Episodic Memory—From Brain to Mind

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ABSTRACT: Neuronal mechanisms of episodic memory, the conscious recollection of autobiographical events, are largely unknown because electrophysiological studies in humans are conducted only in exceptional circumstances. Unit recording studies in animals are thus crucial for understanding the neurophysiological substrate that enables people to remember their individual past. Two features of episodic memoryautonoetic consciousness, the self-aware ability to "travel through time", and one-trial learning, the acquisition of information in one occurrence of the event-raise important questions about the validity of animal models and the ability of unit recording studies to capture essential aspects of memory for episodes. We argue that autonoetic experience is a feature of human consciousness rather than an obligatory aspect of memory for episodes, and that episodic memory is reconstructive and thus its key features can be modeled in animal behavioral tasks that do not involve either autonoetic consciousness or one-trial learning. We propose that the most powerful strategy for investigating neurophysiological mechanisms of episodic memory entails recording unit activity in brain areas homologous to those required for episodic memory in humans (e.g., hippocampus and prefrontal cortex) as animals perform tasks with explicitly defined episodic-like aspects. Within this framework, empirical data suggest that the basic structure of episodic memory is a temporally extended representation that distinguishes the beginning from the end of an event. Future research is needed to fully understand how neural encodings of context, sequences of items/events, and goals are integrated within mnemonic representations of autobiographical events. © 2006 Wiley-Liss, Inc.

KEY WORDS: unit recording; physiology; rats; hippocampus; prefrontal cortex

HUMAN AND ANIMAL MEMORY FOR EPISODES

Different types of memories are used in different circumstances (White and McDonald, 2002). Memory in the everyday sense of the word, the conscious recollection with which we are most familiar, corresponds to **declarative memory**, which includes **semantic memory** for general facts (e.g., "Madrid is the capital of Spain") and **episodic memory** for autobiographic, personally experienced events (e.g., "yesterday I went to the dentist"; Squire, 2004). Both episodic and semantic memories require intact medial temporal lobe brain areas and are characterized

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by the rapid formation of relational representations of highly processed sensory information that are used flexibly and are not necessarily expressed through overt motor behavior. Episodic memory is also sensitive to lesions of the prefrontal cortex (Wheeler et al., 1995; Nyberg et al., 2000; Burgess et al., 2002; Wheeler and Stuss, 2003), develops later in an individual's life, encodes events within a personal framework, and possesses a temporal dimension because it is oriented towards the past and the future (Tulving, 1972, 2001, 2002; Tulving and Markowitsch, 1998). Autobiographic information contains memories about what happened when and where, integrated within the context of other memories (Tulving, 1972). The typical content of an episodic memory is a journey or endeavor taken to accomplish some purpose and is organized as a narrative: each remembered scene includes linked sequences of events with a distinct beginning, middle, and end.

Episodic memory is supported by an extended neural network. While the medial temporal lobe is required for the acquisition and storage of information (Nyberg et al., 2000; Burgess et al., 2002), the prefrontal cortex is activated during, and required for strategic processes such as information search and outcome monitoring, goal selection and pursuit of multiple subgoals, plan formulation, and behavioral monitoring and control (Wheeler et al., 1995, 1997; Nyberg et al., 2000; Buckner and Wheeler, 2001; Burgess et al., 2001a,b; Burgess et al., 2002; Buckner, 2003; Wheeler and Stuss, 2003; Hayes et al., 2004). The hippocampal system is highly conserved across species and recent analyses suggest that at least some aspects of the organization and function of prefrontal cortices in humans, primates, and rodents are also fundamentally similar (for reviews see Kesner, 2000; Granon and Poucet, 2000; Dalley et al., 2004).

Though the neuroanatomy and cognitive properties of human episodic memory are well studied, its neuronal mechanisms remain largely unknown because experimental manipulation of the human brain is limited (Cameron et al., 2001; but see Ekstrom et al., 2003; Quiroga et al., 2005). Thus, the development of animal models suitable to study memory for episodes is crucial. Two factors however raise important problems (Griffiths et al., 1999; e.g., Clayton et al., 2001a). First, the central feature of human episodic memory has been claimed to be autonoetic consciousness, the ability to undergo a self-aware mental time travel, as distinct from awareness of specific knowledge



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per se (Wheeler et al., 1997; Tulving and Markowitsch, 1998; Tulving, 1985, 2002), or from a sense of mere familiarity (Yonelinas, 2001, 2002). This view suggests that central to memory for episodes is the conscious, voluntary navigation backwards or projection forwards along something akin to a personal "movie" (Tulving, 2001; see also Suddendorf and Busby, 2003). Second, episodic memory has been considered eminently a record of unique past events. In the following sections, we argue that neither of these factors is an insurmountable obstacle in gathering relevant information about the neural mechanisms of episodic memory by using animal research.

Autobiographical Information, Conscious Recollection, and Introspection

The validity of animal models of episodic memory has been questioned based on the idea that animals do not posses the central feature of episodic memory: conscious, self-aware mental time travel (e.g., Tulving, 2001). Others have countered that if episodic memory is defined in terms of conscious experience, then by definition the problem has no solution because conscious recollection cannot be assessed in nonverbal animals. However, if episodic memory is defined as memory for *when* and *where* an event (*what*) occurred, as it was initially the case (Tulving, 1972), then behavioral tests suitable for animals can be designed (Griffiths et al., 1999; Clayton et al., 2001a). This line of reasoning describes one of the challenges to creating animal models, but does not provide a strong argument as to why animal research can provide relevant information regarding episodic memory.

In our view, the core problem is that the argument for the centrality of autonoetic consciousness involves introspection. When we remember an autobiographical event, we may perceive the subjective experience of mental time travel as fundamental. Alternatively, we could focus on the equally subjective phenomenological record, event-specific knowledge about nearsensory experience forming a "file" that incorporates both the content of conscious experience and the nonconscious processes that generated it (Conway, 2001a). Objective tests of the validity of these two perspectives are difficult to design because both views rely on introspection, a process affected by first-person subjective factors (e.g., Gallagher and Sørensen, 2006), to determine the centrality of one or another feature of episodic memory. Self-aware, conscious mental time travel seems to be one of the subjective features of memory for episodes in people, but our inability to assess objectively this feature in animals does not entail that they lack episodic memory. The experience of recollection could differ dramatically in people and animals even as the same fundamental psychological and neural processes serve memory for past individually-experienced events across species.

Furthermore, though intuition also suggests that our memories are veridical—an accurate reproduction of past events empirical data indicate that autobiographical memories are in fact **reconstructed** by active processes sensitive to systematic errors based upon inattention, suggestion, expectancy, and familiar cognitive scripts (Schacter, 1999; e.g., Conway, 2001b). Even completely false memories are acquired easily (Loftus, 1997, 2004) and activate the same neural network involved in true memories (Okado and Stark, 2005). These memory distortions show that rather than "traveling down the memory lane" to re-experience past events, memories for episodes are reconstructed representations based on fragmentary data fit together using heuristics (Schacter, 1999; Conway and Pleydell-Pearce, 2000). Like memory content, the temporal context of episodic memories is inferred (Friedman, 1993). People remember when something happened primarily by using general knowledge about time patterns. These patterns include relationships to the beginning, middle, and end of a psychologically-significant series or time intervals such as a day, sequential order of events, and relationship to temporal landmarks or reference points such as other important-personally experiences (Shum, 1998). In contrast, neither calendar dates nor a sense for the temporal interval separating encoding from retrieval (Brown and Chater, 2001) are ordinarily remembered (Friedman, 1993, 2001). For example, people remember better when an event occurred within a day (i.e., morning, noon, evening) than within the year (Friedman and Wilkins, 1985; Friedman, 1987). Thus, the content, place, and time of remembered events are not reproduced or replayed, but reconstructed from a few different types of information.

Together these data suggest that the autonoetic mental experience of "traveling through time" is an illusion, a feature of consciousness analogous to the illusory contours produced by the visual system, and not the central feature of memory for episodes. To the extent that episodic memory is reconstructive, its cognitive features can be examined independent of the processes that generate the conscious experiences and verbal descriptions that may accompany recollection. For example, if people remember when an event occurred partly by encoding what happened before and after, then investigating memory for the sequential order of events in the rat or the monkey should provide important insight into the mechanisms of memory for episodes in humans. Even if animals and humans experience recollection differently, several key features of memory for episodes and their neuronal and computational processes are likely preserved across the animal kingdom, just as the prefrontal and medial temporal brain areas that are required for episodic memory in humans also exist in monkeys, cats, dogs, and rats, with relatively preserved connectivity (e.g., Burwell et al., 1995).

One-Trial Learning

Because we experience and remember episodes as distinct instances, intuition also suggests that brain mechanisms encode and store the content, context, and temporal information of past autobiographical events in "one trial." However, the rapid acquisition of information is neither the sole province, nor a sufficient defining feature, of memory for episodes. Several situations that produce one-trial learning are dissociated from episodic memory. For example, taste aversion learning can be acquired in one trial but does not require remembering anything more than an association between a taste or smell and gastric illness. Conversely, patients with hippocampal lesions show normal and rapid fear conditioning (changes in skin conductance) without memory for the learning episode, whereas patients with amygdala damage remember the learning episode but show no fear conditioning (Bechara et al., 1995). Thus, the outcome of unique events can be remembered even when the content, context, and temporal information that otherwise defines autobiographical events is unavailable.

Furthermore, though the particulars of episodes are unique, memory for episodes depends upon more generic familiarity with situations. In other words, the content of "unique" episodes-their richness, details, and availability to retrieval-vary with prior knowledge. Thus, while a chess expert can remember the position of every chess piece on a board with a single exposure, people unfamiliar with the game will likely remember almost none (cited in Squire, 1987). Finally, as described earlier, episodic memories are not reproductions, but reconstructions, so that memories for unique events are "regularized" to fit familiar schema (Conway and Pleydell-Pearce, 2000; Conway, 2001a). Together, the data suggest that rapid, "one trial" acquisition of information is not unique or fundamental to episodic memory. Unique experiences may be altered in memory to fit more standard schemas and the more common "episodic memories" may in fact be subtle variations in familiar circumstances.

ANIMAL MODELS: EPISODIC-LIKE MEMORY AND TASKS WITH EPISODIC-LIKE ASPECTS

Episodic memory is defined at the level of human cognition and behavior. To use animal models for investigating the neural basis of memory for episodes, the relevant cognitive and behavioral features must be translated into operational definitions and implemented in appropriate behavioral tasks. The most successful example of such an approach defined episodic-like memory operationally as an a) integrated and b) flexible recollection of c) what, when, and where information obtained during a specific past event (cf. Clayton et al., 2003a). Thus, scrub jays were trained to retrieve a preferred food (what) from a hidden location (where) based on when the food was cached (Clayton and Dickinson, 1998). The response was flexible, not based on mere familiarity (cf. Roberts, 2002) and the memory could be used both retrospectively and prospectively (Clayton and Dickinson, 1999a,b,c; Emery and Clayton, 2001; Emery et al., 2004; Clayton et al., 2001b, 2003b, 2005). These data suggest that basic mechanisms for remembering episodes may be available to animals in general.

To investigate the neuronal mechanisms of memory for episodes, an appropriate animal model must be developed that is amenable to neurophysiology. Although action potentials could be recorded from the hippocampus of scrub jays, single unit recording techniques are better developed for mammals, who also provide important neuropsychological models for human memory. A common approach has been to record hippocampal neuronal activity in rats performing tasks such as foraging or running on a linear track and then to extrapolate the results to make inferences about episodic memory coding. The problem with this approach is that episodic memory is not required for performing these tasks (see Suzuki, 2006), while the characteristics of neural activity are modulated by memory demand (Wiener et al., 1989; Markus et al., 1995; Frank et al., 2000; Wood et al., 2000; Lenck-Santini et al., 2002; Ferbinteanu and Shapiro, 2003; Kentros et al., 2004; Bower et al., 2005; Hok et al., 2005; Smith and Mizumori, 2006a). Furthermore, distinguishing necessary from superfluous behavioral correlates of unit activity is a major challenge. Both learning and memory are initiated and expressed during behaviors that require widespread neuronal activity, and only a small subset of that activity is related directly to memory processing. Multiple memory systems are active in parallel, can influence behavior in functionally identical ways (White and McDonald, 2002; McDonald and Hong, 2004; McDonald et al., 2004), and changes in the one memory system that guides behavior can indirectly modify neuronal activity in other memory systems. Therefore, the activity of neurons recorded during an arbitrarily selected behavior cannot reveal conclusively how those neurons contribute to episodic memory. Rather, the cognitive function of interest must be manipulated systematically and recorded unit activity must be analyzed and interpreted with respect to those manipulations.

Given these considerations, what-when-where tasks adapted to rats (Eacott and Norman, 2004; Ergorul and Eichenbaum, 2004; Eacott et al., 2005) provide a natural starting place for investigating the neuronal mechanisms of memory for episodes in an animal model. However, beyond psychological factors, technical aspects of unit recording in the hippocampus impose additional constraints. First, physiological activity is variable (e.g., Fenton and Muller, 1998) so that obtaining reliable data requires multiple recording trials. Second, neuronal activity in these structures is modulated by behavioral parameters such as location within the environment (O'Keefe and Dostrovsky, 1971; O'Keefe, 1976), direction of movement, and speed (McNaughton et al., 1983). To reveal the influence of memory on neuronal activity, these parameters must either be controlled or counterbalanced. Meeting all these cognitive and methodological demands poses a major challenge to any one recording study.

One solution to this problem is suggested by the reconstructive nature of episodic memory. If memory was an exact reinstatement of an original experience, then recording studies examining the correlates of memory for episodes would have to test memory for the complete combination of *what*, *where*, and *when*. Because episodic memory is however a *reconstruction* of events defined by the relationships among different co-occurring items (Eichenbaum et al., 1999) and conjoined from multiple elements of information, recording studies in animals performing tasks that employ only a subset of episodic memory features can still provide relevant information. We define tasks with **episodic-like aspects** as behavioral paradigms that require animals to remember subsets of the defining features of episodic-like memory—*what* and *when, what* and *where,* or *when* and *where*—in an integrated, flexible manner and use this information prospectively or retrospectively to guide goal-oriented responses. Such tasks should demonstrably require the activity of neural networks homologous to those required for episodic memory in people. Although such behavioral tests may not fulfill all the criteria for episodic-like memory, but they can still provide relevant data for investigating the neural correlates of memory for episodes. Within this framework, the remaining part of this article will discuss empirical results indicative of how neural activity may encode episodic memory.

UNIT ACTIVITY AND MEMORY FOR EPISODES

Temporally Extended Representations. I. Prospective and Retrospective Coding

To the extent that the hippocampus contributes to temporally extended, episodic-like memory in rats, hippocampal neuronal activity should form representations that code the past, present, and future. Prospective and retrospective codes are defined operationally as activity modulated by future and past events, respectively, and can be linked to appetitive and consummatory behavior. Goals delimit episodes (Conway, 2001b) and guide appetitive behavior, while consummatory behavior marks the end of a goal-directed behavioral sequence. Neuronal activity during goal-directed appetitive behavior can be modulated by previous experience in the same situation and codes prospective information, whereas neuronal activity immediately preceding consummatory behavior may be informed retrospectively by the history of actions that led to a successful outcome. The difference between prospective and retrospective situations can be sharpened in laboratory experiments. For example, rats trained to obtain food in each arm of a 12-arm radial maze minimize the number of items in memory by switching from a retrospective (arms already visited) to a prospective (arms yet to be visited) memory strategy (Cook et al., 1985). In a T maze task where the animal has to choose a goal arm after being placed in the start arm, the key events behavioral boundaries include placement on the maze, turning in the choice point, and eating the reward at the end of the trial. To enter the correct arm, the rat must remember the location of the goal before it exits the choice point. Thus, the choice point provides a natural boundary between prospective and retrospective coding. While on the goal arm, the rat can remember the behavioral history that led to the food.

Two important studies demonstrated that hippocampal neuronal activity was sensitive to behavioral history and could encode prospective and retrospective information. In one experiment, rats were trained to alternate right and left turns in a modified T-maze occupied the same positions in the central stem while they performed the same overt behavior under similar motivations (Wood et al., 2000). Two thirds of the hippo-

campal cells with place fields on the stem fired differently depending on whether the animal was in a right- or left-turn trial even when the animal occupied the same position in space, and moved at the same speed in the same direction. Although these results suggested that hippocampal neurons encode differently two distinct types of events (right and left turns), the design of the experiment did not distinguish prospective from retrospective coding. In the other experiment, hippocampal neurons were recorded in rats trained to alternate between trajectories from a central stem to the right and left side tracks of a W-shaped maze (Frank et al., 2000). Again hippocampal activity varied with trajectory. Approximately 16% of the CA1 neurons distinguished the different inbound journeys, showing retrospective coding, and 3% of the cells fired selectively during the outbound journeys, showing prospective coding. Though prospective coding by hippocampal neurons was also suggested by earlier experiments, it was not demonstrated conclusively because none of these experiments used hippocampal-dependent tasks (Muller and Kubie, 1989; Skaggs and McNaughton, 1998; Mehta et al., 2000; Battaglia et al., 2004). Indeed, the task used by Wood et al. (2000) was unaffected by hippocampal lesions (Ainge and Wood, 2003). Furthermore, in the Wood et al. (2000) and Frank et al. (2000) studies, the rats followed stereotyped trajectories and therefore could not distinguish whether the neural activity encoded trajectory, the particular spatial path that the rat followed, or *journey*, a flexible representation of origin and goal. Finally, the continuous alternation tasks merged the beginnings with the ends of trials, while episodic memories are characterized by narrative structure, with beginning, middle, and end.

To address these issues we recorded neural activity in rats performing a + maze task designed to emphasize episodic features (Fig. 1A; Ferbinteanu and Shapiro, 2003). North and South arms were designated as start arms and the East and West arms as goal arms. Only one goal arm contained food in a given trial. The rats were trained to go from a start arm, which varied from trial to trial, to the end of a baited goal arm, which switched after the animal responded reliably. The animals were placed on a platform between trials. The task required the rats remember the location of the current goal within the temporal context of a trial block. Performance was reduced to chance by lesions of the fornix, demonstrating that the activity of the hippocampal neurons was indeed necessary for successful performance. The task had episodic-like aspects, since successful performance required remembering where depending upon when and the beginning and end of the trials were clearly delineated. The task also distinguished journeys from trajectories: if the rat mistakenly entered an empty goal arm, he could reach the food by following a path different than the L-shaped route followed during correct trials.

To analyze the influence of memory on hippocampal coding, we compared place field activity during different journeys through the same places, e.g., in the N start arm during NE vs. NW journeys, or in the W goal arm during NW vs. SW journeys. We defined current location, retrospective, and prospective coding operationally. A place field active whenever the ani-

mal was in a given arm showed current location coding; a field in a goal arm whose activity depended upon where the animal started the trial showed retrospective coding; a field in a start arm with activity dependent upon the rat's imminent choice showed prospective coding. In the absence of differences in location, direction of movement, or speed, most cells fired in places during specific journeys (journey-dependent cells): 58% of the fields on the start arm showed prospective coding and 69% of the fields in the goal arm showed retrospective coding (Fig. 1B). Approximately half of the fields that could be assessed during error trials maintained retrospective encoding. These cells clearly encoded journeys rather than trajectories (Fig. 1C). However, overall both retrospective and especially prospective coding diminished when the animal made errors, suggesting thus that the recorded signal was relevant to behavioral performance (Fig. 1D). This particular conclusion is strengthened by the recent finding that on a + maze hippocampal neurons develop differential firing patterns analogous to the prospective and retrospective coding described here only when they perform a memory task very similar to the one we used and not when they engage in random foraging (Smith and Mizumori, 2006a,b).

Prospective coding in the hippocampus has also been observed in human subjects. Patients with electrodes implanted intracranially for seizure control performed a virtual navigation "taxi driver" task while the activity of neurons in the hippocampus, parahippocampal area, amygdala, and frontal lobe was monitored (Ekstrom et al., 2003). Virtual navigation activates the hippocampus (Maguire et al., 1998), and the task likely requires the structure because hippocampal damage impairs spatial memory in people and animals (Olton and Papas, 1979; Murray et al., 1988; Squire, 1992). In close correspondence to studies in rats, while 33% of the neurons recorded from the human hippocampus were significantly associated with places, 49% were modulated by the goal guiding the navigation (Fig. 1E; Ekstrom et al., 2003, Table 2, supplementary material). Thus, hippocampal cells in both rats and humans performing hippocampus-dependent memory tasks fire in patterns that reflect the episodic structure of ongoing behavior in general and the repetitive, goal-directed, prospective demands in particular.

The prefrontal cortex, which is required for key features of human episodic memory (Wheeler et al., 1995), is also active in memory tasks in rats. Cells in the rat medial prefrontal cortex fired differentially on the central stem of a modified T maze depending on whether well-trained animals were on a right turn or left turn trial during a spatial alternation task similar to the one used by Wood et al., 2000 (Jung et al., 1998). Medial prefrontal neurons recorded as rats were learning the same task showed prospective and retrospective coding during task acquisition, when many errors occurred (Baeg et al., 2003). Retrospective coding was shown by discriminative neural activity recorded on the central arm after the rat exited different side arms but went to the same location. Prospective coding was revealed by discriminative activity recorded on the central arm when the rat came from the same side arm but went to different locations. Retrospective coding developed early, after only one day of training; prospective coding developed gradually

across 8 days and correlated with improved performance. Thus, activity in the prefrontal cortex complements the prospective/ retrospective activity recorded in the hippocampus. Together, the data suggest that the potential neural substrate of episodic memory's *when* is a temporally extended representation formed by the neural network required for episodic memory which includes the hippocampus and the prefrontal cortex.

II. Coding the Beginning and End of Episodes

If prospective signals guide behavior by anticipating pending events, and retrospective signals inform behavior by retrieving past events, then these representations must be distinguished clearly by the brain so the past could not be confused with the future (referred here as temporal asymmetry). In other words, if prospective and retrospective activities are indeed part of a temporally extended representation of episodes, then they should be empirically distinguishable. Standard methods for assessing place fields use time averaging to define the mean firing rate of single cells across locations. These methods did not reveal a qualitative difference between neuronal populations that coded prospective and retrospective situations in the start and goal arms. This finding could suggest either that the temporal asymmetry of memory is not coded by hippocampal neurons, or that standard measures of place fields are insensitive to the neural code for that information. How might anticipation be distinguished from recollection? Beyond rate coding, neural groups can in principle convey information through timing codes that distinguish representations based on temporal order, i.e., when each cell fires with respect to others.

Though the exact point in time when hippocampal neurons fire indeed changes with respect to behavior and EEG rhythms (O'Keefe and Recce, 1993; Mehta et al., 1997; Harris et al., 2003; Huxter et al., 2003), changes in temporal patterns of activity had not been previously reported to vary with memory demand. We hypothesized that temporal firing patterns within ensembles of coactive neurons could differentiate the beginning from the end of journeys. We therefore assessed the relative spike timing in pairs of simultaneously active cells with standard, journey-independent place fields recorded in the + maze task (Ferbinteanu and Shapiro, 2003; Shapiro and Ferbinteanu, 2006). Only cells with spatially overlapping fields on either the start or the goal arm were included. Spike timing did not differ at the beginning of different journeys through the start arms. By contrast, when the animal traversed the goal arms, the timing of relative spiking was markedly modulated in pairs of place fields, suggesting a powerful influence of the recent past on the timing of hippocampal neuronal activity. The changes in relative patterns of firing could not be explained by different behaviors across journeys, by different patterns of spatial activity within the place fields, or by a change of timing patterns in firing of individual cells. Rather, hippocampal activity at the start and end of journeys was differentiated by the relative spike timing in simultaneously-active, journey-independent place fields (Fig. 2; Shapiro and Ferbinteanu, 2006). These results













FIGURE 1

support the idea that the activity of hippocampal neurons forms temporally extended representations which are not neutral with respect to the time's arrow, but which, through intrinsic population dynamics, distinguish the beginning from the end of an episode.

Context Coding

Episodic memory is inextricably linked with the contextual elements (spatial, temporal, and internal) present when an event occurred. Thus, single unit recording studies examining how contextual information is represented in relevant neural networks may provide pertinent data regarding the neuronal and computational mechanisms supporting human episodic memory.

The term "context" has been used in many ways in psychology. Here we define context as the set of background features that surround an event (for discussions see Hirsh, 1974; Nadel and Willner, 1980; Good and Honey, 1991; Myers and Gluck, 1994; Nadel et al., 2002; Jeffery et al., 2004). Thus, spatial context describes where an event occurred and is defined by the spatial relationships among, and attributes of, stimuli present in the external environment. Temporal context describes when in the record of experience an event occurred and is defined by what preceded and followed the event or by position within a sequence (see above); internal context describes emotional and motivational states experienced during an event, and is defined by interoceptive signals that can serve as memory retrieval cues in hippocampus-dependent tasks (Hirsh, 1974; Benoit and Davidson, 1996; Hock and Bunsey, 1998; Kennedy and Shapiro, 2004).

Spatial context coding has been widely studied in animal models. Hippocampal neurons clearly encode spatial variables via place fields (Bostock et al., 1991; Tanila et al., 1997; e.g., Skaggs and McNaughton, 1998; Lever et al., 2002; Anderson and Jeffery, 2003; Hayman et al., 2003; Jeffery and Anderson, 2003) but most of these studies were not explicitly designed to test memory for contexts or indeed require memory at all.

Memory demands modulate hippocampal neuronal activity, however, as well as hippocampal responses to spatial context manipulations (Zinyuk et al., 2000; Smith and Mizumori, 2006a). As described earlier, studies that do not vary memory load cannot clarify the precise link between hippocampal neuronal activity, spatial context, and episodic coding (cf. O'Keefe and Speakman, 1987).

More recent evidence shows that hippocampal neurons code both content and context in hippocampus-dependent tasks. Hippocampal neuronal activity was recorded in rats tested after one of two forms of fear conditioning (Moita et al., 2003, 2004). During training, rats were given either paired or unpaired tone-shock presentations in one experimental chamber, to produce either cued or context conditioning, respectively. The hippocampus is required in the latter, but not in the former cases (Rescorla, 1968; Good and Honey, 1991; Kim and Fanselow, 1992; Phillips and LeDoux, 1992; Kim et al., 1993; Maren and Fanselow, 1997). The rats given paired tone-shock presentations showed fear conditioning by freezing during the presentation of the tone, while rats given unpaired tone and shock showed contextual fear conditioning by freezing in the training context (Phillips and LeDoux, 1994). Prior to conditioning, hippocampal neurons in both groups had stable place fields and responded minimally to the tone that subsequently became the conditioned stimulus. After conditioning, the proportion of tone-responsive cells increased significantly in the paired, but not in the unpaired tone-shock group. Furthermore, place fields recorded from rats in the unpaired group were more likely to remap than fields recorded from rats in the paired group, and this partial remapping was specific to the fear conditioning context. Thus, both groups of animals received shock and were exposed to a tone stimulus in the experimental apparatus, but hippocampal activity was differentially modulated depending on what the animal learned. When a hippocampal-independent association was learned, the representation of the environment was unchanged, and hippocampal neurons began to respond to the newly salient cue only when it was presented in a given cell's place field. In contrast, when a hippocampal-dependent association (what-where) was

FIGURE 1. A: Hippocampal-dependent spatial + maze task. Rats were trained to walk from either start arm (North or South) to the end of the baited goal arm. When the animal performed nine times correctly in a succession of 10 trials, the location of the food was switched to the end of the other goal arm. This procedure continued to a maximum of 60 trials in one recording session. B: Hippocampal activity during the performance of the + maze task. Journey-dependent and independent fields were recorded during the same session. Each square shows a location the rat visited, gray lines show the path followed by the rat during a given trial, and dots indicate the firing of the unit whose waveforms are depicted to the left. Insets show the firing rate maps and the statistically defined place fields. Journey-dependent activity was predominant in this experiment. Data from Ferbinteanu and Shapiro, 2003. C: Activity during error trials in the + maze task. Even when the rat reached the goal following a different trajectory, approximately half the fields whose activity could be assessed

maintained a journey selective pattern of firing. These cells encoded journeys, rather than trajectories. D: Overall, both prospective and retrospective coding diminished when the animal made errors, suggesting that the recorded signal was relevant to behavioral performance. Modified from Ferbinteanu and Shapiro, Neuron, 2003, 40, 1227-1239, C Elsevier, reproduced by permission. E: Hippocampal activity in humans performing a virtual spatial navigation task showed prospective coding. Activity in the two relevant locations (highlighted squares) was high when searching for a particular target ('shop C'), but not when searching for other goals. Among all hippocampal cells, approximately half were influenced by the goal either by itself or in conjunction with location or view. Place x goal and place x goal x view activities correspond to prospective coding recorded from the rat hippocampus described above. Modified from Ekstrom et al., Nature, 2003, 425, 184-188, © Nature Publishing Group, reproduced by permission.



FIGURE 2. Relative spike timing in pairs of overlapping journey-independent place fields recorded in the + maze task. At the beginning of the trials (A) the temporal pattern of neuronal activity was consistent across journeys, whereas at the end of trials (B) the temporal pattern of activity was strongly modulated. C: Right panel shows the cross correlation of two cells with overlapping fields recorded on the South start arm. The neurons fired in the same temporal sequence relative to each other in both the SE and the SW journeys and the two curves superimpose well. Left panel

shows the cross correlation of two units with overlapping fields recorded on the West goal arm. In NW journeys, the cell whose data are shown in black fired before the other cell, while in SW journeys the order of firing was reversed. D: Overall, at the end of trials firing rate distributions of individual units were less correlated and corresponding cross-correlations of cell pairs were more variable across journeys than at start of trials. Data from Shapiro and Ferbinteanu, Proc Natl Acad Sci USA, 2006, 103, 4287–4292, © National Academy of Sciences, reproduced by permission.

learned, hippocampal neurons developed an altered representation of the environment in correspondence with the changed emotional valence that defined the context. Together, the studies suggest that the hippocampus encodes salient features of situations, including single cues or contextual features, depending upon the discriminative significance of those features. This view predicts that hippocampal neurons will encode and discriminate contextual variables, including "personal" and temporal contexts, to the extent that they are required for memory discriminations even as spatial context is held constant.

Sequence Coding: Candidate Mechanisms for Episodic Memory Processing

Recollecting the sequential order of events is part of the reconstructive, relational memory processes encoding *when* an

event occurred (Friedman, 1993). In the rat, encoding event sequences requires the hippocampus (Kesner and Novak, 1982; Agster et al., 2002, Chiba et al., 1994; Bunsey and Eichenbaum, 1996; Dusek and Eichenbaum, 1997; Fortin et al., 2002; e.g., Kesner et al., 2002), but the neuronal mechanisms of sequence coding in memory has yet to be determined.

A specifically spatial hypothesis suggests that event sequences are encoded as a succession of locations encountered as a rat moves through regular spatial trajectories (e.g., in a linear track; Buzsaki, 2005). Across multiple trials, the spikes of a given hippocampal neuron progressively advance to an earlier phase of the theta cycle (O'Keefe and Recce, 1993). Within a theta cycle, this "phase precession" generates a repeated activation of a sequence of hippocampal neurons with successive, partially overlapping place fields (compression of temporal sequences; Skaggs et al., 1996). This phenomenon reoccurs during sleep and is proposed to be involved in consolidating the representation (Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; Kudrimoti et al., 1999; Louie and Wilson, 2001; Lee and Wilson, 2002). Recent evidence suggests that the critical factor in memory storage may be the synchronous activity of CA3 and CA1 neurons registered in an EEG recording as sharp waves. Cell pairs in CA1, which fire together or have fields in similar locations, show increased coactivation during both exploratory and subsequent sleep sharp waves, but not during sleep not preceded by exploration (O'Neill et al., 2006). Furthermore, distances between place field peaks generated as a rat runs on the linear track are encoded by the temporal relationships of spikes belonging to the corresponding pairs of neurons. This phenomenon cannot be explained by the synchronous hippocampal activity present during theta rhythm and thus it appears that sequential locations are represented by a dynamic set of cell assemblies (Dragoi and Buzsaki, 2006). Together, these data suggest that the representations of places occupied successively may be linked by the sequential activation of individual neurons within hippocampal cell assemblies (e.g., Mehta et al., 1997; Lee et al., 2004; Buzsaki, 2005).

On the one hand, this hypothesis is powerful because it links the temporal details of hippocampal physiology with important computational theories of spatial information processing. On the other hand, the hypothesis is limited because it ignores the modulation cognitive demand exerts on hippocampal activity (Suzuki, 2006). A rat shuttling back and forth through stereotyped spatial trajectories on a linear track performs a task that lacks episodic-like aspects and is hippocampus-independent. In these conditions the recorded hippocampal activity cannot be linked empirically either to memory for sequences or, more broadly, to memory for episodes. If phase precession and compression of temporal sequences contribute to memory for episodes by coding event sequences, then they should reflect memory demand by coding the order of items in hippocampusdependent tasks (e.g., Fortin et al., 2002).

An alternative hypothesis is suggested by the memory space theory, which proposes that event sequences are encoded by the combined activity of cells that respond to individual events and cells whose activity is extended in time, the latter functioning as a "bridge" between the former (Eichenbaum et al., 1999). Thus, representing a sequence of events in an episode does not derive from, and is not structurally the same as representing a sequence of physical locations, but is produced by the simultaneous firing and sequential activation of hippocampal neurons with different characteristics of activity (Eichenbaum et al., 1999). Empirical evidence supports this theory. Hippocampal neurons encode behavioral history (Wood et al., 2000; Frank et al., 2000; Bower et al., 2005), memory demand (Ferbinteanu and Shapiro, 2003; Ekstrom et al., 2003; Smith and Mizumori, 2006a), and conjunctions of different items (Cameron et al., 2001; Anderson and Jeffery, 2003; Jeffery and Anderson, 2003; Quiroga et al., 2005). These cells correspond well to the "event" cells postulated by the memory space theory. Other hippocampal neurons remain active throughout a series of successive events (Eichenbaum et al., 1987, 1999). Hippocampal activity also distinguishes the beginning from the end of journeys (Shapiro and Ferbinteanu, 2006). Thus, hippocampal neuronal activity seems to parallel the psychological fact that people remember when an event occurred by reconstructing the temporal order between neighboring items, or by the item's relative position to the beginning or end of the sequence.

Little is known about how the prefrontal cortex contributes to sequence coding in episodic memory. Although recent data indicate that neurons in the rat medial prefrontal cortex show phase precession (Jones and Wilson, 2005) and are theta-phase interlocked with hippocampal cells (Hyman et al., 2005; Siapas et al., 2005), no studies have investigated the neural correlates of sequence encoding proper in this brain area. In the monkey, many neurons in the dorsolateral prefrontal cortex show activity selective to specific cue locations and to temporal order (Funahashi et al., 1989, 1993) as well as to conjunctions of two spatial locations, order of presentation of two cues, or a combination of both (Funahashi et al., 1997). More extended sequences of three cues can also be encoded either individually or collectively (Ninokura et al., 2003) and this information is integrated with information about the physical qualities (color and shape) of the items (Ninokura et al., 2004). As monkeys switch from one learned sequence of eye movements to another, neural activity in the prefrontal cortex tracks the behavioral change (Averbeck et al., 2006). Dorsolateral prefrontal neurons fire selectively during approach to a goal, reward retrieval, and walking away from the goal in a delayed alternation task in which the monkeys walked freely among four different location within a room (Ryou and Wilson, 2004). These data suggest that the prefrontal cortex forms a representation of sequences. However, recording studies in the monkey using tasks with episodic-like aspects that require motor responses other than eye movements have yet to be accomplished. Furthermore, if indeed the representation formed by the prefrontal cortex has a functional behavioral role, then lesions of this cortical area should impair the ability to encode the order of events-these studies are yet to be performed.

Neural Encoding of Goals

Individual episodes are delimited by goals, which separate the continuous flow of experience into meaningful chunks (e.g., "while walking to the grocery to get bread I heard the sound of a car accident ... "; Conway and Pleydell-Pearce, 2000). Although goals help to define episodes, precisely how goals are represented as part of memory for episodes remains unknown. Goal-responsive cells have been described in both the hippocampus and frontal cortex of patients performing a virtual spatial navigation task (Ekstrom et al., 2003; see above). Hippocampal neurons in monkeys form conjunctive representations of rewards (which act as goals) and locations when animals perform a hippocampal-dependent task (Rolls and Xiang, 2005). Hippocampal neurons in rats encode goal landmarks when food is located in their vicinity (Gothard et al., 1996), while if the animals perform a spatial alternation task on a + maze, the neurons encode reward sometimes by itself, sometimes in conjunction with spatial location (Smith and Mizumori, 2006a,b).

Neurons in the dorsolateral prefrontal cortex of monkeys performing a delayed response task encode reward, and a conjunction of reward and direction of eye movement (Watanabe, 1996; Wallis and Miller, 2003), a conjunction of reward with temporal delay or reward/temporal delay/direction of eye movement (Tsujimoto and Sawaguchi, 2005). Some of these neurons distinguish among several kinds of reward (Watanabe, 1996), suggesting thus that in these cases the neural activity encoded not just reward in general, but the goal in particular (see also Schultz, 2000). Neurons in the medial prefrontal cortex of rats performing a radial maze spatial task or a figure-eight spatial alternation task show goal-related activity (Jung et al., 1998) and as in the monkey, some of these cells differentially encode relative reward value (Pratt and Mizumori, 2001). Spatially selective activity of medial prefrontal cortex neurons, rare and present only if the rat is engaged in spatial navigation, encodes predominantly the location that is the goal of the behavior (Hok et al., 2005). This finding is similar to the "clustering" of hippocampal place fields around platform location in animals performing an annular water task (Hollup et al., 2001). Together, the data indicate that neurons in both the hippocampus and the prefrontal cortex in rats, monkeys, and humans respond to goals, and may contribute to memories for episodes by directing responses toward these. Goals may be integrally encoded within the temporally extended hippocampal representation (Smith and Mizumori, 2006a), and this suggests that the representation of goals should be affected by changes in the cognitive demand of behavioral tasks.

CONCLUSIONS

Recent developments in episodic memory theory have spurred the development of animal models aimed toward investigating the mechanisms of memory for episodes. Because memory for episodes is reconstructive and relational, animal models can provide relevant information even if animals do not experience memories about their own past in the unique way humans do. Data obtained by combining the neuropsychology of memory with neurophysiology suggests that episodes may be encoded as temporally extended and asymmetric representations formed in part by a distributed neural network that includes the hippocampus and the prefrontal cortex. Many details on the behavioral relevance of these neurophysiological data remain to be confirmed. The mechanisms that represent and process the links among spatial, temporal, and internal contextual information in memory remain unexplored, as is the case with encoding the order of events. Although neuronal activity within the network responds to goals either by themselves or in conjunction with other task parameters such as spatial locations or temporal delays, future research must elucidate other aspects, such as the relationship between goal representation and prospective coding.

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