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The hippocampal complex and long-term memory revisited

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A recent report by Cipolotti *et al.* demonstrates that the hippocampus and perhaps the parahippocampal area are essential for retrieval of remote episodic memory and important for remote semantic memory. This report, along with other recent findings, re-opens the debate about the role of these medial temporal lobe structures, indicating that their role extends much further than traditional theory had suggested.

Although involvement of the hippocampal formation and related structures (entorhinal, perirhinal and parahippocampal cortices) in memory has been known for more than 50 years, the exact nature of this involvement remains a hotly debated subject. In the 1960s the outlines of the central debates were already clearly crystallized in work with amnesic patients such as H.M., which reflected the assumption that it was damage in the medial temporal lobes that was primarily responsible for the amnesia. The focus of attention shifted quickly from the medial temporal lobes to the hippocampal formation, and then to the hippocampus itself. Three major questions emerged: (1) is amnesia a problem of memory storage or memory retrieval?; (2) does the hippocampus play a role in recent or remote memories, or both?; and (3) is the hippocampus important for all, or only some, kinds of memory?

Of these three issues only the last appears to be resolved – most investigators now agree that the hippocampal formation is critical for only some kinds of learning and memory

(e.g. Refs 1,2, but see Ref. 3). The issues of storage versus retrieval, and recent versus remote memory must be discussed within this constraint, even though lively disagreements persist about how to characterize the kinds of memory that are, and are not, dependent on the hippocampal formation.

Recent versus remote memory

The initial report on H.M., and subsequent studies with temporal lobe patients, were taken to show that the hippocampal formation was involved neither in processing short-term memories nor in storing long-term memories. Although they lacked substantial portions of the hippocampus, these individuals had a normal short-term memory as measured by a number of tests, including digit-span performance, which involves repeating back a series of numbers. Similarly, it was reported that deficits in remote memory were limited to retrieval of events within the past few years, suggesting that older memories were stored, and could be retrieved readily, without the hippocampal formation^{4,5}.

Storage versus retrieval

However, reports of quite extensive retrograde amnesia, sometimes extending throughout the patient's remaining lifetime, complicated the picture. Warrington and her colleagues argued that the medial temporal lobe was essential to the retrieval of all remote memories, no matter how old, and that amnesia must reflect the lack of access to memory rather than the loss of the

memories themselves⁶. One concern in this debate (to which we return later) was the extent of damage underlying the amnesic defect. At first it was believed that the damage needed to be restricted to the medial temporal lobes but when reports of extensive retrograde amnesia came to light, the structure viewed as crucial became the hippocampal formation. When such damage was thought to be limited to the hippocampal formation itself, it appeared that the remote memory loss might be restricted (but see Ref. 7 for qualification). Thus, the view emerged that the hippocampus was critical for encoding of memories, and for consolidating memory for a limited period afterwards, but not for storage of memory itself. Over the years, this view became the accepted wisdom.

Recently, this view has come under renewed attack, and the paper by Cipolotti and her colleagues⁸ adds weight to the evidence suggesting that matters are a good deal more complex than many thought. Two lines of evidence have re-opened the debate. First, several studies have shown that activation in the hippocampus, as detected by fMRI studies, is as robust when remote memories are being retrieved as when recent ones are retrieved^{9,10}. This finding would not have been predicted by the traditional theory. Second, the period of retrograde amnesia, even in patients with damage restricted to the hippocampal formation, is now known to extend for years, and possibly decades. This is true also of H.M., whose retrograde amnesia on retesting grew from 3 to 11 years. Even in the case of

remote memories that are retained in people with medial temporal lobe lesions, careful analysis shows that they are not as detailed as in normal individuals¹¹⁻¹³. Traditional theory would demand that remote memories be both quantitatively and qualitatively the same in amnesic and normal individuals.

The patient V.C. is of considerable interest in this renewed debate because his brain damage, although extensive, appears to be largely limited to the hippocampal formation, as the thorough radiological examination indicates. In particular, V.C. shows near total sparing of the entorhinal cortex and adjacent temporal lobe, permitting conclusions to be drawn about the impact of damage in the hippocampal formation itself.

Cipolotti *et al.* carefully studied the memory capacities of V.C. in both the anterograde and retrograde domains. They demonstrated a devastating retrograde defect affecting memories for 40 years prior to the onset of the amnesia. Six different tests were used: (1) the 'dead or alive' test, in which the subject is required to indicate whether a famous person is dead or alive, and when and how they had died (if dead); (2) the famous public events questionnaire, which poses questions about places, names and events that occurred across eight different time periods (5-year intervals between 1960 and 2000); (3) the famous faces test, in which memory for public figures during each of the four decades between 1960 and 2000 is assessed; (4) the famous names familiarity test, in which any possible residual memory for public faces is assessed using the most sensitive implicit measure of familiarity judgments; (5) an autobiographical memory interview, in which the subject is required to generate personal semantic knowledge and autobiographical episodes from childhood, early adult life, and recent life; and (6) tests of memory for both pre- and post-morbidly acquired vocabulary.

Patient V.C. found it almost impossible to recall autobiographical episodes from any period of his life. He was able to recall some personal semantic information, but was impaired at all time points. V.C. was severely impaired on the dead or alive test. He was also impaired on both recall and recognition of famous public events, although on the recognition test the deficit was significant only for the two most recent decades. As the authors pointed out,

this might reflect a floor effect, in that V.C. did not differ from chance for the earlier decades. On the famous faces test much the same results were obtained. On the recall version of the task, V.C. was virtually unable to retrieve the names of famous personalities from any of the time periods tested; on a forced-choice version V.C. was above chance but still impaired relative to controls for the 1980s and 1990s, but not for the earlier decades. On the famous names familiarity task V.C. showed some implicit retention of knowledge from all four decades. On the vocabulary task V.C. showed intact knowledge for words learned pre-morbidly, but a severe impairment in learning new words. (Similar results have also been obtained with another patient by one of the present authors; R. Wesmacott and M. Moscovitch, unpublished data.)

Episodic versus semantic memory

The overall pattern of results with patient V.C. indicates profound and long-lasting retrograde amnesia. The authors argue that this deficit is observed equally with episodic and semantic information, but the data they present favors the view that the deficit is greater with episodic memory, and that a gradient of retrograde amnesia might be observed with semantic information, particularly for vocabulary. This was not tested by decade in V.C., but has been in other patients with equally large medial temporal lobe lesions. Those investigations found a clear temporal gradient for vocabulary acquisition (Ref. 14, and R. Wesmacott and M. Moscovitch, unpublished data).

'the standard model of hippocampal function ... that posits a relatively restricted time-limited role in episode memory, is in need of modification'

The results of this careful analysis of patient V.C. indicate that damage almost completely restricted to the hippocampal formation can cause essentially life-long impairments in retrieval of episodic memories. Thus, the study of V.C. appears to support the notion that the hippocampus is, after all, important for retrieval of remote episodic memories. Its role in retrieval of remote semantic memory is less clear, as the deficit in this domain was less obvious, and there were clear signs of graded retrograde amnesia.

Implications

What are the implications of this fascinating patient? Firstly, the study raises the possibility that the standard model of hippocampal function, one that posits a relatively restricted time-limited role in episode memory, is in need of modification. Secondly, V.C.'s performance on remote semantic memory tests suggests that the hippocampal formation might play a role in consolidating these kinds of memory in other structures, but not in retaining or retrieving them once consolidation is complete. Thus, V.C. provides support for the view that semantic and episodic memory engage the hippocampus in different ways.

Despite such clear evidence, the debate as to whether the hippocampus is needed for retention of remote episodic and semantic memory is likely to continue, and it will center on two lines of evidence: the true extent of the lesion and the types of tests used to assess remote memory. Mindful of this, Cipolotti *et al.* went to great lengths to argue, convincingly in our opinion, that no 'hidden pathology', in any currently accepted use of the term, can account for V.C.'s remote memory loss. One could defend the standard theory by pointing to the parahippocampal damage seen in V.C. Such an argument would, however, represent a significant modification of the standard theory in response to evidence brought against it. Until recently, standard theory assumed the locus of consolidated information to be in lateral and posterior neocortex, not in the parahippocampus or other structures in the medial temporal lobes adjacent to the hippocampus. Those structures were seen as part of the extended hippocampal complex in the medial temporal lobes, whose function was to help consolidate memories rather than be involved permanently in storing and retrieving them. Indeed, as we learn more about the separate functions of these regions, it might make sense to consider the possibility that each of them is involved in retention and retrieval of those aspects of information that they specifically process. For example, Mumby *et al.* found a double dissociation between the effects of hippocampal and perirhinal lesions on remote memory in rats^{15,16}. Thus, damage to the perirhinal cortex led to large and ungraded remote memory loss for objects, but not for spatial location, in keeping with its role in acquisition of object-specific,

but not spatial memory, whereas the reverse was true of the hippocampus (see also Ref. 2 for results with other animal models, and Ref. 17 for evidence that hippocampal lesions produce deficits on remote memory for space and objects). If autobiographical memory is multifaceted, then perhaps we should consider all the medial temporal lobe structures, and not just the hippocampus, as crucial for retention and retrieval of detailed autobiographical memories.

This brings us to the second point, namely the type of tests used to assess remote memory. As Cipolotti *et al.* indicate, their tests of famous and public events has a strong episodic component because the items were chosen to be associated with a restricted context at a given point in time. Other ostensibly similar tests of remote memory might use people and events from a given period but whose notoriety extends long beyond it, becoming more 'semantic', and making one's memory for them less vulnerable to medial temporal lobe lesions. If different regions of the medial temporal lobe contribute to different aspects of remote memory, as they do to newly-acquired memories, then it will be necessary to design tests of remote memory that are as selective as those used in learning. Using such careful tests, we may yet find that lesions to different structures of the medial temporal lobes lead to selective loss of remote memory. These ideas

take us a long way from the standard consolidation theory, but this appears to be the direction in which the field is now heading.

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