Handbook of
Episodic Memory

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CHAPTER 4.4

The hippocampus, context processing and episodic memory

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Abstract: Contextual information plays a critical role in memory. Learned information becomes associated with the learning context and the context can cue the memories and behaviors associated with that context. An extensive literature involving experimental brain lesions has shown that the hippocampus is critically involved in processing contextual information and hippocampal output modulates processing in downstream brain regions in a context-dependent manner. Recent findings indicate that hippocampal spatial firing patterns (place fields) and neuronal responses to task-relevant events are highly sensitive to the context, even when the context is defined by abstract task demands rather than the background environment. Because these neuronal response patterns are unique to a given context, they could serve as a neural representation of the context. These context representations could, through learning processes, become associated with the memories and behaviors that are appropriate to the context. A key feature of episodic memory is the ability to distinguish one event from other similar events. However, neurophysiological data from rodents suggests that hippocampal neuronal responses are better suited to distinguishing contexts than episodic memories for individual training trials. Since episodic memories, by definition, include information about the time and place where the event occurred, contextual information is a necessary prerequisite for episodic memory. It is therefore suggested that episodic memory impairments resulting from hippocampal damage in humans and animals could be secondary to context processing deficits. On the basis of these findings, it is suggested that the primary function of the hippocampus is the identification and encoding of contexts and that the hippocampus likely contributes these context representations to a wider circuitry which mediates episodic memory.

Keywords: hippocampus; context; memory; discrimination; learning; place field

I. Introduction

Episodic memory is a particularly rich, multifaceted form of memory. As discussed in detail elsewhere in this handbook (see Section 1, this volume), episodic memory representations include information about the objects, individuals, and events that comprise an episode as well as the place and time of their occurrence. Thus, a key feature of episodic memory is that it always involves the spatial and temporal context in which events occur. The focus of this chapter is the context processing role of the hippocampus, and the relationship between contextual information and episodic memory.

Contextual information plays a critical role in memory. Revisiting a known context often reminds one of the events that occurred there. For example, returning to one's childhood home or a vacation spot, can elicit particularly vivid memories, often including memories long thought

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to have been lost. Empirical studies of contextual cueing of memory have a long history in psychology. Items learned in one context are more likely to be remembered if testing takes place in the same context (Godden and Baddely, 1975; Baddely, 1987). Even internal mental states can serve as a context (for review see Smith, 1995). For example, items learned while in a particular emotional state are more likely to be remembered when subjects are tested under similar conditions. Simply instructing subjects to think about the learning context improves recall of items learned in that context (Smith, 1979). The context can also serve as a disambiguating cue that allows subjects to retrieve information associated with that context without the interference from items learned in other contexts. For example, subjects who learn two lists in different contexts exhibit better recall than subjects who learn both lists in the same context (for review see Smith and Vela, 2001). Learning the two lists in separate contexts reduces interference at test time, suggesting that the context can serve as a cue that allows subjects to keep learned items separate in memory.

Most of the findings reviewed in this chapter were obtained from studies of experimental animals. A main idea of the following discussion is that the hippocampus is primarily involved in generating context representations, which are one component of episodic memories. However, it is not being suggested that animals do not have the capacity for episodic memory or that context processing is an animal approximation to human episodic memory. Rather, it is proposed that context representations are a key part of episodic memory in animal subjects, just as in humans. A thorough discussion of whether animals possess the capacity for episodic memory is beyond the scope of this chapter (for excellent discussions of this issue see Aggleton and Pearce, 2001; Morris, 2001). However, given the remarkable homology of mammalian nervous systems and the fact that the ability to explicitly recall previous experiences has such obvious adaptive value, it is suggested that, in the absence of contradictory evidence, the most conservative position is to assume that animals possess an episodic memory system that is qualitatively similar to that of humans, although

perhaps not as rich and complex. A number of recent findings are consistent with this idea (Clayton and Dickinson, 1998; Eacott and Norman, 2004; Eacott et al., 2005), see also Easton and Eacott (Chapter 2.3, this volume).

II. The hippocampal role in context processing

An extensive literature involving experimental brain lesions in animals has implicated the hippocampus in context processing (for reviews see Myers and Gluck, 1994; Anagnostaras et al., 2001; Maren, 2001). For example, hippocampal lesions impair conditioned fear responses to contextual stimuli (Kim and Fanselow, 1992; Phillips and LeDoux, 1992). Interestingly, rats with lesions exhibited normal fear responses to phasic conditional stimuli, such as a tone or light, indicating that the lesions did not impair all forms of memory. Instead, the lesions specifically impaired the processing of contextual information. Just as the context can evoke memories, it can also serve as a cue that elicits conditioned responses (Blanchard and Blanchard, 1972; Balaz et al., 1980; Fanselow, 1986). Other studies have shown that lesions of the hippocampus or entorhinal cortex render animal subjects insensitive to changes in the context (Penick and Solomon, 1991; Freeman et al., 1997). In these studies, rats or rabbits were trained in one context and tested in another. Intact subjects exhibited diminished responding when the context is changed. This is an adaptive response to context change since new or altered contexts often have different rules and contingencies. In contrast to controls, subjects with lesions responded at normal levels, suggesting that they did not notice that the context has changed.

The above studies involved Pavlovian and instrumental learning tasks. However, the episodic memory systems of the brain operate automatically, regardless of whether the task at hand specifically requires episodic memory processing. For this reason, studies of behavioral tasks generally thought to have a minimal episodic memory component may nevertheless be fruitful methods for the study of context and, indirectly,

episodic memory. For example, Moita et al. (2003) used a Pavlovian fear conditioning task to study neuronal responses which could be used to link an event to the place in which that event occurred. Consistent with previous studies (Kang and Gabriel, 1998), the authors found that hippocampal neurons respond to an auditory tone that had been paired with shock. Interestingly, the neuronal responses to the tone were enhanced when rats were in the place field for that neuron, suggesting that hippocampal neurons may encode the co-occurrence of an event (the tone) and the place where that event occurred.

Episodic memory is critically dependent on contextual information. However, as the above studies indicate, context representations are not used exclusively for episodic memory. Rather, context representations are important for many forms of learning and memory, including Pavlovian conditioning (Bouton, 1993), instrumental learning (Thomas et al., 1985; Freeman et al., 1997; Smith et al., 2004), priming (Smith, 1990), word list learning (Smith and Vela, 2001), object recognition (e.g., Tsivilis et al., 2001), and face recognition (Thomson et al., 1982). Thus, it would be particularly useful to generate context representations that can be 'exported' to various brain regions which perform different kinds of learning and memory functions. The receipt of this context code could then influence each brain region so that the learned information becomes associated with the context in which the learning occurred.

III. The hippocampal role in context-specific discrimination learning

A recent study examined the importance of hippocampal output to posterior cingulate (retrosplenial) cortical and anterior thalamic brain regions during contextual learning (Smith et al., 2004). This study took advantage of the well-documented role of the cingulate cortex and anterior thalamus in instrumental discrimination learning in rabbits (Gabriel, 1993) and examined whether hippocampal output modulates functioning in these regions in a context dependent manner. Neurons within this circuit develop preferential responses to an auditory conditional stimulus that predicts reinforcement (CS+), relative to a nonpredictive stimulus (CS–). Thus, the neurons come to discriminate between the conditional stimuli with training and these discriminative neuronal responses are necessary for rabbits to learn the discrimination task, since lesions which disrupt the neuronal discrimination also impair learning (Gabriel, 1993; Smith et al., 2004).

Interestingly, the magnitude of these neuronal responses changes systematically over the course of training, with different regions being maximally responsive at early, intermediate, or late stages of training (Fig. 1). Thus, the pattern of tone-evoked neuronal responses varies systematically across brain regions and across training, such that any training stage has a particular topography of neuronal excitation associated with it. Remarkably, these neuronal response patterns are quite distinct in different contexts (Freeman et al., 1996), suggesting that they may reflect context-specific processing of significant stimuli (i.e., the tones) and the behavioral demands relevant to that context. Given the well-documented role of the hippocampus in processing contextual information and the fact that the hippocampus is interconnected with the cingulate cortex and anterior thalamus, it was hypothesized that a hippocampal context code may be sent to the cingulate cortex and anterior thalamus in the interest of context-specific discrimination learning. Since these tone-evoked neuronal firing patterns vary as a function of context and training stage, they may reflect the interactive processing of the cingulate cortical and anterior thalamic circuitry with the hippocampus in the interest of associating a learned discrimination with the appropriate training context.

To test this hypothesis, rabbits with fornix lesions, which partially disconnect the hippocampus from the cingulate cortex and anterior thalamus, were given concurrent training on two different instrumental discrimination tasks, each of which was presented in a different context. In each task, rabbits were trained to respond to one auditory tone which predicted reinforcement (the CS+) and to ignore a nonpredictive tone (CS–).
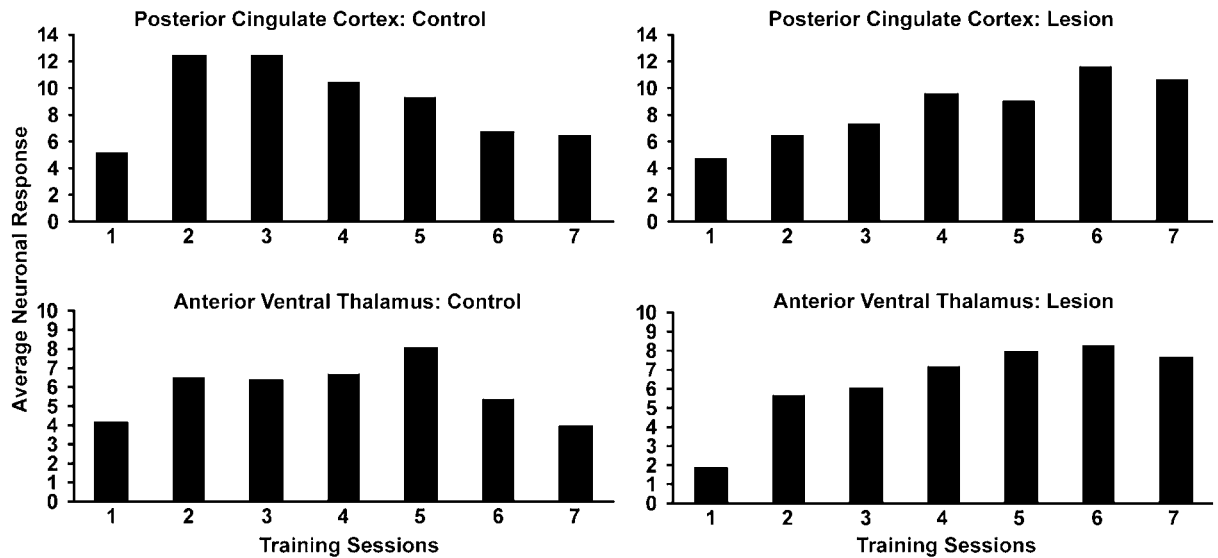
Fig. 1. Average tone-evoked neuronal responses recorded in the posterior cingulate cortex and anterior ventral thalamus during concurrent auditory discrimination learning. The data, in the form of z-scores normalized to pretone baseline, are shown for control subjects (left plots) and subjects with fornix lesions (right plots). Each bar illustrates 400 ms of neuronal firing recorded during the tones. In control subjects, the neurons exhibit an increase in firing rate with training, followed by a return to baseline firing rates in subsequent training sessions. Each of several cingulate cortical and anterior thalamic brain regions (two examples are shown) becomes maximally responsive at a different stage of training, such that the pattern of neuronal responses distributed across a large population of neurons is unique to a given training stage and a particular context. Subjects with lesions exhibit the initial increase in neuronal firing, but they do not show the normal decline. This results in degraded neuronal response patterns in which the neurons respond at high rates throughout the circuitry, rather than exhibiting training stage- and context-specific firing patterns.

The same tone conditional stimuli were used in both tasks, but their predictive value was reversed so that the CS+ in one task was the CS− in the other task. Thus, the rabbits were forced to rely on contextual information to disambiguate the meaning of the tones and to respond accordingly. Rabbits with lesions were severely impaired in learning the two context-specific discrimination tasks. Because the discriminative stimuli were the same in both tasks, the training procedure induced substantial inter-task interference. Intact rabbits were able to use contextual information to defeat this interference and they learned both tasks simultaneously. In contrast, rabbits with lesions exhibited severe inter-task interference, which limited them to improvement in one task or the other, but not in both tasks simultaneously.

Consistent with previous findings, control rabbits developed unique neuronal response patterns in the cingulate cortex and anterior thalamus during learning in each of the discrimination tasks. These response patterns were characterized by an initial increase in tone evoked firing which peaked at a particular stage of training, followed by a decline in neuronal firing in subsequent training sessions (Fig. 1). However, the neuronal response patterns were degraded in rabbits with lesions, indicating that cingulate cortical and anterior thalamic processing was abnormal when these regions were denied access to the hippocampal context code. This degraded processing in the cingulate cortex and anterior thalamus was associated with a deficit in the rabbits' ability to learn the context-appropriate discriminative responses. Thus, the results suggested that the hippocampus generates a neural representation of the context which can be transmitted to extra-hippocampal brain regions to facilitate the interference free retrieval of context-appropriate behavioral responses and memories.

IV. What kinds of "context" does the hippocampus encode?

In the studies described above, the context was defined in terms of the continuously present background cues (i.e., the environment). Despite the fact that this has proven to be a useful operational definition in studies of contextual influences on conditioning, it is unnecessarily restrictive and does not adequately describe the full array of stimuli and task features which subjects use to distinguish one situation from another. Various authors have used the term "context" to describe the spatial geometry of the environment (e.g., Nadel et al., 1985), nongeometric background cues such as colors, odors, or textures (Hayman et al., 2003; Anderson and Jeffery, 2003; Eacott and Norman, 2004; Eacott et al., 2005), the motivational or emotional state of the subject (Kennedy and Shapiro, 2004), the experimenter who presents the target items (Simons et al., 2004), the list in which a target item appears (Anderson and Bower, 1974), the visual scene in which a target stimulus appears (Chun and Phelps, 1999), an ongoing sequence of stimuli (Goldstein et al., 2002) or behaviors (Bower et al., 2005), the strategy demands of the task (Yeshenko et al., 2001), and the mnemonic or response demands of the task (Smith and Mizumori, 2006a, b). Although, there are some important differences between these various kinds of contexts with regard to the impact they have on learning and memory processes, it is suggested here that they all represent different facets of the same underlying function and that all of these various kinds of contexts are encoded by the hippocampus.

The context is more abstract than any particular set of cues. Although the context may be defined by background cues, it can also be defined by the particular task demands, or rules, such as the memory requirements, the required behaviors, or the appropriate strategies. Subjects can readily learn that a particular behavior is appropriate at one time and that different behavior is appropriate at another time, even when the environment has not changed. *Context, as the term will be used in the following discussion, refers to a particular situation or set of circumstances that must be differentiated from other situations in order for subjects to retrieve the correct behavioral or mnemonic output.* Importantly, this definition encompasses the traditional definitions of context used historically in psychology (i.e., background stimuli) as well as the kinds of contexts that are identified by more abstract features, such as the task demands.

This broader definition of context was suggested by findings indicating that hippocampal neuronal responses are not limited to background or spatial stimuli. Instead, hippocampal neurons respond to a variety of stimuli and are sensitive to abstract task features. For example, hippocampal neurons exhibit responses to foreground cues, such as the conditional stimuli and reinforcing stimuli used in learning tasks (e.g., Solomon et al., 1986; Eichenbaum et al., 1987; Kang and Gabriel, 1998; Moita et al., 2003). Hippocampal neurons exhibit remarkably robust spatially localized firing patterns known as place fields (O'Keefe and Dostrovsky, 1971). However, it is now apparent that the firing of these neurons is not controlled solely by the spatial geometry of the environment. Subtle changes in task demands are associated with striking changes in the spatial firing patterns of hippocampal pyramidal neurons even when the background environment is not altered (Markus et al., 1995; Skaggs and McNaughton, 1998; Wood et al., 2000; Song et al., 2005). For example, Markus et al. (1995) found that hippocampal neurons exhibited markedly different spatial firing patterns when rats followed an experimenter-defined search path for rewards, as compared to a random search strategy in the same environment. Remarkably, the neurons even exhibited different firing patterns when rats follow the experimenter-defined path in clockwise or counter-clockwise directions.

More recently, hippocampal neurons have been shown to exhibit different responses depending on upcoming, or previous behavioral responses (e.g., right or left turns on a maze, Wood et al., 2000). Neuronal firing also depends on whether rats are actively or passively moved through the environment (Foster et al., 1989; Song et al., 2005). Some neurons even respond differentially when rats passively ride through the environment on a car

controlled by the experimenter, as compared to trials in which the rats had to press a switch to move the car themselves (Terrazas et al., 2005). Consistent with the idea of state-dependent learning, the hippocampus has even been implicated in selecting behavioral responses on the basis of the rat's internal motivational state (Kennedy and Shapiro, 2004) and preliminary data indicate that hippocampal neurons exhibit different responses in the same environment while performing the same behaviors, depending on whether the rat is motivated to seek water or food rewards (M. Shapiro and P. Kennedy, personal communication).

The data indicate that hippocampal neuronal responses differentiate all of these different aspects of a learning situation. A common feature of all of these findings is that hippocampal neurons responded differentially whenever rats needed to differentiate one situation, or context, from another in order to perform correctly. One recent study found that hippocampal neurons exhibit markedly different response patterns, depending on the problem-solving strategy rats used to obtain rewards (Yeshenko et al., 2001). Remarkably, these differential firing patterns occurred even when the rats were engaged in the same behaviors (e.g., right or left turns) within the same environment. It is suggested here that hippocampal neurons exhibit differential firing patterns whenever subjects must distinguish one context from another in order to retrieve the correct behavioral responses or memories, regardless of whether the defining features of the context are concrete (e.g., the background environment) or abstract (e.g., the task demands).

V. Neurophysiological evidence of hippocampal context processing

The idea that hippocampal neuronal responses could differentiate abstract contexts was explicitly tested in a recent experiment which required rats to distinguish two contexts that differed only in terms of their behavioral requirements (Smith and Mizumori, 2006b). The previous study of context-specific discrimination learning (described above) indicated that the hippocampal input modulates neuronal responses in extrahippocampal brain regions, such as the cingulate cortex and anterior thalamus, in a context-specific manner. However, in that study, neuronal responses in the hippocampus were not recorded and the rabbits in that study were not allowed to move around within the training environment. Thus, it was not possible to record one of the predominant kinds of hippocampal neuronal responses, the place field (O'Keefe and Dostrovsky, 1971). The following experiment was designed to determine whether direct evidence of hippocampal context processing could be found.

In this experiment, rats were trained to retrieve rewards from one location on a plus maze during the first half of each training session and from a different location in the same environment during the second half of the sessions (Smith and Mizumori, 2006b). Specifically, the rats were given daily training sessions during which the reward was always placed at the end of the east arm for the first 15 trials and was always placed at the end of the west arm during the second 15 trials. The start position for each trial was randomly selected from the three non-rewarded arms. In between trials, the rats were placed on an intertrial interval (ITI) platform adjacent to the maze. The position of the ITI platform was constant throughout training. The rats were given identical training sessions each day until they reached a behavioral criterion of 75% correct choices. The two session halves constituted separate contexts defined by their differing task demands. In each block of trials the rats had to remember and approach a different reward location. Neuronal responses were examined to determine whether they differed in the two contexts.

As a control condition, the rats were given a random reward training session before beginning regular training sessions. During the random reward session, the rats started each trial on a randomly designated arm and searched for rewards located on a different randomly designated arm. The random reward session was also divided into two blocks of trials, although all of the trials consisted of searching for randomly placed rewards, and the neuronal responses were compared across these blocks. Since the task demands did not differ across these two blocks,

there was no context manipulation and the neuronal responses were not expected to differ.

Learning to distinguish the two contexts was associated with the development of highly differentiated spatial firing patterns (Fig. 2A–D). These firing patterns became significantly more distinct after learning, relative to the random reward control condition. Importantly, the differential responses developed only in rats that were given context training and not in rats that were given repeated random reward sessions, indicating that the context-specific place fields could not have been due to factors unrelated to learning to distinguish the contexts. The differential responses could not be attributed to differences in the rats' direction of travel in the two contexts, since the firing patterns remained significantly different in the two contexts when direction was controlled. Also, the place fields did not simply rotate 180°, as would be expected if the neurons fired in relation to the reward locations, or if the firing occurred in relation to the rat's position along a given path (e.g., an inbound run, followed by a right turn and an outbound run), a phenomenon known as path equivalence (Frank et al., 2000).

As mentioned previously, hippocampal neurons are known to exhibit responses to task-relevant events and stimuli (e.g., Eichenbaum et al., 1987; Kang and Gabriel, 1998; Moita et al., 2003). In our studies, the neurons developed remarkably different responses to the reward and the beginning of the ITI period in the two contexts (Fig. 2E–H). As was the case with the place fields, these responses developed as the rats learned to differentiate the contexts and they did not develop in rats that were not given context training.

The firing patterns of hippocampal neuronal populations were unique to each context and could therefore serve as a neural representation of the context. Context representations play a critical role in learning and memory because they provide a cue that primes the context-appropriate memories and behaviors (Blanchard and Blanchard, 1972; Godden and Baddely, 1975; Balaz et al., 1980; Fanselow, 1986). When a subject encounters a known context, the hippocampal context code is expressed and the appropriate memories and behaviors are primed. For example, the neuron

in Fig. 2C fired on the north start arm in the Context B but not in Context A. The firing of this neuron and others like it could prime the "right turn" response needed to reach the goal location in Context B. When these neurons do not fire, the right turn response may be suppressed while other neurons presumably prime the left turn response appropriate to Context A. Thus, the output of context-specific hippocampal firing patterns influences processing in extrahippocampal brain regions and, ultimately, the behavioral output of the subject. Through associative learning processes, the context-specific hippocampal firing patterns could become associated with the memories, strategies, and behaviors that are appropriate for a given context. This provides a mechanistic explanation for how contextual information can elicit learned responses and promote the retrieval of relevant memories.

VI. Hippocampal inactivation impairs contextual learning

The idea that hippocampal lesions impair context processing is well documented (Penick and Solomon, 1991; Kim and Fanselow, 1992; Phillips and LeDoux, 1992; Freeman et al., 1997; Smith et al., 2004). To determine whether learning the above described context discrimination task depended on the hippocampus, the $GABA_A$ agonist muscimol ($0.5\,\mu g$ in $0.5\,\mu l$ saline in each hemisphere) was used to temporarily inactivate the dorsal hippocampus before the initial two training sessions (Smith and Mizumori, 2006a). Consistent with previous reports (Eichenbaum et al., 1990; Bunsey and Eichenbaum, 1996; Whishaw and Tomie, 1997; Buckmaster et al., 2004), the loss of hippocampal processing was associated with highly inflexible behavioral strategies. Many of the rats that were given muscimol simply adopted the strategy of always turning right or always turning left. This caused those rats to make many errors from some start positions but few errors from others. For example, because the reward was on the east arm in context A, a rat that always made right turn responses would always perform correctly from the south arm but would always make
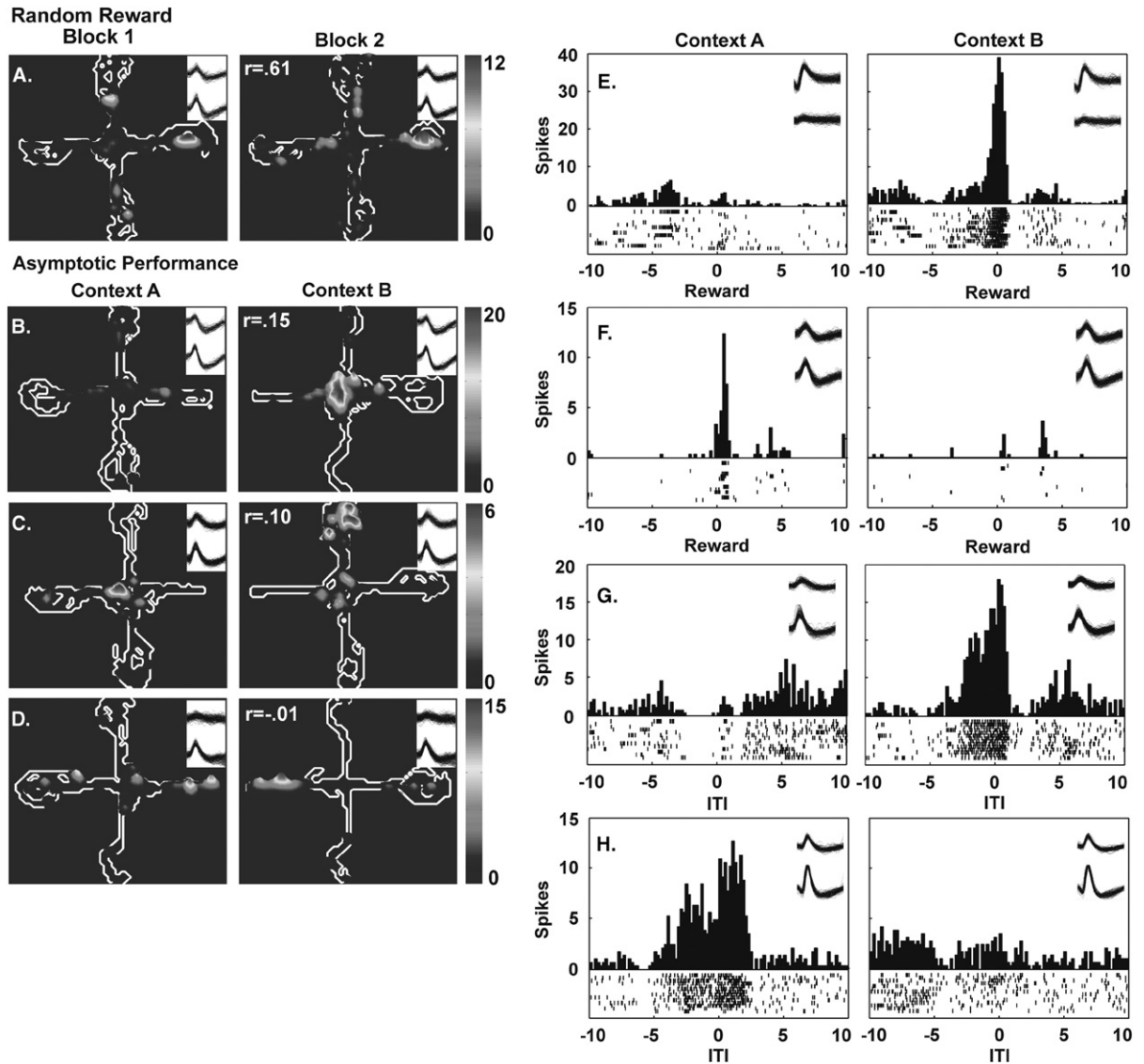
472

Fig. 2. Context-specific neuronal firing patterns. Contour plots (A–D) illustrating the spatial firing patterns during the random reward session and asymptotic performance sessions. The regions of the maze visited by the rat are outlined in white. The firing rates are illustrated by the height and color of the contour peaks, with the scale indicated for each neuron. Plot A illustrates the firing pattern of a neuron recorded during the first and second halves of the random reward session (Block 1 and Block 2). For each trial, rewards were placed at the end of randomly designated arms and the rat started at one of the three non-rewarded arms. Plots B–D illustrate the context-specific firing patterns of neurons recorded during asymptotic performance. Each pair of plots illustrates neuronal firing during the first half of the session (Context A) when the reward was always placed on the east arm, and during the second half (Context B) when the reward was always placed on the west arm. The firing patterns were similar across the two blocks of trials of the random reward session (A) but they were markedly different in the two blocks of trials (contexts) during asymptotic performance (B–D). Spike waveform overlays from both wires of the stereotrodes recorded during each half session and pixel by pixel spatial correlation coefficients (r) are given for each pair of plots. Peri-event time histograms illustrating event related firing of individual neurons recorded during asymptotic performance are shown in plots E–H. For each plot, the firing was summed across the 15 trials of each training block (context) with raster displays illustrating the trial by trial neuronal firing (one row of tick marks per trial). Twenty seconds of data are shown, from 10 s before to 10 s after the event. Examples of neuronal responses at the time of the reward (E and F) and the arrival at the intertrial interval (ITI) platform after training trials (G and H) are shown. The firing patterns during the first half of the session (Context A), when the reward was always placed on the east arm, were markedly different from firing during the second half (Context B), when the reward was always placed on the west arm. (See Color Plate 4.4.2 in Color Plate Section.)

an error from the north arm. In contrast, rats that did not adopt inflexible strategies would be no more likely to make errors from one start position than another. Thus, the difference in the probably of making an error from different start positions was computed and compared could serve as a measure of inflexible strategy use. Using this measure, we found that rats that were given muscimol adopted far more inflexible strategies than controls that were given saline solution. Together, the finding of context-specific neuronal response patterns and impaired context discrimination in rats with hippocampal lesions support context processing accounts of hippocampal function (Hirsh, 1974; Penick and Solomon, 1991; Kim and Fanselow, 1992; Phillips and LeDoux, 1992; Freeman et al., 1997).

VII. Place fields are part of a context representation

In the following discussion, it is proposed that place cells participate in episodic memory processes by providing a neural representation of the context. This idea connects the extensive literature on the hippocampal role in spatial navigation with episodic memory accounts. The relationship between hippocampal place fields and the spatial geometry of the environment has been extensively documented (e.g., Kubie and Ranck, 1983; Muller and Kubie, 1987; Gothard et al., 1996; O'Keefe and Burgess, 1996). The spatial layout of an environment is typically a critical feature of the context and several authors have used the term "spatial context" to denote this relationship (Nadel et al., 1985; Mizumori et al., 1999; Jeffery et al., 2004). It has been suggested that spatial context coding is one example of the general context processing function of the hippocampus (Mizumori et al., 2007; Smith et al., 2004; Smith and Mizumori, 2006b). Indeed, the spatial representations seen in our studies were clearly dependent on nonspatial features of the context (Fig. 2). Place fields were observed but their expression was highly dependent on the current context, as defined by the task demands, suggesting that spatial coding is subordinate to context processing.

Previous authors have debated the issue of whether spatial information has a special status as far as hippocampal processing is concerned (Nadel and Eichenbaum, 1999; O'Keefe, 1999; Shapiro and Eichenbaum, 1999). The spatial firing properties of hippocampal neurons are quite striking and place fields are reliably observed whenever rats are allowed to explore an environment. However, the fact that place fields are a predominant type of response in hippocampal neurons may simply be due to the fact that spatial geometry and context are highly correlated. New places are very likely to be new contexts, with new behavioral and cognitive demands. If the primary function of the hippocampus is to differentiate contexts, then hippocampal neurons should be responsive to any information that provides an efficient means of identifying the context. Spatial information may serve this purpose so reliably that it's inclusion in context representations is largely automatic. However, other kinds of information can also serve this purpose. Consistent with this idea, hippocampal neurons respond to virtually any potentially important stimulus (e.g., Solomon et al., 1986; Eichenbaum et al., 1987; Kang and Gabriel, 1998; Moita et al., 2003).

VIII. Could episodic memory impairments result from context processing deficits?

Although a growing body of data supports the context processing account of hippocampal function, impairment of episodic memory is a well documented consequence of hippocampal damage in humans (Vargha-Khadem et al., 1997; Tulving and Markowitsch, 1998; Rosenbaum et al., 2005) and the effects of lesions in animals are consistent with this idea (Agster et al., 2002; Ergorul and Eichenbaum, 2004). One possible explanation is that these episodic memory impairments are secondary to context processing deficits. Episodic memory, by definition, involves the encoding of the time and place where the event or episode occurred. Thus, contextual information is a necessary prerequisite for episodic memories.

It follows then, that the loss of hippocampal context processing would result in impaired

474

episodic memory functions. Consistent with this idea, recent reports indicate that human subjects with hippocampal damage are impaired in processing contextual information (Chun and Phelps, 1999; Weis et al., 2004; LaBar and Phelps, 2005; Shanks et al., 2005). Interestingly, imagining future situations is associated with hippocampal activity (Addis et al., 2007; Szpunar et al., 2007) and human amnesics have great difficulty imagining themselves in future situations, such as a visit to the beach (Hassabis et al., 2007). This deficit is precisely what would be expected if the subjects were unable to generate the context representations needed as a basis for an imagined future situation. Indeed, although the subjects were specifically encouraged to "see the situation and setting in their mind's eye," they were unable to construct a coherent context for the imaginary future episode.

If the primary function of the hippocampus is to generate context representations, then full blown episodic memory functions must rely on additional brain regions. The hippocampus may contribute contextual information to an extended circuitry which includes, but is not limited to, the hippocampus. It has become increasingly clear that complex learning and memory functions rely on the cooperative interaction of multiple brain regions that form functional circuits (e.g., Gabriel, 1993; Mizumori et al., 2000). Several authors have suggested, variously, that hippocampal memory functions are mediated by circuitry involving the entorhinal cortex, anterior thalamus, prefrontal cortex and posterior cingulate (retrosplenial) cortex (Aggleton and Brown, 1999; Eichenbaum, 2000; Suzuki and Eichenbaum, 2000; Smith et al., 2004; Wiltgen et al., 2004; Siapas et al., 2005).

IX. Hippocampal neuronal responses differentiate contexts but not episodic memories of individual trials

Examination of the spatial and event related neuronal responses recorded during individual training trials also suggested a hippocampal role in differentiating contexts. Fig. 3 illustrates examples of neuronal spike trains emitted when the rats entered a place field or experienced various task
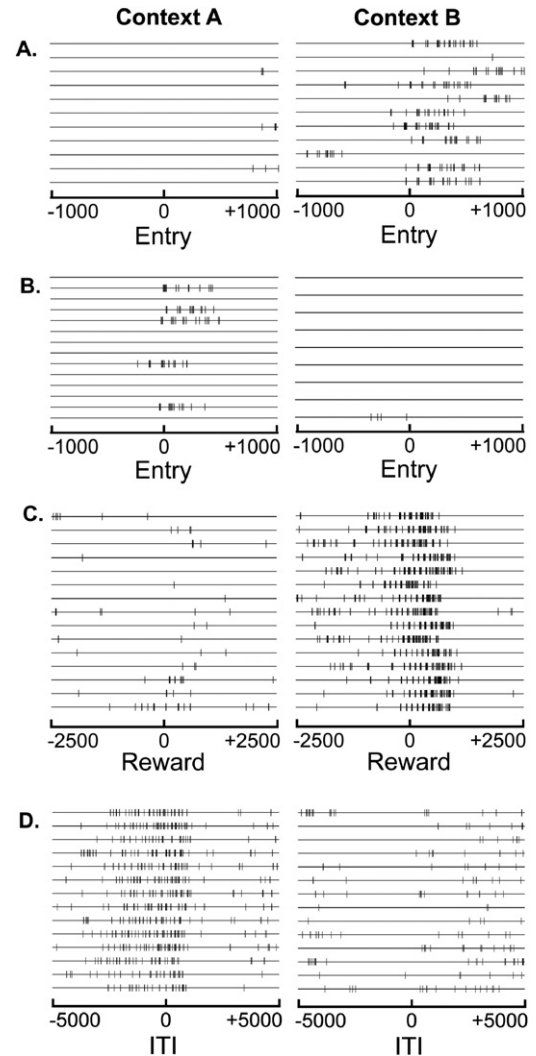

Fig. 3. Spike trains emitted by four different neurons on individual training trials. Each pair of the plots illustrates the firing of an individual neuron during the first half of the session (Context A) when the reward was always placed on the east arm, and during the second half (Context B) when the reward was always placed on the west arm. The plots illustrate neuronal firing at the time of entry into a place field (plots A and B), the reward (plot C), and arrival at the ITI platform after training trials (plot D). Each trial is represented by a horizontal line and each tick mark represents a single spike. The time relative to the event is given in milliseconds. The spike trains were relatively similar from one trial to the next within a particular context, but differed markedly between the two contexts. The neuron in B fired on a subset of the trials because it expressed a place field only when the rat had arrived at the location from a particular start position.

relevant events. The spike trains were remarkably different in the two contexts, but they were relatively similar from one trial to the next. For example the neurons in Fig. 3A and B fired similarly upon the rats' entry into the place field in one context, but fired very little during passes through the same region of space in the other context. The responses to the reward and the return of the rat to the ITI platform after training trials were also similar from one trial to the next, but quite different across contexts (Fig. 3C–D).

Since the neuronal response patterns were relatively similar from one trial to the next, they are more closely associated with differentiating contexts than differentiating individual trials from each other. These data provide additional support for the idea that hippocampal neuronal response patterns could serve to differentiate contexts. However, these observations also have important implications for episodic memory accounts of hippocampal function. A key feature of the episodic memory system is that it allows subjects to distinguish one episode from other similar episodes. Because the neuronal responses were similar from one trial to the next, they are not a good candidate mechanism for differentiating one trial from another. Yet, rats can readily distinguish brief episodes, like an individual training trial, if it is necessary for correct task performance. For example, they can learn spatial alternation tasks which require rats to remember the reward location on the previous trial so they can select the opposite location on the following trial (Aggleton et al., 1986; Wood et al., 2000). Presumably then, rats can form episodic memories of individual training trials. However, the spatial and event-related neuronal responses reported here cannot account for this ability. To date, neurophysiological responses that could reliably differentiate one trial from subsequent similar trials have not been reported.

X. The problem of identifying neurophysiological mechanisms of episodic memory

Identifying the neural correlates of episodic memory presents new challenges for approaches involving measurements of brain activity, from single unit activity to functional magnetic resonance imaging. Because a key feature of episodic memory is the ability to distinguish one event from another, it is necessary to show that hippocampal neuronal activity can distinguish one event from other similar events. It is not currently known how the brain represents unique episodes in a manner that distinguishes them from other episodes. The above described findings suggest that contextual information can be represented by neuronal response patterns distributed across a population of neurons. Similarly, individual episodic memories could be represented by the response patterns of neuronal populations. However, if an episodic memory must differentiate one experience from all others, then the pattern of neural responses that represents that experience would have to be unique, never to occur again except during the retrieval of that specific memory. If this is the case, the identification of these neuronal response patterns presents some formidable experimental difficulties.

The usual approach to studying neurophysiological mechanisms of a given function is to repeatedly present subjects with the item of interest. For example, subjects are typically given several trials involving repeated presentations of a stimulus, repeated passes through a region of space, or repeated behavioral actions. This allows experimenters to sum or average the firing of the neurons across trials which smoothes out minor variation in the spike trains (e.g. Fig. 2E–H). Perhaps more importantly, similar neuronal response seen over repeated trials are taken as an important indication that the responses are reliably associated with the events of the trial. This approach is unlikely to identify neuronal firing patterns that could differentiate individual trials. In contrast, findings of highly differentiated neuronal firing patterns in various contexts have encouraged an approach which stresses the capacity of hippocampal neurons to differentiate among situations (Smith et al., 2004; Smith and Mizumori, 2006b). Recent findings suggest that this may be a fruitful approach to identifying neural response patterns that could encode increasingly specific contexts.
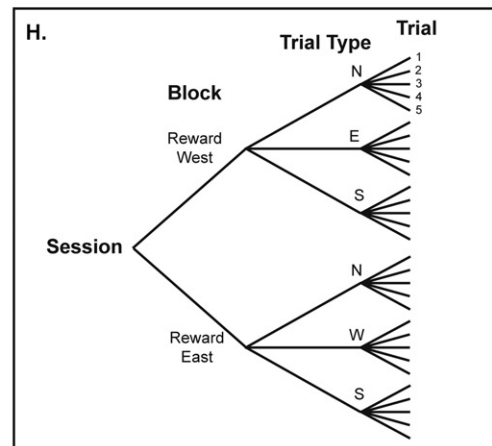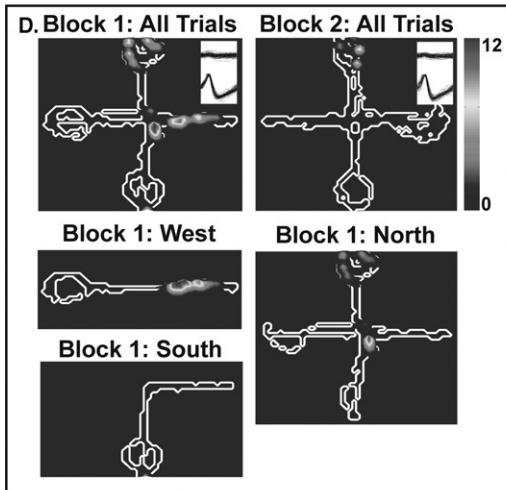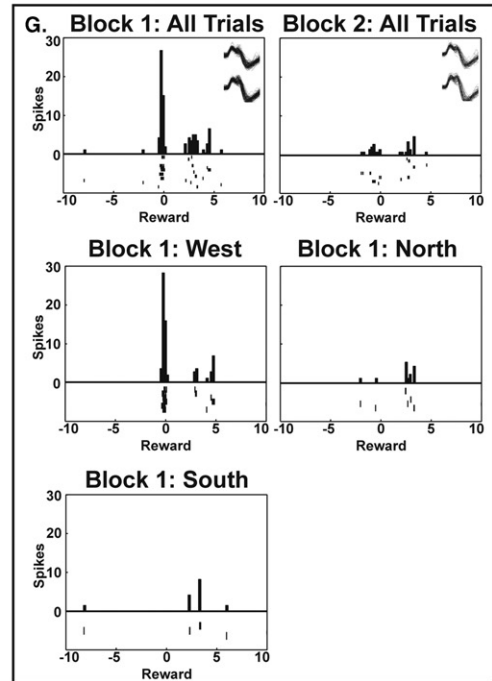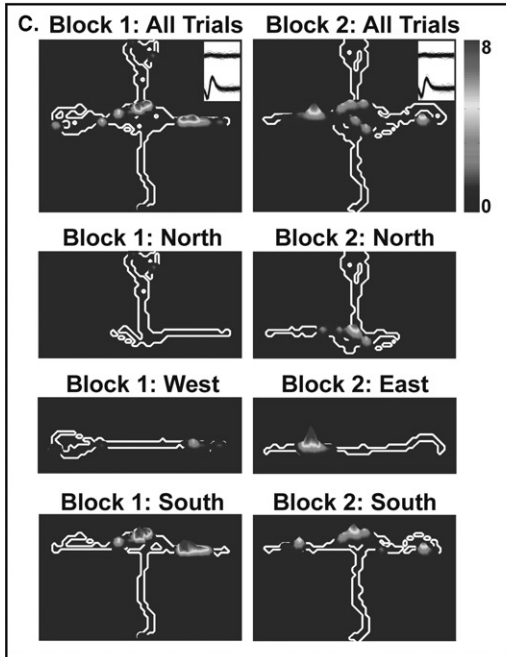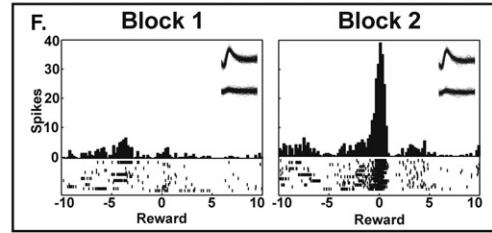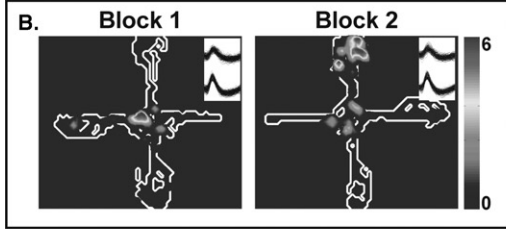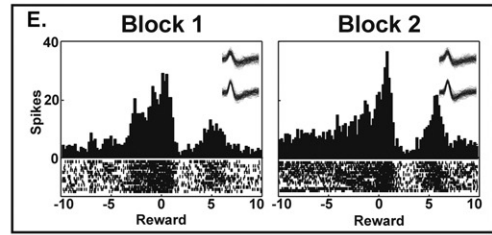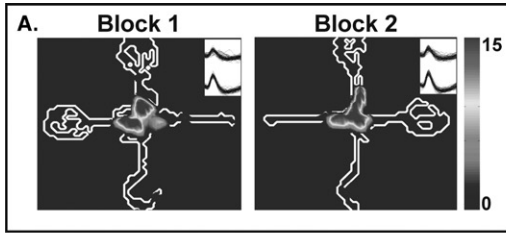
XI. A hierarchical coding scheme for context differentiation

Recent findings indicate that hippocampal neurons exhibit different responses to the same task events or actions, depending on the particular circumstances of the trial (Wood et al., 2000; Ferbinteanu and Shapiro, 2003; Smith and Mizumori, 2006b). For example, some neurons exhibit place fields that are only expressed when the rat arrives at the field from a particular start location. Other neurons only express a place field on trials when the rat is on a journey to a one goal location, but not when the rat is going to a different goal location. These findings suggest that hippocampal neurons may encode events or locations as a particular kind of experience, each of which is an instance of a broader category of experiences. Recent data from our laboratory is consistent with this idea.

Intriguingly, hippocampal neurons seem to differentiate contexts at varying levels of specificity (Fig. 4). Neurons at the most general level responded to the reward throughout the training session, regardless of the reward location. Neurons at the next level of specificity responded differentially, depending on the reward location. These are the responses which were described above as "context specific" because they were sensitive to the intended context manipulation. However, other neurons responded with an even greater degree of specificity. These neurons responded to the reward only when it was presented at a particular location *and* when the rat had arrived at that location from a particular start position. For example, the neuron in Fig. 4G responded during the first half of the training session, when the reward was located on the east arm, but only when the rat had arrived at that location from the west arm. Neurons with place fields exhibited similar varying degrees of specificity. Some neurons exhibited the same place field regardless of the reward location. Others exhibited a field only when the reward was located on the east or west arm. Still others exhibited place fields only when the rat had arrived at the field from a particular start location. Examples of these responses are shown in Fig. 4C–D.

These neuronal responses form a hierarchical coding scheme in which each kind of response represents a subset of the responses at the next highest level of coding. These different kinds of neuronal responses could support progressively finer levels of context differentiation. The intended

Fig. 4. Hippocampal neurons differentiated contexts at varying levels of specificity. Some neurons exhibited similar place fields or reward responses throughout the session, regardless of the reward location or the start position (plots A and E). Other neurons responded differentially in the two contexts, as defined by the location of the reward, which was always placed on the east arm during Block 1 and west arm during Block 2 (plots B and F). Still other neurons responded only during specific trial types, defined by the start position. Plots C and D show the data of two neurons that exhibited place fields that were contingent on the start position. In C, plots that included the data of all of the trials, regardless of the start position, show that the neuron exhibited different place fields during the first and second blocks (Block 1: All and Block 2: All, respectively). However, when the data are plotted separately according to the start position, it is clear that the place field seen in block 1 was only present on trials originating from the south start position (Block 1: South), whereas the place field in block two was only present on trials originating from the east start position (Block 2: East). The neuron in plot D exhibited a place field that was specific to block 1, but only when the rat had arrived at the field from the west arm. Reward responses exhibited similarly varying levels of sensitivity to different kinds of trials. The neuron in plot F responded to the reward on all trials of block 2, regardless of start position but did not respond to the reward during block 1. The neuron in G responded to the reward in block 1, but only on those trials originating on the west arm. The neuronal response illustrated in Fig. 2F also depended on the start position. These different kinds of responses form a hierarchical coding scheme which could differentiate contexts at several levels of specificity. As illustrated schematically in H, some neurons responded at the level of the entire session. Within a given session however, some neurons responded differentially in the two blocks which were characterized by different reward locations (i.e. the intended context manipulation). Within a given block, some neurons responded differentially according to the trial type as characterized by the start position. These neurons may treat the different trial types as separate contexts since they require differing behavioral responses. Neuronal responses that clearly differentiated one trial from another (the Trial level) were not found. (See Color Plate 4.4.4 in Color Plate Section.)

context manipulation involved changing the reward location. This manipulation was effective insofar as many neurons responded differentially in the two session halves which were characterized by different reward locations. However, the rats may have spontaneously differentiated "contexts" at a finer resolution, according to the start position for each trial. Jeffery (2004) observed that different kinds of trials involving varying trajectories may constitute different contexts. Consistent with this idea, the neurons that exhibited start position-specific firing patterns in our studies may have treated the set of trials that began from a given start position as a unique context, distinct from those trials that began from other start positions.

Previous studies have shown that place fields can be dependent on the start or goal positions (Frank et al., 2000; Wood et al., 2000; Ferbinteanu and Shapiro, 2003). Our data illustrate that these responses represent one of several possible levels of differentiation since the trajectory-dependent firing was also context specific. Moreover, the relative importance of each level of differentiation may be indicated by the percentage of the neuronal population dedicated to discriminating at that level. Because our experimental design involved different response requirements in the two blocks of trials that comprised each training session, the ability to differentiate blocks was probably the most important level of context discrimination. Consistent with this idea, most of the neurons responded differentially in the two blocks of each training session (75.6% of the neurons with reward responses and 76.3% of the neurons with place fields).

Neuronal responses that differentiate trial types (on the basis of the start position) could also provide important information that prepares the rat for different behavioral responses. Trials that began from the north start position required one response (e.g., right turn) whereas trials that began from the south position required a different response (e.g., left turn). The need for this level of differentiation is even more apparent in spatial alternation tasks, where the only requirement is that the rat must explicitly distinguish those trials which require a right turn response from those

that require a left turn response. Under these conditions, 67% of the hippocampal neurons differentiated left turn trials from right turn trials (Wood et al., 2000). In our studies, differentiating trial types may have been relatively less important than differentiating blocks. Consistent with this idea, a smaller percentage of the neurons differentiated trial types in our studies (12.8% of the neurons with reward responses and 15.3% of the neurons with place fields). Only 11.5% of the neurons with reward responses and 8.4% of the neurons with place fields responded similarly throughout the session.

The problem of differentiating individual memory episodes from each other is similar to the problem of differentiating individual contexts. Progressively finer levels of differentiation may be critically important for distinguishing different episodes that occur in similar contexts. A hierarchical organization of neural representations may identify a set of rewards which occurred on certain types of trials, which were a subset of the rewards that occurred during a specific block of trials, and which were a subset of the rewards that occurred during a specific training session. The combination of these different levels of processing approximates the ability to remember a specific reward. Clear neuronal responses at the finest level of detail (i.e., the individual trial level) were not observed in our data. However, the addition of temporal information to the above described hierarchy could contribute to an animal's ability to distinguish trials, and could therefore support episodic memory for individual training trials.

XII. Concluding remarks

There is abundant evidence that contextual information plays a critical role in learning and memory functions, including episodic memory. Although the idea that the hippocampus is involved in processing contextual information is not new (Hirsh, 1974), there has been a resurgence of interest in the hippocampal role in context processing (Chun and Phelps, 1999; Mizumori et al., 1999; Jeffery et al., 2004; Johnson, 2004; Smith et al., 2004; Weis et al., 2004; LaBar and Phelps,

2005; Shanks et al., 2005; Smith and Mizumori, 2006a). Recent studies have identified neuronal response patterns that differentiate contexts and could therefore serve as neural representations of the context (Smith and Mizumori, 2006b). When combined with findings indicating that hippocampal neuronal responses are better suited to differentiating contexts than brief episodes, these findings suggest that the primary role of the hippocampus is to identify and encode contexts. A full account of episodic memory processes will therefore require understanding the hippocampal contribution of context representations as well as the broader circuitry that incorporates these context representations into episodic memories.

References

Addis, D.R., Wong, A.T. and Schacter, D.L. (2007) Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. Neuropsychologia, 45(7): 1363–1377.

Aggleton, J.P. and Brown, M.W. (1999) Episodic memory, amnesia, and the hippocampal-thalamic axis. Behav. Brain Sci., 22(3): 425–444; discussion 444–489.

Aggleton, J.P., Hunt, P.R. and Rawlins, J.N. (1986) The effects of hippocampal lesions upon spatial and non-spatial tests of working memory. Behav. Brain Res., 19(2): 133–146.

Aggleton, J.P. and Pearce, J.M. (2001) Neural systems underlying episodic memory: insights from animal research. Philos. Trans. R. Soc. Lond. B Biol. Sci., 356(1413): 1467–1482.

Agster, K.L., Fortin, N.J. and Eichenbaum, H. (2002) The hippocampus and disambiguation of overlapping sequences. J. Neurosci., 22(13): 5760–5768.

Anagnostaras, S.G., Gale, G.D. and Fanselow, M.S. (2001) Hippocampus and contextual fear conditioning: recent controversies and advances. Hippocampus, 11(1): 8–17.

Anderson, J.R. and Bower, G.H. (1974) Interference in memory for multiple contexts. Mem. Cogn., 2(3): 509–514.

Anderson, M.I. and Jeffery, K.J. (2003) Heterogeneous modulation of place cell firing by changes in context. J. Neurosci., 23(26): 8827–8835.

Baddely, A. (1987) Memory and context. In: Gregory, R.L. (Ed.), The Oxford Companion to the Mind. Oxford University Press, Oxford, pp. 20–22.

Balaz, M.A., Capra, S., Hartl, P. and Miller, R.R. (1980) Contextual potentiation of acquired behavior after developing direct context–us associations. Learn. Mem., 12: 383–397.

Blanchard, D.C. and Blanchard, R.J. (1972) Innate and conditioned reactions to threat in rats with amygdaloid lesions. J. Comp. Physiol. Psych., 81(2): 281–290.

Bouton, M.E. (1993) Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. Psychol. Bull., 114(1): 80–99.

Bower, M.R., Euston, D.R. and McNaughton, B.L. (2005) Sequential-context-dependent hippocampal activity is not necessary to learn sequences with repeated elements. J. Neurosci., 25(6): 1313–1323.

Buckmaster, C.A., Eichenbaum, H., Amaral, D.G., Suzuki, W.A. and Rapp, P.R. (2004) Entorhinal cortex lesions disrupt the relational organization of memory in monkeys. J. Neurosci., 24(44): 9811–9825.

Bunsey, M. and Eichenbaum, H. (1996) Conservation of hippocampal memory function in rats and humans. Nature, 379(6562): 255–257.

Chun, M.M. and Phelps, E.A. (1999) Memory deficits for implicit contextual information in amnesic subjects with hippocampal damage. Nat. Neurosci., 2(9): 844–847.

Clayton, N.S. and Dickinson, A. (1998) Episodic-like memory during cache recovery by scrub jays. Nature, 395(6699): 272–274.

Eacott, M.J., Easton, A. and Zinkivskay, A. (2005) Recollection in an episodic-like memory task in the rat. Learn. Mem., 12(3): 221–223.

Eacott, M.J. and Norman, G. (2004) Integrated memory for object, place, and context in rats: a possible model of episodic-like memory? J. Neurosci., 24(8): 1948–1953.

Eichenbaum, H. (2000) A cortical–hippocampal system for declarative memory. Nat. Rev. Neurosci., 1(1): 41–50.

Eichenbaum, H., Kuperstein, M., Fagan, A. and Nagode, J. (1987) Cue-sampling and goal-approach correlates of hippocampal unit activity in rats performing an odor-discrimination task. J. Neurosci., 7(3): 716–732.

Eichenbaum, H., Stewart, C. and Morris, R.G. (1990) Hippocampal representation in spatial learning. J. Neurosci., 10: 331–339.

Ergorul, C. and Eichenbaum, H. (2004) The hippocampus and memory for "what," "where," and "when". Learn. Mem., 11(4): 397–405.

Fanselow, M.S. (1986) Associative vs topographical accounts of the immediate shock-freezing deficit in rats: implications for the response selection rules governing species-specific defensive reactions. Learn. Motiv., 17: 16–39.

Ferbinteanu, J. and Shapiro, M.L. (2003) Prospective and retrospective memory coding in the hippocampus. Neuron, 40(6): 1227–1239.

Foster, T.C., Castro, C.A. and McNaughton, B.L. (1989) Spatial selectivity of rat hippocampal

neurons: dependence on preparedness for movement. Science, 244(4912): 1580–1582.

Frank, L.M., Brown, E.N. and Wilson, M. (2000) Trajectory encoding in the hippocampus and entorhinal cortex. Neuron, 27(1): 169–178.

Freeman, J.H. Jr., Cuppernell, C., Flannery, K. and Gabriel, M. (1996) Context-specific multi-site cingulate cortical, limbic thalamic, and hippocampal neuronal activity during concurrent discriminative approach and avoidance training in rabbits. J. Neurosci., 16(4): 1538–1549.

Freeman, J.H. Jr., Weible, A., Rossi, J. and Gabriel, M. (1997) Lesions of the entorhinal cortex disrupt behavioral and neuronal responses to context change during extinction of discriminative avoidance behavior. Exp. Brain Res., 115(3): 445–457.

Gabriel, M. (1993) Discriminative avoidance learning: a model system. In: Vogt, B.A. and Gabriel, M. (Eds.), Neurobiology of Cingulate Cortex and Limbic Thalamus. Birkhauser, Boston, pp. 478–523.

Godden, D. and Baddely, A. (1975) Context-dependent memory in two natural environments: on land and underwater. Br. J. Psychol., 66: 325–331.

Goldstein, A., Spencer, K.M. and Donchin, E. (2002) The influence of stimulus deviance and novelty on the p300 and novelty p3. Psychophysiology, 39(6): 781–790.

Gothard, K.M., Skaggs, W.E., Moore, K.M. and McNaughton, B.L. (1996) Binding of hippocampal ca1 neural activity to multiple reference frames in a landmark-based navigation task. J. Neurosci., 16(2): 823–835.

Hassabis, D., Kumaran, D., Vann, S.D. and Maguire, E.A. (2007) Patients with hippocampal amnesia cannot imagine new experiences. Proc. Natl. Acad. Sci. USA, 104(5): 1726–1731.

Hayman, R.M., Chakraborty, S., Anderson, M.I. and Jeffery, K.J. (2003) Context-specific acquisition of location discrimination by hippocampal place cells. Eur. J. Neurosci., 18(10): 2825–2834.

Hirsh, R. (1974) The hippocampus and contextual retrieval of information from memory: a theory. Behav. Biol., 12(4): 421–444.

Jeffery, K.J. (2004) Remembrance of futures past. Trends Cogn. Sci., 8(5): 197–199.

Jeffery, K.J., Anderson, M.I., Hayman, R. and Chakraborty, S. (2004) A proposed architecture for the neural representation of spatial context. Neurosci. Biobehav. Rev., 28(2): 201–218.

Johnson, J.D. (2004) Episodic memory and the hippocampus: another view. Med. Hypotheses, 63: 963–967.

Kang, E. and Gabriel, M. (1998) Hippocampal modulation of cingulo-thalamic neuronal activity and discriminative avoidance learning in rabbits. Hippocampus, 8(5): 491–510.

Kennedy, P.J. and Shapiro, M.L. (2004) Retrieving memories via internal context requires the hippocampus. J. Neurosci., 24(31): 6979–6985.

Kim, J.J. and Fanselow, M.S. (1992) Modality-specific retrograde amnesia of fear. Science, 256(5057): 675–677.

Kubie, J.L. and Ranck, J.B. (1983) Sensory-behavioral correlates in individual hippocampus neurons in three situations: space and context. In: Seifert, W. (Ed.), The Hippocampus. Academic Press, New York, pp. 433–447.

LaBar, K.S. and Phelps, E.A. (2005) Reinstatement of conditioned fear in humans is context dependent and impaired in amnesia. Behav. Neurosci., 119(3): 677–686.

Maren, S. (2001) Neurobiology of Pavlovian fear conditioning. Ann. Rev. Neurosci., 24: 897–931.

Markus, E.J., Qin, Y.L., Leonard, B., Skaggs, W.E., McNaughton, B.L. and Barnes, C.A. (1995) Interactions between location and task affect the spatial and directional firing of hippocampal neurons. J. Neurosci., 15(11): 7079–7094.

Mizumori, S.J., Cooper, B.G., Leutgeb, S. and Pratt, W.E. (2000) A neural systems analysis of adaptive navigation. Mol. Neurobiol., 21(1–2): 57–82.

Mizumori, S.J., Ragozzino, K.E., Cooper, B.G. and Leutgeb, S. (1999) Hippocampal representational organization and spatial context. Hippocampus, 9(4): 444–451.

Mizumori, S.J.Y., Smith, D.M. and Puryear, C.B. (2007) Mnemonic contributions of hippocampal place cells. In: Martinez, J.L.J. and Kesner, R.P. (Eds.), Neurobiology of Learning and Memory, 4th edn. Academic Press, San Diego.

Moita, A.P., Svetlana, R., Zhou, Y., LeDoux, J.E. and Blair, H.T. (2003) Hippocampal place cells acquire location-specific response to the conditioned stimulus during auditory fear conditioning. Neuron, 37: 485–497.

Morris, R.G. (2001) Episodic-like memory in animals: psychological criteria, neural mechanisms and the value of episodic-like tasks to investigate animal models of neurodegenerative disease. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci., 356: 1453–1465.

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

Myers, C.E. and Gluck, M. (1994) Context, conditioning, and hippocampal rerepresentation in animal learning. Behav. Neurosci., 108(5): 835–847.

Nadel, L. and Eichenbaum, H. (1999) Introduction to the special issue on place cells. Hippocampus, 9(4): 341–345.

Nadel, L., Willner, J. and Kurz, E.M. (1985) Cognitive maps and environmental context. In: Balsam, P. and Tomie, A. (Eds.), Context and Learning. Erlbaum, Hillsdale, NJ, pp. 385–406.

O'Keefe, J. (1999) Do hippocampal pyramidal cells signal non-spatial as well as spatial information? Hippocampus, 9(4): 352–364.

O'Keefe, J. and Burgess, N. (1996) Geometric determinants of the place fields of hippocampal neurons. Nature, 381(6581): 425–428.

O'Keefe, J. and Dostrovsky, J. (1971) The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res., 34(1): 171–175.

Penick, S. and Solomon, P.R. (1991) Hippocampus, context, and conditioning. Behav. Neurosci., 105(5): 611–617.

Phillips, R.G. and LeDoux, J.E. (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav. Neurosci., 106(2): 274–285.

Rosenbaum, R.S., Kohler, S., Schacter, D.L., Moscovitch, M., Westmacott, R., Black, S.E., Gao, F. and Tulving, E. (2005) The case of k.C.: contributions of a memory-impaired person to memory theory. Neuropsychologia, 43(7): 989–1021.

Shanks, D.R., Channon, S., Wilkinson, L. and Curran, H.V. (2005) Disruption of sequential priming in organic and pharmacological amnesia: a role for the medial temporal lobes in implicit contextual learning. Neuropsychopharmacology (advanced online publication), 1–9.

Shapiro, M.L. and Eichenbaum, H. (1999) Hippocampus as a memory map: synaptic plasticity and memory encoding by hippocampal neurons. Hippocampus, 9(4): 365–384.

Siapas, A.G., Lubenov, E.V. and Wilson, M.A. (2005) Prefrontal phase locking to hippocampal theta oscillations. Neuron, 46(1): 141–151.

Simons, J.S., Dodson, C.S., Bell, D. and Schacter, D.L. (2004) Specific- and partial-source memory: effects of aging. Psychol. Aging, 19(4): 689–694.

Skaggs, W.E. and McNaughton, B.L. (1998) Spatial firing properties of hippocampal CA1 populations in an environment containing two visually identical regions. J. Neurosci., 18(20): 8455–8466.

Smith, D.M. and Mizumori, S.J. (2006a) Hippocampal place cells, context, and episodic memory. Hippocampus, 16(9): 716–729.

Smith, D.M. and Mizumori, S.J.Y. (2006b) Learning-related development of context-specific neuronal responses to places and events: the hippocampal role in context processing. J. Neurosci., 26(12): 3154–3163.

Smith, D.M., Wakeman, D., Patel, J. and Gabriel, M. (2004) Fornix lesions impair context-related cingulothalamic neuronal patterns and concurrent discrimination learning. Behav. Neurosci., 118(6): 1225–1239.

Smith, S.M. (1979) Remembering in and out of context. J. Exp. Psychol. Hum. Learn. Mem., 5(5): 460–471.

Smith, S.M. (1990) Environmental context-dependent homophone spelling. Am. J. Psychol., 103(2): 229–242.

Smith, S.M. (1995) Mood is a component of mental context: comment on each. J. Exp. Psychol.: Gen., 124(3): 309–310.

Smith, S.M. and Vela, E. (2001) Environmental context-dependent memory: a review and meta-analysis. Psychon. Bull. Rev., 8(2): 203–220.

Solomon, P.R., Vander Schaaf, E.R., Thompson, R.F. and Weisz, D.J. (1986) Hippocampus and trace conditioning of the rabbit's classically conditioned nictitating membrane response. Behav. Neurosci., 100(5): 729–744.

Song, E.Y., Kim, Y.B., Kim, Y.H. and Jung, M.W. (2005) Role of active movement in place-specific firing of hippocampal neurons. Hippocampus, 15(8): 8–17.

Suzuki, W.A. and Eichenbaum, H. (2000) The neurophysiology of memory. Ann. N.Y. Acad. Sci., 911: 175–191.

Szpunar, K.K., Watson, J.M. and McDermott, K.B. (2007) Neural substrates of envisioning the future. Proc. Natl. Acad. Sci. U S A, 104(2): 642–647.

Terrazas, A., Krause, M., Lipa, P., Gothard, K.M., Barnes, C.A. and McNaughton, B.L. (2005) Self-motion and the hippocampal spatial metric. J. Neurosci., 25(35): 8085–8096.

Thomas, D.R., McKelvie, A.R. and Mah, W.L. (1985) Context as a conditional cue in operant discrimination reversal learning. J. Exp. Psychol. Anim. Behav. Processes, 11(2): 317–330.

Thomson, D.M., Robertson, S. and Vogt, R. (1982) Person recognition: the effect of context. Hum. Learn., 1: 137–154.

Tsivilis, D., Otten, L.J. and Rugg, M.D. (2001) Context effects on the neural correlates of recognition memory: an electrophysiological study. Neuron, 31(3): 497–505.

Tulving, E. and Markowitsch, H.J. (1998) Episodic and declarative memory: role of the hippocampus. Hippocampus, 8(3): 198–204.

Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W. and Mishkin, M. (1997) Differential effects of early hippocampal pathology on episodic and semantic memory. Science, 277(5324): 376–380.

Weis, S., Specht, K., Klaver, P., Tendolkar, I., Willmes, K., Ruhlmann, J., Elger, C.E. and Fernandez, G. (2004) Process dissociation between contextual retrieval and item recognition. Neuroreport, 15(18): 2729–2733.

Whishaw, I.Q. and Tomie, J.A. (1997) Perseveration on place reversals in spatial swimming pool tasks: further evidence for place learning in hippocampal rats. Hippocampus, 7(4): 361–370.

Wiltgen, B.J., Brown, R.A., Talton, L.E. and Silva, A.J. (2004) New circuits for old memories: the role of the neocortex in consolidation. Neuron, 44(1): 101–108.

Wood, E.R., Dudchenko, P.A., Robitsek, R.J. and Eichenbaum, H. (2000) Hippocampal neurons encode information about different types of memory episodes occurring in the same location. Neuron, 27(3): 623–633.

Yeshenko, O., Guazzelli, A. and Mizumori, S.J.Y. (2001) Differential hippocampal neuronal activity during place or response performance on a t-maze. Soc. Neurosci. Program Number 953.8.
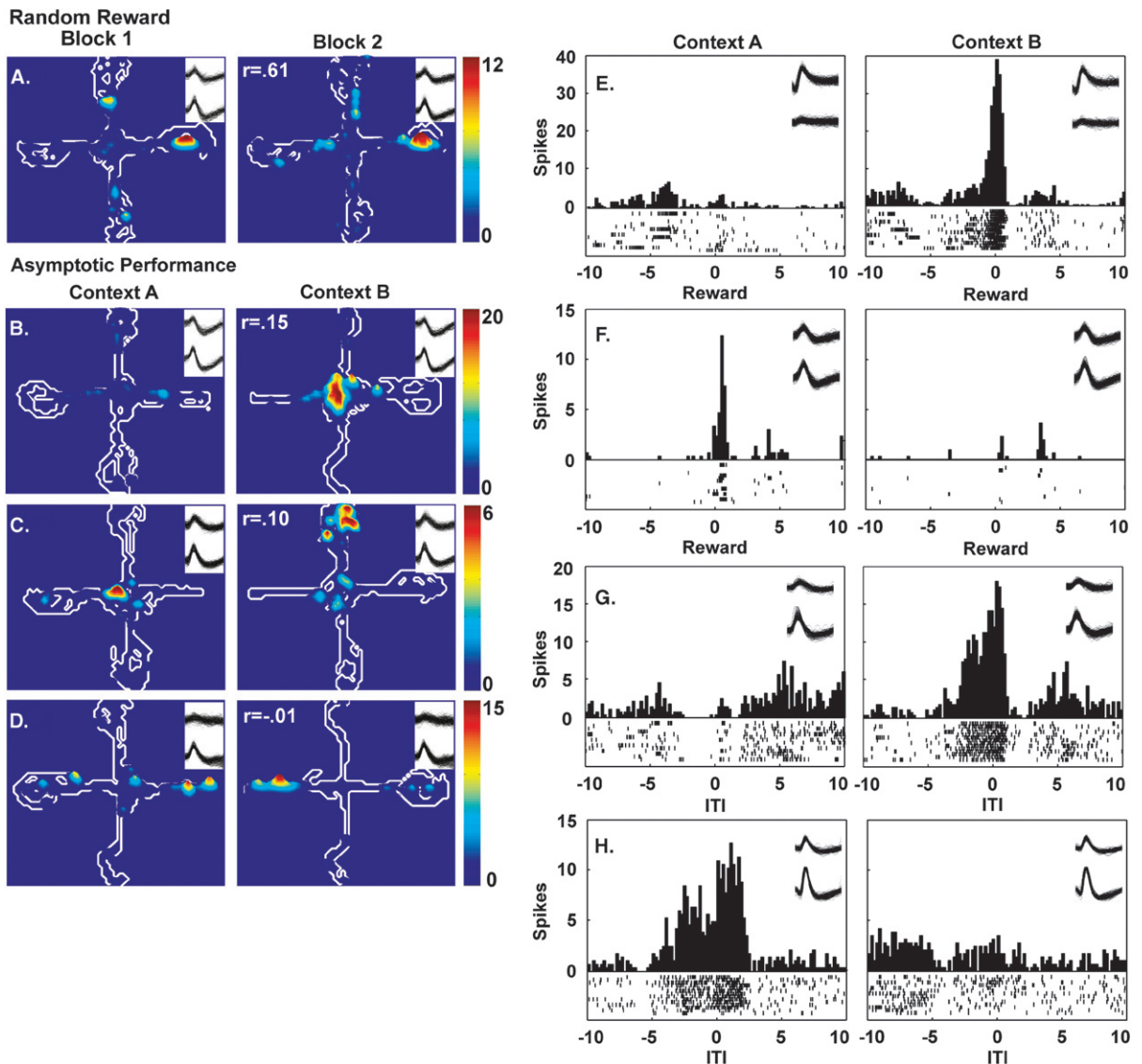
Plate 4.4.2. Context-specific neuronal firing patterns. Contour plots (A–D) illustrating the spatial firing patterns during the random reward session and asymptotic performance sessions. The regions of the maze visited by the rat are outlined in white. The firing rates are illustrated by the height and color of the contour peaks, with the scale indicated for each neuron. Plot A illustrates the firing pattern of a neuron recorded during the first and second halves of the random reward session (Block 1 and Block 2). For each trial, rewards were placed at the end of randomly designated arms and the rat started at one of the three non-rewarded arms. Plots B–D illustrate the context-specific firing patterns of neurons recorded during asymptotic performance. Each pair of plots illustrates neuronal firing during the first half of the session (Context A) when the reward was always placed on the east arm, and during the second half (Context B) when the reward was always placed on the west arm. The firing patterns were similar across the two blocks of trials of the random reward session (A) but they were markedly different in the two blocks of trials (contexts) during asymptotic performance (B–D). Spike waveform overlays from both wires of the stereotrodes recorded during each half session and pixel by pixel spatial correlation coefficients (r) are given for each pair of plots. Peri-event time histograms illustrating event related firing of individual neurons recorded during asymptotic performance are shown in plots E–H. For each plot, the firing was summed across the 15 trials of each training block (context) with raster displays illustrating the trial by trial neuronal firing (one row of tick marks per trial). Twenty seconds of data are shown, from 10 s before to 10 s after the event. Examples of neuronal responses at the time of the reward (E and F) and the arrival at the intertrial interval (ITI) platform after training trials (G and H) are shown. The firing patterns during the first half of the session (Context A), when the reward was always placed on the east arm, were markedly different from firing during the second half (Context B), when the reward was always placed on the west arm.
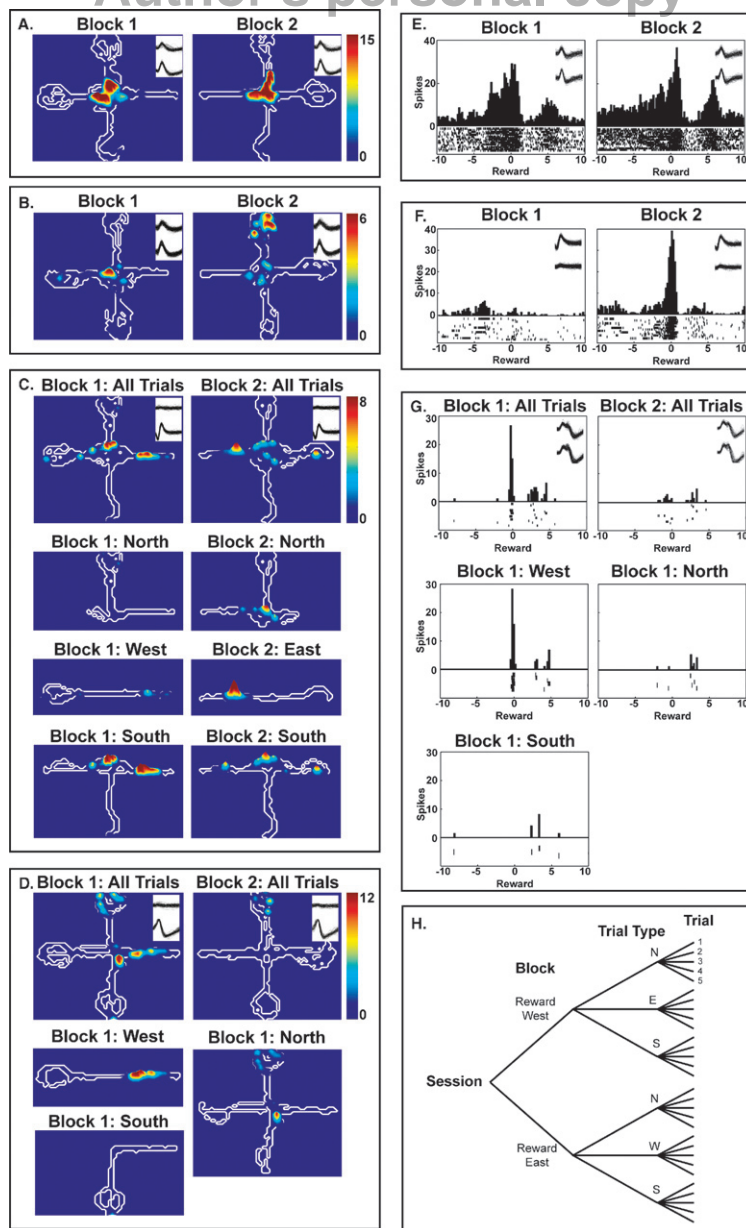
Plate 4.4.4. Hippocampal neurons differentiated contexts at varying levels of specificity. Some neurons exhibited similar place fields or reward responses throughout the session, regardless of the reward location or the start position (plots A and E). Other neurons responded differentially in the two contexts, as defined by the location of the reward, which was always placed on the east arm during Block 1 and west arm during Block 2 (plots B and F). Still other neurons responded only during specific trial types, defined by the start position. Plots C and D show the data of two neurons that exhibited place fields that were contingent on the start position. In C, plots that included the data of all of the trials, regardless of the start position, show that the neuron exhibited different place fields during the first and second blocks (Block 1: All and Block 2: All, respectively). However, when the data are plotted separately according to the start position, it is clear that the place field seen in block 1 was only present on trials originating from the south start position (Block 1: South), whereas the place field in block two was only present on trials originating from the east start position (Block 2: East). The neuron in plot D exhibited a place field that was specific to block 1, but only when the rat had arrived at the field from the west arm. Reward responses exhibited similarly varying levels of sensitivity to different kinds of trials. The neuron in plot F responded to the reward on all trials of block 2, regardless of start position but did not respond to the reward during block 1. The neuron in G responded to the reward in block 1, but only on those trials originating on the west arm. The neuronal response illustrated in Fig. 2F also depended on the start position. These different kinds of responses form a hierarchical coding scheme which could differentiate contexts at several levels of specificity. As illustrated schematically in H, some neurons responded at the level of the entire session. Within a given session however, some neurons responded differentially in the two blocks which were characterized by different reward locations (i.e. the intended context manipulation). Within a given block, some neurons responded differentially according to the trial type as characterized by the start position. These neurons may treat the different trial types as separate contexts since they require differing behavioral responses. Neuronal responses that clearly differentiated one trial from another (the Trial level) were not found.