

Understanding amnesia – Is it time to forget HM?

55 years since the famous amnesic's case was first described, John P. Aggleton questions its value when debating the neuroanatomical basis of memory

The amnesic HM is the most famous single-case in neuropsychology, and possibly the best known case in all of psychology. Over one hundred studies have been published involving HM, and when he died in 2008 it was worldwide news. Interest in Henry Molaison (as we then discovered) was so high that when his brain was sectioned the procedure was filmed for the internet, prompting, among other things, a stage play. Ironically, HM always remained unaware of his fame (Corkin, 2002). The question posed here is whether it is time for us to reciprocate – should we forget HM?

Almost every introduction into the neural basis of memory describes how in 1953 the surgeon William Scoville removed tissue in both medial temporal lobes of HM's brain in an attempt to treat his epilepsy. Immediately thereafter, HM displayed severe anterograde amnesia – a failure to retain new day-to-day events – which remained throughout the rest of his life. This catastrophic outcome ensured that HM's surgery was not repeated, so making him unique.

As has been often described, HM showed preserved IQ despite his loss of long-term memory. He also showed preserved short-term memory (e.g. immediate memory span) and a good knowledge of past factual information. (episodic memory). Subsequent research revealed his spared ability to learn new perceptual-motor skills, e.g. mirror drawing (Corkin, 2002), discoveries that helped to establish emerging distinctions

between explicit and implicit learning. Much of the impact of HM arises, however, from Scoville's surgery and how that inadvertently established the importance of the hippocampus for learning and memory.

Given this impact it seems churlish to question the legacy of HM. Indeed, it must be made clear that this article is not a criticism of research on HM (which has consistently been of an exceptional level and deservedly praised); rather it concerns how key elements of this hugely influential body of research have been more generally interpreted and reported.

Does hippocampal pathology cause anterograde amnesia?

The Russian neurologist Bekhterev is often credited as the first person to signal the involvement of the hippocampus in memory. Bekhterev's research was, however, suppressed after his death, quite probably on the orders of Stalin who may have had Bekhterev killed (Lerner et al., 2005). It is, however, indisputable that Scoville and Milner (1957) drew new attention to the importance of the hippocampal formation for long-term memory, and did so in a way that profoundly altered neuroscience.

It is because HM is regarded as unique that his case has had such influence, yet in their landmark paper, Scoville and Milner (1957) described eight cases in addition to HM who received bilateral removal of tissue in the medial temporal

lobes. Along with HM, one other case had the most 'radical' surgery, intended to remove the full extent of the hippocampus. In six of the remaining cases the surgery was more restricted as it was intended to reach only the front of the hippocampus or only midway through the structure. Within this group of patients, HM was unique as his was the only surgery for the relief of epilepsy. The other patients received psychosurgical treatments intended to relieve schizophrenia ($n = 7$) or bipolar depression ($n = 1$). The failure of Scoville's surgeries to reduce these psychiatric symptoms inevitably posed problems for their cognitive assessments, and the formal testing of three of these schizophrenic cases was incomplete. Added problems would have arisen from the fact that schizophrenia is itself associated with appreciable memory loss.

Despite these issues, several features of the original study on HM seem to create a compelling case for the importance of the hippocampus. Most critically, comparisons among all nine patients revealed that severe memory deficits were only seen after radical resections involving most of the hippocampus. Unfortunately, the real extent of the surgeries could only be subsequently determined for HM, for whom there is structural MRI data (Corkin et al., 1997). We are, therefore, reliant on Scoville's surgical notes for the other eight patients. In fact, we now know that Scoville failed to remove the caudal 2cm of HM's hippocampus, despite his intention to do so (Figure 1). (More precise information will become available when HM's post-mortem findings are published.) It is, therefore, not unreasonable to suppose that there were inconsistencies between the intended and actual extent of tissue removal in these other eight cases.

There are additional concerns. Scoville's surgeries approached the medial temporal lobe from its front (i.e. via the temporal pole), an inevitable consequence of which was the removal of tissue in

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front of the hippocampus. This tissue included most of the amygdala and pyriform cortex. The surgeries also produced variable amounts of tissue loss in other regions adjacent to the hippocampus (the 'parahippocampal region', which includes the entorhinal and perirhinal cortices – see Figure 1). There is no shortage of evidence that additional damage to these adjacent areas can exacerbate memory deficits (Aggleton & Brown, 1999; Diana et al., 2007). A closely related issue concerns the consequences of any white matter damage in HM as the surgical technique used by Scoville would have destroyed both white and grey matter. White matter damage is potentially very important as it might disrupt the functions of sites far removed from the hippocampus.

While MRI data (Corkin et al., 1997) indicate that Scoville probably spared the tract immediately lateral to the hippocampus (the temporal stem), he would have removed fibres linking the temporal pole with the frontal lobe. Other tract damage in HM would almost certainly include those temporal stem fibres that leave the temporal lobe by passing directly through the lateral and dorsal amygdala. Studies with monkeys have shown that cutting these fibres adds to cognitive impairments in tasks such as recognition memory (Bachevalier et al., 1985). It can, therefore, be seen that HM did not suffer selective hippocampal loss and that damage to adjacent areas is very likely to have contributed to his memory problems. As a consequence HM does not confirm that hippocampal cell loss is either 'necessary' or 'sufficient' for temporal lobe amnesia.

Subsequent comparisons using other cases with more localised hippocampal damage (Spiers et al., 2001) have, in fact, often supported the principal insights drawn from HM as these later cases also suffered clear losses of long-term memory that contrasted with spared semantic knowledge acquired prior to the amnesia. That said, HM's amnesia appears appreciably denser than that in cases with more circumscribed hippocampal

HM, it remains highly likely that the combination of additional white matter damage and the loss of tissue in structures adjacent to the hippocampus (e.g. the amygdala) added to his memory problems. Finally, his long-term use of anti-epileptic drugs may have caused cerebellar atrophy (Corkin, 2002). Consequently there are numerous reasons why the amnesia in HM may have been particularly dense, and these reasons reflect more than just hippocampal cell loss.

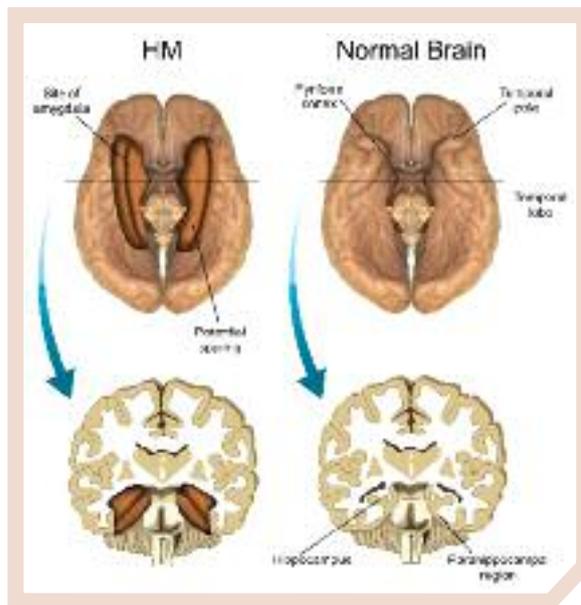


Figure 1. HM's surgery and the medial temporal lobe. The upper level shows views of the underside of a brain (with the cerebellum removed). The brain on the left indicates the intended extent of the medial temporal surgery in HM (region in brown). The dashed line shows approximately how far back Scoville's surgery actually went according to MRI evidence, leaving an area of potential sparing in the posterior hippocampus. The solid line shows the level of the coronal sections in the lower part of the figure. The coronal section on the left indicates the suspected area of tissue loss in HM, which clearly extends well into the parahippocampal region.

damage. While there are several possible explanations for this difference, including the extent of hippocampal

Hierarchical models of medial temporal lobe function

Consult almost any neuropsychological text and there will be a figure highlighting those medial temporal lobe connections most strongly linked to memory. This figure almost always comprises a series of connected boxes, with the hippocampus placed at the top (Figure 2, overleaf). Such figures inevitably convey a hierarchy with the hippocampus overseeing all other medial temporal lobe memory functions.

Although such depictions of medial temporal lobe anatomy were not created by research on HM, the persistent emphasis on hippocampal dysfunction in HM has surely reinforced and maintained this hierarchical view of medial temporal function. This perspective is all the more understandable when it is appreciated that the dominant model of medial temporal lobe memory systems has been one in which other temporal lobe structures are primarily critical for the ingress and egress of information to and from the medial temporal lobe, but it is the hippocampus that orchestrates this information (Squire et al., 2007; Wixted & Squire, 2011). This influential view of medial temporal lobe organisation now looks increasingly untenable.

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Looking back

The pivotal issue is the extent to which other temporal lobe structures have memory functions independent of the hippocampus. Much of this debate originally centred on the relative importance of the hippocampus and the parahippocampal region for recognition memory (the ability to detect when an event is repeated). One highly influential model supposes that the hippocampus is equally important for both recall and recognition, consistent with its position at the top of an anatomical hierarchy (Squire et al., 2007; Wixted & Squire, 2011). This model assumes that damage immediately beyond the hippocampus produces more of the same dysfunction, reflecting this sharing of functions. This concept is very pertinent because it directly implies that any extra-hippocampal damage in HM disrupted processes that primarily depend on the hippocampus, and so do not materially affect his core status as a hippocampal amnesic.

Other models have challenged this view. One class of model supposes that while the hippocampus is vital for recognition memory based on the explicit recall of past experiences, adjacent regions including the perirhinal cortex are independently important for recognition based on the feeling of familiarity (Aggleton & Brown, 1999; Diana et al., 2007). These 'dual-process' models predict that amnesics with pathology restricted to the hippocampus will have disproportionate deficits in recall, as recognition can be partially supported by familiarity. Such cases do exist (Brown et al., 2010). In addition, there is much evidence that the parahippocampal region has cognitive functions independent of the hippocampus (Diana et al., 2007).

With regard to HM, he repeatedly failed to recognise near-neighbours and friends who became acquainted with him after his surgery. HM was impaired on both verbal and non-verbal recognition, and for both yes-no and forced-choice tasks (Corkin, 2002). Consequently, there seems little reason to suppose that HM showed a relative sparing of recognition memory. Unfortunately HM's amnesia is so strongly identified as being fundamentally hippocampal, and his deficits for recall and recognition so widely described, that these two

impairments have become fused.

The problem with conflating these impairments is beautifully highlighted by a pair of experiments with monkeys that

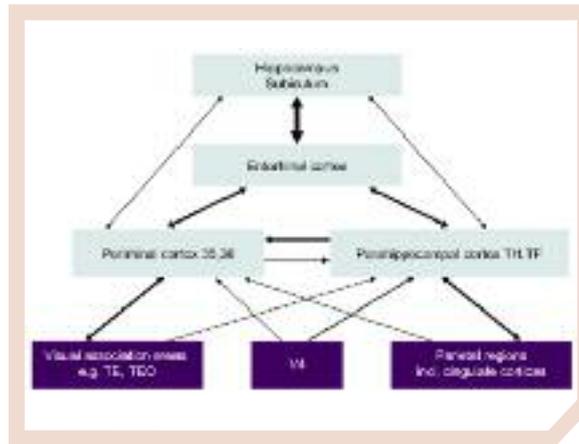


Figure 2. Potentially misleading hierarchical diagram portraying the interconnections between the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex. The cortical regions at the bottom provide sensory information to the region. The thickness of the arrows reflects the strength of the various connections.

sought to replicate the combined amygdala plus hippocampal surgery in HM. When the tissue was removed using Scoville's surgical approach the monkeys were very severely impaired on object recognition memory (Mishkin, 1978). When the same targets were removed by injecting a chemical that kills neurons but spares white matter, the animals were unimpaired on object recognition (Murray & Mishkin, 1998). This contrasting pair of findings underlines the significance of dysfunction in HM beyond the hippocampus, and its likely contribution to recognition memory.

Looking beyond the hippocampus

One legacy of HM is that he reinforced the notion of different brain structures with different roles in processing information, so supporting a modular approach to memory. A related legacy is that the hippocampus has become the keystone for research into long-term memory. One consequence is that research into neurological disorders associated with memory loss, including dementias, remains dominated by hippocampal analyses, despite the potential significance of other areas within the temporal lobe.

Damage beyond the temporal lobe can also cause anterograde amnesia. In

fact the first convincing evidence that damage to a specific brain site can cause amnesia concerns the mammillary bodies (the most posterior part of the hypothalamus), not the hippocampus (Vann & Aggleton, 2004). Remarkable clinical cases, such as BJ who had a snooker cue forced up his nose, damaging the base of this brain, have also specifically implicated the mammillary bodies (see Vann & Aggleton, 2004). Likewise, a large-scale study of memory after tumours in the middle of the brain has highlighted the importance of the mammillary bodies (Tsvilivis et al., 2008).

A number of other sites have been also implicated in amnesia (e.g. the anterior thalamic nuclei, parathalamic thalamic nucleus, medial dorsal thalamic nucleus, retrosplenial cortex), and the fact that many of these structures are directly interconnected with the hippocampus has been given great significance. The assumption has typically been that these other regions are of secondary importance, and that the primary memory influences begin and end with the hippocampus. While such models are anatomically plausible, they have an inherent weakness if they fail to explain why the hippocampus might benefit from such a return circuit. The answer is surely that these other structures provide new information critical for temporal lobe function. Indeed, recent research shows that it might be more insightful to see these other sites as primarily upstream, not downstream, from the hippocampus (Vann, 2010), i.e. reversing the traditional viewpoint. Such findings again emphasise the need to move to a more balanced view of memory substrates.

In many respects, HM remains the prototypical amnesic. (In fact, it could be argued that HM came to define what is now meant by the term amnesic.) There is little doubt that HM was unique, but that uniqueness is a double-edged sword given the multitude of special factors that may have influenced his memory performance. It feels almost sacrilegious to criticise the impact of HM, especially given the quality of the associated research. Nevertheless, the resultant narrow focus on the hippocampus for memory and memory disorders could well have excessively biased our thinking, with far-reaching, unwitting consequences.

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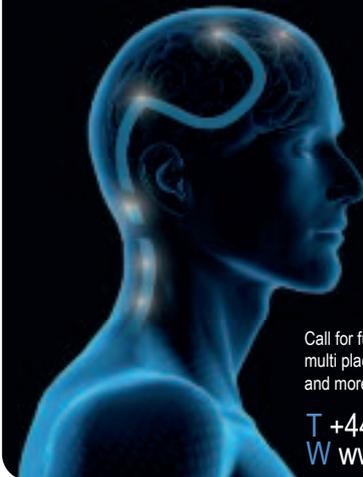
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