Functional Interactions of Prefrontal Cortex and the Hippocampus in Learning and Memory

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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
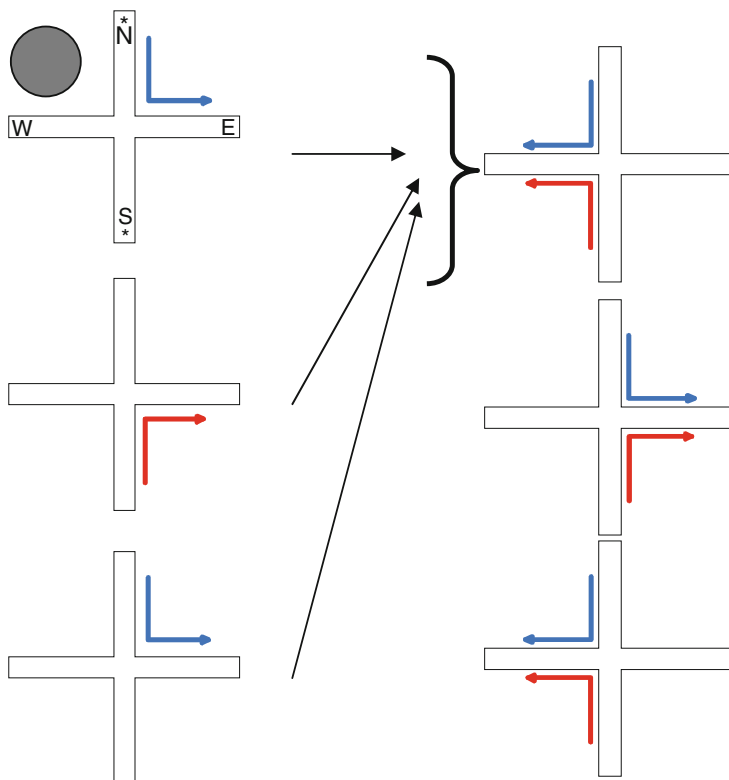
Fig. 19.2 Spatial reversal learning in a + maze. Rats are placed in either the north or south start arm at the start of each trial and learn to find food at the end of either the east or west goal arm (north to east in the first trial shown by the *blue arrow, top*). After each trial the rat is placed 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
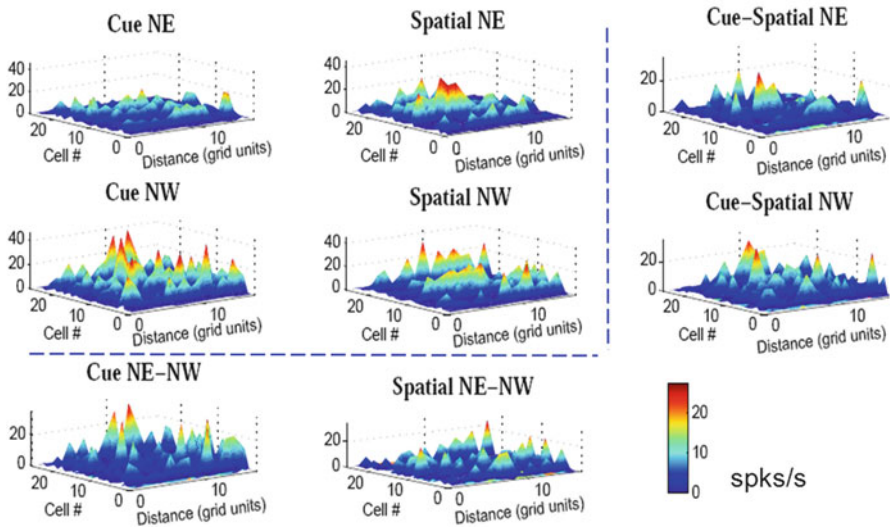
Fig. 19.3 Prospective coding by CA1 neurons signals both task strategy and journeys. The heat plots show the firing rates of an ensemble of ~30 CA1 neurons recorded simultaneously as a rat walked toward the choice point in the north start arm. Though the behavior was identical across conditions, the 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
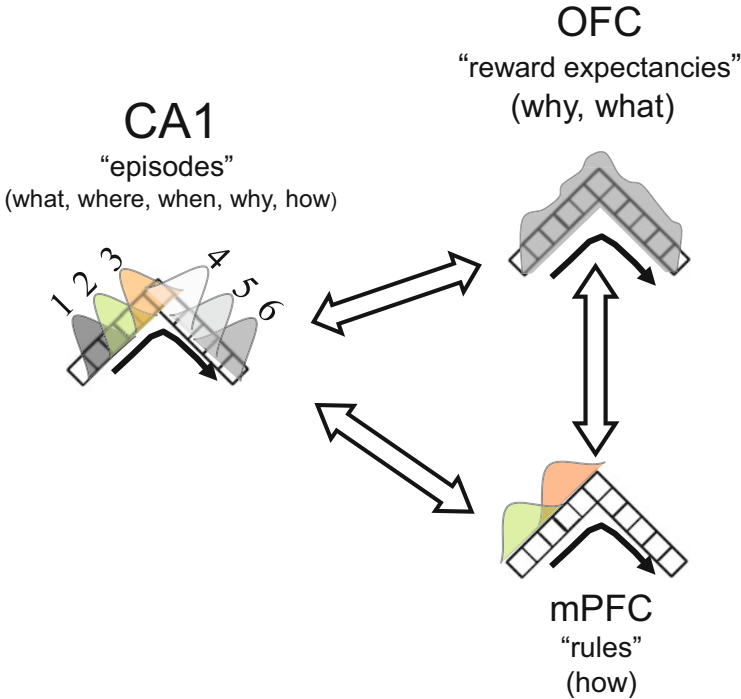
Fig. 19.4 Bidirectional interactions between the PFC and hippocampus link outcome expectancies and memory for episodes. Spatial reversal learning alters OFC population coding (Young and Shapiro 2011a), and switching between memory strategies alters mPFC population coding (Rich and Shapiro 2009). The 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
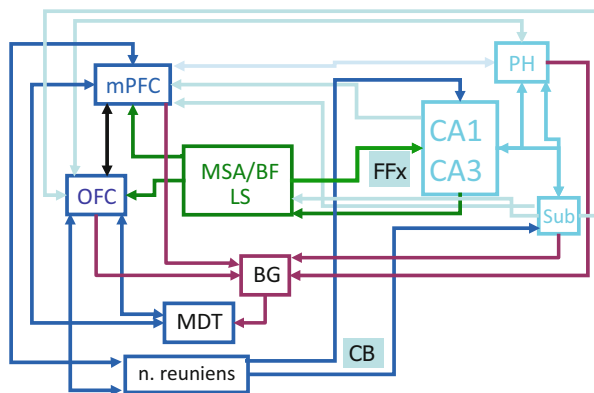
Fig. 19.5 A cartoon showing some of the anatomical connections among key components of the PFC (*dark blue* boxes) and the hippocampal (*light blue* boxes) systems. The PFC is defined by inputs from the medial dorsal thalamus (MDT) which innervates both ventral orbital (OFC) and medial (mPFC) regions 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
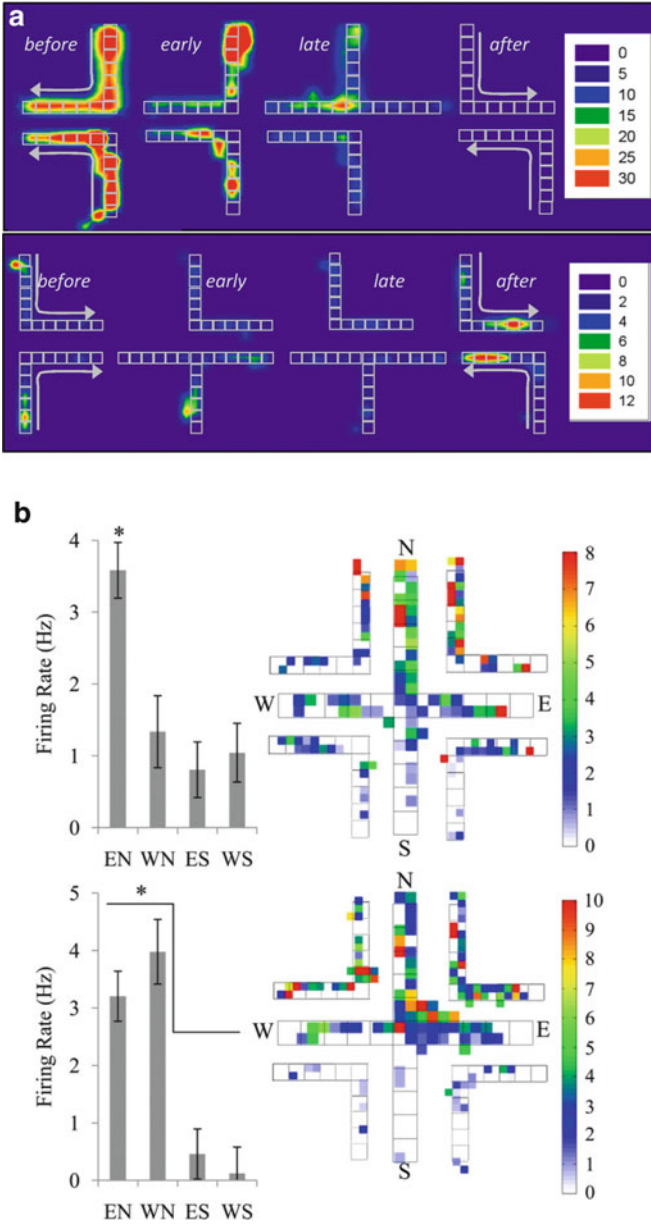
Fig. 19.6 Coding by PFC neurons. (**a**) Rats were trained to approach a spatial goal in the + maze (west) and then adapted to a contingency that rewarded a body turn (go *left*). Learning spatial discriminations requires the hippocampus, whereas learning a body turn requires the dorsolateral striatum (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

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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.
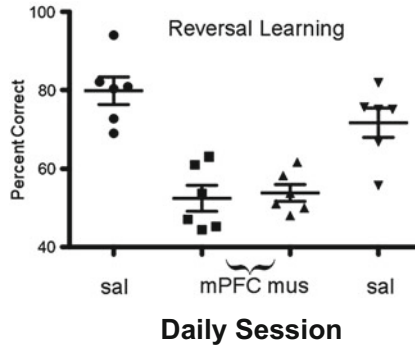
Fig. 19.7 Inactivating mPFC impairs spatial reversal learning in the + maze. Rats were trained in the same tasks shown in Fig. 19.2. Bilateral cannula infused either saline or muscimol into the mPFC before training in the same rats on different days. Saline infusions (sal) did not alter learning or task 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
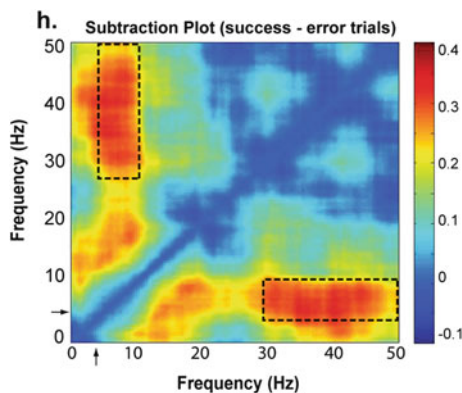
Fig. 19.8 Theta-gamma comodulation in the hippocampus predicts successful memory retrieval. Rats were trained in a matching-to-place task in a radial water maze and implanted with an infusion cannula in the medial septum, a stimulating electrode in the fimbria-fornix, and a recording electrode in the 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
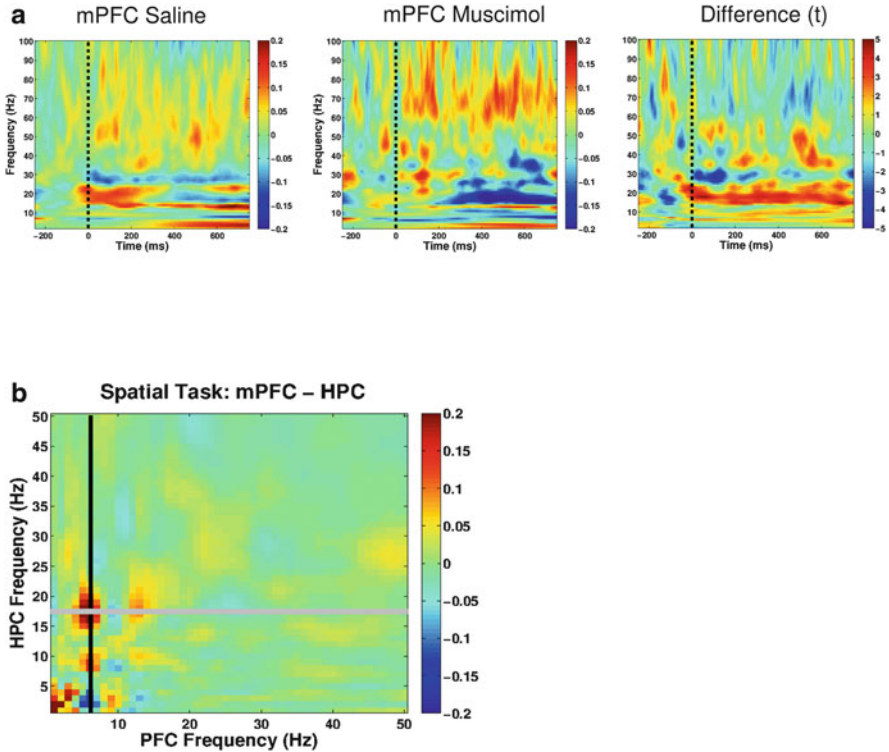
Fig. 19.9 Spatial reversal learning coordinated theta and beta LFPs in the mPFC and CA1. (**a**) Spectrograms show the power of CA1 oscillations recorded as rats learned spatial reversals in the + maze. Each plot shows the power spectrum as the rat moved through the start arm, choice point, and goal 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)
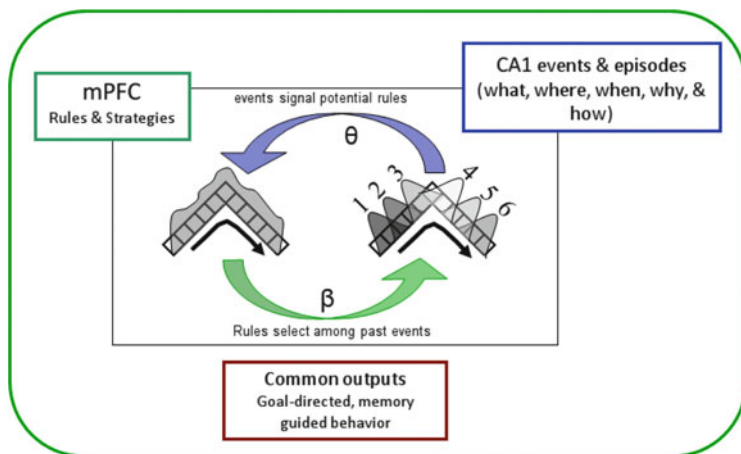
Fig. 19.10 A model of an "intention-recollection" mechanism implemented by coordinated LFP signals in the mPFC and CA1. Hippocampal memory representations associated with the internal or external environment are signaled in theta-gamma modulated bursts and include neurons that help activate mPFC cells. 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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