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Hippocampus: Cognitive Processes and Neural Representations that Underlie Declarative Memory

Review

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The hippocampus serves a critical role in declarative memory—our capacity to recall everyday facts and events. Recent studies using functional brain imaging in humans and neuropsychological analyses of humans and animals with hippocampal damage have revealed some of the elemental cognitive processes mediated by the hippocampus. In addition, recent characterizations of neuronal firing patterns in behaving animals and humans have suggested how neural representations in the hippocampus underlie those elemental cognitive processes in the service of declarative memory.

The domain of memory functions that are mediated by the hippocampus and the surrounding anatomically associated cortical regions was outlined nearly 50 years ago in the case study of H.M., a man who became amnesic following removal of the medial temporal lobe to alleviate his epileptic seizures (Scoville and Milner, 1957; Corkin, 1984). H.M. is severely impaired in declarative memory, but his perceptual and cognitive abilities are intact, as are his capacities for working memory and perceptual and motor skill learning. Furthermore, the deficit in new learning ability is accompanied by a temporally graded retrograde amnesia, such that H.M. can recall information obtained remotely in life but he is impaired in recalling events that occurred recently before the onset of amnesia. These observations suggest that the memory processing mediated by the hippocampal system begins during learning and continues to contribute to the consolidation of memories over a prolonged period.

Succeeding neuropsychological analyses on amnesic patients and functional imaging studies on normal humans have elaborated the domain of capacities that are dependent on the medial temporal region and, in particular, on the hippocampus itself (Aggleton and Brown, 1999; Eichenbaum and Cohen, 2001; Squire et al., 2004). These studies have emphasized the critical role of the hippocampus in two components of declarative memory. The hippocampus plays a critical role in episodic memory, our capacity for the recollection of unique personal experiences; and the hippocampus is involved in particular aspects of the acquisition of semantic or factual knowledge. In addition to detailed characterizations of spared and impaired memory capacities in animals with selective hippocampal damage and recordings of hippocampal neuronal activity in behaving animals and humans, these studies have begun to reveal how the hippocampus mediates these complex memory functions.

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A Simple Model of Hippocampal Information Processing

There are many diverse views about the underlying mechanisms by which hippocampus supports declarative memory. Differing perspectives emphasize the processing of associations among disparate elements of an experience (e.g., Squire and Zola-Morgan, 1991; Rolls, 1990; O'Reilly and Rudy, 2001; Ryan and Cohen, 2003; Morris et al., 2003) and spatial and temporal integration of events into the record of experiences (e.g., Levy, 1989; Kesner, 1990; Wallenstein et al., 1998; Redish, 1999; Burgess et al., 2002; Holscher, 2003). Rather than describing and comparing these alternative perspectives, this review will focus on the common themes among them, guided by a framework for conceptualizing cognitive processes that underlie declarative memory and prominent features of hippocampal circuitry and plasticity. I will discuss three elemental cognitive processes that are mediated by the hippocampus—*associative representation, sequential organization*, and *relational networking*—and a set of characteristic properties of hippocampal circuitry that could support these processes: *convergent afferents, recurrent connections*, and *long-term potentiation* (LTP).

Cognitive Processes

We live our lives through personal experiences, and our initial construction of reality within consciousness is a form of episodic buffer that contains a representation of the stream of events as they just occurred (Baddeley, 2000). Consider, for example, your episodic memory of a day at a recent scientific meeting. You might recall a specific encounter with a colleague, your discussion about personal matters and about specific presentations you and she/he had heard at the conference. Each event within this episodic memory includes a combination of features: yourself, your colleague, what she/he and you said, and where the conversation took place. In addition, a vivid episodic representation for the encounter is organized according to the order of events; it unfolds as a "mental replay" of the encounter extended over time (Tulving, 2002). Thus, that memory can be deconstructed into a series of *associative representations*, wherein each discrete event includes the relevant people, their actions, and the place where that event occurred, and these representations are *sequentially organized* to compose the flow of events in that unique experience (Figure 1).

In addition, episodic memories do not exist in isolation, but instead share many features with other memories that bear common or closely related information. You met that colleague on previous occasions and in different places, and you have discussed related scientific work on each of those occasions. During the current encounter, you can recall both specific previous discussions and general information that you have accrued from many related experiences. A simple and effective way to organize both the specific (episodic) memories and the common (semantic) information accrued across memories is to encode common features of related experiences into the same representational elements (Fig-

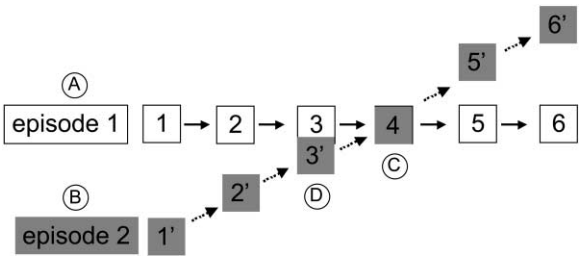

Figure 1. Schematic Diagram of a Simple Relational Network

The network is composed of two episodic memories (A and B), each construed as a sequence of elements (1–6) that represent the conjuction of an event and the place where it occurred. C is an element that contains the same features in both episodes. D is an element that contains only some of the common information.

ure 1). These elements organize memories into a *relational network* that offers two potentially quite useful properties. First, memories for the common features become "timeless" semantic elements, not bound to any particular episode in which they were acquired. Second, the elements that encode common features link memories to one another, allowing one to compare and contrast memories and to make inferences among indirectly related events. These properties of relational memory representation underlie the hallmark "flexibility" of declarative memory expression (Cohen, 1984). Also, the continued abstraction of common features and linking of memories may underlie a more extensive association and interleaving of memories during the prolonged period of consolidation (Ribot, 1882; Burnham, 1903; McClelland et al., 1995).

Hippocampal Circuitry and Plasticity

The elemental cognitive processes of declarative memory introduced above could be mediated by a combination of three well-known properties of hippocampal circuitry; these properties are particularly prominent in region CA3 (Figure 2). (1) The hippocampus receives *convergent afferents* from virtually all cortical association areas, and these inputs are widely distributed onto the cell population in multiple subdivisions of the hippocampus (Amaral and Witter, 1995). Thus, CA3 principal cells have as their main afferents considerable high-level perceptual information about attended stimuli and spatial cues as well as other information from diverse cortical regions. (2) The principal neurons of area CA3 send considerable projections to other CA3 principal cells. These *recurrent connections* are broad across the CA3 population, sparse, and involve mainly excitatory glutamatergic synapses (Amaral and Witter, 1995; Treves and Rolls, 1994). (3) The hippocampus is noted for the prevalence of rapid synaptic plasticity, known as *long-term potentiation* (Bliss and Collingridge, 1993). In particular, a form of LTP that is dependent on N-methyl D-aspartate (NMDA) receptors has been strongly linked to memory (Martin et al., 2000) and to the memory-associated firing properties of hippocampal neurons (Shapiro and Eichenbaum, 1999).

These properties can support the elemental cognitive processes that underlie declarative memory. First, *associative representations* can be formed by simultaneous activation of multiple afferents to CA3 principal cells, leading to LTP of weakly as well as strongly activating inputs (Figure 2A). This associative LTP supports pattern completion, such that subsequent presentation of any part of the representation would fire the cell, constituting retrieval of the entire association (for review, see Nakazawa et al., 2004). In addition, recurrent connections can support pattern completion by spreading the activation of some elements to all elements that compose a previously activated CA3 network (McNaughton and Morris, 1987; Treves and Rolls, 1994).

Second, several recent computational models have emphasized the *sequential organization* of memory representations supported by the hippocampus and, in particular, area CA3. Levy (1989, 1996) proposed that unique characteristics of hippocampal area CA3, specifically the sparseness and largely excitatory nature of its recurrent connectivity, combined with rapid synaptic plasticity, inherently produces asymmetric connections that can represent sequences of information from a single patterned input and can spontaneously reproduce learned sequences. Thus, according to these models, when temporally patterned inputs reach the hippocampus, a rapid LTP mechanism enhances connections between cells that fire in sequence. The likelihood of a reciprocal (backward) connection of forward connected cells is very low due to the overall sparse connectivity. Therefore, the enhancement of recurrent connections is mostly unidirectional, leading to an asymmetry of the enhanced connectivity. When partial inputs are reproduced, the network is more likely to complete the sequence of the full initial input pattern. In addition, when sequences are repeated (practiced) just a few times, cells that represent constant background information provide a context that bridges the firings of neurons representing salient sequential events (Levy, 1989, 1996; Wallenstein and Hasselmo, 1997; Wallenstein et al.,

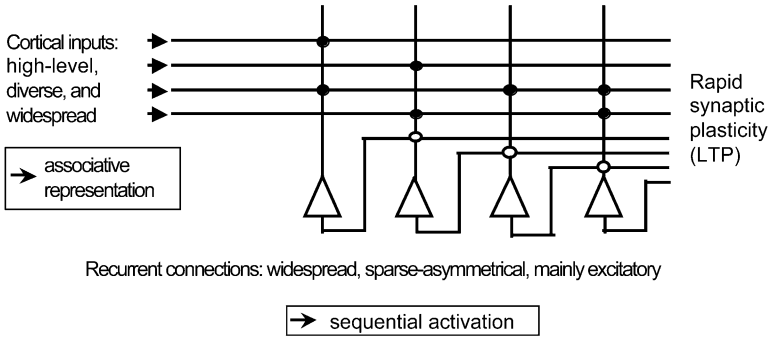

Figure 2. Schematic Diagram of the Circuitry of the Principal Cells in Hippocampal Area CA3 that Could Mediate Properties of Relational Networks

Two major pathways are shown, one pathway involving inputs from diverse neocortical association areas that send widespread projections onto the dendrites of pyramidal cells and the other pathway involving recurrent projections from pyramidal cells projecting sparsely onto other pyramidal cells in the same network. Connections of both of these pathways are subject to activity-dependent rapid synaptic plasticity.

1998). Although sequence storage and recall were initially proposed as characteristics of CA3, subsequent models (Lisman, 1999) have shown how more complex and reciprocally connected recurrent networks in the dentate gyrus and CA3 can coordinate to provide more faithful recall of sequences, leaving CA1 to decode the sequence signals back to the cortex and to compare predictions of the network for the next sequential item to actual information as it arrives.

Third, the same computational models that emphasize temporal organization in episodic memory representations provide a mechanism for linking distinct memory representations into a *relational network*. These networks include cells that receive no external inputs but develop firing patterns that are regularly associated with a particular sequence or with overlapping sequences (Levy, 1996; Sohal and Hasselmo, 1998; Wallenstein et al., 1998). In the situation where episodes are repeated, these cells provide a local temporal context in which items within a particular sequence are linked together. When these links incorporate events that are unique to a particular episode, they can assist the network in disambiguating successive patterns in overlapping but distinct sequences. At the same time, when the links are activated similarly by separate episodes that share a series of overlapping features, they can allow the association of discontiguous episodes that share those features. Thus, the same network properties that support the encoding of episodes as sequences of events also contain the means to link and disambiguate related episodes (see Agster et al., 2002, for an experimental test).

Convergent inputs, recurrency, and LTP are, to differing extents, also properties of other subdivisions of the hippocampus as well as cortical areas (e.g., Bear, 1996). Therefore, the functional mechanisms described here may contribute to memory processing throughout the hippocampus and may support the permanent consolidation of memories within widespread areas of the cerebral cortex (e.g., Frankland et al., 2004; Maviel et al., 2004). The special role of these mechanisms in the hippocampus may be derived from the high extent of diverse convergent inputs, the strong recurrency, and the rapidity of LTP that are prominent within hippocampal circuitry.

Are the elemental cognitive processes of declarative memory that are highlighted in this framework actually mediated by the hippocampus? Do hippocampal neural representations reflect these cognitive processes? The following sections consider the evidence from neuropsychological and physiological studies regarding each of the three elemental cognitive processes of declarative memory introduced above.

Associative Representations

There is a growing body of evidence that suggests that the hippocampus encodes associations among stimuli, actions, and places that compose discrete events. Several functional imaging studies have examined whether the hippocampus is more activated during the encoding or retrieval of associations among many elements of a memory—a characteristic of context-rich episodic memories (for review, see Cohen et al., 1999). For example, Eldridge et al. (2000) found that the hippocampus was activated during correct recollections that included perceptual details or associations made with a word during a previous study phase as compared to a sense of familiarity with the words. In a study that directly compared the encoding of stimuli in combination or separately, Henke et al. (1997) observed greater hippocampal activation when subjects associated a person with a house, as compared to making independent judgments about the person and house. Also, Giovanello et al. (2003a) reported greater hippocampal activation when subjects recognized previously presented word pairings as compared to rearranged word pairs or words studied separately. Davachi and Wagner (2002) found that the hippocampus is activated during the encoding of multiple items and is more activated when subjects are required to link the items to one another by systematic comparisons as compared to rote rehearsal of individual items. Furthermore, the magnitude of hippocampal activation during the comparison and linkage of the items predicted later success in recognition. Other recent studies have revealed activation within subfields of the hippocampus during the encoding of face-name associations (Zeineh et al., 2003) and along the entire longitudinal extent of the hippocampus when subjects studied face-name pairs that they later remembered with high confidence (Sperling et al., 2003). Also, Small et al. (2001) reported that, whereas viewing faces and names independently activated separate areas within the hippocampus, the viewing of faces and names in combination activated a distinct area bridging between the separate face and name activations; and the latter area was also activated during recall of names when cued by the face.

Other studies report activation of the hippocampus during the retrieval of autobiographical experiences (see review in Maguire, 2001). Maguire et al. (2000) reported selective activation in the medial temporal region during the retrieval of multiple aspects of autobiographical events but not the retrieval of public events. Addis et al. (2004) also found that the level of detail, personal significance, and emotionality each contributed to hippocampal activation of autobiographical memories. The involvement of the hippocampus in processing complex material is not limited to autobiographical details but extends broadly, for example, to recollection of the context of learning in formal tests of memory (e.g., Davachi et al., 2003; Ranganath et al., 2003).

Some studies have provided evidence that different components of the medial temporal lobe may play distinct roles in memory. Gabrieli et al. (1997) showed subjects pictures that contained line drawings of common objects and animals. When subjects were again shown the pictures and recalled their names, a part of the hippocampus was selectively activated. In contrast, as had previously been reported by Stern et al. (1996), when subjects were shown novel or highly familiar pictures, the parahippocampal gyrus was activated. Similarly, Davachi et al. (2003) presented subjects with words and asked them either to imagine a spatial scene described by the word (e.g., a garbage dump for "dirty") or to read the word backward. They found that the hippocampus was selectively activated when subjects successfully encoded the contextual cues, whereas the surrounding

cortex was selectively activated during successful encoding of the superficial qualities of single words.

On the other hand, in several of the other studies described above, cortical areas adjacent to the hippocampus, as well as additional cortical areas, were also activated during associative processing. In particular, one recent study emphasized that the hippocampus and adjacent cortex showed equivalent increased activation for associative over nonassociative information (Kirwan and Stark, 2004). These findings are consistent with the view that several areas of the cerebral cortex also process combinations of stimuli, albeit in a different type of processing than that mediated by the hippocampus (Eichenbaum, 1994; O'Reilly and Rudy, 2001; Bussey et al., 2002). Thus, while associative processing may be prominent within the hippocampus, its specific role in representing associations is not clarified by functional imaging (Squire et al., 2004).

Consistent with the notion that the hippocampus is critical for forming associations among items in events, recent neuropsychological studies have found that recognition of associations is impaired even when recognition for single items is spared in amnesic patients (Giovanello et al., 2003b; Turriziani et al., 2004). These studies reported impairment in recognition memory for associations between words or between faces or face-occupation pairs as compared to normal performance in the recognition of single items. On the other hand, Stark et al. (2002) reported that hippocampal damage resulted in impairment in both associative and single-item recognition, highlighting the need to clarify the nature of associative information that composes an "event." The mixture of findings from both functional imaging in normal subjects and from amnesic patients suggests that studies on humans have not conclusively distinguished the specific role of the hippocampus in stimulus association from that of adjacent cortical areas in the same system (Squire et al., 2004).

In animals, there is substantial evidence that selective hippocampal damage results in deficits in forming a memory for the context or location where items were previously experienced. Gaffan (1994) trained monkeys on a set of discrimination problems composed as objects stimuli presented on a computer screen with different kinds of background patterns. Animals with the hippocampus disconnected learned object discriminations at the normal rate when the background simply varied and did not predict the location of the objects or their reward values. By contrast, the same animals were most impaired when the background context predicted the location of the rewarded object. Day et al. (2003) initially allowed rats to find different flavored rewards at specific locations in an open platform, then tested their memory for the location of those events by providing an additional flavored reward associated with one of the locations. After a single exposure to the flavor in a particular location, animals could return to the location where a flavor had previously been consumed when cued by the flavor alone. By contrast, inactivation of the hippocampus or blockade of NMDA receptors prevented encoding of the flavor-place association.

Evidence indicating hippocampal involvement in processing contextual information in recognition memory comes from studies where the overall environment was manipulated independently of the spatial position of an object. In one study, rats were initially exposed to two objects in particular places in one of two environmental chambers (Mumby et al., 2002). In subsequent recognition testing, the place of the object or the context was changed. Normal rats show increased exploration of objects moved to new places or in novel contexts. By contrast, rats with hippocampal damage failed to recognize objects when either the place or contextual information was changed. Another study failed to find a deficit in object-place recognition following hippocampal disconnection, but the same animals had a severe deficit in recognition based on a combination of contextual and place cues (Eacott and Norman, 2004). Perhaps the strongest evidence that the hippocampus is critical for learning the context of important events comes from studies of fear conditioning (Phillips and LeDoux, 1992). These studies are based on the conditioning protocol in which a tone and shock are paired repeatedly such that rats become fearful of the tone. In addition to a conditioned fear for the tone cue, rats also become fearful of the context in which the tones and shock were presented, evidenced as freezing behavior and other indices of fear when the animal is returned to the environment where conditioning occurred. Damage to the hippocampus eliminates the contextual fear conditioning without affecting conditioned fear to the tone.

Finally, the evidence concerning the specific involvement of the hippocampus in recognition for single items assessed within the delayed nonmatch-to-sample (DNMS) test is not clear. In monkeys, some studies report a consistent partial deficit in DNMS performance (Zola et al., 2000), whereas other studies report no deficit (Murray and Mishkin, 1998). The source of this discrepancy is under debate (Baxter and Murray, 2001; Zola and Squire, 2001). By contrast, damage to the cortical areas surrounding the hippocampus produces a consistent severe impairment in DNMS (Zola-Morgan et al., 1989; Meunier et al., 1993). Also, the same animals with selective hippocampal damage that show relatively spared DNMS performance are severely impaired on recognition assessed by novel item exploration (Zola et al., 2000; Nemanic et al., 2004). In rats, reports of impairment or spared performance on DNMS following selective hippocampal damage are also variable, whereas damage to the surrounding cortical areas consistently results in a severe deficit (reviewed in Steckler et al., 1998; Mumby, 2001).

One possible explanation for the different findings on selective hippocampal damage is that there may be two types of memory that contribute to recognition performance, only one of which is affected by hippocampal damage (Brown and Aggleton, 2001). This hypothesis was recently addressed using signal detection techniques to distinguish contributions of recollection of associative information in prior experiences versus a sense of familiarity for the previously experienced items, as has been done in humans (Yonelinas, 2001, 2002). Rats were trained on a variant of DNMS in which they initially sampled a series of odors and then judged old and new test stimuli across a range of response criteria (Fortin et al., 2004). Rats with hippocampal damage showed the typical partial deficit in overall recognition performance. An analysis of receiver operating characteristics

(ROC) indicated that, in normal rats, both recollection and familiarity contributed to recognition. By contrast, in rats with selective hippocampal damage, ROC analysis revealed that recognition was entirely supported by familiarity. These results can explain the overall partial deficit in DNMS observed across species and suggest that the mixed findings across recognition tasks may be a consequence of the differential demands for recollection and familiarity across tasks in animals and in humans (Pascalis et al., 2004).

Sequential Organization

A property of episodic memory that is prominent in computational modeling involves the organization of an episode as a sequence of events that unfolds over time. These studies focus on the observation that vivid episodic memories contain not only a particular item or items that one is attempting to recall, but also the experience of events that precede and follow (Tulving, 2002). A consideration of memory for the orderliness of events in unique experiences, a capacity that can be tested in animals, may provide a fruitful avenue for neurobiological explorations of episodic memory. For example, Honey et al. (1998) provided a simple demonstration of the importance of temporal order in hippocampal processing, reporting that hippocampal lesions disrupted animals' normal orienting response when a pair of stimuli were presented in the opposite order of previous exposures.

To investigate the specific role of the hippocampus in remembering the order of a series of events in unique experiences, recent studies have employed a behavioral protocol that assesses memory for episodes that are composed of a unique sequence of olfactory stimuli (Fortin et al., 2002; see also Kesner et al., 2002). In one of these studies, memory for the sequential order of odor events was directly compared with recognition of the odors in the list independent of memory for their order. On each trial, rats were presented with a series of five odors that were selected randomly from a large pool of common household scents. Memory for each series was subsequently probed using a choice test where the animal was reinforced for selecting the earlier of two of the odors that had appeared in the series or (in later testing) was reinforced for selecting a novel odor against one that had appeared in the series. Normal rats performed both tasks well. Rats with hippocampal lesions could recognize items that had appeared in the series but were severely impaired in judging their order.

A potential confound in any study that employs time as a critical dimension in episodic memory is that memories obtained at different times are likely to differ in the strength of their memory traces due to the inherent decremental nature of memory traces. To what extent could normal animals be using differences in the relative strengths of memory traces for the odors to judge their sequential order? The observation of a temporal gradient in recognition performance by normal animals suggests that memories were in fact stronger for the more recently presented items in each sequence. These differences in trace strength potentially provide sufficient signals for the animals to judge the order of their presentation. However, the observation of the same temporal gradient of recognition performance in rats with hippocampal damage indicated that they had normal access to the differences in trace strengths for the odors. Yet these intact trace strength differences were not sufficient to support consistent discrimination on the order probe tests. These considerations strongly suggest that normal rats also could not utilize the relative strengths of memories for the recently experienced odors and instead based their order judgments directly on remembering the odor sequence. Contrary to the argument that animals lack episodic memory because they are "stuck in time" (Roberts, 2002; Tulving, 2002), these observations suggest that animals have the capacity to recollect the flow of events in unique experiences.

Another major challenge for a robust model of episodic memory is the requirement for a capacity to develop representations that can distinguish two experiences that share common elements. Levy (1996) proposed that memory for the ordering of events mediated by the hippocampus may be especially important when the event sequences have overlapping elements through which memory of earlier elements must be remembered to complete each distinct sequence. In order to test whether sequence disambiguation is a fundamental feature of memory processing dependent on the hippocampus, Agster et al. (2002) trained rats on a sequence disambiguation task designed after Levy's (1996) formal model that involved two series of events that overlap in the middle items. The sequences were presented as a series of six pairwise odor choices where, for each sequence, selection of the appropriate odor at each choice point was rewarded. Each trial began with two forced choices that initiated the production of one of the two sequences. Then the animal was presented with two forced choices that were the same for both sequences. Subsequently, the subject was allowed a free choice and was rewarded for selecting the odor assigned to the ongoing sequence. Normal rats maintained a high level of performance on the critical free choice, indicating that they could remember the beginning of the sequence. By contrast, the rats with hippocampal damage performed poorly on the free choice either when sequences were alternated rapidly (high proactive interference) or when a delay was imposed before the critical choice.

These results are further clarified by a study that examined spatial sequence learning in rats with damage to the hippocampus or striatum. DeCoteau and Kesner (2000) developed two versions of a task where rats entered a series of six arms of a radial maze in which successive choices were controlled by a door to each arm. Striatal lesions resulted in impairment on an "implicit" version of the task where rats simply ran through the fixed sequence of arms opened in order. By contrast, hippocampal lesions resulted in impairment on an "explicit" version of the task where rats had to stand in front of the door to each succeeding arm before it opened. These findings are consistent with the observation that sequence learning can be mediated by declarative and nondeclarative strategies involving distinct memory systems (Keele et al., 2003), and these forms of representation are independent (Reber and Squire, 1998). Furthermore, in humans the hippocampus is implicated in mediating a declarative representation of se-

quence memory that can be established independently of conscious recollection (Schendan et al., 2003; Keele et al., 2003), providing a strong parallel to the observations on rats.

Linking Memories within Relational Networks

The third major feature of the proposed model involves the linking of episodic memories into relational networks in order to abstract the common features among related memories and to mediate flexible memory expression. Within this model, the hippocampus contributes to semantic memory by the construction of relational networks that coordinate memories stored in the cerebral cortex (Eichenbaum et al., 1999). From this perspective, semantic memories are not directly mediated by the hippocampus; rather, the hippocampus links memories in support of the flexibility of their expression through comparisons and generalizations across memories. Therefore, one might expect conditions in which semantic memory might be possible without requisite hippocampal involvement, albeit such memories might differ in the available range of their expression.

Indeed, some recent studies have emphasized the relative sparing of semantic memory in amnesia associated with selective damage to the hippocampal region (e.g., Vargha-Khadem et al., 1997; Verfaellie et al., 2000; O'Kane et al., 2004). However, there is also substantial evidence that the normal acquisition and flexible expression of acquired semantic memories are very much dependent on the hippocampal region. Manns et al. (2003) examined the severity of retrograde and anterograde amnesia for semantic information in patients with damage limited to the hippocampus and adjacent entorhinal area. These patients were impaired in memory for news events for a year or more prior to the onset of amnesia and were impaired for information obtained after they became amnesic. They performed well in recognizing names of famous people but poorly in judging whether these people were living or deceased, and this deficit was apparent even when corrected for names that evoked episodic memory in normal subjects. Complementary evidence from functional brain imaging studies has revealed that a large cortical network, including the hippocampus, is activated during the acquisition of everyday factual information as compared to a baseline task that included similar episodic experience but not general knowledge (Maguire and Frith, 2004).

Still, the patients in Manns and colleagues' study showed evidence of the acquisition of substantial semantic knowledge, albeit less than that of normal subjects. Even in cases of severe amnesia following extensive damage to the hippocampus and surrounding cortical areas, there is compelling evidence of some degree of spared semantic learning. Although several studies have shown the relative sparing of semantic memory in amnesia, the most impressive of these is the O'Kane et al. (2004) report that patient H.M., while impaired compared with normal control subjects, shows a remarkable amount of acquired knowledge about people who become famous following the onset of his amnesia. When prompted with a first name, H.M. recalled the last name of 12 out of 35 famous personalities. Furthermore, in a forced choice recognition task, H.M. discriminated 87% of famous from fictitious names and provided factual details for a third of the recognized people. Similarly, H.M. also shows some spared acquisition of spatial knowledge in that he can draw a reasonably accurate floor plan of the home in which he lived from 5 years to 21 years after he became amnesic (Corkin, 2002).

Does the partial deficit in semantic memory following hippocampal damage reflect a *quantitative* difference in an overall declarative memory capacity of the medial temporal lobe system (Manns et al., 2003) or full and selective loss of some *quality* of semantic processing? McClelland et al. (1995) and, more recently, O'Reilly and Rudy (2001) proposed that the hippocampus and cortical areas both have powerful learning capacities for learning stimulus combinations that compose declarative knowledge. However, they argue, these systems differ in their information processing mechanisms, such that the hippocampus rapidly learns about individual experiences and prevents interference by separating representations of those experiences, whereas the cortex gradually extracts regularities over many experiences. This view suggests no ultimate difference in the nature of memory representations with or without hippocampal participation but, rather, differences in how memories are formed and in the success rate following only a single experience.

To address this issue, Bayley and Squire (2002) trained a patient (EP) with extensive medial temporal lobe damage on factual information by presenting novel three-word sentences repeatedly in several sessions across three months. EP learned more slowly than controls but showed clear gradual improvement in both cued recall and recognition of the last word in learned sentences. Furthermore, unlike control subjects, EP never consciously recalled the items, showing no increased confidence for correct choices and no difference in response times for correct and incorrect responses, both of which typically accompany conscious recollection in normal subjects. Also, EP failed when a target word was replaced with a synonym, showing that, unlike normal subjects, EP's memory did not emphasize the semantic content of the sentences. These findings are consistent with previous reports of spared capacities of amnesic patients in learning computer language routines (Glisky et al., 1986) in which successful performance is rigidly tied to the circumstances of initial learning. These observations indicate that spared semantic memory in amnesia is qualitatively different than that of normal subjects, leading Bayley and Squire (2002) to characterize the preserved verbal learning abilities as nondeclarative.

Animal models have also provided clues about how information processing by the hippocampus might explain the findings on semantic memory in amnesic patients. In particular, some studies have focused directly on the learning of multiple related problems and their integration into networks of memory that support flexible, inferential judgments. One study compared the ability of normal rats and rats with selective damage to the hippocampus on their ability to learn a set of odor problems and to interleave the representations of these problems in support of novel inferential judgments (Bunsey and Eichenbaum, 1996). Animals were initially trained on two sets of overlapping odor paired associates (e.g., A goes with B, B goes with C). Then the rats

were given probe tests to determine if they could infer the relationships between items that were only indirectly associated through the common elements (A goes with C?). Normal rats learned the paired associates and showed strong transitivity in the probe tests. Rats with selective hippocampal lesions also learned the pairs over several trials but were severely impaired in the probes, showing no evidence of transitivity.

In another experiment, rats learned a hierarchical series of overlapping odor choice judgments (e.g., A > B, B > C, C > D, D > E) and then were probed on the relationship between indirectly related items (B > D?). Normal rats learned the series and showed robust transitive inference on the probe tests. Rats with hippocampal damage also learned each of the initial premises but failed to show transitivity (Dusek and Eichenbaum, 1997). The combined findings from these studies show that rats with hippocampal damage can learn even complex associations, such as those embodied in the odor paired associates and conditional discriminations. But, without a hippocampus, they do not interleave the distinct experiences according to their overlapping elements to form a relational network that supports inferential and flexible expression of their memories.

Recently, the same findings were reported in a study on monkeys (Buckmaster et al., 2004). The same animals were trained on both transitivity problems described above, using visual instead of olfactory stimuli. Monkeys with lesions of the entorhinal cortex learned visual paired associates, albeit more slowly than normal monkeys. However, whereas normal monkeys showed strong transitivity on indirect associations, monkeys with entorhinal lesions did not. Also, normal monkeys and monkeys with entorhinal lesions learned a series of overlapping discrimination problems as rapidly as the controls. Normal monkeys also showed robust transitive inference on probe trials, but the monkeys with entorhinal lesions performed no better than chance.

Complementary evidence on the role of the hippocampus in the networking of memories comes from two recent studies indicating that the hippocampus is selectively activated when humans make inferential memory judgments. In one study, subjects initially learned to associate each of two faces with a house and, separately, learned to associate pairs of faces (Preston et al., 2004). Then, during brain scanning, the subjects were tested on their ability to judge whether two faces that were each associated with the same house were therefore indirectly associated with each other and on whether they could remember trained face pairs. The hippocampus was selectively activated during the performance of the inferential judgment about indirectly related faces as compared to during memory for trained face-house or face-face pairings. In the other study, subjects learned a series of choice judgments between pairs of visual patterns that contained overlapping elements, just as in the studies on rats and monkeys, and as a control they also learned a set of nonoverlapping choice judgments (Heckers et al., 2004). The hippocampus was selectively activated during transitive judgments as compared to novel nontransitive judgments. Under some circumstances, it may be possible to indirectly relate items without a relational network (O'Reilly and Rudy, 2001; Van Elzakker et al., 2003), but the above described results provide compelling evidence of hippocampal involvement across species in the flexible expression of memories using relational networks.

Combined, these findings suggest that, whereas the cerebral cortex can mediate that acquisition of complex stimulus conjunctions that compose semantic knowledge, the hippocampus performs an additional type of processing that contributes to the networking of cortical memories. The results on the transitive inference paradigm indicate that the hippocampus plays a critical role in linking related memories according to their common features, and this linkage results in a network that can support inferences between items in memory that are only indirectly related. Such performance suggests how a general networking of memories can underlie the flexibility of declarative memory expression.

Observations on the Firing Patterns of Hippocampal Neurons

Additional evidence on the nature of information processing by the hippocampus is provided by characterizations of the firing patterns of hippocampal neurons in animals and humans performing memory tasks. Observations from rats, monkeys, and humans and across many different behavioral protocols show that hippocampal neuronal activity reflects each of the three fundamental features of declarative memory discussed above: the combinations of event features, the sequencing of events in specific experiences, and the representation of common features of events that could link distinct memories.

Associative Representations

A large body of evidence shows that hippocampal neurons encode an animal's location within its environment (Muller et al., 1999; Best et al., 2001). In addition, however, many studies have shown that hippocampal neurons fire associated with the ongoing behavior and the context of events as well as the animal's location (Eichenbaum et al., 1999). The combination of spatial and nonspatial features of events captured by hippocampal neuronal activity is consistent with the view that the hippocampus encodes many features of events and the places where they occur.

Two recent studies highlight the associative coding of events and places by hippocampal neurons. In one study, rats were trained on an auditory fear conditioning task (Moita et al., 2003). Prior to fear conditioning, few hippocampal cells were activated by an auditory stimulus. Following pairings of tone presentations and shocks, many cells fired briskly to the tone when the animal was in a particular place where the cell fired above baseline. Another recent study examined the firing properties of hippocampal neurons in monkeys performing a task where they rapidly learned new scene-location associations (Wirth et al., 2003). Just as the monkeys acquired a new response to a location in the scene, neurons in the hippocampus changed their firing patterns to become selective to particular scenes. These scene-location associations persist even long after learning is completed (Yanike et al., 2004).

Wood et al. (1999) directly compared spatial and nonspatial coding by hippocampal neurons by training animals to perform the same memory judgments at many

locations in the environment. Rats performed a task in which they had to recognize any of nine olfactory cues was placed in any of nine locations. Because the location of the discriminative stimuli was varied systematically, cellular activity related to the stimuli and behavior could be dissociated from that related to the animal's location. A large subset of hippocampal neurons fired only associated with a particular combination of the odor, the place where it was sampled, and the match/nonmatch status of the odor. Similarly, Ekstrom et al. (2003) recorded the activity of hippocampal neurons in human subjects as they played a taxi driver game, searching for passengers picked up and dropped off at various locations in a virtual-reality town. Many of these cells fired selectively associated with specific combinations of a place and the view of a particular scene or a particular goal. Hippocampal cells that represent specific salient objects in the context of a particular environment have also been observed in studies of rats engaged in foraging (Gothard et al., 1996; Rivard et al., 2004) and escape behavior (Hollup et al., 2001) in open fields. Thus, in rats, monkey, and humans, a prevalent property of hippocampal firing patterns involves the representation of unique associations of stimuli, their significance, specific behaviors, and the places where these events occur.

Sequences of Events

Another common observation across species and many different behavioral protocols is that different hippocampal neurons become activated during virtually every moment of task performance, including during simple behaviors such as foraging for food (e.g., Muller et al., 1987) as well as learning-related behaviors directed at relevant stimuli that have to be remembered (e.g., Hampson et al., 1993). This general pattern is also observed in a broad range of learning protocols, from studies that involve classical conditioning, discrimination learning, and nonmatching or matching to sample tasks to tests and a variety of maze tasks (for review, see Eichenbaum et al., 1999). In each of these paradigms, animals are repeatedly presented with specific stimuli and reinforcers, and they execute appropriate cognitive judgments and conditioned behaviors. Corresponding to each of these regular events, many hippocampal cells show time-locked activations associated with each sequential event. Also, as described above, many of these cells show striking specificities corresponding to particular combinations of stimuli, behaviors, and the spatial location of the event. Thus, within the overall network, cellular activity can be characterized as a sequence of firings representing the step-by-step events in each behavioral episode.

Furthermore, these sequential codings can be envisioned to represent a series of events and their places that compose a meaningful episode, and the information contained in these representations both distinguishes and links related episodes. Recent studies on the spatial firing patterns of hippocampal neurons provide compelling data consistent with this characterization. In one study, rats were trained on the classic spatial alternation task in a modified T maze (Wood et al., 2000; see also Frank et al., 2000). Performance on this task requires that the animal distinguish left turn and right turn episodes and that it remember the immediately preceding episode to guide the choice on the current trial, and in that way, the task is similar in demands to those of episodic memory. If hippocampal neurons encode each sequential behavioral event and its locus within one type of episode, then most cells should fire only when the rat is performing within either the left turn or the right turn type of episode. This should be particularly evident when the rat is on the "stem" of the maze, when the rat traverses the same locations on both types of trials. Indeed, virtually all cells that fired when the rat was on the maze stem fired differentially on left turn versus right turn trials. The majority of cells showed strong selectivity, some firing at over ten times the rate on one trial type, suggesting they were part of the representations of only one type of episode. Other cells fired substantially on both trial types, potentially providing a link between left turn and right turn representations by the common places traversed on both trial types.

Recently, Ferbinteanu and Shapiro (2003) also reported that many hippocampal neurons fire associated with serial locations occupied as rats traverse different routes within the same environment. Furthermore, they modified the task to distinguish whether the activity of these cells reflected the immediate past experience of the animal (retrospective coding) or predicted its future path (prospective coding). They found that these cells encode both past events and future goals of each route, with some cells encoding both kinds of information on the same trials. Furthermore, retrospective and prospective coding diminished on error trials, and some cells fired associated with the intention to proceed to a particular location even when a detour was required. These findings indicate that the overall hippocampal representations are neither retrospective or prospective per se and do not necessarily capture the precise details of behaviors or places that distinguish qualitatively similar episodes. Rather, the hippocampal network encodes routes through space as a meaningful sequence of events that characterize a particular spatially extended experience. Additionally, the processing of previous spatial experiences as the sequential activation of places may continue offline for a substantial period (Louie and Wilson, 2001; Lee and Wilson, 2002; Nadasdy et al., 1999).

Relational Networks

In virtually all of the studies described above, some hippocampal neurons encode features that are common among different experiences—these representations could provide links between distinct memories. In Moita et al. (2003) study of auditory fear conditioning, whereas some cells only fired to a tone when the animal was in a particular place, others fired associated with the tone wherever it was presented across trials. In the Wood et al. (1999) study on odor recognition memory, whereas some cells showed striking associative coding of odors, their match/nonmatch status, and places, other cells fired associated with one of those features across different trials. Some cells fired during a particular phase of the approach toward any stimulus cup. Others fired differentially as the rat sampled a particular odor, regardless of its location or match/nonmatch status. Other cells fired only when the rat sampled the odor at a particular place, regardless of the odor or its status. Yet other cells fired differentially associated with the match and

nonmatch status of the odor, regardless of the odor or where it was sampled. Similarly, in the Ekstrom et al. (2003) study on humans performing a virtual navigation task, whereas some hippocampal neurons fired associated with combinations of views, goals, and places, other cells fired when subjects viewed particular scenes, occupied particular locations, or had particular goals in finding passengers or locations for drop off. Also, in the Rivard et al. (2004) study of rats exploring objects in open fields, whereas some cells fired selectively associated with an object in one environment, others fired associated with the same object across environments.

The notion that these cells might reflect the linking of important features across experiences and the abstraction of common (semantic) information was highlighted in recent studies on monkeys and humans. Hampson et al. (2004) trained monkeys on matching-to-sample problems, then probed the nature of the representation of stimuli by recording from hippocampal cells when the animals were shown novel stimuli that shared features with the trained cues. They found many hippocampal neurons that encoded meaningful categories of stimulus features and appeared to employ these representations to recognize the same features across many situations. Kreiman et al. (2000a) characterized hippocampal firing patterns in humans during presentations of a variety of visual stimuli. They reported a substantial number of hippocampal neurons that fired when the subject viewed specific categories of material, e.g., faces, famous people, animals, scenes, houses, across many exemplars of each. A subsequent study showed that these neurons were activated when a subject simply imagined its optimal stimulus, supporting a role for hippocampal networks in the recollection of specific memories (Kreiman et al., 2000b). This combination of findings across species provides compelling evidence for the notion that some hippocampal cells represent common features among the various episodes that could serve to link memories obtained in separate experiences.

These observations are consistent with the notion that hippocampal neuronal representations are organized to represent behavioral sequences across a broad range of behavioral protocols and species. A subset of hippocampal neurons is selectively activated at every moment throughout task performance across a broad range of behavioral protocols. Furthermore, the contents of hippocampal neuronal representations can be characterized as each and every regularity of the events that is salient during the performance of any task. The full scope of information encoded by the hippocampal population is precisely as broad as the set of attended and regular events that compose the behavioral protocol. Hippocampal population activity can thus be viewed as a continuous and automatic recording of attended experiences (Morris and Frey, 1997) encoded as sequences of events that define both rare experiences and common stimuli, places, and events that are shared across episodes (Eichenbaum et al., 1999).

Conclusions

The findings reviewed here combine aspects of many current ideas about hippocampal information processing, providing substantial preliminary support for the framework outlined at the outset of this review. The hippocampus is envisioned as critically involved in the rapid encoding of events as associations among stimulus elements and context, in the encoding of episodes as sequences of events, and in linking episodes by common features into relational networks that support flexible inferential memory expression. The details of memory representations are likely contained within widespread areas of the cortex, such that the properties of declarative memory described here involve a combination of hippocampal and cortical processing. Furthermore, repeated activation of the hippocampal-cortical network during rehearsal, recall, and new related experiences, as well as during offline periods, could provide the basis for a prolonged period of organization and consolidation of memories within the cerebral cortex (Buzsaki, 1996; Eichenbaum, 2000; Lee and Wilson, 2002).

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