The Hippocampus Book

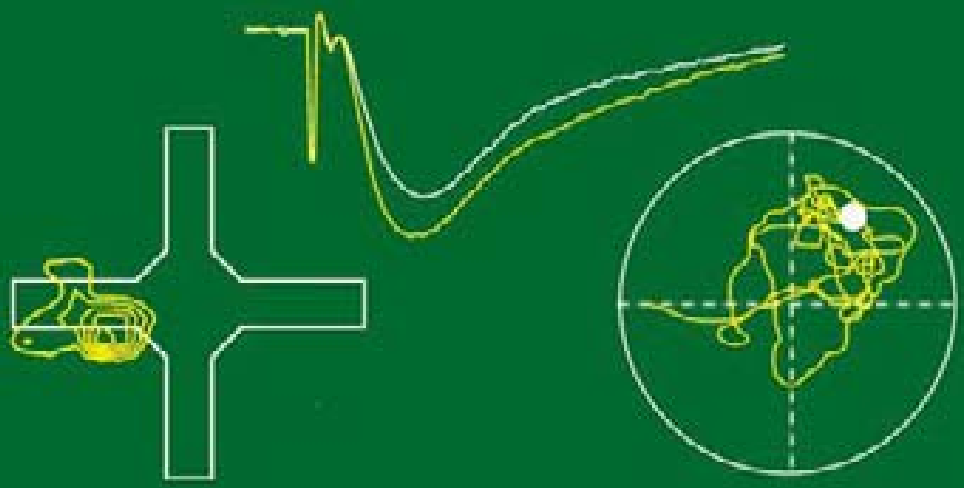
Per Andersen

Richard Morris

David Amaral

Tim Bliss

John O'Keefe



11 John O'Keefe

Hippocampal Neurophysiology in the Behaving Animal

11.1 Overview

This chapter addresses a central question in the study of the hippocampus: What information is represented in hippocampal electrical activity? When asking this question, we are immediately confronted with one of the central problems in neuroscience, the nature of how information is coded in the nervous system. Historically, there have been two answers to this question: On the one hand is the view that the nervous system is composed of a large set of individual computing elements, the neurons, and that these neurons interact with each other by passing discrete bundles of information along their axons. An alternative view is that the system is organized on more holistic principles, with large numbers of cells acting in concert perhaps reflected in synchronous neuronal firing or in rhythmical electroencephalographic (EEG) activity.

The general position taken in this chapter is that the hippocampus uses both strategies. There is ample evidence that individual hippocampal pyramidal cells code for specific locations in an environment by a marked increase in firing rate; but, equally, that part of the code for location involves the timing of cell firing relative to a clock wave, represented by the EEG theta wave and associated interneurons, and that groups of pyramidal cells can act cooperatively in an ensemble fashion. On this view, each pyramidal cell acts as an oscillator, and a sophisticated set of mechanisms exists for producing these oscillations. Each cell has the biophysical machinery to oscillate in isolation from other cells or external inputs. These individual oscillators are stabilized and synchronized by a set of inhibitory feedback circuits primarily involving inhibitory interneurons. Neurons in the septum and brain stem provide the neuromodulatory inputs necessary for hippocampal pyramidal cells to enter the oscillatory state and may also provide a driving signal that sets the overall frequency of the oscillations.

One powerful approach to the study of the functions of a brain region is to correlate the electrical activity of its neurons with some aspect of observed behavior or inferred cognition. This approach reveals what information is available to that part of the brain and when it is available. Furthermore, it is sometimes possible to record both the inputs and the outputs of an area, and under these conditions it may be possible to compute what transfer function is being performed.

Several patterns of electrical activity have been recorded from the hippocampus, and they have been correlated with behavioral or psychological states. During the mid-1960s, Vanderwolf placed a relatively large electrode into the hippocampus of the freely moving rat and recorded the EEG activity during a wide range of behaviors (Vanderwolf, 1969). He identified three distinct states: the rhythmical theta state, the large irregular amplitude activity (LIA) state, and the small irregular amplitude activity (SIA) state. Theta, in turn, could be classified into two subtypes on the basis of behavioral correlate and pharmacological sensitivity. In this chapter, these two types are called a-theta (for arousal/attention theta), which is sensitive to anticholinergic drugs such as atropine, and t-theta (for translation movement theta), which may be serotoninergic and glutamatergic.

The behavioral/psychological correlates of the two types of theta activity have been characterized best in rats: In this animal, the atropine-resistant component or t-theta occurs during a class of movements that may be loosely characterized as those that normally change the spatial relation between the animal's head and the environment. The correlates of the atropine-sensitive theta, or a-theta, are less well defined and are best summed up as psychological states such as arousal, attention, or intention to move. The behavioral correlates of LIA are those that do not change the animal's location in the environment: quiet sitting, eating, drinking, and grooming in the absence of postural shifts. The SIA state occurs during behavioral transitions, often when the animal awakens from

slow-wave or rapid-eye-movement (REM) sleep or when it abruptly stops running. It has not received much attention, and its behavioral correlates and physiological function are less well understood.

The rhythmical theta state reflects the synchronous membrane oscillations of large numbers of pyramidal cells in the CA1 field and dentate gyrus that are locked into synchrony by the inhibitory interneuronal network. One of its functions is to provide a clock signal against which the action potentials of the individual pyramidal cells can be timed. Another function might be to set up the optimal circumstances for the induction of long-term potentiation (LTP) (see Chapter 10). The nonrhythmical LIA state has a more random, broader spectrum especially in the lower-frequency range and may represent an inactive, relaxed state of the same network when it is not being driven. Alternatively, it may be an active state in its own right in which memories previously encoded in the hippocampus are strengthened and/or transferred to other regions of the brain. LIA is characterized by sharp waves of about 100 ms duration that occur randomly, with an average interval of 1 second. Associated with them are higher-frequency "ripple" oscillations of 100 to 200 Hz, which also may reflect the operation of the inhibitory network. In addition to oscillations in the theta and ripple bands, oscillations at intermediate frequencies (beta: 12–30 Hz; gamma: 30–100 Hz) have been recorded in association with various aspects of olfactory behavior.

Placing a microelectrode rather than a gross electrode into the CA1 hippocampal cell layer reveals a much richer and surprising set of behavioral correlates correlations between physiology and behavior. On the basis of the EEG recordings one might expect to see cell-firing patterns that are correlated with the animal's movements, and indeed this is observed. However, it is not the whole story. Ranck (1973) placed microelectrodes into the pyramidal cell layers of CA3 and CA1 and found two classes of cellular response. One type, which he called the theta cell, fired at frequencies ranging from 10 Hz (when the animal sat quietly or engaged in other "LIA" behaviors) to as high as 100 Hz (as it ran around the environment or engaged in other "theta" behaviors). Furthermore, they burst at the same frequency and showed consistent correlations with different phases of the various EEG waves. Here, at the level of the single cell, was one clear correlate of the EEG patterns, banishing forever any lingering skepticism about their functional significance. The second class of cell, the complex spike cell, had a much lower baseline firing rate, and many were effectively "silent" for long periods of time. Their defining characteristic is the occasional short burst of action potentials with successively decreasing amplitudes. Their major behavioral correlate was first identified by O'Keefe and Dostrovsky (1971) as the animal's location. They reported that these place cells were typically silent as the rat moved around the environment until it entered a small patch of the environment when the cell began to fire (the place field). It is now recognized that, within the place field, these cells also fire in a rhythmical bursting pattern during the EEG theta state. Unlike the theta cells, however, the frequency of bursts is slightly higher than the gross EEG theta, causing each successive burst to precess to earlier phases of the theta cycle as the animal moves through the place field. This temporal code works together with the overall rate code to identify the animal's location. In addition, variations in firing rate can signal aspects of behavior that occur in the place field or the presence (or absence) of objects encountered there. The same cells often fire in different environments, but the preferred locations are unrelated if the environments are sufficiently dissimilar to each other. One notable feature of these place cells is that in unconstrained open fields—environments in which the animal is free to move in all directions—the cells fire in the place field irrespective of the direction in which the animal is facing. In environments that constrain the animal's behavior, the cells become directionally sensitive and may be said to represent the successive locations along a path. In addition to the animal's location, some pyramidal cells signal the presence or absence of particular objects within the place field or the performance of particular behaviors there.

In addition to *representing* locations and features of the environment, the place cells have been shown to *learn* about new environments or changes in a familiar environment. For example, place cells initially treat similar environments as identical but can learn to differentiate between them with repeated exposure.

Place cells are typically recorded from the hippocampus proper but have also been recorded from other parts of the hippocampal formation, namely the subiculum, presubiculum, parasubiculum, and entorhinal cortex as well as the hippocampus. The properties of cells in these various regions vary, and it is still not clear how this diverse population of place cells is organized into a functional network or which functions are performed by each region.

Two other major classes of spatial cell have been found in the hippocampal formation: the head direction (HD) cell and the grid cell. The HD cell is sensitive to the orientation of the rat's head with respect to the environmental frame, irrespective of the animal's location in that environment. These cells have been found in several regions, most notably the anterior thalamus and dorsal presubiculum. Different cells have different preferred directional orientations. The animal's orientation is given partly by environmental cues and partly by interoceptive cues derived from vestibular and/or proprioceptive inputs. In addition to directly controlling behavior based on environmental directions, these cells may provide directional information to the place cells. The third major class of spatial cell, the grid cell, provides a metric for marking off distances in the environment. These cells have been found in layers 2/3 of the medial entorhinal cortex, which sends a major projection to the hippocampus proper, and in the lower layers, which receive inputs from the hippocampus. Each of these cells lays a grid-like pattern of firing on top of every environment the animal encounters. The orientation and spacing of the grid varies in a

systematic fashion from cell to cell and appears to depend on information generated by the animal's self motion.

Place cells have also been described in primates including humans, as have a variety of other spatial cells: HD cells and spatial view cells, which respond when the animal looks at a particular location.

Nonspatial behavioral correlates of hippocampal complex spike cells have also been reported in rodents and primates. Simple sensory stimuli, such as tones or somatosensory stimuli, appear to be relatively ineffective in the untrained animal, although there are several reports that pyramidal cells respond to these stimuli following classic conditioning or discrimination learning tasks. Furthermore, increased firing in complex-spike cells has been reported to correlate with different aspects of behavior in approach tasks, such as whether the animal is approaching an area containing cues to be recognized or discriminated or containing a reward. Some authors have argued that these findings support the idea that the hippocampus is involved in many types of relational processing in addition to those in the spatial domain. As we shall see, it is sometimes difficult to decide whether the firing of a hippocampal cell in a particular task is spatial or nonspatial. Whether these nonspatial correlates can eventually be explained within a spatial framework or alternatively, signal the need for an extension of the functions attributed to the hippocampus into nonspatial domains is discussed.

11.2 Hippocampal Electroencephalogram Can Be Classified into Distinct Patterns, with Each Providing Information About an Aspect of Hippocampal Function

If an electrode is placed in the hippocampus and electrical activity in the frequency range 1 to 200 Hz is recorded as the animal goes about its daily business, distinct patterns of electrical activity are seen that vary as a function of state of alertness, sensory stimulation, behavior, and anatomical location. These patterns of electrical activity are known collectively as the "electroencephalogram," or EEG. The EEG reflects the activity of large numbers of neurons and probably includes contributions from action potentials in disparate cell types, excitatory and inhibitory synaptic potentials, and dendritic and glial slow potentials. As such, it can provide a measure of information about the overall function of a brain region but not at the same level of precision as the activity of single units. It is probably most useful for signaling when large numbers of neurons are acting together synchronously. Because this is an important mode of operation of cortical areas such as the hippocampus, it follows that different EEG patterns can serve as a bridge between behavior on the one hand and single or multiple unit activity on the other. As we shall see in this chapter, there are several types of hippocampal EEG pattern, and each type provides information about a different aspect of hippocampal function, although none tells the whole story on its own. Theta and LIA have been studied most and so receive the most attention here.

11.2.1 Hippocampal EEG Can Be Classified into Four Types of Rhythmical and Two Types of Nonrhythmical Activity

In the hippocampus of the freely moving rat, six prominent EEG patterns have been identified: four rhythmical and two nonrhythmical. Rhythmical patterns (and their frequency ranges) include theta (6–12 Hz), beta (12–30 Hz), gamma (30–100 Hz), and ripple (100–200 Hz) waves. Nonrhythmical patterns include LIA and SIA. Figure 11–1 shows examples of each. Some patterns can co-occur (e.g., LIA with ripples, theta with gamma), whereas others appear to be mutually exclusive (e.g., theta, LIA, and SIA). The latter three waveforms appear to correspond to mutually exclusive states of hippocampal functioning.

Theta consists of rhythmical, often sinusoidal oscillations that vary in frequency from 6 to 12 Hz in the rat but can be as low as 4 Hz in the rabbit and cat (Fig. 11–1A, traces 1–4). The frequency power spectrum is narrow (Fig. 11–1B, walking), with a sharp peak around 7 to 10 Hz and often associated with higher harmonics (second peak around 16 Hz in Fig. 11–1B, walking). The LIA pattern looks much more random and is often characterized by sharp waves that resemble the spike and wave of epileptiform tissue (see Fig. 11–1A, traces 6, 7). The LIA power spectrum is flatter, with fewer peaks than are seen in theta and more power in the lower (1–5 Hz) frequencies (Figs. 11–1B, still and 11–2G). High-frequency 200-Hz ripples occur on the LIA sharp waves (Fig. 11–1C). SIA is a low-amplitude pattern that contains a broad spectrum of high frequencies and occurs only occasionally (Figs. 11–1A, 7, pencil tap and 11–2C). Beta waves occupy the frequency range 12 to 20 Hz (Fig. 11–1D) and gamma waves the frequency range 20 to 100 Hz (Fig. 11–1E). Either can occur alone or in combination with theta, LIA, or SIA.

11.2.2 Each EEG Pattern Has Distinct Behavioral Correlates

The simplest behavioral correlates of the various EEG patterns occur in the rat, and here we follow Vanderwolf's general description (Whishaw and Vanderwolf, 1973; Vanderwolf, 2001). It should be noted, however, that theta, in particular, has slightly different behavioral correlates in different species. In the awake rat, theta occurs primarily during movements that can loosely be described as "translational"—those that change the location of the animal's head with respect to the environment: walking, running, swimming, jumping, exploratory head movements, struggling (see examples in Fig. 11–1A, 1–4). Theta also occurs during REM sleep and occasionally during immobile attention or arousal. In the rabbit and guinea pig, this immobile attention-related theta

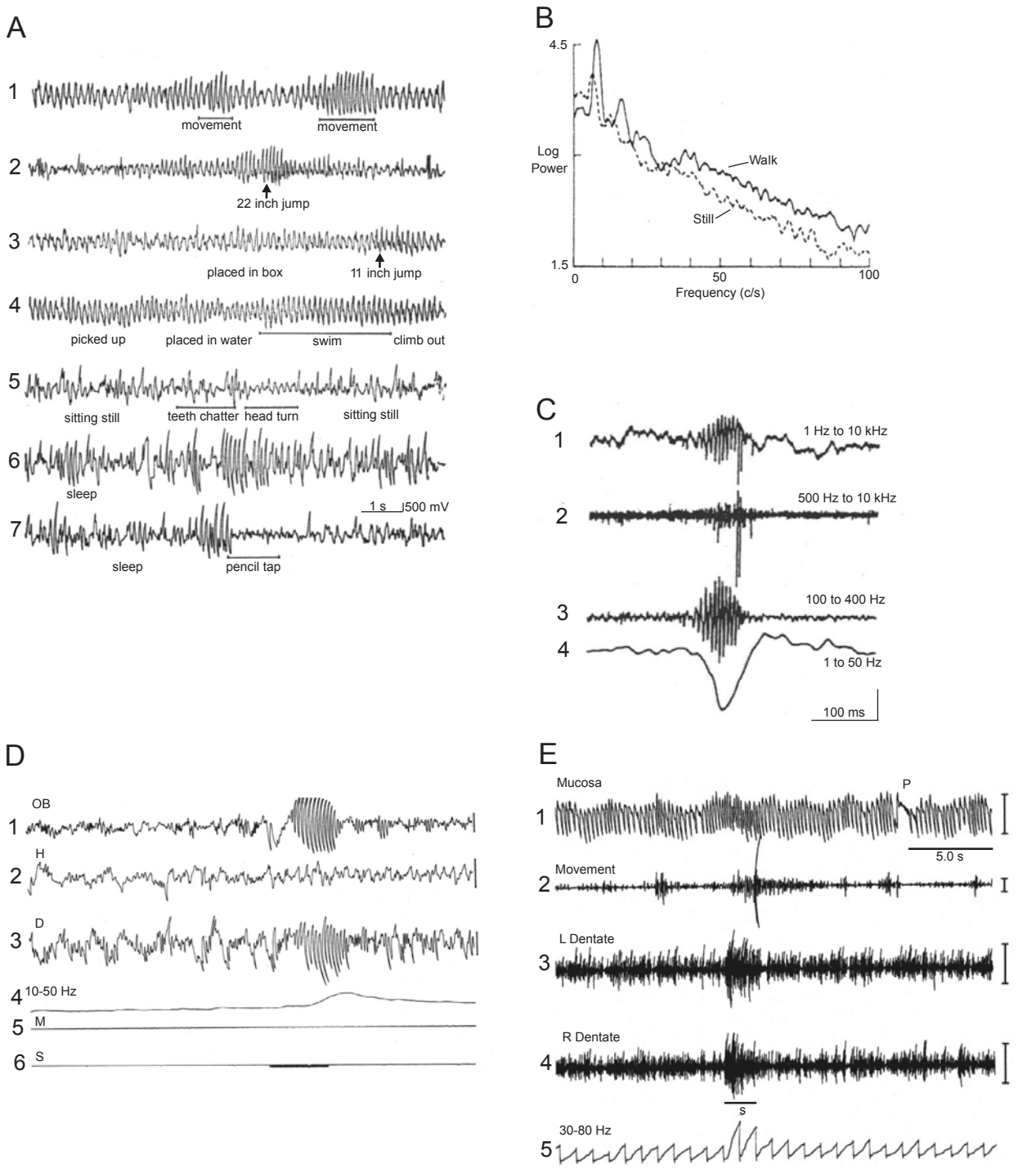


Figure 11–1. Hippocampal electroencephalography (EEG) patterns. *A*. Theta during rapid-eye-movement (REM) sleep (trace 1), jumping (2, 3), and swimming (4). Large irregular amplitude activity (LIA) during quiet sitting (5) and slow-wave sleep (6, 7). Note the large amplitude sharp waves especially prominent during slow-wave sleep. Small irregular amplitude activity (SIA) during brief arousal from slow-wave sleep after a pencil tap (7). (*Source*: Whishaw and Vanderwolf, 1973.) *B*. Frequency power spectrum during walking and standing still. Note the peaks around 8 and 16 Hz and the generally higher amplitude in the beta and gamma bands during walking. (*Source*: Leung, 1992.) *C*. LIA ripples and sharp waves in broad-band (trace 1) and filtered (2–4) recordings. Ripples (3) and sharp waves (4) are accompanied by bursts of action potentials (2) in hippocampal interneurons (small spikes) and principal cells (large spikes). (*Source*: Buzsaki et al., 1992.) *D*. Beta activity in the olfactory bulb (OB) and dentate gyrus (D) during sniffing toluene (thickening of s in trace 6). Note the absence of beta in the hippocampus (2, H) and the absence of gross movement (5, M). *E*. Gamma activity (3, 4) in the dentate during sniffing (s). Trace 5 shows the increase in breathing recorded during sniffing. (*Source*: Vanderwalf, 2001.)

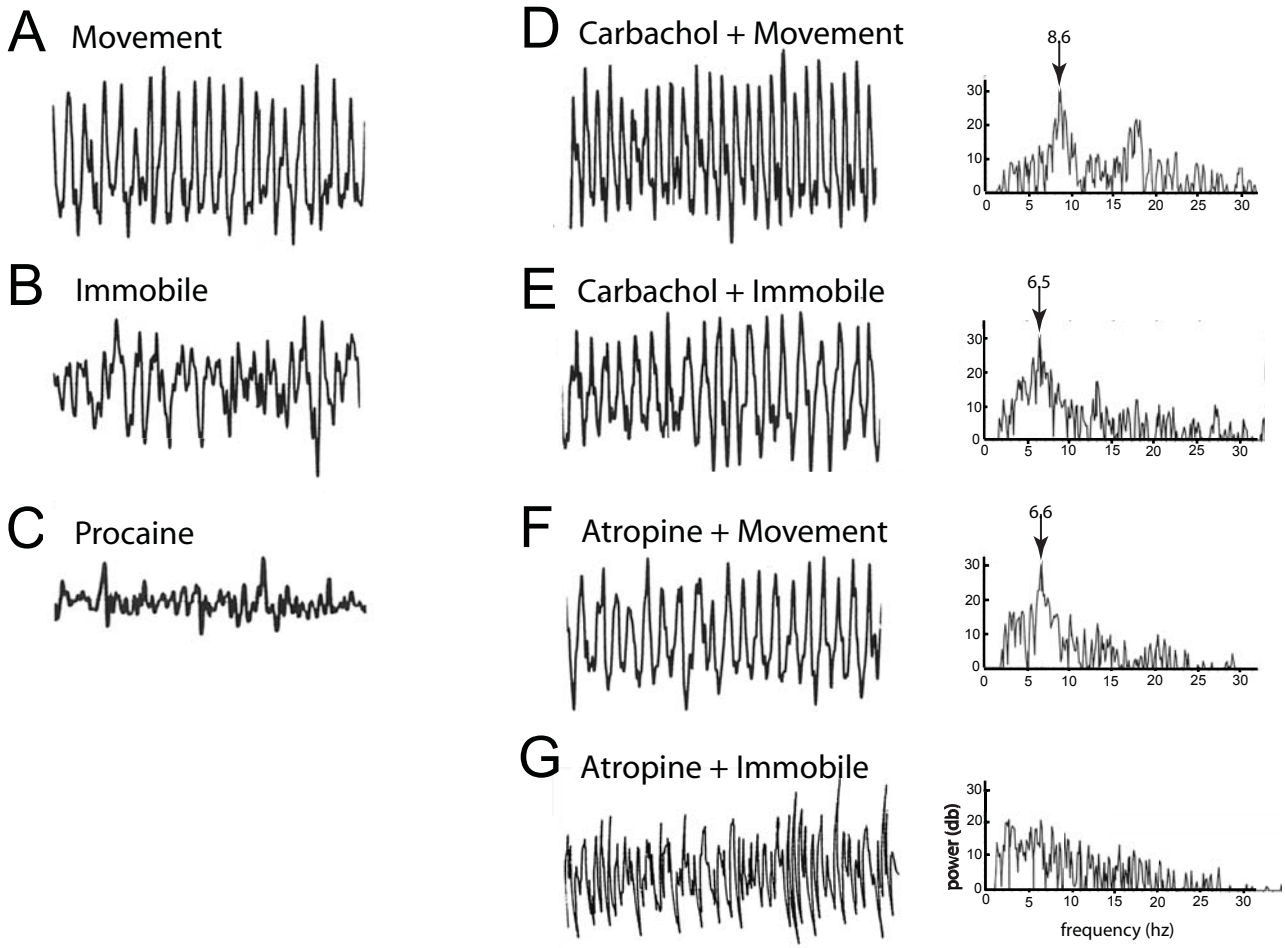


Figure 11–2. EEG patterns and frequency power spectra during movement and immobility in the rat. *A*. Theta during spontaneous movement. *B*. LIA during quiet immobility. *C*. All theta is abolished by a procaine injection into the medial septum. *D*.Theta during movement following intraseptal injection of the cholinomimetic carbachol. *E*. a-Theta during immobility following intraseptal injection of the cholinomimetic carbachol has a lower frequency than in *D*. *F*. t-Theta during movement is not blocked by an intraseptal injection of the anticholinergic atropine. *G*. LIA during immobility following intraseptal atropine. All EEG traces are 3 s long except *C*, which is 2 seconds. Arrows in *D*, *E*, and *F* indicate peak theta frequency in hertz. (*Source*: After Lawson and Bland, 1993, with permission.)

occurs more often. In the cat, it is related to active exploratory eye movements.

LIA occurs during behaviors that do not change the animal's location, such as sitting quietly, eating, drinking, grooming, and during slow wave sleep (SWS) (Fig. 11–1A, 5–7). SIA is seen infrequently: in the awake rat when ongoing movement is abruptly halted after a long train of theta, during sudden, motionless transitions from rest/sleep to alertness (Fig. 11–1A, 7, pencil tap), and during periods of SWS after REM episodes. Much less is known about the full range of behavioral correlates of beta and gamma, but they both have been shown to be associated with different types of olfactory input. Gamma occurs when the animal sniffs at a wide range of odors (Fig. 11–1E), whereas beta waves have been observed only during the sniffing of odors associated with predators (Fig. 11–1D).

11.3 Hippocampal Theta Activity

11.3.1 Hippocampal Theta Activity: Historical Overview

Theta activity and its behavioral correlates have been studied extensively ever since its discovery in the rabbit hippocampus by Jung and Kornmuller in 1938 (Jung and Kornmuller, 1938). The initial skepticism about the possibility that such regular large amplitude waves could be generated in the brain was overcome when Green and Arduini (1954) repeated the observations during the 1950s and showed that the theta pattern correlated inversely with neocortical desynchronization, suggesting that it represented the hippocampal arousal pattern. Later, attempts were made to correlate the theta rhy-

thm with aspects of learning: Adey et al. (1960) in the United States reported frequency shifts during simple discrimination learning, and Grastyan et al. (1959) in Hungary found high-frequency theta during orienting behavior early in auditory-reward conditioning but a desynchronized SIA pattern later, after the animal had learned to approach the reward. Studies by Gray (1971) in Britain suggested that particular frequencies of hippocampal theta activity (ca. 7.7 Hz) in the rat may also occur in association with reactions to nonreward.

These differences of opinion from different laboratories led to speculation that the behavioral correlate of theta varied from species to species and perhaps from task to task. Some measure of order was brought to the field by Vanderwolf's careful observations of the strictly behavioral correlates of hippocampal EEG patterns (Vanderwolf, 1969). He made the important point that changes of the kind seen by Adey and Grastyan that appeared to be correlated with different phases of learning were also correlated with specific changes in behavior at the same time. The changes in theta frequency seen by Adey, for example, tended to be correlated with changes in motor behavior during the course of learning. Vanderwolf argued that it was the strictly behavioral correlate of these EEG patterns that was primary. In various rodent species, he and his colleagues observed that theta activity was associated with what he termed "voluntary movements," whereas LIA occurred during stereotyped "fixed-action patterns." His subsequent observation that there were two types of theta, each with different behavioral correlates, clarified matters further (Kramis et al., 1975). One type is associated with arousal or attention, whether in association with movement or immobility, and the other with a class of movement alone. These two types are expressed to different degrees in different species and depend on different neuromodulatory inputs. The changes in hippocampal EEG during classic conditioning in the rabbit are examined in more detail in the section on nonspatial learning and memory (see Section 11.11).

11.3.2 Hippocampal Theta Activity Is Comprised of Two Components, a-Theta and t-Theta, Which Can Be Distinguished on the Basis of Behavioral Correlates and Pharmacology

In addition to differences in their behavioral correlates, the two components of theta recorded in freely moving animals also differ in their pharmacology. One is affected by drugs that act at cholinergic synapses, such as the antagonists atropine and scopolamine, the agonist carbachol, and the anticholinesterase, eserine. Vanderwolf and colleagues (Kramis et al., 1975) called this component atropine-sensitive theta, but we refer to it here by the more psychological name, arousal- or attentional-theta (*a-theta* for short). The second component of theta is correlated with translational movements and is unaffected by cholinergic drugs. There is some evidence that it is dependent on the transmitters serotonin and glutamate. It is called translation-movement theta (*t-theta* for short).

Theta is not uniformly distributed in the hippocampal formation but varies in both phase and amplitude in different parts. Whereas synchronous, large-amplitude theta waves are prominent in the dentate gyrus and CA1 areas of the hippocampus, most mapping studies report the absence of theta in area CA3. Despite this, CA3 cells can show good phase correlates to the EEG recorded elsewhere (e.g., in CA1 or the dentate gyrus). The implication is that the presence or absence of theta waves in the EEG is not a simple function of the underlying single-cell activity. The presence of theta must depend, at least in part, on other factors, such as the anatomical arrangement of the cells and the phase relations of their activity (see Buzsaki, 2002 for a recent review of the cellular basis of theta).

11.3.3 Both Types of Theta Activity Are Dependent on the Medial Septal/DBB but Only t-Theta Is Dependent on the Entorhinal Cortex

As discussed in Chapter 3, the major cholinergic input to the hippocampal formation arises from the medial septal nucleus and the nucleus of the diagonal band of Broca. The relative contributions of the medial septal nucleus and entorhinal cortex to the overall hippocampal theta pattern have been dissected using a combination of lesions and pharmacological manipulations (Bland and Oddie, 2001; Buzsaki, 2002). Lesions of the medial septal nucleus and associated diagonal band eliminate both types of theta activity. Injection of various drugs into the septum reveals differences in the pharmacological basis of a- and t-theta (Lawson and Bland, 1993). Inactivation by intraseptal injections of the local anesthetic procaine or the γ-aminobutyric acid (GABA)ergic drug muscimol eliminates all theta from the hippocampus (Fig. 11–2 C). Intraseptal injection of cholinergic antagonists (such as atropine) also block both thetas if the animal sits quietly (Fig. 11–2G) but leave movement-related t-theta intact (Fig. 11–2F). Conversely, injections of cholinergic agonists such as carbachol produce a state of continuous theta in the hippocampus regardless of whether the animal is moving (Fig. 11–2D) or sitting quietly (Fig. 11–2E). The frequency of the a-theta that occurs during immobility is about 2 Hz lower than when the animal is moving (compare power spectra in Fig. 11–2, D and E).

Lesions of the entorhinal cortex, in contrast, eliminate t-theta but leave a-theta intact (Kramis et al., 1975). Following such lesions, injections of atropine eliminate the remaining theta. Chronic injections of para-chlorophenylalanine (PCPA) or reserpine, both of which reduce the levels of serotonin in the brain, appear to eliminate t-theta. Because the *N*-methyl-D-aspartate (NMDA) receptor blocker ketamine also eliminates t-theta and results in a depth profile similar to urethane, it is likely that the glutamatergic afferents from the entorhinal cortex to the distal dendrites of CA1 and CA3 are responsible for this subcomponent of theta (Buzsaki, 2002).

The simplest explanation of these findings is that t-theta depends on fibers that pass through, or synapse in, the medial septum on their way to the entorhinal cortex with onward connection to the hippocampus. On the other hand, a-theta

requires the integrity of the direct cholinergic projection from the medial septal-diagonal band of Broca to the hippocampus perhaps through the activation of networks of inhibitory interneurons (see Chapter 8).

11.3.4 t-Theta Occurs During Movement Through Space

Following Vanderwolf's observational studies, the tight coupling between t-theta and certain types of movement was strengthened by the results of "theta-conditioning" experiments by Black (1975). The idea was to reward animals for producing short trains of theta activity under two training conditions: In one they were allowed to move, but in the other they were forced to hold still. Training to produce theta with frequencies greater than 7 Hz (t- theta) was successful only when movement was allowed. Thus, movement is necessary for t-theta, but what aspect of such movement is being signaled by theta activity?

Vanderwolf's original suggestion that theta was correlated with some aspect of voluntary behavior is not operational enough because it is not clear whether, in the case of animals, a movement can ever be said to be truly volitional. Considering the movements during which theta occurs most readily—walking, running, swimming, jumping—the likely common factor is translation through space. The fact that small head movements during exploratory sniffing are also accompanied by theta suggests that the crucial factor is the translation of the *head* through space or, more specifically, the generation of motor outputs that would normally result in translation of the head through space. Changes in the frequency of theta activity are correlated with either the animal's speed of movement through the environment (Rivas et al., 1996; Slawinska and Kasicki, 1998) or the rapidity with which a movement is initiated. The latter has been shown in experiments in which rats have been trained to jump up onto a ledge or to initiate running in a runway (Whishaw and Vanderwolf, 1973).

The behavioral correlate of theta amplitude is less clear. Although Vanderwolf and colleagues failed to find a positive correlation between amplitude and speed, Rivas et al. (1996) reported a positive correlation between both the frequency and the amplitude of theta and the speed of movement in the guinea pig when movements are initiated in simple runways. On the other hand, there is no correlation in jumping experiments between amplitude and speed of movement. It seems that there are many factors contributing to the amplitude of theta, such that a consistent correlate of amplitude is not always seen.

11.3.5 a-Theta Occurs During Arousal and/or Attention as well as Movement

a-Theta may correlate with psychological states such as arousal or attention. It rarely occurs in isolation in the rat but is much more common in rabbits, guinea pigs, and cats. In rats, it occurs naturally only when the animal freezes following a noxious stimulus, in response to an aversive conditioned stimulus, or when the animal is immobile but preparing to move (such as just before a jump). It also co-occurs with t-theta during movement. In rabbits and guinea pigs, it is readily produced in immobile animals by innocuous visual, auditory, or tactile stimuli. Repeated stimulation, however, leads to habituation of this response. Sainsbury and colleagues (1987a,b) have shown that the ability of a stimulus to elicit hippocampal a-theta is dependent on the preexisting level of arousal. A relatively neutral stimulus such as a tone, which ordinarily has little effect, readily elicits a-theta if the animal has previously been "sensitized" with an arousing stimulus such as the sound of an owl or the sight of a predator. One possibility is that a-theta represents a subthreshold activation of the motor system. Experiments in support of this idea have been carried out by Sinnamon and his colleagues (Sinnamon, 2000; Sinnamon et al., 2000). They recorded theta activity in urethane-anesthetized rats before, during, and after hind-limb stepping movements elicited by electrical stimulation of the hypothalamus or pharmacological block of the midbrain raphe nucleus. Both manipulations elicited low-frequency premovement (presumptive a- type) theta activity as well as the higher-frequency (presumptive t- type) theta, which accompanied the hind-limb stepping movements. It might be that a- theta reflects the activation of movement programs in the absence of the movement itself. Alternatively or in addition, it might reflect the organization of sensory inputs as reflected in the correlation of single-unit activity in different sensory nuclei with hippocampal theta (see Section 11.3.7).

11.3.6 Theta and Sleep

Theta occurs during the REM phase of sleep; LIA and SIA occur during slow-wave sleep; and SIA bursts frequently come at the termination of an REM episode. Pharmacological studies have shown that the theta recorded during the actual eye movements of the REM phase of sleep is unaffected by cholinergic drugs and therefore resembles t-theta, and that outside of these episodes is a-theta.

11.3.7 Theta Activity in Nonhippocampal Areas

In the rat, the theta system is centred on the hippocampal formation, taken here to include the septum, subicular area, and entorhinal cortex (Alonso and Garcia-Austt, 1987a,b; Brankack et al., 1993). However there are also reports of EEG and cellular activity phase-locked to theta in the cingulate cortex (Leung and Borst, 1987), prefrontal cortex (Hyman et al., 2005; Jones and Wilson, 2005; Siapas et al., 2005), perirhinal cortex (Muir and Bilkey, 1998), posterior hypothalamus including the mammillary bodies (Kirk and McNaughton, 1991; Bland et al., 1995; Slawinska and Kasicki, 1995; Kocsis and Vertes, 1997), brain stem reticular formation (Nunez et al., 1991), amygdala (Paré and Gaudreau, 1996; Seidenbecher et al., 2003), and superior (Natsume et al., 1999) and inferior (Pedemonte et al., 1996) colliculi. Some of these areas, such as the posterior hypothalamus and the brain stem reticular

formation, are involved in the circuitry that generates the hippocampal theta rhythm and might be expected to show activity synchronized with theta, whereas others are part of the sensory systems (the colliculi) or the limbic system (amygdala and cingulate cortex). These latter correlations must represent a fairly widespread function for theta, such as the synchronization or binding together of neurons in many sensory, motor, and emotional/motivational centers as well as those involved in spatial perception and memory.

11.3.8 Does the Hippocampal EEG in Monkeys and Humans Have a Theta Mode?

Although theta patterns are readily observed in cats, dogs, and rodents, it has been difficult to establish whether a clear rhythmic theta pattern can been recorded from either monkey or human hippocampus. There have been hints over the years that it might exist. For example, Stewart and Fox (1991) reported a theta-like pattern (7–9 Hz) in the hippocampal EEG of urethane-anesthetized monkeys. In an earlier study, Watanabe and Niki (1985) reported the existence of the rhythmical theta-like firing patterns in monkey hippocampal cells. Similarly, rare experiments using depth electrodes in the human hippocampus have observed activity at theta frequencies, although their behavioral correlates were not clear (Halgren et al., 1978; Arnolds et al., 1980). This paucity of data has led some authors to suggest that theta may not exist in monkeys and primates or may not have the same behavioral correlates as in other mammals. Some reasons for the failure to record prominent theta patterns in the primate EEG are examined in the next section.

First, the existence of an oscillatory theta pattern in the EEG depends not only on the rhythmical firing of cells but also on the correct cytoarchitectonic orientation of pyramidal cells to create the appropriate electrical dipole. As was seen in the section on theta activity in field CA3, cells can burst with a theta pattern in the absence of pronounced theta waves in the EEG. Different neuroarchitecture could account for a theta system in primates in the absence of rodent-like theta patterns in the gross EEG.

A second problem is that most monkey and human recording is done while the subject is immobile, a condition that is not conducive to recording t-theta. Thirdly, most recordings in humans have been from the scalp, and it is possible that the skull and scalp are acting as filters, effectively screening out the theta patterns. Some evidence to support the last two possibilities comes from recent findings (Kahana et al., 1999) that theta patterns could be recorded from electrodes placed on the surface of the human neocortex while subjects navigated through a virtual reality maze. Theta activity was recorded from several cortical regions, but temporal lobe theta showed the best correlation with maze difficulty. More theta activity was seen during traverses through more difficult 12-choice mazes than through simpler 6-choice mazes. The same group has used depth as well as subdural electrodes in humans performing a virtual taxi driver task (Caplan et al., 2003) to show that theta oscillations in humans are found during virtual movement, exploratory search, and goal-seeking. One difference from the rat is that human theta bursts tend to be of shorter duration. These kinds of studies confirm the suspicion that the difficulty recording primate theta has more to do with inappropriate behavioral paradigms and recording techniques than with the absence of a theta system per se.

There has also been recent interest in the related field of frequency analysis of EEGs recorded from scalp electrodes. For example, increases in the power present in the EEG at theta frequencies have been shown to be related to the successful encoding of new information (for a review see Klimesch, 1999). However, these studies typically do not demonstrate the peak in the power spectrum at theta frequencies or the long continuous records of trains of theta activity shown by Kahana and colleagues in their virtual reality study. Localizing the source of theta in scalp-recorded EEGs is even more problematical than with subdural electrodes; one experiment where it was attempted implicated the anterior cingulate rather than the hippocampus (in a task showing increased theta with increased working memory load) (Gevins et al., 1997). Spectral peaks at theta frequencies have been found in experiments using magnetoencephalography and have been interpreted as consistent with a generator near the hippocampus (Tesche and Karhu, 2000), although this technique also suffers from problems of accurate source localization. Nevertheless, these findings, and particularly the subdural recordings of Kahana et al., clearly show that theta activity exists in the human brain and tempt one to speculate that it might be related to the hippocampal system. There is a more extensive discussion of recording of the EEG and evoked potentials from the human brain in Chapter 12.

11.3.9 Functions of Theta

Work on the rat hippocampus suggests three possible functions for theta. First, it acts as a global synchronizing mechanism, essentially locking the entire hippocampal formation into one global processing mode and organizing the activity in each hippocampal region with respect to the others. Simultaneous recordings of the EEG in different hippocampal locations have shown that theta activity at comparable locations (e.g., in the CA1 pyramidal layer) is in synchrony and coherent across large areas of the hippocampal formation (Mitchell and Ranck, 1980; Fox et al., 1986; Bullock et al., 1990). This means that if two cells have firing patterns that are systematically related to the local theta cycle, they have systematic temporal relations to each other, even if they are located far apart in the hippocampus. Although the theta rhythm is centered on the hippocampal formation, sensory and motivational areas are also brought under its sway. We begin to see here evidence for a widespread system of oscillations that organizes the activity of many disparate brain areas.

A second function of the theta oscillations is to provide a periodic clocking system for the timing of hippocampal spikes. As set out in greater detail in Section 11.7.9, the phase

relation of each pyramidal cell measured against the concurrent theta activity is not constant but can vary from one cycle to the next (O'Keefe and Recce, 1993; Skaggs et al., 1996). As a rat runs through the firing field of a spatially coded pyramidal cell (the place field), the cell fires bursts of spikes at an interburst frequency slightly higher than that of the concomitant EEG theta. This leads to a precession of the phase of firing to earlier points on each successive cycle. Over the course of the five to seven theta cycles that comprise the typical place field, the phase of the EEG at which the cell fires may precess through a full 360°, although smaller amounts of precession are also seen. Furthermore, the phase of firing is highly correlated with the animal's location within the place field (more so than with the duration spent in the field). Thus, temporal variation in spike firing conveys information about the animal's spatial location. An analysis of this phenomenon (Jensen and Lisman, 2000) shows that the temporal information provided by the phase precession can improve localization of the animal's position by more than 40% compared to that obtained by the use of firing rates alone.

A third function for theta is to provide temporal control over long-term potentiation (LTP) induction and, by inference, the storage and retrieval of information from the hippocampus. As noted in Chapter 10, theta-burst electrical stimulation of hippocampal afferents is an effective way to induce LTP. Furthermore, there is some evidence that volleys arriving at different phases of the ongoing theta are differentially effective (Pavlides et al., 1988; Huerta and Lisman, 1995; Holscher et al., 1997; Hyman et al., 2003). Inputs arriving at the positive phase of CA1 theta result in synaptic potentiation, whereas those arriving at the negative phase yield depotentiation or depression. On the basis of this and other evidence, Hasselmo (2005) proposed that the various phases of theta oscillation represent different modes of operation. Specifically, the peak of the CA1 theta is the period during which encoding of new information entering the hippocampus from the entorhinal cortex takes place, and the trough is the period during which retrieval of information from the hippocampus to the entorhinal cortex occurs.

11.4 Non-theta EEG Patterns in the Hippocampal EEG: LIA, SIA, Ripples, Beta, and Gamma

11.4.1 Sharp Waves, Ripples, and Single Units During Large Irregular Activity

During LIA, large sharp waves occur in the hippocampal EEG (Fig. 11–1A, traces 5–7 and Fig.11–1C, trace 4). In CA1, the sharp waves occur most frequently during slow wave sleep and quiet sitting, less frequently during eating and drinking, and least frequently during grooming. They appear to occur during periods of low arousal and are often, but not always, inhibited by arousing stimuli. They may represent a resting state of the hippocampus as a whole or the absence of some aspect of hippocampal function such as the theta state; functionally, it has been suggested that they represent a neural correlate of memory consolidation. Each sharp wave lasts 50 to 100 ms and has a maximum amplitude in the stratum radiatum that can be as large as 1 mV or more. Their resemblance to the interictal spike and wave complex of epileptogenic cortex may give some clues to the peculiar susceptibility of the hippocampus to seizure activity (Bragin, 1999; Draguhn et al., 2000; Buzaki and Draguhn, 2004). They occur more or less synchronously over large areas of the CA1 field of the dorsal hippocampus: Recordings at different points along the septotemporal axis of the hippocampus have shown that they are in phase over the entire extent (Buzsaki et al., 1992; Chrobak and Buzsaki, 1996). They reverse polarity in the pyramidal cell layer and reach their maximum amplitude several hundred microns into the stratum radiatum (O'Keefe and Nadel, 1978, pp. 150–153). Buzsaki and colleagues have suggested that sharp waves originate in the CA3 field and that the sharp waves recorded in CA1 are the summated extracellular excitatory postsynaptic potentials (EPSPs) of the Schaffer collaterals that result from synchronous firing of the CA3 pyramidal cells (Csicsvari et al., 2000). Direct stimulation of these fibres results in evoked potentials with similar shape and depth profiles.

Around the time of the negative peak of the sharp wave, there is a high-frequency oscillation of between 120 and 200 Hz whose peak amplitude occurs in the CA1 pyramidal cell layer (O'Keefe and Nadel, 1978, pp. 150–153; Buzsaki et al., 1992) (Fig. 11–1C). During these "ripples" there are synchronous bursts in almost all theta interneurons and in about 1 in 10 of the complex-spike pyramidal cells. Intracellular recordings from the soma of pyramidal cells during ripples reveals intracellular oscillations that mirror the extracellular pattern. Hyperpolarization results in a reduction of ripple amplitude at −70 mV, with a reversal at more negative potentials. This sequence of events suggests that the sharp wave itself reflects the synchronous barrage of afferent activity from CA3 cells onto the apical dendrites of CA1 cells. The rapid activation of inhibitory interneurons causes synchronized hyperpolarizing inhibitory postsynaptic potentials (IPSPs) in the somata of pyramidal cells.

Are sharp waves and ripples confined to the hippocampus proper, or do they spread to other structures? Recordings in the subiculum and the deep layers of the entorhinal cortex show that sharp waves also occur in these structures at about the same time as those in hippocampus. The sharp wave in layers V and VI of the entorhinal cortex, which receive inputs from the hippocampus, followed those in the hippocampus by 5 to 30 ms (Chrobak and Buzsaki, 1996). In contrast, the presence of hippocampal sharp waves is not reflected in the activity of the upper layers (II and III) of the entorhinal cortex, which project to the dentate gyrus, hippocampus, and subiculum. Recordings from the dentate gyrus show that the granule cells are also influenced by the sharp-wave activity of CA3. The anatomical basis for this retrograde effect is not entirely clear.

There are projections from CA3 into the polymorph layer, and these fibers may be ending on mossy cells, which in turn project to the dentate granule cells. In the ventral tip of the hippocampus, there appear to be some CA3 pyramidal cells that project directly into the molecular layer of the dentate gyrus.

11.4.2 Dentate EEG Spikes During LIA

Sharp-wave activity during LIA also occurs in the granule cell layers of the dentate gyrus. It is also associated with a high-frequency ripple, although the frequency is not as high as that of the CA1 ripple. Most granule cells do not fire during dentate sharp waves, but intracellular recordings have shown that they are nevertheless depolarized at this time. Surprisingly, the overall effect of dentate spikes on CA3 cells is inhibitory. This presumably reflects the heavy innervation of interneurons by the mossy fibers (Acsady et al., 1998) (see Chapter 5, Section 5.7).

11.4.3 Pharmacology of LIA

Little is known about the pharmacology of LIA, the sharp waves, or the ripples. Ripples are eliminated under halothane anesthesia, and their frequency is reduced under urethane and ketamine to around 100 Hz (Ylinen et al., 1995). In the mouse, sharp waves and ripples can be elicited by application of KCl to the dendrites of pyramidal cells following pharmacological block of $GABA_A$ receptors, making it unlikely that they are due to activity in networks of the inhibitory interneurons (Nimmrich et al., 2005). Synchronization between ripples appears to depend on gap junctions. Consistent with the idea that the LIA state is a passive absence of theta, procaine or muscimol suppression of the medial septum, which inhibits theta activity, has only a small effect on the power of hippocampal LIA (Bland et al., 1996). Recordings of medial septal and diagonal band cells during LIA show that the firing rates of most of these cells are reduced relative to theta, strengthening this suggestion. On the other hand, cholinergic activation of the septum completely suppresses hippocampal LIA, replacing it with low-frequency theta even in the immobile animal (Fig. 11–2E). Theta appears to be the active state driven from the medial septum, and LIA is the passive state that occurs in its absence.

11.4.4 Behavioral Correlates and Functions of LIA

In their discussion of hippocampal sharp waves and ripples during LIA, O'Keefe and Nadel (1978, pp. 150–153) suggested that one way to think about this EEG state was as an absence of the theta state—it is the hippocampus in a non-theta idling mode. This suggestion was based partly on the observation that there was always a period of at least a few seconds between the onset of an LIA-associated pattern of behavior (such as immobility) and the onset of the sharp wave and ripples. They also argued that the nearly synchronous bursts in a sizable percentage of the pyramidal cells, when compared with their highly differentiated patterns of activity during the theta state as the animal moved around an environment, would be unlikely to convey much information. Perhaps most tellingly, it was found that lesions of the fornix decreased neither the frequency nor the amplitude of ripples and sharp waves; if anything, they increased them—again suggesting release of the hippocampus from an activated theta state. In this view, the LIA state is the passive activity of a system with extensive positive and negative feedback loops and other oscillatory mechanisms.

An alternative hypothesis is that LIA is an active, rather than an idling, state of the hippocampus whose function is to strengthen synaptic modifications that have occurred during the immediately prior periods (Buzsaki, 1989). Pointing to the similarity between the synchronous volleys of afferent activity impinging on the dendrites of CA1 dendrites during LIA and the type of tetanic stimulation known to cause LTP, Buzsaki suggested that synaptic potentiation occurs naturally during LIA. He went on to propose that this potentiation acts as a boost to synapses that had been only weakly modified during the previous theta behaviors and perhaps plays a role in a memory consolidation process. Evidence in support of this idea comes from experiments by Skaggs and McNaughton (1996). They looked at pairs of CA1 pyramidal cells with overlapping place fields in freely moving rats that were running around a small triangular runway. When identified cells were recorded before and after the animal had run around for extended periods, they observed during LIA an increase in the cross-correlation between cells that had been simultaneously active during the previous period. That is, cells with firing fields that were close together in the environment were more likely to fire close together in time during an ensuing period of slow-wave sleep than cells with more distant fields. The small number of collateral fibers between CA1 pyramidal cells suggests that this effect might be due to an increase in the efficacy of the common input from CA3 or the entorhinal cortex onto these cells, rather than to the direct connections between them. In the consolidation view of LIA, the uncoupling of the hippocampus from the septum during LIA is merely a necessary condition for hippocampal consolidation to occur.

A related idea is that LIA is a period involving transfer of information from hippocampus to neocortex. Support for this view comes from experiments (Siapas and Wilson, 1998) that showed a correlation between hippocampal sharp waves and neocortical spindle waves during slow-wave sleep. The hypothesis that information might be transferred from the hippocampus to the neocortex as a result of LIA-associated sharp waves is consonant with evidence from behavioral experiments addressing the question of long-term storage of memory "traces" in or outside of the hippocampus. Chapter 12 presents evidence that lesions to the hippocampus in animals and humans can sometimes cause temporally graded amnesia. One interpretation of such a gradient is that memory traces are stored only in the hippocampus for a short period before being sent to the neocortex for permanent stor-

age (see Chapter 13, Section 13.3 for a more extensive discussion of consolidation). After this period, damage to the hippocampus would no longer result in memory loss. Although the sharp waves may be part of such a mechanism, there is some evidence against this general idea. For example, Leonard and colleagues (1987) have shown that LTP cannot be induced in the hippocampus during slow-wave sleep. If this finding can be generalized to other parts of the brain, it would greatly reduce the attractiveness of the hypothesis that sharp waves could serve as a basis for consolidation because no new LTP-based learning could take place. There is clearly much more to understand about ripple/sharp-wave states. A possible role in memory formation may not be restricted within the confines of the currently dominant theory of intrahippocampal consolidation or hippocampo-neocortical trace transfer during sleep. For example, ripple/sharp-wave events may have a purely intrahippocampal *housekeeping* function. To take just one possibility, synaptic renormalization or overall gain control processes might occur during LIA.

11.4.5 Small Irregular Activity

Small irregular activity (SIA) is characterized by low-amplitude irregular activity in the hippocampus and desynchronization in the neocortical EEG. In 1967, Pickenhain and Klingberg reported low-amplitude irregular activity in the hippocampus of rats during transitions to alertness where no orienting movements were made, such as when a click awakened them from sleep. Vanderwolf and Whishaw (Whishaw and Vanderwolf, 1971) noted a similar pattern during transitions to alertness but added the observation that SIA, as they called it, occurred when rats abruptly halt voluntary movement.

Jarosiewicz and colleagues (2002) have extended the characterization of SIA to include periods during sleep. Sleep SIA bursts occur repeatedly during all periods of slow-wave sleep and after nearly every REM episode. Each burst typically lasts a few seconds, with a range from 200 ms to many seconds. A brief tone presented in sleep routinely elicited an increase in electromyographic (EMG) and neocortical arousal accompanied by hippocampal SIA, suggesting that it is a state intermediary between LIA and theta (Jarosiewicz and Skaggs, 2004b). Sleep SIA is characterized by the cessation of firing in most pyramidal cells. The 3% to 5% that continue to fire do so actively and repeatedly over successive bursts. These place cells are probably continuing to represent the location where the rat fell asleep because rotating the platform and the sleeping rat away from a given cell's place field location relative to the testing laboratory did not have an effect on SIA firing (Jarosiewicz and Skaggs, 2004a).

11.4.6 Beta/Gamma Activity in the Hippocampus

In addition to the low-frequency EEG activity seen during theta and LIA, and the higher frequency ripple activity characteristic of sharp waves and dentate spikes, intermediate frequency 10- to 100-Hz waves have also been described. This band is further divided into beta (10–20 Hz) (Leung, 1992) (Fig. 11–1D) and gamma (20–100 Hz) (Fig. 11–1E) activity. Gamma waves were first described in the cat amygdala by Lesse in 1955 and have since been reported in widespread brain regions of animals and humans (Singer and Gray, 1995). It has been suggested that gamma synchrony between various regions of the neocortex binds together the simple elements of a complex representation. In the hippocampal formation, they occur most clearly in the entorhinal cortex and dentate but have also been reported in the CA fields (Csicsvari et al., 2003). They may be related to 40-Hz oscillations that have been reported in the olfactory (Freeman, 1975) and visual (Singer and Gray, 1995) systems.

Gamma activity is slightly depressed in the rat by both septal lesions and cholinergic antagonists (Leung, 1985). In rabbits, drugs that stimulate a-theta during immobility (e.g., physostigmine) increase the amount of this intermediate frequency. However, this increase does not seem to occur in immobile rats. Seizures cause a dramatic increase in the amount of beta/gamma activity, an effect blocked by cholinergic antagonists and unaffected by the animal's ongoing behavior (Leung, 1992). The extent to which this beta/gamma activity is a reflection of the underlying behavior of neural elements (principal cells or interneurons) is unclear, although it may be a correlate of the activity of hilar theta cells.

11.4.7 Olfactory Stimulation Can Elicit Hippocampal Gamma and Beta Waves

In the rat hippocampal formation, both beta and gamma waves occur preferentially during olfaction. The dentate gamma waves appear to occur during the sniffing of odors in general but do not occur during odorless sniffing or other sensory stimulation (Vanderwolf, 2001) (Fig. 11–1E). The behavioral correlates of the CA1/CA3 gamma have not been established. In general, gamma and theta occur independently, but under some (undefined) circumstances they become synchronized, with the gamma occurring preferentially at the positive peak of the dentate theta waves. The dentate, but not the CA1, gamma is dependent on the perforant path input from the entorhinal cortex, as lesions of the entorhinal cortex abolish the dentate gyrus gamma but enhance the CA1/CA3 gamma (Bragin et al., 1995). Dentate gamma waves may be part of the mechanism for synchronizing the olfactory inputs arriving via the entorhinal cortex with the hippocampal theta. Beta waves have a more restricted olfactory correlate than gamma waves. They occur in the dentate gyrus in response to olfactory inputs that signal, or mimic those that signal, the presence of predators (Fig. 11–1D) (Vanderwolf, 2001): compounds found in the anal scent gland secretions of weasels and foxes, most organic solvents including toluene and xylene, and phytochemicals derived from plants such as eucalyptol and salicylaldehyde. In general, these odors also elicit a fear response and behavioral avoidance. Other strong smells, such as ammonia, cadaverine, or

putrescine, which are either approached or not avoided, do not elicit dentate beta waves. Vanderwolf has argued that these olfactory correlates of gamma and beta waves in the hippocampus suggest a primary olfactory function for this structure, but it is more likely that, like the theta waves, they represent one aspect of a more complex overall function, such as cognitive mapping or associative memory formation.

11.5 Single-cell Recording in the Hippocampal Formation Reveals Two Major Classes of Units: Principal Cells and Theta Cells

Although EEG recordings provide some information about the circumstances under which large numbers of neurons in a brain region become synchronously active, it is generally accepted that a complete understanding of function can be gained only by looking at the behavioral correlates of single units. One reason for this is that although neighboring neurons often share common functional properties they may not always respond to the same specific stimulus or behavior. As we shall see, this is particularly true of the hippocampus, where neighboring pyramidal cells share the property of representing places in an environment. However, because different cells become active in different parts of an environment, this property is not revealed in the hippocampal EEG.

The recording of individual neuronal responses in the hippocampus of the awake freely moving rat began during the early 1970s with the work of Ranck (1973) and O'Keefe (O'Keefe and Dostrovsky, 1971). They both encouraged their animals to move around the environment, engaging in everyday tasks such as eating, drinking, sleeping, and searching for food and water. This emphasis on naturalistic behavioral correlates led to several important discoveries. The first was that they noticed that there were two major classes of cells that could be distinguished by differences in their anatomical and physiological properties (e.g., firing rates, action potential width, and relative locations in the hippocampus). Ranck termed these two classes complex-spike and theta cells, and these terms are still in general usage. We describe their properties in a subsequent section. Perhaps more importantly, they discovered that the firing patterns of the two cell types had repeatable behavioral correlates. Ranck had trained his animals to approach one location to obtain food and another to get water, and emphasized the relation of the complex-spike cell firing pattern to the behavioral approach to reward. O'Keefe was more impressed by the spatial correlate and named the cells *place* cells. It is now widely accepted that the location of the animal in a familiar environment is the major determinant of when such cells fire.

The second class of neurons, the *theta* cells, has less specific behavioral correlates. As the name implies, their behavioral correlates are closely related to those of the gross EEG waves and in particular theta. They tend to change rate during hippocampal EEG theta, and many display strong phase locking to the individual theta waves.

Extracellular recordings in the freely moving rat enable complex-spike and theta cells to be distinguished on the basis of differences in their wave shapes, firing rates, and other properties (Fig. 11–3). Complex-spike place cells have a much broader action potential than theta cells (Fig. 11–3B–D), often display a complex-spike burst pattern in which the later spikes in a burst are smaller in amplitude and of longer duration than the first (Fig. 11–3A), and have a lower spontaneous

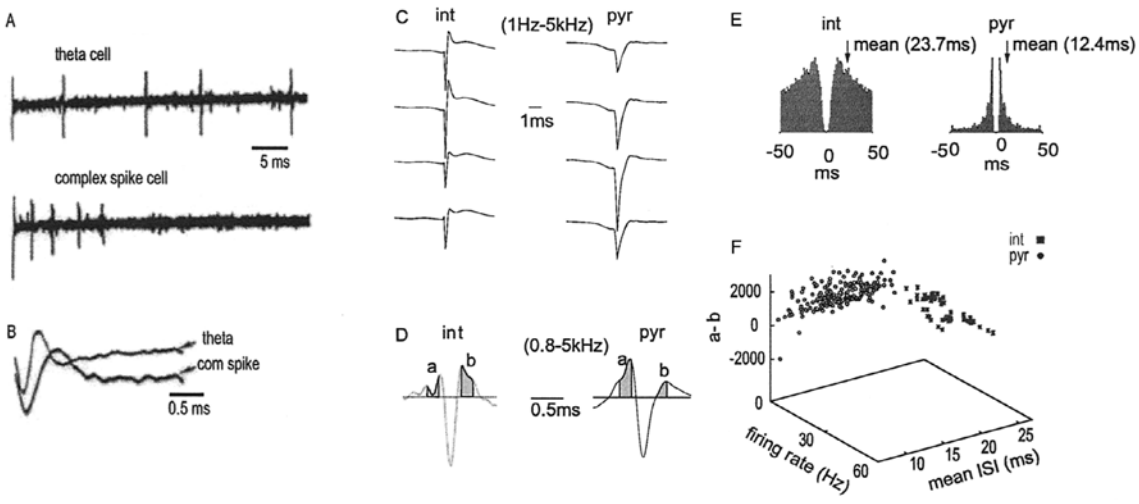


Figure 11–3. Complex-spike cells and theta cells have different physiological properties. *A*. Theta cells have a steady firing rate and constant size amplitude spikes, whereas C-S cells sometimes emit a complex-spike burst in which the later action potentials in the burst are lower in amplitude and broader. *B–D*. Action potentials of C-S cells (pyr) are broader and have a larger initial hump than those of theta cells (int). *E*. C-S cells have a narrower range of interspike intervals (ISI) *F*. Three-dimensional plot of firing rate against mean ISI and spike asymmetry (a-b in *D*) separates the overall population into two clusters. (*Source*: *A*,*B*. After Christian and Deadwyler, 1986; *C–F*. After Csicsvari et al., 1998 with permission.)

background firing rate (generally about 1 Hz) (Fig. 11–3F). In contrast, theta cells have a much higher firing rate (10–100 Hz) (Fig. 11–3F) with all action potentials being of the same amplitude (Fig. 11–3A) and of shorter duration (Fig. 11–3B-D). An important caveat is that in the rabbit this separation of spikes into two nonoverlapping classes is less clear as there appears to be a large subclass of complex-spike cells with spontaneous firing rates as high as 6 Hz.

It is highly likely that in the rat the complex spike cells are pyramidal cells and the theta cells are one or more types of interneuron. Intracellular staining of neurons that display complex spikes in brain slices reveals they have the morphology of pyramidal cells, whereas those without complex spikes are interneurons. Sometimes it is possible to activate complex spike cells antidromically from electrodes placed in hippocampal outflow pathways, but the theta cells can only be driven orthodromically (Berger and Thompson, 1978; Fox and Ranck, 1981; Christian and Deadwyler, 1986). Another strong piece of evidence in support of the idea that complex-spike cells are pyramidal cells and theta cells are interneurons comes from the temporal relation between their firing patterns. Most pyramidal cells innervate neighboring interneurons via an axon collateral, which should give rise to an increased probability of firing in the theta cell shortly after an action potential in the pyramidal cell. Just such a relation has been reported. Some theta cells tend to fire a few milliseconds after a complex-spike cell recorded on the same tetrode (see Box 11–1), and this is reflected in a short latency cross-correlation between their spike trains (Csicsvari et al., 1998) (Fig. 11–4B-D and Box 11–2).

The same generalizations can be made for rabbits. However, there appears to be an additional group of intermediate cells that exhibit complex spikes and that can be antidromically activated by stimulation of projection pathways; but they have a resting firing rate that is intermediate between the theta and complex-spike cell firing rates shown in rats (Berger et al., 1983).

11.5.1 Distinctive Spatial Cells—Complex-spike Place Cells, Head-direction Cells, and Grid Cells—Are Found in Various Regions of the Hippocampal Formation

Discovery of the place cells led to the development of the *cognitive map theory* of hippocampal function by O'Keefe and Nadel (1978), which has guided much of the subsequent research and theorizing on hippocampal function (see Chapter 13, Section 13.4). Equally important for our understanding of the spatial functions of the hippocampal formation was the discovery of two other classes of spatial cell: In

Box 11–1
Microelectrode Recording Technique

Microelectrodes placed in the extracellular space in the vicinity of a neuron detect the current flow associated with action potentials. Experience has shown that relatively large electrodes with flat tips are preferable for recording in chronic animals because they do not puncture the cells and therefore do less damage during small movements of the electrode relative to the brain. One problem with the use of single electrodes in a structure such as the hippocampus is that it is difficult to isolate single units on the basis of action potential amplitude and shape. This is because of the close packing of the identically sized and shaped cells. Action potentials from all cells on a sphere with the electrode at the center are identical. There is a danger that all such spikes are considered to have come from one neuron. Template-matching algorithms, which are so useful when different cell types are in close proximity, offer no way out of this ambiguity and also have difficulty coping with the fact that a single pyramidal cell sometimes fires simple spikes and sometimes complex spike bursts in which the later action potentials in the burst have reduced amplitude and broader waveforms than the initial spike (Fig. 11–3A). One solution, introduced by McNaughton et al. (1983b), is to use multiple electrodes whose tips are close enough to sense the action potentials from a group of neurons but, being spaced a short distance apart, cannot both be at the center of a notional sphere. Each electrode tip is a slightly different distance from a given cell and, consequently, records its action potential with a slightly different amplitude and shape. These sometimes subtle differences can be used to distinguish a multiunit recording from several electrodes into spikes emanating from different cells. The principle is analogous to a "stereophonic" recording in which two or more microphones are used to capture the sound of an orchestra; hence, the earliest electrodes of this type used two wires and were called "stereotrodes." In general, $n + 1$ electrodes are necessary to identify uniquely the action potential from a neuron in n-space. In the hippocampus, "triotrodes" with three tips oriented in the plane of the quasi-two-dimensional pyramidal cell layer would probably suffice; but in practice, "tetrodes" are commonly used to ensure adequate isolation (O'Keefe and Recce, 1993; Wilson and McNaughton, 1993). Figure 11–4A shows the profile of action potentials of complex-spike and theta cells on the four electrodes of a tetrode.

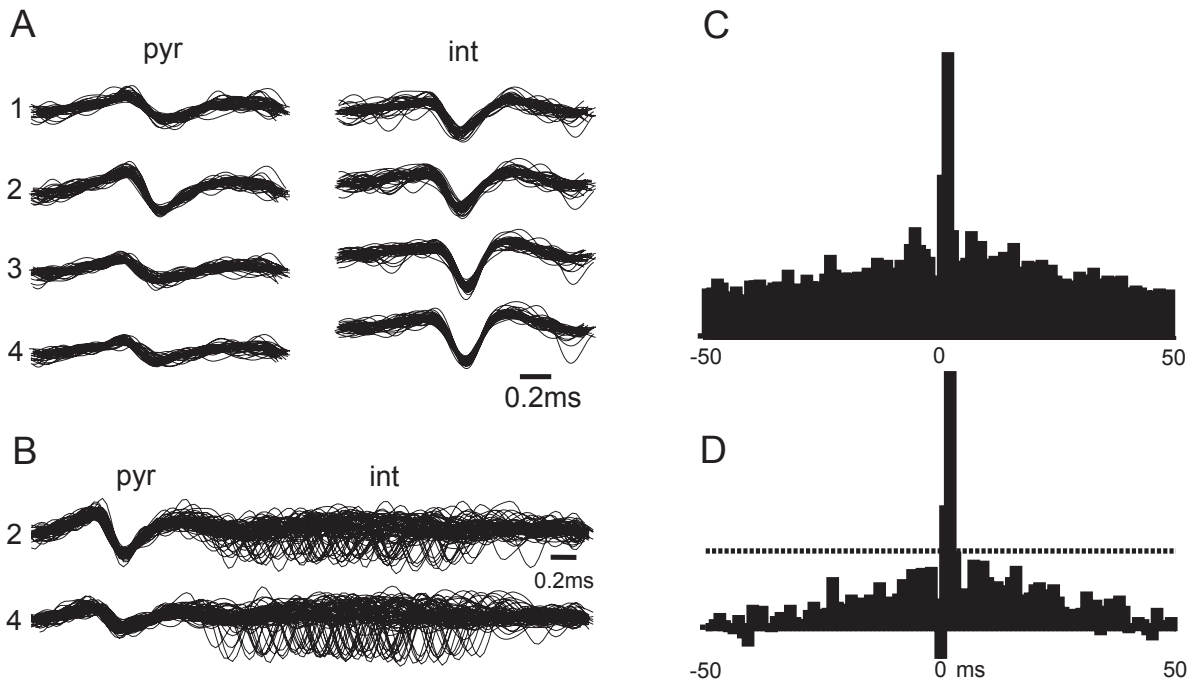


Figure 11–4. Hippocampal interneurons sometimes fire a few milliseconds after neighboring pyramidal cells. *A*. Waveforms of a pyramidal (pyr) and an interneuron (int) recorded on the same tetrode (traces 1–4). *B*. Multiple sweeps triggered on the pyramidal cell show that the interneuron often fired at a short but variable latency shortly after, suggesting a monosynaptic coupling between the two. *C*. Cross-correlogram between the firing trains of the two cells in *B* shows the interneuron fires at a peak latency of 2 ms following the spike in the pyramidal cell. *D*. Controlling for the repetitive rhythmical pattern of firing within each of the spike trains does not eliminate the short-term causal relation between the two. Horizontal line in *D* indicates a significance level above which the correlation is highly significant. (*Source*: After Csicsvari et al., 1998, with permission.)

Box 11–2
Auto-correlation and Cross-correlation Functions

Correlation techniques are used to investigate the temporal relations of spike occurrences to themselves (auto-correlation) (Fig. 11–3 E), to the occurrence of spikes in other neurons (cross-correlation) (Fig. 11–4C,D), and to other brain events (e.g., theta waves) (Fig. 11–5) or to sensory and motor events in the environment (e.g., peristimulus event histogram) (see Fig. 11–17, later). The auto-correlation function is useful for revealing repetitive or rhythmical patterns of firing. A graph is constructed in which the x-axis represents time intervals before and after each spike event, and the y-axis represents the probability that the cell will fire during each interval before or after that spike event. A period of 50 ms is a useful period of time for looking at the complex spike properties of principal cells in which the cell fires repetitively within 10 ms (Fig. 11–3A,E); 500 ms is a useful length of time for demonstrating the rhythmical pattern of theta cell firing. The cross-correlation function reveals the tendency of two cells to fire with a particular temporal relation to each other. Here one cell is chosen as the target, and its spikes fix the zero point on the time axis. The probability of the other cell firing at times earlier and later is calculated and displayed as a histogram. This type of analysis is useful for identifying potential synaptic relations between cells or the existence of common inputs to the cells. The cross-correlogram between a complex-spike cell and a theta cell is shown in Figure 11–4C,D. The peak at 2 ms suggests that there is a short-latency excitatory synaptic connection from the pyramidal cell to the theta cell. The probability associated with this peak gives some indication of the strength of this connection. The correlation between hippocampal units and the phase of the global EEG theta signal is useful for showing the temporal relations of different types of unit to the EEG and to each other (Fig. 11–5). A final use of correlation techniques is to look for a relation of spike firing to a sensory event or motor action in the external world or to another brain event. Illustrated in Figures 11–17 to 11–19 are peristimulus histograms of hippocampal unit responses to auditory stimuli as a result of conditioning experiments and in Figure 11–20 (see later) the increase in activity during different aspects of the behavioral learning paradigm.

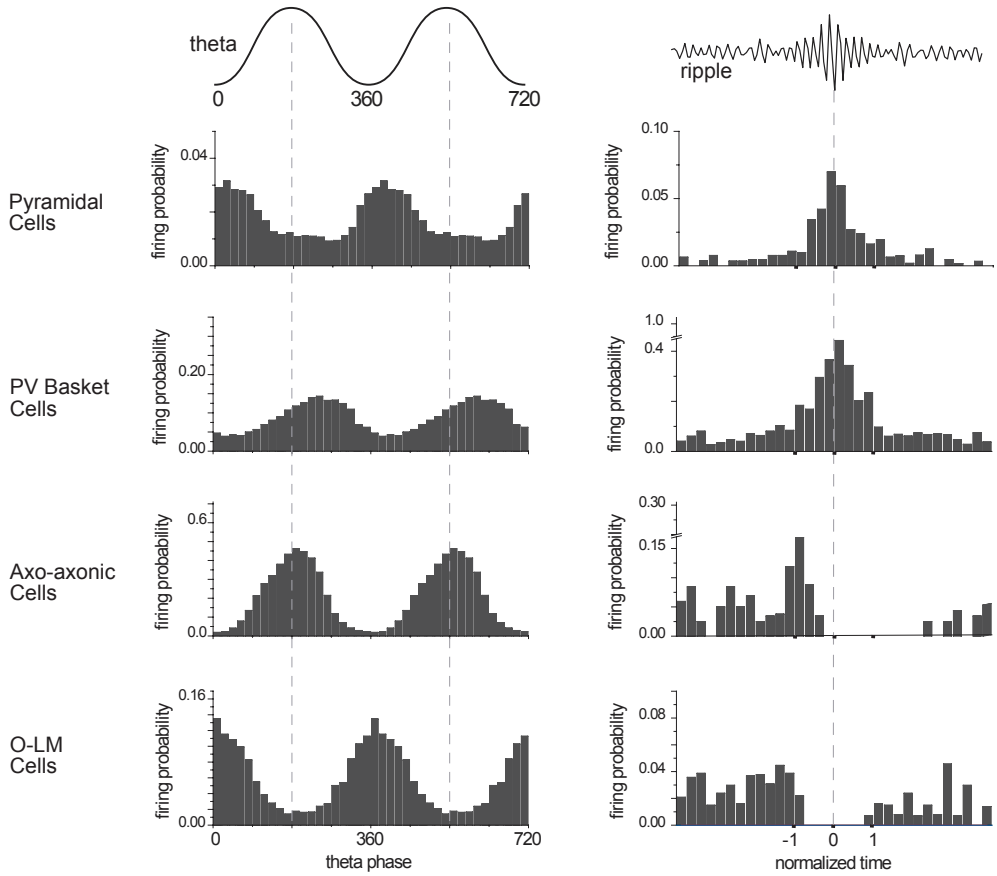


Figure 11–5. Phase relations of pyramidal cells and various classes of interneurons for theta (*top left*) and sharp-wave ripples (*top right*). Note that the various interneurons have phase relations different from those of theta activity. Note also that pyramidal cells and basket cells fire during the ripples, axo-axonic cells fire slightly before, and both they and the O-LM cells are silent during the ripples. (*Source*: After Klausberger et al., 2003.)

1984, Ranck described the *head direction* units, and in 2005 Hafting and colleagues discovered the *entorhinal grid* cells. The availability of directional and distance information to the mapping system was a prediction of the theory, and the discovery of these cell types in the hippocampal formation provides strong support for it.

Head direction cells were first discovered in the dorsal presubiculum (or postsubiculum) (Ranck, 1984; Taube et al., 1990a). The activity of these cells complements that of the place cells: They do not take into account the animal's location but signal the direction in which it is pointing relative to the environmental frame. They are rarely found in the hippocampus proper but mainly in another part of the hippocampal formation, the dorsal presubiculum, which has strong anatomical connections to the hippocampus via its projections to the entorhinal cortex, perhaps to the grid cells located there. The best estimate is that about 25% of the cells in this area are sensitive to head direction, whereas other cells there have angular head velocity, running speed, locational, and both directional and locational correlates (Sharp, 1996; Cacucci et al., 2004). They are discussed in Section 11.9.

The grid cells are found in the medial entorhinal cortex. Their firing maps lay down a regular pattern of locations across all environments the animal encounters. They are well suited to provide the self-motion or idiothetic information for the construction of place cells, as well as the distances and directions between them. They are considered in greater detail in Section 11.7.7.

Not everyone who has recorded from principal cells in the hippocampus agrees with this spatially conditioned way of looking at the data. For example, there have been reports of temporal correlates between pyramidal cell firing with eyelid responses during nictitating membrane conditioning and sensory, motor, and task-related correlates during olfactory learning and memory tasks. These reports have suggested a function for the hippocampus broader than spatial memory and navigation, perhaps as a storage device for nonspatial as well as spatial relations. Several authors, most notably Eichenbaum and Cohen (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001), have returned to the original Ranck description of these cells as having behavioral approach as well as spatial and relational correlates. The next

sections focus on the extensive literature on place cells, theta cells, and on other spatially related cells in particular, head-direction cells, and grid cells. Work on nonspatial correlates is described in later sections (see Section 11.11).

11.6 Theta Cells

The second major class of cells in the rodent hippocampal formation is the theta cell. These cells are distinguishable from the complex-spike cells by having a briefer action potential, a higher firing rate, and a different anatomical location (Fig. 11–3). They also have a different relation to the hippocampal EEG. Given the predominance of theta EEG activity during certain behaviors, it is not surprising to find that many cells in the hippocampus have a rhythmical pattern of firing that is related to theta. Theta cells were originally defined by their strong, consistent phase correlation to the EEG theta pattern and by their increased firing rate during theta, irrespective of the animal's location. Subsequently, the class was broadened to include cells that decrease their firing rates during theta. In contrast, the timing of complex-spike action potentials relative to the theta waves is more complex and changes as the animal moves through the place field (see Section 11.7.9). In the rest of this section, the relation of theta cells to the EEG, their pharmacology, and their correlation with behavior are described.

11.6.1 Theta Cells Fire with a Consistent Phase Relation to EEG Theta

The defining feature of theta cells is their close relation to the hippocampal EEG. Bland and his colleagues (Colom and Bland, 1987) have identified four classes of theta cell, theta-on and theta-off cells, each of which is subdivided into phasic and tonic subtypes. Theta-on cells increase their firing rates during theta activity, whereas theta-off cells decrease their activity. Phasic cells have strong constant phase relations to theta; tonic ones do not. The theta-off cells are found much less frequently than theta-on cells and are particularly rare in the freely moving rat.

In the urethane-anesthetized rat, both CA1 and dentate theta cells fire close to the negative peak of the dentate theta. In contrast, in the awake animal, maximal firing is found much closer to the positive peak of the dentate theta (Fox et al., 1986). In addition, there is a broad range of preferred phases in the various cells pointing to a heterogeneous population of theta cells. It is likely that more than one class of interneuron is involved, corresponding to the different classes of hippocampal interneuron identified in Chapter 8. Different types of interneuron have different phase correlates to theta and the LIA sharp waves. For example, Klausberger (2003) reported that the basket cells, which have their cell body in the pyramidal cell layer and inhibit the perisomatic region of the pyramidal cells, preferentially fire on the positive/negative part of the theta wave and on each wave of the sharp-wave ripple oscillation; oriens/lacunosum-moleculare cells, with their somata in the stratum oriens and their axons targeted on the distal dendrites of the pyramidal cells, fire on the negative phase of the theta wave and are silent during sharp waves; axo-axonic cells, which target the axon hillock of the pyramidal cells, fire on the positive theta wave and are also silent on the sharp waves (Fig. 11–5).

In the rabbit, the same cells take part in both a-theta and t-theta. Typically, the firing rate during a-theta is lower than during t-theta even for the same frequency of theta. Within each type of theta, the firing rates of the theta cells vary as a function of the frequency of theta. In Section 11.7.9, we discuss in greater detail the temporal relation between the complex-spike and theta cells and the EEG theta.

11.6.2 Pharmacology of Theta Cells

As we have seen in Chapters 3 and 8, interneurons in the hippocampus receive both GABAergic and cholinergic inputs from the septal nuclei, GABAergic and endorphin peptidergic inputs from other inhibitory interneurons, and glutamatergic inputs from the pyramidal cells. Finally, they receive catecholaminergic inputs from the brain stem and might be expected to respond to transmitters such as noradrenaline (norepinephrine). Firing rates of theta cells recorded in the urethane-anesthetized rat decreased by up to 75% following iontophoretic application of atropine or scopolamine (Stewart et al., 1992). There was, however, no change in the phase relation between the remaining spikes and the EEG theta. This is markedly different from the effect of the same drugs on complex-spike cells, which did not change their rate of firing but altered their patterns of firing from the usual complex-spike burst pattern to more continuous firing. This suggests that the cholinergic input to the hippocampus from the medial septal nucleus makes direct contact with the theta cells and increases their firing rate but has no influence on their theta burst mode of firing. It further suggests that the pattern of activity in complex spike cells, in contrast to the rate, has only a modest influence on the pattern of firing of the theta cell interneurons. Opiates have a different effect: They directly inhibit the interneurons and indirectly disinhibit the pyramidal cells, increasing their discharge rate firing (Pang and Rose, 1989). Finally norepinephrine has an effect that is broadly opposite to that of the opiates, exciting interneurons and inhibiting the principal cells in both the CA1 field (Pang and Rose, 1987) and the dentate gyrus (Rose and Pang, 1989).

11.6.3 Hippocampal Theta Cells Have Behavioral Correlates Similar to Those of the Hippocampal EEG

In the rat, theta-on cells increase their firing rates during the EEG theta and begin to fire in a bursting pattern in phase with the theta rhythm. This normally occurs during behaviors such as walking and swimming, which change the animal's location in an environment. During LIA behaviors (e.g., slow-wave

sleep, quiet sitting, eating, drinking, grooming), theta cell firing is lower in frequency and more random in pattern. Interestingly, low-frequency theta mode firing occurs during the postural shifts of grooming, such as changes from face-washing to flank-grooming.

Theta-off cells have the opposite behavioral correlates, increasing their firing rate during LIA and decreasing their rates during theta. There are differences between the behavioral correlates of theta in the rat and rabbit (see above), and similar differences are found in the correlates of theta cells in these two animals. For example, a-theta in the rabbit occurs much more readily in response to arousing stimuli in the absence of movement. It is no surprise, then, that the theta cells also fire during arousing stimuli as well as during movements such as walking and hopping. As we shall see in the section on conditioned responses in single hippocampal units (11.11.5), this a-theta related firing may help explain the involvement of the hippocampus in the timing of such responses to the (arousing) conditioned stimulus.

An important pointer to one function of the theta cells comes from an interesting observation by Nitz and McNaughton (2004). They found that a large number of CA1 theta cells turn off during the first exposure to a novel environment, whereas the dentate interneurons increased firing rates. Perhaps the CA1 interneurons are part of a mechanism for identifying familiar and novel environments and for controlling the processes of learning that occur in CA1 pyramidal cells when the animal is confronted with environmental novelty.

11.7 Complex-spike Cells and Spatial Processing

The primary correlate of hippocampal complex-spike cell firing is the animal's location in an environment. For this reason they have been called *place* cells (Fig. 11–21A, see color insert). This section begins with a description of the properties of place cells, followed by the factors that control the location, size, and shape of place fields. Both exteroceptive sensory cues and internal proprioceptive/vestibular cues play a role in determining place field structure and location. The frame of reference for the spatial coordinates of place fields can vary depending on the environment. It is known that the spatial code is conveyed by the temporal firing pattern of the complex-spike cells as well as by their absolute rate of firing. The animal's location in an environment is not given by the activity of a single place cell but by the pattern of firing across a large number of such cells. It follows, therefore, that it is important to look at the network properties of place cells. Place cells have been found in areas outside of the hippocampus, in particular in the subiculum and entorhinal cortex; and the properties of these cells and how they differ from those in hippocampus are discussed. The final section examines the data suggesting that place cell firing is controlled by activity in brain regions outside the hippocampal formation and in particular by cells in the septal region and in the thalamus.

11.7.1 Place Cells Signal the Animal's Location in an Environment

Place cells were discovered by O'Keefe and Dostrovsky in 1971 (O'Keefe and Dostrovsky, 1971). After recording from rat CA1 complex-spike cells during various behavioral tasks and in response to various types of sensory stimulation, they noticed that the activity of some cells was more closely related to the animal's location than to any aspect of the task in which it was engaged. O'Keefe (1976) confirmed and extended these observations by recording from rats as they ran between the arms of a three-arm maze to obtain different rewards. He christened these cells *place cells* and called the location where each cell fired its *place field*. There were several aspects of the firing patterns of these cells that suggested they were signaling the abstract concept of place rather than acting as simple sensory cells. First, it was not possible to identify any single sensory stimulus that reliably controlled the cell's activity. Second, after the rat had some experience with running on the maze in the dark as well as in the light, many of the complex-spike cells continued to fire in the appropriate location with the lights out. Third, on the broad-armed maze used by O'Keefe, many cells fired equally well as the animal faced in any direction. Finally, place field firing did not seem to depend on the animal's motivation or incentive for visiting a location. For example, interchanging the food and water rewards at the ends of the different arms of the maze had no effect on place cell firing. Thus, complex-spike cells did not appear to be tuned to specific sensory stimuli, they tolerated radical changes in lighting, and they were omnidirectional and uninfluenced by reward. The notion that something more abstract was being signaled—such as location—seemed an appropriate conclusion.

Some skepticism greeted the first qualitative reports of the properties of these cells. However, the introduction of photographic methods and, later, the development of computational methods of obtaining objective data gradually convinced the most ardent skeptics (Box 11–3 and Fig. 11–6). Over the years, improvements in single-cell isolation (see Box 11–2), coupled to ever more sophisticated behavioral procedures and unusual bits of apparatus (e.g., "morph" boxes with walls that can be reconfigured), have helped unravel many of the properties and determinants of place cells.

O'Keefe (1976) noted that although many complex-spike cells could be classified as simple place cells, others had more complex properties. For these cells, the firing rate was dependent on factors in addition to location. For example, some cells increased their firing rates if the animal experienced an object in their place field or engaged in a particular type of behavior there (e.g., running or sniffing). The clearest example of this type of cell was one that fired maximally when the animal went to a specific location on the maze and either failed to find something that had been there often before or found something new. These complex spatial cells were called *mis-*

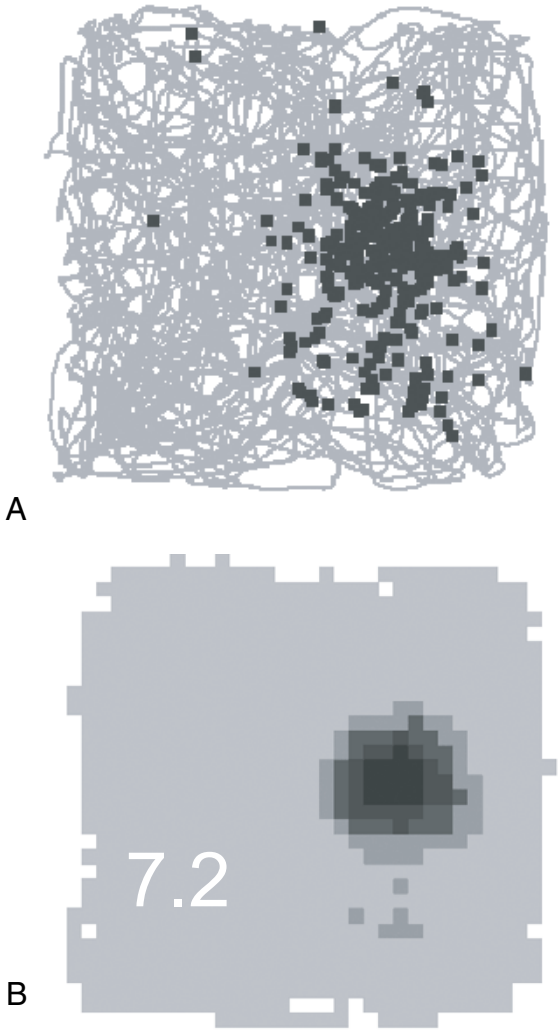


Figure 11–6. Firing field of a CA1 place cell. *A*. Raw data from a rat foraging for food in a square box for 10 minutes. Gray line traces the animal's path through the environment; black boxes show firing of place cell. *B*. Place firing field as a grayscale map where darker colors represent higher firing rates. Inset number in white gives the peak firing rate. (*Source*: After Wills et al., 2005, with permission.)

place cells. Whether the firing of these misplace cells was due to the absence of the expected object or reward or to the myostatial (exploratory) sniffing elicited by the mismatch was not clear. Ranck (1973) noted similar behavioral correlates of hippocampal complex-spike cells but did not identify their spatial properties. He labeled one class "approach-consummate" cells because they fired as the animal ran toward the food or the water reward. Another class he called "approach-consummate mismatch" cells because they fired maximally when the animal sniffed around the reward location when the reward was withheld. It now seems likely that many and perhaps all of Ranck's first class of cells are synonymous with O'Keefe's category of place cells and his second class synonymous with the misplace cells. Eichenbaum and his colleagues have recorded cells during odor discrimination tasks with properties similar to those described by Ranck and questioned whether all of these cells are best described as having spatial fields. This work is described in more detail later (see Section 11.11).

Box 11–3
Quantitative Recording of Place Fields

An objective description of the firing field of a place cell is achieved by constructing a map of firing frequencies across the surface of an environment (see Fig. 11–6). The location of a small light fixed to the animal's head is monitored by an overhead television camera, and the animal's position is recorded throughout the trial. The environment is broken up into a set of squares, and two independent measures are computed for each square: the amount of time the animal spent there and the number of times the cell fired while the animal occupied that square. A firing rate per square can be calculated by dividing the number of spikes in each square by the amount of time the animal spent there. Spatial firing rates are often portrayed as false color or grayscale maps in which different colors or shades of gray represent different firing rates. In some laboratories, the data are spatially averaged and smoothed before this step. The colors or grayscales allocated to the different firing rates are usually adjusted relative to each cell's peak firing rate (auto-scaling) to give comparable field pictures from high- and low-firing cells. When fields are created for the same cell across different conditions, it is often useful to fix all of the color map levels to the first one to facilitate comparisons. In some experiments, two differently colored lights or infrared lights of different intensities are fixed at different positions on the animal's head so the computer monitoring the animal's movements can compute the instantaneous heading direction as well as location. The best estimates of spatial firing are achieved during tasks in which the animal visits each section of the environment for an equal amount of time.

11.7.2 Basic Properties of Place Fields

The size and shape of place fields vary with the shape and perhaps also the size of the testing enclosure as well as with the part of the hippocampus from which the recordings are taken. In the dorsal hippocampus, fields on small, open platforms have a tendency to be located along the edges or just off them (seen when the animal peers over the edge), whereas those in closed cylinders or rectangular boxes tend to be equally distributed around the environment (Muller et al., 1987) (Fig. 11–7). On mazes, fields may be located anywhere, with no tendency for them to cluster in particular arms or in particular parts of the maze such as at choice points (O'Keefe, 1976; Olton et al., 1978; McNaughton et al., 1983a; O'Keefe and Speakman, 1987). There are, however, occasional reports that provide exceptions to this generalization: Hetherington and Shapiro (1997) reported that fields tended to cluster closer to walls than in the center of rectangular boxes, and Hollup et al. (2001) found a greater representation of fields in the region of the goal in an annular-shaped swimming pool.

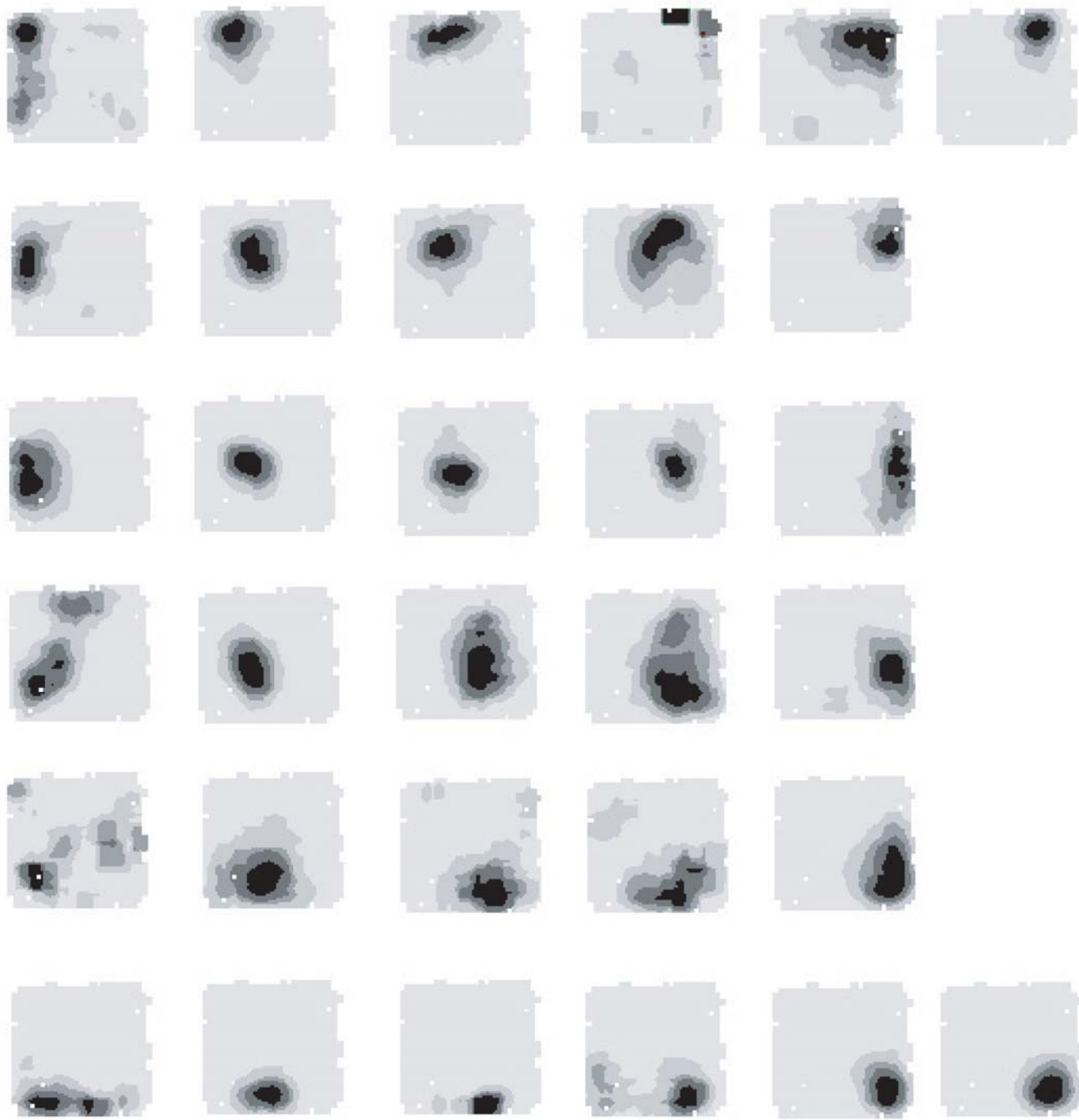


Figure 11–7. Firing fields of 32 place cells simultaneously recorded while a rat foraged for food in a 62-cm^2 box. The place field maps are arranged topographically so fields in the northwest of the box are located at the upper left, fields in the southwest are located at the lower left, and so on. In reality there is no topographical relation between the location of cells in the hippocampus and the location of their fields in an environment. (*Source*: After Lever et al., 2002, with permission.)

One distinctive feature of the representation of any particular environment by the hippocampal place cells is the absence of topographical mapping of function onto anatomy, such as is seen in the neocortex. That is, place cells located next to each other in the hippocampus are no more likely to have fields located next to each other than those far away (O'Keefe et al., 1998). In contrast, there have been some reports that neighboring cells have fields closer than expected by chance (Eichenbaum et al., 1989) or that cells in the hippocampus are functionally organized in bands separated by 300 to 400 μm along the long axis (Hampson et al., 1999). A definitive resolution of the question seems to have been given by Redish and colleagues (2001). Using tetrodes to ensure adequate spike isolation, they collected a large number of recordings of pairs of complex-spike cells during tasks in which the animals ran along circular or linear tracks. They compared the place fields of cells recorded from the same tetrode (see Box 11–2) and therefore anatomically neighboring each other, with those of cells from different tetrodes and therefore more distant from each other. They found no tendency for the place fields of neighboring cells to be closer to each other than would be expected for cells located at any two points in the hippocampus. They also recorded the activation of the immediate early gene *Arc*, which identifies active cells, as the animal explored two different environments. In neither case did they find any evidence for clustering of cells with similar spatial or temporal correlates. One is tempted to speculate that there must exist some mechanism for preventing neighboring cells with their overlapping inputs from adopting similar place fields in any environment. Perhaps one function of the inhibitory interneuronal networks is to allow some pyramidal cells to capture a territory in an environment and to exclude their neighbors from firing in that region.

Place cells rarely have more than one field in a single environment (typical testing environments are less than 1 m^2). The best current estimate is that cells with double fields comprise no more than about 5% to 10% of the total. The sizes of place fields in the dorsal hippocampus vary considerably. To some extent, field size is a function of the threshold used for separating signal from noise and the location of the recording site along the dorsal septo-temporal axis of the hippocampus. Using a 1-Hz threshold as the minimum rate within a place field, field sizes in a cylinder of 76 cm radius ranged from a minimum of 4% of the surface area to a maximum of 62%, with a median size of 18% (Muller et al., 1987). (These data were obtained with single-electrode recording techniques; it is likely that the actual place field sizes are even smaller.) As can be seen from Figure 11–7, there appears to be a slight tendency for the fields in the center of the environment to be larger than those toward the periphery, but this has not been quantified.

The average size of the place field varies with location along the long axis of the hippocampus. As the recording electrode is moved to more ventral portions of the hippocampus, the size of place fields expands. Fields in the middle region of the hippocampus are almost twice as large as those in the septal hippocampus (Jung et al., 1994). The most ventral regions of the hippocampus were not extensively explored in these studies, but a small number of cells recorded there (Maurer et al., 2005) appear to have fields twice the size of those in the middle region. It seems reasonable to assume, therefore, that field sizes increase as one goes from the dorsal to the ventral hippocampus; and some fields in the most ventral hippocampus might be very large, covering areas the size of the usual laboratory testing enclosures or even larger. This wide range of field sizes has important implications for analysis of the sensory correlates of hippocampal cells and for analysis of the differences in behavioral functions of the dorsal versus ventral hippocampus. Some authors have claimed that hippocampal complex-spike cells respond to specific sensory inputs (e.g., an odor) in the absence of a spatial correlate because the cells did not fire at higher rates in one part of the testing apparatus than in any other (e.g., Wood et al., 1999). Clearly, however, if some spatial firing fields can be as large as or even larger than the size of the apparatus, this conclusion is not warranted. At the very least, it is necessary to test sensory responses in two enclosures located in different laboratories. Similarly, when trying to discern the differences in function between the dorsal and ventral hippocampi, it is important to take this average field size difference into account. Fields that cover an entire testing enclosure might be described as spatial context neurons and in conditioning paradigms, for example, might have the primary function of distinguishing between two testing boxes rather than identifying different locations within the same testing box.

How quickly are place fields formed, and how do they develop? The answers to these questions can provide some indication of whether some or all of the representation of an environment is prefigured and what rules govern the plasticity involved in the initial development of the spatial representation. Several studies have provided reasonably good answers. On a small sample of 15 place cells, Hill (1978) found that 11 had fully fledged fields on the first entry into the relevant part of the environment. On a larger sample of cells and using tetrode recordings, Wilson and McNaughton (1993) allowed their rats to explore one-half of an open field box until it was familiar; they then removed a partition wall of the box, giving access to the whole. They reported that all place fields had stabilized within 10 to 15 minutes of entry into this new part of the enclosure. Frank et al. (2004) looked at the development of fields on a three-arm maze when one of the usual arms was closed and a new one with a different angular orientation was opened. They found that about one-quarter of the new fields on the novel arm developed rapidly within the first 2 minutes and that most fields had stabilized after 5 to 6 minutes of experience with this arm. Interestingly, cells that had less than 4 minutes of novel experience on the first day showed considerable plasticity on the second day, whereas those with more than 4 minutes' experience were much more stable. The firing in some fields strengthened in the initial location, that of others weakened, and some shifted to a new location altogether. Still others were initially silent on the arm, but after several minutes of exposure to the new arm turned on from this zero baseline and began to fire. The authors

pointed out that the latter phenomenon is incompatible with a role for postsynaptic spike timing-dependent plasticity in the recorded cells as the mechanism underlying place field development. This mechanism suggests that presynaptic activity coincident with postsynaptic spiking strengthens the active synapses, and the absence of postsynaptic cell firing prior to the development of the full-blown place field rules it out. Of course, it could be that the changes are taking place in an earlier part of the circuit with postsynaptic cells that are initially active. Our own studies (Lever, Cacucci, Burton, O'Keefe, unpublished) have examined CA1 place field dynamics during the first exposure to an entirely novel environment: a 60-cm sided square box located in a curtained environment of which the animal had no prior experience. In agreement with Frank and colleagues, we found that place field establishment was rapid and could occur within 2 to 3 minutes. Most of the CA1 cells that developed fields during the first exposure to an environment maintained these fields, but some stopped firing or changed field location. This is reminiscent of the process of place field development upon exposure to a new part of a familiar environment, described above. Setting up a representation of a new environment or part of an otherwise familiar environment seems to involve a competitive competition among a group of neighboring cells perhaps mediated by the inhibitory interneuronal networks. Initially, a small number of seed cells have place fields from the moment the animal enters the environment, although the field firing rate may increase or decrease with continued experience. These cells prevent neighbors from firing in their territories through activation of inhibitory interneurons. Other cells gradually fill in the unclaimed territory until the entire space is represented, at which point no other cells are allowed to develop place fields in that environment and the representation stabilizes. Both Wilson and McNaughton (1993) and Frank and colleagues (2004) noted that some theta cells showed a marked reduction in firing rate during the first entry into the novel environment, although according to Frank et al. this lasted only for the first minute of exploration. In a subsequent section, evidence is presented in support of O'Keefe's (O'Keefe, 1976) original idea that place cells could be activated in the place field by sensory cues experienced there or by path integration signals that compute the distance and direction from other locations. McNaughton et al. (1996) has speculated that when an animal first enters a novel environment the firing of place cells is driven by the path integration inputs and that only subsequently are the environmental stimuli experienced in each location associated with these place fields. A plausible alternative is that the small number of seed cells are driven by the appropriate combination of environmental cues from the first exposure (perhaps including the animal's own urine), and the rest of the cells are subsequently co-opted by the path integration system as the animal moves around the environment relative to these known locations. Further experimentation is needed to distinguish between these alternatives.

11.7.3 Place Fields are Nondirectional in Unrestricted Open-field Environments but Directional When Behavior Is Restricted to Routes

Place field firing sometimes depends on the direction in which the animal faces and sometimes it does not. In open-field environments, the place fields are nondirectional (Muller et al., 1994) (Figs. 11–8A; see Fig. 11–21A, color insert); on radial arm mazes (McNaughton et al., 1983a; Muller et al., 1994; Markus et al., 1995) and narrow linear tracks (O'Keefe and Recce, 1993; Gothard et al., 1996a), they are highly directional (Fig. 11–8B). Whereas in the first situation each cell may be said to represent a location, in the second it might more properly be described as representing a serial position along a path.

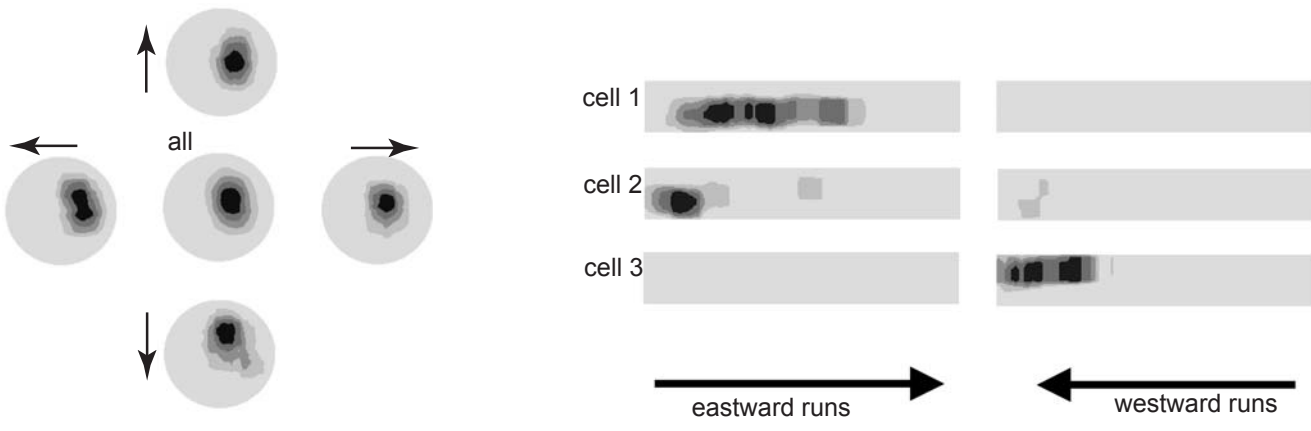


Figure 11–8. Place fields are nondirectional in open-field environments but directional on linear tracks. *A*. Central panel shows the firing field of a place cell in a 78 cm diameter cylinder regardless of the direction in which the rat is facing. The four outer panels show the field when the animal is facing in the four cardinal directions: northward at the top, eastward to the right, and so on. (Peak rates are shown in black: 12 center, 10 north, 12 east, 9 south, 9 west.) *B*. Firing fields of three cells recorded simultaneously as the rat runs back and forth on a 1.5-m linear track for food reward at each end. Cells 1 and 2 fired as the animal ran from left to right but not in the opposite direction; cell 3 fired during right to left runs. (Peak rates shown in black: 9 top, 10 middle, 7 bottom.) (*Source*: Courtesy of O'Keefe.)

The difference between the two situations appears to be due, in part, to the constraints that the shape of the testing apparatus places on the animal's behavior. It is not a matter of sampling from two cell populations because the same cells can have directional or nondirectional fields in different testing apparatuses or under different behavioral constraints (Muller et al., 1994; Markus et al., 1995). The most important variables appear to be whether the animal can turn around in any given location and if it approaches the same location from many directions. If it can, cells are relatively nondirectional. However, if the animal always runs through the same location along the same one or two paths, place cells tend to be directional. Note that one can induce narrow and stereotypical pathtaking in open fields by reward shaping. Markus et al. (1995) originally trained rats to perform random foraging in an open cylinder and then retrained them to take direct paths in the same cylinder among four reward locations in either clockwise or anticlockwise sequences. The proportion of place fields defined as directional doubled from about 20% in the random foraging condition to 40% in the direct path condition. An important study has reexamined directionality in CA1 cells (Battaglia et al., 2004). These authors trained rats to run on narrow linear and circular tracks of the kind that would normally induce a high proportion of unidirectional place fields. Their finding across experiments was that placing various proximal multimodal cues along the tracks significantly increased the proportion of bidirectional place fields. This is puzzling because there are usually no distinctive local cues in open fields where the cells are typically nondirectional. The dynamics of (non)directionality need further study; there are no published reports examining directionality on first exposures in linear tracks. Does omnidirectionality appear as soon as a place field develops, or do the fields start out with a directional bias and only lose this directionality with further experience of the environment (Kali and Dayan, 2000)?

The existence of both directional and nondirectional modes of spatial representation raises the question of whether the hippocampus is providing fundamentally different types of information in these two situations. Specifically, does the spatial localization system, of which the place cells are a part, "know" that the rat is in the same location when, say, traveling east as when traveling west? Perhaps it is only acting to its fullest capacity when the cells are omnidirectional and is showing limited functionality when they are unidirectional. Against this is the recent demonstration (Rosenzweig et al., 2003) of a good correlation between the degree to which place cells recorded on a linear track used a particular reference frame and the animal's ability to localize an unmarked location defined within that framework. Place cells were recording on a linear track where locations could be identified in one of two conflicting frameworks: in the framework of (1) a goal box that changed location along the track from trial to trial or (2) stable room cues. The target location remained fixed relative to the stable room cues but moved from trial to trial relative to the moving goal box. The authors showed that the higher the percentage of place cells that related to the framework of the stable room cues in each rat's hippocampus, the more likely the animal was to be successful at the task. The relation of place fields to different environmental reference frames is considered at greater length in a subsequent section.

One major difference between directional and nondirectional field firing is the influence on the firing rate within the field of the overall trajectory of the path in the former but not, so far as is known, in the latter. During behavioral tasks that promote directional firing and require the rat to traverse the same part of the apparatus as part of two different paths, place cells fire differently in the place field on the two paths (Frank et al., 2000; Wood et al., 2000; Ferbinteanu and Shapiro, 2003). For example, Wood and colleagues (2000) trained animals on a continuous alternation task in a T maze that had been fitted with return tracks from each goal to the start of the stem so the animal could run in a continuous figure-of-eight path by turning left or right alternatively at the choice point of the T junction. Activity in two-thirds of the place fields in the stem of the T varied markedly depending on whether the animal entered the stem following a return from the left-hand or right-hand goal. In the Wood et al. study, it was not possible to distinguish between firing owing to the previous part of the path (retrospective coding) and the future part of the path (prospective coding). Two of the three studies (Frank et al., 2000; Ferbinteanu and Shapiro, 2003), however, did allow for this distinction and reported that, in addition to the retrospective effect of the previous path on place cell firing, the subsequent path (i.e., the upcoming turn to be made at the T junction) also had an effect on firing in the stem (a prospective effect), although the effect was seen in only a few hippocampal cells in the Frank et al. study and was much more prominent in cells in the entorhinal cortex.

These effects appear to be due to the animal repeatedly running in a continuous trajectory in the same direction through the entire path and thus activating a fixed sequence of place cells. These prospective and retrospective effects have not been reported in nondirectional fields in open-field environments, suggesting they have something to do with the stereotyped ballistic nature of the paths taken on linear tracks. In the one study in which the effect was not seen, the animals were trained to alternate on a Y maze with broad arms (Lenck-Santini et al., 2001a). They had to return to the start arm following each visit to a goal arm, resulting in a start arm → left goal → start arm → right goal → start arm, etc. alternation pattern. This behavioral pattern would activate the same cells in a different order on successive runs, and the wide arms would allow the rat to take slightly differing paths on each run. Interestingly, one observation in the Ferbineatu and Shapiro study suggests that the effect is not due solely to the activation of the immediately prior place cell in the sequence or the execution of the immediately preceding turn. On error trials in which the animal first visited an incorrect arm before entering the correct goal arm for that trial, about one-half of the cells with place fields in the goal arm continued to fire correctly. This shows that small deviations from the standard path through the environment do not disrupt the effect. The authors suggested that it is the overall journey from one place

to another that is important, not the actual sequence of locations traversed. Buzsaki (2005) has speculated that the firing of any given place cell may be influenced by place cells from early stages in the path and not just by the immediately preceding cell in the sequence. At this stage, it is not clear how much these effects are due to the beginning and end points of the path and how much to particular motor behaviors, such as body turns made during the path. One possibility is that the firing of many cells on these tracks is driven by the path integration system (see Section 11.7.7), and activation of the motor, proprioceptive, and vestibular systems at the turn into the stem of the T maze marks an important location on the path and is carried over to the rest of the path. This would explain some of the retrospective effects but would not explain the prospective effects unless there is activation of the turning machinery some period of time prior to reaching the turn itself.

These studies have been interpreted by their authors as pointing to a place cell basis for the episodic functions of the hippocampus (see Chapter 13, Section 13.4). O'Keefe and Nadel (1978, 1979) originally suggested that the spatial functions of the rat hippocampus could be elaborated into a spatiotemporal episodic memory in humans by adding a temporal time-stamp signal, which would allow each set of events occurring in the same location to be distinguished from each other on the basis of their time of occurrence. The present results, however, do not provide evidence for this unique time-stamp signal, which would enable different runs to be identified as independent episodes. Rather, it seems to be more appropriately interpreted as evidence of the organization of place cells into integrated, ordered sequences, as might be expected for the representation of paths.

To conclude this section, it is clear that the place cells can be directional or nondirectional depending on the specific circumstances in which they are recorded. It is important to emphasize that the nondirectional mode of place cell activity rules out the possibility that they are simply responding to a particular configuration of distal sensory cues. They cannot be responsive just to a particular view or scene in front of the animal (sometimes called the "local view"), as this would change radically as a function of the heading direction. Moreover, as these experiments routinely control for local sensory inputs such as intramaze smells and textures, nondirectionality is evidence in favor of the idea that these cells can signal something quite abstract.

11.7.4 What Proportion of Complex-spike Cells Are Place Cells?

To estimate the proportion of complex-spike cells that are place cells, it is necessary to record from the same cells in several environments. This is because most place cells do not have a place field in every environment. For example, early studies (O'Keefe and Conway, 1978; Kubie and Ranck, 1983) reported that whereas some complex-spike cells had fields in two or more recording environments others had fields in one but not the other. A second problem is that many complex-spike cells are silent most of the time, making it difficult to estimate the population number. Thompson and Best (1989) tried to get an accurate estimate of the population by recording during slow-wave sleep or while the rat was under light barbiturate anesthesia. Both procedures are known to enhance the spontaneous firing rates of complex-spike cells and may therefore provide a better estimate of the total population under the recording electrode than can be obtained during the active, awake state. They also recorded complex spikes in three environments: an elevated eight-arm radial maze, an enclosed cylinder, and an enclosed rectangular environment. They concluded that slightly more than a third of the cells that could be identified under barbiturate anesthesia had place fields in at least one of the three environments. Almost all of the other cells recorded had very low spontaneous rates in all environments (and were thus termed "silent cells"), with many firing no spikes for the entire period of testing. Only 14% of cells had fields in two environments, and only 1% had fields in all three environments. That is, many cells with fields in one environment acted like silent cells in the other environments. On the basis of the physiological similarities between the place cells and the silent cells, and the distribution of fields across the three boxes, Thompson and Best suggested that if enough environments were tested every complex-spike cell would have a field in at least one of them. In several studies, McNaughton and his colleagues (Wilson and McNaughton, 1993a; Gothard et al., 1996a) have sampled large groups of complex-spike cells and find that 30% to 70% have place fields in a given environment. Their group (Guzowski et al., 1999) has used the immediate early gene *Arc* to label all of the CA1 cells active in two groups of animals, each exploring a different environment. In one group 44% of CA1 cells were active and in the other group 45%—in broad agreement with the results from single-unit recordings. In animals that were allowed to explore both boxes and in which double staining was carried out, 22% of the cells were active in one environment, 23% in the other, and 16% in both. These studies make it clear that a large proportion of complex-spike cells have a place field in some environments, consistent with the view that spatial representation is one of the primary functions of the hippocampus.

Is there any relation between the size or shape of the place fields that a cell displays in one environment and those obtained in another? The answer depends on the similarity between the environments and the amount of experience the animal has had with them. When the environments are sufficiently different, such as the eight-arm radial maze without walls and a small enclosed rectangular box used in the study of Thompson and Best (1989), and the animal has had considerable experience in both, the fields are very different. In contrast, when both environments have walls and the animal is inexperienced, most fields are initially similar in shape and location despite differences of shape or color between boxes. With experience, the place cells begin to differentiate between the two environments, and after a period of time most cells fire differently in the two boxes (Bostock et al., 1991; Lever et al., 2002; Wills et al., 2005). This phenomenon is called remapping and is a good example of a type of learn-

ing that is reflected in hippocampal cell firing. Most of the remapping that occurred between square and circular environments involves the cessation of firing in one of the two environments; more rarely, there is a shift in field location between the two (Lever et al., 2002). One important factor influencing whether a complex-spike cell has a place field in any given environment might be the overall level of inhibition experienced by that cell in that environment. Thompson and Best found higher background rates in environments in which the cell had a place field than in environments in which it did not. A reasonable speculation, therefore, is that silent cells are potential place cells whose level of inhibition is high in the "silent" environment perhaps due to enhanced excitatory inputs to its inhibitory interneurons from place cells with maintained fields in that environment.

11.7.5 Frame of Reference of Place Fields

If place cells identify an animal's location, they must do so ultimately on the basis of sensory information. In this section, this issue is addressed from the perspective of frames of reference. In the next, the role of specific sensory modalities is examined. The framework to which place fields are referenced might be egocentric or allocentric. An egocentric framework is one that is anchored to the animal's body (or some part of it, such as the trunk, head, or eye) and that travels with the animal as it moves through the environment. An allocentric framework, on the other hand, is one that is fixed to some part of the environment. It is therefore a framework in which the animal's position changes as it traverses the environment. The fact that complex-spike cells recorded in an open field environment fire in their place field irrespective of the direction in which the animal is facing appears to rule out a purely egocentric reference framework. On the other hand, the fact that complex-spike cells can sometimes be directional (e.g., on linear tracks) shows that under some circumstances they can be egocentric or that the inputs to these cells may be coded in egocentric frameworks.

In open fields, where place cells appear to be anchored within an allocentric reference frame, it has been shown that this frame can be a reference to the room, the testing box, or the maze in which the animal has been placed. When recording takes place on symmetrical elevated mazes or open fields with low side-walls, the room generally provides the overall framework. This is readily revealed by rotating the testing apparatus. The usual result is that place fields follow cues located outside the apparatus (O'Keefe, 1976; Olton et al., 1978) (see Fig. 11–12B, later). This is not to say that the intra-apparatus, or what are commonly referred to as "intramaze," cues are without influence. They ordinarily may contribute to place field size or location but be overshadowed in importance by more distal, or "extramaze," cues when the two types are put in opposition. Maze rotation, however, sometimes gives rise to locational ambiguity. A cell may develop two place fields immediately after the rotation, but they quickly resolve into one field with repeated experience of the new configuration (O'Keefe, 1976; Thompson and Best, 1989).

In boxes with high walls and limited views of the room, place cells often use the box itself as the frame of reference. Rotation of the box or rotation of a "cue-card" suspended prominently on the interior wall of the box, generally causes equal rotation of the place fields (Kubie and Ranck, 1983; Muller and Kubie, 1987). On multi-arm mazes with high walls, the fields sometimes take their reference from specific arms and not from the entire maze. Under these circumstances, interchanging arms can result in the fields following a specific arm of the maze irrespective of its allocentric location (Shapiro et al., 1997). In this situation, the cells do not fire all over the surface of the arm but maintain a localized firing field relative to the "frame of the arm" and can thus still be said to be spatially coded. It should not be thought, however, that there is a sharp distinction between extramaze and intramaze cues and frameworks or that any given cell is forced to choose between them. In an experiment described in more detail later, O'Keefe and Burgess (1996) found that although most place fields were controlled by either the animal's location relative to the walls of the testing box or relative to the laboratory frame, some were responsive to combinations of one wall of the testing box and an extramaze cue, such as the wall of the testing room. Bures and colleagues (Rossier et al., 2000) developed an elegant behavioral paradigm for dissociating intramaze from extramaze frames of reference. Rats are trained to avoid a prohibited area of a static circular platform with a good view of the surrounding laboratory. Under these circumstances, the prohibited area can be defined with reference to the extramaze laboratory reference frame or the intramaze frame of the platform itself. Recording from place cells with the platform rotating slowly showed that the firing fields of some are fixed to the extramaze room cues, whereas those of others remain with the rotating intramaze cues. Turning off the lights increased the number of intramaze fields. A large proportion of place fields disintegrated when the two frames of reference were dissociated, suggesting that information from both was required.

In a subsequent experiment, Zinyuk et al. (2000) demonstrated that the proportion of cells related to the extramaze frame, the intramaze frame, or both depended on whether the animal was trained to navigate within the environment. The animals in the navigation group were trained to use the extramaze environmental cues to go to an unmarked location in the static open-field box to receive food pellets. Each entry into this target zone triggered the release of a food reward into a random location for which the rats had to forage. When the intra- and extramaze frames of reference were dissociated by rotating the box at 1 rpm, 38% of the place fields stayed with the extramaze framework, 9% with the rotating intramaze framework, and 31% with the conjunction of both. Cells in this last category fired only at that point of the cycle when the two frameworks coincided. The firing fields of only one-fifth of the cells were disrupted during rotation. In contrast, when another group of animals carried out a random foraging task in the same environment without the navigational component, almost three-fifths of the cells were disrupted by rotating the platform. Of the small number of intact fields, 21%

stayed with the extramaze environment framework, 14% with the rotating intramaze framework, and 7% with both. This study makes several important points. First, it confirms that place cells can be anchored by the extramaze environmental cues, the intramaze box cues, or both, in agreement with previous findings. Second, it shows that training the animals to pay attention to the extramaze cues increases the proportion of place cells that use these cues, alone or in combination, from less than one-third to more than two- thirds. Third, somewhat surprisingly, training to attend to the extramaze cues markedly increases the proportion of cells responsive to the conjunction of the relevant extramaze cues and the irrelevant intramaze framework. It appears that in the absence of explicit training to attend to the spatial aspects of the environment many place cells take their inputs from combinations of a small number of weak distal and local intra-maze cues which are easily disrupted by the rotation. In animals trained to attend to the distal cues the cells incorporate much more robust information especially about the extra-maze cues and are less easily disrupted when these cues are placed into conflict. Support for this interpretation comes from experiments in the same testing paradigm using blockade of one hippocampus by injection of tetrodotoxin. This has no effect on the ability of rats to avoid a place successfully on the basis of either extramaze or intramaze cues alone but blocks their ability to avoid a place on the basis of extramaze cues *in the face of* conflicting intramaze cues (Wesierska et al., 2005). The effects of unilateral blockade are probably due to the disruptive effect of the procedure on the other intact hippocampus (Olypher et al., 2006). These results should serve as a warning that some of the conclusions drawn from studies on animals foraging in the open fields in the absence of an explicit requirement to encode the spatial aspects of the environment might not be providing an accurate picture of the full range of the spatial capacities of the hippocampus.

Interestingly, this group has also shown that training rats to use room-based but not arena-based cues to navigate increases the amount of total variance in place cell firing that is accounted for by position (Olypher et al., 2002). Accordingly, they speculated that some of the variance in place cell firing not accounted for by position (Fenton and Muller, 1998) is attributable to attentional switches between alternative spatial reference frames. Their analysis may provide an interesting window into ostensibly unstable coding of place by hippocampal cells in some experiments.

11.7.6 Place Fields Can Be Controlled by Exteroceptive Sensory Cues

What sensory information does a place cell use to determine where it fires? O'Keefe (1976) suggested that two sources of information were available.

> Each place cell receives two different inputs, one conveying information about the large number of environmental stimuli or events, and the other from a navigational system which calculates where an animal is in an environment independently of the stimuli impinging on it at that moment. The input from the navigational system gates the environmental input, allowing only those stimuli occurring when the animal is in a particular place to excite a particular cell. One possible basis for the navigational system relies on the fact that information about changes in position and direction in space could be calculated from the animal's movement. When the animal had located itself in an environment (using environmental stimuli), the hippocampus could calculate subsequent positions in that environment on the basis of how far, and in what direction the animal had moved in the interim. . . . In addition to information about distance traversed, a navigational system would need to know about changes in direction of movement either relative to some environmental landmark or within the animal's own egocentric space. . . . (O'Keefe, 1976, pp. 107–108)

Both hypotheses have received experimental support: Place fields can be controlled by exteroceptive information from the environment or by movement-generated proprioceptive and vestibular stimuli. This section looks at the external sensory information arising from the environment and asks: Are some sensory modalities privileged over others? Which cues determine the angular orientation of a field in a symmetrically shaped environment, and do these differ from those that control its distance from the borders of the environment? The following section examines the role of internal cues generated by the animal's own behavior in providing estimates of distance and direction traveled.

We begin by asking: Are some sensory modalities privileged over others? There are two ways to identify the role of sensory inputs in controlling place fields. The first follows the pioneering methods of Honzik (1936) in his study of the sensory control of maze learning. Here, a specific sensory modality is eliminated by lesion or occlusion and the consequences examined. The second approach is to construct artificial environments in which there are a few controlled cues that can be experimentally manipulated. Various manipulations have been explored: Cues have been rotated; the distance between them changed; the geometry of the environment altered; associative value or cue meaning taken into account. The results show that many place cells receive information from more than one sensory input; they can use subsets of this total input to identify correctly the preferred place; and geometrical information about distance to features of the environment is particularly important.

A simple manipulation to test the role of vision is to turn out the room lights (O'Keefe, 1976; Quirk et al., 1990; Markus et al., 1994). Some cells are unaffected, but others show a more interesting response. For example, the field may disappear on the first visit to the preferred area but return on the second or third visit. In a cylindrical open-field apparatus, place fields tend to remain intact if the animal is in the environment when

the lights are extinguished. However, if the animal is removed from the environment and then put back into it in the dark, about half of the fields change (Quirk et al., 1990). New fields may appear, and they are maintained even if the lights are now turned on. In contrast, there are many fewer cells that retain similar fields in the light and the dark on the radial arm maze. Furthermore, of the cells firing in both light and dark, the firing in the light was more reliable. Such observations offer yet another indication that place cells act in distinct ways in differing environments. It appears that, in a cylindrical arena or rectangle, once a pattern of place fields is set up for a particular environment it is relatively stable to alterations of exteroceptive cues—unless the animal is removed from the environment. In contrast, place cells are more sensory-bound on radial arm mazes and in other situations that restrict an animal's movements to a linear path.

Eliminating sensory modalities by occlusion or using lesions indicates that there are still place cells after the elimination of olfactory, visual, or both visual and auditory inputs. Save and colleagues (1998) found that rats blind from birth have completely normal place fields when tested as adults. The only discernible difference was a decreased firing rate of place cells compared to controls. Hill and Best's study (1981) of animals deprived of both vision and audition during adulthood revealed they also had apparently normal place fields. However, rotating the arms of the maze showed that, on average, these animals were much more "bound" to the local cues of an arm. Further experiments on the small group of cells that had fields anchored to the allocentric room frame of reference showed that rapid rotation of the animal for 20 to 30 seconds prior to running on the maze caused their fields also to come under the control of the intramaze cues. On the assumption that the rotation primarily affected the vestibular system, these results suggest that, in the absence of distal visual and auditory cues, the angular orientation of place cells can be controlled by olfactory/tactile cues on the maze and by vestibular cues. The latter may be mediated by inputs from the head direction system (see Sections 11.9 and 11.10).

Several studies have attacked the problem of cue control by constructing environments in which the distal stimuli were explicitly identified and controlled. O'Keefe and Conway (1978) trained animals on a T maze located within a set of curtains that excluded visual cues from the rest of the laboratory. Four objects were hung around the periphery of a T maze inside the curtains, and the animal was taught to choose an arm of the maze. The four cues were rotated from trial to trial. Place fields always rotated with the cues (see Fig. 11–12B, later, for a similar result). Removal of one or more cues on each trial showed that a few fields depended on one specific cue, but most were maintained so long as any two of the four cues were present. Muller and colleagues (Muller and Kubie, 1987) showed similar cue dependence of place fields recorded from rats foraging for food in cylinders or rectangular boxes. A single white cue-card fixed to the wall exerted control over the angular location of the field but not its distance from the wall. Rotation of the card rotated the fields by the same amount. Neither the shape of the field nor its distance from the walls of the box was affected, but there was a slight loss of place specificity.

The location of the controlling cues within the environment can be important. Cressant et al. (1997) found that three objects placed in a triangular configuration in the center of a cylinder did not control the orientation of place fields, but they did do so when these same objects were moved to the periphery. This result was interpreted as suggesting that distal peripheral landmarks are more important for fixing the orientation of the place fields, perhaps because the animal's movement relative to centrally placed local cues causes constant reordering of their positions relative to each other within the egocentric frameworks of the distal sensory modalities, whereas movements relative to distal cues do not. Central object A is sometimes seen to the left of central object B and sometimes to its right.

If the angular orientation of a place field in a symmetrical environment is controlled by distal cues, what determines its shape and size and its radial distance from the walls of the environment? The first clue came from an experiment (Muller and Kubie, 1987) that showed that doubling the dimensions of a cylinder or a rectangular box had two effects: In many cells, the fields remapped to unpredictable shapes and locations; in about one-third of the place cells, however, field size increased to about twice the original size without significant effect on field shape. This is less than the fourfold increase that would have represented an exact proportion to the increased area of the recording chamber. Factors other than simple scaling seemed to be at work. A related experiment (Wilson and McNaughton, 1993b) looked at field changes after a partition was removed, converting a square box to a rectangular box whose long dimension was twice that of its short one. Here cells with fields in the square were maintained, whereas other cells began to fire in the new section of the box. It appears, then, that under some circumstances the field sizes are influenced by the size of the testing environment, but under others they are not. The factors controlling this difference are still unclear, but they may relate to whether the animal is, or is not, in the box when the change is made. If in it, the animal is better placed to see the change happening in front of him, which triggers exploration. Under these circumstances the existing fields are maintained intact and new ones created to represent the new part of the environment. However, when the animal is removed from a recording chamber with which it is familiar and placed in a dilated version of it, the system may be tricked into treating this as the "same" environment with the resulting alteration of existing fields.

O'Keefe and Burgess (1996) employed the second procedure to look at the effect of changing box size and shape on established place fields. Combining features of the preceding studies, the same cell was studied while the rat foraged for food in four differently shaped boxes: two squares, one with double the dimensions of the others; and two rectangles, each with its small side taken from the dimensions of the small square and its large side from the large square (Fig. 11–9). One

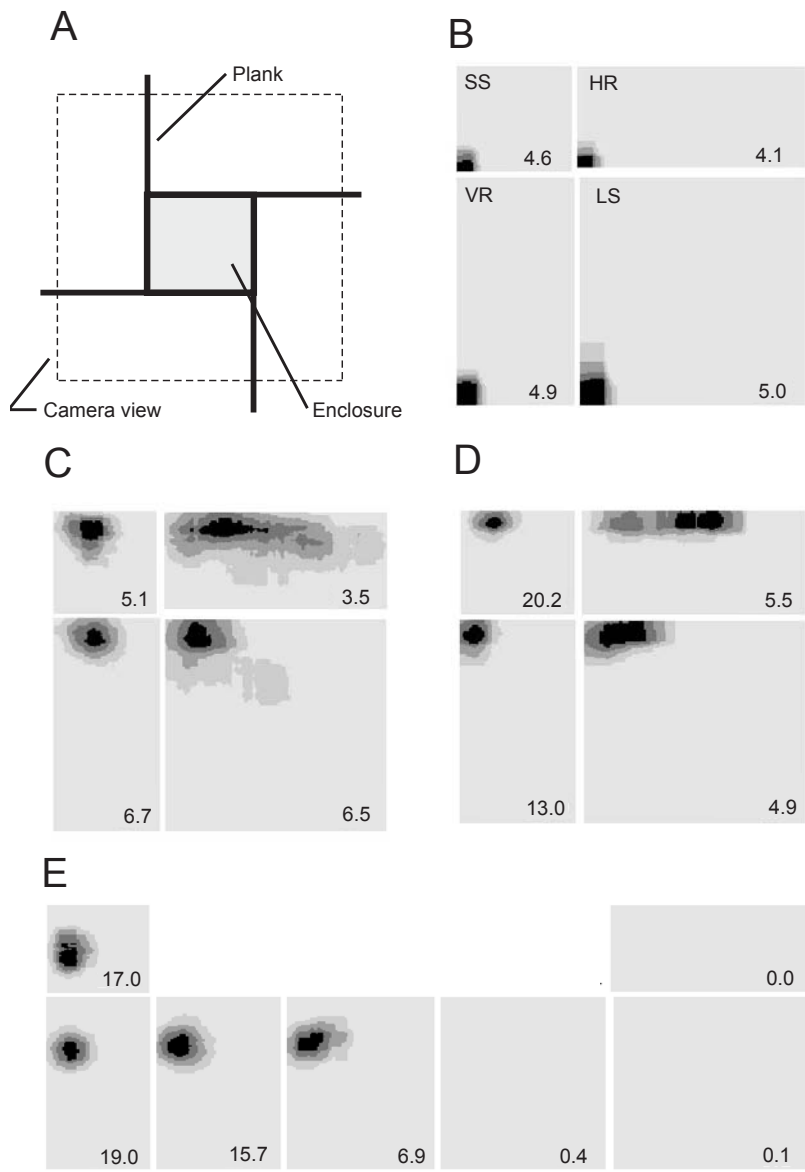


Figure 11–9. Place fields in four rectilinear enclosures reveal that each field is comprised of several subcomponents. *A*. Layout of the testing area shows how the small square (61 cm^2) is constructed from four wooden planks set on their edges. The same set of planks can be joined in different configurations to make rectangular (61 by 122 cm) and large square (122 by 122 cm) enclosures. *B*. Place field with strong inputs from the left and bottom walls does not change its relative location in the various boxes. *C*. A different place field with strong inputs from the top, left, and right walls is elongated in the horizontal rectangle. *D*. A field similar to that shown in *C* breaks into two components in the horizontal rectangle. *E*. A cell with fields in the small square and vertical rectangle (two left-hand panels) shows steadily diminishing firing rates in the boxes intermediate to the vertical rectangle and the large square. Numbers in each panel represent the peak field firing rate (shown in black). (*Source*: After O'Keefe and Burgess, 1996, with permission.)

rectangle was oriented with its long side parallel to the long dimension of the testing laboratory and the other with its long side perpendicular to this dimension. The same construction materials were used, and the floor covering was interchanged frequently, eliminating local olfactory and tactile cues as determinants of field shape and location. The important finding was that for most cells the field location and shape was determined by the distance to two or more walls usually of the box but, more rarely, of the room itself. Some cells were controlled by the distance to two box walls in orthogonal directions (e.g., the south and west walls) (Fig. 11–9B); others were sensitive to the distance to three or four walls (e.g., Fig. 11–9C,D). The expansion of field width along one dimension sometimes resulted in double peaks or even the apparent splitting of a field into two (Fig. 11–9D). Some cells (e.g., Fig. 11–9E) that had a field in one box (vertical rectangle) but were silent in an adjacent box (big square) could be shown to reduce their rates in an incremental way in boxes intermediate to these two. A small number of cells had one of their field dimensions determined by the distance to the room walls and the other by a wall of the box. One important observation was that no cells used the framework of the shape of the box itself. If this had been the case, one would expect to see cells with fields that rotated by 90° in the two rectangular configurations or that fired only in the small and large squares. These patterns were never observed. The experiment shows that in environments in which the animal has sufficient distal information to fix its directional orientation it is not the geometry of the testing box that is being captured by the place field but the intersection of distances to two or more elongated features of the environment (see Chapter 13 for a further discussion of the geometry of the spatial representation and Chapter 14 for a discussion of a computational model that accounts for these findings).

Gothard and her colleagues obtained similar results (Gothard et al., 1996b). Place cells were recorded while the rat attempted to find a reward hidden at a fixed distance and direction from two large objects. Each trial began with the rat leaving a small box and ended when it returned to it where it was also rewarded. The location of the box, like that of the objects, was moved around the room from trial to trial. Cells were found that fired as the rat entered or exited the start/goal box; others fired relative to one or other of the goal objects; and a third group maintained their field location relative to the framework of the room, regardless of the location of the goal or start box. This study complemented that of Burgess and O'Keefe in showing that relative location to objects or walls is important. It also reinforced the notion that different place cells recorded at the same time may use two or more frames of reference in a single environment.

In another study, Gothard et al. (1996a) examined the "frame of reference" issue further by recording cells in rats trained to run back and forth on a linear track for food reward at each end. The goal at one end of the track remained fixed relative to the room, whereas that at the other end was a box that could be moved between one of five locations along the track from trial to trial. Recall that on linear tracks or narrow-armed radial mazes many place cells tend to have directional fields. In the present experiment just over 42% fired in one of the two directions, another 45% in the opposite direction, and just over 12% in both directions and these usually did not bear a close spatial relation to each other. Place fields closer to the goal box were tied to it and moved with it, whereas those closer to the other end of the track tended to stay fixed with respect to the room and the fixed goal location. A number of cells were influenced by both the moving box and the fixed goal. In these cases, as the box was moved farther away from the other end of the track there was evidence for the stretching and splitting of the fields described by O'Keefe and Burgess in their expanding two-dimensional world.

Two interpretations of these results are possible. Gothard and her colleagues suggest that there are two representations or charts of the space on the track: one related to the framework of the box and the other to the room. As the animal runs along the track, it switches from one map or chart of the environment to the other. The animal was, in some sense, treating this single runway as two separate environments: a world in which it was located relative to the goal box while it was in its vicinity and a world in which it was located in the room frame as it got farther from the moving box. These authors further interpreted the constant distance of the box- related fields from the box as evidence for a path integration mechanism.

O'Keefe and Burgess favor the alternative view: that under the conditions of these experiments, the normal map-like omnidirectionality and connectedness between place cells has been lost, and they are essentially acting as isolated individuals. Each individual cell is influenced by the box and the fixed goal in proportion to the distance of its field from each. Cells close to the box are almost entirely controlled by a box, whereas those far from it are controlled by the fixed room cues. The distance from each set of cues could be computed on the basis of sensory inputs from that cue or from path integration signals (see Chapter 14, Section 14.3 for a more detailed discussion of this model).

Fenton et al. (2000a,b) investigated the problem of cue-control of place fields in a different experimental paradigm. They recorded while rats foraged for food pellets in cylinders with two distinct cue cards on the wall and varied the angle between the cards by small amounts. Removal of either card had no effect on place fields, and rotation of the remaining card caused equal rotation of the place fields, demonstrating independent control over the fields by each card. In contrast, changing the angle between the cards from 135° to either 160° or 110° caused subtle changes in the location and shape of the fields. In general, fields shifted and transformed in the direction of card movement. Fields closer to the cards were more influenced than those farther away. An interesting finding was that the peak firing rate was highest for the original card configuration and decreased as the cards were brought closer together or placed farther apart. Although carried out under different experimental circumstances and interpreted somewhat differently by the authors, these results are broadly in line with those of O'Keefe and Burgess and of Gothard et al. in showing that place fields are determined by distances from specific environmental features.

An overview of all the experiments reviewed in this section suggests that there are at least two independent exteroceptive determinants of place fields. The directional orientation of a place field in a symmetrical enclosure is controlled by polarizing distal cues in the room or at the periphery of the testing box. On the other hand, the location and shape of the field is determined by the distance of the animal from two or more walls or by other features of the environment. In addition, it is clear that interoceptive cues can influence place field shape and location, which we discuss in the next section.

11.7.7 Idiothetic Cues Can Control Place Fields

Place fields can also be located on the basis of idiothetic cues generated by an animal's own movements, which consist of interoceptive stimuli such as head, neck and limb proprioceptors, vestibular signals, and motor reafference signals from intended movements together with exteroceptive stimuli derived from optic flow and whisker-detected airflow. We noted earlier that rats blind from birth have completely normal place fields when tested as adults (Save et al., 1998). Detailed analysis of the behavior of these animals suggested that they used olfactory and tactile information to recognize objects in the recording environment and then "updated" the locations of place fields on the basis of interoceptive cues associated with their own movements. Whereas some 80% of place cells in the sighted control rats in this study fired in the appropriate location before the animal had made contact with any of the objects, none of the place cells in the blind rats did so. However, after contact with one of the objects, 60% of cells fired appropriately in a single place, and 75% did so after

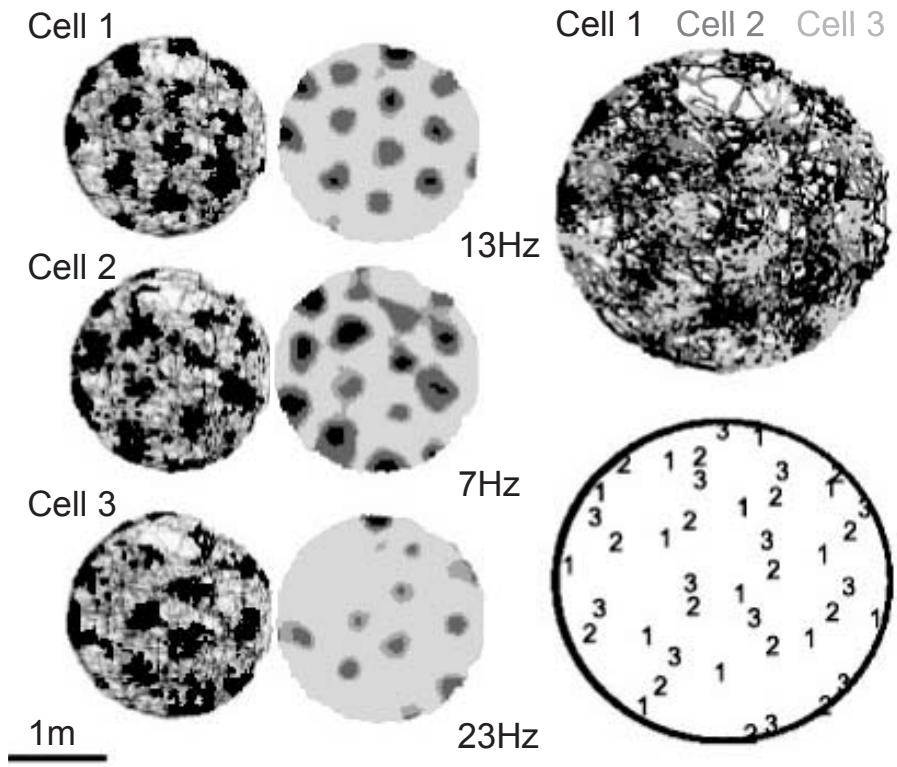


Figure 11–10. Entorhinal cortex grid cells. Raw data (left) and firing fields (right) for three grid cells. Note the regularity of the firing, which forms a triangular grid pattern in each cell. Numbers indicate the peak rate. Peaks of the three cells (top in grayscale, bottom as numbers 1–3) are slightly offset from each other so when superimposed they tend to tesselate the space. (*Source*: After Hafting et al., 2005, by permission.)

exploring two objects. Completely normal firing patterns were seen after contact with all three objects.

Maintaining spatial specificity in this way represents a form of "memory." It is presumably an "active" or "working" memory that is maintained by some form of inertial navigation or path-integration mechanism. Once an animal had identified its location in an environment on the basis of exteroceptive cues, a path integration mechanism could continuously update its position by calculating the changes in distance and direction from the original position resulting from the animal's movements. This type of mechanism might explain the short-term memory properties of place cells, which are discussed in greater detail in Section 11.8.

Further evidence for idiothetic influences on place fields comes from experiments in which animals have been passively rotated. As we saw in the experiment of Hill and Best, rotating animals deprived of vision and audition before placing them on a radial arm maze results in the rotation of place fields. Several groups (Sharp et al., 1995; Wiener et al., 1995; Bures et al., 1997; Jeffery et al., 1997) have studied the effect of rotating the testing enclosure, or parts of it, with the animal inside it. Sharp et al. (1995) rotated the cylinder walls or floor separately at a fast or slow speed and in the light or dark. It was assumed that the slow rotations were below the speed detectable by the vestibular system and would not be compensated for: The fields rotated with the rotating enclosure relative to the laboratory frame. Both visual and vestibular signals influenced the angular location of place fields to about the same extent. Slow rotation of the rat in a separate chamber outside of the testing enclosure also led to rotated place fields when the rat was replaced into the enclosure (Jeffery et al., 1997). In both experiments the rotations were brief, and their effects were subsequently assessed in a stationary environment. Similar findings with head direction cells (Blair and Sharp, 1996) raise the possibility of a coupling between the spatial localization and head direction system. The interactions between the two are discussed in Section 11.10.

A movement-generated estimate of distance and direction would explain the instances of place cell stability in the shift from light to dark in memory tasks and following lesions that limit access to exteroceptive cues. The source of this "path-integration" signal is either input from interoceptive cues or "collateral discharges" arising from motor structures actively generating movements. This information arrives at the hippocampus via several routes. Information about the animal's heading direction is carried by the head direction cells and enters the hippocampal system through the presubiculum projection to the medial entorhinal cortex. We discuss the properties of the head direction cells in greater detail in Section 11.9 and their interaction with the place cells in Section 11.10. When it arrives to the medial entorhinal cortex, head direction information is combined with distance information in a set of grid cells (Hafting et al., 2005). One of the functions of the grid cells is to convey information about distances in specific environmental directions. Each grid cell fires in several locations in an environment, with the locations forming a regular pattern as though they were nodes on a triangular grid (Fig. 11–10; see also Fig. 11–21D, color centerfold). Different cells recorded at the same location have the same grid spacing and orientation relative to the environment. They differ, however, in the loca-

tion of the nodes such that the firing peaks of one cell are slightly shifted from those of its neighbor. The multiple interdigitated fields of several such cells together cover the environment (Fig. 11–10, right). For each cell, the size of the grid appears to be independent of the size or shape of the environment. The orientation of the grid relative to the environment, however, is dependent on the location of a polarizing visual cue on the wall of the enclosure in much same way as are the postsubicular head direction (Taube et al., 1990b) and the hippocampal place cells (Muller and Kubie, 1987). It seems likely, then, that the orientation of each grid is controlled by the head direction cells of the presubiculum. Cells located at increasing depths from the postrhinal border form grids whose nodes have fields of increasing size and spacing. In summary, the grid cells probably do not form a map of a given environment by themselves but provide the Euclidean distance and direction metric postulated by the cognitive map theory of hippocampal function (O'Keefe and Nadel, 1978). This idiothetic information is combined with sensory information about each environment to create the specific map of that environment in the hippocampus.

To maintain the appropriate distance between grid points as the animal moves around the environment, the grid cells must take its speed into account. Information about speed may arise in posterior hypothalamic areas that are known to provide theta-related inputs to the hippocampus and where electrical stimulation produces running or jumping, with the speed of the movement increasing as a function of the stimulation intensity (Bland and Vanderwolf, 1972). Integration of a speed signal over time as the animal ran in a constant direction would give a measure of distance traveled during that time. There is direct evidence that information about an animal's speed of movement is available to the hippocampus. A small number of nonprincipal "speed" cells have been recorded in the hippocampus. The firing rates of these cells directly correlates with the animal's speed of running regardless of direction or location (O'Keefe et al., 1998). Second, higher running speeds tend to increase place cell firing rates (McNaughton et al., 1983a; Wiener et al., 1989; Zhang et al., 1998). Furthermore, the firing frequencies of many place cells from a stationary animal running in a wheel located in the place field were positively correlated with the speed of running (Czurko et al., 1999; Hirase et al., 1999). Some cells asymptoted within the range of speeds reached in the wheel. Cells that wholly or partially code for speed have also been found in the presubiculum (Sharp, 1996), which projects to the hippocampus via the medial entorhinal cortex. In all, we can conclude that information about both an animal's heading direction and its speed of movement through the environment is available to the hippocampal formation, and this information most likely is combined in the medial entorhinal grid cells.

The path integration system suffers from the fact that errors accumulate rapidly as the animal's heading direction and distance from the original location are continuously updated. On the basis of data from several studies in which attempts were made to remove exteroceptive information after initial localization or make it irrrelevant, it has been estimated that place fields can be maintained for only 1 to 2 minutes on the basis of path integration information alone (Save et al., 2000).

11.7.8 Are Place Cells Influenced by Goals, Rewards, or Punishments?

If place cells are part of a navigational system that can guide an animal to locations containing desirable objects such as food and water or to avoid dangerous places, one might expect to find goal cells whose activity was sensitive to goal location or navigation to a goal or, more generally, a change in place cell firing following a shift in the valence of parts or all of an environment. These "goal" or "valence" cells might exhibit any of several characteristics: The location of their place fields might alter when the valence of the environment changes, and it might happen in a way that reflects the goal location in an environment; there might be a disproportionate number of place cells with fields located at reward sites; or there might be nonlocational cells whose firing rate depended on which goal was being sought or navigated toward. Several experiments have searched for the first type by shifting goal locations: Some reported no effect (O'Keefe, 1976; Speakman and O'Keefe, 1990; Zinyuk et al., 2000), while others found concomitant place field shifts (Breese et al., 1989; Kobayashi et al., 1997; Hollup et al., 2001). Here we need to bear in mind that rewards have both sensory and incentive properties, and field shifts might be due to the former rather than the latter. Three recent studies employed experimental paradigms in which the goal was not marked by any physical stimulus. The rats in the Hollup et al (Hollup et al., 2001) experiment searched for a hidden platform in a modified annular watermaze and the fields of some cells shifted when the goal location was changed. Kobayashi used rewarding brain stimulation of the hypothalamus in order to designate particular locations as goals and reported that six of 31 place cells either developed additional new fields in the rewarded location or shifted their place field to that location {Kobayashi *et al.,* 1997}. Finally, Zinyuk et al. (2000) used a paradigm similar to that of Kobayashi et al. but rewarded the animals with random food pellets rather than electrical brain stimulation; they found no changes in place fields when the reward location was moved. Because there was no physical reward at the goal locations in these experiments, the explanation of the discrepancies cannot rely solely on the perceptibility of the goal or its role as a sensory cue. We note that many of the cells that shifted fields in the Kobayashi et al. experiment had very low (< 1 Hz) place field rates, below those normally accepted in these types of experiment. These considerations, however, do not apply to the Hollup findings (Hollup et al., 2001).

Moita et al. (2004) used aversive electrical stimulation of the orbit of the eye to condition rats to an auditory conditioned stimulus (CS) or to the background context. They found that as a result of training some place fields were altered. More place cells changed their firing fields in the context than in the cue-conditioned group and more in the conditioning box than in a different control box. Furthermore,

they found that following cue conditioning the place cells began to fire with a short latency response to the auditory cue but only if the animal was in the place field of that cell when the CS was delivered (Moita et al., 2003). This result is discussed further in Section 11.11.3.

Evidence for the second type of goal representation comes from Hollup et al. (2001), who found twice as many cells representing the unmarked goal in their annular watermaze than would be expected by chance. The third type of active goal cell was reported in a study of temporal and frontal cells recorded in human epileptic patients while they played a taxicab game in which they searched for passengers in a small virtual reality town and took them to their destinations in the form of specific storefronts (Ekstrom et al., 2003). About one-fifth of the cells recorded were sensitive to the goal being sought, almost three-fourths of which responded while searching for a specific location. An additional 7% were involved as the subject searched for more than one store and 22% while searching for passengers. A small number of cells showed a place by goal interaction, firing in a particular location if the subject crossed it en route to a particular goal. These goal cells were located throughout the temporal and frontal lobes and not concentrated in the hippocampus or parahippocampal gyrus as were the place and spatial-view cells (see below) recorded in the same study.

It seems clear, then, that changing the valence of an environment or regions within that environment can cause the firing fields of some place cells to shift. The functional significance of this is not clear, unless it turns out that the cells that changed had fields where the animal was located during the occurrence of the rewarding or punishing event. At present, it is not clear exactly how goals are represented or whether goal location is stored in the hippocampus or outside of it. When no distal sensory information is available, the sensory qualities of rewards may be used to locate place fields. In a "richer" environment, food and water may be "categorized" as objects that are potentially unstable over time. Food sources become depleted and new ones become available, and this happens over a time scale quite different from that of other cues such as trees or bushes. Nonetheless, the locations of reward have to be stored somewhere. However, on balance, the experimental results, although not conclusive, suggest that the information about goal location is probably not stored in any simple fashion in the CA3 or CA1 areas of the hippocampus itself. Regions such as the lateral septum subiculum, nucleus accumbens, or prefrontal cortex, which receive inputs from the hippocampal formation, might be the site of such place-reward cells. In support of this hypothesis is a recent study strongly suggesting that one type of goal cell can be found in the prelimbic/infralimbic areas situated in the rat's medial prefrontal cortex (Hok et al., 2005). Rats were trained in a cylinder to spend a short period of time in a localized but unmarked region to receive a pellet of food elsewhere. The pellets dropped from an overhead dispenser into a localized zone but then bounced elsewhere, ending up all over the enclosure. There were thus two localized but unmarked zones, a goal zone, which upon entry triggered the reward, and a landing zone, where the pellets initially dropped. Most pellets, however, were retrieved and eaten elsewhere. One-fourth of the cells in the prelimbic/infralimbic areas had place fields and these were about three to four times larger than those found in the hippocampus. The centers of a large percentage of these fields were concentrated in the trigger (36%) and landing (42%) zones. Rotating the cue card on the wall of the enclosure rotated the animal's representation of the trigger zone location, as judged by its behavior, but had no effect on the landing zone place fields. Conversely, changing the location of the pellet dispenser and thus the location of the landing zone caused a shift in the landing zone fields to the new area but had no effect on the behavioral approach to the trigger zone. The large size of the prefrontal place fields and the concentration of their centers at goal regions to which the animal navigated make them much better potential candidates for goal cells than hippocampal neurons. They bear some resemblance to the goal cells postulated in the models of spatial navigation of Burgess and colleagues (Burgess et al., 1994; Burgess and O'Keefe, 1996) (see Chapter 14, Section 14.4).

11.7.9 Temporal Patterns of Place Cell Firing

Complex-spike cells do not fire in a continuous pattern when the rat runs through a place field but burst with a frequency close to that of the EEG theta rhythm. In several studies (Fox and Ranck, 1975; Buzsaki et al., 1983) recordings were made while the rats were running on a treadmill. Unfortunately, pyramidal cells do not fire at their maximal rate in such a situation unless the animal is in that part of the environment that the cell represents (its place field). On a treadmill, CA1 complex-spike cells often fire at a low rate and display a preference for the positive peak of the dentate gyrus theta. Phase correlates have also been studied on narrow tracks as the rat runs through a cell's place field (O'Keefe and Recce, 1993; Skaggs et al., 1996; Harris et al., 2002; Mehta et al., 2002; Yamaguchi et al., 2002; Huxter et al., 2003), and a different, more interesting pattern has emerged. O'Keefe and Recce first noted that instead of remaining correlated to a constant phase of the EEG theta cycle, as on treadmills, the phase of firing changed in a systematic way. When the rat entered the cell's place field, the cell began firing at a particular phase of theta. However, as the animal progressed through the field, the bursts of unit firing occurred on an earlier phase of each successive theta cycle (Fig. 11–11C). The phase of firing correlates with the animal's location in the place field (Fig. 11–11B,D), and this correlation is higher than for time after entry into the field (Fig. 11–11E) or instantaneous firing rate (Fig. 11–11F). This *phase precession* phenomenon is partly explained by cells firing rhythmically at a frequency higher than that of theta. Dentate granule cells also phase shift but by a lesser amount, and the onset of firing is at an earlier phase of the theta cycle than that seen in the CA1 cells (Skaggs et al., 1996).

Is there information in the phase correlate of place cell firing beyond that contained in the firing rate? If there is, does it add greater precision to the locational information contained in the rate, or are the two coding for independent variables

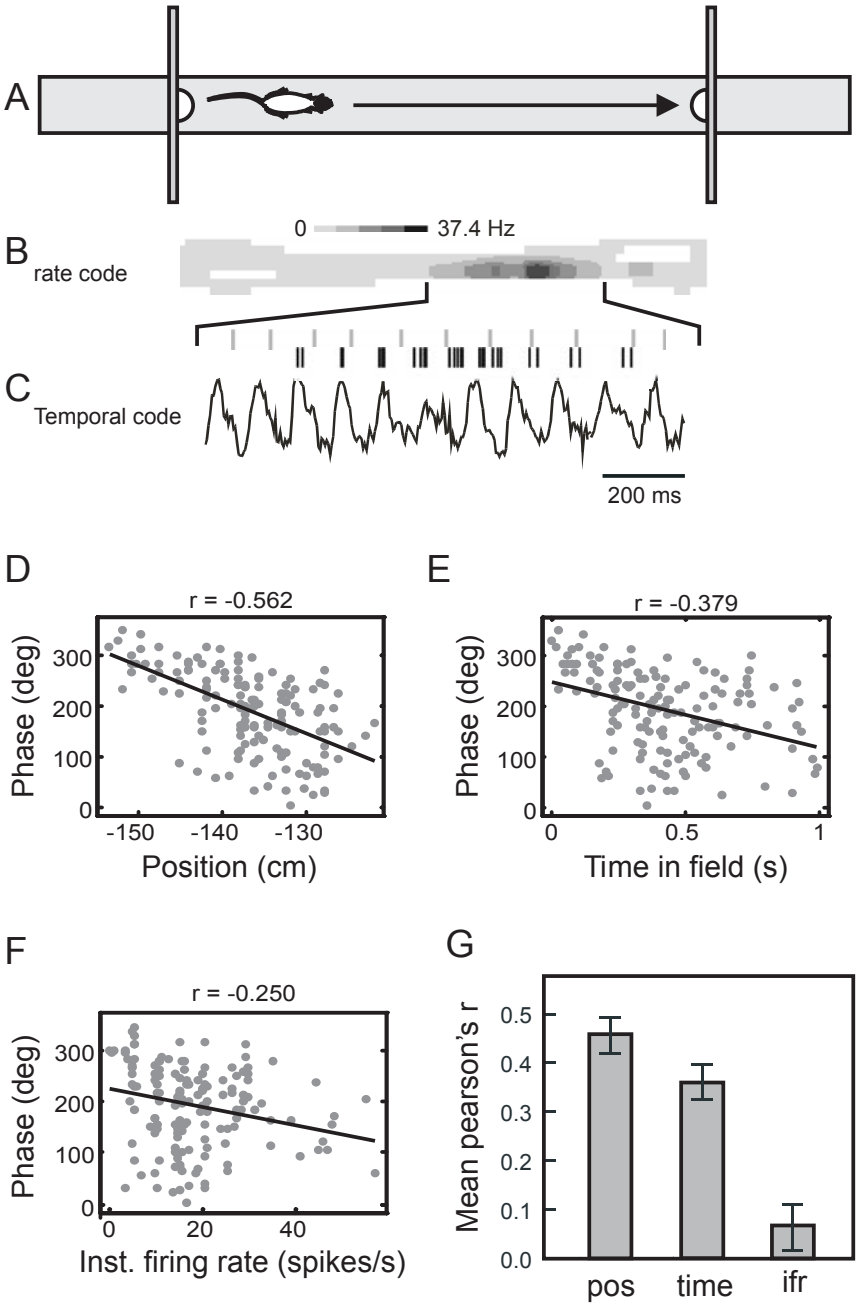


Figure 11–11. Temporal coding of location in hippocampal pyramidal cells. *A*. Rat shuttled from left to right and then back again to receive a food reward at each end wall of a linear track. *B*. Firing rate field map of the cell based on multiple runs. *C*. Spikes on a single run through the field show phase precession, moving to earlier phases of the EEG theta cycle with each successive wave. Spikes are shown in black; lighter tick marks above identify the zero crossing point of the EEG. *D*. Plot of theta phase versus the position for multiple runs through the field of an example cell. The correlation between phase and position (*D*) is higher than the correlation with the time in field (*E*) or the instantaneous firing rate (*F*) for an average cell. *G*. Correlation of phase with position, time, and instantaneous firing rate across a population of 94 place fields. Best correlation is with position. (*Source*: After Huxter et al., 2003, by permission.)

(O'Keefe, 1991)? Jensen and Lisman (2000) have used data collected by Skaggs et al. (1996) and shown that, with certain assumptions, the accuracy of locating an animal's position on a narrow track can be increased by more than 40% when phase is taken into account in addition to rate. In this view, phase acts like a vernier, permitting finer-grain location of the animal within the place field. Evidence for the dual coding hypothesis comes from a linear track study showing that phase and rate could vary independently (Huxter et al., 2003). The rate within the field varied as a function of the animal's running speed, and phase coded for the proportion of the place field the animal had traversed. Changing the size of the field by changing the distance between the walls at the ends of the track increased the rate of phase precession to maintain the correlation between phase and a fixed proportion of the total field size. Whether phase and rate can represent variables other than location and speed is an open question. It has been known for some time that the firing rate in the place field can vary considerably from one traverse to the next (see above), and there is some evidence that different odors located in a place can be coded by different rates (Wiebe and Staubli, 1999; Wood et al., 1999a). Some evidence in support of the idea that phase can represent a nonspatial as well as a spatial variable comes from the running wheel experiments of Hirase et al. (1999) and Harris et al. (2002). They found that whereas the rate of firing of the place cells was a function of the animal's speed of running, the phase with respect to theta was relatively constant at low firing rates but occasionally changed at higher

rates in the absence of changed location. One variable that caused a change in phase in some cells was the directional orientation of the wheel, and thus the animal, to the room.

One important consequence of the phase precession effect is that the spatial overlap between the firing fields of two place cells is represented within each theta cycle by the amount of time the bursting pattern in the cell of the first field entered precedes that of the second field. This temporal difference can be demonstrated in the cross correlation between the firing patterns of the two cells (Skaggs et al., 1996). The farther apart the field borders, the larger is the temporal gap between firing peaks within each theta cycle.

Part of the phase precession effect might be explained by a coupling between the amount of cellular depolarization and the time of firing of the cell (Harris et al., 2002; Mehta et al., 2002). As the animal advances farther toward the center of the field, the cell would be more depolarized, fire more spikes on each cycle, and begin firing at an earlier phase of the cycle. This cannot be the whole story, however, as the phase continues to precess in the latter part of the field when the firing rate (and presumably the level of depolarization) is falling. An alternative explanation for phase precession invokes a mechanism based on the interaction of two theta-like waves (O'Keefe and Recce, 1993; Lengyel et al., 2003). These waves would normally be of the same frequency but 180° phase-reversed so that, when added together, they cancel each other. A slight increase in the frequency of one of these oscillators relative to the other would result in an interference pattern when the two waves are added together. If it is assumed that the extracellular EEG represents the lower frequency of the two oscillators, and that place cells fire on the peaks of the interference pattern, the precession phenomenon would be seen. The dual oscillator model predicts that the size of the place field is dependent on the difference between the frequencies of the two oscillators. The closer the two frequencies are together, the larger is the field. An article by Maurer et al. (2005) provides experimental evidence in support of this predicted relation between field size and the oscillatory frequency of the pyramidal cell. They showed that the average sizes of place fields are not uniform along the long (septo-temporal) axis of the hippocampus but increase in the temporal direction. In parallel with this field expansion, place cells in the dorsal hippocampus have a higher (intrinsic) frequency of oscillation than those located more ventrally despite no differences in the frequency of the EEG theta or the theta cells in the two regions. The dual oscillator interference model suggests there is a causal link between these two phenomena, with the dorsoventral gradient in intrinsic frequency (higher in the dorsal hippocampus) leading to the gradient in the spatial extent of the firing fields (smaller fields in the dorsal hippocampus).

The origin of the two separate but interacting theta rhythms and the site of their interaction are unknown. The latter may be in the hippocampus proper. One may be internal to CA3 and CA1 pyramidal cells, which can oscillate under the cholinergic influence of the septal nuclei. The other theta rhythm might arise from the direct projection from the entorhinal cortex to the CA3 and CA1 areas. Kamondi et al. (1998) studied the oscillations inside the dendrites of CA1 cells during theta and showed that they are 180° phase-shifted with respect to those in the soma, as predicted by the wave interference hypothesis. They also found that depolarization of the dendrites causes an increase in the frequency of these oscillations. This and other models of the phase shift are considered in greater detail in Chapter 14.

Alternatively, the site of phase shift generation may ultimately be found in areas outside of the hippocampus but projecting to it, such as the entorhinal cortex. A study by Zugaro and colleagues (2005) lends strong support to the idea of an extrahippocampal origin. They trained rats to shuttle between two ends of a linear track and recorded the phase precession in hippocampal place cells. During some runs through the place field, a single 0.1 ms duration electric shock was delivered to the fibers of the ventral hippocampal commissure. This had the effect of resetting the phase of the hippocampal theta and inhibiting all recorded cells for approximately 200 to 250 ms. They found that when the cells recovered and began firing again they did so at the correct phase of the (reset) theta to code correctly for the animal's location at that point. This finding appears to argue against a primary role for the hippocampus itself in the phase precession and points in the direction of structures afferent to the hippocampus that might not have been affected by the brief intervention. The most likely source of this preserved positional information is the entorhinal cortex, which has direct projections to the CA3 and CA1 pyramidal cells as well as to the dentate granule cells and which was probably not affected by the electrical shock to the ventral hippocampal commissure. Evidence that it escaped comes from an observation by Zugaro et al. They looked for but did not see a rebound evoked potential in the hippocampus in response to the shock, suggesting that the entorhinal-hippocampal pathways were not greatly affected via the CA1-to-entorhinal return pathway. As we have seen, the medial entorhinal cortex contains grid cells that are theta-modulated and might be able to identify changes in the animal's location in the environment independent of the hippocampus.

11.7.10 Place Fields in Young and Aged Animals

In altricial animals, which depend on their mother after birth (such as the rat), the brain and in particular the hippocampus continues to develop for considerable periods of time after birth. For example, the dentate gyrus continues to generate large numbers of new granule cells for several weeks after birth and at a lesser rate throughout life (see Chapter 9), and inhibitory processes do not reach their full adult level of functioning until postnatal age 28 days (P28). Tests of spatial memory and navigation suggest that the hippocampus is not fully functioning until P40. Schenk (1985) trained rats of different ages on two versions of the Morris watermaze: the standard version in which the platform was hidden and the animal had to use distant spatial cues throughout learning and a version in which the platform was hidden but its location was marked by a visible proximal cue. This meant the task

could be learned by a hippocampal or a nonhippocampal strategy. Which of these methods was used was probed by trials in which the proximal cue was removed. Schenk found that animals aged P28 took longer to learn a new platform task than did adults and reached adult levels of performance only at ages greater than 40 days. Animals at age P35 could perform the version of the task with the proximal visual cue; but when the cue was removed, they failed to show transfer to the distal cues. This finding suggests that they had developed all of the abilities necessary to solve the watermaze task except formation of the distal cue-based spatial representation needed to navigate to the goal in the absence of the visible proximal cue. A longitudinal study in which rats were originally trained on the hidden platform version of the watermaze at age 21 and then given daily trials for 69 days put the development of spatial navigation ability somewhat earlier (Clark et al., 2005). They found that the performance of the animals rose above chance level after the second day of training and steadily increased over the next 10 days to asymptote at adult levels at approximately P35. It is reasonable to conclude that the ability to form allocentric spatial memories and to perform spatial navigation does not fully develop until around 35 to 40 days of age in rats.

In the only study of the development of place cells in young animals, Martin and Berthoz (2002) recorded complex-spike cells from animals at ages P27, P29, P34, P40, and P52 and above while they were searching for random food pellets on an open field platform. They found that the place fields of younger animals were larger and more diffuse than those of adults and became more compact with age, finally reaching adult values at about P52. Furthermore, the place fields recorded on successive 10-minute trials were unstable in younger animals, shifting location from one trial to the next, and reached adult levels of stability only at age P52. In contrast, a small number of head direction cells, which signal the orientation of the animal's head relative to environmental cues (see Section 11.9), were recorded from the cingulum at P30 and appeared to be indistinguishable from those reported in the adult. Previous work on the development of hippocampal theta had suggested that theta waves could be recorded on the hippocampal EEG as early as P10, developing to adult levels over the next 2 weeks (Leblanc and Bland, 1979). It seems reasonable to conclude from both the behavioral and the electrophysiological data that the rat hippocampus continues to develop over the first month of life and reaches the mature adult level of functioning only at ages 40 to 50 days after birth. The head direction and the theta systems, on the other hand, appeared to be functioning at earlier ages, reaching maturity by P30.

At the other end of the life cycle, when animals get older, their spatial learning abilities decrease (for a review see Rosenzweig and Barnes, 2003) and their hippocampal place cells appear to undergo changes. There seems to be little overall agreement as to whether place fields get larger or become less reliable as animals age. In the first study that compared the sizes of place fields in adult and aged animals, it was reported that the older animals had larger firing fields (Barnes et al., 1983). Subsequent studies, however, have not been able to replicate this change but have found that the field sizes of the aged animals were normal or, under some circumstances, even more compact than those of the adult controls (Mizumori et al., 1996; Tanila et al., 1997a). There is also disagreement as to whether the place fields in aged animals are more or less reliable than in younger animals. Whereas Barnes and colleagues (1983, 1997) found that the CA1 place fields in aged animals are less reliable, Tanila et al. (1997a) found that, if anything, they were more reliable. Mizumori et al. (1996) found that they were more reliable in the CA1 pyramidal cells but less reliable in the hilar cells. Barnes et al. (1997) has suggested a reconciliation of these apparently conflicting results. They also found no difference in field size between groups but found that older animals spontaneously remapped between trials in the absence of any environmental changes. In the earlier Barnes et al. study, data were averaged across trials. If spontaneous remapping occurred between trials, it might lead to the impression that the firing fields were more dispersed and less reliable. The cause of the spontaneous remapping is not clear but may signal weakening of control of the head direction system over the hippocampal place fields with age. Spatial behavior in the watermaze also appears to reflect a decrease in the consistency of the spatial representation in older animals in that they sometimes head directly for the hidden platform and on some trials take much longer to get there, resulting in a bimodal distribution of scores (Barnes et al., 1997).

Tanila and colleagues (1997a) looked at whether cue control over place fields changed with aging. Aged animals were divided into spatial memory-impaired and spatial memory-unimpaired groups following testing in the Morris watermaze. They were then trained on the four-arm radial maze, with both distal visual cues and local visual, tactile, and olfactory cues available on the arms of the maze. Their place cells were then recorded. Probe trials in which either set of cues was rotated or scrambled were also conducted to determine which set of cues was controlling the fields. About two-fifths of the fields of young animals remapped when the distal and local cues were rotated by 90° in opposite directions, and approximately another third followed the distal cues. A smaller percentage (about one-fifth) followed the local cues. In contrast, more than three-fourths of the place fields in the aged animals with memory deficits followed the distal cues with fewer than one-fifth remapping. Scrambling the distal cues caused the latter group of place cells to become responsive to the local cues, showing that the predominant influence of the distal cues in the double rotation probes was not due to a sensory deficit. It appears as though the cells of the younger animals were relying on all of the cue information, whereas those of the memory-impaired aged animals were selectively attending to the distal visual cues. It is not clear why this shift should occur with age or how to explain it. It is especially puzzling because the aged animals were selected on the basis of their deficits in the Morris watermaze, which requires attention to

distal cues for its solution. The authors noted that all of the animals had adopted a strategy of entering adjacent arms of the maze to solve the task and therefore may not have been using a spatial strategy. Whether forcing them to use a spatial strategy would have made a difference is not clear.

Rosenzweig and colleagues (2003) looked at environmental control of place fields in a different way and compared it with the animal's performance in a spatial task. They trained animals in a task where they (and their place fields) could locate themselves within one of two frameworks (Gothard et al., 1996a). The goal at one end of a linear track was fixed relative to the room cues, whereas the goal at the other end was located inside a box that moved along the track from one run to the next. Place fields located close to the moving box tended to move with the box, whereas those distant from it stayed fixed relative to the room framework. As the animal ran from the box to the fixed end of the track, the population of cells could be said to switch frameworks. Rosenzweig et al. trained the rats to slow down at an unmarked location on the track to receive positively rewarding electrical brain stimulation. This goal location stayed fixed relative to the room cues and thus would be better located after the population response of the cells had switched into the room frame of reference. They found that the adult animals learned the task better than the aged animals and that as a group the adult animals switched from the box framework to the room framework earlier on the track than the aged animals. Furthermore, on an animal-by-animal basis there was a good correlation between the point at which the ensemble of place cells recorded switched and the ability of the animal to distinguish between the goal location and a control location. Although it was not formally tested, it seems reasonable to conclude that the ability to switch into the fixed room framework was at least in part dependent on the ability of room cues to influence the place fields and that this was deficient in the aged animals.

11.7.11 Hippocampal Place Cell Firing Is Influenced by Other Areas of the Brain

Lesions of the septal or entorhinal projections to the hippocampus have been reported to cause a decrease in the number of place cells that are found and, in the case of entorhinal lesions, to a shift in the stimulus control of place field firing (Miller and Best, 1980). Following entorhinal cortex lesions, the fields rotated with the maze, unlike the fields of normal animals, which remain anchored to extramaze cues. These findings are consistent with the idea that CA1 and CA3 cells have access to distal sensory input via the entorhinal cortex. The importance of direct entorhinal–CA1 connections has been highlighted by Brun et al. (2002), who removed the input from CA3 (and thus the dentate gyrus as well) onto CA1 cells and showed that CA1 place cells could still form well defined, stable place fields in repeated exposures to a familiar environment.

The influence of the medial septal nucleus is somewhat different from that of the entorhinal cortex. Recall that it provides powerful cholinergic and GABAergic inputs to the hippocampal formation and has a major influence on hippocampal theta activity. As we shall see in Section 11.12.6, many medial septal cells are theta cells that have a good phase relation with the hippocampal theta. Its role in the control of place field firing has been studied by Mizumori et al., 1989). They trained rats in an eight-arm radial maze and recorded from place cells in CA1 and CA3 during performance of the task. Surprisingly, blocking the medial septum with the anesthetic procaine left place fields intact despite disrupting maze performance. Subsequent experiments have suggested that firing in the subiculum is disrupted and that this area of the hippocampal formation thus contributes to the control of behavior in this task. Leutgeb and Mizumori (1999) replicated this observation but found a difference between the place cells in the lesioned animals and controls when the animals were placed in a new environment or faced with altered spatial cues. Interestingly the place fields of the lesioned animals showed less transfer from light to dark and slightly greater transfer between rooms.

Lesions or temporary inactivation of other regions have been shown to affect place fields in different ways. Lesions of the perirhinal cortex, which projects to the entorhinal cortex and therefore might be providing sensory information to the hippocampal place cells, have no effect on basic field parameters but reduce the consistency of locational firing (Muir and Bilkey, 2001): In contrast to the stability of field locations in the control animals, field centers in the lesioned rats frequently moved from one exposure to the testing box to the next. A similar effect on the stability of hippocampal place fields was found after lesions of the prefrontal cortex (Kyd and Bilkey, 2005), and this may have been mediated by frontal projections to the entorhinal/perirhinal cortex.

Temporary inactivation of the retrosplenial cortex (Cooper and Mizumori, 2001) disrupt an animal's performance on the radial arm maze in the dark and during the initial learning phase in the light. During inactivation, the location of place fields shift on the maze. There are head direction (HD) cells and more complex HD, location, and movement cells in retrosplenial cortex (Chen et al., 1994; Cho and Sharp, 2001). This suggests that the retrosplenial cortex is more involved in nonvisual (perhaps path integration) control of place cells and spatial behavior. On the other hand, the role of objects placed at the periphery of the environment in controlling the orientation of place fields in a symmetrical environment seems to be mediated, at least in part, by the visual and the parietal cortices. After lesions of the visual cortex, 70% of place fields did not rotate in step with the rotation of the landmarks. In comparison, 100% of place fields in the controls did so (Paz-Villagran et al., 2002) (see Section 11.7.6 regarding how place fields can be controlled by exteroceptive sensory cues). When the objects were removed, the fields in both lesioned and control animals remained in the standard position fixed relative to the room. The parietal cortex also seems to be involved in the control of place cell orientation relative to the landmark objects but in a different way (Save et al., 2005). Following

lesions to the parietal cortex, most cells (78%) still rotated with the objects but, unlike in control animals, did not maintain this rotated location when the objects were subsequently removed. This type of short-term memory for the visual location of landmarks is discussed in greater detail in Section 11.8 and appears to be dependent on the integrity of the parietal cortex.

11.7.12 Primate Hippocampal Units also Exhibit Spatial Responses

The spatial properties of single units in the hippocampus of primates including humans have been studied. This is important because it establishes the generality of the spatial nature of the hippocampus and shows that the findings in rodents are not unique. However, if there is broadening of the function of the human hippocampus to include episodic memory as well as spatial memory, it might be expected that the cells in humans and, more generally, primates might have a broader spectrum of response properties than those found in rodents. Furthermore, the standard approach to recording single units in primates is markedly different from that found in the freely moving rat. Primates are usually restrained with their heads fixed, and stimuli are often presented in ways that make it difficult to identify a spatial correlate or to dissociate the different frames of reference that might be used for the localization. It is also known that restraining rats severely depresses the locational correlate of the hippocampal complex-spike cells (Foster et al., 1989). These constraints have been partially overcome in a few studies by giving the animals increased mobility either in movable chairs or carts or by allowing them to move freely around a large cage. We should not be surprised, then, if there are differences between the unit/behavioral correlates found in primates and those in rodents. The spatial responses are described in this section; the nonspatial responses are described separately in Sections 11.11. 1 and 8.

Several types of spatial response have been found in primate hippocampal units. Responses to the location of the stimulus on a VDU screen, spatial-view cells that respond to the location at which the animal is looking, and place cells similar to those in the rodent have all been described. When the response of hippocampal units to the identity of a stimulus is compared to its spatial location, considerably higher percentages of units are found to the latter variable. Rolls and his colleagues (1993) tested monkeys on object recognition tasks and compared unit responses to object familiarity with those to object location. They reported that about 9% of cells in the hippocampal region responded differentially to the location of the stimulus on a display screen. In contrast, only a small percentage (2%) of cells responded to familiar objects (see Section 11.11.8). Colombo et al. (1998) recorded units in the primate hippocampus during a similar delayed matching to sample task in which either the spatial location or the object identity of the sample stimulus had to be remembered. They found 41 neurons that responded during the delay period, and of these 15(37%) were related exclusively to spatial position and 5 (12%) to object identity. The remaining 21 responded to both. Most of the responses were inhibitory. Interestingly, the spatial neurons were more heavily concentrated in the posterior hippocampus, which is the analogue of the dorsal hippocampus in rodents. Ringo and colleagues (Ringo et al., 1994; Sobotka et al., 1997; Nowicka and Ringo, 2000) investigated the role of eye movements in hippocampal single unit responses. Monkeys were trained to look to one of five locations in the light or in the dark to receive rewards. In an early study, about one-third of the units changed their rate during saccades; in a subsequent study, 13% of the cells were shown to be sensitive to position and another 17% were shown to be sensitive to direction. Because the animal's head was fixed in these experiments, it is not possible to say whether the effective saccades were to locations in the laboratory or in a head-centered framework. Remembering the location of a stimulus on a computer screen might not be the same type of spatial task as locating oneself in an environment and might more easily be solved using egocentric spatial strategies dependent on parietal than hippocampal cortex (Burgess et al., 1999). Wirth et al. (2003) studied the responses of hippocampal neurons during a task that required the monkeys to learn the association between specific scenes and specific locations. Novel pictures of scenes were presented on a VDU screen, and the animal's task was to learn to move its eyes to one of four locations on the screen at the end of the presentation to obtain a reward. Each scene was presented for 0.5 second followed by a 700-ms delay during which the screen was blank before the animal was allowed to move its eyes to the required location. In all, 61% of the hippocampal cells recorded had firing rates that were significantly altered during the presentation of one of the scenes, during the delay that followed it, or both. Furthermore, there was a good correlation between the altered firing during the trial and the learning of the behavioral response. Changes in firing rate preceded the behavioral learning by a small number of trials for 14 cells, occurred at the same time in 4 cells, and followed learning in 19 cells. This suggests that although the firing rate of some cells may have been related to the learning of the scene-location association it may have been involved in learning other aspects of the scene in others. Control trials involved the presentation of familiar scenes that required the same eye movement as the novel scene. This rules out the possibility that the hippocampal firing was related to a particular eye movement or to a specific location on the screen. Although it is possible to describe this task as learning an arbitrary association between a scene and an eye movement to a location defined relative to the VDU screen, it is also possible that the animals were learning to attend to a particular location in each new scene, to remember the scene and the location during the delay, and to look at the location when allowed to do so after the delay. On this view, these cells would be closely related to the spatial-view cells, which respond when an animal looks at a location rather than goes there (Rolls et al., 1997) (see next paragraph).

Several groups have also looked for spatially coded cells in the hippocampus of monkeys free to move around the envi-

ronment. Rolls and colleagues (1997) have found a type of spatial cell not described in the rodent: the spatial-view cell. Spatial-view cells respond selectively when the animal looks at particular locations in the testing room irrespective of where the animal is situated in the room when it looks at that location. For example, one cell increased its firing rate markedly when the animal looked at a particular corner of the room regardless of where it was located in the room itself and regardless of the orientation of gaze required to look there. Some of these cells continued to respond when the target location is screened off by curtains, suggesting that the cells are not responding to particular sensory features in that location. This group has also reported the existence of whole body motion cells (O'Mara et al., 1994), which may be related to the speed cells in the rat described above. In contrast, this group has looked for but not found place cells comparable to those seen in rats. The existence of spatial-view cells might be an indication that primates have developed the ability to identify places and their contents without physically visiting those places, an important step in the evolution of the spatial mapping system.

Ono and his colleagues (1993) found place-coded neurons in the hippocampal formation of monkeys that could visit different locations in an environment while performing different tasks. The monkeys were trained to sit in an enclosed cart and to move it to nine different locations in the testing environment by pressing a lever. About 13% of the cells fired more when the animal was at one location than when it was in other locations. In a subsequent task, the animals were required to perform an object-in-place discrimination. The cart was moved to a particular location and the view window was opened, allowing the animal a sight of an object at that location. About one-fourth of cells responded when objects were shown to the animal in this task. A subset of these cells (5% of the total) were object-in-place cells that responded differentially when the animal was shown an object in a particular location and not in other locations. These cells were also not interested in a different object in the preferred location. They appear to have properties similar to those of the place and object-in-place cells described in the rat. Further evidence that the cells are appropriately described as place cells comes from an experiment by Nishijo et al. (1997) in the same laboratory. Here the animal in the cart was moved backward as well as forward through the environment, and the cells continued to fire at the same location. This manipulation reverses the cues in egocentric space but leaves allocentric cues unchanged. This group has also used virtual reality environments to provide testing environments more related to the open field tasks used with rodents (Hori et al., 2005). Monkeys were trained to use a joystick to move between five reward locations in a large 100 m virtual diameter space containing a 20 m diameter arena surrounded by landmarks such as a tree, a house, and the building. Almost one-third of the hippocampal units displayed spatial fields. When the distal cues were rearranged, two-thirds of the cells tested remapped by either ceasing to fire or by changing the spatial pattern of firing. The monkeys were also trained in a two-dimensional screen-based task in which they had to move a pointer to different parts of the screen. A subset of cells were recorded in both the virtual reality task and the screen-based task. Of the cells with spatial responses in either or both tasks, about one-third had spatial activity in both, one-half in the virtual reality task alone, and only 15% in the screen-based task. It appears that large-scale allocentric spatial tasks are better for activating primate hippocampal neurons than are screen-based egocentric tasks.

If we are to compare hippocampal physiology in rodents and primates appropriately, more recordings are needed from primates whose heads are unrestrained and who are free to locomote around a complex environment (see Section 11.2). There has been some interesting progress along these lines. In the first study in completely freely moving monkeys, rodent-like place cells with high signal-to-noise ratios in the hippocampus proper were found in squirrel monkeys performing a spatial memory task in three dimensions (Ludvig et al., 2004). Interestingly, many of these cells had fields that involved the walls of the wire-mesh testing cage, areas that would not have been sampled in the floor-bound experiments of Rolls and Ono.

Another approach has been to record units from human epilepsy patients (awaiting determination of seizure foci). In early studies the responses to faces, objects, and scenes were studied (see Section 11.11.9). Of relevance here is a study of unit activity during virtual locomotion in a taxi-driver game (Ekstrom et al., 2003). This study recorded units from the temporal lobe and frontal cortex and looked for evidence of cell activity responsive to the variables of place, view, and goal-seeking and of conjuctions between these variables. Place responses clustered in the hippocampus to a greater extent than in the parahippocampus (24% of hippocampal cells being "pure" place cells versus 8% in the parahippocampus), and "pure" location-independent spatial-view cells clustered in the parahippocampus (17% vs. 5% in the hippocampus). The goal cells were distributed evenly throughout the temporal and frontal cortices (see above). The place-responsive cells were found to be nondirectional, as would be predicted from the rodent literature, given that the subjects were free to move through areas in the virtual town from different directions. In an important control, Eckstrom et al. looked for unit responses to isolated landmarks before the patients learned to use them to navigate in a virtual reality environment; they failed to find any.

11.8 Place Cells Are Memory Cells

A role for the hippocampal formation in memory is suggested by activity-dependent synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD) (see Chapter 10) and the profound amnesia associated with damage to the medial temporal lobe (see Chapters 12 and 13). Is this mnemonic capability also reflected by place cells? This

chapter presents evidence that these cells can maintain their firing fields over a period of a few minutes in a working memory task, that place field characteristics can change with experience over the course of a day, that sensory control of place cell firing can become more differentiated with experience over days and weeks or can shift from exteroceptive to interoceptive cues when the animal learns that the former are unstable, that place cell activity during sleep reflects experience in the prior waking period and may be involved in consolidation of recently acquired spatial memories, and finally that several properties of normal place cell behavior in familiar and novel environments, such as place field stability, are based on memory and depend on the NMDA receptor implicated in LTP.

11.8.1 Hippocampal Place Cells "Remember" the Animal's Location for Several Minutes During a Spatial Working Memory Task

When discussing the properties of place cells, we saw that they displayed "memory" properties such as continuing to fire in appropriate places when the lights have been turned off. The cells use environmental cues to set up their firing pattern, but once established the pattern is sometimes surprisingly free of environmental influences. The clearest demonstration of this "memory" phenomenon was in experiments in which the environmental cues controlling place fields have been identified; and it was shown that place fields were maintained following the removal of these cues (Muller and Kubie, 1987; O'Keefe and Speakman, 1987; Save et al., 2005). We concentrate here on the O'Keefe and Speakman experiment in which place cell firing pattern was shown to be correlated with the animal's behavior.

O'Keefe and Speakman (1987) recorded cells during a spatial memory task in a cue-controlled environment (Fig. 11–12). Rats were first trained on a plus shaped elevated maze to go to a goal defined by a set of cues within the curtained environment (Fig. 11–12A). Rotation of the cues and goal between trials ensured that the rats learned to use these cues. Place fields rotated in step with the cue rotations (Fig. 11–12B). On some trials, the cues were removed while the rat was still in the start arm before it was allowed to choose. Tests on normal rats had established that well trained animals could remember the location of the goal for periods as long as 30 minutes after the cues were removed. Of 30 cells with fields on the maze, 27 maintained these fields following removal of the cues (Fig. 11–12C). Cells with fields on the nonstart arms for a particular trial also fired in the correct place, demonstrating that place cell "memory" is more than the continuous persistence of a trace set up during the registration period; the system can, in addition, compute the correct location on the maze of place fields for cells that are inactive in the start arm. One explanation for this memory phenomenon points to a role for the distal cues at the periphery of an environment in orienting the head direction system. Once this has been set by the orientation of the control cues on a given trial, exteroceptive and interoceptive cues other than these might be capable of maintaining it (see Section 11.9). As we saw in Section 11.7.11, a role for the parietal cortex in this short-term spatial memory has been demonstrated (Save et al., 2005).

A final observation on these cells was made during control trials in which the animal was not placed in the start arm until after the controlled cues had been removed, preventing the animal from knowing which arm contained the reward. Under these circumstances, choice performance falls to chance levels, but the pattern of place cell firing still stayed appropriate for the animal's choice of goal (Fig. 11–12D). This constitutes strong evidence that these cells are not firing to the actual environmental location but to where the animal "thinks" it is. Other studies have also found a good relation between place field activity and behavioral choices (Zinyuk et al., 2000; Lenck-Santini et al., 2001a, 2002; Rosenzweig et al., 2003) but there has also been failure to find this (Jeffery et al., 2003). In the latter experiment, rats continued to perform a hippocampus-dependent spatial task, albeit at a reduced level, following a change in the testing box that caused remapping of most of the CA1 place fields. Here, it is plausible to assume that place cells in other areas of the hippocampal formation did not remap and continued to support the behavior.

11.8.2 Place Field Plasticity During Unidirectional Locomotion

One interesting line of investigation has involved changes in place field characteristics over time as rats run along a track. When animals are run on narrow tracks, many of the fields are directional, firing in one direction of movement but not the other. The experiments described in this section test models describing the effects of temporally asymmetrical LTP and the encoding of sequence-related information (see discussion in Chapter 14; see also Section 11.7.3). Mehta and colleagues (1997, 2000) have shown that over the course of a few dozen traverses in the same direction along a track, CA1 place fields shift backward relative to that direction of motion and become larger. They also found that an experience-dependent skewness develops in the place fields; that is, on the animal's first runs of the day a given cell's place field is symmetrical, but with continued exposure the place cell tends to fire at a higher rate when the animal leaves the place field than as it enters it. However, this increased skewness in CA1 place fields has not been found by others (Huxter et al., 2003). The development of place field expansion and backward shift has been shown to depend on NMDA receptors (Ekstrom et al., 2001). An intriguing aspect of the phenomenon in CA1 is that the effect resets overnight, as if the cells do not remember the previous day's experience on the track (Mehta et al., 2000). Evidence from Lee et al. (2004) confirms and extends this finding but in addition shows a difference betweeen the CA3 and CA1 fields: CA3 fields develop skewness and shift backward immediately on exposure to a newly altered track and maintain these changes on subsequent days, whereas CA1 fields shift back-

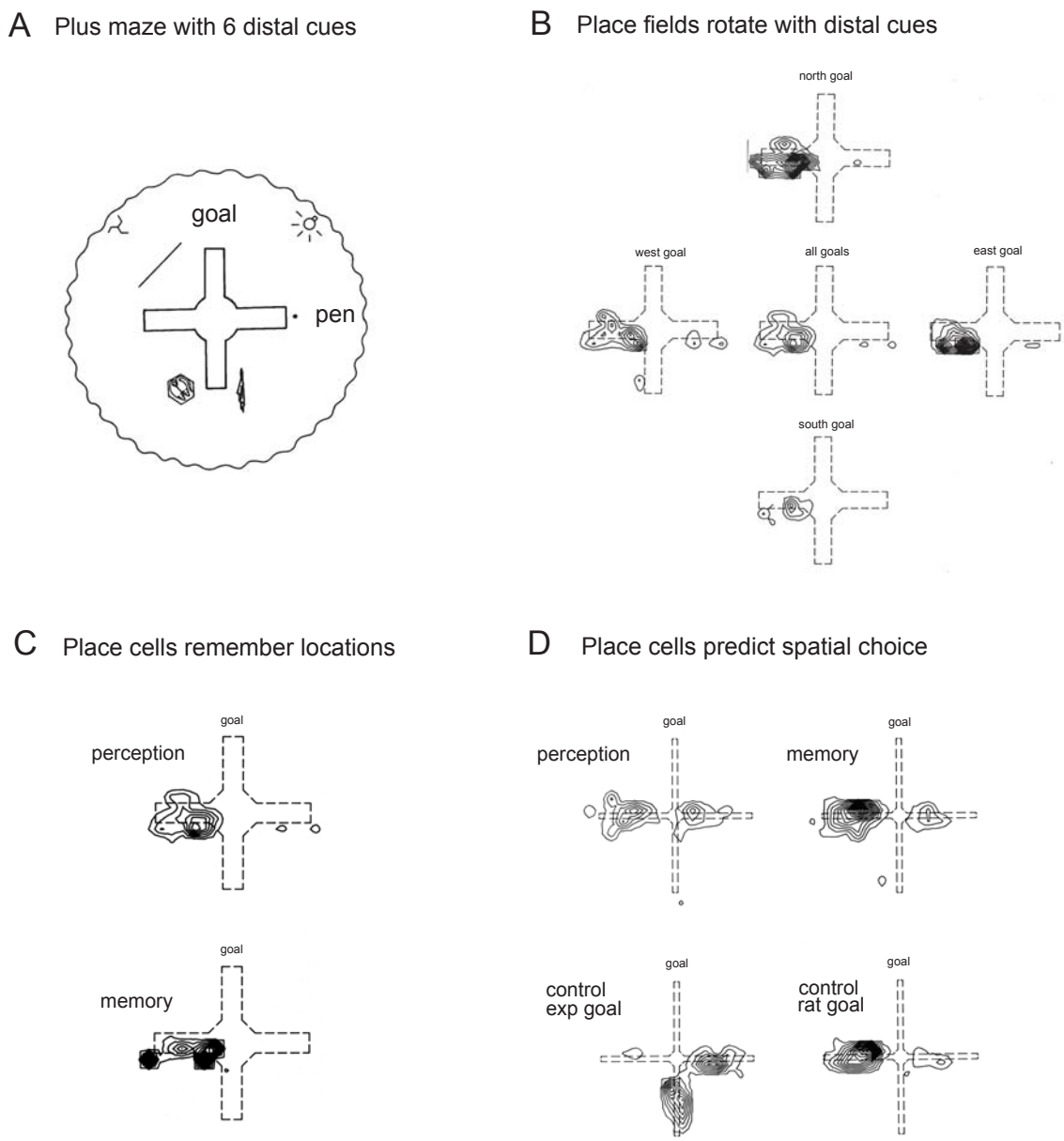


Figure 11–12. Place cell activity during a spatial working memory task. *A*. Layout of the testing environment showing an elevated plus-shaped maze surrounded by six cues and a set of curtains. *B*. Place cell with a field on the arm 90° counterclockwise to the goal (−90°, inner panel). The firing field remains constant with respect to the distal cues and goal as they are rotated by multiples of 90° relative to the laboratory frame (outside panels). Trials have been rotated so the goal is always shown at the top. More contours indicate a higher firing rate. *C*. Same cell as in *B* maintains its field during the perceptual (top) and memory (bottom) phases of the experiment. *D*. A different place cell fires strongly in the −90° arm and weakly in the +90° arm on both perceptual and memory trials (upper left and right). During control trials, it fails to fire with correct relation to the (unknown) goal (lower left) but fires with correct relation to the animal's choice of goal arm at the end of the trial (lower right). In *B* and *C*, each contour = 0.7 spikes s^{-1}; in *D*, each contour = 1.5 spikes s^{-1}. (*Source*: After O'Keefe and Speakman, 1987, with permission.)

ward only from the second day of testing and do *not* maintain the changes. Lee et al. interpreted these findings as suggesting that the CA3, but not the CA1, network can store sequence information in the long term, and that CA1 is more involved in novelty detection. Note that CA1 cells can show long-term plasticity in other paradigms (see Section 11.8.3).

11.8.3 Cue Control over Hippocampal Place Cells Can Change as a Function of Experience

Experience with an environment can change which features of that environment control place fields. Such features include the color of a polarizing cue and the geometrical shape of the

environment. Bostock et al. (1991) studied place fields in two recording chambers that were identical except for a white or black polarizing card at the periphery. They found that when the black card was first substituted for the white card most of the place fields remained the same. However, as the rat continued to experience the white and black card environments, the place cells began to distinguish between them. The remapped fields fell into three classes: (1) the field in the black card environment was a rotation of that in the white card environment, or (2) the cell ceased to fire in the black card environment, or (3) the fields in the two environments were completely different in location and shape. The second and third classes were described as "complex remapping" and were found to be all-or-none: If one place cell showed complex remapping, so did another simultaneously recorded cell. Learned remapping can also occur between environments of different geometrical shapes (Muller and Kubie, 1987).

Lever et al. (2002) and Wills et al. (2005) studied the development of shape remapping in CA1 place cells in detail. Both experiments studied remapping between square and circular enclosures. In the Lever et al experiment, the enclosures differed only in shape and were identical in color, texture, and odor; in the Wills experiment they differed across all four dimensions. The activity of several hippocampal place cells was recorded on each day of the experiment; often they were different cells, but in some cases recordings were taken from the same cells over many consecutive days. Remapping was rapid and coherent in the latter experiment but slow and individualistic in the former. As in the Bostock et al. experiment described above, Lever found that on first exposure to a circular and a square environment most place fields were identical in the two shapes. With continued exposure, however, the cells began to differentiate between the environments. Unlike Bostock et al., they found that different cells differentiated between the environments at different rates, so after a few days some of the place fields were still similar in the two environments whereas others had clearly remapped. After 1 to 3 weeks of exposure to both environments, most of the cells had different fields in the two. Recording from individual cells through their remapping transition period showed that it took one of three forms. The most common form involved a gradual reduction of firing rate in one of the two shapes until it reached zero. Other forms of remapping involved the development of a new field in one of the shapes in tandem with the decline of the original field in that shape or, more rarely, a shift of the field in one shape to a new location. Once the cells had learned to differentiate between the two different-shaped boxes, rats were placed back in their home cages for delay periods of up to 39 days without any exposure to the shapes; upon reexposure, most of the cells continued to discriminate the two shaped boxes. CA1 place cells thus demonstrated long-term memory for this learned discrimination. Note that in both this and the Bostock et al. study the rats were not trained to discriminate the environments but were equally rewarded in both. Thus, the learning is *incremental* (see also Tanila et al., 1997b), *latent* because it does not necessarily manifest in behavior, and *incidental* because it takes place in the absence of explicit reward.

In the Wills et al. study (2005a), the boxes were more different from each other to begin with, differing not only in shape but also in the color, odor, and texture of the walls. Original training took place in a white wooden circle and a brown morph square. Under these circumstances, the remapping took place over a period of minutes, and most of the cells had differentiated between the two environments by the end of the first few exposures. Furthermore, the remapped cells act in a unitary ensemble fashion, as was revealed by challenging them with shapes intermediate between the circle and the square. After several days' experience with the original training enclosures the animals were transferred to circles and squares constructed from the same brown morph box. It was then possible to probe the basis for each cell's differentiation between circle and square by recording in a series of octagons that vary systematically from the circle-like (regular octagon, adjacent side ratio 4:4) to the square-like (adjacent side ratio 7:1) (Fig. 11–13). Most of the remapped cells shifted abruptly from a square to circle firing pattern (for example, by treating the 6:2 octagon as a square and the 5:3 octagon as a circle). Furthermore, in all animals tested on this probe, all of the simultaneously recorded cells show the abrupt shift at exactly the same point in the sequence of octagons. This suggests that there are two mechanisms at work: pattern separation and pattern association (see Chapter 14). The first would permit the abrupt switch from the circle to square pattern despite a very small change in the geometry of the boxes. The second would be based on some type of cooperation among the active subset of place cells, perhaps revealing the operation of an attractor network and would account for the coherent behavior of the network.

11.8.4 Control of the Angular Orientation of Place Cells in a Symmetrical Environment Can Be Altered by the Animal's Experience of Cue Instability

In a symmetrically shaped environment such as a cylinder, an animal's sense of direction can be controlled by distal polarizing cues, such as a card on the wall of the environment, or by internal path integration cues, such as the amount it has turned around. Commonly, the visual information provided by a distal cue overshadows the internal cues, and rotating the cue causes an equal rotation of the fields (see Section 11.7.6). Jeffery and collegues (Jeffery et al 1997; Jeffery 1998) showed that given certain experiences the animal could learn to give priority to internal path integration signals over the external cue. They tested the effectiveness of the cue card by rotating it when the animal was out of the enclosure and the effectiveness of the internal path integration system by slow rotations (subvestibular threshold) of the animal relative to the framework of the enclosure. As expected, they found that, initially, the visual cue card controlled place field orientation.

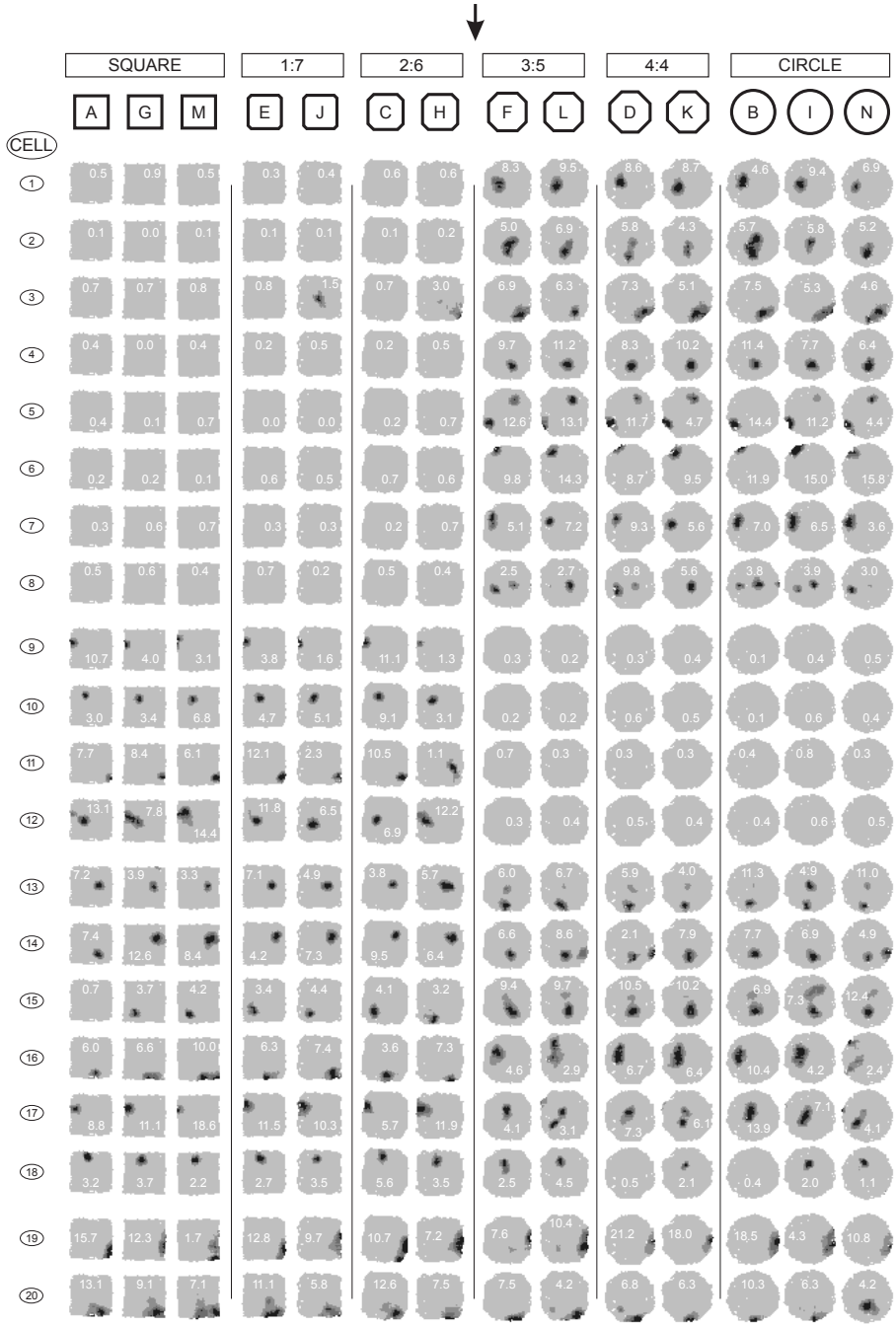


Figure 11–13. Abrupt coherent switch from square-like pattern to circle-like pattern in an incrementally changing series of octagons. Fields of 20 simultaneously recorded place cells following fast remapping training. Cells 1–17 met the criterion for remapping, and all switched abruptly from the square-like to circle-like pattern at the same point in the series between the 2:6 and 3:5 octagon (arrow at top). The order in which the octagons were experienced is indicated by the letters A to N in the second row. Numbers in panels are peak rates. (*Source*: After Wills et al., 2005, with permission.)

However, following experience in which the rat could see the cue card move relative to the background environment and therefore was not a stable landmark, control of place field orientation passed from this visual cue to the interoceptive path integration system. Now the fields were no longer controlled by rotations of the visual cue but could be shifted by slow rotations of the animal relative to the framework of the enclosure, demonstrating that they were under the control of the vestibular system. Rotations of the cue when the animal could not see it move did not produce the shift away from cue control. It seems likely that the site for this cue-instability learning is in the head-direction system itself (see Sections 11.9 and 11.10), perhaps in the presubiculum. This is suggested by two key features of the data. First, all the cells

behave as a map-like ensemble, following *either* exteroceptive cues *or* interoceptive cues. Second, once the path integration system surplants the visual cue card in the control of orientation, it generalizes to novel situations. Following remapping induced by changing the color of the environment's walls, the newly remapped population of CA1 cells immediately follows the interoceptive rather than the visual cues, without needing to relearn the cue instability (Chakraborty et al., 2004).

11.8.5 Complex-spike Cell Firing and Connectivity During Sleep Is Modulated by Prior Spatial Learning Experiences

It has been suggested that consolidation of memories might take place during sleep and, in particular, during REM sleep (Maquet, 2001; Stickgold et al., 2001). Therefore, one might expect neuronal firing patterns to reflect this consolidation activity. Furthermore, if consolidation involves the transfer of information from hippocampus to neocortex (an idea developed further in Chapters 12 and 13), one might expect there to be increased interaction between cells in these brain areas during and after sleep. Experiments have suggested that the cell activity during ripples and sharp waves, or that related to the theta waves of REM sleep, could be the neural signature of this information transfer/consolidation process.

Pavlides and Winson (1989) recorded pairs of place cells in rats during sleep sessions that followed experience on a radial arm maze. The rats were allowed to visit the place field of one of the two cells prior to each sleep session but not the other. Remarkably, there was a selective increase in firing during both the slow-wave sleep and REM sleep periods of the cell that had been allowed to be active in its place field prior to sleep. The other cell showed no change in firing rate. In another study following place cell activation on a runaway during waking, the theta phase at which these cells fired during subsequent REM sleep shifted to the positive peak (Poe et al., 2000). Because LTP is more likely to occur at this phase, this finding might be an indication that recently experienced cells are more susceptible to plastic modification. Evidence for such changes comes from studies on changes in cell connectivity. Wilson and McNaughton (1994) examined the effects of spatial experience on changes in functional connectivity between CA1 cells. Using cross-correlation techniques (see Box 11–2), they found an increase in the correlation between pairs of cells with overlapping place fields in slow-wave sleep *after*, compared to before, the environmental experience; these correlations were more pronounced during ripples (see also (Kudrimoti et al., 1999). There was evidence from another study (Qin et al., 1997) that some of this increased connectivity takes place between cells that were already connected prior to the environmental experience. Skaggs and McNaughton (1996) ran rats in one direction on a narrow triangular track and found that the temporal ordering of firing between cells with partially overlapping fields was replicated in a compressed form during slow wave sleep. Firing sequence replay has been replicated by Wilson's group for slow-wave sleep (Lee and Wilson, 2002) and for REM sleep (Louie and Wilson, 2001). It should be emphasized that the replay time scales relative to the waking spatial experience differ markedly for these types of sleep, involving about 20-fold compression during slow-wave sleep and basically no compression during REM sleep. Second, it seems that slow-wave sleep replays sequences immediately after they were experienced, whereas REM sleep replays experience at least a day old. Finally, cross-correlational analysis showed that increased correlations were found between pairs of neocortical cells as well as pairs of hippocampal cells and, most intriguingly, between pairs of hippocampal and neocortical cells (Qin et al., 1997; Siapas and Wilson, 1998). The latter finding may be taken as evidence for increases in the "functional connectivity" between, as well as within, structures.

In all, these results indicate selective, orderly reactivation of cells that have recently taken part in a spatial experience. They also suggest that co-activation of place cells during the waking experience might lead to increased connectivity and further consolidation during sleep states. These studies have involved CA1 cells. A future goal is to compare CA3 and CA1 cells and relate these findings to the experience-dependent place field changes during unidirectional track running described above in this section. The mechanisms that immediately produce sequence replay during sleep in CA1 appear to reset (Lee and Wilson, 2002), like the CA1 place field changes such as skewness and backward shift. Given that these are maintained on subsequent days in CA3 cells (Lee et al., 2004), one might predict that experience-dependent changes in CA3–CA3 connectivity in sleep would also be less transient.

What is needed to take these results forward and demonstrate a causal relation between the sleep phenomenon and subsequent memory capacity is a physiological or pharmacological technique for selectively disrupting postexperience LIA or REM theta activity or, even better, altering the patterning of place cell activity during these periods.

11.8.6 NMDA Receptor Confers Mnemonic Properties on Place Cell Firing

Several studies have pointed to a role for the NMDA receptor (NMDAR) in conferring mnemonic properties on place cell function (reviewed by Nakazawa et al., 2004). McHugh et al. (1996) studied the place cells of mice in which the NMDA receptor subunit NR1 had been knocked out only in CA1 pyramidal cells. Deletion of this subunit renders the receptor inoperable. Rotenberg et al. (1996) looked at the fields of place cells in animals that transgenically expressed a mutated calcium-independent form of CAMKII, part of the intracellular signaling pathway that mediates the effects of the NMDA receptor. Both groups of animals had deficits in LTP and spatial memory (Rotenberg et al., 1996; Tsien et al., 1996). In both experiments fewer place cells were found in the mutants and the quality of the mutant place fields was degraded, a result that has also been seen in other mutant mice with disrupted

NMDAR-dependent plasticity (Cho et al 1998). In a different mutant. Rotenberg et al found that place fields were less stable over repeated exposures to the environment (Rotenberg et al., 2000). In the McHugh et al. experiment, the place cells showed an interesting loss of the usual temporal relation between the firing patterns of cells with overlapping place fields. As we saw in Section 11.7.9, place cells fire with a theta-like bursting pattern as the animal runs through the firing field, which is revealed by strong periodicity in the cross-correlogram of the two spike trains (see Box 11–2). The absence of this periodicity in the McHugh et al. experiment suggests a fundamental breakdown in the temporal firing pattern of the place cells or the temporal relations between cells lacking a functional NMDA receptor.

The global role of the NMDA receptor in the long-term stability of place fields was studied by Kentros et al. (1998). They showed that systemic administration of the competitive NMDA channel blocker CPP had no effect on established place fields in an environment long familiar to the rats or on the formation of newly "remapped" place fields in a novel environment, nor on the short-term stability of these new, remapped place fields, as measured over a couple of hours. However, on the second day of exposure to the novel environment, the previous day's place fields had been "forgotten": Again the cells remapped the new environment, but the new patterns of firing bore no relation to those of the previous day. This finding suggests that the NMDA receptor is more important for the stability of place fields in the long term than it is in their initial establishment or their short-term maintenance.

Highly informative studies have used conditional CA3-restricted NMDA receptor knockout mice to explore the contribution of long-term CA3 plasticity to CA1 place cell firing and spatial behavior (Nakazawa et al., 2002, 2003). These studies suggest two important roles for CA3 plasticity: pattern completion (see Chapter 14), whereby only a subset of cues are sufficient to reinstate a pattern of firing originally associated with the full cue set; and rapid, single-exposure, learning. Pattern completion is suggested by the finding that although CA1 cells in the mutants showed normal firing in full-cue reexposures to an environment they showed significantly reduced levels of firing (albeit in the appropriate locations) in partial-cue reexposures. Impaired behavior was also seen in probe trials during the watermaze task under partial-cue conditions. A CA3 plasticity-dependent role in rapid environmental learning is suggested by the poorer quality of the mutants' CA1 place fields in novel environments and by impaired performance in the delayed match-to-place version of the watermaze (see Chapter 13).

11.8.7 Summary of Place Cell Plasticity

The evidence summarized in this section indicates that place cells show several forms of plasticity, some of which can be correlated with the animal's behavior in spatial memory tasks. These various forms of plasticity last for markedly different periods of time, ranging from a few minutes to longer than a month. Some of them are activity-dependent and temporary, lasting only the length of a single trial in a working memory task or a session on a maze, whereas others appear to be permanent, such as the differentiation between two boxes following slow remapping. Some of these changes clearly depend on the integrity of the NMDA receptor in different parts of the hippocampus, but others may not. Indeed, for many of these changes it has not yet been firmly established that the underlying synaptic plasticity takes place in the hippocampus itself rather than in structures afferent to the hippocampus and is merely being passively reflected by the cells there. Finally, there is substantial evidence that some type of consolidation process takes place during sleep following an experience, and it is reflected in place cell firing. Whether this involves intrahippocampal processes, such as the strengthening of synapses between cells with overlapping fields, or involves the transfer of information from hippocampal stores to neocortical ones, must await further experimentation. It is clear that there are sufficient examples of plasticity reflected in place cell firing to make them one of the more fruitful targets in the study of the neural basis of memory. In a subsequent section (see Section 11.11), we examine the evidence for changes in hippocampal cell activity during nonspatial learning and memory tasks.

11.9 Head Direction Cells

Another well characterized class of spatial cells recorded in the hippocampal formation of freely moving awake animals is the head-direction (HD) cells, found in the dorsal presubiculum and regions connected with the presubiculum, such as the anterior thalamus (Ranck, 1984; Taube et al., 1990a; Taube, 1995a, 1998). As already noted, HD cells fire whenever the rat's head points in a specific direction relative to the environment, irrespective of its location or whether it is moving or still (see Fig. 11–21C, color centerfold). The primary correlate is the azimuthal orientation of the head in the horizontal plane. Pitch and roll appear to be relatively unimportant, as is the orientation of the rest of the body. Figure 11–14A shows the firing rate for three of these HD units plotted as a function of the direction of heading. Each cell has a single preferred direction, and firing falls off rapidly, symmetrically, and almost linearly as the head direction rotates away from the preferred direction. We refer to these directions in terms of compass headings but do not imply that these cells are sensitive to geomagnetism. The portion of the 360° circle covered by a given cell ranges from about 60° to 140°, with the average being about 90° (Fig. 11–14A). An impressively Euclidean property of HD cells is that the preferred direction is remarkably independent of position (Taube et al., 1990a; Burgess et al., 2005); the preferred direction vectors in the various parts of an environment appear *not* to converge (e.g., upon a salient distal cue, as one might have expected) but are parallel. The distribution of peak firing directions across the population of cells is uniform, with no direction preferred over any other.

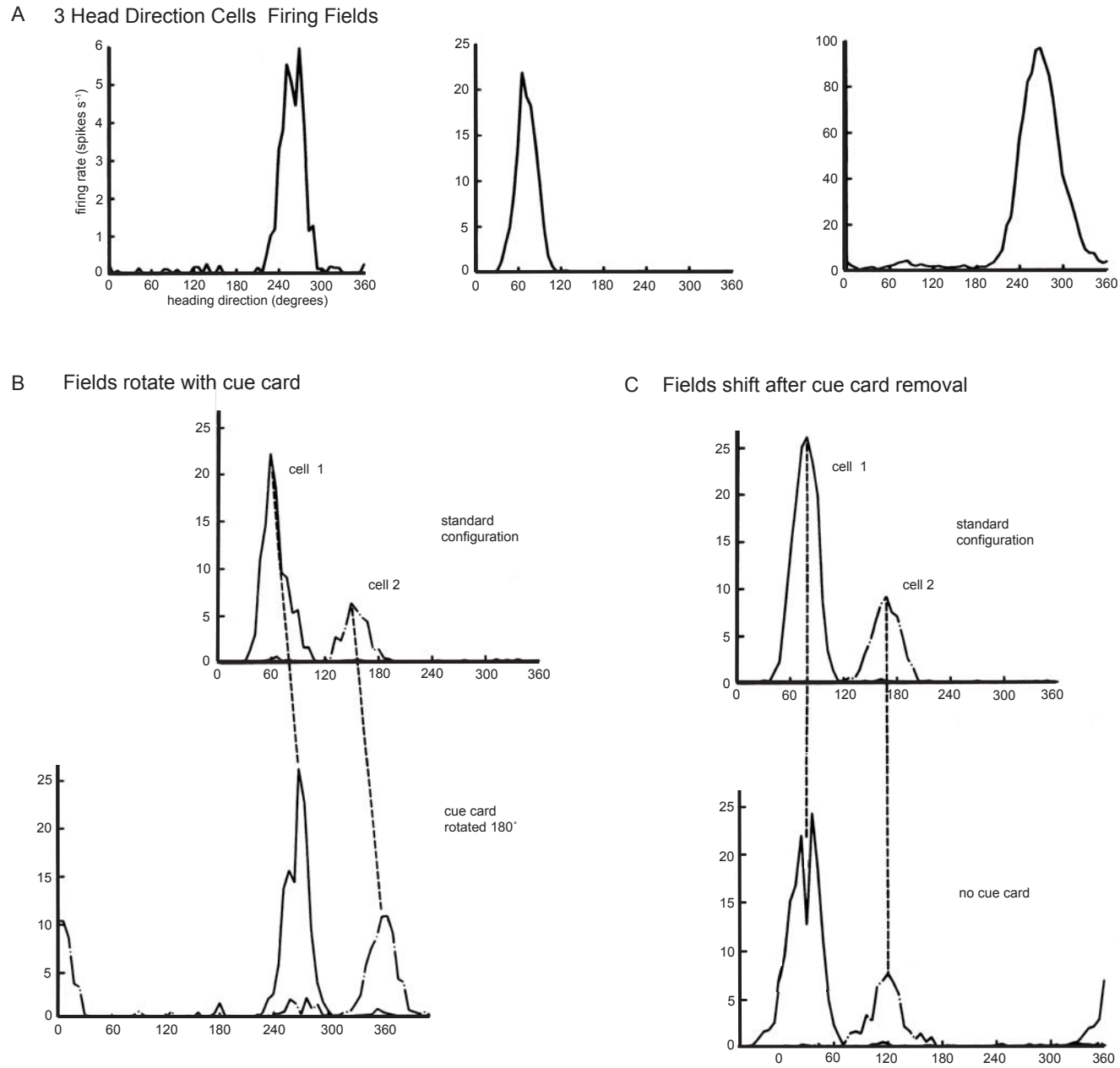


Figure 11–14. Head direction cells in the dorsal presubiculum. *A*. Firing fields of three cells as a function of the animal's heading direction. Note that each firing field subtends an angle of about 90° but that the firing rates differ. (*Source:* After Taube et al., 1990a.) *B*. Rotation of a cue card on the wall of the cylindrical enclosure by 180° rotates the angular orientation of two simultaneously recorded fields by a similar amount. Note that the relative angle between the two fields tends to remain the same, as shown by the dashed parallel lines. *C*. Removal of the cue card shifts firing fields of two cells recorded at the same time. Again, both fields shift by approximately 40° and maintain a constant difference in their preferred heading directions. The x axes in the bottom figures of *B* and *C* have been extended beyond 360°, and part of the field is duplicated to show the entire shape of the firing fields around 0/360°. (*Source: B*, *C*. Afer Taube et al., 1990b, both with permission.)

Similarly, there does not appear to be any topography to the directions represented by neighboring neurons, an arrangement reminiscent of the lack of environmental topography in the layout of place cells. Importantly, unlike hippocampal place cells, which signal location in some locations but are silent in others, HD cells fire in all environments tested.

11.9.1 Head Direction Cells are Controlled by Distal Sensory Cues

Taube et al. (1990a) found that rotations of a cue card fixed to the apparatus wall by multiples of 90° produced almost commensurate rotations of the directional firing field (Fig.

11–14B). Slight deviations from perfect rotation, however, suggested that in the experimental setup used the card was not the only environmental cue exerting stimulus control over the preferred direction. This was confirmed in tests in which the card was removed altogether. Card removal revealed two interesting properties of these cells (Fig. 11–14C). First, the width of the directional firing field remained the same, as did the peak firing rate. This suggests that these properties depend on factors intrinsic to the cell itself or to the network in which it is embedded, not on environmental inputs. Second, the preferred direction shifted to a new unpredictable compass point in almost two-thirds of the cells. Shifts ranged from 108° in the clockwise direction to 66° in the counterclockwise direction. The preferred direction appeared to remain approximately the same in the remaining one-third of cells. Zugaro et al. (2001) tested the relative influence of distal and proximal cues in determining the orientation of HD cells. As Cressant et al. (1997) had shown with place field orientation, Zugaro found that the rotation of three distinct objects at the periphery of a platform, bounded by a cylindrical enclosure, caused an equal rotation in the preferred directions of all anterior thalamus HD cells tested. The cylinder prevented the rats from seeing more distal background cues, such as geometrically configured black curtains along the walls of the room. When the same object-set rotation was performed in the absence of the cylinder, the preferred directions of all the HD cells were essentially unaltered. Although the cylinder-absent, background-visible condition was always performed second, the consistency of the responses provides further evidence that the orientation system is preferentially controlled by the most distal cues available.

In addition to cue card shifts, Taube and colleagues (1990b) found that changing the shape of the testing enclosure from a cylinder to a square or rectangle also caused changes in the preferred direction. In both right-angled boxes, the polarizing cue card occupied the same location relative to the environment as it had in the cylinder. When tested in the rectangular enclosure, most cells (8/10) shifted directions by large amounts; but on subsequent testing of these cells in the square enclosure, fewer than half (3/8) had preferred directions shifted relative to those they had displayed in the cylinder. As with card removal, the peak firing and angular width remained constant. Golob and Taube (1997) found that only 2 of 11 cells changed their preferred direction by more than 18° from the standard cylinder to a square box. As previously, more radical shape changes (i.e., from the cylinder to triangular or rectangular enclosures) caused large shifts in directional preference; all 17 cells tested shifting by at least 36°. (One minor caveat: This study tested HD cell activity in hippocampal-lesioned animals only.)

Goodridge et al. (1998) looked at the role of sensory modalities other than vision on the firing of head direction cells. Whereas a simple auditory cue, such as a localized series of clicks or bursts of noise, was ineffective, a localized smell did exert a small but significant control over the preferred direction. Rotation of the walls and floor of the testing chamber in blindfolded rats also had a small effect that subsequent tests revealed was mostly attributable to the floor. There was also some evidence that the preferred direction in blindfolded rats was less stable.

11.9.2 Angular Distance Between any Given Pair of Head Direction Cells Always Remains Constant

An important property of HD cells is "obligatory coupling"—the angular distance between the preferred directions of pairs of HD cells is remarkably resistant to alteration (Fig. 11–14B,C). Regardless of the cue-control manipulation, both cells of a simultaneously pair are always found to rotate by the same amount. Figure 11–14C illustrates this nicely: Following cue removal, the preferred head direction of cell 1 rotates by approximately 40° accompanied by a similar rotation in cell 2. The important implication of this coupling of preferred directions between cells is that there must be some kind of "hard-wiring" of the network of HD cells such that the population of cells firing at any one time gives an accurate and, above all, unambiguous representation of heading direction. The maintenance of a constant angular distance between HD cell pairs in the face of environmental change is well modeled by attractor networks (e.g., Redish and Touretzky, 1996; Zhang, 1996) (see Chapter 14).

11.9.3 Head Direction Cells Can also Be Controlled by Idiothetic Cues

In a fashion similar to the place cells, some HD cells maintain their preferred direction following removal of the cue card. One interpretation of this finding is that the sense of direction is continually updated in the absence of environmental cues on the basis of idiothetic or inertial navigation cues including those from the vestibular and proprioceptive systems. Consistent with this possibility is the finding that vestibular lesions cause cells to lose their preferred direction (Stackman and Taube, 1997). It must be stressed, however, that idiothetic cues *alone* are almost certainly insufficient to maintain a constant preferred direction over a long period of nonstereotyped locomotion. For instance, in darkness, olfactory signals from the cylinder and/or floor are probably required in tandem with idiothetic cues for stable orientation, as suggested by the place cell results of Save et al. (2000) (Section 11.7.7).

Additional evidence for the role of vestibular cues on preferred heading direction comes from experiments in which the floor (and therefore the rat) and the black-and-white striped walls of the recording chamber were rotated together in tandem or independently (Blair and Sharp, 1996). There were two rates of rotation, one above and the other below that assumed to be detectable by the vestibular system. These manipulations were carried out both in the light and in the dark in an attempt to dissociate visual motion cues from vestibular effects. In the light, slow rotation of the wall and floor together resulted in the comparable rotation of the

preferred heading direction in all cells tested. In contrast, rapid rotation of the wall or floor individually or together was ignored by most cells, which maintained their preferred direction relative to the laboratory frame. A few cells did show partial or complete rotations under these conditions, revealing some influence of idiothetic cues. The picture was different in the dark. Now both fast and slow rotations changed the preferred heading direction for many but not all of the cells. This pattern of results suggests that the preferred direction is controlled by several factors, which include visual information from the laboratory itself and visual motion and vestibular information derived from the animal's movements. The latter become more effective in the absence of the distal visual cues.

Disorientating or disruptive rotations of the animal carried out before it is placed in the environment have also been examined. If these are carried out on a routine daily basis for several weeks prior to recording, HD cells have a less stable relation to the frame of the laboratory both within and across recording sessions. They are also less well controlled by explicit visual cues (Knierim et al., 1995). Even in animals that had not been disorientated in this way and that displayed strong stable control by visual cues, subsequent introduction of the disorienting procedure prior to each daily recording session caused the HD cells to become progressively uncoupled from strong visual control. Knierim and colleagues suggested that this is evidence that path integration navigation cues predominate when an animal first enters a new environment and that environmental cues gain control over the head direction system only after a period in which they maintain a stable relation to the path integration system. Stability, it is thought, initially derives from the path integration system. On this argument, the association of the head direction system to environmental cues would provide corrections for the inevitable accumulation of errors to which the path integration system is subject. This requires that the system, which originally used the path integration system as the basis for assigning stability (or a direction) to the visual cue, would then be able to use that cue to correct the drift in the system. This boot-strap operation appears to require rapid association of specific cues (e.g., those provided by a cue card) to an otherwise stable but preexisting framework. The amount of exposure time for a visual cue card to gain control over preferred orientation was studied in passing in earlier studies. Goodridge et al. (1998), for instance, found that 8 minutes was sufficient for all cells tested, but that as little as 1 minute sufficed for some cells. Zugaro et al. (2000) found that preferred directions shifted to a new, fairly stable orientation within 15 seconds of a cue card rotation. More recently, an interesting study designed specifically to examine this issue (Zugaro et al., 2003) has shown that reorientation induced by 90° rotation of a peripheral cue card in the dark can occur with a latency on the order of 100 ms after the cue-card shift becomes visually apparent. The authors reasonably concluded that such latencies are more compatible with an abrupt jump from one preferred direction to another than with a gradual rotation through intermediate directions. In familiar environments, control of the head direction system by visual stimuli can be rapid indeed. Perhaps the slower figures are due to the time it takes for the animal to notice the changed position of the cue card.

11.9.4 Head Direction Cells Are Found in Different Anatomically Connected Brain Areas

Head-direction cells have been recorded in areas of the brain in addition to the dorsal presubiculum, where they were first discovered. These areas include the anterior dorsal thalamic nucleus (Taube, 1995a), lateral mammillary nucleus (Stackman and Taube, 1998), lateral dorsal thalamic nuclei (Mizumori and Williams, 1993), retrosplenial cortex (Chen et al., 1994; Cho and Sharp, 2001), and striatum (Wiener, 1993). Apart from the striatum, these areas are all strongly interconnected. The HD cells in the lateral mammillary nucleus, anterior thalamus, and dorsal presubiculum have been most studied, and this section concentrates on the differences in their properties. Do they tell us anything about the way in which the head direction signal is constructed? What is the contribution of each part of the circuit? In addition to the characterization of the properties of the HD cells in each area, two additional approaches to these questions have been used. The first looks at the relative timing of the signal in the various areas, and the second asks what the effect of a lesion in one area is on the activity in another. With the first approach, the best temporal correlation between the HD cell firing and the animal's heading direction is computed. The idea is to see whether cell firing is better related to the animal's current heading or to its heading in the immediate past or future. The assumption is that if the best correlated cell firing precedes the current heading direction, it is more likely to reflect some aspect of neural activity in the motor system that is producing the head movements; conversely, if the best correlated cell firing lags behind the behavior, it is more likely to reflect sensory feedback generated by the movement. The latter assumption is not infallible, however, because it is equally possible that lagged cell firing represents aspects of the neural control of movement shifted by a time delay.

The second use of time shift correlation analyses is to compare the temporal relations between the areas in which HD cells are found. If the cells in one area show a firing pattern that is earlier relative to the current heading direction than those of a second area, it is reasonable to suppose that the first brain area makes computations that come "earlier" in the circuit than the second. In a modular system with strictly serial connections between the modules, the relative latencies with respect to an external event may be taken as an indication of the functional and perhaps causal connectivity between brain areas.

There is a clear consensus that, on average, the firing of HD cells in the dorsal presubiculum is approximately in synchrony with the current direction of heading. HD cells in the lateral

mammillary nucleus lead those of the anterior dorsal thalamus (by about 60–70 ms), and the anterior dorsal thalamus leads the dorsal presubiculum (by about 20–30 ms) (Blair et al., 1997; Stackman and Taube, 1998; Taube and Muller, 1998). Although it is clear that there are average time shifts between the areas, there is also a wide distribution of shifts within any area, resulting in an overlap of shifts between areas. The pattern of temporal correlations suggests a functional pathway that originates in the lateral mammillary nucleus, passes information to the anterior dorsal thalamic nucleus, and thence to the dorsal presubiculum. Remarkably, this is part of the classic Papez circuit originally believed to provide the neural substrate for emotions (see Chapter 2), and there is abundant evidence of its anatomical basis from numerous tract tracing studies (see Chapter 3). It is important to remember, however, that there are also substantial connections in the opposite direction and, as we shall see in the next section, good reason to be cautious when putting forward any simple serial theory of the elements of the head direction system in rodents.

A similar story emerges from lesion experiments. Lesions of the anterior dorsal thalamic nucleus abolish the head direction signal in the dorsal presubiculum (Goodridge and Taube, 1997). In contrast, lesions in the dorsal presubiculum do not abolish the anterior dorsal thalamic nucleus signal but have more subtle effects on it. The clearest of these is an increase in the amount of time by which anterior dorsal thalamic nucleus HD cell firing anticipates the animal's heading direction. This suggests that a contribution of the feedback from the dorsal presubiculum to the anterior dorsal thalamic nucleus is to reduce the anticipatory interval expressed in the anterior dorsal thalamic nucleus leg of the system. A second effect of dorsal presubiculum lesions is to abolish the control of a cue card over the preferred heading direction of anterior dorsal thalamic nucleus cells (Goodridge and Taube, 1997) and to reduce the consistency and stability of the preferred heading direction between recording sessions.

Blair and colleagues (1999) investigated the effects of bilateral or unilateral lesions of the lateral mammillary nuclei on the properties of HD cells in the anterior thalamus. Following unilateral lesions, thalamic cells still had preferred directions, but they sometimes differed from prelesion ones, the peak firing rates were often reduced, and the turning curves were broader. In general, the HD cell firing properties shifted to resemble those in the mammillary bodies. Following bilateral lesions, no directional cells could be found in the anterior thalamus.

The overall pattern of changes following lesions of various nuclei support the notion that directional signals travel from the hypothalamus through the thalamus to the cortex. Furthermore, they are consistent with the idea that the dorsal presubiculum is the site at which visual sensory information gains access to the HD system, and the lateral mammillary nucleus/anterior dorsal thalamic nucleus pathway is the source of path integration control based on vestibular information.

11.9.5 Dorsal Tegmental Nucleus of Gudden Provides Information About the Direction and Angular Velocity of the Animal's Head Rotation

The midbrain nucleus called the dorsal tegmental nucleus of Gudden (DTN) is reciprocally connected to the lateral mammillary nucleus and contains cells whose firing rate correlates with the angular velocity of the head (Bassett and Taube, 2001; Sharp et al., 2001). Integration of the angular velocity over time would produce a signal proportional to the change in angular direction, which could be used to update the current heading direction. There appear to be several types of angular velocity cell in the DTN: Many show strong correlations with velocity of movement regardless of the direction of the movement, increasing their firing rates in both directions, whereas others are asymmetrical, increasing their firing rates in one direction and decreasing them or firing at a constant rate in the other. In addition to these angular velocity cells, the DTN contains a small number of HD cells, and there is evidence that some of the angular velocity cells also show head direction or head pitch correlates.

11.10 Interactions Between Hippocampal Place Cells and Head Direction Cells

What is the relation between place cells and HD cells? In the original formulation of the cognitive map theory, O'Keefe and Nadel suggested that the map of an environment consisted of a set of place representations bound together by information about the direction and distance between them (O'Keefe, 1976; O'Keefe and Nadel, 1978) (see Section 11.7). In this view a place representation could be activated either by direct sensory information impinging on the animal when it occupied that place or by activation of a different place representation together with the appropriate distance and direction inputs between that place and the target place. The theory was extended in 1991 (O'Keefe, 1991a,b) by the suggestion that place cells were dependent on the input from two or more HD cells for directional information and that rotation of the HD system relative to the environmental frame would produce the rotation of place fields seen in these experiments. McNaughton and colleagues (1996) suggested that the place cell firing field was determined by the distance to a single object in a specific direction and that this directional signal was provided by the HD system. Evidence in favor of the idea that the place system is dependent on the HD system comes from the following.

Both place and HD cells respond similarly to rotation and removal of polarizing cues, such as the cue card in the standard cylinder (Muller and Kubie, 1987; Taube et al., 1990b; Cressant et al., 1997; Zugaro et al., 2001). Vestibular lesions abolish anterior thalamic directional firing and location-specific firing in hippocampal place cells (Stackman and

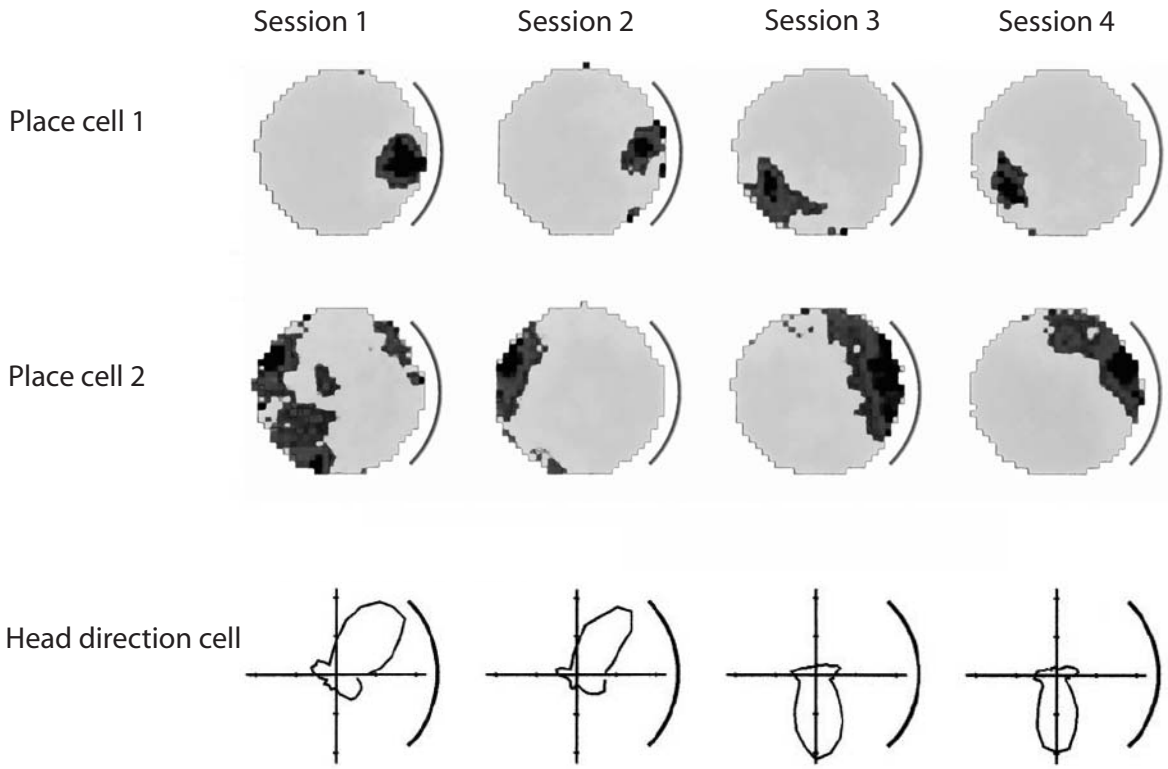


Figure 11–15. Place and head direction cells recorded simultaneously maintain the same angular orientation despite both rotating relative to the environment. Top two rows show the place fields of two cells that rotate by about 135° following disorientation of the animal by gentle spinning between sessions two and three. Bottom row shows the field of a head-direction (HD) cell recorded at the same time, which also rotates. Both place fields and preferred direction of the HD cell are stable before (sessions one and two) and after (sessions three and four) the intervention. Note that the fields of both place cells and the HD cell maintain a constant angular relation to each other. (*Source*: After Knierim et al., 1995, with permission.)

Taube, 1997; Stackman et al., 2002; Russell et al., 2003). In the one experiment (Knierim et al., 1995) in which HD cells and place cells were recorded simultaneously, they stayed in register even under circumstances where the control by environmental stimuli was lost: Rotating the animal prior to the recording session often led to unpredictable rotation of both the preferred heading direction of the HD cell and the angular orientation of the place cell, but they maintained their fixed relation to each other (Fig. 11–15).

Lesions to the anterior thalamus or the dorsal presubiculum significantly increased the directionality of place fields recorded in the cylinder in comparison with control animals (Calton et al., 2003). Recall that in normal rats the place fields are essentially nondirectional in this testing apparatus (Muller et al., 1994) (see Section 11.7). Such lesions also reduce the spatial coherence of the place fields. The relation between the standard cue card and the place fields depends on the lesion locus. Note that in intact animals, as discussed above, rotation of the card causes the preferred direction of most HD cells to reorient rapidly so as to maintain a fixed relation to the card. Calton et al. (2003) found that in animals with lesions of the dorsal presubiculum the angular locations of hippocampal place fields were not controlled by the cue card but shifted unpredictably from trial to trial. Although intertrial variability was also reliably seen in anterior thalamus-lesioned animals, the effect was mild in these cases. Similarly, removing the cue card caused large shifts in the place fields' angular location in the dorsal presubicular animals but minor shifts in the anterior thalamic lesioned animals.

In contrast to the large effect that dorsal presubicular lesions have on hippocampal place cells, there is little evidence that hippocampal lesions have a major effect on the basic firing characteristics of HD cells. Golob and Taube (1997) reported that about the usual number of HD cells were recorded in the anterior thalamic nuclei and dorsal presubiculum following hippocampal lesions, and that they were under control of the visual cue card to the same extent. Furthermore, changes in the preferred firing direction in novel enclosures of different shapes were broadly similar to previous studies of nonlesioned animals. In a follow-up experiment, the effect of combined lesions of the hippocampus and overlying neocortex on the control of the HD cells by idiothetic path integration signals was examined (Golob and Taube, 1999). The preferred head direction was monitored as the animals moved from a familiar environment to an unfamiliar one. In normal animals, the self-movement cues provided sufficient information to maintain the heading direction in the new environment consonant with that in the old familiar one, con-

sistent with previous work (Taube and Burton, 1995). HD cells in lesioned animals, however, were not able to do this and, furthermore, took up to 4 minutes to reach a stable preferred orientation in the new environment. On the other hand, a cue card in the new environment was capable of establishing control over the HD preferred orientation, showing that there was no deficit in this part of the system. The primary influence of the hippocampus on the head direction system appears to be to maintain a consistent preferred direction in the HD cells as an animal moves between different enclosures in the same laboratory, presumably on the basis of path integration signals or context information about the laboratory. The only caveat here is that lesions of the overlying neocortex resulted in effects that were similar but of lesser magnitude, and it is not possible therefore to rule out a role for the neocortex or a more general, nonspecific effect of the lesions.

As we shall see in Chapter 13, there is evidence that hippocampus-lesioned rats can learn an allocentric spatial memory task in which they are required to go to a location defined by its distance from a single object in a specific environmental direction. This capability appears to depend on the HD system but not, because it depends on a single vector, on the hippocampal system.

In summary, the evidence strongly suggests that the place system relies on the HD system to provide it with the directional basis of a fixed framework, which acts as the scaffolding for the representation of an environment. Two HD cell characteristics are crucial to this: First, the angular distance between HD cells remains constant; and second, the vectors created by the signaling of each HD cell firing in different portions of an environment are parallel. Whereas environmental changes can cause the distance between different place fields to shift relative to each other, the HD cells appear to be rigidly fixed relative to each other, and it is only the relation between the total constellation of cells and the environment that can be altered. Rotation of the HD system rotates the entire place system. The most likely route for the influence of the HD system on the hippocampal place cells is via the medial entorhinal cortical grid cells whose orientation relative to the environment is also controlled by distal cues (see Section 11.7.7). The contribution of the hippocampal place system to the HD system is less clear. It may be the origin of information about the wider context that allows the animal to maintain a constant heading direction relative to distant cues as it moves from a familiar part of a territory to an unfamiliar one.

11.11 Hippocampal Complex-spike Cells Have Been Implicated in Nonspatial Perception and Learning

In addition to the widely reported spatial and movement correlates of hippocampal cells, there have been reports of other correlates from several laboratories. They have suggested to some that the functions of the hippocampus are more general than the processing and storage of specifically *spatial* information. We return to this question in Chapter 13 on lesion results, as a successful theory must account for the data from several experimental domains. Suffice it to mention here that nonspatial responses in hippocampal units do not per se argue against a spatial function for the hippocampus. A spatial system would need to incorporate information about the locations of objects, rewards, and dangers as well as using nonspatial information in the construction of place representations.

The data on nonspatial unit responses fall into two primary classes: those suggesting a role in nonspatial sensory processing and those showing a correlation with some aspect of a nonspatial learning process. They are discussed in separate sections.

11.11.1 Hippocampal Cells Have Been Implicated in the Processing of Nonspatial Sensory Information

Studies by McLean, Ranck, and O'Keefe during the 1960s and early 1970s looked for, but could not find, selective sensory inputs to the hippocampal complex-spike cells. On the other hand, Vinogradova (1977) and colleagues reported a nonspecific effect of sensory stimulation in the awake rabbit; however, it appears likely from the firing rates of her cells, the absence of complex spikes, and subsequent work on the correlates of theta cells in the rabbit (Sinclair et al., 1982) that many of her cells were theta cells. As pointed out above, theta cells in the rabbit increase their firing during theta EEG episodes, and in the rabbit these episodes occur during nonmovement arousal as well as during movement.

Ranck (1973) and O'Keefe (1976) studied the role of sensory inputs in the freely moving rat and, aside from a few olfactory responses reported by O'Keefe, neither found much evidence for these inputs. However, some of the unit responses to the cues used in more recent learning experiments could be interpreted as unlearned responses to the stimuli themselves. For example, Wood et al. (1999a) reported that 8% of cells in the rat hippocampus responded to the olfactory cues in an olfactory recognition task. Likewise, Tamura et al. (1992) reported that 10% of units in the hippocampus and surrounding regions of the monkey responded to specific objects. Creutzfeldt and colleagues (Vidyasagar et al., 1991; Salzmann et al., 1993) found that as many as 38% of hippocampal and parahippocampal units in the monkey changed activity in response to arousing stimuli such as the presentation of a raisin or the sight of the experimenter. It is not clear whether these are perceptual, learned, or general arousal responses. These studies are examined in more detail in the section on nonspatial learning, below.

Perceptual responses to stimuli have also been reported in studies on the human hippocampal formation. In one experiment (Kreiman et al., 2000b), subjects viewed a series of pictures drawn from nine classes: household objects, unknown faces portraying different emotions, famous faces,

spatial layouts including the facades of houses and natural scenes, animals, drawings of famous people or cartoon characters, cars, food items, and abstract drawings. Overall, 14% of units from medial temporal lobe sites showed a visual response to one or more stimuli. Interestingly, of the 32 hippocampal units responsive to visual stimuli, 29% responded selectively to spatial layouts, 12% to famous faces, and less than 10% to stimuli drawn from the other categories. Therefore, although hippocampal cells responded to famous faces and other stimuli, pictures portraying the layout of environments or buildings were by far the most effective of these visual stimuli. The human hippocampus, like that of the rodent and nonhuman primate, appears to prefer information about spaces over faces and objects.

11.11.2 Hippocampal Unit Activity May Show Correlations with Different Aspects of Nonspatial Learning Tasks

In pioneering studies conducted during the 1960s, Jim Olds and Menahem Segal recorded unit activity in the hippocampus during classical conditioning to a tone. They saw an increase in firing to the tone following conditioning. These studies were the first of a number that have looked at the responses of hippocampal neurons during or after nonspatial learning, primarily using conditioning paradigms or discrimination learning. Some of these studies were carried out using multiunit recording techniques, which, like EEG, register only the collective properties of a group of neurons. As we have seen, the spatial coding of environmental features in complex-spike cells is carried out at the single-cell level, and group recordings would not reveal this spatial code. We therefore concentrate primarily on studies that have recorded single-unit activity and refer to the multiunit studies only when they add something different.

Two types of behavioral paradigm have often been used to look at nonspatial learning: (1) classical conditioning in which the animal's response has no effect on the stimulus-reward contingencies and (2) signaled operant conditioning in which it does. A good example of the former are experiments on classical conditioning of the rabbit nictitating membrane (NM) response; a good example of the latter would be a nose poke, go/no-go instrumental task taught to a rat. In the sections that follow, we turn first to classical conditioning experiments in the rat and rabbit and then examine the somewhat more extensive literature on operant conditioning in rats and monkeys.

11.11.3 Hippocampal Unit Activity During Aversive Classical Conditioning

Hippocampal unit activity has been recorded during aversive classical conditioning: a single conditioned stimulus (CS) followed after a short period by an unconditioned stimulus (US) consisting of a shock or other noxious stimulus. After sufficient pairings, the CS comes to elicit a conditioned response (CR) such as an eyeblink or suppressed heart rate. In a more complicated differential conditioning paradigm, two stimuli (CS^+ and CS^-) are interspersed randomly, one followed by the US and the other not. In this latter paradigm, the animal learns to discriminate between the stimuli, coming eventually to respond to the first but not the second. Typically, during the early stages of learning, both stimuli elicit responses and only subsequently does the animal learn to inhibit its response to the CS^-. In addition, there is a learned arousal response that is not specific to the hippocampus but can be reflected in the activity of hippocampal cells.

Delacour (1984) trained rats on an aversive differential conditioning paradigm. During slow-wave sleep two different tones served as the conditioning stimuli and mild electric shock to the neck as the unconditioned stimulus. He recorded increased neck muscle tone as the conditioned response (CR) and the cortical EEG as an independent measure of arousal. During the early stages of training, both the CS^+ and CS^- elicited a muscle activation CR that was associated with cortical arousal; during the later stages, there was a decrease in the cortical arousal to both stimuli as well as the development of a differential neck muscle response, with the response to the CS^+ remaining high and that to the CS^- steadily declined to baseline (Fig. 11–16A). The initial increase in the EMG activation to both stimuli was thought to reflect general arousal, whereas the later differentiation between them reflected movement to the CS^+. Unit responses to the CSs of single hippocampal complex-spike cells, hippocampal theta cells, and dentate granule cells were monitored. During the early phase of training, all cell types increased activity to both stimuli in parallel with EMG activation, the complex-spike cells somewhat faster than the theta cells. During the latter phases, however, they acted differently: The hippocampal complex-spike cells ceased firing to both positive and negative conditioning stimuli, paralleling the decrease in cortical arousal. Like the cortical arousal, at no time during training did they differentiate between the two CSs (Fig. 11–16B). In contrast, the responses of the hippocampal theta and dentate granule cells followed the pattern of the EMG response and began to differentiate between the stimuli as the behavioral differentiation developed (Fig. 11–16C). As a control for the specificity of these responses, Delacour recorded from thalamic cells as well and found that they also divided into two classes: Those in the centre median acted similiar to the complex spike cells, whereas those recorded in the dorsomedial nucleus resembled the theta cells. On the basis of these results, Delacour argued rather convincingly that the response of the complex-spike cells was a reflection of general arousal, whereas the pattern of activity of the theta/granule cells was a reflection of the learned differential increase in neck muscle activation to the two conditioned stimuli. The latter response may reflect the movement correlates of the hippocampal theta cells. He further argued that these were not specific responses but were representative of more general responses in arousal and movement systems that could be recorded elsewhere in the brain as well. Laroche and Bloch (Bloch and Laroche, 1981; Laroche et

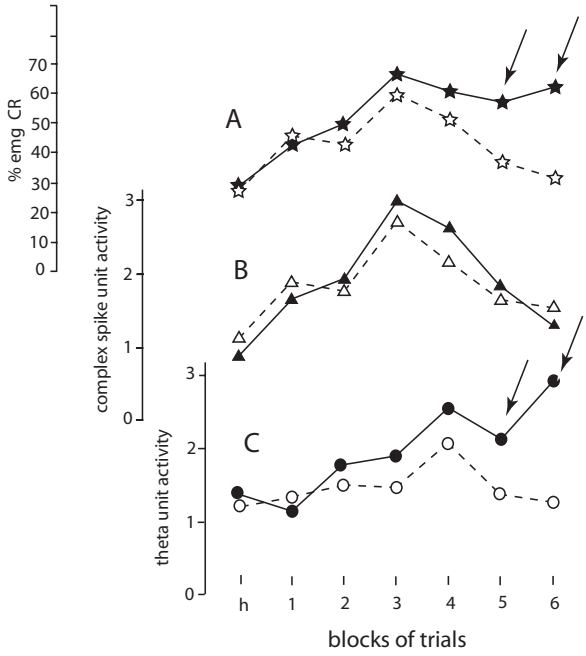


Figure 11–16. Two types of response in hippocampal unit activity during classic conditioning of the arousal response to positive and negative tones. *A*. Neck electromyography (EMG) increases during the early trials and then begins to differentiate between the CS^+ (black stars) and CS^- (open stars) by the last two blocks of trials (arrows). *B*. Principal hippocampal neurons increase their firing rate during the early part of the trial in parallel with the EMG response but then fall off to both stimuli. *C*. Hippocampal theta cells and dentate granule cells also show an initial increase but then differentiate between the CSs in a manner that parallels the EMG activity. Solid symbols are CS^+ responses, and open symbols are CS^- responses in all panels. h, habituation trials. (*Source*: Delacour, 1984.)

al., 1983) found a similar increase to a CS in the dentate multiple unit response after conditioning.

Moita and colleagues (2003, 2004) have carried out an important classical conditioning experiment in the rat that may throw further light on the role of hippocampal cells in these tasks. They recorded the responsiveness of complex-spike and theta cells to an auditory stimulus before and after delay classical conditioning in which the stimulus was paired with a brief electric shock to the eyelid. No complex-spike cells responded with a short latency to the tone prior to conditioning, but many did so after conditioning. However, they did so only if the animal was located in the place field of the cell during CS presentation (Fig. 11–17). As Figure 11–17 shows, the same cell might give a strong, brisk response to the auditory stimulus when the animal was in the place field but respond little or not at all to the same stimulus when the animal was outside the field. The animal's location in the place field appeared to gate the response to the CS rather than simply summate with it. Moita and colleagues (2004) also found that place cells can develop a place field or can shift field location in the conditioning box following conditioning, and this effect was greater following conditioning to the context of the box than when there was an explicit auditory stimulus. These results may give some insight into the role of the hippocampus in this behavioral paradigm, at least in the rat. It is possible that, in addition to the conditioning of arousal responses, some conditioned responses in hippocampal units in immobile animals reflect the fact that during conditioning some cells shift their place fields to the animal's location and begin to respond to the CS in that location. Against this interpretation is the fact that restraining the rat abolishes the firing in the place field (Foster et al., 1989). However the possibility remains that restraint may not abolish the gating function on conditioned stimuli. We return to this possibility following a discussion of unit activity during the nictitating conditioning paradigm.

11.11.4 Nictitating Membrane Conditioning in the Rabbit: Role of Theta

Conditioning of the rabbit nictitating membrane (NM) has been used successfully as a model system for studying the neural bases of learning and memory since it was introduced by Richard Thompson in 1976 (Thompson, 1976). In this paradigm, the CS (e.g., a 6 KHz tone) is paired with a US, which can be a puff of air to the eye or a small electric shock to the orbit. By varying the temporal relation between the CS and US, one can investigate various types of classical conditioning. In delay conditioning, the US overlaps the last portion of the CS, so both terminate together. In trace conditioning, the CS ends before the US begins, and there is a temporal gap between the two. As we saw with classical conditioning in the rat (Delacour, 1984), there is an important role for arousal in this form of learning. There is clear evidence that theta activity gets conditioned to various aspects of the task during classical conditioning experiments in the rabbit. Powell and Joseph (1974) conditioned the corneoretinal potential in the rabbit using a mild electric shock to the eye as the US. This was preceded by a CS. A second stimulus was not followed by the US and served as a CS^-. During the early stages of learning, before differential responses to these two stimuli had been established, there was a high incidence of theta to both CSs; after differential conditioning, when the CS^+ but not the CS^- consistently elicited the US, a considerably higher amount of theta occurred to the CS^+. During this second phase of conditioning there was a differential response of the neck EMG to the CS^+. This pattern of responses is similar to that seen in the rat (see above) and indicates that the early theta activity was related to general arousal, and the later theta activity was related, at least in part, to the motor response. Experiments that manipulate the animal's arousal have shown that it has a strong effect on learning rates and that this effect may be mediated in part via its effect on the baseline rate of theta activity. Berry and colleagues (Berry, 1989) showed that the pretraining background amount of hippocampal theta was a good predictor of NM conditioning rates and that this variable was strongly influenced by the level of arousal. Following

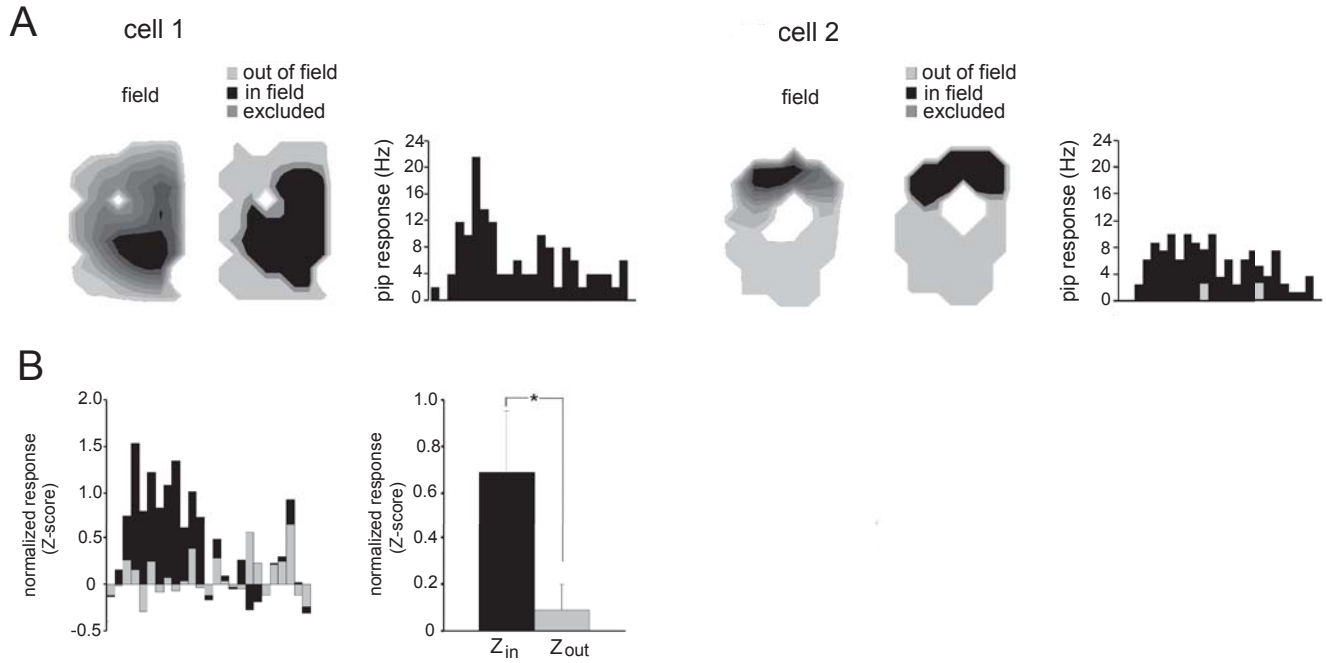


Figure 11–17. Response of hippocampal complex spike cells to auditory CS following classic eyeblink conditioning. The cells respond only when the animal is in the place field. *A*. Responses in two individual cells. On the left of each panel, place fields are shown with the higher firing rates in the darker colors; on the right of each panel are histograms of the unit responses while the animal is inside the place field (black color) and outside the field (light color). The middle panels show the portion of the environment included as part of the field, the portion considered to be outside the field, and an immediate zone not considered as part of either. Both cells showed a strong response to the stimulus inside the field and no (cell 1) or few (cell 2) spikes outside the field. *B*. Population response histograms to stimulus presented inside (dark shading) and outside (light shading) the field of each cell. Across the population there is a significant difference between the in-the-field and out-of-field responses (histogram, right). The x-axes in the unit response histograms are 250 ms in total, which was the period of CS presentation. (*Source*: Moita et al., 2003.)

mild water deprivation, there was a faster rate of learning. A similar pattern was found with trace conditioning (Kim et al., 1995).

11.11.5 Single-unit Recording in the Hippocampus During Nictitating Membrane Conditioning of Rabbits

Several laboratories have recorded the activity of single units and multiple units from the hippocampus of rabbits during classical conditioning of the NM response. Berger and colleagues (1983) recorded single units in the rabbit hippocampus during simple delay NM conditioning. Pyramidal cells were identified by their antidromic activation from fornix stimulation. They comprised the largest proportion of cells recorded; and following conditioning, many increased their firing rates during the CS period (Fig. 11–18A–C). They typically emitted one or more bursts of spikes during each trial, some showing a pattern of activity that closely modeled the NM response (Fig. 11–18A) whereas others were more selective, firing during different time epochs of the trial (Fig. 11–18B,C). One type of theta cell increased its overall level of activity during the trial (Fig. 11–18D,E), whereas another type showed an overall decrease in activity (Fig. 11–18F,G). Theta cells were typically activated by the CS to fire a series of theta-like bursts, which often continued throughout the trial and in some cases continued beyond the termination of the trial. Berger and colleagues also reported a third category of cells, "silent" cells, which constituted 11% of the neurons recorded; they had exceptionally low spontaneous firing rates (< 0.2/second), were not activated by fornix stimulation, and did not participate in the conditioned response. As we shall see below, this estimate of the percentage of cells in this category may be low.

Weiss et al. (1996) recorded single units from rabbit hippocampus during trace conditioning of the NM, a version of the conditioning task that is sensitive to hippocampal lesions: Either the CR is abolished, or its timing is altered (see Chapter 12). They also reported the existence of the same three classes of cells reported by Berger and colleagues in their delay conditioning experiments; but in other respects the results differed markedly. Weiss et al. found a much larger percentage of cells that did not participate in the conditioning (40% in contrast to Berger's 11%) and relatively few units that were significantly excited (in contrast to inhibited) during the CS or trace period in the conditioned animals in comparison with unpaired controls. Thus, in CA1, 14% of pyramidal cells were excited during the CS period in contrast to 9% of the unpaired

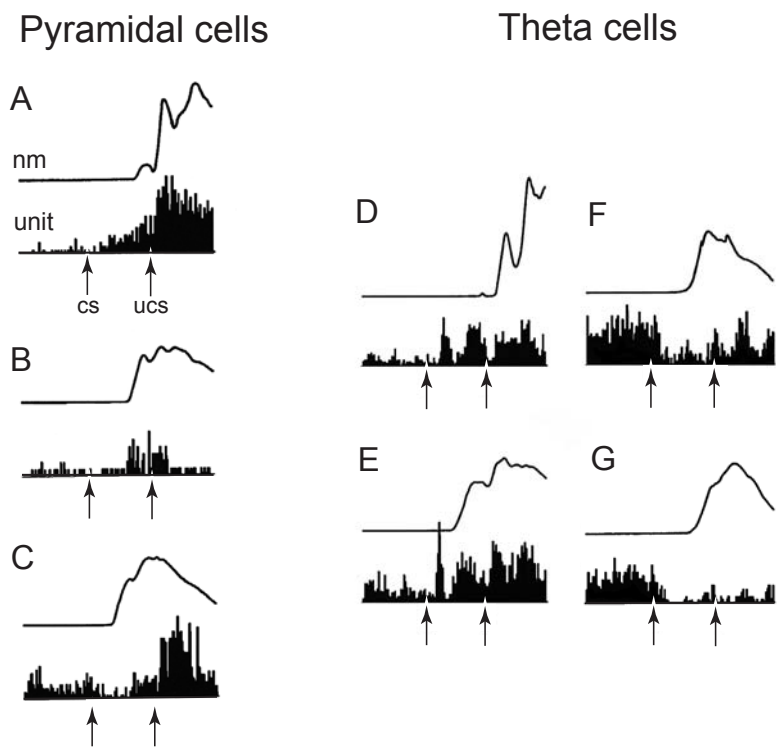


Figure 11–18. Firing patterns of hippocampal units following nictitating membrane conditioning in the rabbit. *A–C*. Pyramidal cells. *D*, *E*. Excited theta cells. *F*, *G*. Inhibited theta cells. Top trace in each panel is the nictitating membrane record; bottom trace is the histogram of the average unit response. The first arrow indicates CS onset and the second arrow UCS onset, an interval of 250 ms. Note the theta bursting at approximately 8 Hz following the CS onset in the theta cells. (*Source*: Berger et al., 1983.)

controls; and 11% were excited during the trace period in contrast to 9% of the controls. In contrast to the findings of Berger and colleagues, the increase in inhibitory responses relative to the controls was twice as large as the increase in excitatory responses. McEchron and Disterhoft (1997) obtained similar results in animals conditioned in a trace paradigm when recordings were taken after asymptotic performance had been reached. In addition, they recorded from some animals during the earlier stages of learning. They found that the maximal activation in complex spike units occurred on the trials just *prior* to the onset of learning; as behavioral conditioning proceeded and the conditioned responses appeared more frequently, these unit responses actually diminished. Finally, when looked at on a trial-by-trial basis, there was no correlation between the unit activity and the occurrence of the conditioned response. This pattern suggests that the hippocampus may not be involved directly in the generation or timing of the motor response. Rather, it may be involved only indirectly, perhaps playing a role in the creation of a temporary behavioral state that precedes the motor learning but is a necessary condition for it to occur. Lesions of the hippocampus do not generally affect delay conditioning but do affect trace conditioning, changing the timing of the conditioned response in the trace version of the task (for a review see O'Keefe, 1999). Thus, if we compare the effects of hippocampal lesions on the NM conditioning with the results of single-unit recording experiments, we are left with a paradox. Delay conditioning, in which there are a sizable number of pyramidal cells whose temporal activation profile precedes and models the CR, does not require the hippocampus, whereas trace conditioning, during which few such unit responses are found, does require an intact hippocampus.

How might the hippocampus be involved in trace but not delay conditioning? There are three distinct but related possibilities. The first suggests that the hippocampus provides the information that the animal is in a frightening place, the second that the animal is in a place where frightening events happen, and the third that it provides information about the timing of the unpleasant event. The first two make clear links to the spatial functions of the hippocampus, whereas the third does not necessarily do so. We deal with these in turn.

Our first two mechanisms relate to ones suggested by Nadel and colleagues (1985). According to them, the spatial functions of the hippocampus might lead to its being involved in conditioning in two ways: as the substrate for a direct association between the background cues and the US or less directly as the basis for an association between the CS–US event and the overall context. Evidence for a hippocampal role in conditioning to the background cues (the fearful context hypothesis) comes from experiments showing that animals with hippocampal lesions do not condition to the context (Phillips and LeDoux, 1994; Kim et al., 1995). This could come about either because there is an association of fear with the entire testing box or with specific locations in it. Recall that the ventral hippocampus contains place cells with large fields that may extend to an entire testing environment, and they could provide the basis for context conditioning. An alternative is that the more localized place fields in the dorsal hippocampus could shift following context conditioning so

the overall pattern of place cell firing was different, perhaps signifying a dangerous environment (Moita et al., 2004).

The second possibility is that the cells showing conditioned responses are place cells whose fields coincide with the location of the testing box, and the responses to the CS are signaling the occurrence of an event in that place. As we have seen above in the experiments of Moita and colleagues (2003), complex-spike cells in the rat, which are normally not responsive to auditory stimuli, begin to respond to the CS following delay conditioning but only if the animal occupies the firing field of that cell. If the same changes are occurring in the rabbit, this might explain the increased responsiveness of cells with fields in the conditioning location; moreover, the fields of some cells might shift to that location following conditioning. With this interpretation, the increased responsiveness might reflect the fact that the hippocampus is now signaling that the animal is in a dangerous location and, furthermore, that the auditory cue predicts the onset of danger in that place. More evidence for a role for the hippocampus in contextual gating of CS–US events comes from a context shift experiment. Although lesions of the hippocampu have no obvious effect on simple delay conditioning, they do affect the role the background cues (i.e., the room in which conditioning takes place) play in that conditioning. Penick and Solomon (1991) showed that simple delay conditioning was disrupted in normal rabbits when the animal was moved into a new room after conditioning was completed but hippocampal-lesioned animals were not affected. This result fits nicely with the idea that the hippocampus provides spatial contextual information that gates the conditioning of fear to the CS. This information might not be necessary for simple delay conditioning, but it might be essential for trace conditioning.

The third possibility is that the hippocampus provides information about the timing of the US. The interpretation of the altered timing response in trace conditioning following dorsal hippocampal lesions is unclear. Why, for that matter, does the conditioned unit response occur just prior to the unconditioned stimulus in normals? The original rationale of the NM learning paradigm was to rule out any instrumental contribution to the learning and in particular the possibility that the conditioned response would protect the eye from the US or otherwise attenuate its impact (Thompson, 1976). If, on the other hand, one accepts that the conditioned response in these conditioning paradigms is a reflection of the prediction of the US, the timing of the CS is important; and the lesion results suggest that the hippocampus is involved in setting up the conditions under which the short-term prediction of stimuli can occur. Both Rawlins (1985) and Wallenstein and colleagues (1998) have suggested that the hippocampus is needed to bridge a temporal gap between two stimuli to be associated. This role would be particularly important in paradigms such as trace conditioning, where there is a CS–US interval and normal animals generate a CR just prior to the US. What might the underlying mechanism be? One possibility is that hippocampal a-theta is being used as a timing mechanism to allow a short-term signal to bridge the CS–US gap. Theta oscillations, with their relatively constant period, could act as a clock over short intervals. During conditioning of the rabbit NM response, this clock signal can be reset by the CS and could therefore be used to predict the occurrence of the US. Even here there might be a secondary role for the spatial functions of the hippocampus. Recall that a-theta in the rabbit can be driven by arousing stimuli (e.g., the CS) much more easily than in the rat (see Section 11.3). That required level of arousal might be based on conditioning to the apparatus and other nonspatial cues, but it might also be driven by hippocampus-mediated fear conditioning to the background context as well. Under circumstances where the arousal level is appropriate, pyramidal cells may be able to count theta cycles and use this clock signal to predict the timing of the US. This timing signal would then be available to brain stem regions to control the occurrence of the CR. In the absence of this signal (e.g., following hippocampal damage), conditioning would still occur but the timing of the CR would be controlled by other factors. Some support for this view comes from an experiment on trace conditioning of the heart rate in rabbits (McEchron et al., 2003). Pairing a CS with an aversive US results in slowing of the heart rate in anticipation of the US; this can be conditioned with trace intervals as long as 20 seconds. McEchron and colleagues used trace intervals of 10 and 20 seconds in two groups of animals and found that one-fourth of complex-spike cells showed a burst of activity timed to coincide with the end of the trace interval. The effect was weak on any given trial; but when summed over trials there was a discernible response. The problem for the theta-counting hypothesis is that 10 seconds is a long time to count theta cycles. For further discussion of the contributions that contexts make to learning, see Chapter 13.

11.11.6 Hippocampal Unit Recording During Operant Tasks

During operant conditioning tasks, the animal must emit a response to gain a reward or avoid punishment. Often the availability of reinforcement is signaled by a sensory stimulus such as a tone. Christian and Deadwyler (1986) recorded from complex-spike and theta cells during an appetitive operant conditioning task. They trained thirsty rats to poke their noses into a small antechamber in the wall of a box to receive a water reward. For some animals, the availability of reward was signaled by a tone, and no sensory discrimination was required; for others, a differential CS^+/CS^- procedure was used. Following successful conditioning to the single tone stimulus (Fig. 11–19A), theta cells showed a consistent increase in firing rate during the 200 ms following tone onset (Fig. 11–19A, theta). In contrast, no change from the background rate was seen in the complex spike cells (Fig. 11–19A, complex spike). During two-tone differential conditioning, the theta cells showed an increase to both stimuli with a greater increase to the CS^+ (Fig. 11–19B, theta). In contrast, the pyramidal cells registered a marginal but nonsignificant change to the CS^+ (Fig. 11–19B, complex-spike). Recordings

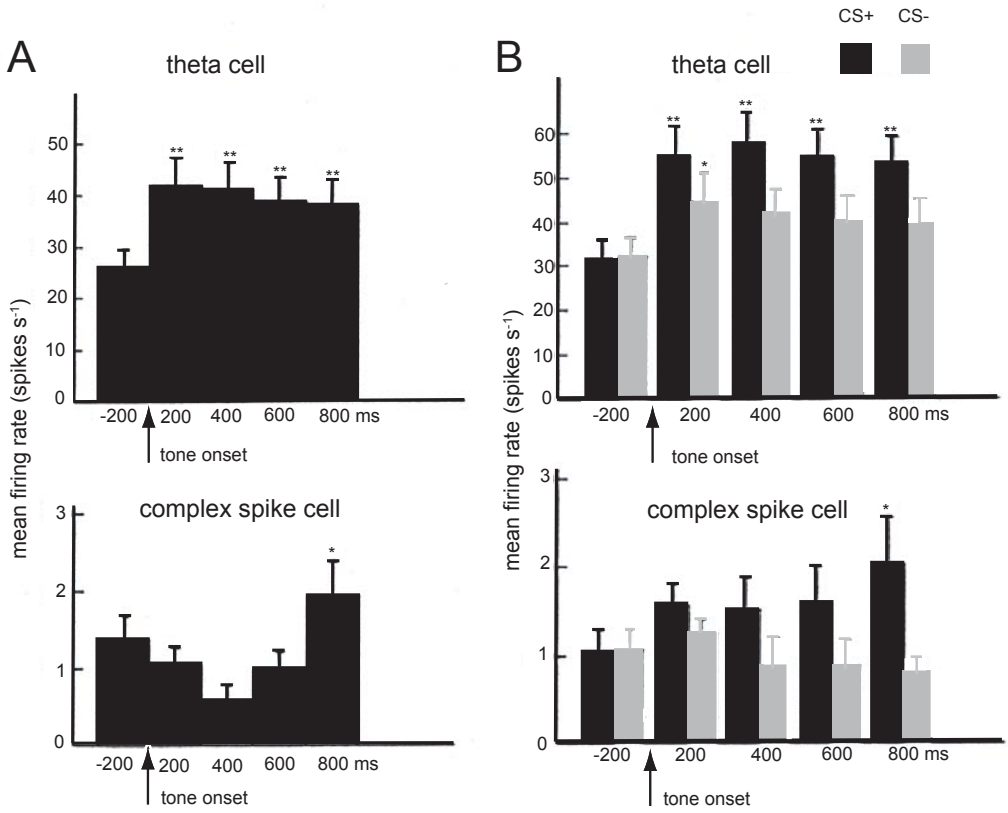


Figure 11–19. Theta and complex spike cell responses following nose-poke conditioning to tones. Theta cells (top) show increased firing above the pre-tone background rate in response to the tone in both simple (*A*) and compound (*B*) conditioning paradigms. In the latter, the unit response to the CS^+ is more marked than to the CS^-. Complex spike cells (bottom) do not respond in either the simple conditioning paradigm (*A*) or the complex compound conditioning paradigm (*B*). Single asterisks indicate a significant difference from pre-tone firing rates at the 0.05 level of significance and double asterisks at the 0.01 level of significance. The apparent increase in firing rate in the complex spike cells 800 ms following the tone in both *A* and *B* is an artifact from the reward dispenser. (*Source*: Christian and Deadwyler, 1986.)

taken from animals while they acquired the task showed that the changes in theta cell firing occurred in parallel to acquisition of the conditioned EMG response and disappeared with subsequent extinction. Again no changes were seen in complex-spike cells during the course of acquisition.

In a subsequent experiment from the same laboratory, Foster and colleagues (1987) did find a small but significant increase in firing in their population of complex-spike cells to both conditioned stimuli but still no differential activity to the CS^+. A more detailed look at the differential response that did occur in the theta cell group revealed that the difference in response to the two stimuli was due to an initial increase in firing to both stimuli, which peaked at about 80 to 100 ms after tone onset and was then maintained throughout the 1-second tone period to the CS^+ but fell back to baseline in response to the CS^-.

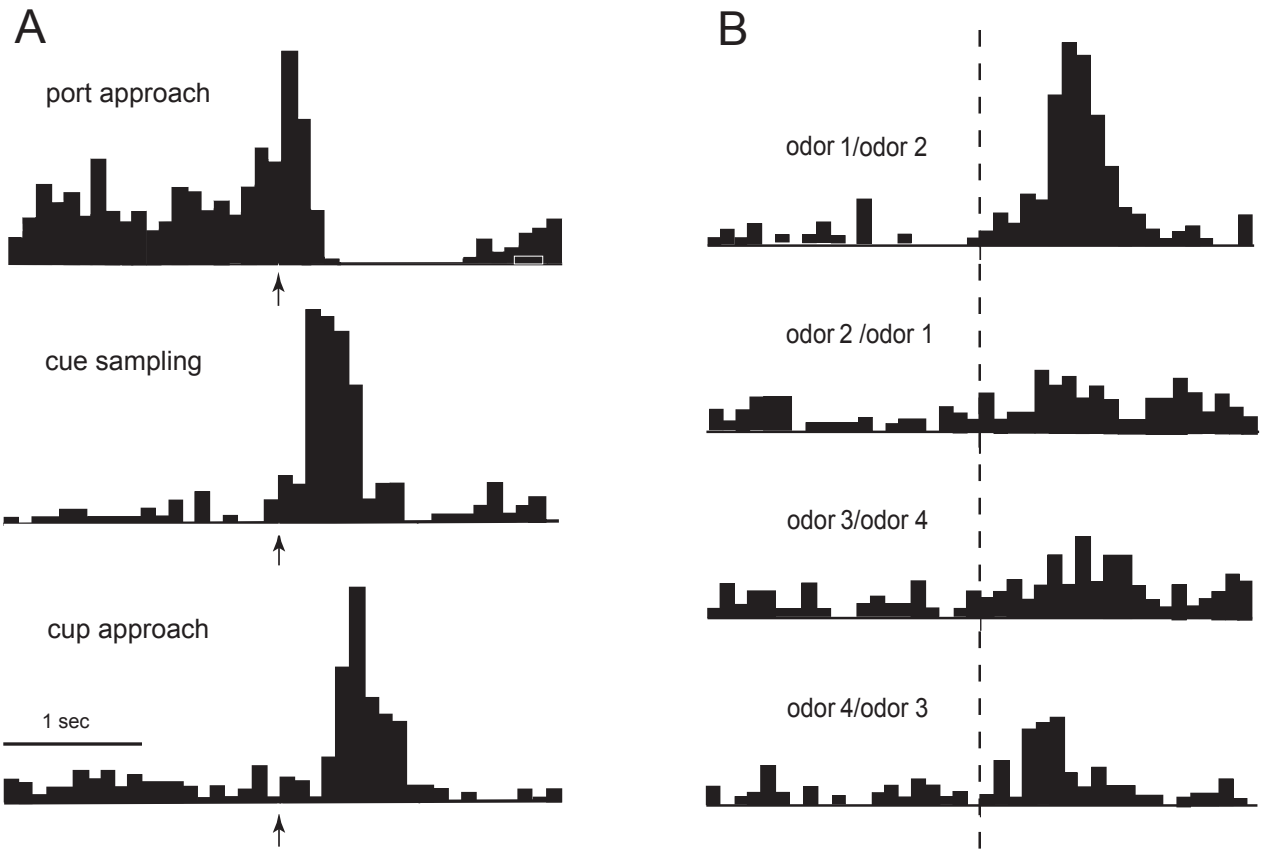
The simplest explanation for the pattern of results observed in these studies is that there are two independent factors operating during conditioning: arousal and preparation for the motor response. Both contribute to the firing of theta cells, but only one of them, arousal, influences the pyramidal cells. The initial short-latency response of hippocampal interneurons and granule cells to either a CS^+ or a CS^- is presumably activation reflecting an arousal input from the brain stem; at about the same time, a small percentage of pyramidal cells, in some studies, also show an arousal response. Depending on the stage and type of training, this can either be an inhibitory or a weak excitatory response. The later phase ($>$ 200 ms after CS onset) of the unit activity is related to the behavioral response. For the theta and granule cells there is prolonged activation continuing throughout the CS^+ period but no such response to the CS^-. The pyramidal cells do not participate in this second longer-latency phase.

Eichenbaum and his colleagues have studied the behavioral correlates of hippocampal cells in various olfactory recognition and discrimination tasks. They recorded two major behavioral correlates: Some cells fired when the animal sniffed at the odor cues, whereas others changed their firing rates during various stages of the approach to the cues or to the goal. In a successive go/no-go discrimination task (Eichenbaum et al., 1987), the rat was presented with one odor of a pair and had to poke its nose into the single-odor

port in response to the CS^+ but not to the CS^-. Water reward was available on the other side of the testing box, requiring the animal to shuttle continuously between opposite sides of the box. Three behavioral correlates of unit response were identified: cells that fired when the animal was sniffing at the odor ("cue sampling" 15%); cells that fired when the animal approached the sniff port or ran from the sniff port to the water cup at the other end of the box ("reward/port approach" 60%) (Fig. 11–20A); and theta cells (10%). Many of the cue sampling units had firing patterns that were maximally synchronized to the onset of cue sniffing. No evidence was found for cells that preferred one odor over others. Almost all cue sampling cells fired more to the positive stimulus that signaled the availability of water reward in another part of the environment. In addition, there was evidence that in the trials that followed a CS^- trial the cells gave a larger response than in those that followed a CS^+. A follow-up study (Otto and Eichenbaum, 1992) looked at complex-spike cell firing during a continuous recognition olfactory memory task in which any one of 32 odors could be presented, and the availability of water nearby was signaled by a mismatch between the current and previous stimulus. Again, cells that had peak firing rates at different points in the task were found, including 12% that peaked during the cue sampling period. Somewhat disappointingly however, only eight cells (3%) had firing patterns that could be unambiguously classified as signaling a mismatch between successive stimuli. As we shall see below in the section on primate studies of delayed nonmatch to sample, there are also very few cells in these studies that responded selectively to the familiarity or unfamiliarity of a stimulus.

In a forced-choice discrimination trial, Wiener and colleagues (1989) used simultaneous rather than successive odor discrimination. Both the CS^+ and CS^- were presented at the same time from two adjacent odor ports. In total, 22% of complex-spike cells had increased activity during cue sampling (Fig. 11–20A, center panel). However, closer examination of these data showed that only 13% of cue-sampling cells discriminated between odors irrespective of location, and 44% took the stimulus location into account. Figure 11–20B

Figure 11–20. Hippocampal cell firing correlates with various aspects of an odor discrimination task. *A*. Firing rate histograms of cells that fired best when the animal approached the odor sampling port (top trace), sniffed at the odors (middle trace), and approached the reward cup (bottom trace). Arrows in the top two traces indicate initiation of the behavior; arrow in the bottom trace indicates a nose-poke into the reward cup. *B*. Firing pattern of an odor/spatial cell that responded maximally when the animal sniffed at a particular odor (odor 1) on the left side of the odor sampling port and a second (different) odor (odor 2) on the right side. Top trace: best response to odor 1 on the left and odor 2 on the right; second trace: same odors from the opposite ports gives a lower response; third and fourth traces: different odors are also less effective. Dotted line marks initiation of the trials. (*Source*: Wiener et al., 1989.)



shows an example of a cell that had a strong spatial component. It fired best to a particular odor pair when one was presented on the left and the other on the right. Somewhat more surprising, 44% of cup-approach cells signaling approach to the reward cup on the opposite side of the box also had responses that depended on the position of the prior nose poke or the odor/position interaction. It is difficult to interpret these data, but one possibility is that the rats may have been turning in different directions away from the odor port as they headed toward the reward. If this is true, the cup approach response in this ostensibly nonspatial task may depend on whether the animal turns toward the left or right on its exit from the sniff port and thus passes through a place field on one side of the sniff port as it turns in one direction but not in the other. Alternatively, this may be an example of the dependence of some place cells firing on the prior turn taken by the animal before entry to the place field (see Section 11.7.3). One can conclude that a small number of complex-spike cells respond to the CS^+ in a differential go/no-go discrimination but that, in general, few hippocampal cells code for the specific odor quality, and that many cells take the location of the odor into account.

On the basis of these and other results (see Chapter 13), Eichenbaum and his colleagues proposed that the hippocampus stores information about a wide range of relations, both nonspatial and spatial. Unit responses to odors and approaches to the odor port or reward dispenser might be taken as evidence of nonspatial representations and unit responses signaling the identity between two successive stimuli as evidence of one type of nonspatial relationship: the identity relation between two stimuli experienced at different times.

As described earlier in the chapter (see Section 11.7.1), many place cells fire more when the animal sniffs at a location when the stimulus in that location has been altered in some way, and these results from odor discrimination paradigms may provide additional information about the conditions under which this mismatch response occurs. To identify cell responses as being due to the odor cue independently of its location, it is necessary to present the same odor in two or more locations. The demonstration that place fields can be rather large, encompassing a large part of the testing box (see Section 11.7.2), means that it may be necessary to test the same odors in two different laboratories as well as in two testing boxes in the same laboratory before concluding that hippocampal cells do not have a spatial correlate. Similarly, the cells that fire selectively during port approach and cup approach have much in common with place cells recorded on linear tracks. Recall that under conditions that constrain the animal to move along narrow pathways, the place cells are unidirectional. To distinguish a goal-oriented response from a motivationally neutral place response, it is necessary to have two identical goals in the environment or two different goals that can be interchanged. O'Keefe (1976) reported that interchanging the water and food at the end of a three-arm maze did not change the location of complex-spike firing fields on the maze. O'Keefe and Recce (1993) used a linear track with identical food reward at both ends and found that some cells fire in one direction and other cells fired in the opposite direction. Even if one were tempted to describe these cells as goal approach cells, it is not the approach to the food or the food container per se that is being signaled but their locations at different ends of the track. It does not seem warranted to describe the cells reported in the experiments of Eichenbaum and colleagues as cue-sampling or goal-approach cells in the absence of similiar manipulations.

Two experiments have provided evidence about the efficacy of cues and goals in isolation from their location (Wiebe and Staubli, 1999; Wood et al., 1999). Wood et al. recorded from hippocampal cells during a variant of a continuous olfactory recognition task in which they tried to dissociate location, odor, and the match/mismatch aspects of the task. Rats were trained on an open platform to approach a small cup containing sand scented with one of nine odors. In each trial the cup was placed in one of nine locations. If a cup had an odor different from that of the previous one, it contained food for which the animal could dig (nonmatch); if the odor was the same, there was no food (match), and digging went unrewarded. Cells were recorded during the 1 second prior to arrival at each cup. An analysis of variance showed that of the total 127 cells, 8% responded to odor in the absence of any other correlate, 11% solely to location, and 10% solely to the match/mismatch aspect of the task. The remainder of the responsive cells took interactions between these variables into account. In all, 20% of cells had nonspatial correlates, and 32% took location into account. (Another 20% changed their firing rate as the animal approached any of the cups. The latter may simply be movement- or speed-related—because this was not measured, it is not discussed further.) These results are notable as a higher percentage of cells with a match/mismatch correlate irrespective of location was found than in the previous reports from the same laboratory (see above). Furthermore, there are fewer purely spatially coded cells than are usually found. This may be because the experimental design required the animal to approach each cup from a different angle during different trials and therefore via different locations; this might lead to a significant underestimation of the number of place cells. Approaching a cup from the north would not force the animal to cross the same region of space as approaching the same cups from the south. It is also not clear how much of the difference between cellular match and nonmatch responses can be attributed to the different behaviors of digging and turning away from the cup that were used as the response measures, rather than the relational judgment itself. Nevertheless, taken at face value, these results provide evidence for the more general relational theory. Significantly, this task has been shown by the authors of the Wood et al. study themselves (Dudchenko et al., 2000) not to be disrupted by selective hippocampal damage.

Wiebe and Straubli (1999) used a Y maze task that forced the animal to traverse the same locations on the approaches to the goals and came to a conclusion different from that of

Wood and colleagues. Animals were trained on a delayed nonmatch-to-sample odor task with each trial comprised of three discrete periods: a sampling period during which the animal sniffed one of two odors in the start arm, a delay period during which it was confined to the start arm and had to remember the recently smelled odor, and a test period during which it was required to choose one of the other two arms containing the odor it had not recently experienced. During the first two periods, everything happened within the same arm, and cellular activity could be correlated only with the odor presented on that trial and with subsequent correct or incorrect performance on the choice part of the trial. During the third (test) period the animal could enter one of two goal arms, and therefore a correlation with location as well as odor and performance could be sought. Overall, most of the 1101 cells recorded from the dentate gyrus, CA3, and CA1 had significant correlations with one or more aspects of the task. Some of the results are shown in Table 11–1. Several conclusions can be drawn from these results. First, during the sample phase, which always took place in the same arm and therefore did not allow the contribution of location to be examined, a small percentage of cells had significant changes in firing rate to the specific odor presented (5%), to whether the subsequent choice would be correct or incorrect (2%), or to the interaction between two (4%). None of these firing rate changes, however, carried over into the delay phase of the trial (Table 11–1, delay) suggesting that the hippocampus does not maintain an active trace of the correct odor choice, as it does of location in a comparable spatial memory task (O'Keefe and Speakman, 1987). Second, in marked contrast to what was seen in the sample phase, during the test phase only a tiny percentage of cells fired to the odor, to the correctness of the choice, or to the interaction between them (all $< 1\%$). This represents a large discrepancy with the odor and performance correlates found in the sample arm. Third, in contrast to the weak representation of odor or performance in the test arms, there was a strong representation of the animal's location. Of the 571 cells with behavioral correlates in the test arms either alone or as an interaction with another correlate, 70% had a spatial correlate, whereas only 27% had an odor correlate and 21% a performance correlate. More significantly, 37% of the cells with spatial correlates were pure place cells with no other correlates, whereas most of the cells with olfactory and performance correlates also had spatial correlates (92% and 93%, respectively). It is difficult to escape the conclusion that when the testing situation allows them to be identified spatial responses predominate either as pure place responses or as place combined with some other aspect of the task, even in tasks where the spatial component is irrelevant to the solution.

Table 11–1.
Percentages of Total Number of Recorded Cells with Significant Correlates to Various Aspects of an Olfactory Delayed Nonmatch-to-Sample Task

Parameter	Sample phase (%)	Delay phase (%)	Test phase phase (%)
Odor	4.8	0	0.9
Performance	2.1	0	0.6
Odor × performance	4.3	0	0.2
Position	–		26.8
Position × odor	–		8.4
Position × performance	–		5.6
Position × odor × performance	–		4.5
Position exclusively	–		13.5
Odor exclusively	2.4		0.8
Performance exclusively	2.1		0.4

After Wiebe & Staubli, 1999.

A potential criticism of the Wiebe and Straubli experiment is that they only used two odors, but there might be more than one location in each of the test arms. This points up an important methodological problem in these studies. To equate two tasks on the number of odors and locations, it is important to have an accurate measure of these items. It might be thought, for example, that the number of place fields in each arm of the maze is greater than the number of odors, but the odors used in the tasks are typically compounds and may be distinguished on the basis of many different elemental aspects of the compound. In the absence of more information about the elemental components of locations and smells in any given task, the best one can do is try to vary each variable systematically to see what effect it has on the results.

11.11.7 Comparison of Hippocampal Cells During Operant Conditioning and Place Tasks in Rats

Are the neurons that show place responses the same as those that take part in nonspatial learning tasks conditioning, or are there two separate populations of cells? Several studies have compared the response of the same hippocampal neurons during place tasks and conditioning tasks. Three studies have asked whether complex-spike cells might be specifically involved in the place task and the theta cells might be specifically involved in the conditioning tasks. Christian and Deadwyler (1986) used antidromical stimulation of projection pathways to identify complex-spike cells as pyramidal cells. They found a clear double dissociation of the cells involved in the two tasks. In total, 81% of complex-spike cells had place fields in the place task in comparison with none of the theta cells. Conversely, 81% of the theta cells participated in the conditioning task whereas none of the complex-spike cells did. In two experiments, Eichenbaum and his colleagues (Eichenbaum et al., 1987; Wiener et al., 1989) asked whether cells that were related to events in their olfactory discrimination task also had place fields in the same or different tasks. In the first study, they found that 43% of cells with correlates in the odor discrimination task had place fields in the same

environment; in the second study, they recorded some complex-spike cells in a spatial task, some in the odor discrimination task, and a third group in both tasks. They found 75% of the complex-spike cells had place fields in the spatial task compared to 58% with correlations in the odor discrimination task. Of cells collected in both tasks, 85% had place fields in contrast to 54% that had correlates in the odor task.

We can conclude that in conditioning tasks involving rats that were not required to move around the environment to any great extent, most or all hippocampal cells taking part in the conditioning response were theta cells. Complex-spike cells, by contrast, either did not take part or showed slight inhibition of their resting firing rate. In discrimination conditioning tasks in which the animal is required to move, the complex-spike cells also become engaged. The clearest example of cells that may not have a spatial correlate are the cue-sampling cells reported in the Eichenbaum studies. However, even some of these responses may be covert place responses, as clearly suggested by the Wiebe and Straubli experiments.

11.11.8 Hippocampal Units During Nonspatial Learning in Nonhuman Primates

Tamura et al. (1991) reported that 10% of cells in the hippocampal formation responded differentially to the presentation of three-dimensional objects, some of which had been conditioned to rewarding (3%) or aversive (2%) stimuli. In a follow-up study (Tamura et al., 1992), they showed that 61% of object-responsive cells tested in the same apparatus varied their response as a function of the location of the stimulus in egocentric or allocentric space. The latter study indicates that apparently perceptual responses in the hippocampus may be spatially modulated. Such responses may underlie object-in-place associativity, which like odor-place associativity, is often shown to be hippocampus-dependent, unlike odor-object associativity, which is hippocampus-independent (Gilbert and Kesner, 2002).

Hippocampal units have been recorded from primates while they performed in one of the paradigmatic relational tasks: delayed match or non-match-to-sample. On these tasks, the animal must signal whether two successive stimuli separated by an interval are the same or different. It is now widely accepted that these tasks can be solved in two ways. The animal can either assess the strength of the familiarity of the two stimuli presented during the test phase and choose the least familiar, or it can remember which stimulus was previously presented in the present situation or context and choose the one it has not experienced there before. The second strategy is clearly both spatial and relational, but it could be argued that the first strategy is also relational although clearly nonspatial. To judge a stimulus as familiar or novel, it is necessary to compare it to the representation of a previous stimulus and to decide whether the relation between the two is one of equality. Recognition tasks of this sort were originally thought to depend on the integrity of the hippocampus but are now known to depend on the perirhinal/parahippocampal cortices and only minimally (Alvarez et al., 1995) or not at all (Murray and Mishkin, 1998) on the hippocampus itself (see Chapter 13) (Aggleton and Brown, 1999). In keeping with the lesion results, it has been found that only a small number of cells show a differential response to the familiarity of the stimuli (0%–2.3% in various studies (Riches et al., 1991; Tamura et al., 1992; Rolls et al., 1993; Salzmann et al., 1993; Brown and Xiang, 1998). In contrast, Wilson et al. (1990) found that 40% of their hippocampal cells in this task correlated with the response, signaling whether the animal was reaching to the left or right position during their task. Salzmann and Creutzfeldt (Salzmann et al., 1993) reported that 28% of hippocampal and 33% of parahippocampal neurons responded to both presentations of the visual stimuli in a delayed match-to-sample task but that even more cells (38% in each area) fired when the animal was presented with a raisin. Vidyasagar and Creutzfeldt (Vidyasagar et al., 1991) reported similar results but that arousing events such as the cage door being opened or closed or the experimenter entering or leaving the room also produced a response in these cells. On the basis of these findings, they attributed hippocampal single-unit activity to the animal's behavioral state rather than to any specific memory. These studies provide no evidence for the representation of stimulus familiarity in the hippocampus.

In contrast and in keeping with the lesion results, there is evidence that cells in the rhinal cortex are involved in familiarity judgments. Brown and colleagues (Brown and Xiang, 1998) reported that about one-fourth of cells in the rhinal cortex and area TE showed a decreased response to the second presentation of the stimulus in a delayed match-to-sample task.

Rolls and his colleagues (Rolls et al., 1993) have tested monkeys on object recognition tasks and compared unit responses to object familiarity with those to object location. Only a small percentage (2%) of cells responded to familiar objects (see above). In contrast, they reported that about 9% of cells in the hippocampal region responded differentially to the location of the stimulus on a display screen. As part of a study of the place properties of primate hippocampal neurons, Ono and his colleagues (1993) found that 17% of cells responded to objects such as a moving experimenter or apple when presented in a particular part of the visual field. Just over half of these were object-in-place cells, which responded differentially when the animal was shown the object in a particular location and not in other locations. They appear to have properties similar to those of the misplace cells described in the rat (O'Keefe, 1976).

11.11.9 Hippocampal Units During Nonspatial Learning in Humans

Single units have been recorded from medial temporal lobe regions in patients with intractable epilepsy during both recognition and recall memory tasks (Heit et al., 1988; Fried et

al., 1997, 2002; Cameron et al., 2001) as well as during the perceptual categorization tasks described in Section 11.11.1. In general, a sizable percentage of hippocampal units was found to participate in both types of memory task. In a recognition memory task, Fried and colleagues (2002) presented a set of male and female faces portraying various emotions; and after an interval of 1 to 12 hours they showed the same faces again together with an equal number of foils. A significant number of hippocampal neurons responded to faces during encoding (25%) and a somewhat larger percentage during the recognition phase (41%). Perhaps surprisingly, a large proportion of the hippocampal responses (62%) consisted of firing rate decreases. Almost one-half the hippocampal neurons with an excitatory response but only one-sixth of those with an inhibitory response showed some selectivity for gender or emotion. Similar findings were reported by Heit and colleagues (1988), who used lists of words to be remembered and found most hippocampal units selective for one of the words on the list. When tested with a second list of different words, slightly less than half of these cells (13/30) were also selective for a word in that list. As the authors remarked, this suggests that rather than being preordained to respond to specific stimuli the cells were tuning into the current context and selecting one aspect of it (such as position along a list?). The result is reminiscent of the way in which a given pyramidal cell in the rat hippocampus may have unrelated place fields in two or more environments. Hippocampal units have also been recorded during a paired-associate recall task (Cameron et al., 2001). A series of word pairs were presented, and after 1 to 2 minutes the subject had to respond with the second of the pair when prompted with the first: 29% of hippocampal units responded during stimulus encoding and 44% during recall. These percentages are similar to those found in the entorhinal cortex and amygdala in the same study and in the face recognition study of Fried et al. (2002) but significantly higher than the response to faces and other nonspatial visual stimuli in the perceptual classification study of Kreiman et al., 2000a), suggesting a specific role for learning. An interesting aspect of the study was that one-fifth of the hippocampal cells showed a differential firing rate during encoding between word pairs that were subsequently remembered correctly and those that were forgotten. Most intriguingly, most of these cells showed a *smaller* increase in firing rate to the word pairs that were subsequently remembered than to the ones that were forgotten. Whatever the role being played by the hippocampus in these tasks, it cannot simply be that increased firing in hippocampal neurons during encoding leads to a stronger memory trace and therefore to better recall.

Although one must be cautious when comparing across studies, even from the same laboratory, the results can be summarized as follows. (1) The percentage of cells responding to faces and words is higher when they are part of a memory task than when they are simply perceived; (2) these stimuli are equally well represented in both recognition and recall memory tasks; and finally (3) the response of hippocampal units to a stimulus during the encoding phase of a recall test correlates with subsequent recall of that stimulus but in a counterintuitive fashion. The cells increase firing to both remembered and forgotten stimuli but the increase is smaller to the subsequently remembered stimuli than to those forgotten.

11.11.10 Conclusions

In all species tested, a small percentage of hippocampal cells have been reported to fire to nonspatial stimuli. The data are clearest in humans, where about 12% of cells responded to the sight of famous faces, but this fell well below the proportion (29%) that responded to spatial stimuli such as pictures of houses or interiors. Hippocampal unit responses to stimuli used as discriminanda in learning experiments have been reported in all species tested: rats, rabbits, monkeys, and humans. There is some suggestion that the responses in the rat may be due to a place-gated mechanism because the one study that tested this carefully found that the conditioned stimuli only elicited a pyramidal cell response after conditioning if it was presented while the animal was in the place field of the cell (Moita et al., 2003). Theta cells are much less sensitive to location and may account for a large percentage of the responses reported in the early studies, which did not distinguish between cell types. In general, monkey experiments reported few cells responding to objects per se but more to location or object-in-places. In keeping with the lesion results (see Chapter 13), units responding to objects and their familiarity were more plentiful in the rhinal cortex than in the hippocampus.

There are clearly cells in the human medial temporal lobe that respond to words as well as faces and other stimuli in both recognition and recall paradigms. Furthermore, in one study of verbal paired associate learning, hippocampal unit responses during encoding of a pair predicted the success of subsequent recall (Cameron et al., 2001). Somewhat surprisingly, there was only a hint of lateralization of these responses to the left hemisphere, as might be expected from the lesion data. It is clear that the human hippocampus is involved in the storage of verbal as well as nonverbal material.

In general then, there is evidence that nonspatial information is represented in the hippocampus but that the number of cells involved is considerably smaller than those involved in spatial information and often the nonspatial responses are secondary to a primary spatial correlate. The larger percentage of responses to nonspatial stimuli reported in humans is consonant with the wider function attributed to the human hippocampus in narrative and episodic memory (O'Keefe and Nadel, 1978; O'Keefe, 1996, 2001; Burgess et al., 2002).

11.12 Other Distinctive Cells in the Hippocampal Formation and Related Areas

As we have seen, the hippocampal formation is part of a widespread system of anatomically related regions involved in memory and navigation. In addition to the CA fields and the dentate gyrus, the hippocampal formation contains two

anatomically distinct regions: the subicular complex and the parahippocampal cortex. Response properties of cells in some of these other regions have been touched on at different points in this chapter where appropriate. For example in Sections 11.9 and 11.10, we summarized the properties of head-direction (HD) cells found in the presubiculum and, in addition, regions of the Papez circuit, which forms the inputs to these cells. In this section, we briefly summarize the properties of cells in some of these other related brain regions and touch upon the question of whether these cells are afferent to the hippocampal formation, providing spatial information, or alternately should be thought of as efferent output structures, receiving spatial and memory information from the hippocampal formation.

There are three ways this question might be approached. The first is to look at the effects of lesions elsewhere in the circuit on hippocampal place cell firing (Brun et al., 2002; Calton et al., 2003) and presubicular HD cell firing (Golob and Taube, 1997) as described in Sections 11.7.4 and 11.9/11.10, respectively. The second examines the relative latency of the neurons in each area to respond to the stimulus or behavior under study. This approach depends on the assumption that neurons in a region that projects to a second region in a serial fashion, on average, fire earlier in response to the appropriate stimulus or during the relevant behavior than the neurons in that second region. On the assumption that many cells in the hippocampal formation and related areas have spatial aspects of behavior as their primary correlate, it is possible to compare the temporal correlation of cells in different hippocampal regions in response to manipulations of these spatial variables to estimate the temporal relation between cells in different regions indirectly. For example, one might study the latency to onset of firing of HD cells with the same preferred orientation in different parts of the Papez circuit. Ideally, this ought to be done with simultaneous recording from the two (or more) regions in question to control for variations between rats in behavior and location of the tracking lights on the head. The third method is based on a comparison of the place correlates of the neurons in the two areas. If one has a serial model of place field construction, it might be possible to attribute some neuronal responses to earlier stages in that process than others. For example, Barnes and colleagues (1990) compared the field sizes of place cells in different regions of the hippocampal formation and subiculum. As we shall see, some generalizations arise from this third type of analysis. The locational code in the CA fields of the hippocampus is more environment-specific than in other regions. Hippocampal place cells often fire in distinct patterns in different environments ("remapping"); indeed, many hippocampal cells are or become silent in a given environment (see Section 11.7.4). By contrast, the locational region(s) signaled by nonhippocampal cells are much more likely to be in similar places across dissimilar environments. Moreover, in other regions, such as the subiculum and superficial entorhinal cortex, principal cells are never silent.

Taking the results of all three methods into account, it is difficult but not impossible to make suggestions about the functional circuit diagram of the interconnections between these regions of the hippocampal formation that underlies spatial behavior and memory.

11.12.1 Subicular Region Has Fewer Place Cells than the Hippocampus Proper, and Their Properties Differ

Place cells and theta cells have been recorded from several subdivisions of the subicular region. We consider the similarities and differences between cells in the next sections. The subiculum contains both place cells and theta cells (Sharp and Green, 1994; Sharp, 1997). The percentage of theta cells is approximately the same as found in the hippocampus proper (10%), and most of the remaining cells have strong spatial signals. There are no complex-spike cells, but one group (29% of total) shows a bursting pattern with a peak interspike interval of 2 to 4 ms. These cells do not seem to differ in any other respect from the nonbursting types except that they have a stronger theta modulation. The field sizes and average firing rates of the subicular place cells are much larger when compared to those in the hippocampus. A typical subicular cell fires over the entire environment with an average rate of 5 to 15 Hz (in contrast to 0.5–2.5 Hz in the hippocampus) and has one or more areas of increased firing. Like the place cells of the hippocampus, subicular place cells recorded in a cylinder are under the influence of a cue card on the wall and rotate in step with it. It has been claimed that the subicular cells have a stronger directional component than the hippocampal cells, but this claim must be treated with caution. The amount of variance in subicular firing rate that is explained by direction is actually very small (Sharp and Green, 1994).

One important difference from hippocampal place cells is that subicular cells are far less likely to remap across environments that differ in shape (Sharp and Green, 1994), shape and visual markings (Sharp, 1997), or size (Sharp, 1999b). For instance, whereas many of the hippocampal cells displayed markedly different fields in a cyclinder and a rectangle, the subicular fields were similar in the two environments. This is reminiscent of what is found in the spatially coded cells in the superficial layers of the entorhinal cortex (see below) and to hippocampal place cells during the animal's initial experiences of the two (see Section 11.8.3). A study of the timing of subicular cell firing relative to the animal's location suggests that subicular cells fire slightly earlier on average than CA1 cells (70 vs. 40 ms), perhaps indicating that they come earlier in the computational chain (Sharp, 1999a). This result may seem paradoxical in light of the strong connections from CA1 to the subiculum, but it is consistent with the data showing that subicular cells do not remap the environments that CA1 cells do.

In conclusion, various approaches to the functional relation between the subiculum and the hippocampus proper suggest that the subicular place cells cannot receive their spatial properties solely by virtue of their inputs from the hippocampus proper. They may be more dependent on direct

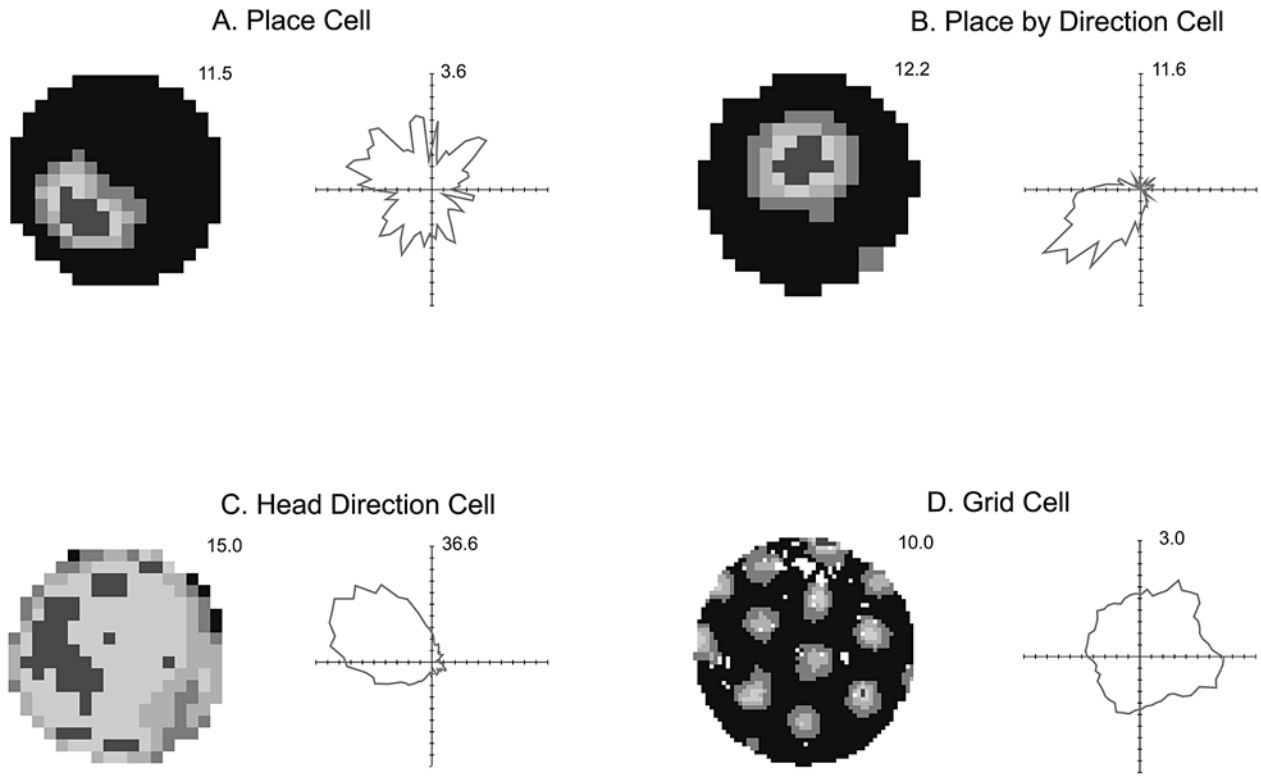
inputs from the entorhinal cortex and/or they themselves may provide a source of spatial inputs to the entorhinal cells.

11.12.2 Presubiculum Contains Several Classes of Spatial Cell

The dorsal presubiculum (or postsubiculum in some authors' terminology) contains other types of spatial cell in addition to the HD cells described above (see Section 11.9). A survey study (Sharp, 1996) of presubicular cells in the standard cylinder also reported cells with correlates for angular velocity, running speed (see also Lever et al., 2003), location and direction, and location. The nature of these correlates suggests an important role for the presubiculum in navigation and spatial memory. One class of these cells, called theta-modulated place-by-direction (TPD) cells, has been examined in detail (Cacucci et al., 2004) (Fig. 11–21B, see color insert). TPD cells generally have a strong tendency to fire at or just before the trough of the local theta oscillation. Their depth of theta modulation is high and comparable to that of cells in the medial septum/diagonal band of Broca (King et al., 1998). The quantitative analyses of Cacucci et al. indicate that both locational and directional signals are stable and robust in TPD cells, with the directional signal carrying more information. The directional and locational signals are dissociable in different environments. The preferred direction of a given TPD cell appears to be environment-invariant, being similar across different locations in the testing room (like the HD cells) and across different enclosures in the same location (cylinder versus an open circular platform). In contrast, the locational fields tend to differ more between environments; notably, TPD cells generally have different locational fields in the cylinder and open circular platform. TPD cell firing represents an integration of location-related and direction-related information. It is possible that directional information may have to be incorporated into and distributed in theta wave packets to be used by the navigation system. Neither anterodorsal thalamic nor presubicular HD cells show theta modulation. Cacucci et al. provided evidence that a robust orientation signal operating in theta mode exists in the hippocampal formation.

There have been no published reports of cells recorded from the ventral portions of either the presubiculum or the parasubiculum. By analogy with the differences between dor-

Figure 11–21. Four spatial cell types in the hippocampal formation. False color firing field maps (left) show the firing rate as a function of the animal's location in cylindrical environments irrespective of heading direction; directional polar plots (right) show the firing rate for the same cell as a function of the animal's heading direction irrespective of location. *A*. Place cell has single localized field and no directional selectivity. *B*. Place by directional cell has single localized field and strong directional selectivity. *C*. Head direction cell does not have localized firing but has strong directional selectivity. (*Source*: *A–C*. Courtesy of Francesca Cacucci.) *D*. Grid cell has multiple place fields and no directional selectivity. Directional grid cells also exist. Numbers associated with the firing rate plots represent the maximum firing rate (red regions in firing rate maps and peak x and y values in polar plots). Diameter of cylinders in *A– C* is 79 cm; diameter in *D* is 2 m. (*Source*: Edvard and May-Britt Moser.)



sal and ventral hippocampus (Jung et al., 1994), these ventral regions might be expected to contain lower levels of spatial signaling and/or larger spatial fields.

11.12.3 Parasubiculum

The parasubiculum contains location-specific neurons, although in much lower percentages (ca. 10%) than are found in the hippocampus proper or the subiculum (Taube, 1995b). In contrast, it contains a much higher percentage of theta cells (41%). No complex-spike cells have been found there. In comparison with the hippocampus, the firing fields of the parasubicular place cells are significantly larger and have less spatial information content. In common with all place and HD cells recorded thus far, their place fields rotate in step with the rotation of the cue card on the wall of the environment. Analysis of the temporal relations of the firing fields of these cells to the animal's location showed a variety of relations, but on average the cell firing preceded the animal's location by about 60 ms. This is less than the average of about 120 ms for hippocampal cells, suggesting that the parasubicular neurons may be later in the circuit than the hippocampal cells.

11.12.4 Spatial Cells in the Entorhinal Cortex

Quirk and colleagues (1992) recorded from cells in layers 2 and 3 of the medial entorhinal cortex under conditions similar to those in which hippocampal place cells have been recorded (Muller et al., 1987). They found both place-coded and theta cells. Two properties of the spatial cells were different from those displayed by the hippocampal place cells but similar to those found in the subiculum. The entorhinal cortex (EC) fields were larger and less spatially compact; and unlike the hippocampal cells but like the subicular cells, they showed less sensitivity to the shape of the enclosure. Whereas many of the hipppocampal place cells displayed markedly different fields in the cyclinder and the square, the EC cell fields were similar in the two environments. Unlike the hippocampus, where this similarity between fields in the two boxes occurs only during the initial experience of the environments, the EC cells appear not to learn to discriminate. As we saw earlier (Mizumori et al., 1992; Jeffery et al., 1995), the theta cells in the EC are dependent on the integrity of the medial septum in the same way as the hippocampal theta cells.

As discussed in Section 11.7, work by Fynn, Hafting, and colleagues (Fyhn et al., 2004; Hafting et al., 2005) suggests that at least one class of cells in the superficial layers of the medial entorhinal cortex lays a grid-like structure on every environment the animal visits. Each grid cell fires in several locations in each environment, with the locations forming a regular pattern as though they were nodes on a triangular grid (see Figs 11–10 and 11–21D, see color insert). Different cells recorded at the same location have the same grid spacing and orientation relative to the environment but differ in the location of the nodes, such that the firing peaks of one cell are slightly shifted from those of its neighbor. The result is that the overall set of fields of several such cells covers the entire environment. For each cell, the size of the grid appears to be independent of the size or shape of the environment. As one goes more ventral in the medial entorhinal cortex, the size of the grid gets larger. This grid system appears to be based on path integration inputs generated by the animal's own movements and may provide the hippocampal mapping system with distance and directional information on which to construct maps of individual environments.

Frank and colleagues (2000) recorded from neurons in the hippocampus proper and in the superficial and deep layers of the entorhinal cortex while rats ran along single or double U-shaped tracks (the latter termed W-shaped tracks). On the single U-shaped track, the animal shuttled back and forth between the two prongs of the U to receive rewards at each end; on the W track it shuttled first between the left-hand and middle prongs and then between the middle and right-hand ones and vice-versa. Similar to the findings of Quirk et al. (see above), they found that: (1) EC cells fire at rates about five times those of CA1 cells; (2) the locational fields of cells in both the superficial and deep layers of the entorhinal cortex were larger (by about three times) and contained less locational information than those in CA1. Deep EC cells contained more locational information than superficial EC cells. Some cells in all three regions were sensitive to the place from which the animals had recently come (retrospective coding) or to which they were intending to go (prospective coding) (cf. Section 11.7.3 for a discusssion of retrospective and prospective coding in hippocampal cells). However, the deep entorhinal cortex contained a significantly higher proportion of prospectively coding cells than the CA1 or the superficial entorhinal cortex. Cells in the deep entorhinal layers were also more likely to reflect environment-invariant aspects of the paths taken along these tracks. For instance, one deep EC cell fired on both the U and W tracks as the animal ran away from a prong and turned left into the adjacent arm. These findings suggest that the deeper layers of the entorhinal cortex, which receive strong inputs from the CA1 field and the subiculum, may be using spatial information provided by these regions to construct routes between known locations. Alternatively, the results may be related to the regular field structure of grid cells reported by Hafting and colleagues (see above).

11.12.5 Cells in the Perirhinal Cortex Code for the Familiarity of Stimuli

Cells in the perirhinal cortex of the monkey and rat (Brown et al., 1987) are sensitive to the familiarity of the stimulus. The amplitude of the cell's response to the second and subsequent repetitions of an object is smaller than that to the first presentation, and this decreased response recovers as a function of the time and number of intervening items since the previous exposure to that stimulus. This fits with the suggestion that the deficit in delayed non-match-to-sample in the monkey or human following large lesions in the mesial temporal lobes is due primarily to the involvement of these rhinal structures

(Brown and Aggleton, 2001) (see Section 11.11.8 and Chapter 13 for further discussion).

11.12.6 Cells in the Medial Septum Are Theta Cells

Cholinergic and GABAergic cells in the medial septum and diagonal band of Broca (DBB) supply the driving inputs that set the frequency of hippocampal theta. As we saw in Section 11.3.3, lesions of this region abolish hippocampal theta. Ranck (1973) recorded from cells in the medial septum of freely moving rats and confirmed earlier reports by Petsche and Stumpf that cells there had a rhythmical bursting pattern that was phase-locked to hippocampal theta. About 50% of the septal cells showed this pattern. Attempts have been made to classify septal cells into those likely to be cholinergic or GABAergic on the basis of their waveform (Matthews and Lee, 1991; King et al., 1998). Cells have also been classified on the basis of the strength of their correlation to the hippocampus theta. In one study (King et al., 1998) , 47% showed a strong phase relation to the hippocampal theta with strong peaks in the auto-correlation at the theta period. Each cell had its own individual preferred phase, which was constant over days. The rest of the septal cells show weaker relations to theta. There is, however, only a slight preference for a particular phase across the whole population with all phases represented. Putative cholinergic cells (on the basis of wave shape) tended to be concentrated in the less rhythmical class than putative GABAergic cells. On the other hand, GABAergic medial septal neurons, which selectively target hippocampal inteneurons, appear to form two distinct populations tightly coupled either to the trough (178°) or the peak (330°) of hippocampal theta waves (Borhegyi et al., 2004).

As we saw in Section 11.3.4 on the theta rhythms and the EEG, there is some evidence that the frequency of theta is correlated with the speed with which an animal moves in an environment. A similar correlation was found in the rhythmical theta cells of the septum (King et al., 1998). Rhythmical cells showed a burst frequency that was correlated with the speed of movement on a linear track. The slope of the regression linear curve was about 0.9 Hz/m/s with an intercept at 8.4 Hz. A small number of rhythmical septal cells had an interesting directional response. They fired with a strong rhythmicity when the animal ran in one direction but lost their rhythmicity when it ran in other directions.

11.12.7 Summary of Extrahippocampal Place Field Properties

The firing of extrahippocampal cells tends to be more environment-invariant than hippocampal place cell firing, generalizing across the various environments explored and routes taken. Thus, cells in the subiculum and entorhinal cortex may signal broadly equivalent locations, or similar points along a route, in different environments. Whereas extrahippocampal cells generalize, hippocampal place cells basically discriminate (especially after experience). This is revealed at the population level: In any single environment, half or more of the cells in the hippocampus proper are silent. Outside the hippocampus proper, principal cells are generally not silent and indeed tend to fire at higher rates than hippocampal place cells. Further study is required to disentangle the particular role played by each of the regions in the hippocampal formation.

Relative to hippocampal place cells, cells in some neighboring extrahippocampal regions tend to, have larger fields, and are less sensitive to environmental changes such as alterations in the shape of the enclosure. It seems reasonable to suggest that the presubicular HD cells are afferent to the medial EC grid cells, which in turn are afferent to the hippocampal place cells; and the anatomical connections between these regions are consonant with this functional relation. Less clear is the relation between the subiculum and the hippocampus. The greater susceptibility of hippocampal place cells to environmental change and the latency data suggest that the subiculum provides environmental inputs to the hippocampus perhaps in the form of the distance to one or more boundaries; on the other hand, the anatomy suggests a strong projection from the CA1 field to the subiculum that is not reciprocated. The perirhinal and lateral entorhinal cells most likely provide information about environmental landmarks and other objects to the hippocampus where it is integrated with the place information to support behavior based on object-in-place knowledge. The deeper layers and the lateral septum are the major efferent targets of the CA1 and CA3 pyramids, respectively. Little is known about the behavioral correlates of deep layers of the entorhinal cortex and the prefrontal cortex, but they may be the first stages in the transformation of the hippocampal signal into environmentally specific route information or where it is used to program the approach to goal locations. The hippocampal projection to the EC may stabilize the grid cell location relative to a given environment.

11.13 Overall Conclusions

This chapter has focused on the neural correlates of hippocampal EEG and single-unit activity. We found that the EEG could be categorized into several frequency bands: theta, beta, gamma, and the high-frequency ripples. Each of these has a different behavioral correlate and is reflected by different firing patterns in hippocampal interneurons. In rodents, the beta and gamma oscillations relate primarily to olfactory stimuli, but theta and the ripples have much broader correlates. There are two types of theta, which are differentially sensitive to cholinergic drugs: a-Theta is activated during periods of arousal or attention, and t-theta is related to movements (e.g., walking, swimming, jumping) that translate the animal's position relative to the environment. Hippocampal interneurons fire in synchrony with the concurrent theta; and various types of interneuron, targeting different parts of the pyramidal cell, preferentially fire on different phases of theta. One function of theta activity is to coordinate and perhaps bind

together neural activity in different parts of the nervous system. Theta-related firing patterns have been found in cells in such disparate regions of the nervous system as the prefrontal cortex, amygdala, and inferior colliculus. Theta also organizes the temporal relation between the firing of cells in the hippocampus such that inputs to a cell at one phase of theta produce larger synaptic modifications (LTP) than at other phases. Finally, each theta cycle acts as a timing cycle against which the phase of hippocampal pyramidal cell firing can be measured. This phase coding complements the locational signal carried in the gross firing rate and allows rate modulations above the baseline to code for variables such as the speed of running in addition to location (see below). Dual phase and firing rate coding may be a general strategy for binding together the representations of different aspects of the world in the train of action potentials of a single cell. The high-frequency ripples occur in conjunction with the large irregular activity (LIA) state of the hippocampal EEG, which occurs during nontranslational activities such as sleeping, quiet resting, grooming, drinking, and eating. Theta and LIA/ripples appear to be mutually exclusive states of the hippocampus, never occurring at the same time. It has been suggested that the synchronized bursts of activity that occur in hippocampal neurons during the ripples may reflect the transfer of information from the hippocampus to the neocortex as part of a memory consolidation process.

Three classes of cells with spatial correlates have been reported in the hippocampal formation: the place cells in the hippocampus itself (Fig. 11–21A, see color insert); the head direction (HD) cells in the dorsal presubiculum (Fig. 11–21C, see color insert); and the grid cells in the medial entorhinal cortex (Fig. 11–21D, see color insert). In addition, there are cells that combine two types of information, such as the "place by direction" cells found in the presubiculum (Fig. 11–21B, see color insert). Place cells signal the animal's location, HD cells signal the animal's direction of heading, and grid cells provide information about distances moved in particular directions. It seems reasonable to assume that the place cell firing patterns are constructed from combinations of grid cell inputs, which in turn get their directional orientation from the head direction input. Together these three cell types provide the information required to construct a mapping system that identifies the animal's location in an environment and relates these locations to each other on the basis of the distance and direction from one to the other. It should also allow the animal to move from one location in that environment to another along any available path, supporting flexible navigation. As we mentioned above, hippocampal pyramidal cells also code for events or stimuli that occur in particular places, laying the basis for the more general episodic memory system seen in the human hippocampus. A true episodic memory system would incorporate the time of occurrence of events as well as their location.

Encoding of events as well as locations in hippocampal pyramidal cells is made possible by a dual coding strategy: Location is conveyed by a combination of increased firing rate above a low-level baseline and the phase of firing relative to the ongoing hippocampal EEG theta activity; events and stimuli occurring in that location are signaled by variations in the firing rate above the baseline. The existence of temporal coding strategies in the nervous system means that one must be cautious when interpreting the results of recording techniques that reflect only relative rates of neural activity in contrast to the timing of action potentials. This is especially true when the representation is distributed across a population of cells with some cells increasing and others decreasing their firing rates in addition to shifting phases.

Several types of learning have been demonstrated in hippocampal pyramidal cells: short-term changes in the orientation of place fields relative to the environment lasting for the duration of the trial; longer changes in the shape of the place field lasting for the duration of the testing session; and long-term discrimination between similar environments that appears to be permanent. One type of environmental discrimination appears to involve the collective behavior of pyramidal cells, perhaps operating as a discrete attractor in which the behavior of neighboring pyramidal cells, in addition to environmental inputs, is taken into account in the final representation.

The location of place fields depends on factors in addition to the animal's physical location in an environment. Under certain circumstances, fields may depend on the animal's previous behavior, such as the turn that it has just made at a choice point or one that it intends to make. Training on aversive tasks such as eyeblink conditioning in the rat has also been shown to shift the location of fields. Whether this means that the animal conceives of these environments as different is not clear at present.

It has also been reported that pyramidal cells respond to nonspatial stimuli such as the odors used in a running recognition task or the auditory cues in a nictitating membrane conditioning task. The existence of such responses together with deficits in some types of conditioning tasks (e.g., trace conditioning following hippocampal lesions) has suggested a broader function for the hippocampus than purely spatial. On the other hand, several studies have suggested that when the locations in which these stimuli occur are varied, these "nonspatial" responses are gated by the animal's location. In a rat eyeblink conditioning experiment, the auditory conditioned stimulus only elicited short latency response in hippocampal cells when the animal was in the place field of that cell. In an olfactory delayed match-to-sample task, cells appeared to respond to the olfactory cues alone when position was not varied in the start arm of a Y maze; in contrast, only olfactory responses gated by position were seen in the two goal arms where position was available as a factor. To rule out position as a contribution to hippocampal unit responses, it is important to provide the stimulus in more than one location.

Studies of single-unit activity in monkey hippocampus suggest that although place responses also dominate there is evidence of nonspatial inputs as well. As primate research moves in the direction of the use of freely moving monkeys, and especially when the animal can explore the walls as well as

the floor of the environment, we will begin to get a better picture of the relation between these nonspatial and spatial inputs. There are also a small number of studies of hippocampal unit activity in humans. Units responding to pictures of faces and household objects have been reported, but the percentage of cells responding to pictures of houses and locations in the same studies has been higher. Responses to words have been reported frequently, especially when they are presented in a learning paradigm. This may be an indication that the function of the human hippocampus is broader than purely spatial. This is in line with the original suggestion of the cognitive map theory that the incorporation of verbal and temporal inputs into its original spatial functions would result in employment of the hippocampus as an episodic and narrative memory system as well a spatial one.

ACKNOWLEDGMENTS

I am grateful to my co-editors for extensive and helpful comments on earlier drafts of the chapter. I also thank Dr. Colin Lever (Leeds University) who made extensive comments and suggestions on an earlier version. Support for the research from my own laboratory cited in this chapter came from the Medical Research Council UK, Wellcome Trust, and the BBSRC.

REFERENCES

Acsady L, Kamondi A, Sik A, Freund T, Buzsaki G (1998) GABAergic cells are the major postsynaptic targets of mossy fibers in the rat hippocampus. *J Neurosci* 18:3386–3403.

Adey WR, Dunlop CW, Hendrix CE (1960) Hippocampal slow waves: distribution and phase relations in the course of approach learning. *Arch Neurol* 3:74–90.

Aggleton JP, Brown MW (1999) Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behav Brain Sci* 22: 425–490.

Alonso A, Garcia-Austt E (1987a) Neuronal sources of theta rhythm in the entorhinal cortex of the rat. I. Laminar distribution of theta field potentials. *Exp Brain Res* 67:493–501.

Alonso A, Garcia-Austt E (1987b) Neuronal sources of theta rhythm in the entorhinal cortex of the rat. II. Phase relations between unit discharges and theta field potentials. *Exp Brain Res* 67: 502–509.

Alvarez P, Zola-Morgan S, Squire LR (1995) Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys. *J Neurosci* 15:3796–3807.

Arnolds DE, Lopes da Silva FH, Aitink JW, Kamp A, Boeijinga P (1980) The spectral properties of hippocampal EEG related to behavior in man. *Electroencephalogr Clin Neurophysiol* 50: 324–328.

Barnes CA, McNaughton BL, O'Keefe J (1983) Loss of place specificity in hippocampal complex spike cells of senescent rat. *Neurobiol Aging* 4:113–119.

Barnes CA, McNaughton BL, Mizumori SJ, Leonard BW, Lin LH (1990) Comparison of spatial and temporal characteristics of neuronal activity in sequential stages of hippocampal processing. *Prog Brain* Res 83:287–300.

Barnes CA, Suster MS, Shen J, McNaughton BL (1997) Multistability of cognitive maps in the hippocampus of old rats. *Nature* 388:272–275.

Bassett JP, Taube JS (2001) Neural correlates for angular head velocity in the rat dorsal tegmental nucleus. *J Neurosci* 21:5740–5751.

Battaglia FP, Sutherland GR, McNaughton BL (2004) Local sensory cues and place cell directionality: additional evidence of prospective coding in the hippocampus. *J Neurosci* 24: 4541–4550.

Berger TW, Thompson RF (1978) Identification of pyramidal cells as the critical elements in hippocampal neuronal plasticity during learning. *Proc Natl Acad Sci USA* 75:1572–1576.

Berger TW, Rinaldi PC, Weisz DJ, Thompson RF (1983) Single-unit analysis of different hippocampal cell types during classical conditioning of rabbit nictitating membrane response. *J Neurophysiol* 50:1197–1219.

Berry SD, Swain RA (1989) Water deprivation optimizes hippocampal activity and facilitates nictitating membrane conditioning. *Behav Neurosci* 103:71–76.

Black A (1975) Hippocampal electrical activity and behavior. In: *The hippocampus: a comprehensive treatise* (Isaacson RL, Pribram KH, eds), pp 129–167. New York: Plenum Press.

Blair HT, Sharp PE (1996) Visual and vestibular influences on head-direction cells in the anterior thalamus of the rat. *Behav Neurosci* 110:643–660.

Blair HT, Lipscomb BW, Sharp PE (1997) Anticipatory time intervals of head-direction cells in the anterior thalamus of the rat: implications for path integration in the head-direction circuit. *J Neurophysiol* 78:145–159.

Blair HT, Cho J, Sharp PE (1999) The anterior thalamic head-direction signal is abolished by bilateral but not unilateral lesions of the lateral mammillary nucleus. *J Neurosci* 19:6673–6683.

Bland BH, Oddie SD (2001) Theta band oscillation and synchrony in the hippocampal formation and associated structures: the case for its role in sensorimotor integration. *Behav Brain Res* 127:119–136.

Bland BH, Vanderwolf CH (1972) Diencephalic and hippocampal mechanisms of motor activity in the rat: effects of posterior hypothalamic stimulation on behavior and hippocampal slow wave activity. *Brain Res* 43:67–88.

Bland BH, Konopacki J, Kirk IJ, Oddie SD, Dickson CT (1995) Discharge patterns of hippocampal theta-related cells in the caudal diencephalon of the urethane-anesthetized rat. *J Neurophysiol* 74:322–333.

Bland BH, Trepel C, Oddie SD, Kirk IJ (1996) Intraseptal microinfusion of muscimol: effects on hippocampal formation theta field activity and phasic theta-on cell discharges. *Exp Neurol* 138:286–297.

Bloch V, Laroche S (1981) Conditioning of hippocampal cells: its acceleration and long-term facilitation by post-trial reticular stimulation. *Behav Brain Res* 3:23–42.

Borhegyi Z, Varga V, Szilagyi N, Fabo D, Freund TF (2004) Phase segregation of medial septal GABAergic neurons during hippocampal theta activity. *J Neurosci* 24:8470–8479.

Bostock E, Muller RU, Kubie JL (1991) Experience-dependent modifications of hippocampal place cell firing. *Hippocampus* 1:193–205.

Bragin A, Engel J Jr, Wilson CL, Fried I, Buzsaki, G (1999) High-frequency oscillation in human brain. *Hippocampus* 9: 137–142.

Bragin A, Jando G, Nadasdy Z, Hetke J, Wise K, Buzsaki G (1995) Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. *J Neurosci* 15:47–60.

Brankack J, Stewart M, Fox SE (1993) Current source density analysis of the hippocampal theta rhythm: associated sustained potentials and candidate synaptic generators. *Brain Res* 615:310–327.

Breese CR, Hampson RE, Deadwyler SA (1989) Hippocampal place cells: stereotypy and plasticity. *J Neurosci* 9:1097–1111.

Brown MW, Aggleton JP (2001) Recognition memory: what are the roles of the perirhinal cortex and hippocampus? *Nat Rev Neurosci* 2:51–61.

Brown MW, Xiang JZ (1998) Recognition memory: neuronal substrates of the judgement of prior occurrence. *Prog Neurobiol* 55:149–189.

Brown MW, Wilson FA, Riches IP (1987) Neuronal evidence that inferomedial temporal cortex is more important than hippocampus in certain processes underlying recognition memory. *Brain Res* 409:158–162.

Brun VH, Otnass MK, Molden S, Steffenach HA, Witter MP, Moser MB, Moser EI (2002) Place cells and place recognition maintained by direct entorhinal-hippocampal circuitry. *Science* 296:2243–2246.

Bullock TH, Buzsaki G, McClune MC (1990) Coherence of compound field potentials reveals discontinuities in the CA1-subiculum of the hippocampus in freely-moving rats. *Neuroscience* 38:609–619.

Bures J, Fenton AA, Kaminsky Y, Rossier J, Sacchetti B, Zinyuk L (1997) Dissociation of exteroceptive and idiothetic orientation cues: effect on hippocampal place cells and place navigation. *Philos Trans R Soc Lond B Biol Sci* 352:1515–1524.

Burgess N, O'Keefe J (1996) Neuronal computations underlying the firing of place cells and their role in navigation. *Hippocampus* 6:749–762.

Burgess N, Recce M, O'Keefe J (1994) A model of hippocampal function. *Neural Networks* 7:1065–1081.

Burgess N, Jeffery KJ, O'Keefe J (1999) Intergrating hippocampal and parietal functions: a spatial point of view. In: *The hippocampal and parietal foundations of spatial cognition* (Burgess N, Jeffery KJ, O'Keefe J, eds), pp 3–29. Oxford, UK: Oxford University Press.

Burgess N, Maguire EA, O'Keefe J (2002) The human hippocampus and spatial and episodic memory. *Neuron* 35:625–641.

Burgess N, Cacucci F, Lever C, O'Keefe J (2005) Characterizing multiple independent behavioral correlates of cell firing in freely moving animals. *Hippocampus* 15:149–153.

Buzsaki G (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience* 31:551–570.

Buzsaki G (2002) Theta oscillations in the hippocampus. *Neuron* 33:325–340.

Buzsaki G (2005) Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus* 15:827–840.

Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. *Science* 304: 1926–1929.

Buzsaki G, Leung LW, Vanderwolf CH (1983) Cellular bases of hippocampal EEG in the behaving rat. *Brain Res* 287:139–171.

Buzsaki G, Horvath Z, Urioste R, Hetke J, Wise K (1992) High-frequency network oscillation in the hippocampus. *Science* 256:1025–1027.

Cacucci F, Lever C, Wills TJ, Burgess N, O'Keefe J (2004) Theta-modulated place-by-direction cells in the hippocampal formation in the rat. *J Neurosci* 24:8265–8277.

Calton JL, Stackman RW, Goodridge JP, Archey WB, Dudchenko PA, Taube JS (2003) Hippocampal place cell instability after lesions of the head direction cell network. *J Neurosci* 23:9719–9731.

Cameron KA, Yashar S, Wilson CL, Fried I (2001) Human hippocampal neurons predict how well word pairs will be remembered. *Neuron* 30:289–298.

Caplan JB, Madsen JR, Schulze-Bonhage A, Aschenbrenner-Scheibe R, Newman EL, Kahana MJ (2003) Human theta oscillations related to sensorimotor integration and spatial learning. *J Neurosci* 23:4726–4736.

Chakraborty S, Anderson MI, Chaudhry AM, Mumford JC, Jeffery KL (2004) Context-independent directional cue learning by hippocampal place cells. *Eur J Neurosci* 20: 281–292.

Chen LL, Lin LH, Green EJ, Barnes CA, McNaughton BL (1994) Head-direction cells in the rat posterior cortex. I. Anatomical distribution and behavioral modulation. *Exp Brain Res* 101:8–23.

Cho J, Sharp PE (2001) Head direction, place, and movement correlates for cells in the rat retrosplenial cortex. *Behav Neurosci* 115:3–25.

Cho YH, Giese KP, Tanila H, Silva AJ, Eichenbaum H (1998) Abnormal hippocampal spatial representations in alphaCaMKIIT286A and CREBalphaDelta mice. Science 279:867–869.

Christian EP, Deadwyler SA (1986) Behavioral functions and hippocampal cell types: evidence for two nonoverlapping populations in the rat. *J Neurophysiol* 55:331–348.

Chrobak JJ, Buzsaki G (1996) High-frequency oscillations in the output networks of the hippocampal- entorhinal axis of the freely behaving rat. *J Neurosci* 16:3056–3066.

Clark RE, Broadbent, Squire LR (2005) Imparied remote spatial memory after hippocampal lesions despite extensive training beginning early in life. *Hippocampus* 15:340–346.

Cohen NJ, Eichenbaum H (1993) *Memory, amnesisa and the hippocampal system*. Cambridge, MA: MIT Press.

Colom LV, Bland BH (1987) State-dependent spike train dynamics of hippocampal formation neurons: evidence for theta-on and theta-off cells. *Brain Res* 422:277–286.

Colombo M, Fernandez T, Nakamura K, Gross CG (1998) Functional differentiation along the anterior-posterior axis of the hippocampus in monkeys. *J Neurophysiol* 80:1002–1005.

Cooper BG, Mizumori SJ (2001) Temporary inactivation of the retrosplenial cortex causes a transient reorganization of spatial coding in the hippocampus. *J Neurosci* 21:3986–4001.

Cressant A, Muller RU, Poucet B (1997) Failure of centrally placed objects to control the firing fields of hippocampal place cells. *J Neurosci* 17:2531–2542.

Csicsvari J, Hirase H, Czurko A, Buzsaki G (1998) Reliability and state dependence of pyramidal cell-interneuron synapses in the hippocampus: an ensemble approach in the behaving rat. *Neuron* 21:179–189.

Csicsvari J, Hirase H, Mamiya A, Buzsaki G (2000) Ensemble patterns of hippocampal CA3-CA1 neurons during sharp wave-associated population events. *Neuron* 28:585–594.

Csicsvari J, Jamieson B, Wise KD, Buzsaki G (2003) Mechanisms of gamma oscillations in the hippocampus of the behaving rat. *Neuron* 37:311–322.

Czurko A, Hirase H, Csicsvari J, Buzsaki G (1999) Sustained activation of hippocampal pyramidal cells by 'space clamping' in a running wheel. *Eur J Neurosci* 11:344–352.

Delacour J (1984) Two neuronal systems are involved in a classical conditioning in the rat. *Neuroscience* 13:705–15.

Draguhn A, Traub RD, Bibbig A, Schmitz (2000) Ripple (approxi-

mately 200-Hz) oscillations in temporal structures. *J Clin Neurophysiol* 17:361–376.

Dudchenko PA, Wood ER, Eichenbaum H (2000) Neurotoxic hippocampal lesions have no effect on odor span and little effect on odor recognition memory but produce significant impairments on spatial span, recognition, and alternation. *J Neurosci* 20:2964–2977.

Eichenbaum H, Cohen N (2001) *From conditioning to conscious recollection*. Oxford, UK: Oxford University Press.

Eichenbaum H, Kuperstein M, Fagan A, Nagode J (1987) Cuesampling and goal-approach correlates of hippocampal unit activity in rats performing an odor-discrimination task. *J Neurosci* 7:716–732.

Eichenbaum H, Wiener SI, Shapiro ML, Cohen NJ (1989) The organization of spatial coding in the hippocampus: a study of neural ensemble activity. *J Neurosci* 9:2764–2775.

Ekstrom AD, Meltzer J, McNaughton BL, Barnes CA (2001) NMDA receptor antagonism blocks experience-dependent expansion of hippocampal "place fields." *Neuron* 31:631–638.

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I (2003) Cellular networks underlying human spatial navigation. *Nature* 425:184–188.

Fenton AA, Muller RU (1998) Place cell discharge is extremely variable during individual passes of the rat through the firing field. *Proc Natl Acad Sci USA* 95:3182–3187.

Fenton AA, Csizmadia G, Muller RU (2000a) Conjoint control of hippocampal place cell firing by two visual stimuli. I. The effects of moving the stimuli on firing field positions. *J Gen Physiol* 116:191–209.

Fenton AA, Csizmadia G, Muller RU (2000b) Conjoint control of hippocampal place cell firing by two visual stimuli. I. A vector-field theory that predicts modifications of the representation of the environment. *J Gen Physiol* 116:211–221.

Ferbinteanu J, Shapiro ML (2003) Prospective and retrospective memory coding in the hippocampus. *Neuron* 40:1227–1239.

Foster TC, Christian EP, Hampson RE, Campbell KA, Deadwyler SA (1987) Sequential dependencies regulate sensory evoked responses of single units in the rat hippocampus. *Brain Res* 408:86–96.

Foster TC, Castro CA, McNaughton BL (1989) Spatial selectivity of rat hippocampal neurons: dependence on preparedness for movement. *Science* 244:1580–1582.

Fox SE, Ranck JB Jr (1975) Localization and anatomical identification of theta and complex spike cells in dorsal hippocampal formation of rats. *Exp Neurol* 49:299–313.

Fox SE, Ranck JB Jr (1981) Electrophysiological characteristics of hippocampal complex-spike cells and theta cells. *Exp Brain Res* 41:399–410.

Fox SE, Wolfson S, Ranck JB Jr (1986) Hippocampal theta rhythm and the firing of neurons in walking and urethane anesthetized rats. *Exp Brain Res* 62:495–508.

Frank LM, Brown EN, Wilson M (2000) Trajectory encoding in the hippocampus and entorhinal cortex. *Neuron* 27:169–178.

Frank LM, Stanley GB, Brown EN (2004) Hippocampal plasticity across multiple days of exposure to novel environments. *J Neurosci* 24:7681–7689.

Freeman WJ (1975) *Mass action in the nervous system*. San Diego: Academic Press.

Fried I, MacDonald KA, Wilson CL (1997) Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron* 18:753–765.

Fried I, Cameron KA, Yashar S, Fong R, Morrow JW (2002) Inhibitory and excitatory responses of single neurons in the human medial temporal lobe during recognition of faces and objects. *Cereb Cortex* 12:575–584.

Fyhn M, Molden S, Witter MP, Moser EI, Moser MB (2004) Spatial representation in the entorhinal cortex. *Science* 305:1258–1264.

Gevins A, Smith ME, McEvoy L, Yu D (1997) High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. *Cereb Cortex* 7:374–385.

Gilbert PE, Kesner RP (2002) Role of the rodent hippocampus in paired-associate learning involving associations between a stimulus and a spatial location. *Behav Neurosci* 116:63–71.

Golob EJ, Taube JS (1997) Head direction cells and episodic spatial information in rats without a hippocampus. *Proc Natl Acad Sci USA* 94:7645–7650.

Golob EJ, Taube JS (1999) Head direction cells in rats with hippocampal or overlying neocortical lesions: evidence for impaired angular path integration. *J Neurosci* 19:7198–7211.

Goodridge JP, Taube JS (1997) Interaction between the postsubiculum and anterior thalamus in the generation of head direction cell activity. *J Neurosci* 17:9315–9330.

Goodridge JP, Dudchenko PA, Worboys KA, Golob EJ, Taube JS (1998) Cue control and head direction cells. *Behav Neurosci* 112:749–761.

Gothard KM, Skaggs WE, McNaughton BL (1996a) Dynamics of mismatch correction in the hippocampal ensemble code for space: interaction between path integration and environmental cues. *J Neurosci* 16:8027–8040.

Gothard KM, Skaggs WE, Moore KM, McNaughton BL (1996b) Binding of hippocampal CA1 neural activity to multiple reference frames in a landmark-based navigation task. *J Neurosci* 16:823–835.

Grastyan, E., Lissak, K., Madarasz, I, Donhoffer, H. (1959) Hippocampal electrical activity during the development of conditioned reflexes. *Electroencephalogr Clin Neurophysiol* 11:409–430.

Gray JA (1971) Medial septal lesions, hippocampal theta rhythm and the control of vibrissal movement in the freelymoving rat. *Electroencephalogr Clin Neurophysiol* 30:189–197.

Green JD, Arduini AA (1954) Hippocampal electrical activity in arousal. *J Neurophysiol* 17:533–557.

Guzowski JF, McNaughton BL, Barnes CA, Worley PF (1999) Environment-specific expression of the immediate-early gene Arc in hippocampal neuronal ensembles. *Nat Neurosci* 2:1120–1124.

Hafting T, Fyhn M, Molden S, Moser MB, Moser EI (2005) Microstructure of a spatial map in the entorhinal cortex. *Nature* 436:801–806.

Halgren E, Babb TL, Crandall PH (1978) Human hippocampal formation EEG desynchronizes during attentiveness and movement. *Electroencephalogr Clin Neurophysiol* 44:778–781.

Hampson RE, Simeral JD, Deadwyler SA (1999) Distribution of spatial and nonspatial information in dorsal hippocampus. *Nature* 402:610–614.

Harris KD, Henze DA, Hirase H, Leinekugel X, Dragoi G, Czurko A, Buzsaki G (2002) Spike train dynamics predicts theta-related phase precession in hippocampal pyramidal cells. *Nature* 417:738–741.

Hasselmo ME (2005) What is the function of hippocampal theta rhythm? Linking behavioral data to phasic properties of

field potential and unit recording data. *Hippocampus* 15:936–949.

Heit G, Smith ME, Halgren E (1988) Neural encoding of individual words and faces by the human hippocampus and amygdala. *Nature* 333:773–775.

Hetherington PA, Shapiro ML (1997) Hippocampal place fields are altered by the removal of single visual cues in a distance-dependent manner. *Behav Neurosci* 111:20–34.

Hill AJ (1978) First occurrence of hippocampal spatial firing in a new environment. *Exp Neurol* 62:282–297.

Hill AJ, Best PJ (1981) Effects of deafness and blindness on the spatial correlates of hippocampal unit activity in the rat. *Exp Neurol* 74:204–217.

Hirase H, Czurko HH, Csicsvari J, Buzsaki G (1999) Firing rate and theta-phase coding by hippocampal pyramidal neurons during 'space clamping.' *Eur J Neurosci* 11:4373–4380.

Hok V, Save E, Lenck-Santini PP, Poucet B (2005) Coding for spatial goals in the prelimbic/infralimbic area of the rat frontal cortex. *Proc Natl Acad Sci USA* 102:4602–4607.

Hollup SA, Molden S, Donnett JG, Moser MB, Moser EI (2001) Accumulation of hippocampal place fields at the goal location in an annular watermaze task. *J Neurosci* 21:1635–1644.

Holscher C, Anwyl R, Rowan MJ (1997) Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. *J Neurosci* 17:6470–6477.

Honzik CH (1936) The sensory basis of maze learning in rats. *Comp Psychol Monogr* 13:1–113.

Hori E, Nishio Y, Kazui K, Umeno K, Tabuchi E, Sasaki K, Endo S, Ono T, Nishijo H (2005) Place-related neural responses in the monkey hippocampal formation in a virtual space. *Hippocampus* 15:991–996.

Huerta PT, Lisman JE (1995) Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. *Neuron* 15:1053–1063.

Huxter J, Burgess N, O'Keefe J (2003) Independent rate and temporal coding in hippocampal pyramidal cells. *Nature* 425:828–832.

Hyman JM, Wyble BP, Goyal V, Rossi CA, Hasselmo ME (2003) Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. *J Neurosci* 23:11725–11731.

Hyman JM, Zilli EA, Paley AM, Hasselmo ME (2005) Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behavior. *Hippocampus* 15:739–749.

Jarosiewicz B, Skaggs WE (2004a) Hippocampal place cells are not controlled by visual input during the small irregular activity state in the rat. *J Neurosci* 24:5070–5077.

Jarosiewicz B, Skaggs WE (2004b) Level of arousal during the small irregular activity state in the rat hippocampal EEG. *J Neurophysiol* 91:2649–2657.

Jarosiewicz B, McNaughton BL, Skaggs WE (2002) Hippocampal population activity during the small-amplitude irregular activity state in the rat. *J Neurosci* 22:1373–1384.

Jeffery KJ (1998) Learning of landmark stability and instability by hippocampal place cells. *Neuropharmacology* 37:677–687.

Jeffery KJ, Donnett JG, O'Keefe J (1995) Medial septal control of theta-correlated unit firing in the entorhinal cortex of awake rats. *Neuroreport* 6:2166–2170.

Jeffery KJ, Donnett JG, Burgess N, O'Keefe JM (1997) Directional control of hippocampal place fields. *Exp Brain Res* 117:131–142.

Jeffery KJ, Gilbert A, Burton S, Strudwick A (2003) Preserved performance in a hippocampal-dependent spatial task despite complete place cell remapping. *Hippocampus* 13:175–189.

Jensen O, Lisman JE (2000) Position reconstruction from an ensemble of hippocampal place cells: contribution of theta phase coding. *J Neurophysiol* 83:2602–2609.

Jones MW, Wilson MA (2005) Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol* 3:e402.

Jung MW, Wiener SI, McNaughton BL (1994) Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. *J Neurosci* 14:7347–7356.

Jung R, Kornmuller AE (1938) Eine methodik der ableitung lokalisierter Potentialschwankungen aus subcorticalen Hirngebieten. *Arch Psychiatry* 109:1–30.

Kahana MJ, Sekuler R, Caplan JB, Kirschen M, Madsen JR (1999) Human theta oscillations exhibit task dependence during virtual maze navigation. *Nature* 399:781–784.

Kali S, Dayan P (2000) The involvement of recurrent connections in area CA3 in establishing the properties of place fields: a model. *J Neurosci* 20:7463–7477.

Kamondi A, Acsady L, Wang XJ, Buzsaki G (1998) Theta oscillations in somata and dendrites of hippocampal pyramidal cells in vivo: activity-dependent phase-precession of action potentials. *Hippocampus* 8:244–261.

Kentros C, Hargreaves E, Hawkins RD, Kandel ER, Shapiro M, Muller RV (1998) Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. *Science* 280:2121–2126.

Kim JJ, Clark RE, Thompson RF (1995) Hippocampectomy impairs the memory of recently, but not remotely, acquired trace eyeblink conditioned responses. *Behav Neurosci* 109:195–203.

King C, Recce M, O'Keefe J (1998) The rhythmicity of cells of the medial septum/diagonal band of Broca in the awake freely moving rat: relationships with behavior and hippocampal theta. *Eur J Neurosci* 10:464–477.

Kirk IJ, McNaughton N (1991) Supramammillary cell firing and hippocampal rhythmical slow activity. *Neuroreport* 2:723–725.

Klausberger T, Magill PJ, Marton LF, Roberts JD, Cobden PM, Buzsaki G, Somogyi P (2003) Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. *Nature* 421:844–848.

Klimesch W (1999) EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Brain Res Rev* 29:169–195.

Knierim JJ, Kudrimoti HS, McNaughton BL (1995) Place cells, head direction cells, and the learning of landmark stability. *J Neurosci* 15:1648–1659.

Kobayashi T, Nishijo H, Fukuda M, Bures J, Ono T (1997) Task-dependent representations in rat hippocampal place neurons. *J Neurophysiol* 78:597–613.

Kocsis B, Vertes RP (1997) Phase relations of rhythmic neuronal firing in the supramammillary nucleus and mammillary body to the hippocampal theta activity in urethane anesthetized rats. *Hippocampus* 7:204–214.

Kramis R, Vanderwolf CH, Bland BH (1975) Two types of hippocampal rhythmical slow activity in both the rabbit and the rat: relations to behavior and effects of atropine, diethyl ether, urethane, and pentobarbital. *Exp Neurol* 49:58–85.

Kreiman G, Koch C, Fried I (2000a) Category-specific visual responses of single neurons in the human medial temporal lobe. *Nat Neurosci* 3:946–953.

Kubie JL, Ranck JB Jr (1983) Sensory-behavioral correlates of individual hippocampal neurons in three situations: space and context. In: *Neurobiology of the hippocampus* (Siefert W, ed), pp 433–447, New York: Academic Press.

Kudrimoti HS, Barnes CA, McNaughton BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. *J Neurosci* 19:4090–4101.

Kyd RJ, Bilkey DK (2005) Hippocampal place cells show increased sensitivity to changes in the local environment following prefrontal cortex lesions. *Cereb Cortex* 15:720–731.

Laroche S, Falcou R, Bloch V (1983) Post-trial reticular facilitation of associative changes in multiunit activity; comparison between dentate gyrus and entorhinal cortex. *Behav Brain Res* 9:381–387.

Lawson VH, Bland BH (1993) The role of the septohippocampal pathway in the regulation of hippocampal field activity and behavior: analysis by the intraseptal microinfusion of carbachol, atropine, and procaine. *Exp Neurol* 120:132–144.

Leblanc MO, Bland BH (1979) Developmental aspects of hippocampal electrical activity and motor behavior in the rat *Exp Neurol* 66:220–237.

Lee AK, Wilson MA (2002) Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* 36:1183–1194.

Lee I, Rao G, Knierim JJ (2004) A double dissociation between hippocampal subfields: differential time course of CA3 and CA1 place cells for processing changed environments. *Neuron* 42:803–815.

Lenck-Santini PP, Save E, Poucet B (2001a) Evidence for a relationship between place-cell spatial firing and spatial memory performance. *Hippocampus* 11:377–390.

Lenck-Santini PP, Save E, Poucet B (2001b) Place-cell firing does not depend on the direction of turn in a Y-maze alternation task. *Eur J Neurosci* 13:1055–1058.

Lenck-Santini PP, Muller RU, Save E, Poucet B (2002) Relationships between place cell firing fields and navigational decisions by rats. *J Neurosci* 22:9035–9047.

Lengyel M, Szatmary Z, Erdi P. (2003) Dynamically detuned oscillators account for the coupled rate and temporal code of place cell firing. *Hippocampus* 13:700–714.

Leonard BJ, McNaughton BL, Barnes CA (1987) Suppression of hippocampal synaptic plasticity during slow-wave sleep. *Brain Res* 425:174–177.

Leung LW (1985) Spectral analysis of hippocampal EEG in the freely moving rat: effects of centrally active drugs and relations to evoked potentials. *Electroencephalogr Clin Neurophysiol* 60:65–77.

Leung LS (1992) Fast (beta) rhythms in the hippocampus: a review. *Hippocampus* 2:93–98.

Leung LW, Borst JG (1987) Electrical activity of the cingulate cortex. I. Generating mechanisms and relations to behavior. *Brain Res* 407:68–80.

Leutgeb S, Mizumori SJ (1999) Excitotoxic septal lesions result in spatial memory deficits and altered flexibility of hippocampal single-unit representations. *J Neurosci* 19:6661–6672.

Lever C, Cacucci F, Wills TJ, Burton S, McClelland, Burgess N, O'Keefe J (2003) Spatial coding in the hippocampal formation: input, information type, plasticity, and behavior. In: *The neurobiology of spatial behavior* (Jeffrey KJ, ed), pp 199–225. Oxford, UK: Oxford University Press.

Lever C, Wills T, Cacucci F, Burgess N, O'Keefe J (2002) Long-term plasticity in hippocampal place-cell representation of environmental geometry. *Nature* 416:90–94.

Louie K, Wilson MA (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron* 29:145–156.

Ludvig N, Tang HM, Gohil BC, Botero JM (2004) Detecting location-specific neuronal firing rate increases in the hippocampus of freely-moving monkeys. *Brain Res* 1014:97–109.

Maquet P (2001) The role of sleep in learning and memory. *Science* 294:1048–1052.

Markus EJ, Barnes CA, McNaughton BL, Gladden VL, Skaggs WE (1994) Spatial information content and reliability of hippocampal CA1 neurons: effects of visual input. *Hippocampus* 4:410–421.

Markus EJ, Qin YL, Leonard B, Skaggs WE, McNaughton BL, Barnes CA (1995) Interactions between location and task affect the spatial and directional firing of hippocampal neurons. *J Neurosci* 15:7079–7094.

Martin PD, Berthoz A (2002) Development of spatial firing in the hippocampus of young rats. *Hippocampus* 12:465–480.

Matthews RT, Lee WL (1991) A comparison of extracellular and intracellular recordings from medial septum/diagonal band neurons in vitro. *Neuroscience* 42:451–462.

Maurer AP, Vanrhoads SR, Sutherland GR, Lipa P, McNaughton BL (2005) Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus. *Hippocampus* 15:841–852.

McEchron MD, Disterhoft JF (1997) Sequence of single neuron changes in CA1 hippocampus of rabbits during acquisition of trace eyeblink conditioned responses. *J Neurophysiol* 78:1030–1044.

McEchron MD, Tseng W, Disterhoft JF (2003) Single neurons in CA1 hippocampus encode trace interval duration during trace heart rate (fear) conditioning in rabbit. *J Neurosci* 23:1535–1547.

McHugh TJ, Blum KI, Tsien JZ, Tonegawa S, Wilson MA (1996) Impaired hippocampal representation of space in CA1-specific NMDAR1 knockout mice. *Cell* 87:1339–1349.

McNaughton BL, Barnes CA, O'Keefe J (1983a) The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Exp Brain Res* 52: 41–49.

McNaughton BL, O'Keefe J, Barnes CA (1983b) The stereotrode: a new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records. *J Neurosci Methods* 8:391–397.

McNaughton BL, Barnes CA, Gerrard JL, Gothard K, Jung MW, Knierim JJ, Kudrimoti H, Qin Y, Skaggs WE, Suster M, Weaver KL (1996) Deciphering the hippocampal polyglot: the hippocampus as a path integration system. *J Exp Biol* 199(Pt 1):173–185.

Mehta MR, Barnes CA, McNaughton BL (1997) Experience-dependent, asymmetric expansion of hippocampal place fields. *Proc Natl Acad Sci USA* 94:8918–8921.

Mehta MR, Quirk MC, Wilson MA (2000) Experience-dependent asymmetric shape of hippocampal receptive fields. *Neuron* 25:707–715.

Mehta MR, Lee AK, Wilson MA (2002) Role of experience and oscillations in transforming a rate code into a temporal code. *Nature* 417:741–746.

Miller VM, Best PJ (1980) Spatial correlates of hippocampal unit

activity are altered by lesions of the fornix and endorhinal cortex. *Brain Res* 194:311–323.

Mitchell SJ, Ranck JB Jr (1980) Generation of theta rhythm in medial entorhinal cortex of freely moving rats. *Brain Res* 189:49–66.

Mizumori SJ, Williams JD (1993) Directionally selective mnemonic properties of neurons in the lateral dorsal nucleus of the thalamus of rats. *J Neurosci* 13:4015–4028.

Mizumori SJ, Barnes CA, McNaughton BL (1989) Reversible inactivation of the medial septum: selective effects on the spontaneous unit activity of different hippocampal cell types. *Brain Res* 500:99–106.

Mizumori SJ, Ward KE, Lavoie AM (1992) Medial septal modulation of entorhinal single unit activity in anesthetized and freely moving rats. *Brain Res* 570:188–197.

Mizumori SJ, Lavoie AM, Kalyani A (1996) Redistribution of spatial representation in the hippocampus of aged rats performing a spatial memory task. *Behav Neurosci* 110:1006–1016.

Moita MA, Rosis S, Zhou Y, LeDoux JE, Blair HT (2003) Hippocampal place cells acquire location-specific responses to the conditioned stimulus during auditory fear conditioning. *Neuron* 37:485–497.

Moita MA, Rosis S, Zhou Y, LeDoux JE, Blair HT (2004) Putting fear in its place: remapping of hippocampal place cells during fear conditioning. *J Neurosci* 24:7015–7023.

Muir GM, Bilkey DK (1998) Synchronous modulation of perirhinal cortex neuronal activity during cholinergically mediated (type II) hippocampal theta. *Hippocampus* 8:526–532.

Muir GM, Bilkey DK (2001) Instability in the place field location of hippocampal place cells after lesions centered on the perirhinal cortex. *J Neurosci* 21:4016–4025.

Muller RU, Kubie JL (1987) The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. *J Neurosci* 7:1951–1968.

Muller RU, Kubie JL, Ranck JB Jr (1987) Spatial firing patterns of hippocampal complex-spike cells in a fixed environment. *J Neurosci* 7:1935–1950.

Muller RU, Bostock E, Taube JS, Kubie JL (1994) On the directional firing properties of hippocampal place cells. J *Neurosci* 14:7235–7251.

Murray EA, Mishkin M (1998) Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J Neurosci 18:6568–6582.

Nadel L, Willner J, Kurz E (1985) Cognitive maps and environmental contex. In: *Context and learning* (Balsam P, Tomie A, eds), pp 385–406. Hillside, NJ: Erlbaum.

Nakazawa K, Quirk MC, Chitwood RA, Watanabe M, Yeckel MF, Sun LD, Kato A, Carr CA, Johnston D, Wilson MA, Tonegawa S (2002) Requirement for hippocampal CA3 NMDA receptors in associative memory recall. *Science* 297:211–218.

Nakazawa K, Sun LD, Quirk MC, Rondi-Reig L, Wilson MA, Tonegawa S (2003) Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. *Neuron* 38:305–315.

Nakazawa K, McHugh TJ, Wilson MA, Tonegawa S (2004) NMDA receptors, place cells and hippocampal spatial memory. *Nat Rev Neurosci* 5:361–372.

Natsume K, Hallworth NE, Szgatti TL, Bland BH (1999) Hippocampal theta-related cellular activity in the superior colliculus of the urethane-anesthetized rat. *Hippocampus* 9:500–509.

Nimmrich V, Maier N, Schmitz D, Draguhn A (2005) Induced sharp wave-ripple complexes in the absence of synaptic inhibition. *J Physiol* 563(Pt 3):663–670.

Nishijo H, Ono T, Eifuku S, Tamura R (1997) The relationship between monkey hippocampus place-related neural activity and action in space. *Neurosci Lett* 226:57–60.

Nitz D, McNaughton B (2004) Differential modulation of CA1 and dentate gyrus interneurons during exploration of novel environments. *J Neurophysiol* 91:863–872.

Nowicka A, Ringo JL (2000) Eye position-sensitive units in hippocampal formation and in inferotemporal cortex of the macaque monkey. *Eur J Neurosci* 12:751–759.

Nunez A, de Andres, I, Garcia-Austt E (1991) Relationships of nucleus reticularis pontis oralis neuronal discharge with sensory and carbachol evoked hippocampal theta rhythm. *Exp Brain Res* 87:303–308.

O'Keefe J (1976) Place units in the hippocampus of the freely moving rat. *Exp Neurol* 51:78–109.

O'Keefe J (1991a) The hippocampal cognitive map and navigational strategies. In: *Brain and space* (Paillard J, ed), pp 273–295. Oxford, UK: Oxford University Press.

O'Keefe J (1991b) An allocentric spatial model for the hippocampal cognitive map. *Hippocampus* 1:230–235.

O'Keefe J (1996) The spatial prepositions in English, vector grammar and the cognitive map theory. In: *Language and space* (Bloom P, Peterson M, Nadel L, Garrett M, eds), pp 277–316. Cambridge, MA: MIT Press.

O'Keefe J (1999) Do hippocampal pyramidal cells signal non-spatial as well as spatial information? *Hippocampus* 9:352–364.

O'Keefe J (2001) Vector grammar, places, and the functional role of the spatial prepositions in English. In: *Axes and vectors in language and space* (van der Zee E, Slack J, eds). Oxford, UK: Oxford University Press.

O'Keefe J, Burgess N (1996) Geometric determinants of the place fields of hippocampal neurons. *Nature* 381:425–428.

O'Keefe J, Conway DH (1978) Hippocampal place units in the freely moving rat: why they fire where they fire. *Exp Brain Res* 31:573–590.

O'Keefe J, Dostrovsky J (1971) The hippocampus as a spatial map: preliminary evidence from unit activity in the freely-moving rat. *Brain Res* 34:171–175.

O'Keefe J, Nadel L (1978) *The hippocampus as a cognitive map*. Oxford, UK: Oxford University Press.

O'Keefe J, Nadel L (1979) Precis of O'Keefe and Nadel's The Hippocampus as a Cognitive Map. Behav Brain Sci 2:487–533.

O'Keefe J, Recce ML (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3:317–330.

O'Keefe J, Speakman A (1987) Single unit activity in the rat hippocampus during a spatial memory task. *Exp Brain Res* 68:1–27.

O'Keefe J, Burgess N, Donnett JG, Jeffery KJ, Maguire EA (1998) Place cells, navigational accuracy, and the human hippocampus. *Philos Trans R Soc Lond B Biol Sci* 353:1333–1340.

O'Mara SM, Rolls ET, Berthoz A, Kesner RP (1994) Neurons responding to whole-body motion in the primate hippocampus. *J Neurosci* 14:6511–6523.

Olton DS, Branch M, Best PJ (1978) Spatial correlates of hippocampal unit activity. *Exp Neurol* 58:387–409.

Olypher AV, Lansky P, Fenton AA (2002) Properties of the extra-positional signal in hippocampal place cell discharge derived from the overdispersion in location-specific firing. *Neuroscience* 111:553–566.

Olypher AV, Klement D, Fenton AA (2006) Cognitive disorganization in hippocampus: a physiological model of the disorganization in psychosis. *J Neurosci* 26:158–168.

Ono T, Nakamura K, Nishijo H, Eifuku S (1993) Monkey hippocampal neurons related to spatial and nonspatial functions. *J Neurophysiol* 70:1516–1529.

Otto T, Eichenbaum H (1992) Neuronal activity in the hippocampus during delayed non-match to sample performance in rats: evidence for hippocampal processing in recognition memory. *Hippocampus* 2:323–334.

Pang K, Rose GM (1987) Differential effects of norepinephrine on hippocampal complex-spike and theta-neurons. *Brain Res* 425:146–158.

Pang K, Rose GM (1989a) Differential effects of methionine5-enkephalin on hippocampal pyramidal cells and interneurons. *Neuropharmacology* 28:1175–1181.

Paré D, Gaudreau H (1996) Projection cells and interneurons of the lateral and basolateral amygdala: distinct firing patterns and differential relation to theta and delta rhythms in conscious cats. *J Neurosci* 16:3334–3350.

Pavlides C, Winson J (1989) Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *J Neurosci* 9:2907–2918.

Pavlides C, Greenstein YJ, Grudman M, Winson J (1988) Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. *Brain Res* 439:383–387.

Paz-Villagran V, Lenck-Santini PP, Save E, Poucet B (2002) Properties of place cell firing after damage to the visual cortex. *Eur J Neurosci* 16:771–776.

Pedemonte M, Pena JL, Velluti RA (1996) Firing of inferior colliculus auditory neurons is phase-locked to the hippocampus theta rhythm during paradoxical sleep and waking. *Exp Brain Res* 112:41–46.

Penick S, Solomon PR (1991) Hippocampus, context, and conditioning. *Behav Neurosci* 105:611–617.

Phillips RG, LeDoux JE (1994) Lesions of the dorsal hippocampal formation interfere with background but not foreground contextual fear conditioning. *Learn Mem* 1:34–44.

Pickenhain, L., and Klingberg, F. (1967) Hippocampal slow wave activity as a correlate of basic behavioural mechanisms in the rat. In *Progress in brain research,* Vol. 27 (Adley WR, Tokizane T, eds), pp 218–27. Elsevier, Amsterdam.

Poe GR, Nitz DA, McNaughton BL, Barnes CA (2000) Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain Res* 855:176–180.

Powell DA, Joseph JA (1974) Autonomic-somatic interaction and hippocampal theta activity. *J Comp Physiol Psychol* 87:978–986.

Qin YL, McNaughton BL, Skaggs WE, Barnes CA (1997) Memory reprocessing in corticocortical and hippocampocortical neuronal ensembles. *Philos Trans R Soc Lond B Biol Sci* 352: 1525–1533.

Quirk GJ, Muller RU, Kubie JL (1990) The firing of hippocampal place cells in the dark depends on the rat's recent experience. *J Neurosci* 10:2008–2017.

Quirk GJ, Muller RU, Kubie JL, Ranck JB Jr (1992) The positional firing properties of medial entorhinal neurons: description and comparison with hippocampal place cells. *J Neurosci* 12: 1945–1963.

Ranck JB (1973) Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. I. Behavioral correlates and firing repertoires. *Exp Neurol* 41:461–531.

Ranck JB (1984) Head-direction cells in the deep cell layers of the dorsal presubiculum in freely moving rats. *Soc Neurosci Abstr* 10:599.

Rawlins JNP (1985) Associations across time: the hippocampus as a temporary memory store. *Brain Behav Sci* 8:479–496.

Redish AD, Touretzky DS (1996) Modeling interactions of the rat's place and head direction systems. In: *Neural information processing systems 8* (Touretzky DS, Mozer MC, Hasselmo ME, eds), pp 61–67. Cambridge, MA: MIT Press.

Redish AD, Battaglia FP, Chawla MK, Ekstrom AD, Gerrard JL, Lipa P, Rosenzweig ES, Worley PF, Guzowski JF, McNaughton BL, Barnes CA (2001) Independence of firing correlates of anatomically proximate hippocampal pyramidal cells. *J Neurosci* 21:RC134.

Riches IP, Wilson FA, Brown MW (1991) The effects of visual stimulation and memory on neurons of the hippocampal formation and the neighboring parahippocampal gyrus and inferior temporal cortex of the primate. *J Neurosci* 11:1763–1779.

Ringo JL, Sobotka S, Diltz MD, Bunce CM (1994) Eye movements modulate activity in hippocampal, parahippocampal, and inferotemporal neurons. *J Neurophysiol* 71:1285–1288.

Rivas J, Gaztelu JM, Garcia-Austt E (1996) Changes in hippocampal cell discharge patterns and theta rhythm spectral properties as a function of walking velocity in the guinea pig. *Exp Brain Res* 108:113–118.

Rolls ET, Cahusac PM, Feigenbaum JD, Miyashita Y (1993) Responses of single neurons in the hippocampus of the macaque related to recognition memory. *Exp Brain Res* 93:299–306.

Rolls ET, Robertson RG, Georges-Francois P (1997) Spatial view cells in the primate hippocampus. *Eur J Neurosci* 9:1789–1794.

Rose GM, Pang KC (1989) Differential effect of norepinephrine upon granule cells and interneurons in the dentate gyrus. *Brain Res* 488:353–356.

Rosenzweig ES, Barnes CA (2003) Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. *Prog Neurobiol* 69:143–179.

Rosenzweig ES, Redish AD, McNaughton BL, Barnes CA (2003) Hippocampal map realignment and spatial learning. *Nat Neurosci* 6:609–615.

Rossier J, Kaminsky Y, Schenk F, Bures J (2000) The place preference task: a new tool for studying the relation between behavior and place cell activity in rats. *Behav Neurosci* 114:273–284.

Rotenberg A, Mayford M, Hawkins RD, Kandel ER, Muller RU (1996) Mice expressing activated CaMKII lack low frequency LTP and do not form stable place cells in the CA1 region of the hippocampus. *Cell* 87:1351–1361.

Rotenberg A, Abel T, Hawkins RD, Kandel ER, Muller RU (2000) Parallel instabilities of long-term potentiation, place cells, and learning caused by decreased protein kinase A activity. *J Neurosci* 20:8096–8102.

Russell NA, Horii A, Smith PF, Darlington CL, Bilkey DK (2003) Long-term effects of permanent vestibular lesions on hippocampal spatial firing. *J Neurosci* 23:6490–6498.

Sainsbury RS, Harris JL, Rowland GL (1987a) Sensitization and hippocampal type 2 theta in the rat. *Physiol Behav* 41:489–493.

Sainsbury RS, Heynen A, Montoya CP (1987b) Behavioral correlates of hippocampal type 2 theta in the rat. *Physiol Behav* 39:513–519.

Salzmann E, Vidyasagar TR, Creutzfeldt OD (1993) Functional comparison of neuronal properties in the primate posterior hippocampus and parahippocampus (area TF/TH) during dif-

ferent behavioral paradigms involving memory and selective attention. *Behav Brain Res* 53:133–149.

Save E, Cressant A, Thinus-Blanc C, Poucet B (1998) Spatial firing of hippocampal place cells in blind rats. *J Neurosci* 18: 1818–1826.

Save E, Nerad L, Poucet B (2000) Contribution of multiple sensory information to place field stability in hippocampal place cells. *Hippocampus* 10:64–76.

Save E, Paz-Villagran V, Alexinsky T, Poucet B (2005) Functional interaction between the associative parietal cortex and hippocampal place cell firing in the rat. *Eur J Neurosci* 21:522–530.

Schenk F (1985) Development of place navigation in rats from weaning to puberty. *Behav Neural Biol* 43:69–85.

Seidenbecher T, Laxmi TR, Stork O, Pape HC (2003) Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. *Science* 301:846–850.

Shapiro ML, Tanila H, Eichenbaum H (1997) Cues that hippocampal place cells encode: dynamic and hierarchical representation of local and distal stimuli. *Hippocampus* 7:624–642.

Sharp PE (1996) Multiple spatial/behavioral correlates for cells in the rat postsubiculum: multiple regression analysis and comparison to other hippocampal areas. *Cereb Cortex* 6:238–259.

Sharp PE (1997) Subicular cells generate similar spatial firing patterns in two geometrically and visually distinctive environments: comparison with hippocampal place cells. *Behav Brain Res* 85:71–92.

Sharp PE (1999a) Comparison of the timing of hippocampal and subicular spatial signals: implications for path integration. *Hippocampus* 9:158–172.

Sharp PE (1999b) Subicular place cells expand or contract their spatial firing pattern to fit the size of the environment in an open field but not in the presence of barriers: comparison with hippocampal place cells. *Behav Neurosci* 113:643–662.

Sharp PE, Green C (1994) Spatial correlates of firing patterns of single cells in the subiculum of the freely moving rat. *J Neurosci* 14:2339–2356.

Sharp PE, Blair HT, Etkin D, Tzanetos DB (1995) Influences of vestibular and visual motion information on the spatial firing patterns of hippocampal place cells. *J Neurosci* 15:173–189.

Sharp PE, Tinkelman A, Cho J (2001) Angular velocity and head direction signals recorded from the dorsal tegmental nucleus of gudden in the rat: implications for path integration in the head direction cell circuit. *Behav Neurosci* 115:571–588.

Siapas AG, Wilson MA (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron* 21:1123–1128.

Siapas AG, Lubenov EV, Wilson MA (2005) Prefrontal phase locking to hippocampal theta oscillations. *Neuron* 46:141–151.

Sinclair BR, Seto MG, Bland BH (1982) Theta-cells in CA1 and dentate layers of hippocampal formation: relations to slow-wave activity and motor behavior in the freely moving rabbit. *J Neurophysiol* 48:1214–1225.

Singer W, Gray CM (1995) Visual feature integration and the temporal correlation hypothesis. *Annu Rev Neurosci* 18:555–586.

Sinnamon HM (2000) Priming pattern determines the correlation between hippocampal theta activity and locomotor stepping elicited by stimulation in anesthetized rats. *Neuroscience* 98:459–470.

Sinnamon HM, Jassen AK, Ilch C (2000) Hippocampal theta activity and facilitated locomotor stepping produced by GABA injections in the midbrain raphe region. *Behav Brain Res* 107:93–103.

Skaggs WE, McNaughton BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science* 271:1870–1873.

Skaggs WE, McNaughton BL, Wilson MA, Barnes CA (1996) Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 6: 149–172.

Slawinska U, Kasicki S (1995) Theta-like rhythm in depth EEG activity of hypothalamic areas during spontaneous or electrically induced locomotion in the rat. *Brain Res* 678:117–126.

Slawinska U, Kasicki S (1998) The frequency of rat's hippocampal theta rhythm is related to the speed of locomotion. *Brain Res* 796:327–331.

Sobotka S, Nowicka A, Ringo JL (1997) Activity linked to externally cued saccades in single units recorded from hippocampal, parahippocampal, and inferotemporal areas of macaques. *J Neurophysiol* 78:2156–2163.

Speakman A, O'Keefe J (1990) Hippocampal complex spike cells do not change their place fields if the goal is moved within a cue controlled environment. *Eur J Neurosci* 7:544–555.

Stackman RW, Taube JS (1997) Firing properties of head direction cells in the rat anterior thalamic nucleus: dependence on vestibular input. *J Neurosci* 17:4349–4358.

Stackman RW, Taube JS (1998) Firing properties of rat lateral mammillary single units: head direction, head pitch, and angular head velocity. *J Neurosci* 18:9020–9037.

Stackman RW, Clark AS, Taube JS (2002) Hippocampal spatial representations require vestibular input. *Hippocampus* 12: 291–303.

Stewart M, Fox SE (1991) Hippocampal theta activity in monkeys. *Brain Res* 538:59–63.

Stewart M, Luo Y, Fox SE (1992) Effects of atropine on hippocampal theta cells and complex-spike cells. *Brain Res* 591:122–128.

Stickgold R, Hobson JA, Fosse R, Fosse M (2001) Sleep, learning, and dreams: off-line memory reprocessing. *Science* 294: 1052–1057.

Tamura R, Ono T, Fukuda M, Nishijo H (1991) Role of monkey hippocampus in recognition of food and nonfood. *Brain Res Bull* 27:457–461.

Tamura R, Ono T, Fukuda M, Nakamura K (1992) Spatial responsiveness of monkey hippocampal neurons to various visual and auditory stimuli. *Hippocampus* 2:307–322.

Tanila H, Shapiro M, Gallagher M, Eichenbaum H (1997a) Brain aging: changes in the nature of information coding by the hippocampus. *J Neurosci* 17:5155–5166.

Tanila H, Shapiro ML, Eichenbaum H (1997b) Discordance of spatial representation in ensembles of hippocampal place cells. *Hippocampus* 7:613–623.

Taube JS (1995a) Head direction cells recorded in the anterior thalamic nuclei of freely moving rats. *J Neurosci* 15:70–86.

Taube JS (1995b) Place cells recorded in the parasubiculum of freely moving rats. *Hippocampus* 5:569–583.

Taube JS (1998) Head direction cells and the neuropsychological basis for a sense of direction. *Prog Neurobiol* 55:225–256.

Taube JS, Burton HL (1995) Head direction cell activity monitored in a novel environment and during a cue conflict situation. *J Neurophysiol* 74:1953–1971.

Taube JS, Muller RU (1998) Comparisons of head direction cell activity in the postsubiculum and anterior thalamus of freely moving rats. *Hippocampus* 8:87–108.

Taube JS, Muller RU, Ranck JB Jr (1990a) Head-direction cells recorded from the postsubiculum in freely moving rats.

I. Description and quantitative analysis. *J Neurosci* 10: 420–435.

Taube JS, Muller RU, Ranck JB Jr (1990b) Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations. *J Neurosci* 10: 436–447.

Tesche CD, Karhu J (2000) Theta oscillations index human hippocampal activation during a working memory task. *Proc Natl Acad Sci USA* 97:919–924.

Thompson LT, Best PJ (1989) Place cells and silent cells in the hippocampus of freely-behaving rats. *J Neurosci* 9:2382–2390.

Thompson RF (1976) The search for the engram. *Am Psychol* 31:209–227.

Tsien JZ, Huerta PT, Tonegawa S (1996) The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. *Cell* 87:1327–1338.

Vanderwolf CH (1969) Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr Clin Neurophysiol* 26:407–418.

Vanderwolf CH (2001) The hippocampus as an olfacto-motor mechanism: were the classical anatomists right after all? *Behav Brain Res* 127:25–47.

Vidyasagar TR, Salzmann E, Creutzfeldt OD (1991) Unit activity in the hippocampus and the parahippocampal temporobasal association cortex related to memory and complex behavior in the awake monkey. *Brain Res* 544:269–278.

Vinogradova OS, Brazhnik ES (1977) Neuronal aspects of septo-hippocampal relations *Ciba Found Symp* 145–177.

Wallenstein GV, Eichenbaum H, Hasselmo ME (1998) The hippocampus as an associator of discontiguous events. T*rends Neurosci* 21:317–323.

Watanabe T, Niki H (1985) Hippocampal unit activity and delayed response in the monkey. *Brain Res* 325:241–254.

Weiss C, Kronforst-Collins MA, Disterhoft JF (1996) Activity of hippocampal pyramidal neurons during trace eyeblink conditioning. *Hippocampus* 6:192–209.

Wesierska M, Dockery C, Fenton AA (2005) Beyond memory, navigation, and inhibition: behavioral evidence for hippocampus-dependent cognitive coordination in the rat. *J Neurosci* 25:2413–2419.

Whishaw IQ, Vanderwolf CH (1971) Hippocampal EEG and behavior: effects of variation in body temperature and relation of EEG to vibrissae movement, swimming and shivering. *Physiol Behav* 6:391–397.

Whishaw IQ, Vanderwolf CH (1973) Hippocampal EEG and behavior: changes in amplitude and frequency of RSA (theta rhythm) associated with spontaneous and learned movement patterns in rats and cats. *Behav Biol* 8:461–484.

Wiebe SP, Staubli UV (1999) Dynamic filtering of recognition memory codes in the hippocampus. *J Neurosci* 19:10562–10574.

Wiener SI (1993) Spatial and behavioral correlates of striatal neurons in rats performing a self-initiated navigation task. *J Neurosci* 13:3802–3817.

Wiener SI, Paul CA, Eichenbaum H (1989) Spatial and behavioral correlates of hippocampal neuronal activity. *J Neurosci* 9:2737–2763.

Wiener SI, Korshunov VA, Garcia R, Berthoz A (1995) Inertial, substratal and landmark cue control of hippocampal CA1 place cell activity. *Eur J Neurosci* 7:2206–2219.

Wills TJ, Lever C, Cacucci F, Burgess N, O'Keefe J (2005) Attractor dynamics in the hippocampal representation of the local environment. *Science* 308:873–876.

Wilson FA, Riches IP, Brown MW (1990) Hippocampus and medial temporal cortex: neuronal activity related to behavioral responses during the performance of memory tasks by primates. *Behav Brain Res* 40:7–28.

Wilson MA, McNaughton BL (1993) Dynamics of the hippocampal ensemble code for space. *Science* 261:1055–1058.

Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* 265:676–679.

Wirth S, Yanike M, Frank LM, Smith AC, Brown EN, Suzuki WA (2003) Single neurons in the monkey hippocampus and learning of new associations. *Science* 300:1578–1581.

Wood ER, Dudchenko PA, Eichenbaum H (1999) The global record of memory in hippocampal neuronal activity. *Nature* 397:613–616.

Wood ER, Dudchenko PA, Robitsek RJ, Eichenbaum H (2000) Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* 27:623–633.

Yamaguchi Y, Aota Y, McNaughton BL, Lipa P (2002) Bimodality of theta phase precession in hippocampal place cells in freely running rats. *J Neurophysiol* 87:2629–2642.

Ylinen A, Bragin A, Nadasdy Z, Jando G, Szabo I, Sik A, Buzsaki G (1995) Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms. *J Neurosci* 15:30–46.

Zhang K (1996) Representation of spatial orientation by the intrinsic dynamics of the head-direction cell ensemble: a theory. *J Neurosci* 16:2112–2126.

Zhang K, Ginzburg I, McNaughton BL, Sejnowski TJ (1998) Interpreting neuronal population activity by reconstruction: unified framework with application to hippocampal place cells. *J Neurophysiol* 79:1017–1044.

Zinyuk L, Kubik S, Kaminsky Y, Fenton AA, Bures J (2000) Understanding hippocampal activity by using purposeful behavior: place navigation induces place cell discharge in both task-relevant and task- irrelevant spatial reference frames. *Proc Natl Acad Sci USA* 97:3771–3776.

Zugaro MB, Tabuchi E, Wiener SI (2000) Influence of conflicting visual, inertial and substratal cues on head direction cell activity. *Exp Brain Res* 133:198–208.

Zugaro MB, Berthoz A, Wiener SI (2001) Background, but not foreground, spatial cues are taken as references for head direction responses by rat anterodorsal thalamus neurons. *J Neurosci* 21:RC154.

Zugaro MB, Arleo A, Berthoz A, Wiener SI (2003) Rapid spatial reorientation and head direction cells. *J Neurosci* 23:3478–3482.

Zugaro MB, Monconduit L, Buzsaki G (2005) Spike phase precession persists after transient intrahippocampal perturbation. *Nat Neurosci* 8:67–71.