Cognitive Critique

H.M. IN CONTEXT

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INTRODUCTION

Henry Gustav Molaison is arguably one of the most important figures in the history of neuroscience. He lived from 1926 to 2008, and for most of his life suffered from a severe anterograde amnesia, or inability to form new memories. He developed epilepsy in his teens, experiencing his first grand-mal seizure on his 16th birthday. Over time, Molaison's epileptic condition became so disabling and intractable that he and his family finally consented to an experimental treatment offered by William Beecher Scoville. The operation was conducted in 1953, when Molaison was 27. The operation was a medial temporal lobectomy, in which parts of the hippocampus and nearby brain structures were removed bilaterally. Molaison was the first and last non-schizophrenic patient in history to undergo this operation, since his resulting amnesia was immediately clear after the surgery. Postoperatively, he was able to carry out normal conversations and appeared normal to the casual observer, except for being extremely forgetful. Among other things, he did not know whether his hair was black or gray. Celebrated qualities of this subject were his great willingness to be studied and his desire to help others learn about his condition. He is most widely known by his initials, H.M.

This paper provides an overview of H.M.'s condition, with enough historical and conceptual context that the reader is able to appreciate why this subject was important, what he meant to psychology and neuroscience during his life, and what he continues to tell us about how the brain and mind work. One possible characterization of what is now known as the *medial temporal lobe memory system* will also be discussed.

OVERVIEW OF H.M.'S CONDITION

The primary reason H.M. has been important to the neuroscientific study of memory is that both his surgical lesions and his cognitive impairment were well circumscribed. When Scoville performed the surgery, he removed contiguous areas of H.M.'s medial temporal lobe (MTL), including the uncus, amygdala, and anterior portions of the hippocampal formation (Scoville and Milner 1957). The ablation was symmetrical bilaterally (Corkin et al. 1997), allowing for cleaner attribution of cognitive function to specific brain structures. As for cognitive function, the specific defect resulting from the surgery was a severe anterograde amnesia that was originally characterized as global in the sense that all modalities of memory were affected: verbal, visual, auditory, olfactory, etc. Nevertheless, this defect did not appear to have brought with it any intellectual deficits. H.M. still spoke and performed routine tasks normally, and his Verbal, Performance, and Full Scale IQ scores on the Wechsler-Bellevue scale actually rose postoperatively, perhaps due to reduced cognitive interference from epileptic activity (Milner et al. 1968). Researchers were therefore able to posit a direct connection between MTL structures and the ability to commit information to long-term memory, which was profoundly impaired after H.M.'s operation.

A major aspect of H.M.'s impact was not only that scientists could point to a correspondence between the MTL and normal memory function, but that they could now demonstrate that memory function of the kind impaired in H.M. could be localized. While brain areas lesioned in H.M. were clearly important for formation of long-term memories, they were apparently not the seat of the memory store itself. H.M.'s memory for events antedating his operation was largely spared. For example, he could recall incidents from his school years or jobs that he held in his late teens and early twenties (Milner et al. 1968). This pattern suggests that MTL damage impairs storage of new memories, not retrieval of old memories

(Marslen-Wilson and Teuber 1975). Moreover, evidence from other amnesic patients shows a double dissociation between anterograde and retrograde amnesia. A comparison between patients EP and KC (discussed below) reveals that EP performs better in remote autobiographical recollection, whereas KC performs better acquiring new information (Bayley and Squire 2002). However, this picture is complicated by the fact that MTL lesions often induce a recent retrograde amnesia. H.M. had memory loss for events in the two years prior to his operation, and objective tests showed some impairment in recall of events that occurred up to 11 years before his surgery (Corkin 1984; Corkin et al. 1983; Sagar et al. 1985). These recall deficits for immediate preoperative time periods are typically attributed to processes of memory consolidation, where memories are only gradually redistributed to the neocortex and become independent of the MTL (Squire 2009).

Another important distinction is between long-term and immediate recall memory. Although he was unable to reproduce information after an extended interval, H.M. was able to retain conversations and narratives in short-term memory, and he had a low-normal digit span. H.M.'s immediate retention was not determined by any fixed period of time; rather, continued retention depended on conditions affecting attention. He could remember a three-digit sequence or other information for as long as 15 minutes by continuous repetition. But when information could not be rehearsed, as in the case of faces or designs, it faded quickly, becoming irretrievable in less than a minute (Squire 2009). Retained information was also lost when H.M.'s attention was diverted or when his attention span was exceeded even by a single item (Corkin 1984; Drachman and Arbit 1966).Although short-term memory is dissociable from long-term memory, it is doubtful that one would find a brain module in charge of short-term memory. Instead, deficiencies in immediate recall such as those exhibited by patients with Alzheimer's disease and Korsakoff's syndrome are produced by widespread pathologic changes in the brain (Corkin 1984; Corkin 1982). While long-term memory encoding is accelerated by MTL structures, there is reason to think that immediate retention may be site-specific. Immediate retention may not even depend on synaptic plasticity, a point explored in more depth below.

ANATOMICAL CONSIDERATIONS

Initially, a correspondence between the hippocampus and memory function was implicated in Scoville and Milner's 1957 report of amnesia in several patients who had undergone MTL resections, in most cases to treat schizophrenia. The central thesis of this paper was that the posterior extent of the resection was positively related to the severity of the resulting memory impairment. Specifically, patients in which only the uncus and amygdala were removed exhibited no persistent memory deficit, whereas patients suffering damage to the hippocampus and hippocampal gyrus had impaired recall. The greatest memory deficits appeared in patients, such as H.M., with the most extensive hippocampal lesions.

Work in following decades provided a more nuanced picture of the brain areas involved in memory function. Scoville (1957) noted that all of his patients with bilateral hippocampal lesions exhibited considerable memory deficits, while a patient with an extensive unilateral resection in which the right inferior temporal lobe and hippocampus were removed showed only transient memory impairment. It has since been speculated that other patients with amnesia following unilateral MTL ablations, such as Penfield's patient PB, had preexisting lesions in the opposite hemisphere. Indeed, at autopsy, a histological examination of PB's brain confirmed that, along with surgical ablations of the anterior hippocampus and other MTL structures on the left, there was cell loss in the hippocampus and dentate gyrus due to epilepsy-associated hippocampal sclerosis in the right hemisphere (Corkin et al. 1997; Margerison and Corsellis 1966). PB's case also helped identify the key brain structures involved in the amnesic syndrome. While the 1957 report certainly implicated the hippocampus in memory functions, it was not clear whether the uncus and amygdala played a role, since they were removed in each of Scoville's MTL resections. But the bilateral component of PB's lesions was limited to the hippocampus and dentate gyrus.

The hippocampal formation consists of the hippocampus, dentate gyrus, subicular complex, and entorhinal cortex. The entorhinal cortex receives about 60% of its input from the perirhinal and parahippocampal cortices, which in turn receive input from sensory cortex. The entorhinal cortex sends projections to the intraventricular aspect of the hippocampal formation, consisting of the hippocampus, dentate gyrus, and subicular complex. Primate studies have indicated that all of these connected structures — but not the

amygdala — are implicated in recognition memory[1] (Corkin et al. 1997; Leonard et al. 1995; Zola-Morgan et al. 1989a, b, c; Suzuki et al. 1993). Damage to the mammillary bodies, which receive strong projections from the hippocampus, has also been connected with Korsakoff-type amnesia[2] (Scoville and Milner 1957; Gamper 1928).

Questions then arise as to how these various structures contribute to memory function. There is some support for the idea that damage to each of these structures impairs memory function by degree. That is, bilateral damage confined to the hippocampus and dentate gyrus, as with PB, results in considerable memory impairment, but not as severe as that seen with H.M., whose lesions also included anterior portions of the parahippocampal gyrus. Lesions extending to more posterior parts of the parahippocampal cortex produce an even more profound amnesic condition than H.M.'s, as observed in patient EP (Squire 2009). Another possibility is that the structures in the MTL have different functions, and that the more structures are damaged, the fewer the strategies available for conducting a task. For example, perhaps the hippocampus is responsible for conscious recollection of episodes whereas the perirhinal cortex handles familiarity judgments absent of episodic context (Corkin 2002; Brown and Aggleton 2001).

Connectivity is also an important factor in ascribing functions to various brain areas. Since the parahippocampal and perirhinal cortices, the entorhinal cortex, the intraventricular hippocampal formation, and the mammillary bodies are to some extent organized in a feed-forward chain, disruption at different points on that chain could result in similar functional defects. For example, although the posterior 2 cm (approximately 50%) of H.M.'s hippocampus was spared, it was atrophic and was most likely deafferented and, therefore, nonfunctional due to the total ablation of his entorhinal cortex (O'Kane et al. 2004; Corkin et al. 1997). Interestingly, cortical connections to the hippocampus appear to be more important to normal memory function than subcortical ones. Interruption of the descending fibers from the hippocampus by sectioning the fornix

[1] The studies cited here primarily made use of the delayed nonmatching-to-sample (DNMS) task to assess recognition memory performance in primates with lesions in brain areas of interest. Some studies also used other tasks including object retention, concurrent discrimination, and delayed response.

[2] Korsakoff's is a syndrome whose various symptoms include retrograde and anterograde amnesia. It is caused by a deficiency of thiamine (vitamin B1) in the brain and is often attributed to chronic alcohol abuse.

bilaterally produces at most a transient memory deficit (Scoville and Milner 1957). Conversely, although the fornix and mammillary bodies were spared in H.M., these were not sufficient to maintain normal memory function (Corkin et al. 1997).

EARLY PROGRESS OF OUR UNDERSTANDING OF ANTEROGRADE AMNESIA

H.M.'s mnemonic pathology was originally thought to encompass all aspects of long-term memory encoding, but an important challenge to this notion came with Milner's (1962) discovery that H.M. exhibited normal learning of mirror-tracing, a perceptual-motor task. H.M. traced a star pattern reflected in a mirror, a task which,

> "…requires subjects to inhibit and reverse powerful associations between vision and motor control of hand and arm movements." (Gabrieli et al. 1993)

H.M. showed improvement on this task over a period of three days, and normal retention over time. It soon became clear that amnesics could improve their performance on a range of motor tasks, such as rotary pursuit, where subjects are required to keep a stylus in contact with a target on a spinning disc (Corkin 1968). In the early years following these discoveries, motor learning was regarded as an exception to the global nature of MTL-associated amnesia.

An interesting point about such motor learning was that H.M. gained these skills without awareness of any previous exposure to the task, a phenomenon referred to as source amnesia (Schacter et al. 1984; Shimamura and Squire 1987). Amnesic subjects had no conscious recollection of the events in which they had learned the skills. This was an intriguing dissociation, and H.M.'s amnesic syndrome presented an opportunity to examine the boundaries of apparently different memory functions. In time a significant amount of anecdotal evidence for other forms of mnemonic sparing in amnesic patients was amassed. For example, in 1966 H.M. was able to draw the floor plan of a house that he had moved to postmorbidly and lived in for eight years (Corkin 2002). On different occasions he exhibited limited awareness of certain public events, such as the fact that Kennedy had been assassinated (O'Kane et al. 2004).

With additional information about impaired versus spared memory in anterograde amnesia came new categorical distinctions

among classes of memory. One influential proposal by Tulving (1972) made a distinction between episodic and semantic memory. Episodic memory records personal and autobiographical events, and semantic memory deals with general facts or ideas. Although there is considerable overlap between the two memory types, they are contrasted by their content and organization. Episodic memories detail the perceptible properties of the events they represent, whereas semantic memories operate on a more abstract basis. Perceptible attributes of events are important to semantic memory since they allow identification of semantic symbols or referents within the knowledge store. Also, since episodic memory records an ongoing sequence of physical events, its contents are organized in temporospatial relation to one another, whereas semantic memories are presumably organized in a more flexible, multidimensional system of relationships.

Although some researchers have pointed to a lack of evidence for the dissociability of episodic and semantic memory (Gabrieli et al. 1988), it is important to note that Tulving presented these categories as *orienting attitudes* or *pre-theoretic positions* akin to the distinction between sensory and perceptual processes. No one challenges the idea that sensation and perception are tightly intertwined domains, but,

> "…nevertheless, it frequently makes good sense to talk about laws and principles governing one set of phenomena independently of those applicable to the other." (Tulving 1972)

In other words, the episodic-semantic distinction may provide a descriptively useful set of labels without a demonstration of its psychological reality. Albeit on a severely impaired basis, H.M. and other amnesics have shown significant learning of semantic-type information, both in laboratory teaching experiments and upon examination of postmorbidly accumulated knowledge such as names of famous individuals (Gabrieli et al. 1988; Hayman and Macdonald 1993; Bayley and Squire 2002; O'Kane et al. 2004). Even in the face of these small semantic achievements, one is struck by the profundity of the episodic deficit that results from MTL damage. One study indicates that children with bilateral hippocampal pathology can undergo apparently normal language development and can accumulate in their knowledge store an impressive array of facts about word meanings, famous people, and other cultures in spite of episodic losses,

> "…so disabling that none of the patients can be left alone, much less lead lives commensurate with their age, circumstances, and aspirations." (Vargha-Khadem et al. 1997)

Another landmark development in the evolving categorization of memory functions was a reevaluation of motor and other types of skill learning. Cohen and Squire (1980) proposed a distinction between *declarative* and *procedural* forms of knowledge after conducting an experiment involving mirror-reading. Amnesic subjects' learning was comparable to that of normal controls on a task condition where subjects read novel (non-repeated) triads of words backwards in a mirror, whereas on a task condition in which word triads were repeated, normal controls showed greater improvement than amnesics. This showed that while amnesic subjects could engage in reverse remapping of the letters or writing, they were less effective than the controls at remembering specific words already seen. Since mirror-reading minimizes perceptual-motor involvement, it was cited along with several other skills such as numerical rule learning or eye-blink conditioning as examples of non-motor tasks governed by rules or procedures that were learnable by amnesics. Consequently, a procedural category of knowledge which encompassed both motor and non-motor skills was needed, to be contrasted with declarative or data-based knowledge.

MODALITY OR SOMETHING ELSE?

The declarative-procedural dichotomy in particular raises questions about whether the modality of the information, or something else, constitutes the dividing line between spared and impaired memory in anterograde amnesia. Declarative knowledge will often coincide with episodic, semantic, auditory or visual modalities while procedural knowledge will often coincide with motor or perceptual skills. There are striking counterexamples which show that modality is not the fundamental difference between the two categories. Patient EP suffers from a more extreme anterograde amnesia than H.M., a consequence of contracting viral encephalitis (Stefanacci et al. 2000), but was able to obtain enough information to produce the third word in a word triad (e.g., *TRAIN frightened KANGAROO*) when prompted with the first two, in an experiment by Bayley and Squire (2002).

EP's accomplishment is interesting because the semantic knowledge gained appeared to be non-declarative in nature, although semantic memory would ostensibly fit in the declarative category. There are several ways in which EP's knowledge of the word triads indicates non-declarative patterning. First, the knowledge was engrained through massive repetition: he was exposed to 48 training trials over a period of 12 weeks. More important, EP's recall and use of the knowledge differed from that of controls. Despite his ability to complete triads in a free recall condition with 18.8% accuracy, he expressed no awareness of giving the right answer, and assigned the same confidence ratings to right answers as to wrong answers. Similarly, when tested on the material in a binary forced-choice condition, EP's percentage of correct answers was measurably above chance. But unlike normal controls, who on average give correct responses more quickly than incorrect ones, EP's response times for right and wrong answers were identical. This suggests that EP lacked conscious control over his knowledge, a property inconsistent with the accepted view of declarative memory. Furthermore, EP's learned responses did not generalize as one would expect of declarative knowledge. After learning a triad such as *VENOM caused FEVER*, subjects were tested on the trained triad (*VENOM caused ???*) as well as a synonym-swapped triad (*VENOM induced ???*). Normal controls' performance on the synonym test diminished only slightly in comparison with the standard test, whereas EP's performance was abysmal when synonyms were introduced. The massive repetition needed for learning, the lack of conscious access to memory, and the rigidity of the knowledge were interpreted as evidence that the information, though semantic in nature, was acquired by non-declarative means.

Even within a modality, changes in how the information is presented can have an effect on whether an amnesic subject can learn the material. This is seen in a study involving patient KC, who developed anterograde and retrograde amnesia after a motorcycle accident (Hayman and Macdonald 1993). The stimulus used in this experiment consisted of creative definitions for 96 familiar target words, for example, *an underpaid textile worker — SILKWORM*. Aside from repetition, a major factor affecting KC's successful memorization was interference. Subjects exhibit *negative transfer* when, after having acquired an A-B association, an attempt is made to train an A-C association (Martin 1971). An important point of this study was to compare an error-free learning condition in which

subjects simply studied the definition-word associations with an error-prone condition where subjects read a definition, ventured a guess as to the associated word, and only then were shown the word along with the definition. The errors elicited by the second condition presumably would thwart the learning effort by introducing competing associations. The experiment showed that both pre-experimental interference in the form of pre-existing cue associations and intra-experimental interference in the form of error-prone learning methods additively attenuated performance. The difference was considerable, with a retention rate of 29% in the presence of both sources of interference, and 84% in the presence of neither.

The authors argued that most past studies had used error-prone methods to teach semantic material, which had probably sabotaged retention. For example, the widely cited results of a study conducted by Gabrieli et al. (1988) may not be a decisive indicator of amnesics' inability to learn new semantic information. In this study, subjects were shown a word along with the definitions of all eight words in the set, and had to choose from among them until all the definitions were eliminated. This method encourages a large number of errors (Hayman and Macdonald 1993), which may place erroneous associations in the way of correct ones. This consideration carries with it the suggestion that amnesics' past failures to acquire new semantic information might have less to do with the modality and more to do with how the information is presented or organized. In contrast, motor skills are typically trained through massive repetition of a sequence of actions, and not through repeated presentation of a choice among different potential actions.

TOWARD A DEEPER UNDERSTANDING

Studies of H.M. and of other patients with MTL damage have shed light on how memory functions are organized in the brain. But ideally we would like to gain knowledge of what exactly is going on in the hippocampus or nearby structures that makes them vital to the formation of long-term memories.

One idea is that since most types of information seem to be learnable in spite of MTL damage when one resorts to massive repetition, perhaps MTL structures somehow simulate or operate in lieu of repetition. For example, it could be that the hippocampus acts as a temporary information buffer that quickly stores memories and then replays them over time so as to train the representation in

neocortex. Indeed, there is evidence that hippocampal representations replay during sleep states (Kudrimoti et al. 1999; Nádasdy et al. 1999; Pavlides and Winson 1989; Skaggs and McNaughton 1996; Wilson and McNaughton 1994), although presently the evidence is inconclusive as to whether hippocampal replay affects neocortical representations (Redish 2001). Alternatively, it could be that the hippocampus is responsible for the disinhibition of neocortical nodes active in a representation, which should allow for long-term potentiation (LTP) processes to occur very quickly, whereas LTP would be stymied in a normal, inhibited state[3] (MacKay et al. 2007). Both of these ideas are essentially degree-oriented with the role posited for the hippocampus related to the speed or magnitude of information retention.

A problem remaining after these explanations have been invoked is that information stored with the benefit of MTL structures often possesses a different character than that stored through brute engrainment. Among the more striking examples of this was patient EP's lack of conscious access to trained semantic sequences, and the rigidity of the information. H.M. has shown similar rigidity in regard to newly acquired memories. When tested on his ability to memorize a path through a grid-like maze, he was able to succeed only when the maze was small enough that the potential wrong turns in the sequence did not exceed his immediate attention span. Through repetition he was able to learn a path in a small, truncated version of a larger maze. But when faced again with the larger maze, he was not able to retain any portion of the path through it, even though the larger path incorporated the smaller path H.M. had already memorized (Milner et al. 1968). Similarly, H.M. often showed patchy recall of postmorbidly acquired semantic knowledge. He sometimes recalled Kennedy as having been assassinated, and at other times he thought Kennedy was still alive (O'Kane et al. 2004).

It is difficult to attribute these failings to on-line performance defects, since the patients can reason about the material in apparently normal ways. During training EP frequently commented on the stimuli;

[3] Long-term potentiation (LTP) is a process in which the synaptic connection weight between two neurons grows stronger when they fire simultaneously. LTP is often thought of as the neural correlate of associative learning.

> "...when presented with the sentence *TRAIN frightened KANGAROO*, he regularly commented that he had visited Australia during his time in the Merchant Marines and that this kind of incident could indeed occur." (Bayley and Squire 2002).

The defect, therefore, apparently relates to how the information is represented in memory. Especially when one considers that different cues seem to elicit recall of different details in amnesics, it becomes plausible to think that MTL structures could play a role in organizing memories in the brain, beyond simply accelerating storage.

The necessary perspective on this issue could come from a surprising source. Although we have been entirely concerned so far with the role of MTL structures in amnesia, a debate has been raging for several decades about whether the hippocampus is involved in memory or spatial mapping (Eichenbaum 2000; Redish 2001). The *cognitive map* perspective was sparked by the discovery of place cells in 1971 (O'Keefe and Dostrovsky). In its simplest conception, a place cell is a neuron that fires every time an animal — typically a rat — goes near a particular place within an environment.

Two important ideas about place cells could make them relevant to the current discussion. First, place cells are not really place cells, or at least not exclusively. A growing body of research is uncovering properties of place cells that are inconsistent with a Cartesian-style representation of space. For one reason, the places coded by place cells are not uniformly distributed within a space, as one would expect of spatial mapping, but instead they congregate near salient cues within the environment. Also, place cells are not necessarily connected in a coherent topology that mirrors the space itself; instead, different place cells within a population appear to be tied to specific features of the environment. For example, in a double rotation task, where proximal cues in the environment are rotated 90 degrees one way, and distal cues are rotated 90 degrees the other way, different cells in a population will maintain their place-coding in relation to different sets of cues, such that two cells which coded the same place originally will code two different places after rotation (Shapiro and Eichenbaum 1999). Moreover, it has been found that place cells do not necessarily code places in the environment reliably, but rather what seem to be places within a larger task framework. In spontaneous alternation tasks, rats run a W-shaped maze and are trained to alternate left turns and right turns upon reaching

the end of the center track. In these experiments, a majority of cells coding places on the center track do so only for left turns or only for right, but not both (Eichenbaum 2000; Wood et al. 2000). This pattern is more consistent with the repeating temporo-spatial topology consequent to task design than it is with the physical space itself. Furthermore, hippocampal cells respond to a much greater range of stimuli than just places, including olfactory stimuli and even reward valence of odors (Wood et al. 2000). Considerations like these have prompted some researchers to view hippocampal cells as coding a *memory space* or episodic mapping domain and not merely a spatial map (Eichenbaum 2000; Wood et al. 1999).

Second, place cells are interesting both in their remapping properties and in their apparent functioning as a sort of world model or spatial map. When a rat is introduced to a new environment, cells within its hippocampus begin to code specific places. These places are *stable* in that when the rat returns to the environment after a period of absence, each cell codes the same place as it did before. However, when LTP is prevented by blocking NMDA receptors, place fields do not remain stable, but they do form. The key is that if NMDA receptor antagonists are applied and the rat is then placed in a new environment A, hippocampal cells will code place fields; when put in an intervening environment B and then re-introduced to environment A, cells code different place fields than the previous ones. This *forgetting* can occur during an intervening hiatus of as little as five minutes. But, importantly, cells that already code places in an environment before NMDA-antagonistic treatment continue to code those same places when the rat is again placed in that environment (Shapiro and Eichenbaum 1999; Austin et al. 1990). This shows that synaptic plasticity is needed for hippocampal cells to form stable place fields, but is not needed simply for the formation of place fields, or for the activation of existing, stable place fields.

Rats' performance on the radial maze exhibits what appear to be the effects of these hippocampal representations. Radial mazes are circular tracks with arms extending distally in different directions. Efficient retrieval of food rewards from the arms of the maze requires a mental representation of which arms have already been visited. Interestingly, after rats are allowed to learn the task and familiarize themselves with the radial maze, knocking out their NMDA receptors has no effect on their subsequent ability to effectively navigate the maze, despite the fact that working memory is required. However, if NMDA receptors are knocked out prior to

learning the radial maze environment, the rats' performance is drastically impaired compared with that of normal controls (Shapiro and Eichenbaum 1999; Shapiro and O'Connor 1992). This suggests that synaptic plasticity is required to build a representation of the space, but not to use working memory given an adequate representation.

Additional support for the view that spatial representations are built in the hippocampus comes from the finding that hippocampal lesions impair performance on the radial maze when rats are required to build a spatial representation of the environment and remember which arms consistently contain food (the PLACE task), but that the same lesions do not impair performance when placement of rewards was randomized among the arms on each trial but marked by textured floor inserts (the CUE task). These two tasks appeared to be of comparable difficulty for unlesioned rats. After lesions, rats regained criterion in the CUE task but not the PLACE task (Nadel and MacDonald 1980). This finding implicates the hippocampus in formation of spatial representations, and is further reinforced by a more recent finding that hippocampal cells appear to function as a cognitive map for *model-based* decision-making, whereas the dorsal striatum and ventral striatum appear to code *model-free* situation-action representations and action-outcome representations, respectively (Van der Meer et al. 2010).

A POSSIBLE SYNTHESIS

Taken together, the above two important findings about hippocampal cells suggest tantalizing correspondences with human learning as observed in anterograde amnesia. In the spatial domain, it appears that hippocampal cells form structured representations of the environment quickly, that these structured representations become stable on the basis of synaptic plasticity, and that working-memory use of these representations does not depend on synaptic plasticity. Additionally, since hippocampal cells encode a great deal more than just spatial layouts –a sort of integrated episodic memory map — it is possible that the phenomena observed in the spatial domain may extend to a much wider range of domains, especially in humans, who engage in a more sophisticated array of tasks and behaviors than do rats.

Phenomena observed in rat studies resemble those observed in MTL-associated amnesia. Specifically, since working memory used in a radial maze task functions in the absence of synaptic plasticity

suggests that immediate memory in amnesics may do the same, and would provide an explanation of why the information is lost when attention is diverted. A new activation pattern replaces the old one, and the old one can only be recalled if there exists a record of it in the form of synaptic connection weights. If the hippocampus or other MTL structures are important for rapid formation of structured representations of the environment or events, it is understandable that episodic memory in particular suffers such a devastating impact when MTL structures are destroyed. The arbitrary events and stimuli constituting episodic experiences either fail to be recorded or are recorded piecemeal, rendering them worthless when it comes to reconstructing an episode.

This explanation would also shed some light on the declarative-procedural distinction and the rigidity of information learned by amnesics. A failure to form structured representations could cause problems encoding associations in general, which might make it difficult to integrate information that would be dynamically accessible, like declarative information. A loss of the system of relationships in which a piece of factual knowledge embeds could essentially deprive one of the cues or conceptual pathways needed to retrieve that knowledge. Meanwhile, massive repetition could be used to train associations which would essentially exist in isolation, disallowing retrieval of the memories through the broader system of declarative associations to which most of us are accustomed.

But invoking this explanation raises a question. Aside from memory deficits, failure to form the kinds of representations suggested above should result in on-line performance deficits similar to the rats' inability to efficiently navigate an unfamiliar radial maze. Yet much of the literature on H.M. shows an intact ability to perform a wide range of tasks. Beyond normal IQ and digit span, H.M. understood jokes and puns, and a recent battery of linguistic evaluations showed normal performance compared to that of controls on such tasks as spelling, picture naming, past tense, plural production, and syntax or thematic role comprehension (Kensinger et al. 2001). Similarly, even in the visual-spatial domain, H.M. quickly detected anomalous features of cartoon drawings, and performed normally on tachistoscopic tests of letter recognition and letter masking (Milner et al. 1968). H.M. also showed strong performance on the Mooney face perception task, in which subjects are required to give the gender and approximate age of a person whose face is shown as a somewhat abstract set of black and white contours (Milner et

al. 1968; Mooney 1956). In initial trials of an incomplete pictures task (Gollin 1960), H.M.'s performance was comparable to that of controls, indicating that his perceptual abilities were intact in this regard (Milner et al. 1968). On an anecdotal level, to those with whom he interacted, H.M. appeared to be cognitively intact, except for his extreme forgetfulness.

But it should be noted that the tasks listed above are those in which successful performance might depend on chunked representations or highly over-trained rules or procedures. The constellation of tasks on which H.M. showed impaired performance are those that require dynamic integration of multiple elements, rules, or references frames. H.M. showed deficient performance when copying the Rey-Osterrieth figure or when attempting to navigate from one room to another using the floor plan of a building (Corkin 1984). H.M. was also impaired on a hidden-figures task in which *particular geometric patterns have to be discovered and traced out within a network of embedding and overlapping lines* (Milner et al. 1968). It would be difficult to rely on chunked patterns for these types of tasks, where shapes must be coordinated with one another or allocentric-egocentric transformations must be computed.

In a linguistic domain as well, H.M. showed performance deficits detecting ungrammatical sentences where grammatical errors could only be identified by evaluating several words in a sentence (it was not enough to recognize that one word was problematic). An example would be, *John gave me the car that he couldn't drive by ourselves*, in which detecting the error requires an evaluation of whether pronouns agree. In contrast with these subtler combinatorial problems, H.M. made no errors identifying scrambled sentences as ungrammatical: *Has house she decided to a buy*. H.M.'s solid performance on these more blatantly problematic sentences showed that he understood the task and was following the instructions. A number of other deficits were exhibited in the same set of experiments, all involving sentences where H.M. encountered some novel usage, ambiguity, or combination of elements (MacKay et al. 2007). This again underscores that integration of multiple elements, frames, or rules causes H.M. problems when negotiating the task. Consistent with this interpretation are the observations that H.M. uses a large quantity of clichés or stock phrases in his speech (MacKay et al. 2007), and that,

> "...when asked to repeat an unrelated word string exceeding his normal span, (he) will produce large numbers of recombination errors; for example, he will substitute the response waste for the list words wake and taste." (Marslen-Wilson and Teuber 1975).

This suggests a reliance on chunked or over-trained patterns in the absence of an ability to organize multiple elements or combinatorial information.

The constellations of tasks on which H.M.'s on-line performance was either impaired or spared can be regarded as reinforcement for the idea that MTL damage results in an impaired ability to build and maintain structured representations relying on the association or integration of multiple chunks or elements. Lacking this ability, individuals have difficulty negotiating novel situations in which coordination of multiple combinatorial elements or reference frames is needed. Moreover, failure to construct representational frameworks leaves learned factual and experiential knowledge isolated and often irretrievable, and has an especially grave impact on episodic memory. These representational frameworks likely depend on quickly emerging tuning properties in hippocampal or other cells, and their stability over time — mediated by synaptic plasticity — probably corresponds to long-term memory. Importantly, this view goes beyond the hypothesis that the hippocampus increases the speed or magnitude of memory encoding, instead positing a role for MTL structures in the structured organization of memory, with clear implications for the flexible nature of declarative knowledge.

FINAL THOUGHTS

H.M.'s contribution to neuroscience continues to be important as we investigate the role and function of the MTL memory system. Our knowledge of his condition increased throughout his lifetime and continues to deepen with time. The line of research and questions posed by H.M.'s amnesia now runs parallel with other investigations into hippocampal or MTL function related to spatial mapping. As these two major lines of research inform one another, it may be possible to ascribe a parsimonious functional account to the brain structures involved. This paper has outlined one such account. Whatever the case, it is clear that H.M.'s contribution to science will continue to be a central one in the coming decades.

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REFERENCES

Austin KB, Fortin WF, Shapiro ML (1990) Place fields are altered by NMDA antagonist MK-801 during spatial learning. Soc Neurosci Abstr 16:263

Bayley PJ, Squire LR (2002) Medial temporal lobe amnesia: gradual acquisition of factual information by nondeclarative memory. J Neurosci 22:5741-5748

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

Cohen NJ, Squire LR (1980) Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. Science 210:207-210

Corkin S (1968) Acquisition of motor skill after bilateral medial temporal-lobe excision. Neuropsychologia 6:255-265

Corkin S (1982) Some relationships between global amnesias and the memory impairments in Alzheimer's disease. In: Corkin S, Davis KL, Growdan JH, Usdin E, Wurtman RJ (eds) *Alzheimer's disease: a report of progress in research*. Raven Press, New York, NY, pp 149-164

Corkin S, Cohen NJ, Sagar HJ (1983) Memory for remote personal and public events after bilateral medial temporal lobectomy. Soc Neurosci Abstr 9:28

Corkin S (1984) Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M. Seminars in Neurol 4:249-259

Corkin S, Amaral DG, González G, Johnson KA, Hyman BT (1997) H.M.'s medial temporal lobe lesion: findings from magnetic resonance imaging. J Neurosci 17:3964-3979

Corkin S (2002) What's new with the amnesic patient H.M.? Nat Rev Neurosci 3:153-160

Drachman DA, Arbit J (1966) Memory and the hippocampal complex. Arch Neurol 15:52-61

Eichenbaum H (2000) Hippocampus: mapping or memory? Curr Biol 10:R785-R787

Gabrieli JDE, Cohen NJ, Corkin S (1988) The impaired learning of semantic knowledge following bilateral medial temporal-lode resection. Brain and Cogn 7:157-177

Gabrieli JDE, Corkin S, Mickel SF, Growdon JH (1993) Intact acquisition and long-term retention of mirror-tracing skill in Alzheimer's disease and in global amnesia. Behav Neurosci 107:899-910

Gamper E (1928) Zur frage der polioencephalitis haemorrhagica der chronischen alkoholiker. Anatomische befunde beim alkoholischen Korsakow und ihre beziehungen zum klinischen bild. Deutsche Zeitschrift für Nervenheilkunde 102:122-129

Gollin ES (1960) Developmental studies of visual recognition of incomplete objects. Perceptual and Motor Skills 11:289-298

Hayman CAG, Macdonald CA (1993) The role of repetition and associative interference in new semantic learning in amnesia: a case experiment. J Cogn Neurosci 5:375-389

Kensinger EA, Ullman MT, Corkin S (2001) Bilateral medial temporal lobe damage does not affect lexical or grammatical processing: evidence from amnesic patient H.M. Hippocampus 11:347-360

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

Leonard BW, Amaral DG, Squire LR, Zola-Morgan S (1995) Transient memory impairment in monkeys with bilateral lesions of the entorhinal cortex. J Neurosci 15:5637-5659

MacKay DG, James LE, Taylor JK, Marian DE (2007) Amnesic H.M. exhibits parallel deficits and sparing in language and memory: systems versus binding theory accounts. Lang Cogn Proc 22:377-452

Margerison JH, Corsellis JAN (1966) Epilepsy and the temporal lobes. Brain 89:499-529

Marslen-Wilson WD, Teuber HL (1975) Memory for remote events in anterograde amnesia: recognition of public figures from news photographs. Neuropsychologia 13:353-364

Martin E (1971) Verbal learning theory and independent retrieval phenomena. Psychol Rev 78:314-332

Milner B (1962) Les troubles de la mémoire accompagnant des lésions hippocampiques bilatérales. In: Passouant P (ed) *Physiologie de l'Hippocampe*. Centre Nationale de la Recherche Scientifique, pp 257-272

Milner B, Corkin S, Teuber HL (1968) Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. Neuropsychologia 6:215-234

Mooney CM (1956) Closure with negative after-images under flickering light. Canad J Psychol 10:191-199

Nádasdy Z, Hirase H, Czurkó A, Csicsvari J, Buzsáki G (1999) Replay and time compression of recurring spike sequences in the hippocampus. J Neurosci 19:9497-9507

Nadel L, MacDonald L (1980) Hippocampus: cognitive map or working memory? Behav Neural Biol 29:405-409

O'Kane G, Kensinger EA, Corkin S (2004) Evidence for semantic learning in profound amnesia: an investigation with patient H.M. Hippocampus 14:417-425

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

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

Redish AD (2001) The hippocampal debate: are we asking the right questions? Behav Brain Res 127:81-98

Sagar HJ, Cohen NJ, Corkin S, Growdon JH (1985) Dissociations among processes in remote memory. Ann NY Acad Sci 444:533-535

Schacter DL, Harbluk JL, McLachlan DR (1984) Retrieval without recollection: an experimental analysis of source amnesia. J Verbal Learn Verbal Behav 23:593-611

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11-21

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

Shapiro ML, O'Connor C (1992) N-methyl-D-aspartate receptor antagonist MK-801 and spatial memory representation: working memory is impaired in an unfamiliar environment but not in a familiar environment. Behav Neurosci 106:604-612

Shimamura AP, Squire LR (1987) A neuropsychological study of fact memory and source amnesia. J Exp Psychol 13:464-473

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

Squire LR (2009) The legacy of patient H.M. for neuroscience. Neuron 61:6-9

Stefanacci L, Buffalo EA, Schmolck H, Squire LR (2000) Profound amnesia after damage to the medial temporal lobe: a neuroanatomical and neuropsychological profile of patient E.P. J Neurosci 20:7024-7036

Suzuki WA, Zola-Morgan S, Squire LR, Amaral DG (1993) Lesions of the perirhinal and parahippocampal cortices in the monkey produce long-lasting memory impairment in the visual and tactual modalities. J Neurosci 13:2430-2451

Tulving E (1972) Episodic and semantic memory. In: Tulving E, Donaldson W (eds) *Organization of memory*. Academic Press, New York, NY, pp 382-402

Van der Meer MAA, Johnson A, Schmitzer-Torbert NC, Redish AD (2010) Triple dissociation of information processing in dorsal striatum, ventral striatum, and hippocampus on a learned spatial decision task. Neuron 67:25-32

Vargha-Khadem F, Gadian DG, Watkins KE, Conelly A, Van Paesschen W, Mishkin M (1997) Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277:376-380

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

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

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

Zola-Morgan S, Squire LR, Amaral DG (1989a) Lesions of the amygdala that spare adjacent cortical regions do not impair memory or exacerbate the impairment following lesions of the hippocampal formation. J Neurosci 9:1922-1936

Zola-Morgan S, Squire LR, Amaral DG (1989b) Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkeys. J Neurosci 9:898-913

Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA (1989c) Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci 9:4355-4370