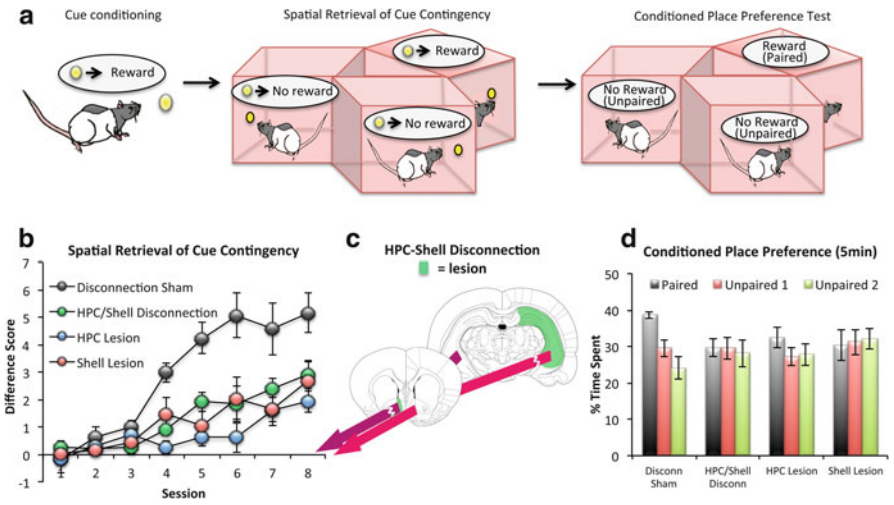

Fig. 18.2 HPC-shell disconnection study using an appetitive Y-maze task. (**a**) Rats were first trained to expect to receive a sucrose reward with the presentation of a light cue at various locations in a Y-maze apparatus (all three chambers). They were then trained to learn that only cues presented in one spatial location (one of three chambers) would be associated with reward delivery. Rats would typically develop a discriminative approach behavior towards the cue presented in a reward-associated location but avoid the cue presented in non-reward-associated locations (expressed as difference score). They were then tested for conditioned place preference in extinction (and without the cues) to specifically assess the acquisition of place-reward associations. Disconnection excitotoxic lesions of the HPC and shell of the vStr (**c**), as well as bilateral lesions of the HPC and shell, led to an impairment in the ability to use spatial information to guide a cue approach/avoidance response (**b**), as well as a deficit in forming place-reward associations (**d**). Figure based on data from Ito et al. (2006, 2008)

Floresco et al. (1997) took a similar disconnection approach, this time by pharmacologically and transiently inactivating the ventral CA1/subiculum and vStr on a radial arm maze task that required learning place-reward associations. They found that this disconnection led to a specific impairment under circumstances in which rats were required to develop an efficient strategy to forage for reward in trial-unique spatial locations. They did not, however, observe a deficit when rats were required to use previously learnt place-reward associations for reward foraging after a 30 min delay period (win-shift strategy). Taken together, these disconnection studies demonstrate the importance of the HC/vSub-vStr pathways in allowing spatial information represented in the HC to guide goal-directed responses but may also highlight subtle differences in the functions subserved by different hippocampal regions (HC versus vSub).

18.4 Function: Connection to Dopamine

The projection from hippocampus to the ventral striatum plays an important role in regulating the activity of dopaminergic neurons in the VTA. Stimulation of the vHC/vSub activates VTA neurons in a manner that does not depend on mPFC, but rather seems to be polysynaptic through vStr and, in part, the ventral pallidum (Legault et al. 2000; Floresco et al. 2001; but see Blaha et al. 1997; Papp et al. 2012). The result is increased dopamine levels in vStr itself, which can lead to acute effects such as hyperactivity, reinstatement of drug seeking (Bast et al. 2001; Vorel et al. 2001), and preferential gating of HC inputs to the vStr (Ito and Hayen 2011). vHC stimulation can also increase DA in other projection targets of the VTA (Gurden et al. 2000; Bast and Feldon 2003). Several studies have noted that stimulation of the ventral hippocampus is more effective in eliciting DA release compared to stimulation of the dorsal hippocampus (Howland et al. 2004; Peleg-Raibstein and Feldon 2006), in line with the anatomical gradient in projection density (Fig. 18.1).

The functional relationship between vHC/vSub activity and dopamine levels has led to proposals that the HC-Str projection can set the gain of alerting and learning signals arising from the VTA (Grace 2010) and implicates its dysregulation in DA-associated disorders such as addiction and schizophrenia (Vorel et al. 2001; Ito and Canseliet 2010; Lodge and Grace 2011; Britt et al. 2012). It is important to note, however, that there are multiple possible pathways for the hippocampus to influence DA release. Contributions of HC inputs to presynaptic DA terminals in vStr have been suggested (Sesack and Pickel 1990; Blaha et al. 1997) and alternative polysynaptic pathways, through the amygdala and mPFC, and from dorsal CA3 to lateral septum to VTA, have also been noted (Luo et al. 2011).

18.5 Mechanisms: Electrophysiology

Early work recording neural activity from the hippocampus and ventral striatum simultaneously established that relationships between neural activity in the two structures are modulated by behavior. Two such studies (Martin 2001: subiculum and accumbens; Tabuchi et al. 2000; CA1 and accumbens) found increased coordination in spiking activity as rats approached reward locations. Specifically, the Tabuchi et al. study used cross-correlations between HC and vStr neurons, noting a theta component in the cross-correlation increased during reward approach.

Theta scale coordination between the hippocampus and ventral striatum during reward approach also forms a major theme in a recent simultaneous HC-vStr recording study (Van der Meer and Redish 2011b). In this study, rats performed a continuous T-maze task where the rewarded strategy (left rewarded, right rewarded, or alternation rewarded) was chosen randomly at the start and in the middle of each recording session. On this task, a sizeable proportion of ventral striatal neurons (15–20 %) showed a characteristic anticipatory "ramping" pattern of increasing firing rate during approach to reward sites [Fig. 18.3a, Schultz et al. (1992),

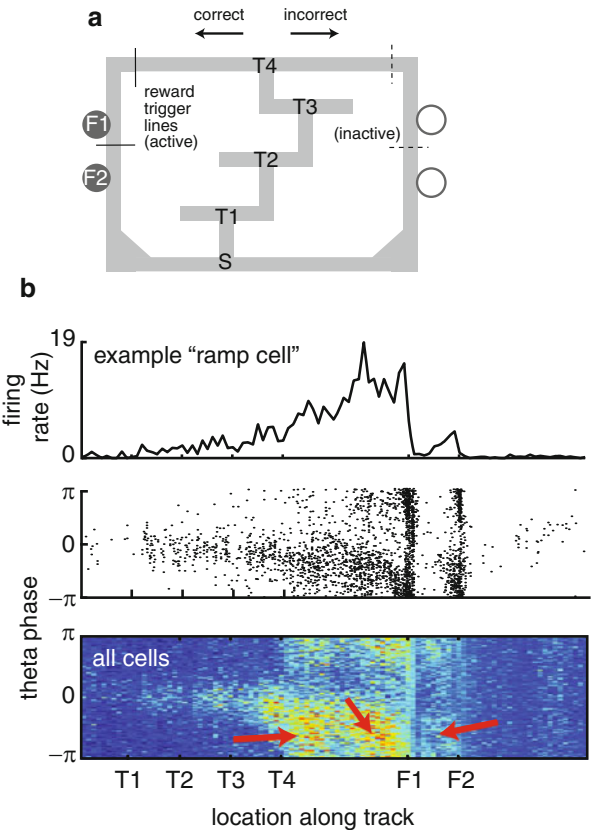

Fig. 18.3 (**a**) Layout of the Multiple T-maze (Schmitzer-Torbert and Redish 2002) on which multiple units and local field potentials were recorded simultaneously from the rat hippocampus and ventral striatum. Rats ran laps up the central stem of the maze, which consisted of three low-cost choices (T1–T3) and a high-cost choice point (T4). Only one choice at T4 was rewarded for any given lap; the reward policy was changed between left rewarded, right rewarded, or alternation at the start and in the middle of a recording session. (**b**, *top panel*) Theta phase precession in a ventral striatal anticipatory "ramp" cell with increasing activity up to the reward sites (F1 and F2). "Ramp" firing was accompanied by systematic changes of spike phase relative to the hippocampal theta rhythm (*middle panel*). (*Bottom panel*) Pseudocolor histogram of theta phase across the track for all recorded cells ($n = 277$); note phase precession is restricted to certain locations, including the final choice point (T4) and the reward locations (F1, F2, *red arrows*). Adapted from van der Meer and Redish (2011b)

see Malhotra et al. (2012) and Pennartz et al. (2011) for discussion of other studies of anticipatory ramping in vStr].

Anticipatory ramping neurons on this task tended to display clear theta phase precession [Fig. 18.3b, see Lever et al. (2014), for an introduction to this phenomenon, nearly ubiquitous in the hippocampal formation]. Phase precession, also apparent in the population average phase histogram (Fig. 18.3b), was not uniformly

distributed across ventral striatal cells or across locations on the track, but preferentially occurred in anticipatory ramping cells. Other common cell types, such as those responding during or following reward delivery, or with diffuse firing fields on the track, did not display phase precession.

Since there is no evidence for local theta generation in the ventral striatum (see Malhotra et al. 2012 for discussion), these results suggest that phase precession in the ventral striatum is derived from the hippocampus. In that case, HC-vStr coordination is not only specific to particular behaviors but also to a specific population of vStr neurons with particular task-related firing.

One of several open issues arising from the above studies is the relative contribution of increased hippocampal drive on the one hand and increased ventral striatal sensitivity on the other to increased HC-vStr coordination during reward approach. Van der Meer and Redish (2011b) recorded simultaneous ensembles of dorsal CA1 neurons and found no evidence for increases in firing rate or temporal coordination (phase precession) upon reward approach such as those seen in vStr.[3] However, this study did not examine ventral hippocampal regions, which may be expected to be the primary contributor to ventral striatal phase precession. Future studies must determine to what degree ventral hippocampal activity shares the reward-related features present in vStr phase-precessing neurons.

18.6 Comparison of Spatial Representations in the Hippocampus and Ventral Striatum

Lansink et al. (2012) recorded HC and vStr activity in the same Y-maze as used by Ito et al. (2008). In this electrophysiological study, the first question was to what extent vStr neurons—in comparison to the hippocampus—express spatial information in a setting where spatial navigation is driven by path integration, without discrete cues that distinguish different parts of the environment. This setup allowed to test two contrasting hypotheses (i) vStr neurons "inherit" spatial information from the hippocampus in the sense that they, like CA1 neurons, will express location-specific firing patterns, similar to the place fields of CA1 neurons, as suggested by some previous studies (Lavoie and Mizumori 1994; Shibata et al. 2001; notably, these previous studies examined vStr firing in the presence of landmark cues); (ii) vStr neurons do not express place fields or similar patterns but will utilize spatial-contextual information from the hippocampus to drive spatially dependent behavior, for instance, because spatial information contributes to reward prediction.

The results showed that, in contrast to CA1 neurons, vStr cells exhibited little or no spatial selectivity in the Y-maze, in line with hypothesis (ii) (Fig. 18.4a). Instead,

[3] We note that the extent to which dorsal CA1 place cells show reward-related organization is an issue of long-standing debate. For instance, Hollup et al. (2001) found increased place cell density near reward sites, but this effect does not always manifest (e.g., Lansink et al. 2009; Van der Meer et al. 2010). This debate would benefit greatly from a single study identifying the conditions under which such effects are present and absent.

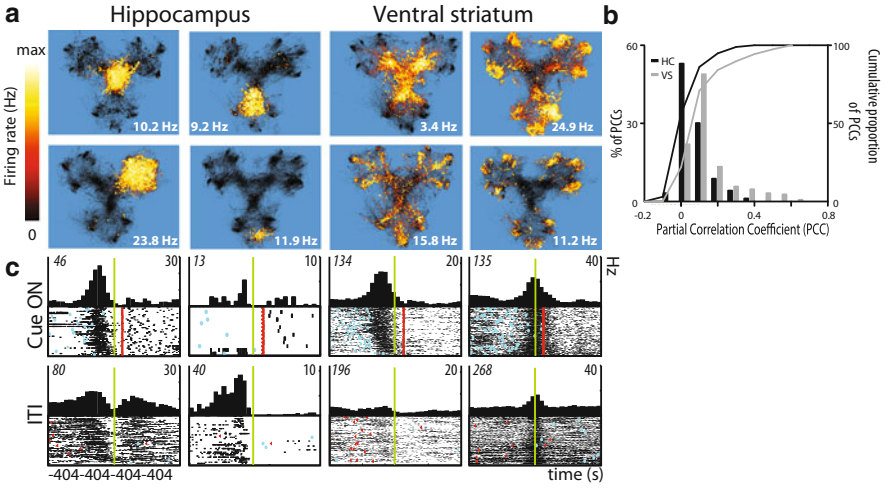

Fig. 18.4 Hippocampal and ventral striatal firing patterns in a Y-maze. (**a**) Whereas hippocampal neurons showed location-specific firing patterns ("place fields"), the firing of the ventral striatal neurons was more rotationally symmetric. Each *blue panel* shows the color-coded local instantaneous firing rate of a single hippocampal (*left four panels*) or ventral striatal (*right four panels*) neuron, superimposed on the occupancy map of the rat (*black*). Firing rates range from very low values shown in *dark red colors* to increasingly higher values shown in *yellows* and *whites*. Maximal firing rate on the maze is noted in the lower right corner. Examples were taken from different recording sessions. (**b**) This difference in spatial firing patterns was quantified by computing the spatial symmetry of single-neuron firing patterns. First, the rate and occupancy maps of each chamber were rotated such that all chambers overlapped in the same region of space. The similarity between the binned rate maps of two Y-maze chambers was then assessed with a partial correlation coefficient, in which the behavioral occupancy for each chamber was partialled out. Spatial symmetry was determined by averaging the partial correlation coefficients of all chamber pairs. The ventral striatal distribution of coefficients and the cumulative distribution (*grey bars and line*, respectively) were significantly shifted towards higher values than for hippocampus (*black bars and line*). This demonstrates that the ventral striatum is not simply co-expressing spatial information inherited from the hippocampus. (**c**) Reward-predictive cues modulate the firing rate of both hippocampal and ventral striatal neurons. Firing rate histograms and rasters for reward approaches during periods in which the cue light was on (*top row*; Cue On) and behaviorally similar approaches in the intertrial intervals (i.e., periods in between cue light presentations when all cues were off; bottom row; ITI). Histograms and rasters are associated to the rate maps shown in the *bottom row* of panel **a**. Firing patterns are aligned to nose poke events in reward ports (*green line*; $t = 0$). *Cyan dots*: cue onset; *red triangles*: reward delivery. Each *row* represents an individual trial, with the first trial plotted at the bottom. The total number of trials is shown in *italics in the upper left corner* of the histograms. Firing rates are relative to the scale maximum noted on the *top right*. Neurons often showed a response in either the intertrial interval (*right* hippocampus column; *bottom* reward port only; see **a**) or the Cue ON phase (*left* ventral striatum column; all reward ports; see **a**). If cells responded in both phases, hippocampal responses generally showed higher peak firing rates and shorter durations in the Cue ON then in the intertrial interval phase (*left* hippocampus column; *upper right* reward ports only; see **a**). Ventral striatal responses were often more similar between the two conditions (*right* ventral striatal column; all reward ports) then hippocampal responses. Adapted from Lansink et al. (2012)

vStr neurons fired strongly in association with specific phases of executing the Y-maze task, such as during the initial or final phases of approach to the light (which could indiscriminately appear at each of nine locations in the three compartments of the Y-maze) and reward port. In addition, some neurons fired in response to the onset of the reward-predictive cue light or to reward consumption, although these were less frequent. Although these task-phase correlates were found indiscriminately in the compartment the rat entered upon approach of a cue light, these results by no means imply that hippocampal information would not be used to drive motivated behavior or vStr firing. For instance, the task requires that the rat, when perceiving a cue light, has knowledge of its place relative to a goal location to determine the next best action. When situated in the middle of the Y-maze and seeing the cue, initiation of approach behavior is appropriate whereas licking behavior is dysfunctional. The converse is true when the animal is situated at a reward port. In brief, hippocampal inputs to the vStr may contribute spatial-contextual information to the shaping of reward-predictive activity in the vStr, expressed amongst others in the form of "ramps" in firing rate (Schultz 2006; Lansink et al. 2008; van der Meer and Redish 2011b; see also Fig. 18.3).

A second question addressed by simultaneous hippocampal-ventral striatal recordings in the Y-maze was to study the impact of temporally discrete, reward-predictive cues on firing patterns in both structures. Whereas stationary landmark cues, often used by animals as visual beacons during spatial navigation, are known to heavily influence place cells and to give rise to "remapping" when salient properties are changed, the effect of time-limited stimuli was largely unknown. Cue lights induced an effect in both hippocampus and ventral striatum that strongly resembles rate remapping previously described in the hippocampus (Leutgeb et al. 2005). This effect was apparent from the different firing rate responses during reward port approaches when a cue light was illuminated compared to behaviorally similar approaches in the intertrial intervals, i.e., the periods between cue light presentations when all cues were off (Fig. 18.4c). Neurons often expressed an elevated firing rate during cued approaches, although in both structures individual neurons were also seen to decrease their discharge frequency. This indicates that reward-predictive cues induce state changes in both HC and vStr ensembles and that a rise in reward expectancy, due to cue onset, does not invariably or consistently correlate with a rise in firing rate.

18.7 Off-Line Interactions

Apart from interactions during behavior, it is also clear that HC and vStr interact "off-line." Results on ventral striatal reactivation during sleep are generally in line with replay characteristics previously reported for the hippocampus (Wilson and McNaughton 1994; Skaggs and McNaughton 1996, see Jadhav and Frank 2014) but have yielded additional new insights. As in the hippocampus, post-task replay following a T-maze or triangle-track running task with reward search has been found to be prominent in slow-wave sleep, but not in REM sleep (Pennartz

et al. 2004; Lansink et al. 2008). Within slow-wave sleep epochs, vStr reactivation is stronger during hippocampal ripples than outside these events (Lansink et al. 2008). VStr neurons also exhibit a forward direction of replay and a roughly 10× temporal compression in replayed spike sequences as compared to the behavioral state, also in line with hippocampal findings (if theta phase precession phenomena are not taken into account; Euston et al. 2007).

New insights, emphasizing powerful hippocampal-vStr interactions during replay, have emerged especially by considering the physiology of the two brain structures together. When the hippocampus generates ripples in CA1—accompanied by sequential replay of place cells—the firing rate of a substantial subset of vStr neurons (25 %) is elevated up to about 0.5 s following ripple onset. This ripple-modulated subset reactivates strongly, whereas the non-modulated subset does not show significant reactivation (Pennartz et al. 2004). When, in addition to LFPs, ensembles are recorded in area CA1 together with the vStr, the pattern of hippocampal-vStr cross-correlations is significantly reactivated during post-task slow-wave sleep as compared to pre-task sleep. This reactivation is most powerful in those HC-vStr cell pairs in which the hippocampal cell has a place field and the vStr cell a reward-related firing correlate, underscoring the behavioral significance of the neural codes being replayed (Lansink et al. 2009; Fig. 18.5).

Both vStr and HC-vStr reactivation appear to outlast "hippocampal-only" replay when the duration of enhanced pattern similarity following post-task sleep is studied. Perhaps the most striking finding comes from studying the temporal order in which HC and vStr cell pairs fired during behavior versus post-task sleep (Lansink et al. 2009). During behavior, there was no clear preference for HC to fire in advance of vStr cells (or vice versa; because place-field firing naturally alternates with reward-related activity in the cyclic task used). In contrast, the bulk of replay in HC-vStr patterns was accounted for by pairs in which the hippocampal member fired first and the vStr cell followed (84 %). This result suggests a preferential role for the HC to initiate replay processes when these are taken to occur cross-structurally, extending beyond the hippocampus.

Taken together, dual-structure ensemble recordings suggest that hippocampal inputs to the ventral striatum selectively target neurons that signal rewards or other motivationally relevant, reward-predictive information. Coordination between the two structures is modulated not only during the performance of specific behaviors—reward approach in particular—but also during post-task rest periods, indicating a possible role not just in directing and invigorating place and context-dependent reward seeking but also in the consolidation of place-reward associations (Carr and White 1983; Dalley et al. 2005; Ito et al. 2008).

18.8 Speculative Synthesis

The hippocampus and striatum are often viewed as distinct systems that learn in parallel and compete for behavioral control based on different strategies (Packard and McGaugh 1996; Poldrack and Packard 2003; van der Meer et al. 2012). This

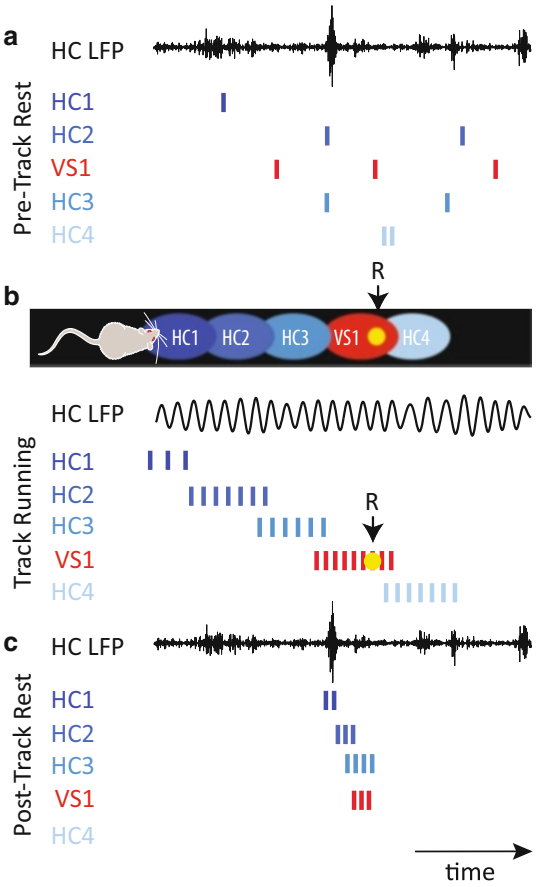

Fig. 18.5 Schematic representation of spontaneous cross-structural reactivation of place-reward information. Neural activity is shown for 4 hippocampal neurons (HC1-4; *blue ticks* represent spikes) and 1 ventral striatal neuron (VS1; *red ticks*) together with hippocampal local field potentials for a period of rest and sleep (**a**) preceding food searching on a triangular track (**b**; one side shown) and a period of post-behavioral rest and sleep (**c**). As a rat runs along a track, place fields of hippocampal neurons (represented by *blue ellipses*) are sequentially activated, whereas a ventral striatal neuron is firing around a reward delivery site (*red ellipse and ticks*; R, reward site). Hippocampal-ventral striatal ensembles show coherent cross-structural reactivation of behavior-related firing patterns during post-behavioral rest and slow-wave sleep, whereas firing patterns appeared uncorrelated in pre-behavioral rest and sleep. Reactivation was particularly strong for cell pairs that expressed both a place field and a reward-related correlate, which did not have to overlap in time in order to be reactivated. Another predictive factor of strong reactivation was the cell pair's firing order during behavior in which the hippocampal cell fired in advance of the ventral striatal neuron. This firing order was maintained during post-behavioral rest in which the information is replayed on a 10× accelerated time scale

view accounts for a wealth of data on the dissociable effects of HC and *dorsal* striatal manipulations. However, as reviewed in this chapter, the relationship

between the hippocampus and the *ventral* striatum is not well captured in this light. Rather, we have reviewed substantial evidence, ranging from anatomical and electrophysiological to functional/behavioral, demonstrating that HC and vStr cooperate.

In this respect, and in the context of this volume, it is particularly notable that interactions between the HC and vStr appear to span the full range of hippocampal processing phenomena at multiple timescales. At the long end of this scale, the coordination between the hippocampus and ventral striatum during off-line processing (sleep) suggests the possibility that this interaction may contribute to cellular and/or systems consolidation (Lisman and Grace 2005; Morris 2006).

A different role for the HC-vStr projection in learning is suggested by the influential idea that the ventral striatum is part of a reinforcement learning (RL) system, perhaps a variant of the "actor-critic" architecture (Joel et al. 2002; Atallah et al. 2007; van der Meer and Redish 2011a). This architecture is an example of "model-free" systems, which rely on assigning expected reward values to different actions and situations (or "states") based on previous experience; inputs from the hippocampus that include location, context, and other aspects of the current situation are likely a useful input for such a reinforcement learning system (Pennartz et al. 2011; Malhotra et al. 2012). The ramping activity observed in many ventral striatal cells is reminiscent of a "state value" signal in these RL architectures, but it is unlikely that complex state value functions are encoded by single neurons (Khamassi et al. 2008; Pennartz et al. 2011).

In addition, the hippocampus exhibits a number of faster-timescale phenomena, including remapping, theta sequences, and sequential (re)activation during sharp wave-ripple complexes (see Lever et al. 2014; Jadhav and Frank 2014). These phenomena are often related to past and/or potential future trajectories (or more generally, behavioral sequences) and thus can at least in principle provide an informative cue for directing and invigorating ongoing behavior. This conceptualization is more in line with "model-based" reinforcement learning models, which rely on the on-line prediction and evaluation of possible future outcomes (Daw et al. 2005; van der Meer and Redish 2010). On the Multiple-T task (Fig. 18.3) hippocampal and ventral striatal activity display such covert representations specifically at the high-cost decision point (Johnson and Redish 2007; van der Meer and Redish 2009; van der Meer et al. 2010).

Interestingly, the ventral striatum is known to be important for the expression of so-called Pavlovian-instrumental transfer (PIT) effects, in which a Pavlovian cue previously associated with a certain outcome can bias instrumental behavior directed towards obtaining that outcome (in "specific" PIT; Kruse and Overmier 1983; Cardinal et al. 2002). For instance, a rat that has experienced a Pavlovian pairing of light and food reward may be biased to pressing a lever associated with food reward, rather than a lever associated with water reward, when presented with the light. A similar mechanism may apply to hippocampal inputs to the ventral striatum, whereby representations of a specific place may bias the animal towards that place (Van der Meer and Redish 2010).

In sum, it is clear that the HC-vStr projection participates in a rich set of phenomena relevant to understanding the influence of the many facets of HC processing over learning, memory, and behavior. Challenges in the further understanding of this projection include (1) the heterogeneity of both HC and vStr subregions spanned by their interaction (Berendse et al. 1992; Pennartz et al. 1994; Voorn et al. 2004), (2) the relatively poor understanding of information processing in the ventral hippocampus (however, see Kjelstrup et al. 2008; Royer et al. 2010), and (3) the complex interactions between hippocampal inputs to the vStr, converging projections from other sources, and their relationship to downstream targets. Stimulation of specific afferent fibers and simultaneous multistructure recordings are expected to further elucidate the function of these inputs and their interactions (e.g. Britt et al. 2012).

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Functional Interactions of Prefrontal Cortex and the Hippocampus in Learning and Memory

19

Matthew L. Shapiro, Justin S. Riceberg, Kate Seip-Cammack, and Kevin G. Guise

Abstract

The prefrontal cortex (PFC) is associated with "executive function" and the hippocampus with declarative and episodic memory. Yet both the PFC and the hippocampus are described as "specialized for representing events that are extended in time" (Wilson et al. Trends Neurosci 33:533–540, 2010) and encoding sequences "of events that unfold over time" (Eichenbaum, Neuron 44:109–120, 2004). Bidirectional interactions between the two structures in an "intention-recollection" cycle (cf. Fuster et al. Brain Res 330:299–307, 1995) may describe how their complementary and distinct functions contribute to goal-directed learning and memory. Beyond "what, where, and when," the external facts that define episodes (Morris 2001), hippocampal representations include "why and how." These internal features include outcome expectancies and abstract rules computed by the PFC, extracted from outcomes integrated across many behavioral episodes. PFC signals stored along with high-level percepts in hippocampal representations can therefore guide memory retrieval. Hippocampal signals relayed to the PFC let remembered events select associated goal, rule, and procedure representations. The bidirectional interactions associate individual items with multiple goals and individual goals with multiple items. By including outcome expectancies and abstract rules as episodic elements in a content-addressable memory system, an "intention-recollection cycle" reduces proactive interference and guides selective memory retrieval.

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19.1 Introduction

The prefrontal cortex and the hippocampus have long been associated with maintaining the structure of experience through time. Both structures have been described as supporting "working memory" though defining the term somewhat differently (Baddeley 1996; Olton et al. 1979). Both structures have been associated with reducing proactive interference, contributing to behavioral inhibition, using "context" to guide behavior, and playing a key role in episodic memory retrieval, consolidation, and guiding goal-directed behavior (Fuster 2008, 2007). Indeed, recent theories have proposed that the PFC is "specialized for representing events that are extended in time" (Wilson et al. 2010), and the hippocampus is crucial for encoding episodes as sequences "of events that unfold over time" (Eichenbaum 2004). These descriptions have converged despite major differences in the neuropsychology, anatomy, and physiology of the two brain regions, the PFC associated with "executive function" and the hippocampus with declarative and episodic memory.

This chapter describes how bidirectional interactions between the PFC and the hippocampus can account for the differences and similarities in the functional descriptions of these two highest-order association cortices and their roles in learning and memory. The proposal combines three neuropsychological theories, based on the anatomy and physiology of the PFC and the hippocampus that emphasize their computational specializations. The "perception-action cycle" (Fuster 1995) and "guided activation" (Miller and Cohen 2001) theories propose that the PFC helps organize behavior by altering activity in other brain areas, so that appropriate, hierarchically organized sensory, motor, memory, and motivation signals guide successful behavior, especially in changing circumstances. The output of the PFC modulates computation in other brain regions by altering the activity patterns across distributed neural networks and thereby maintaining select, active representations. The outcome expectancy theory proposes that the PFC predicts the sensory and contextual features, together with the value, of eventualities in a particular situation, computed by integrating reward history associated with those circumstances (Schoenbaum et al. 2009). The outcome expectancy theory focuses on the orbitofrontal cortex (Schoenbaum et al. 2009), but the described computation—integrating common aspects of situations over repeated episodes to generate predictions—may generalize to the entire PFC. The relational memory theory (Eichenbaum 2004) proposes that the hippocampus helps guide behavior by encoding hierarchically organized "events" derived from temporally overlapping inputs from highest-order association cortices. Each event, stored by synaptic plasticity, is an "index" (Teyler and DiScenna 1986) to activate cortical representations of items and event sequences that encode behavioral episodes (Eichenbaum et al. 1999).

The neuropsychological proposal here is that beyond "what, where, and when" (Morris 2001), the external facts that define episodes, hippocampal representations include internal factors, such as "why and how" that include motivation, reward expectancies, and remembered actions, including the procedures and more abstract

Fig. 19.1 Memory for episodes includes information about both the internal and external environment. Animal models of episodic-like memory emphasize the ability to remember "what, where, and when" (Clayton and Dickinson 1998), features of the external environment. Memories are also informed by the internal environment, such as deprivation and other motivational states, outcome expectancies, and the rules and strategies that guided successful behavior in the past. If the hippocampus stores relational memory representations that include these internal variables and each item that comprises an event can serve as a retrieval cue for every other event that includes that item, then internal variables can contribute importantly to discriminative learning and selective memory retrieval. The prefrontal cortex computes expectancies, rules, and strategies by integrating the history of situations, actions, and outcomes. Interactions between the prefrontal cortex and hippocampus allow "episodic" information, "outcome expectancies, and inferred rules" to influence one another and guide adaptive behavior

rules that guide successful behavior (Fig. 19.1). The internal factors, especially reward expectancies and abstract rules, are computed in part by the PFC and relayed to the hippocampus where they are linked with external factors computed by posterior cortical areas. Populations of hippocampal neurons, "assemblies" activated by temporally overlapping inputs and linked by synaptic plasticity, form "relational representations" that allow each item that comprises an event to serve as a retrieval cue for every other event that includes that item (Eichenbaum et al. 1999). Because signals from the PFC are stored along with perceptual information in hippocampal representations, internal factors become retrieval cues. Goals, rules, and procedures computed by the PFC select among different memory representations in otherwise ambiguous situations, e.g., when different responses are required at different times in the same place. This view predicts that place fields that distinguish different behavioral histories, e.g., firing rate codes for prospective and retrospective information, are established by and depend upon PFC-hippocampus interactions. The same logic suggests that these interactions will be crucial for real-time hippocampal firing sequences that accompany memory-guided behavior. Hippocampal firing patterns that track multiple goals

simultaneously (Kelemen and Fenton 2010) "preplay" and "replay" past and future locations (Pfeiffer and Foster 2013), "vicarious trial and error" signals that occur in CA3 at the choice point of mazes (Johnson and Redish 2007), and goal-related firing in CA1 during sharp-wave ripples and other brief events (Jadhav et al. 2012) likely depend on interactions with the PFC. The strong prediction is that goal-directed "journey coding," "task coding," "vicarious trial and error," and sequence replay and "preplay" are established during learning and activated by PFC circuits in unfamiliar circumstances that contain familiar elements. Because episodic codes associate highest-order perceptual information with internal factors, hippocampal representations activated by environmental features will include information about "why and how." These hippocampal signals modulate the PFC, associating the representations of goals, rules, and procedures associated with remembered events. In this way, new situations that resemble familiar ones can help guide choices. Beyond reducing proactive interference—the detrimental effects of prior learning on memory—the interaction between the PFC and hippocampus integrates memory with potential actions. Familiar elements in new situations can activate representations of prior episodes and their outcomes so that the consequences of actions in new situations can be anticipated. Similarly, new elements encountered in familiar situations can be integrated with prior episodes and their associated outcomes.

19.2 Hippocampal Function and Memory for Episodes

People, monkeys, and rats need hippocampal circuits to remember events in place and time. The hippocampus supports homologous memory functions across mammalian species. Memory for recent events, such as where a car was parked earlier in the day, depend upon hippocampal function; difficulty with these tasks is a common complaint early in Alzheimer's disease when observable brain damage is restricted to the hippocampal system (Hyman et al. 1984). The hippocampus is crucial for remembering new facts and recent events, and without it episodic memories are lost almost as quickly as experiences unfold. Memories acquired long before hippocampal damage remain accessible, and immediate or working memory is limited to what can be maintained by verbal rehearsal (Sidman et al. 1968), and items that can be distinguished only by comparing relationships among their parts are forgotten quickly (Hannula et al. 2006).

Spatial reversal learning in a plus-shaped maze (+ maze) poses an analogous cognitive challenge for rats (Fig. 19.2). The + maze has two start arms (north and south) that meet in a choice point leading to two goal arms (east and west). A hungry rat who finds food at the end of the east goal arm will return to that arm readily after a few trials, clearly demonstrating learning. Training the rat to "go east" from both of the start arms enforces a spatial strategy. *Reversal learning* requires subjects to withhold a previously rewarded response and emit one that was previously not rewarded. Spatial reversal learning in the + maze entails making the opposite response at the choice point, so that an animal trained to "go east" would

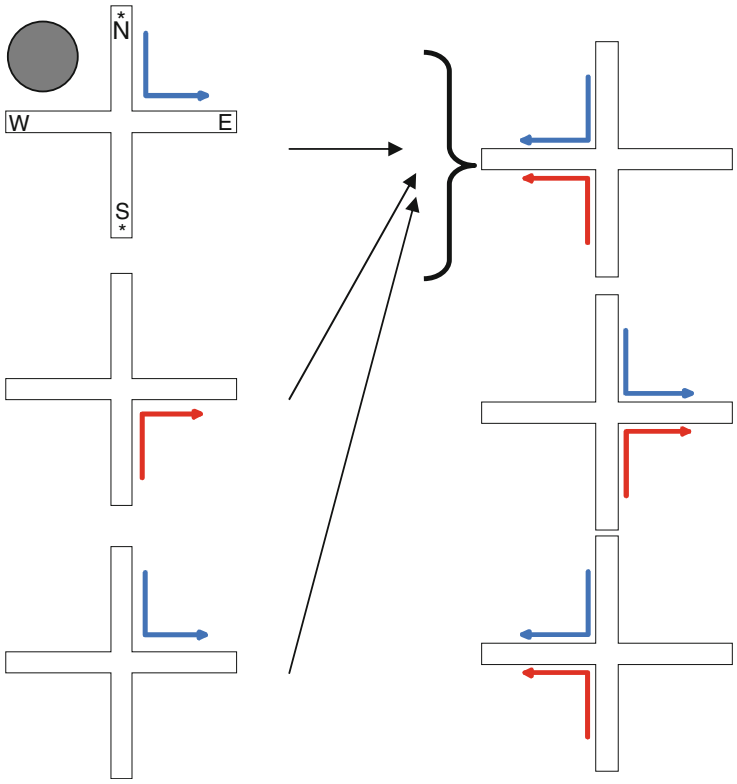

Fig. 19.2 Spatial reversal learning in a + maze. Rats are placed in either the north or south start arm at the start of each trial and learn to find food at the end of either the east or west goal arm (north to east in the first trial shown by the *blue arrow, top*). After each trial the rat is placed on a waiting platform (*gray circle*). Within a block of trials, the start arm is changed pseudorandomly, and the goal is kept constant, shown by the sequence of *red* and *blue arrows* below. After the rat chooses the correct arm reliably, the contingencies change so that the rat must learn to enter the opposite goal arm to find food for that block of trials (*upper right*). The figure shows four blocks and three reversals. Different experiments include different numbers of trials within a block and reversals within a testing session, both of which vary proactive interference and the relative influence of outcome expectancies

learn to find reward in the west goal arm. Because the correct response in the choice point varies in space and time (Olton et al. 1979), spatial reversal learning in the plus maze is highly sensitive to hippocampal dysfunction. Lesions of the fimbria-fornix or neurotoxin lesions of the hippocampus proper reduce choice accuracy to chance (Ferbinteanu et al. 2011; Ferbinteanu and Shapiro 2003). The impairment is selective to remembering recent events, however, as rats with hippocampal dysfunction seek and consume food as vigorously as intact animals. The same lesions had no effect on learning or performance if the task required approaching a visual stimulus rather than remembering a changing location (Ferbinteanu et al. 2011), tasks that require the dorsolateral striatum (McDonald and White 1993) (see van der Matthijs et al. 2014).

19.3 Information Coding by Hippocampal Neurons

Memory lets us recall past events and mentally reconstruct past experiences, and people with damage to the temporal lobe are unable to recall past events or imagine potential futures (Maguire and Hassabis 2011). Since the 1970s we have known that hippocampal neurons signal locations, but only now are we beginning to understand how these cells contribute to memory in the everyday sense of the word. Neurons in the dorsal hippocampus recorded as rats explore open environments fire at high rates in specific places, one or two small patches defined by local regions in the environment, and are otherwise mostly silent (O'Keefe and Speakman 1987; O'Keefe and Dostrovsky 1971). Such *place fields* recorded from 60 CA1 neurons can predict the location of a rat's head to within 1 square inch (Wilson and McNaughton 1993). Repeated exposure to an environment "tunes" place fields into stable representations, and treatments that prevent this stabilization or disrupt temporal firing sequences impair spatial learning and memory (Kentros 2006; Robbe and Buzsaki 2009).

19.3.1 Place, Time, and Goals

Beyond signaling location, hippocampal neurons respond to the unfolding history of behavior, linking the "here and now" to "before and after," the start and end of goal-directed actions. Rats demonstrate memory in mazes by returning to places associated with reinforcement, and hippocampal neurons distinguish identical spatial trajectories that either lead from different starting points to the same goal or to different goals from the same starting point (Frank et al. 2000; Wood et al. 2000; Ferbinteanu and Shapiro 2003) (see Dudchenko and Wood 2014). We recorded hippocampal neurons as rats performed a hippocampus-dependent spatial reversal task in a + maze. Along with place fields, we found that CA1 firing rates were modulated by memory discriminations even while the external environment and overt behavior were identical (Ferbinteanu and Shapiro 2003; Shapiro and Ferbinteanu 2006). In the + maze, the rat approaches a choice point using the same spatial trajectory on the way to different goals, e.g., from the north start arm to either the west or east goal arm. In the + maze, the rat approaches a choice point using the same spatial trajectory on the way to different goals, e.g., from the north start arm to either the west or east goal arm. Thus, journeys through each maze arm are identical, "behaviorally clamped," while memory discriminations vary. Some CA1 cells fired in a start arm only when the rat was about to enter a specific goal arm; the same cells fired less or not at all if the rat was about to enter the other goal arm. During "behaviorally clamped" approaches to the choice point the cells fire at different rates, showing "prospective" coding that predict the pending goal arm selection (Ferbinteanu and Shapiro 2003). Prospective coding declined during memory errors, as though providing a mechanism for retrieving temporally extended sequences (Ferbinteanu et al. 2006). Behavior is also "clamped" after the rat exits the choice point until it obtains reward in the goal arm. In this situation

hippocampal neurons fired at different rates depending on the start of the journey, showing "retrospective" coding, e.g., by distinguishing paths to the east goal depending on whether the rat exited the north or the south start arm. As described below, the spatial reversal learning in the + maze task also requires the PFC.

Beyond place, retrospective and prospective coding, CA1 activity also distinguishes the task strategies (Ferbinteanu et al. 2011). Rats were trained to perform two tasks in the same + maze, the spatial discrimination and reversals just described and a cue-approach task in which the rats selected the goal by approaching a visual cue. The tasks and goals were switched several times daily across blocks of trials, and the rats performed accurately on all the discriminations. As in prior experiments, CA1 cells distinguished overlapping journeys in the start arm on the way to different goals and different goal arms after leaving different start arms. Furthermore, the proportions of retrospective and prospective fields were equivalent in the two tasks, showing that the hippocampus coded temporally extended representations whether or not the structure was required for task performance. The most surprising result, however, was that CA1 activity distinguished the place and cue-approach tasks that guided identical journeys (e.g., north to west) (Fig. 19.3). As described below, memory for switching between strategies also requires the PFC (Rich and Shapiro 2009).

19.3.2 Time and Sequence Coding

In addition to distinguishing the same place across different behavioral episodes, CA1 neuronal activity changes in time and signals unfolding temporal sequences. During hippocampus-dependent trace eyelid conditioning, CA1 cells model the timing of CS-CR intervals (McEchron and Disterhoft 1997). In spatial nonmatching-to-place tasks, CA1 and CA3 neurons encode the sample, and decay of the sample code during the delay predicts performance errors (Hampson et al. 2002). CA1 cell ensembles fire in sequences that predict pending spatial choices when rats are trained to run on a treadmill between choices in a delayed spatial alternation task (Pastalkova et al. 2008). CA1 neurons also signal temporal sequences and intervals during the delay in a nonspatial object association tasks (MacDonald et al. 2011). In this experiment, rats performed an object-odor delayed association task in a modified T-maze. In each trial, the rat was placed in a starting area, presented briefly with one of two objects, and allowed to enter a waiting area for a 6–10 s delay, after which it approached a scented, sand-filled flowerpot. Each object-odor pair was associated with a different response. In "go" trials, the reward was obtained by digging in the flowerpot; in "no-go" trials, the reward could be found in a different place by not digging. To obtain reward, the rat had to remember which object had been presented before the delay. Many CA1 neurons had place fields; ~30 % of the neurons distinguished between the objects, the odors, and the response or had conjunctive properties, e.g., firing most when a specific odor was sampled after a particular object. CA1 firing rates changed during the delay, so that different populations of neurons were maximally active in "time fields," as though

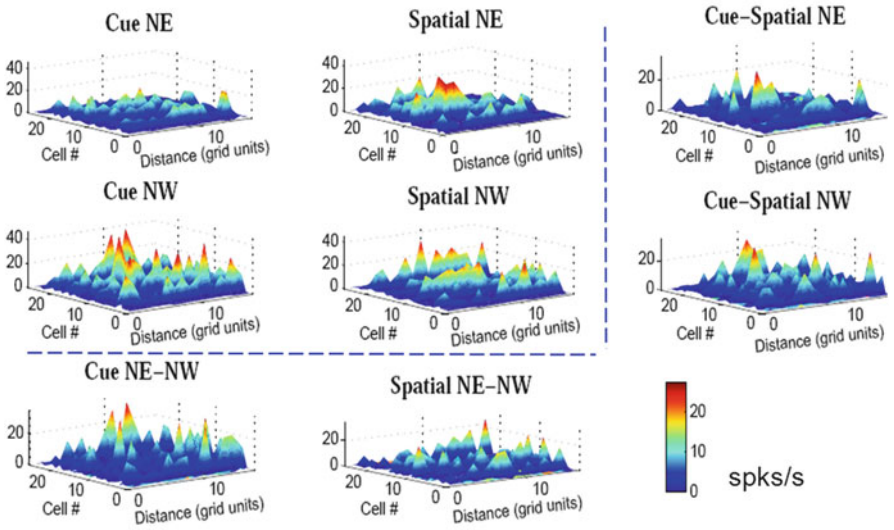

Fig. 19.3 Prospective coding by CA1 neurons signals both task strategy and journeys. The heat plots show the firing rates of an ensemble of ~30 CA1 neurons recorded simultaneously as a rat walked toward the choice point in the north start arm. Though the behavior was identical across conditions, the memory discrimination differed as the rat would soon select one or the other goal arm to approach either a visual cue (*left column*) or a spatial goal (*middle column*). The implied height and color show the firing rate; distance along the start arm is plotted against the cell number. The bottom row shows the arithmetic difference in firing rates between the journeys in the cue task (*bottom left*) and the spatial task (*bottom right*). The *right-hand* column shows the arithmetic difference in firing rate between identical journeys guided by different memory strategies. Adapted from Ferbinteanu et al. (2011)

the hippocampus coded the passage of time in an otherwise static environment. Moreover, the ensemble firing patterns distinguished object-delay-choice associations, as though the hippocampus parsed goal-directed, temporally extended event sequences. In other words, the active hippocampal representation of "here and now" was influenced by "before and after": a particular sample stimulus presented some time ago selects future actions (MacDonald et al. 2011). During the delay in a nonmatching-to-place task, CA1 activity varied with place, time, and treadmill walking distance (Kraus et al. 2013). Moreover, CA1 cells encode time linearly over days, so that different subpopulations signal consistent locations, even as CA3 place fields were stable over the same interval (Mankin et al. 2012) (see Eichenbaum et al. (2014) for discussion of these issues). Hippocampal representations thus encode the unfolding history of events and distinguish among goal-directed actions supported by identical behaviors in static environments. Distinguishing identical spatial trajectories requires a mechanism

for linking hippocampal representations to behavioral goals and strategies, information that may be provided by PFC mechanisms.

19.3.3 Hippocampal Coding at Behavioral Timescales

Mean firing rates averaged over many trials determine the trigger features of neurons and identify the type of information the cells encode. These time-averaged signals cannot explain how spiking guides behavioral discriminations, such as actions at the choice point of a maze, which occur in some hundreds of milliseconds. However, neuronal activity on this timescale is now known to reflect recent behaviors and predict pending choices. When rats track two different reference frames, different groups of CA1 neurons that predict the location in each frame fire in alternating ensembles (Kelemen and Fenton 2010) (see Leutgeb and Leutgeb 2014). When rats walk back and forth on a linear track, groups of CA1 neurons fire in ~150 ms bursts during reward consumption before and after journeys (Foster and Wilson 2006). Many of the neurons active during bursts that accompany sharp-wave ripples (SWR) are also active in place fields in the track. The sequential firing within SWRs recapitulates the sequence of place fields occupied by a rat during a journey. Reverse sequences "replayed" the occupied locations from the current reward cup backwards in time toward the start, and forward sequences "preplayed" sequences from the current reward cup forward toward the next goal (Foster and Wilson 2006; Diba and Buzsaki 2007). CA1 cells fire in analogous sequential bursts during slow-wave sleep, as though rats dream about recent experiences (Pavlides and Winson 1989; Wilson and McNaughton 1994; Skaggs et al. 1996; Lee and Wilson 2002; Diba and Buzsaki 2007) (see Jadhav and Frank 2014). Moreover, precisely timed electrical stimulation that disrupts sharp-wave-ripple events during sleep impairs subsequent memory for information acquired before sleep; identical stimulation delivered between sharp-wave-ripple bursts leaves learning and memory intact (Girardeau et al. 2009). Memories acquired over many seconds during behavior are replayed in "compressed" time during sleep (Skaggs et al. 1996); disrupting this "replay" during sleep impairs consolidation.

The importance of compressed hippocampal spike sequences for memory-guided behavior is not yet fully known, but the evidence reported so far is promising. During behavior pauses in or before the choice point, groups of CA3 neurons fire in 150 ms bursts in an order that recapitulates the sequence of place fields that would be occupied if the rat entered one or the other goal (Johnson and Redish 2007). The firing patterns occur during slow waves with strong theta and gamma power (described below) and resemble a neuronal correlate of "vicarious trial and error," as though the rat was "thinking ahead" about potential futures consequent to a choice. In an open-field test of spatial memory, CA1 neurons fired in ~100 ms population bursts that again corresponded to place field sequences, in this case the sequence of neuronal spikes predicted future and recapitulated past trajectories starting at the current location of the rat (Pfeiffer and Foster 2013). The sequences appeared to be strongly related to goal-directed memory retrieval,

because they coded multiple paths from many different locations toward a reliable food location; when the rats learned a new goal location the next day, the prospective codes pointed to the new goal. Disrupting these CA1 population bursts during behavior as rats were trained in a spatial alternation task impaired recent memory performance (Jadhav et al. 2012). Together, the results suggest that hippocampal circuits encode events during learning over many minutes, "parse" behavior into segments lasting seconds, and replay these limited episodes as spike sequences during compressed bursts lasting ~100 ms. The compressed burst sequences reflect the recent past, anticipate the imminent future, and could serve as mechanisms for integrating learning, memory consolidation, and retrieval with prospective action.

19.3.4 Hippocampal Coding Summary

During behavior guided by memory retrieval, time-averaged firing rates of hippocampal neurons distinguished different behavioral histories as rats perform identical behaviors on the way to different goals. Analogous coding has been observed in the human hippocampal system. Neurons recorded from the hippocampal system in people with epilepsy encode learned concepts, e.g., places (Ekstrom et al. 2003), the name, photo, and caricature cartoon of an individual (Quiroga et al. 2005), and distinguish temporally extended episodes such as movie clips. Moreover, the same neurons that respond as people watch specific movie clips fire in anticipation of the free recall of that information (Gelbard-Sagiv et al. 2008). "Real-time" bursts of hippocampal activity recapitulate or reconstruct elements from recent experience, whether in rats navigating to a remembered goal or in people recalling recently viewed movie clips. Indeed, these real-time bursts may drive the synaptic plasticity that modifies hippocampal circuits so that time-averaged firing rates distinguish different journeys. Whether or not these particular neuronal signals code memory retrieval events, a fundamental question remains concerning how specific memories are retrieved in a given circumstance.

19.3.5 Relational Memory

A "relational memory" theory of hippocampal function provides a conceptual framework for investigating selective memory retrieval (Eichenbaum et al. 1999). This view suggests that temporally overlapping inputs from cortical and subcortical areas code feature collections that converge in the medial temporal lobe where "cell assemblies" form via synaptic plasticity that represent events, relationships among internal or external environmental features, such as a view from a particular location. Successive activation of subpopulations of hippocampal neurons code sequences of events that represent temporally extended episodes, analogous to journeys taken to accomplish a goal (Ferbinteanu and Shapiro 2003) . Events that recur commonly in many episodes represent "nodes," such as an office—a place that contains many episodes. The integrated inputs provide the "content" that

"addresses" hippocampal memory representations. Subsequently, subsets of environmental inputs trigger these hippocampal "assemblies" and activate reciprocal, divergent outputs from the hippocampal system that innervate the same cortical and subcortical networks. The activation of recurrent hippocampal-cortical networks thereby provides "recognition" or "recall" signals as items in the internal or external environment trigger memory retrieval (Wickelgren 1992; Teyler and DiScenna 1986). Relational memory representations are powerful in principle because they allow each item that comprises an event to serve as a retrieval cue for every other event that includes that item. The same properties that give relational memory its powerful flexibility, however, present a computational challenge: what neural mechanisms guide retrieval toward relevant items among the wide range of potential associations presented by a given situation? Without some selection mechanism, flexible associations could leave an animal "lost in memory space," e.g., at the choice point of a + maze when the correct goal arm changes in different trials.

An obvious psychological solution is to include signals derived from action and motivation—needs, goals, or desires—as elements of relational memories. Human memory includes information about motives and goal satisfaction (e.g., "I had a great meal last night with ...."), and recall can "induce motivation" (think about your favorite food). Deprivation state can guide contextual memory retrieval that requires the hippocampus (Kennedy and Shapiro 2004) and modulate CA1 representations during identical behaviors in the same external environment (Kennedy and Shapiro 2009). Goals are obtained using procedures, rules, and schemas, coordinated plans and actions that organize structured sets of predictions based on prior experience. The predictions are generalized over many prior episodes and used to anticipate the consequences of actions in new situations. Together, motivation, outcome expectancies, and schemas can guide selective memory retrieval if they are integrated with episodes, e.g., as another aspect of "content" that "addresses" hippocampal memory representations. Interactions between the PFC and hippocampus may implement the bidirectional signaling mechanisms that integrate memories and goals (Fig. 19.4).

19.4 Learning, Memory, and the PFC

19.4.1 PFC Comparative Neuroanatomy

Although the PFC is not required for memory in the everyday sense of the word, it is crucial for working with memory in people, monkeys, and rats. For example, while PFC dysfunction does not impair memory for items or recent events per se, it does impair remembering the temporal order of items and actions, distinguishing among sources of information (e.g., which of two lists included a word or odor), and predicting the accuracy of memories. Extensive PFC damage in people impairs "executive function," the ability to engage appropriate and effective goal-directed behavior. PFC dysfunction impairs integrating expected events and their likely

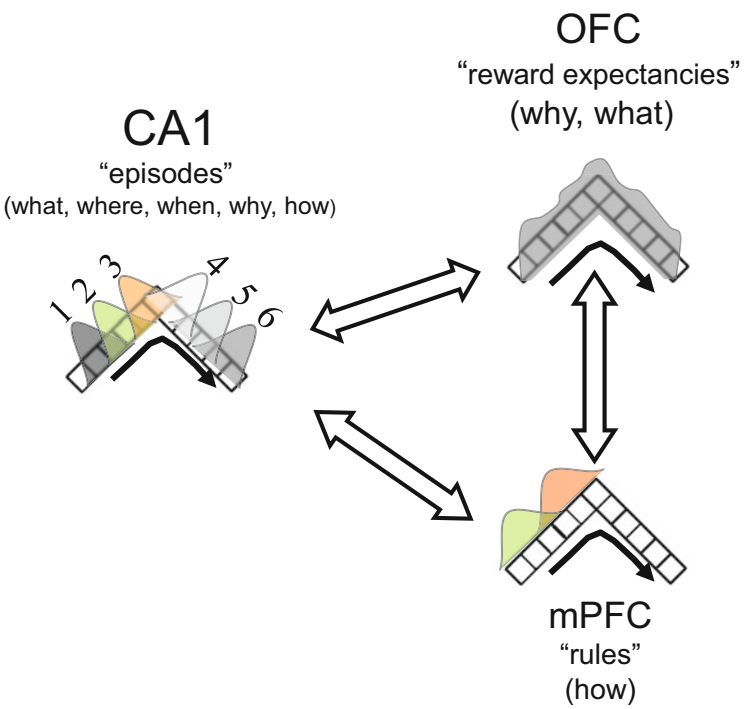

Fig. 19.4 Bidirectional interactions between the PFC and hippocampus link outcome expectancies and memory for episodes. Spatial reversal learning alters OFC population coding (Young and Shapiro 2011a), and switching between memory strategies alters mPFC population coding (Rich and Shapiro 2009). The cartoon suggests that task and journey prospective coding in CA1 may be selected by PFC input depending on the relevance of adaptive strategy our outcome expectancy signals conveyed by mPFC and OFC codes

outcomes with appropriate, temporally organized actions even when people can describe each of these cognitive domains in words (Teuber 2009). Specific signs of PFC damage include problems with mood, planning, attention, behavioral and emotional inhibition and control, temporal ordering, working with memory, and initiating directed movement. Few of these signs are obligatory (Teuber 2009), and the varied outcomes of PFC damage may be due to its size and complexity, which in humans includes ~13 distinct cytoarchitectonic maps (Petrides et al. 2012). The maps in primates are located in dorsolateral, ventrolateral, and orbital regions (dlPFC, vlPFC, and OFC, respectively), are interconnected in patterns that correspond to these anatomical subdivisions, and have partially overlapping and largely bidirectional connections with other cortical areas (Yeterian et al. 2012).

Though strong homology exists between PFC cytoarchitectonic and connectivity in humans and monkeys (Petrides et al. 2012), the homology of specific PFC subregions between rats and primates is debated (Preuss 1995). The PFC in

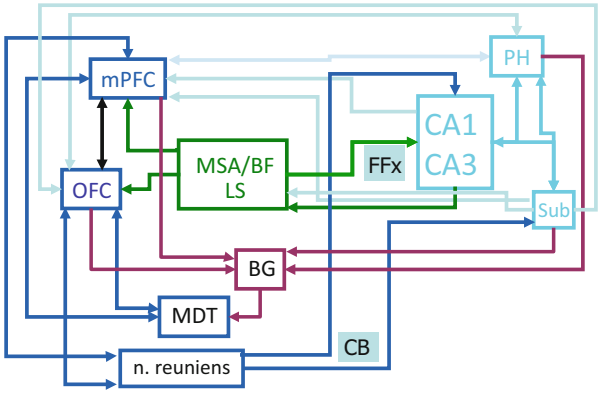

Fig. 19.5 A cartoon showing some of the anatomical connections among key components of the PFC (*dark blue* boxes) and the hippocampal (*light blue* boxes) systems. The PFC is defined by inputs from the medial dorsal thalamus (MDT) which innervates both ventral orbital (OFC) and medial (mPFC) regions in the rat. Output from both PFC regions is relayed to temporal lobe structures via cortico-cortical connections that project to parahippocampal (PH) cortices and by the nucleus reuniens, which innervates the subiculum (Sub) and CA1 via the cingulate bundle (CB). The hippocampal system projects to the PFC indirectly via the parahippocampal cortices and directly by connections from the subiculum and CA1 to the PFC. The hippocampal system also conveys signals to the PFC via projections through the fimbria-fornix (FFx) to the mammillary bodies and anterior thalamus (not shown). Both systems project to the striatum, the input structure of the basal ganglia (BG) that returns signals to the PFC via the thalamus. Both the PFC and hippocampal systems receive cholinergic and GABAergic input from the basal forebrain (medial septal area/basal forebrain, MSA/BF) that is crucial for theta oscillations in the hippocampus

human and nonhuman primates has regions with a prominent granular layer IV; rats do not (Preuss 1995). Other anatomical and neuropsychological homologies suggest nonetheless that rats provide a good animal model for investigating basic aspects of PFC function (Uylings et al. 2003). Anatomical connections between the rat PFC and other brain areas resemble those in primates, in particular patterns of brain stem innervation, reciprocal innervation with the medial dorsal thalamus, topographically organized basal ganglia-thalamocortical loops, and cortico-cortical links (Uylings et al 2003). As in primates, the rat PFC interconnects strongly with the basal ganglia via the medial dorsal thalamus (Uylings and Van Eden 1990). Connections between the PFC and other cortical regions of monkeys and rats are similar, with strong bidirectional connections with highest-order association areas including the entorhinal and perirhinal cortices and the hippocampus (Uylings et al. 2003) (Fig. 19.5). Across the species, the anatomical connectivity supports interactions between the PFC and the hippocampal system. We will return to this idea after a brief review of the neuropsychology and physiology of two major subdivisions, the orbital and the lateral regions of the PFC.

The dlPFC/mPFC and OFC make dissociable contributions to behavioral flexibility—higher-order learning and memory—that are functionally homologous in people, monkeys, and rats, using similar circuits and neural coding mechanisms.

The OFC may compute outcome expectancies by integrating the history of reinforcement, affect, and other value signals associated with the sensory and contextual features of experience (Schoenbaum et al. 2009). The OFC is crucial for generating neural representations of a stimulus or a response and its associated value. In contrast, the dlPFC/mPFC may compute abstract rules or strategies that select actions by mapping contingencies that either generalize across different or discriminate between similar situations. In other words, the dlPFC/mPFC is crucial for both applying old rules to new situations and selecting among different rules in highly familiar ones. As described below, both PFC regions use memory, the collected history of experiences, to predict how best to accomplish current goals. Together, the mPFC and OFC compute the means and ends of goal-directed actions. The OFC links otherwise neutral items to desired ends, whereas the m/dl-PFC links those items to selected actions, the means.

19.5 OFC and Expected Outcomes

People with OFC damage have difficulty using expected value outcomes to guide their actions. Thus, the Iowa gambling task requires choosing decks of cards associated with different probabilities of rewards and penalties (Bechara et al. 1994). Normal subjects initially choose the decks associated with large rewards and penalties, but learn to choose the other decks associated with smaller rewards and penalties but a net-positive expected value. Like normal subjects, people with OFC dysfunction initially choose the high reward/penalty deck, but unlike normal subjects they do not respond to the net benefit of the deck with smaller rewards. Episodic memory is available, but the memories are ineffective for guiding adaptive behavior. The deficit is one of changing expectancies, because patients who experience cards associated with the full range of outcomes from the start learn to select advantageous cards (Fellows and Farah 2005).

Imaging studies have linked BOLD activity changes in the OFC with the subjective value of expected outcomes (Levy and Glimcher 2012), and OFC dysfunction has been associated with gambling and drug abuse (London et al. 2000). Monkeys with OFC lesions learn initial contingencies normally, but are relatively insensitive to contingency changes that reassign stimulus-reward associations (Dias et al. 1996). Physical lesions of the OFC in monkeys impair value tracking (Walton et al. 2010), and neurotoxin lesions of the OFC impair stimulus-reward revaluation (Murray and Rudebeck 2013). In reinforcer devaluation experiments, animals are trained to associate a cue with a reward, and then the reward is associated with satiety or nausea. Normal animals stop responding to the cue after devaluation, whereas those with OFC dysfunction continue responding (Murray and Rudebeck 2013). Neurons in area 13 of the monkey OFC encode expected value outcomes associated with an arbitrary stimulus (Padoa-Schioppa and Assad 2006; Kennerley and Wallis 2009). Like monkeys, rats with OFC dysfunction are also impaired in reinforcer devaluation experiments (Pickens et al. 2003). During the course of initial stimulus-reward training, neurons in the

rat OFC "learn" to distinguish stimuli that predict different outcomes, but the coding changes lag behavior and develop slowly after stimulus-reward associations change (Schoenbaum et al. 1998). Reversal learning is impaired by OFC dysfunction when outcome expectancies guide the reversals (Schoenbaum et al. 2009). Lesions or inactivation of the OFC impairs reversal learning without affecting learning of initially rewarded associations in people (Hornak et al. 2004; Tsuchida et al. 2010), monkeys (Mishkin 1964; Dias et al. 1996; Izquierdo et al. 2004; Jones and Mishkin 1972), and rodents (Kim and Ragozzino 2005; Schoenbaum et al. 2002; Schoenbaum et al. 2003; Stalnaker et al. 2007; McAlonan and Brown 2003).

OFC activity recorded in people, monkeys, and rats corresponds to task-related changes in outcome expectancies. As in other tasks that require adjusting outcome expectancies, reversal learning increases the BOLD signal in the human OFC (O'Doherty et al. 2001). OFC unit activity in monkeys (Wallis and Miller 2003) and rats (Young and Shapiro 2011a) are strongly altered by the expected reward values of cues including during reversal learning (Ghods-Sharifi et al. 2008). When an odor associated with food becomes associated with no food, and vice versa, rats with OFC dysfunction adapt more slowly than intact animals to the new contingency (Schoenbaum et al. 2003; McAlonan and Brown 2003; Kim and Ragozzino 2005; Schoenbaum et al. 2007). Spatial reversal learning is similarly impaired (Boulougouris et al. 2007; Ghods-Sharifi et al. 2008; Young and Shapiro 2009). The deficit is general, in that olfactory, visual, auditory, and spatial discriminations are learned normally while reversal learning within those modalities is impaired. During olfactory discrimination learning, OFC neurons acquire stimulus-selective activity associated with reward that changes during reversal learning (Schoenbaum and Eichenbaum 1995a; Schoenbaum and Eichenbaum 1995b; Alvarez and Eichenbaum 2002; Ramus and Eichenbaum 2000; Schoenbaum et al. 1999; Roesch et al. 2007). OFC neurons recorded in the + maze during spatial learning fired in patterns that distinguished different rewarded paths in the same start arm, and population coding changed immediately when contingencies reversed (Young and Shapiro 2011a).

Reversal learning is not always impaired by OFC dysfunction, however, and the deficit depends on the extent to which outcome expectancies guide behavior. Indeed, OFC dysfunction can either impair, improve, or have no effect (Rudebeck et al. 2013) on reversal learning, depending in part on the history and schedule of contingency changes (Fellows and Farah 2005). Rats with OFC lesions learn rapid reversals faster than control animals, perhaps because frequent contingency changes minimize the significance of integrated reward history and prevent the development of stable outcome expectancies (Riceberg and Shapiro 2012). As stable outcome expectancies lose relevance to the behavioral discrimination, so does the influence of the OFC. Rapid reversals increase proactive interference, and the rat needs to keep track of current "task rules." At the limit, rapid "reversal learning," tasks in the + maze become "delayed nonmatching-to-sample" tasks, operationally defined tests of spatial working memory (Olton et al. 1979) that require both hippocampal and mPFC function.

19.6 dlPFC/mPFC and Strategy Switching

People with lateral PFC damage are typically impaired when required to "work with memory." PFC damage impairs normal rule learning in humans (Owen et al. 1991; Gershberg and Shimamura 1995; Levine et al. 1998; Bunge et al. 2005). People with vlPFC damage have trouble suppressing information in memory, and imaging studies show selective activation of vlPFC during "retrieval and selection of task-relevant representations," i.e., reducing memory interference (Badre and Wagner 2006). Dorsolateral PFC (dlPFC) damage impairs people's ability to select or organize information to guide actions. The Wisconsin Card Sorting Task is a canonical test of dlPFC function in people. Subjects are shown four stimulus cards that differ in the number and color of four different shapes (stars, crosses, triangles, and circles) (Berg 1948). The subject is given a pack of response cards, asked to place them one at a time into the correct group, and is told after each response whether the classification is correct (Berg 1948). Because the cards can be grouped by each of three dimensions (number, shape, and color), the subject must learn by trial and error the appropriate sorting strategy. After the subject makes the correct response five times in a row, the experimenter changes the category, and the subject has to switch the sorting strategy. People with dlPFC damage typically learn the first rule normally, but are impaired when required to switch sorting rules, e.g., from number to color (Grant and Berg 1948; Milner 1963); imaging studies find the same region is activated during task performance (Blumenfeld and Ranganath 2007). Homologous deficits follow lateral PFC damage in nonhuman animals. Monkeys with dlPFC lesions are impaired in switching responses between different stimulus dimensions (Dias et al. 1996; Bussey et al. 2001; Gaffan et al. 2002). Rats with mPFC damage are impaired in learning or remembering tasks that require attending to (Birrell and Brown 2000) and changing the perception-action category that guides adaptive behavior (Ragozzino et al. 1999a; Ragozzino et al. 1999b; Ragozzino et al. 2003; Dalley et al. 2004; Rich and Shapiro 2007). mPFC lidocaine infusions impaired learning new strategies, but not reversal learning in the + maze (Ragozzino et al. 1999a; Ragozzino et al. 1999b; Ragozzino et al. 2003); the opposite dissociation was produced by inactivating the OFC (Kim and Ragozzino 2005; Young and Shapiro 2009).

PFC neurons in monkeys are sensitive to rules that guide behavior including abstract stimulus categories (White and Wise 1999; Wallis et al. 2001; Fuster et al. 2000; Asaad et al. 2000). Even as stimuli and overt responses are identical, PFC neurons differentiate the rules guiding behavior. In rodents, the medial PFC (mPFC), particularly the infralimbic (IL) and prelimbic (PL) regions, corresponds to the dlPFC in primates, and though the anatomical homology of the rat and primate prefrontal is debated (Preuss 1995), the circuits support similar classes of behavior (Uylings et al. 2003). Rats can be trained to switch strategies in tasks that require extra dimensional shifts, such as learning to discriminate the shape vs orientation of visual objects (Shepp and EIMAS 1964), odor vs texture of material in bowls (Birrell and Brown 2000), and between body turn and place approach strategies in the + maze (Ragozzino et al. 1999b). As in the lateral PFC of

nonhuman primates, mPFC neurons fire in patterns that correspond to task rules (Fig. 19.6). In spatial mazes neurons in the rat mPFC tend to fire in relation to goals and other aspects of task structure (Jung et al. 1998; Pratt and Mizumori 2001). Beyond goal-related firing in the + maze, mPFC firing rate dynamics reflected changes in strategy as rats switched between place approach and body-turn response rules (Rich and Shapiro 2009). The firing rate of rat mPFC neurons correlated with task rules even when the stimulus environment and overt behavior were identical (Durstewitz et al. 2010; Rich and Shapiro 2009). Moreover, mPFC population activity that changed markedly during strategy switching was relatively stable during spatial reversal learning (Rich and Shapiro 2009). Neurons in the rat mPFC are especially important for signaling abstract rules, in this case defined by using different memory systems.

19.6.1 PFC Operations: Delay Tasks and Consolidation

19.6.1.1 Working Memory and "Delay Cells"

The delayed response task was one of the first reliable indicators of PFC damage in monkeys and suggested that the PFC was crucial for short-term memory (Jacobsen 1935). In this task, monkeys learn to observe where food is placed in one of two adjacent but otherwise identical food wells that are then covered by cards. After a variable delay, the monkey is given access to the cards and can move one to retrieve the hidden food. Intact monkeys remember and choose the correct location after delays as long as several minutes, but monkeys with lesions of the PFC perform poorly if the delay exceeds a few seconds (Jacobsen 1935). Analogous deficits have been reported in rats with PFC dysfunction (Winocur 1992; Ragozzino et al. 1998; Floresco et al. 1999; Ragozzino and Kesner 2001; Lee and Kesner 2003; Yoon et al. 2008), but the results are inconsistent (Dias and Aggleton 2000) and, as in monkeys, may depend on proactive interference (Gisquet-Verrier and Delatour 2006; Horst and Laubach 2009). For example, inactivating neurons and fibers of passage in the mPFC with lidocaine had no effect on a standard test of spatial working memory in the radial maze, but caused a marked impairment when a 30-min delay was imposed between the first and last 4 choices (Floresco et al. 1997). If proactive interference rather than the passage of time alone is responsible for this deficit, then increasing interference in other ways, e.g., having the rat perform a working memory test on a different maze, should impair performance at shorter delays.

Neurons recorded in the dlPFC of intact monkeys performing delay tasks fire at high rates after the presentation of a discriminative cue and before the related response, called "delay cells" (Fuster and Alexander 1971; Fuster and Alexander 1973). Delay tasks require attending to and coding stimuli, maintaining discriminative information during the delay, and response selection, and PFC neuronal activity correlates with each of these cognitive demands. Many single-PFC neurons respond to signals indicating the start of the trial, some discriminate the stimuli and maintain firing during the delay, others fire during the delay independent of the

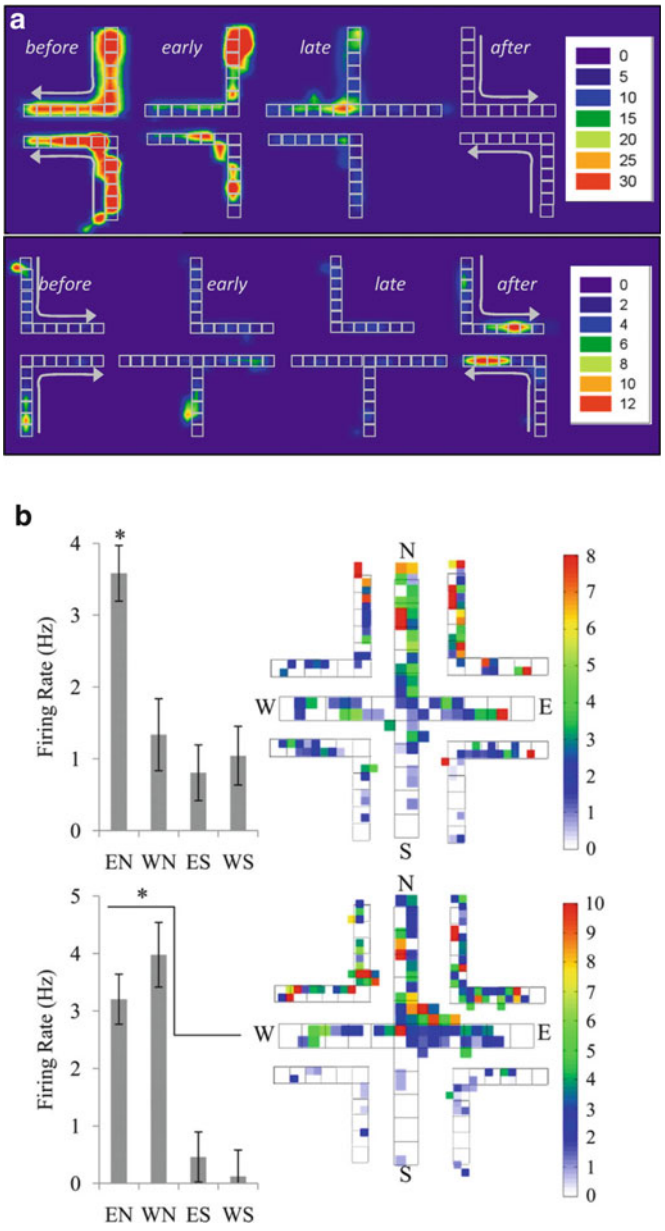

Fig. 19.6 Coding by PFC neurons. (**a**) Rats were trained to approach a spatial goal in the + maze (west) and then adapted to a contingency that rewarded a body turn (go *left*). Learning spatial discriminations requires the hippocampus, whereas learning a body turn requires the dorsolateral striatum (White 2008). mPFC inactivation impairs memory for switching between these two

stimulus, and others only increase firing prior to response initiation (Fuster 2008). Delayed response tasks based on saccades activate delay cells in the principal sulcus of the PFC with directionally tuned signals, and error trials are associated with failure of the delay activity (Funahashi et al. 1990). The delay firing is associated with stimulus quality (Constantinidis et al. 2001) or location rather than saccade direction, dissociating memory for past events from motor preparation (Funahashi et al. 1993). In paired associate tasks, PFC neurons show prospective coding by firing with increasing rates toward the end of the delay that predicts the expected stimulus. The prospective coding did not depend on the particular sample or the discriminative response (Rainer et al. 1999). In monkeys trained to remember sequences of two visual stimuli, the same population of PFC neurons encoded both stimuli with changed firing rates (Warden and Miller 2007). Moreover, the same population of PFC neurons code stimulus sequences differently depending on whether the monkeys had to recognize repeated sequences or indicate the stimulus series by recapitulating them using eye movements (Warden and Miller 2010). During delay tasks, each PFC neuron can signal combined information about recent, current, and pending stimuli, task rules, and discriminative responses (Rigotti et al. 2013).

These responses reflect the multidimensional input to the PFC from the entire cortical mantle. Delay cells are recorded in many neocortical areas in monkeys and depend upon reciprocal links with the PFC. For example, when monkeys perform a delayed matching-to-sample task, neurons in the inferotemporal cortex (IT) fire during the delay in patterns that vary with the color of the stimulus to be remembered (Fuster and Jervery 1981). Cooling the PFC reduces discriminative signals in IT delay activity, cooling IT reduces discriminative activity of the PFC delay cells, and both treatments impair memory performance (Fuster et al. 1985). Delay activity has been observed in the rat auditory cortex (Sakurai and Sugimoto 1986; Sakurai 1990; Sakurai 1994), but PFC recording experiments report inconsistent results (Euston et al. 2012; Euston and McNaughton 2006). We looked for but did not observe delay activity in the mPFC while rats performed recent memory tasks in a radial maze. The discrepancies between studies may depend on precisely which region of the PFC is recorded, the task demands, and the statistical methods used to analyze the data (Narayanan and Laubach 2009). For example, the temporal organization of mPFC firing predicts memory performance in a delayed response tasks in rats, but not mean firing rate (Hyman et al. 2010). During delay tasks the

Fig. 19.6 (continued) memory strategies (Rich and Shapiro 2007b), and mPFC neuron activity is better correlated with memory strategy than location, a specific goals, or overt behavior. The figure shows the firing rate of two mPFC neurons recorded before, during, and after the rat switched strategies. Both neurons fired in different patterns as the rats followed different strategies despite using identical behaviors in consistent paths (turning *left*/approaching the west goal in the *top panel*, turning *right*/approaching the east goal in the *lower panel*). The heat plots show firing rate. Adapted from Rich and Shapiro (2009). (**b**) Rats were trained to approach a spatial goal in the + maze (*north*) and then adapted to a reversed contingency that rewarded the opposite goal arm (*south*). The firing rate of OFC neurons distinguished either single paths (*top*) or multiple paths to the same goal (*bottom*). Adapted from Young and Shapiro (2011a)

active population of PFC cells encodes the full range of information needed to meet task demands, and individual neurons contribute to multiple components. Taken together, PFC activity encodes interactions among task parameters that predict outcomes.

19.6.1.2 Enduring Flexible Encoding and Consolidation

The results suggest that during learning the PFC can modulate other brain areas across several timescales. As reflected in delay tasks with rapidly changing contingencies, PFC activity can guide discriminations directly by helping to maintain active representations across distributed circuits (Fuster and Bressler 2012). When contingencies changed more slowly, e.g., across many minutes during typical reversal or strategy switching tasks, the PFC may alter distributed circuits so that learning endures (Rich and Shapiro 2009; Rich and Shapiro 2007a). mPFC inactivation during learning did not affect the acquisition of strategy switches or spatial reversals, but selectively impaired memory for strategy switches and not reversals the following day (Rich and Shapiro 2007b). The retention, but not the acquisition, of spatial reversal learning, was impaired by inactivating the OFC with muscimol during learning a treatment that left memory for strategy switches intact (Young and Shapiro 2009). The double dissociation produced by muscimol infused during learning into either the OFC or the mPFC suggests that the two structures contribute to memory for reversal learning and strategy switching, respectively (Young and Shapiro 2011a, b). Enduring memory required mPFC activity during learning itself, because muscimol infused immediately after learning had no effect on subsequent memory performance (Rich and Shapiro 2007). In both tasks PFC neurons developed new population codes when rats were presented with new contingencies. mPFC neurons responded to changing task strategies that generalized across spatial goals and trajectories (Rich and Shapiro 2009), while OFC neurons generalized across paths to a spatial goal (Young and Shapiro 2011a). In these cases signals from the mPFC and OFC during learning may establish patterns of synaptic weights in the hippocampus that bias prospective coding and guide goal selection 24 h later. In some cases long-term memory retrieval requires mPFC activity. Trace eyeblink conditioning in rats requires the hippocampus, and not the mPFC (though it does in rabbits and may depend on specific subregions (Siegel et al. 2012)), but inactivating the mPFC several weeks after training impaired memory retention (Takehara-Nishiuchi et al. 2006; Takehara-Nishiuchi and McNaughton 2008). OFC inactivation causes analogous impairments in establishing the social transmission of food preference and its long-term persistence (Lesburgueres et al. 2011).

19.7 Theories of PFC Function

The neuropsychology and neurophysiology of the PFC suggest that the structure computes expectancies related to goals and rules. “Perception-action” cycle and “guided activation” theories propose that PFC neurons contribute to behavioral flexibility by altering activity in other brain areas so that newly appropriate sensory,

memory, and motor circuits guide successful behavior in changing circumstances (Fuster 1989; Miller and Cohen 2001). The basic idea is that processing streams in frontal and posterior cortical regions connect and interact most strongly at similar levels of sensory and motor abstraction. Visual information that begins with a retinal map is recoded across cortical regions to extract regular statistical features or dimensions: retinocentric location, oriented lines, color, spatial frequency, etc. As the signal is processed through higher-order association cortices, the features are combined into more complex trigger features, culminating in the medial temporal lobe where visual information can trigger representations about the individual's behavior within a spatial, temporal, and personal context. The processing hierarchy is analogous in frontal cortex, with simple movement vector signals by neurons in the precentral sulcus (Georgopoulos et al. 1986) influenced by premotor and ultimately prefrontal cortical circuits that include goals, plans, and schemas. The frontal and posterior processing systems are connected at each level of the hierarchy so that actions and perceptions inform and constrain one another (Fuster 2008; Fuster 1995). At the highest and most abstract level, the perception-action cycle might be considered as an "intention-recollection" cycle that spans multiple environments and timescales, such as planning to give a talk on another continent.

The PFC integrates information provided by many cortical inputs and modulates processing in those circuits. The spatial integration across anatomical circuits is accompanied by temporal integration over repeated experiences, as illustrated by the proposed role of the OFC in computing outcome expectancy. From this view, the OFC integrates the history of reward-associated past experiences, and its output provides a "teaching signal" that modulates activity and plasticity in other brain structures when predicted and actual features differ (Schoenbaum et al. 2009). The output from OFC activates other brain regions, so that representations of similar events, actions, and outcomes from the past can guide response selection (Young and Shapiro 2011b). Like outcome expectancies, abstract rules are generalizations acquired during many experiences that can either provide a teaching signal when contingencies change or activate prospective representations in new circumstances. The integration of repeated perception-action-outcome cycles into common patterns or "regularities," e.g., rules, strategies, or expectancies, may reflect the generalized computational function of the PFC (Miller and Cohen 2001). The modulation of other brain regions by "teaching" during learning or activating prospective codes during memory retrieval may be the generalized output signals from the PFC. Both of these functions are reflected in the contribution of the PFC to consolidation and working with memory, especially during learning and selective memory retrieval that are susceptible to proactive interference.

PFC dysfunction increases susceptibility to proactive memory interference in people, monkeys, and rats. Peters et al. (2013), for example, found that inactivating the mPFC in rats does not impair learning to discriminate between eight pairs of odors if each pair is learned one at a time. The same treatment slows learning when the eight odor pairs are interleaved during training and seems to block learning altogether if a second list is presented that includes familiar items with reversed contingencies. In other words, mPFC reduces interference during learning. mPFC

also seems to be crucial for reducing interference during memory retrieval. Rats first trained to high levels of performance with intact mPFC function are impaired if the structure is later inactivated during testing, showing that the structure is important for normal memory retrieval (Peters et al. 2013). Tasks that require learning or remembering lists of items concurrently, reversing contingencies, switching strategies, shifting response dimensions, and ignoring irrelevant stimuli have in common the need to compute selective outcome expectancies to reduce proactive interference.

In summary, PFC activity can initiate processing during behavioral episodes that has important effects long after the events, likely by modifying activity in distributed brain structures. The areas include key components in different memory systems, specifically the striatum and the hippocampus (White 2008). This perspective suggests a framework for investigating the functional interactions between the PFC and the hippocampus. Spatial discrimination and reversal learning require rats to navigate first to one and then to another goal defined by location, and both require hippocampal function. Spatial reversal learning, however, can be impaired by either the hippocampal or PFC dysfunction. Converging neuropsychological and physiological evidence shows that interactions between the PFC and the hippocampus are crucial when circumstances require reorganizing the relationships among familiar items.

19.8 PFC- Hippocampus Interactions and Memory

The previous sections described the neuropsychology and physiology of the PFC and the hippocampus. In broad strokes, the PFC computes the general patterns common to repeated experiences, e.g., outcome expectancies that activate representations of objects and their value (Schoenbaum et al. 2009) or abstract rules that link common features of objects into categories that guide responses (Miller and Cohen 2001). PFC neurons encode these general patterns and maintain goal-directed signals across distributed neural networks throughout delays and despite interference, "monitoring performance" about actions and their outcomes (Horst and Laubach 2012). When contingencies change, these signals modulate other brain regions, perhaps by providing a teaching signal that helps correct errors. In new situations the PFC may activate prospective codes in those brain regions based on rules and expectancies acquired during similar circumstances in the past (Young and Shapiro 2011b). The hippocampus, in contrast, encodes records of specific event sequences that includes "what, where, when, why, and how," the internal and external context of behavior. During memory-guided behavior, hippocampal neurons replay time-compressed sequences of places occupied during recent journeys and project sequences of places about to be entered. Hippocampal neurons fire in temporal sequences (Pastalkova et al. 2008) with "time cells" that differentiate intervals during delays (MacDonald et al. 2011). Unlike PFC "delay cells" that often fire in similar patterns during different delays (Fuster and Alexander 1971) based on task rules that generalize across stimuli (Wallis et al. 2001),

CA1 "time fields" fire in unique patterns based on specific stimulus associations and delay duration (Kraus et al. 2013; MacDonald et al. 2011). Both regions contribute to memory via reciprocal connections with widely distributed cortical areas, but according to different computational roles. The hippocampus encodes and consolidates unique episodes by linking event features; the PFC encodes and consolidates the commonalities across episodes by linking outcomes into rules and expectancies.

An extended view of relational memory theory suggests that the two regions interact in an "intention-recollection" cycle (Fuster 1995): items in the environment trigger the retrieval of episodic memories that in turn help activate representations of "goals and means to achieve them" (Miller and Cohen 2001). From this view, overall goals coded by the PFC help retrieve hippocampal representations of episodic memories that included obtaining those goals (Fig. 19.4), strategies, reward expectancies, and journey coding.

Memory strategy and reward expectancy signals recorded in the mPFC (Rich and Shapiro 2009) and OFC (Young and Shapiro 2011a, b) may influence the hippocampus either directly or indirectly. Strategy switching alters mPFC population codes and modulates CA1 journey coding (Ferbinteanu et al. 2011). mPFC signals may inform CA1 codes about abstract task features, such as matching-to-sample rules, and cognitive structures that allow one place, e.g., a start arm, to be parsed and represented as a common path to different goals. In the + maze, rats select between journeys to the current goal, which changes across trial blocks. Reversal learning can be guided by reward expectancies or by parsing memories of recent episodes. Reward expectancies are signaled by OFC neurons where "path coding" changes during both reversal learning and strategy switching (Young and Shapiro 2011a, b). "Rules" signaled by mPFC neurons may track which of two goals has been rewarded most recently, mitigating interference and maintaining rewarded responses in the settings that require flexibility. Combined, mPFC neurons convey memory strategy and the matching-to-sample (or win-stay/lose-shift) rules to CA1 that parse different journeys ("what" and "how"), while OFC neurons convey integrated reward history signals that link journeys to expected outcomes ("what" and "why"). Frontotemporal interactions thereby identify available goals, activate relevant memories, and engage appropriate strategies.

This view helps account for how familiar task rules facilitate learning in new circumstances and explain learning-related changes in hippocampal firing patterns. We trained two groups of rats in a standard (STD) spatial win-stay task with serial reversals in a + maze as described above. The rats were implanted with bundles of unit recording electrodes targeting dorsal CA1 and CA3. Place fields recorded in the STD had similar current, prospective, and retrospective coding distributions (Bahar and Shapiro 2012b; Bahar et al. 2011) as described before (Ferbinteanu and Shapiro 2003). The same cells were recorded as one group of rats learned to apply the same "win-stay with serial reversals" rules but moving in opposite directions from switched start and goal arms. In this "switch" task (SW), the rats were trained to take opposite trajectories (e.g., from east and west start arms to either south or north goal arms) in the same maze and room. Another group of rats followed the same initial procedures, but were tested in an unfamiliar environment (UN).

Because both strategies and rules (e.g., matching to place) were identical to the STD, the rats learned both the SW and the UN tasks rapidly. The rats learned the SW within a few trials. Though the basic task rules were preserved, learning the SW required adjusting the link between outcome expectancies and spatial episodes—the different journeys in the same environment. Hippocampal place fields remapped instantaneously and stably in the SW compared to the STD. Moreover, ~50 % of CA1 and ~75 % of CA3 cells had place fields in both tasks. The two place field populations "compared and contrasted" the STD and SW tasks: most CA3 cells had place fields that shifted within the same maze arm in both tasks, as though preserving their spatial identity, while CA1 place field maps were anticorrelated between the tasks (Bahar et al. 2011). In contrast, journey-dependent activity declined during SW sessions, as though the OFC lagged in computing new reward expectancies, or those signals did not integrate with a well-established representation of strategy and place. From this view, the brief decline in SW performance reflected the violation of reward expectancies and reduced coherence between the hippocampal and OFC coding (Young and Shapiro 2011a, b). This phase of learning coincides with the time when novel sequences of familiar places (journeys) must be linked with reward and generate novel OFC path codes. Familiar rules and environmental representations could support rapid learning, but path coding needed adjusting.

In contrast, performance in the UN task only reached criterion after many trials in one day of training. Familiar rules and non-discordant reward expectancies were insufficient to support rapid learning, which required establishing memory representations of the new environment. The more severe impairment in the UN task and the marked instability of place fields reflected the formation of new hippocampal representations in an unfamiliar environment: 60 % of CA1 and 80 % of the CA3 cells had place fields exclusively in either the STD or the UN (Bahar et al. 2011). In contrast to the SW, journey-dependent CA1 place fields were largely maintained in the UN despite the instability of the active CA1 population and a dramatic reduction of CA3 place fields (Bahar and Shapiro 2012a).

We propose that journey coding was maintained in the UN by familiar strategies that, unlike in the SW, were unencumbered by reversed contingencies. In other words, journey coding by CA1 may have been maintained by coherent interactions between the hippocampus and both the mPFC (Guise and Shapiro 2012) and OFC (Young and Shapiro 2011a, b). This interpretation is consistent with a striking loss of CA3 place fields in the UN task: PFC neurons strongly innervate CA1, but not CA3, both directly (Cenquizca and Swanson 2007) via the nucleus reuniens (Vertes 2006) and the entorhinal cortex (Prasad and Chudasama 2013).

In familiar situations, strategy and reward expectancy signals converge on stable memory representations. In the STD + maze task, hippocampal representations included "where, when, and which" in place and journey codes as rats made familiar approaches to established goals. In the SW task, reward expectancies were violated, established spatial memory sequences inverted, and journey coding vanished. In the UN task, reward expectancies were neither established nor violated, novel path codes were generated rapidly, and journey coding emerged

as quickly as it could be measured. Interactions between the PFC and the hippocampus may link strategies and reward expectancies with memory codes. If bidirectional interactions between the PFC and the hippocampus in fact help select memory representations, then the structures should be strongly interconnected. Recording both structures simultaneously during tasks that require both should reveal coactivation that predicts selective memory retrieval, and disconnecting them should impair performance of those tasks.

19.8.1 Functional Anatomy

The PFC and the hippocampus are interconnected through both cortico-cortical and subcortical routes, and these reciprocal connections support functional interactions. The PFC and the medial temporal lobes are strongly connected ipsilaterally, and commissural pathways are weak. The mPFC and OFC project directly to the entorhinal cortex and to septal and temporal CA1 via one subcortical route through the nucleus reuniens, a midline thalamic nucleus that is strongly interconnected with both regions (Vertes et al. 2007; Vertes 2006). Temporal CA1, the entorhinal cortex, and the subiculum innervate the PFC directly and indirectly via the nucleus reuniens and other midline thalamic nuclei (McKenna and Vertes 2004). Projections from ventral CA1 to PFC are powerful enough to induce LTP (Jay et al. 1996), and stimulating the nucleus reuniens generates evoked potentials in CA1 of equal magnitude to those produced by Shaffer collaterals (Di Prisco and Vertes 2006). Output from the hippocampal system is also relayed to the PFC via the fornix, mammillary bodies, and anterior thalamus (Fig. 19.5).

19.8.2 PFC-Hippocampus Interactions: Neuropsychology

If PFC-hippocampus interactions are crucial for selective memory encoding and retrieval to mitigate against proactive interference, then their coactivity should predict memory performance. Frontal and temporal lobe activation levels predict the accuracy of subsequent memory for recent events in people. During presentation of visual scenes, fMRI signal increases in the lateral PFC-hippocampus and parahippocampal gyrus, but not other brain areas, predict the extent to which a scene is later remembered (Brewer et al. 1998; Kao et al. 2005). Parahippocampal cortex and the lateral PFC activity predicts memory accuracy for temporal sequences of events (Jenkins and Ranganath 2010), and dlPFC and hippocampus activity predict subsequent memory for relationships between items more than individual items (Blumenfeld et al. 2011). PFC and hippocampus activity levels are temporally correlated during memory maintenance (Gazzaley et al. 2004), encoding, and retrieval (Miller and D'Esposito 2012). Interactions between the PFC and hippocampus are especially crucial when learning or memory retrieval conditions are prone to interference, such as in highly familiar circumstances when choices can be disambiguated only by the current goal. My choice between

on-ramps to a local highway depends on remembering whether my goal is to work or to shop. Tasks that increase proactive interference strongly activate the human PFC in fMRI experiments (Jost et al. 2012). When people navigate to different virtual spatial goals that include overlapping routes, performance varies with coactivation of the hippocampus and the OFC (Brown et al. 2010). The coactivation of the OFC and hippocampus is not limited to spatial tasks but generalizes to disambiguation of other types of overlapping sequences, such as when people learn and remember two overlapping sequences of faces (Ross et al. 2011). In this case temporal changes in activity in the hippocampus and OFC correlate with performance, as though interactions between the structures help people distinguish two social groups that share some common members. Interference reduction and selective memory retrieval reflect the same "intention-recollection" cycle, the reciprocal activation of goals and episodes.

Frontal-temporal interactions are necessary for similar memory operations in nonhuman animals. Dysfunction of the PFC on one side of the brain and temporal lobe structures on the other side deprives each hemisphere of functional interactions between the two regions even though each is intact unilaterally. Lesions of fiber tracts that interconnect prefrontal and temporal lobe structures caused severe memory impairments in monkeys (Wilson et al. 2008). Contralateral lesions of the PFC and inferotemporal cortex selectively impair delayed nonmatching-to-sample performance in monkeys that perform consistent discriminations normally (Browning et al. 2013). The same lesions impair reversal learning when items are presented serially, i.e., one stimulus at a time in sequence, but not when the same type of stimulus pairs are presented simultaneously (Wilson and Gaffan 2008). PFC-temporal lobe interactions are required when monkeys respond to items presented in temporally separated sequences (Browning and Gaffan 2008). Again interference is a key variable, as monkeys with lesions performed well in a visual object-delay task in which a blank screen filled the delay interval. When a visual object was presented on the screen during the delay, performance was impaired even though the intervening object was irrelevant to the discrimination (Browning and Gaffan 2008). Interactions between the PFC and the temporal lobes are necessary for maintaining goal-directed memory operations despite interference.

Lesions of the anterior thalamus in rats, which conveys signals from the hippocampal system via the mammillary bodies to the mPFC, increase susceptibility to memory interference (Dumont and Aggleton 2013; Law and Smith 2012). Excitotoxic lesions of the nucleus reuniens, a thalamic link from the PFC to CA1 and subiculum, impair working memory in the 8-arm radial maze (Hembrook and Mair 2011) and long-term spatial memory but not learning in the water maze (Loureiro et al. 2012). Inactivating the rat nucleus reuniens impairs switching between body turn and spatial strategies in a modified water maze (Cholvin et al. 2013). Contextual fear conditioning and its extinction is mediated by interactions between the hippocampus, the amygdala, and the PFC (Sierra-Mercado et al. 2011; Milad and Quirk 2002; Milad et al. 2004). Inhibiting nucleus reuniens cells innervated by the mPFC during contextual fear conditioning increased stimulus generalization, so that the mice were afraid and froze in an unfamiliar testing

chamber that resembled the conditioning context; normal mice did not. Phasic but not tonic low-frequency stimulation of the same cells had similar effects as inhibition and increased generalization (Xu and Sudhof 2013). The result is consistent with prior findings that disconnecting the PFC and hippocampal system increases interference, in this case between environments and reinforcement, and predicts that the PFC helps selective retrieval of hippocampal memory representations (Komorowski et al. 2013).

Interactions between the mPFC and hippocampus in rats are crucial for performing a delayed nonmatching-to-place task in the T-maze (Wang and Cai 2006) and 8-arm radial mazes (Churchwell et al. 2010). Both experiments require changing discriminative responses across trials and therefore resolving proactive interference. Memory performance was impaired after bilateral inactivation of each structure as well as by crossed unilateral inactivation of both. In the 8-arm maze, rats were trained to enter one maze arm for food and then return to the center of the apparatus where they were held in an inverted bucket for either a 10-s or 5-min delay and then allowed to choose either the same or the opposite goal arm. Each rat was implanted with cannula targeting the mPFC and CA1 bilaterally, and muscimol or saline was delivered to either one structure bilaterally, both structures ipsilaterally, both structures contralaterally, or both structures bilaterally. Inactivating either structure bilaterally impaired memory after a 5-min delay, as did crossed ipsilateral inactivation, whereas inactivating both structures ipsilaterally had no effect. The results show that both the mPFC and CA1 were necessary for task performance, as was their interaction. Only bilateral inactivation of both PFC and CA1 impaired memory at the 10-s delay, suggesting that either structure alone could help the rest of the brain maintain spatial memory for this short term (Churchwell et al. 2010).

Recent work in our laboratory concurs that interactions between the PFC and hippocampus are crucial for rapid spatial reversal learning. Temporary bilateral inactivation of the mPFC impairs spatial reversals in the + maze (Guise and Shapiro 2012) (Fig. 19.7). The infusions do not impair spatial discrimination learning or performance, but do impair learning when more than one discrimination is presented in the same testing session, as proactive interference increases. Bilateral hippocampal inactivation impairs spatial discrimination and reversal learning, whereas crossed inactivation of the mPFC in one hemisphere and the dorsal hippocampus in the other selectively impairs reversals. Unilateral connections between the structures in the intact hemisphere is sufficient to support normal learning, as neither unilateral mPFC infusions nor combined ipsilateral infusions of both structures affected behavior (Seip-Cammack et al. 2013). Interactions between the PFC and the hippocampus link goal-related expectancies with memory for recent behavioral episodes.

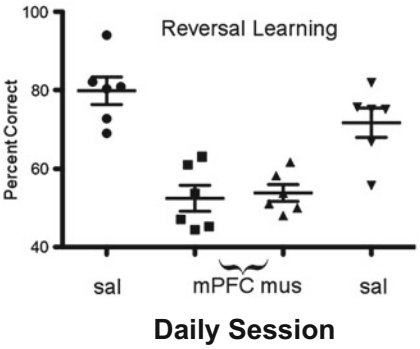

Fig. 19.7 Inactivating mPFC impairs spatial reversal learning in the + maze. Rats were trained in the same tasks shown in Fig. 19.2. Bilateral cannula infused either saline or muscimol into the mPFC before training in the same rats on different days. Saline infusions (sal) did not alter learning or task performance. Muscimol infusions (mus) did not impair learning one spatial discrimination (not shown), but impaired reversal learning (Guise and Shapiro 2012)

19.8.3 PFC-Hippocampus Interactions: Physiology

Lesion and inactivation studies demonstrate that interactions between the PFC and the hippocampus are necessary for selective memory retrieval in ambiguous situations. For example, Komorowski et al. (2009) trained rats to use spatial context to guide odor discriminations. The rats learned to find food by digging in one of two distinctly scented cups, each placed in a distal corner of one recording chamber; the odor signaled food and the cups were moved between the two corners across trials. A second, highly similar recording chamber contained identically scented cups, but in that environment the odor-reward contingencies were reversed. Some dorsal hippocampal CA1 and CA3 neurons had stable place fields throughout training, while others developed selective activity patterns that distinguished "items-in-place" as rats learned the task (Komorowski et al. 2009). Ventral CA3 cells developed "context fields," large place fields that distinguished the two chambers but fired similarly in both corners and in response to both cups (Komorowski et al. 2013). Performance in this contextual retrieval task requires both the mPFC and the entorhinal cortex for different reasons, and CA1 coding reflects the distinct and necessary type of information provided by each (Navawongse and Eichenbaum 2013). Inactivating the entorhinal cortex causes "global remapping" of CA1 place fields and reorganized object sampling correlates. In other words, entorhinal inactivation "scrambled" place fields and selective object-in-place firing correlates so that neither was related to the previously established representation. In contrast, inactivating the mPFC reduced object-in-place selectivity without altering place fields. For example, before mPFC inactivation a CA1 neuron fired selectively while the rat sampled one odor in one corner in one context. After inactivating the mPFC, the same neuron fired when the rat sampled either odor in that corner or stopped firing altogether (Navawongse and Eichenbaum 2013). The PFC is important for

selective, goal-directed memory retrieval, especially when responses to the same stimuli vary across circumstances. Interactions between the PFC and the hippocampus implement a retrieval mechanism by which PFC signals about goals modulate hippocampal memory representations.

19.8.4 Communication Between the PFC and the Hippocampus

PFC-hippocampus interactions require communication between widely distributed neuronal networks, and the mechanisms that support such communication are not well understood. Logic and evidence suggest that the interactions between distributed circuits require precise spike timing, so that action potentials generated by groups of cells in one region arrive when relevant groups of "downstream" neurons are responsive to inputs. Recent findings suggest that such spike timing is organized by coordinated oscillations reflected by coherent LFPs. Communication between networks is most likely to occur when spikes generated by the "sending" arrive at the peak excitability phase of the "receiving" network, at maximal depolarization LFPs phases (Buzsaki 2010). Together with synaptic input, the probability of spike generation is timed by coordinated oscillations in neuronal excitability, reflected in local field potentials (LFPs). LFPs correspond to fluctuations in dendritic currents recorded either locally by electrodes implanted in particular brain areas or on the scalp as electroencephalograms (EEGs). LFPs often oscillate in characteristic frequency ranges that correlate with behavior and cognitive demands in different brain areas. Hippocampal theta rhythm, for example, is a 4–12 Hz oscillation that is prominent during appetitive behavior and stimulus sampling but not consummatory behavior (Vanderwolf 1969). Other predominant oscillation frequencies include delta ~2 Hz, beta 12–25 Hz, and gamma 30–100 Hz. Oscillation amplitudes reflect relative synchrony in local groups and are modulated by networks of inhibitory interneurons; oscillation frequencies are determined by the intrinsic excitability of the neurons, the time constant of ion channel controlling currents (e.g., GABA receptors), HCN channels, and extrinsic inputs (Buzsaki and Wang 2012; Buzsaki 2002; Buzsaki et al. 2012) (see Lever et al. 2014; Stark et al. 2013).

LFPs reveal PFC-hippocampus interactions. During learning and memory performance in rats, PFC-hippocampus interactions include dynamic, cross-network synchronization and coordinated spike timing within and between the structures. mPFC neurons fire in phase with hippocampal theta rhythm in behaving rats (Siapas et al. 2005; Hyman et al. 2005), and the temporal organization is modified by memory demand. Pairs of mPFC and CA1 neurons were recorded simultaneously in rats performing a delayed spatial association task, and their activity was most strongly cross-correlated when behavior was guided by memory (Jones and Wilson 2005). In other words, spike timing across mPFC and hippocampal networks was best synchronized when memory guided behavior. Firing of mPFC and CA1 cells was locked to theta phase, the phase locking was stronger when prospective choices were being guided by memory than when memory was irrelevant, and the peak

inter-spike interval corresponded to one theta cycle (~150 ms) (Jones and Wilson 2005). Moreover, the temporal coordination of mPFC spiking with respect to theta rhythm predicted memory accuracy in rats performing a spatial nonmatching-to-position task (Hyman et al. 2010). Learning rate was predicted by the magnitude of PFC-hippocampus theta coherence in mice performing a working memory task in a T-maze. Furthermore, interfering with theta coherence between the PFC and the hippocampus impairs learning. Phase locking of mPFC neurons to hippocampal theta was markedly reduced in mice with impaired spatial working memory (Sigurdsson et al. 2010). Mice tested in the T-maze task have higher amplitude theta oscillations in the mPFC on the central stem of the maze, when behavior is guided by spatial working memory (O'Neill et al. 2013). During error trials, theta power in the mPFC declined, especially as the mice approached the choice point of the maze, and inactivation of the ventral hippocampus with muscimol reduced theta frequency coherence between the mPFC and the dorsal hippocampus (O'Neill et al. 2013).

Complementary results were obtained in rats performing spatial discriminations in a + maze. LFPs were recorded simultaneously in the OFC and the dorsal hippocampus as the rats approached the choice point, so that memory guided behavior throughout the recording. The key comparison was between stable memory performance that requires the hippocampus, and spatial reversal learning requires the OFC for remembering the reversed contingencies the next day (Young and Shapiro 2009). OFC-hippocampus coherence was high during stable performance and declined during reversal learning, as population coding in the OFC changed to reflect new reward expectancies (Young and Shapiro 2011a). Note that in this experiment the OFC was not required for reversal learning per se, but, for its persistence, a process that could depend on suppressing old, rather than activating current spatial memory representations, or on modifying synaptic connectivity in the hippocampal system. Future experiments will determine the range of physiological interactions between the PFC and the hippocampus across learning and memory conditions, as different patterns of temporal coordination may contribute to each.

19.8.5 Coordinated Oscillations: Network Handshaking?

If communication between neural networks is organized by oscillations, then functionally interconnected circuits should have temporally correlated oscillations. Endogenous oscillations include a spectrum of simultaneous LFP frequencies that can covary in power and phase. Because action potentials are generated by voltage-gated ion channels, they occur typically in phase relation to LFPs, and the comodulation of different frequencies may provide a mechanism for coordinating local and distant neuronal networks (Buzsaki 2006). For example, hippocampal LFPs often show power and phase comodulation; the faster gamma rhythm subdivides each cycle of theta, and the magnitude of the gamma cycles are largest at the peak of the theta rhythm (Lisman and Buzsaki 2008). Hippocampal neurons

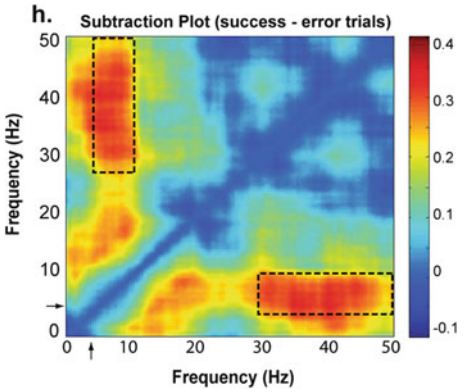

Fig. 19.8 Theta-gamma comodulation in the hippocampus predicts successful memory retrieval. Rats were trained in a matching-to-place task in a radial water maze and implanted with an infusion cannula in the medial septum, a stimulating electrode in the fimbria-fornix, and a recording electrode in the dorsal hippocampus. Memory performance was impaired by septal inactivation, which decreased theta power, and ameliorated by simultaneous "theta burst" stimulation of the fimbria-fornix. The comodulation of theta and gamma LFP power predicted memory retrieval from trial to trial across all infusion and stimulation conditions. The graph shows the arithmetic difference in power comodulation between correct and error trials. The *comodulogram* shows the temporal correlation of LFP power across frequencies and is diagonally symmetric. Subtracting the comodulograms obtained from success and error trials emphasizes the comodulation patterns associated with successful memory retrieval. The *rectangles* shown by *dashed lines* indicate theta-gamma comodulation. The *heat map* indicates correlation values. Adapted from Shirvalkar et al. (2010)

fire at gamma cycle "peaks" in sequences that recapitulate the ordered series of occupied place fields within one theta cycle (Skaggs et al. 1996; Nadasdy et al. 1999; Foster and Wilson 2007). Theta-gamma comodulation may therefore provide a mechanism that allows the hippocampus to link coactive cortical representations into gamma-separated "events" and within theta "sequences" (Lisman and Redish 2009). Different patterns of LFP comodulation within a given structure may reflect communication between specific networks. For example, CA1 oscillations are comodulated by theta and a wide range of gamma frequencies (~25–150 Hz). In CA1, theta-low gamma (25–50 Hz) comodulation synchronizes with low gamma in CA3; theta-high gamma (65–140 Hz) comodulation synchronizes with high gamma in the medial entorhinal cortex (Colgin et al. 2009). Various comodulation patterns may thereby segregate (or combine) CA1 responses initiated by different networks and support rapidly interleaved representations for memory encoding and retrieval (Hasselmo et al. 2002). Comodulation may reveal a crucial timing mechanism for memory function. Hippocampal theta-gamma comodulation predicted trial-wise memory performance in a matching-to-place task, septal inactivation reduced the comodulation and impaired memory, and brain stimulation patterns that induced comodulation improved memory in otherwise amnestic rats (Shirvalkar et al. 2010) (Fig. 19.8). LFP comodulation within a local circuit may reflect its functional

interaction with other brain areas, so that information flow between particular circuits is accompanied by specific comodulation patterns. This view suggests that specific comodulation "signatures" in each structure should accompany interactions between the PFC and CA1, perhaps varying across different learning and memory demands.

Sometimes behavior guided by the prefrontal cortex requires hippocampus-dependent memory, and other times it does not though both structures process information nonetheless. A fundamental question in neuroscience concerns how functional links between active structures are controlled, i.e., how communication between neural networks is established, maintained, and stopped. "Handshaking" describes how Internet communication is established between two computers and requires exchanging "synchronization" and "acknowledgment" signals. If computer A transmits a synchronize packet to computer B, computer B returns a synchronize-acknowledgment packet to A, and A replies with an acknowledgment packet, then communication between the two computers is established. Clearly the brain is not a digital computer, but the analogy is helpful because it indicates that handshaking can be initiated by any node and emphasizes the importance of the sequential exchange of signals to establish communication. Handshaking between mPFC and CA1 may occur during sequential changes in LFP comodulation that reflect the function of the "intention-recollection cycle."

Combined inactivation, multisite recording, and behavior studies can specify what, how, and when signals are conveyed from one structure to the other to guide information processing. Ongoing experiments in our lab combine local inactivation and simultaneous recording in both the mPFC and the hippocampus. Preliminary results suggest that coordinated changes in LFP oscillations accompany behavior and may be crucial for spatial reversal learning (Guise and Shapiro 2012). We analyzed the physiological activity recorded as the rat approach the choice point of the + maze, when behavior was "clamped" and learning proceeded. Some oscillation frequencies were relatively consistent throughout each trial. Hippocampal theta (7–10 Hz) and low-gamma (25–35 Hz) power were high throughout the trials, as were mPFC beta (12–25 Hz) and high gamma. Other frequencies changed dynamically with behavior as the animal initiated its response, approached the choice point, and reached the goal. These events are defining features of behavioral episodes, and LFP dynamics may coordinate handshaking among key brain structures to support selective, memory-guided action.

The "handshaking" may begin when the rat initiates a goal-directed response. As soon as the rats started moving in the start arm, delta (1–4 Hz) power increased simultaneously in the mPFC and CA1; it declined about one third of the way down the start arm and remained low for the remainder of the trial. The delta rhythm may establish a fundamental baseline for communication among structures, analogous to the "listen" state in TCP connections. Hippocampal theta and mPFC beta activity increased just after the delta power increases, as soon as the rats began walking along the maze arm. An increase in mPFC theta power coincided with the decline in delta power, which may reflect the first step in coordinating mPFC and hippocampal communication, analogous to the "synchronize" state. About one theta cycle

after mPFC theta power increased, (130 ms) beta power increased in CA1, as though synchronizing with mPFC, analogous to the "synchronize-acknowledgment" state. CA1 beta power remained high until the rat reached the choice point when it declined. Correlated power fluctuations in the two structures verified beta synchrony, suggesting that the mPFC and CA1 communicate when both structures oscillate in this range, as do OFC and CA1 (Young and Shapiro 2011a). Cross-comodulation analysis quantified the extent to which different oscillations frequencies covaried in time and may reflect full bandwidth communication between the mPFC and CA1, analogous to "full-duplex" communication (Fig. 19.9). The CA1 beta increase was blocked by inactivating the ipsilateral mPFC, suggesting that the coordinated beta oscillations are triggered by the mPFC (Fig. 19.9) (Guise and Shapiro 2012).

From this view, the mPFC "guides" hippocampal "activation" by coordinating activity in beta frequency in both structures (Fig. 19.10). In other words, communication between the structures may be bidirectional and organized by sequential changes of dominant frequencies. According to this sketch, behavior is initiated when both structures (and presumably the entire perception-action system) oscillate in delta rhythm—the "listen" state. As soon as the rat begins moving, the hippocampus oscillates in theta, and bursts of hippocampal spikes timed by delta-theta comodulation transmit a "synchronization" signal that triggers theta oscillations in the mPFC. Bursts of mPFC spikes timed by beta-theta comodulation transmitted to the hippocampus provide the "synchronize-acknowledgment" signal that triggers beta oscillations in CA1. Communication between the two structures proceeds as hippocampal neurons fire at the peaks of theta-beta complex waves. Future experiments will test these predictions.

19.9 Summary and Future Directions

An extended view of relational memory theory suggests that the PFC and hippocampus interact in a bidirectional "intention-recollection" cycle (Fuster 1995). Goals and expected outcomes coded by the PFC help activate hippocampal representations that include episodes relevant to the goals and environmental features that trigger hippocampal representations help activate PFC representations of "goals and means to achieve them" (Miller and Cohen 2001). As the highest-order association areas in the motor and perceptual processing streams, the PFC and the hippocampus both operate on highly abstract information collected over extended time periods. Whether or not they depend on "network handshaking," PFC-hippocampus interactions should be needed when memories that distinguish ambiguous situations are established or retrieved. When the mPFC is required for reversal learning in a familiar environment, the signal from the mPFC may select prospective codes in CA1 (Ferbinteanu et al. 2011) and CA3 (Bahar and Shapiro 2012a). Similar outcomes should apply to hippocampal coding features that correlate with memory retrieval, such as disambiguating overlapping odor sequences (Fortin et al. 2002), tracking more than one reference frame simultaneously

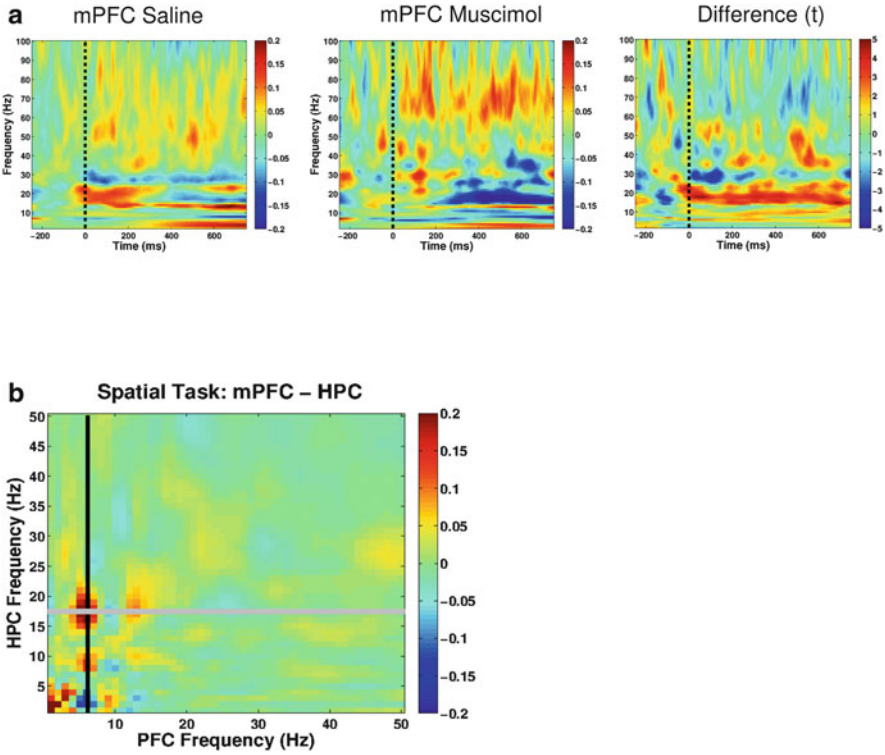

Fig. 19.9 Spatial reversal learning coordinated theta and beta LFPs in the mPFC and CA1. (**a**) Spectrograms show the power of CA1 oscillations recorded as rats learned spatial reversals in the + maze. Each plot shows the power spectrum as the rat moved through the start arm, choice point, and goal arm in ~1 s. The *dashed vertical line* indicates when the animal was ~1/3 the way to the choice point. The horizontal axis shows time in milliseconds around the *dashed line*, and the choice point was reached at the ~300 ms mark. Each frequency band was normalized by subtracting the power before the *dashed line* from the power afterwards. The mPFC was infused ipsilaterally either with saline or muscimol. CA1 beta power increased as the rat approaches the choice point after mPFC saline infusion (*left panel*). Infusing muscimol into the mPFC prevented the beta power increase in CA1 (*middle panel*). Paired *t*-tests compared the different effects of saline and muscimol mPFC infusions on CA1 oscillations, illustrating that the beta power increase in CA1 was blocked by inactivating the ipsilateral mPFC. Unilateral infusions did not impair learning or performance. The heat plot in the *left* and *middle* spectrograms shows power; the difference plot on the *right* shows *t* values. B. The spectrograms recorded from the mPFC and CA1 were cross-correlated to assess how LFP power varied concurrently in the two structures. Reversal learning was accompanied by high, synchronous theta and beta power in both structures (*not shown*). The heat plot shows power correlations in the mPFC (horizontal axis) 110 ms before CA1 (vertical axis), i.e., time shifted by ~ one theta cycle. The intersection of the vertical *black* and horizontal *pink lines* indicates that maximal CA1 beta power followed maximal mPFC theta power by 110 ms, ~one theta cycle (Guise and Shapiro 2012)

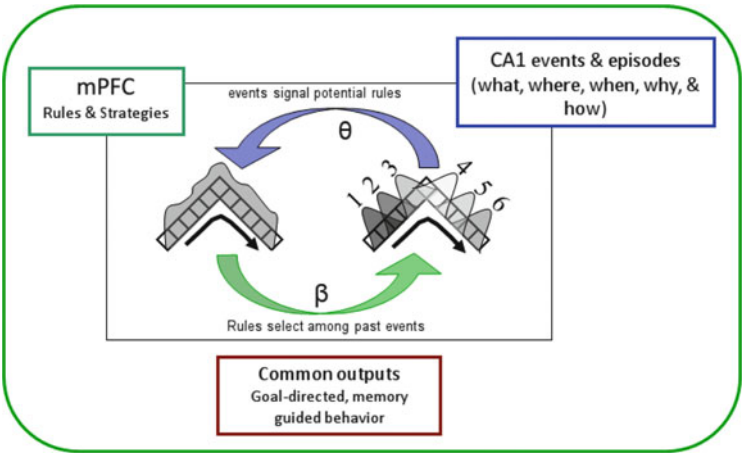

Fig. 19.10 A model of an "intention-recollection" mechanism implemented by coordinated LFP signals in the mPFC and CA1. Hippocampal memory representations associated with the internal or external environment are signaled in theta-gamma modulated bursts and include neurons that help activate mPFC cells. Neurons in the mPFC responsive to current goals that also receive hippocampal input become active, represent action outcomes associated with these memories, and synchronize in theta-beta modulated bursts. Neurons in the active mPFC circuits include neurons that innervate CA1, trigger CA1 beta, and modulate the hippocampal representation based on goals and expected outcomes. In unfamiliar circumstances CA1 neurons respond to new relationships among familiar features and automatically represent associated memories. Neurons in the mPFC responsive to current goals and hippocampal "memory items" modulate hippocampal activity and trigger prospective codes in CA1 based on outcomes from similar situations in the past (Bahar and Shapiro 2012a)

(Kelemen and Fenton 2010), populations of "time cells" that bridge delays between different pairs of associated items, and real-time hippocampal codes including "preplay," "replay," and vicarious trial and error that predict memory discriminations. The strong prediction in each of these cases is that inactivation of the PFC should reduce discriminative signals represented by hippocampal firing patterns.

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Index

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