What H.M. Taught Us

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Abstract

■ Studies on H.M. generated five main findings: that memory is a distinct psychological function, that amnesia spares short-term and working memory, that amnesia is an impairment of declarative and episodic memory, that the hippocampus is a core brain structure supporting memory, and that the hippocampus supports the permanent consolidation of memories. Each of these basic findings has recently been challenged, but a consideration of these studies suggests the new observations serve to support the original findings on H.M. and improve our understanding of the memory functions of the hippocampal system. ■

The discoveries generated in studies on H.M. by Suzanne Corkin, Brenda Milner, and their many students and colleagues launched a new era of research on memory. Prior to H.M., memory was not localized in the brain and the function of the hippocampus was generically just a part of the "limbic" emotional circuit. The studies on H.M. changed all that. We now know that memory is a distinct neuropsychological function, that the hippocampus is central to that function, and much more. This commentary is a reflection on those findings and on where they have led us today. I will argue that the key observations on H.M. began to answer the most fundamental questions about memory and gave us direction toward a full understanding of how memory works.

Here I will outline five main findings about memory discovered through the studies on H.M. I will argue that each finding offered an insight and, at the same time, raised a key question, and I will suggest that current research is addressing those questions. I will not attempt to be comprehensive in my coverage of the relevant literature, but instead I will be selective in summarizing research highlights that are answering those questions. I will cite the large literature on memory sparingly—readers interested in the details and further studies on each issue are referred to relevant reviews and books (Corkin, 1984, 2002; Eichenbaum & Cohen, 2001; O'Keefe & Nadel, 1978). My hope is that this missive will serve to sum up where we are and point to what we still need to understand about hippocampus and memory and, in doing so, do justice to some of the major contributions of Suzanne Corkin toward this enterprise.

FINDING 1. MEMORY IS A DISTINCT PSYCHOLOGICAL FUNCTION

Before H.M., it was thought that memory was not localized to any particular part of the brain. Instead, a large literature on the effects of damage to specific areas of the cerebral cortex indicated that each brain area was responsible for a particular modality of information processing (verbal, visual, auditory, etc.) and, in doing so, supported memories for that type of material. Memory, specifically, could not be localized. Back in the early 1950s, there was a quote from Karl Lashley, whose studies famously failed to identify any particular cerebral area or pathway critical to memory. He concluded, "I sometimes feel, in reviewing the evidence on the localization of the memory trace, that the necessary conclusion is that learning just is not possible. It is difficult to conceive of a mechanism which can satisfy the conditions set for it. Nevertheless, in spite of such evidence against it, learning does sometimes occur" (Lashley, 1950, pp. 477–478).

In direct contrast to those views at the time, H.M.'s memory impairment was "global" in that the deficit extended to all modalities, verbal and nonverbal, visual and auditory (summarized in Corkin, 1984). He performed very poorly in standard neuropsychological tests of memory and had virtually no memory for everyday events. This severe deficit stood in striking contrast to H.M.'s intact abilities in other psychological faculties as commonly tested, including perceptual and cognitive capacities measured in numerous neuropsychological tests. This observation was highlighted by a rise in his postoperative IQ. The dissociation between intact perception and cognition and impaired memory is one of the most compelling aspects of the findings on H.M.

Are perception and cognition intact in amnesia? Some studies have suggested that perceptual processing of complex objects that ambiguously include some of the same features may be affected in amnesic patients (Graham et al., 2006). In these experiments, amnesic subjects are impaired in detecting an "odd" object among an array of identical objects that differ in a single feature and in several other tasks that require discrimination of stimuli that contain overlapping features. Most impressive is evidence that amnesic patients are impaired in discriminating virtual

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reality scenes composed of slight changes in the contents of the scenes. These findings led to the proposal that the hippocampal region may be involved in higher-order processing of perceptual configurations. This proposal is controversial (Suzuki, 2009), and a full consensus seems unlikely. It is notable that amnesic patients perform well in discriminating faces, so the deficit in perceptual discrimination is not generalized to all complex stimuli. Instead, the deficit is highly selective to stimuli that contain overlapping elements. While surely the impairment is an exception to memory loss per se, it remains poorly understood what perceptual or cognitive processing is impaired. One possibility is that disambiguation of stimulus elements in complex and overlapping patterns reflects an on-line information processing function of the same brain region that supports memory.

Consistent with this view, a related finding is that amnesic patients are abnormal in their exploration strategies for stimulus arrays (Voss, Warren, et al., 2011). Thus, when normal patients scan arrays in which multiple stimuli can be examined only individually, they frequently look back at previous stimuli and this "spontaneous revisitation" engages the hippocampus. Amnesics are deficient in spontaneous revisitation, even though the demand for memory of these stimuli is within the range of working memory that is typically intact in amnesic individuals. Furthermore, whereas normal patients benefit in subsequent memory for stimulus arrays by volitional control of their scanning, amnesic patients do not (Voss, Gonsalves, Federmeier, Tranel, & Cohen, 2011). Thus, abnormality in on-line exploration of the elements of a complex stimulus array could underlie a deficit in memory.

Another line of evidence that challenges the claim that cognition is intact in amnesia involved the observation that the ability to imagine future scenarios is impaired in amnesia (Hassabis, Kumaran, Vann, & Maguire, 2007; Schacter, Addis, & Buckner, 2007). Such a finding seems at odds with the general view that cognition is not impaired in amnesia. In these studies, participants were asked to construct new imagined experiences based on brief cues about the nature of those experiences. Whereas normal individuals could easily create rich scenarios for everyday events, amnesic individuals could not. Thus, for example, when asked to imagine lying on a white sandy beach on a beautiful day, normal participants imagined an elaborate arrangement of objects on the beach, a boat moving by, and personal feelings of the sun and sand. By contrast, an amnesic patient could only see blue sky and white sand without an elaborate array of objects or events contained in the scene. Schacter and colleagues (2007) have argued that the deficit in imaging the future may reflect impairment in creatively interrelating memory fragments from the past to compose a novel future event.

In a review of memory systems, Neal Cohen and I struggled with a dilemma in our efforts toward a unifying characterization of the distinctions between brain systems that support different forms of memory (Eichenbaum & Cohen, 2001). We argued that each brain system has a distinct information processing function and that memory supported by each system reflects the plasticity of that information processing function. This characterization of brain and memory systems was straightforward for habit, emotion, and perceptual systems, but not for the hippocampal system damaged in H.M., where there is no clear nonmemory information processing function! Thus, we wondered, there must be an information processing function supported by the hippocampus that is somehow inherently so tied to everyday memory that the nature of its function cannot be distinguished from memory per se. In my view, these recent studies are beginning to clarify the nature of information processing by the hippocampus that begins during the acquisition of new memories. As will be discussed in greater detail below, the studies introduced above have a common thread suggesting that hippocampal information processing involves relating elements of an experience to one another within the context of composing memories of the whole experience.

FINDING 2. AMNESIA SPARES SHORT-TERM AND WORKING MEMORY

Another major observation on H.M. was that neuropsychological assessments showed fully intact memory for a normal amount of material over a brief period, typically until he was distracted by intervening mental activities (Corkin, 1984). Thus, H.M. could repeat a phone number and had a normal digit span. He could carry on a conversation as long as the discourse did not require reference to an event that had been left behind earlier in the conversation. Nevertheless, recent studies have called into question whether the hippocampus is engaged during short-term or working memory. Now several studies that require participants to retain novel information across brief delays strongly engages the hippocampus and hippocampal activation contributes to subsequent memory performance (Ben-Yakov & Dudai, 2011; Schon, Hasselmo, LoPresti, Tricarico, & Stern, 2004; Ranganath & D'Esposito, 2001). These observations seem to directly contradict the many reports of intact short-term and working memory in amnesia.

In reconciling the new findings with the observations on H.M., it is important to consider a major distinction between the interpretations of studies on amnesia and those on functional imaging. The observation of intact short-term and working memory in amnesia allows us to conclude that other brain areas and systems can support performance in short-term and working memory tasks; they do not inform us about whether the hippocampus is normally engaged. The studies using brain imaging in normal individuals tell us, in complementary fashion, that the hippocampus is engaged during short-term and working memory, but they do not tell us whether that activity was necessary for performance. The combination of these lines of evidence indicates that the hippocampus is actively

processing information immediately after acquiring new material and that processing normally contributes to memory, even if compensatory systems can support performance in the absence of hippocampal function. Importantly, there is considerable evidence that the role of the hippocampus briefly after learning can be extended backward to events before short-term and working memory. Pioneering studies by Brewer, Zhao, Desmond, Glover, and Gabrieli (1998) and Wagner et al. (1998) showed that hippocampal activation even during the acquisition of new information predicts subsequent memory. Thus, one major implication of the "subsequent memory effect" is that the hippocampus begins information processing of value to memory during the learning experience itself.

Furthermore, studies by Hannula, Tranel, and Cohen (2006) have shown that the impairments in memory for objects that have been manipulated in scenes and memory for pairings of faces and scenes can be detected at short delays and an additional study, using an analysis of eye movement patterns to measure memory for face–scene associations, revealed an impairment in amnesic subjects within 500–750 msec. A similar impairment appeared within seconds in a test of memory for object–location relations.

It is also notable that animal studies have consistently shown that hippocampal neurons are activated on-line as animals investigate their environment and highly specific spatial firing patterns of these neurons develop rapidly (Eichenbaum, 2004). In addition, as animals learn new object associations, hippocampal neurons develop robust representations that reflect these associations in parallel with learning and predictive of performance (Komorowski, Manns, & Eichenbaum, 2009). In animals performing tests of memory for once presented lists of objects, hippocampal neural populations active during the study of the lists carry information about temporal organization, and these representations predict performance (Manns, Howard, & Eichenbaum, 2007). In humans, temporal patterns of hippocampal neural activity that are observed during encoding events also replay during subsequent memory retrieval (Gelbard-Sagiv, Mukamel, Harel, Malach, & Fried, 2008). Taken together with the above-described observations on amnesia, the findings on neural activity during learning suggest that it is naive to think that the hippocampus is not normally involved until after short-term and working memory has ended. Rather, hippocampal memory processing that contributes to subsequent memories begins during the experiences that will become memories and its involvement persists for some time.

FINDING 3. AMNESIA IS AN IMPAIRMENT OF DECLARATIVE AND EPISODIC MEMORY

The early investigations on H.M. by Suzanne Corkin (1965, 1968) and Brenda Milner (1962) revealed an exception to his otherwise severe memory impairment, specifically intact learning of motor skills, and this was followed by discoveries of other exceptions to amnesia including intact perceptual learning, priming, and cognitive skills (Corkin, 1984, 2002). It has become clear that amnesia associated with hippocampal region damage is selective to declarative memory, the ability to recall facts and events (Cohen & Squire, 1980), and for H.M. the deficit includes the complete absence of episodic memory, defined as the ability to remember specific personal experiences (Steinvorth, Levine, & Corkin, 2005). By contrast, other brain structures and systems support different types of memory performance, including perceptual learning and memory and the acquisition of skills and emotional memories (reviewed in Eichenbaum & Cohen, 2001).

A central issue in defining declarative and episodic memory is how to characterize the kind of memory lost in H.M. Some argue that declarative/episodic memory is fundamentally defined as explicit and conscious recollection of prior events, and indeed conscious awareness is a common feature of the memories observed in normal individuals that is lost in amnesia (Clark & Squire, 1998). Although amnesia is most often observed in tests that require an explicit form of memory expression, such as verbal or gestural responses indicating awareness of the memory, there are now important observations of impairment even for memory that is implicit and for which normal subjects are not consciously aware. A particularly striking example is where eye movement patterns were used to measure memory (Ryan, Althoff, Whitlow, & Cohen, 2000). In this experiment, individuals studied scenes, then were shown the same scenes with an object added, removed, or moved in the scene. Normal participants' eye movement patterns reflected memory in disproportional viewing of the altered parts of the scenes. Notably, the disproportionate viewing effect was observed only in the absence of awareness of the change, even though it was precisely this effect that was eliminated in amnesic subjects. These observations provide compelling evidence that conscious awareness is not a requisite feature of declarative and episodic memory supported by the hippocampal region.

These and other findings have led Neal Cohen and I to suggest that the core deficit in amnesia is a loss of the ability to relate distinct elements of memories, and distinct memories, to one another—we called this *relational representation*—and consequently the ability to use the acquired memories inferentially in novel situations—we called this *relational flexibility* (Cohen & Eichenbaum, 1993; Eichenbaum, Cohen, Otto, & Wible, 1992). If declarative memory involves encoding of relations among events, then amnesia would be expected to result in deficits in encoding as well as short-term maintenance and working memory for relations among percepts, as observed in the studies on perception of complex scenes and short-term memory for distinct percepts that must be related. Furthermore, to the extent that imagining future scenarios typically involves recall and novel rearrangement of remembered events and their relations

from previous experiences, this ability should be affected in amnesia, as observed. Also, if conscious awareness of the memories is an emergent phenomenon that accompanies but does not drive relational processing, then it should be possible to observe relational memory deficits in amnesia even in situations where memories do not reach consciousness. These observations improve our understanding of amnesia as a relational processing deficit that begins at the outset of encoding, plays an important role in the organization of short-term as well as long-term storage, reflects the inherent relational organization of memories even without conscious awareness, and can be called upon in cognitive functions such as imagining future events.

FINDING 4. THE HIPPOCAMPUS IS A CORE BRAIN STRUCTURE SUPPORTING MEMORY

H.M.'s surgery removed approximately two thirds of the hippocampus plus substantial parts of the perirhinal and entorhinal cortex (Corkin, Amaral, González, Johnson, & Hyman, 1997). A key assumption in much of the early work on H.M. assumed that damage to the hippocampus was central to the disorder. Subsequent case studies that involve damage isolated to the hippocampus have confirmed the observation of amnesia following damage limited to the hippocampus (Bartsch et al., 2010; Zola-Morgan, Squire, & Amaral, 1986), but the memory deficit is less severe. Early studies on animals replicated the finding of severe deficits in object recognition memory following large medial temporal lobe lesions including the hippocampus and surrounding cortical areas (Mishkin, 1978). However, later studies revealed that the deficit following damage selective hippocampal lesions was modest (Zola et al., 2000) or not observed (Murray & Mishkin, 1998) in one version of object recognition memory but severe in a different version of a formally identical task. By contrast, damage to the perirhinal cortex resulted in severe recognition memory deficits in multiple versions of the task (Nemanic, Alvarado, & Bachevalier, 2004). These findings are consistent with the view that the hippocampus and the surrounding cortical areas interconnected with the hippocampus support distinct roles in memory (Eichenbaum, Yonelinas, & Ranganath, 2007; Eichenbaum, Otto, & Cohen, 1994).

Considerable subsequent research on humans with selective damage in the medial temporal area, using functional imaging in normal human subjects, and studies on animals with selective damage to medial temporal areas, as well as single neuron recording studies, have largely converged on the view that the hippocampus makes a unique contribution to memory and that other surrounding cortical areas make distinct contributions (Eichenbaum et al., 2007). Considerable anatomical, physiological, and behavioral evidence indicates that the functional organization of the medial temporal lobe involves a convergence of the classic "what" (dorsal) and "where" (ventral) cortical streams onto distinct medial temporal cortical areas, and information about objects and events (what) and their spatial-temporal context (where) converge within the hippocampus. Thus, the perirhinal cortex and lateral entorhinal cortex represent important objects, people, actions, and other specific events can hold these representations in for substantial periods of time and can support a sense of familiarity of those events. In contrast, the parahippocampal cortex and medial entorhinal cortex represent the spatial environment in which important events occur and may also represent the temporal context in which events occur. Subsequently, the hippocampus integrates the "what" and "where" information into composite events, sequences event codes into representations of temporally extended experiences, and then compares and relates these individual event and episode representations to other memory representations, creating or modifying the overall memory organization according to the relevant relations between new memories and the structure of any already established memory organization that involves those items. Processing of this information by the full circuit including the hippocampus supports the experience in recollection of events, their associates, and the context in which they occurred. The combination of these processing functions comprises the basis of declarative memory.

This view of the functional organization of the medial temporal lobe has been disputed, suggesting instead that all components of the medial temporal lobe contribute to both familiarity for object and events and for recollection of associated context albeit their activity differentially reflects the strength of memories (Squire, Wixted, & Clark, 2007). However, there are now multiple double dissociations of the roles of the areas within the medial temporal lobe that support the functional organization described above and are inconsistent with a common function of all medial temporal areas. For example, Guillen Fernandez and colleagues (Qin et al., 2009) scanned individuals as they learned a large number of associations between objects, then subsequently tested their memory for the objects and associations. In addition, participants rated the strength of their memories for the items and associations, allowing the investigators to equate the strength of memory of items and associations in their analysis of the data. The main findings were that memory for items was predicted by activation of the perirhinal cortex whereas memory for the associations was predicted by activation in the hippocampus. Therefore, even when memory strength is taken into account, the perirhinal cortex is specialized for processing memories of single items whereas the hippocampus is specialized for processing item associations. In another study, Davachi, Mitchell, and Wagner (2003) explored activation of medial temporal areas in humans during the study of objects and the general context in which they were imagined to occur as predicting subsequent memory. Participants initially studied pictures of objects and an adjective and imagined a spatial scene in

which the adjective applied. For example, while viewing a teddy bear and the word "dirty," they might imagine the teddy bear in a garbage dump. Later participants were shown the objects and asked whether they recognized them from the study period, and if so, whether they could recall the scene in which they were imagined. Activation of the perirhinal cortex predicted whether individuals correctly remembered seeing the objects, but not the scene. Conversely, activation of the hippocampus and parahippocampal cortex predicted subsequent success in remembering the scene but not in remembering the object. These studies and many others (see Eichenbaum et al., 2007) provide compelling evidence in humans of a direct dissociation of memory processing functions in the hippocampal region. The perirhinal cortex is activated during memory processing of objects whereas the parahippocampal cortex is activated during the processing of contextual information, and the hippocampus is activated during the processing of associations, consistent with the functional organization introduced above.

Recently, studies in animals have also dissociated the roles of medial temporal areas in the contributions to recollection and familiarity (Eichenbaum, Fortin, Sauvage, Robitsek, & Farovik, 2009; Fortin, Wright, & Eichenbaum, 2004). These studies employed a variant of receiver operating characteristics (ROC) analysis of recognition memory that distinguishes recollection and familiarity components of recognition. Although this distinction is also contested (Squire et al., 2007), the studies on rodents have doubly dissociated recollection and familiarity components of the ROC function in intact animals. Moreover, damage isolated to the hippocampus eliminated the recollection component of the ROC sparing familiarity, whereas damage that removed amygdala inputs to perirhinal cortex selectively reduced familiarity while sparing recollection (Farovik, Place, Miller, & Eichenbaum, 2011). These findings cannot be explained by differential contributions of specific medial temporal areas to the strength of memory but are entirely consistent with the view that convergent information about events and their context converge on the hippocampus in support of recollective memory.

FINDING 5. THE HIPPOCAMPUS SUPPORTS THE PERMANENT CONSOLIDATION OF MEMORIES

The early findings on amnesia in H.M. were characterized as a severe and selective impairment in "recent memory" in the face of spared memory for knowledge obtained remotely prior to the surgery, and formal tests on H.M.'s memory for public and personal events showed that his retrograde amnesia extends back at least 11 years (Corkin, 1984). More recent studies of patients with damage limited to the hippocampal region also report temporally graded retrograde amnesia for factual knowledge and news events over a period extending up to 10 years (Bayley, Hopkins, & Squire, 2006; Manns, Hopkins, Reed, Kitchener, & Squire, 2003). There remains debate about whether there is a temporal gradient for retrograde amnesia after hippocampal damage for all categories of memory. However, it is consensual that damage restricted to the hippocampal region results in temporally retrograde graded amnesia for semantic information.

A major limitation on studies of retrograde amnesia in humans is that there is no control over the extent of exposure to events during acquisition as well as no control over how often the memories for those events are re-experienced or remembered. This problem has been addressed in several "prospective" studies on amnesia in animals, where hippocampal damage occurs at different time points after learning and temporally graded amnesia emerges across multiple species and memory tasks (reviewed in Milner, Squire, & Kandel, 1998). The evidence for temporally limited hippocampal involvement is compelling; however, this observation does not provide direct evidence on what brain areas support memory when the hippocampus is no longer necessary.

Insights about the relative engagement of other brain areas over the course of consolidation have come from recent experiments that have measured brain activation during memory retrieval at different times after learning in humans and animals. In humans, activation of the hippocampus during accurate memory retrieval in normal subjects was maximal for the most recent news stories and declined over approximately nine years, parallel with the course of retrograde amnesia (Smith & Squire, 2009). Conversely, activation of widespread cortical areas was lowest for the most recent accurately remembered events and increased for more remote memories (for a review, see McKensie & Eichenbaum, 2011). Recent "prospective" studies using functional imaging have identified greater activation of the hippocampus during recall of recently over remotely studied paired associations and the opposite temporal gradient in cortical areas. Furthermore, in the latter study, functional connectivity between the hippocampus and cortical areas decreased, whereas connectivity within the cortical network increased, over time following learning.

There is current debate about whether the hippocampus remains involved in episodic memory, whereas memories that become "semanticized" become independent of the hippocampus over time. The multiple trace theory proposes that memories are qualitatively transformed from episodic memories into semantic memories during the consolidation period (Nadel & Moscovitch, 1997). On this view, memories that are initially stored in cortical–hippocampal circuitry are episodic, defined as context-specific, and repeated "off-line" reactivations create multiple distinct traces from which the common information is extracted and integrated within pre-existing semantic networks in the cortex. Eventually the cortical representations that are common among memories, that is, semantic memories free of episodic/contextual detail, do not depend on the hippocampus, but retrieval of episodic

details continues to depend upon cortical–hippocampal connections. In support of this view are reports that amnesic patients show temporally ungraded retrograde impairment for episodic memories (e.g., Steinvorth et al., 2005). However, contrary to the view that episodic and contextual memories always depend on the hippocampus, there are also findings of spared remote autobiographical memories in patients with medial temporal lobe damage (reviewed in McKensie & Eichenbaum, 2011), and it is argued that flat retrograde gradients for episodic memory occur only following damage extending beyond the hippocampus into cortical areas (Reed & Squire, 1998).

However, functional imaging studies have consistently reported that the hippocampus is activated for both recently and remotely acquired episodic and autobiographical memories (reviewed in McKensie & Eichenbaum, 2011). These findings contrast with the above-described observations of declining hippocampal activation during retrieval of famous faces and names, news events, that is, semantic memories (e.g., Smith & Squire, 2009). A possible reconciliation of these observations is that the hippocampus is consistently engaged whenever detailed associative or contextual information is recalled. Notably, the hippocampus is also involved even when people imagine detailed events that have never occurred, as discussed above. Thus, observations of hippocampal activation during relational processing may fit the expectation that the hippocampus becomes engaged by cues that generate an extensive memory search, regardless of the age or even the existence of a memory.

Consistent with these findings, the hippocampus may support consolidation by integrating new episodic memories into our previously acquired schemas of world and personal knowledge (McKensie & Eichenbaum, 2011). In support of this model, Tse et al. (2007) demonstrated that rats develop a schema of locations where different foods are buried by showing that, once several food/location associations had been formed, new ones could be added within a single trial; however, in a different environment, the learning of new associations was much more gradual. Moreover, when new associations could be integrated within a pre-existing schema, hippocampal lesions after 3 hr, but not 48 hr, impaired subsequent performance, revealing a consolidation gradient considerably steeper than those reported in studies in which learning did not benefit from an existing schema. By examining the organization of related memories that is the foundation of schemas, Bunsey and Eichenbaum (1996) showed that normal rats link overlapping paired associates and make new inferences about indirectly related elements and that this capacity depends on the hippocampus. The same finding has been extended to schemas that involved a hierarchical organization of stimulus elements (Dusek & Eichenbaum, 1997) and the organization of choices in maze behavior (Mingaud et al., 2007).

Many other studies in humans, monkeys, and rats have shown that hippocampal neurons encode both distinct experiences and their common overlapping features, consistent with the existence of networks of related memories (for a review, see Eichenbaum, 2004). In addition, fMRI studies have shown that the hippocampus is engaged as related memories are integrated to support novel inferences in tasks similar to those dependent on the hippocampus in rats (Zeithamova & Preston, 2010; Zalesak & Heckers, 2009; Preston, Shrager, Dudukovic, & Gabrieli, 2004). These lines of evidence suggest that consolidation involves an interleaving of memories into our networks of knowledge, and the process of interleaving continues as long as additional memories can demand a restructuring of our schemas (McKensie & Eichenbaum, 2011).

CONCLUSIONS: WHAT ARE THE COGNITIVE AND NEURAL MECHANISMS OF HIPPOCAMPAL FUNCTION THAT SUPPORT DECLARATIVE/EPISODIC MEMORY?

The discoveries about H.M. and those that have followed this pioneering work have generated multiple hypotheses about the fundamental information processing function of the hippocampus (reviewed in Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001). Most prominent among these, perhaps, is the view that the hippocampus constructs cognitive maps that organize memory, reflected in the prominent role of the hippocampus in spatial memory in animals and suggested to provide a framework for memory in humans (O'Keefe & Nadel, 1978). However, recent evidence indicates that hippocampal circuitry and critical function is equally involved in temporal organization, indicating that a more general "relational," rather than specifically spatial, organization is fundamental (MacDonald, Lepage, Eden, & Eichenbaum, 2011; Fortin, Agster, & Eichenbaum, 2002; see Eichenbaum, Dudchencko, Wood, Shapiro, & Tanila, 1999).

What is the structure of relational representation? I have previously argued that hippocampus encodes three kinds of associations (Eichenbaum, 2004), including associations between objects and other perceptually and conceptually distinct objects, and the spatial-temporal context in which they occurred; sequential associations between events to represent the flow of experiences in whole episodes; and associations among events and episodes linked by their common features into networks of memories. The combination of these properties is embodied in the view that the hippocampus creates a "memory space," a framework of spatial, temporal, and perhaps other stable contextual dimensions in which associations and sequential relations between memories is contained (Eichenbaum et al., 1999). Thus, the relational hypothesis proposes that the hippocampus, first, creates a contextual scaffolding whose parameters involve the stable dimensions of space, time, and other features that characterize an organized schema in which events occurred. Second, distinct events are embedded within the schema at appropriate locations and moments. Third, as newer memories are acquired, they are interleaved into the schema, and this process

constitutes a never-ending evolution and consolidation of the memory space. Furthermore, at all times, the memory space can be scanned or "surfed" to identify associations between elements of memories and among memories, supporting the flexibility of relational representations.

WHAT HAS H.M. TAUGHT US?

Suzanne Corkin and her colleagues made pioneering contributions to our understanding of memory through her years of study on H.M. and other amnesic patients. The basic findings characterizing amnesia as a selective deficit in memory and identifying a key role for medial temporal areas have stood the test of time. In addition, we have come far in understanding the functional organization of the medial temporal memory system and the nature of cognitive processes supported by this system. The hippocampus, along with its intimately connected cortical areas, supports information processing that is defining of the type of memory supported in this system. The entire medial temporal system becomes engaged at the time of learning and begins to process new information organized as relations between events, their context, and sequential events that compose whole episodes. Furthermore, through interactions with cortical areas, these memories are interleaved with related memories to build and elaborate semantic knowledge within the memory space.

A full understanding of the mechanisms of relational processing remains a major goal. How do distinct anatomical components of the hippocampus work together in supporting relational processing? How does the hippocampus guides the retrieval and interleaving of memories stored in the cerebral cortex? The pioneering work of Suzanne Corkin has guided my own work and that of many others and continues to lead us toward a comprehensive understanding of how the brain makes memories.

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