The Legacy of Patient H.M. for Neuroscience

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H.M. is probably the best known single patient in the history of neuroscience. His severe memory impairment, which resulted from experimental neurosurgery to control seizures, was the subject of study for five decades until his death in December 2008. Work with H.M. established fundamental principles about how memory functions are organized in the brain.

In 1952, Brenda Milner was completing her doctoral research at McGill University under the direction of Donald Hebb. At about this time, she encountered two patients (P.B. and F.C.) who had become severely amnesic following unilateral removal of the medial structures of the left temporal lobe for the treatment of epileptic seizures (Penfield and Milner, 1958). This unfortunate outcome was entirely unexpected, and it was proposed that in each case there had been a preexistent, but unsuspected, atrophic lesion in the medial temporal lobe of the opposite hemisphere. In that way, the unilateral surgery would have resulted in a bilateral lesion, an idea that was confirmed at autopsy some years later for patient P.B. After the two cases were presented at the 1955 meeting of the American Neurological Association, Wilder Penfield (the neurosurgeon in both cases) received a call from William Scoville, a neurosurgeon in Hartford, Connecticut. Scoville told Penfield that he had seen a similar memory impairment in one of his own patients (H.M.) in whom he had carried out a bilateral medial temporal lobe resection in an attempt to control epileptic seizures. As a result of this conversation, Brenda Milner was invited to travel to Hartford to study H.M.

H.M. had been knocked down by a bicycle at the age of 7, began to have minor seizures at age 10, and had major seizures after age 16. (The age of the bicycle accident is given as 9 in some reports; for clarification see Corkin, 1984.) He worked for a time on an assembly line but, finally, in 1953 at the age of 27 he had become so incapacitated by his seizures, despite high doses of anticonvulsant medication, that he could not work or lead a normal life. Scoville offered H.M. an experimental procedure that he had carried out previously in psychotic patients, and the surgery was then performed with the approval of the patient and his family.

When Milner first visited H.M., she saw that the epilepsy was now controlled but that his memory impairment was even more severe than in Penfield's two patients, P.B. and F.C. What she observed was someone who forgot daily events nearly as fast as they occurred, apparently in the absence of any general intellectual loss or perceptual disorder. He underestimated his own age, apologized for forgetting the names of persons to whom he had just been introduced, and described his state as "like waking from a dream … every day is alone in itself…" (Milner et al., 1968, p. 217).

The first observations of H.M., and the results of formal testing, were reported a few years later (Scoville and Milner, 1957). This publication became one of the most cited papers in neuroscience (nearly 2500 citations) and is still cited with high frequency. H.M. continued to be studied for five decades, principally by Brenda Milner, her former student Suzanne Corkin, and their colleagues (Corkin, 1984, 2002; Milner et al., 1968). He died on December 2, 2008, at the age of 82. It can be said that the early descriptions of H.M. inaugurated the modern era of memory research. Before H.M., due particularly to the influence of Karl Lashley, memory functions were thought to be widely distributed in the cortex and to be integrated with intellectual and perceptual functions. The findings from H.M. established the fundamental principle that memory is a distinct cerebral function, separable from other perceptual and cognitive abilities, and identified the medial aspect of the temporal lobe as important for memory. The implication was that the brain has to some extent separated its perceptual and intellectual functions from its capacity to lay down in memory the records that ordinarily result from engaging in perceptual and intellectual work.

The Medial Temporal Lobe Memory System

The early paper is sometimes cited incorrectly as evidence that the hippocampus is important for memory, but this particular point could not of course be established from a lesion that, by the surgeon's description, included the hippocampus, amygdala, and the adjacent parahippocampal gyrus. As Milner subsequently wrote, "Despite the use of the word 'hippocampal' in the titles of my papers with Scoville and Penfield, I have never claimed that the memory loss was solely attributable to the hippocampal lesions" (Milner, 1998). Indeed, the original paper ends, quite appropriately, with the statement:

> It is concluded that the anterior hippocampus and hippocampal gyrus, either separately or together, are critically concerned in the retention of current experience. It is not known whether the amygdala plays any part in this mechanism, since the hippocampal complex has not been removed alone, but

> always together with uncus and amygdala. (Scoville and Milner, 1957, p. 21).

The findings from H.M. were initially met with some resistance, especially because of the difficulty for many years of demonstrating anything resembling his impairment in the experimental animal. Efforts to establish an animal model in fact began almost immediately when Scoville himself came to Montreal and did the same surgery in monkeys that he had done with H.M. But these monkeys and others with medial temporal lesions seemed able to learn tasks that H.M. could not learn. Only much later did it become understood that apparently similar tasks can be learned in different ways by humans and monkeys. For example, the visual discrimination task, which is learned gradually by the monkey over hundreds of trials, proved to involve what one would now call habit learning. In the monkey, this kind of learning depends on the basal ganglia, not the medial temporal lobe. Eventually, tasks were developed for the monkey that were exquisitely sensitive to medial temporal lobe lesions (for example, the one-trial, delayed nonmatching to sample task), and an animal model of human memory impairment thereby became available (Mishkin, 1978).

Cumulative work with the animal model over the next decade, together with neuroanatomical studies, succeeded in identifying the anatomical components of what is now termed the medial temporal lobe memory system (Squire and Zola-Morgan, 1991): the hippocampus and the adjacent perirhinal, entorhinal, and parahippocampal cortices that make up much of the parahippocampal gyrus. This information showed which structures within H.M.'s large lesion were important for understanding his impairment and, more broadly, what structures are important for memory. A few years later, an improved description of H.M.'s lesion was obtained with magnetic resonance imaging (MRI) (Corkin et al., 1997). MRI had been delayed because of concerns that clips placed on the dura during surgery made H.M. ineligible for imaging. However, thorough inquiry revealed that the dural clips constituted no risk.

At this juncture, several points became clear. First, H.M.'s lesion was less extensive than described originally by the surgeon in that it extended a little more than 5 cm caudally from the temporal pole (not 8 cm). As a result the posterior parahippocampal gyrus was largely spared (specifically, the parahippocampal cortex or what in the monkey is termed area TH TF). Second, the reason that H.M.'s memory impairment was so severe was that the bilateral damage included the parahippocampal gyrus (anteriorly) and was not restricted to the hippocampus. Damage limited to the hippocampus causes significant memory impairment but considerably less impairment than in H.M. Third, memory impairment more severe than H.M.'s could now be understood, as when the damage includes the structures damaged in H.M. but also extends far enough posteriorly to involve the parahippocampal cortex (patients E.P. and G.P.; Kirwan et al., 2008).

In the early years, the anatomy of the medial temporal lobe was poorly understood, and terms like hippocampal zone and hippocampal complex were often used to identify the area of damage. With the elucidation of the boundaries and connectivity of the structures adjacent to the hippocampus and the discovery that these structures are important for memory, vague terms like hippocampal complex became unnecessary (though one can still find them in contemporary writing). It is now possible to achieve careful descriptions based on anatomical measurement and modern terminology.

H.M. not only motivated the development of an animal model of human memory impairment and the subsequent delineation of the medial temporal lobe memory system. As described next, the study of H.M. also led to fundamental insights into the function of the medial temporal lobe and the larger matter of how memory is organized in the brain.

Immediate Memory and Long-Term Memory

H.M.'s intact intellectual and perceptual functions, and similar findings in other patients with large medial temporal lesions, have been well documented. A key additional finding was that H.M. had a remarkable capacity for sustained attention, including the ability to retain information for a period of time after it was presented. Thus, he could carry on a conversation, and he exhibited an intact digit span (i.e., the ability to repeat back a string of six or seven digits). Indeed, information remained available so long as it could be actively maintained by rehearsal. For example, H.M. could retain a three-digit number for as long as 15 min by continuous rehearsal, organizing the digits according to an elaborate mnemonic scheme. Yet when his attention was diverted to a new topic, he forgot the whole event. In contrast, when the material was not easy to rehearse (in the case of nonverbal stimuli like faces or designs), information slipped away in less than a minute. These findings supported a fundamental distinction between immediate memory and long-term memory (what William James termed primary memory and secondary memory). Primary memory [immediate memory]

> …comes to us as belonging to the rearward portion of the present space of time, and not to the genuine past (James, 1890, p. 647).

Secondary memory [long-term memory] is quite different.

> An object which has been recollected … is one which has been absent from consciousness altogether, and now revives anew. It is brought back, recalled, fished up, so to speak, from a reservoir in which, with countless other objects, it lay buried and lost from view. (James, 1890, p. 648).

Notably, time is not the key factor that determines how long patients like H.M. can retain information in memory. The relevant factors are the capacity of immediate memory and attention, i.e., the amount of material that can be held in mind and how successfully it can be rehearsed. The work with H.M. demonstrated that the psychological distinction between immediate memory and long-term memory is a prominent feature of how the brain has organized its memory functions.

Multiple Memory Systems

Perhaps the most unexpected discovery about H.M., given his profound and global memory impairment, came when Brenda Milner tested his ability to acquire a visuomotor skill (Milner, 1962). H.M. was shown a five-pointed star, with a double contour, and asked to trace its outline with a pencil, but in a condition when he could only see his hand and the star as reflected in a mirror. H.M. acquired this mirror-drawing skill during ten trials and exhibited excellent retention across 3 days. Yet at the end of testing, he had no recollection of having done the task before. This demonstration provided the first hint that there was more than one kind of memory in the brain and suggested that some kinds of memory (motor skills) must lie outside the province of the medial temporal lobe.

For a time, it was rather thought that motor skills were a special case and that all the rest of memory is impaired in patients like H.M. Later it became appreciated that motor skills are but a subset of a larger domain of skill-like abilities, all of which are preserved in amnesia. The demonstration of a fully preserved ability to learn the perceptual skill of mirror reading suggested a distinction between two broad classes of knowledge: declarative and procedural (Cohen and Squire, 1980). Declarative memory is what is meant when the term "memory" is used in everyday language, i.e., conscious knowledge of facts and events. Procedural memory refers to skill-based knowledge that develops gradually but with little ability to report what is being learned.

In the years that followed, other preserved learning abilities began to be reported for amnesic patients, and the perspective shifted to a framework that accommodated multiple (i.e., more than two) memory systems. As Endel Tulving wrote:

> But even if we accept the broad division of memory into procedural and propositional forms … there are phenomena that do not seem to fit readily into such a taxonomy (Tulving et al., 1982, p.336).

Subsequently, the terms declarative and nondeclarative were introduced with the idea that declarative memory refers to the kind of memory that is impaired in H.M. and is dependent on the medial temporal lobe. Nondeclarative memory is an umbrella term referring to additional memory systems. These include systems that support skill learning, habit learning, simple conditioning, emotional learning, as well as priming and perceptual learning. The structures with special importance for these kinds of memory include the basal ganglia, the cerebellum, the amygdala, and the neocortex. The starting point for these developments was the early discovery that motor skill learning was preserved in H.M. This finding revealed that memory is not a single faculty of the mind and led ultimately to the identification of the multiple memory systems of the mammalian brain.

Remote Memory

H.M.'s memory impairment has generally been taken as reflecting a failure to convert transient, immediate memory into stable long-term memory. A key insight about the organization of memory, and medial temporal lobe function, came with a consideration of his capacity to remember information that he had acquired before his surgery. The first exploration of this issue with formal tests asked H.M. to recognize faces of persons who had become famous in different decades, 1920–1970 (Marslen-Wilson and Teuber, 1975). As expected, H.M. was severely impaired at recognizing faces from his postmorbid period (the 1950s and 1960s), but he performed as well as or better than age-matched controls at recognizing faces of persons who were in the news before his surgery. This important finding implied that the medial temporal lobe is not the ultimate storage site for previously acquired knowledge. The early descriptions of H.M. conform to this view. Thus, H.M. was described as having a partial loss of memory (retrograde amnesia) for the 3 years leading up to his surgery, with early memories "seemingly normal" (Scoville and Milner, 1957, p. 17). Similarly, about 10 years later it was remarked that there did not appear

> to have been any change in H.M.'s capacity to recall remote events antedating his operation, such as incidents from his early school years, a high-school attachment, or jobs he had held in his late teens and early twenties (Milner et al., 1968, p. 216).

Subsequently, a particular interest developed in the status of autobiographical memories for unique events, which are specific to time and place, and methods were developed to assess the specificity and the detail with which such recollections could be reproduced. In the earliest efforts along these lines, as summarized by Suzanne Corkin (Corkin, 1984), H.M. produced well-formed autobiographical memories, from age 16 years or younger. It was concluded that H.M's remote memory impairment now extended back to 11 years before his surgery. The situation seemed to change further as H.M. aged. In an update prepared nearly 20 years later (Corkin, 2002), H.M. (now 76 years old) was described as having memories of childhood, but his memories appeared more like remembered facts than like memories of specific episodes. It was also said that he could not narrate a single event that occurred at a specific time and place. Essentially the same conclusion was reached a few years later when new methods, intended to be particularly sensitive, were used to assess H.M.'s remote memory for autobiographical events (Steinvorth et al., 2005). These later findings led to the proposal that, whatever might be the case for fact memory, autobiographical memories, i.e., memories that are specific to time and place, depend on the medial temporal lobe so long as the memories persist.

There are reasons to be cautious about this idea. In 2002–2003, new MRI scans of H.M. were obtained (Salat et al., 2006). These scans documented a number of changes since his first MRI scans from 1992–1993 (Corkin et al., 1997), including cortical thinning, subcortical atrophy, large amounts of abnormal white matter, and subcortical infarcts. These findings were thought to have appeared during the past decade, and they complicate the interpretation of neuropsychological data collected during the same time period. Another consideration is that remote memories could have been intact in the early years after surgery but then have faded with time because they could not be strengthened through rehearsal and relearning. In any case, the optimal time to assess the status of past memory is soon after the onset of memory impairment.

Other work has tended to support the earlier estimates that H.M.'s remote memories were intact. First, Penfield's two patients described above, P.B. and F.C., were reported after their surgeries to have memory loss extending back a few months and 4 years, respectively, and intact memory from before that time (Penfield and Milner, 1958). Second, methods like those used recently to assess H.M. have also been used to evaluate autobiographical memory in other patients, including patients like E.P. and G.P. who have very severe memory impairment (Kirwan et al., 2008). In these cases, autobiographical recollection was impaired when memories were drawn from the recent past but fully intact when memories were drawn from the remote past.

Memory loss can sometimes extend back for decades in the case of large medial temporal lobe lesions (though additional damage to anterolateral temporal cortex may be important in this circumstance). In any case, memories from early life appear to be intact unless the damage extends well into the lateral temporal lobe or the frontal lobe. These findings are typically interpreted to mean that the structures damaged in H.M. are important for the formation of long-term memory and its maintenance for a period of time after learning. During this period gradual changes are thought to occur in neocortex (memory consolidation) that increase the complexity, distribution, and connectivity among multiple cortical regions. Eventually, memory can be supported by the neocortex and becomes independent of the medial temporal lobe. The surprising observation that H.M. had access to old memories, in the face of an inability to establish new ones, motivated an enormous body of work, both in humans and experimental animals, on the topic of remote memory and continues to stimulate discussion about the nature and significance of retrograde amnesia.

Perspective

H.M. was likely the most studied individual in the history of neuroscience. Interest in the case can be attributed to a number of factors, including the unusual purity and severity of the memory impairment, its stability, its well-described anatomical basis, and H.M.'s willingness to be studied. He was a quiet and courteous man with a sense of humor and insight into his condition. Speaking of his neurosurgeon, he once said, "What he learned about me helped others, and I'm glad about that." (Corkin, 2002, p. 159).

An additional aspect of H.M.'s circumstance, which assured his eventual place in the history of neuroscience, was the fact that Brenda Milner was the young scientist who first studied him. She is a superb experimentalist with a strong conceptual orientation that allowed her to draw from her data deep insights about the organization of memory. Because he was the first well-studied patient with amnesia, H.M. became the yardstick against which other patients with memory impairment would be compared. It is now clear that his memory impairment was not absolute and that he was able to acquire significant new knowledge (Corkin, 2002). Thus, memory impairment can be either more severe or less severe than in H.M. But the study of H.M. established key principles about how memory is organized that continue to guide the discipline.

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