



The long and winding road to memory consolidation

Howard Eichenbaum

An imaging study suggests memories may depend briefly on the hippocampus, and for a prolonged period on the entorhinal cortex, before being organized fully within the neocortex.

A cornerstone in the neurobiology of memory is consolidation, the gradual process by which memories acquire permanence¹. Over 100 years ago, neurological observations and behavioral experiments showed that memories are initially impermanent, and therefore susceptible to disruption^{2,3}. Since then, two major phases of consolidation have been identified and partially characterized. The first phase occurs over minutes to hours and involves a cascade of molecular and cellular events that fixes preliminary alterations in synaptic strength in all of the brain's memory systems. The second phase is specific to the brain system that mediates memory for autobiographical events (episodic memory) and worldly knowledge (semantic memory). It occurs gradually over days to years and is believed to involve two-way interactions between the hippocampal region (including immediately adjacent entorhinal cortex and other cortical areas) and widespread areas of the neocortex. In this issue, Haist *et al.*⁴ present functional imaging evidence suggesting that the hippocampus has an initial brief role in consolidation, which is followed by a more extended involvement of entorhinal cortex.

Our initial insights about the prolonged phase of consolidation came from observations on the famous case of H.M. In this patient, removal of most of the hippocampal region resulted in a severe anterograde amnesia, marked by an inability to retain new episodic and semantic memories, plus a graded retrograde amnesia that caused greatest loss for memories acquired recently before the brain damage, less loss for older memories and no loss for remotely acquired childhood memories and knowledge about the world⁵. The temporally graded pattern of retrograde

amnesia suggested that permanent storage takes place outside the hippocampal region. In this view, the limited-capacity hippocampal region temporarily links detailed neocortical representations, and these links eventually become solidified entirely within the neocortex.

Recently, Nadel and Moscovitch⁶ challenged this view, proposing instead that the involvement of the hippocampus is selective for episodic and spatial memory, and that these memory traces always depend on neocortical-hippocampal connections. They found evidence supporting these proposals in clinical cases with selective episodic memory impairment that extended back for the full lifetime, and in animal studies showing time-invariant retrograde loss of spatial memories. They suggested that intact remote memory in H.M.'s and other cases can be explained by incomplete hippocampal damage that spares some of the more numerous traces formed over time for older memories. However, contrary to these observations, Teng and Squire⁷ reported on a clinical case in which a patient retained memory for a town lived in long before the onset of amnesia. This case, involving severe damage to the hippocampal region, demonstrated a graded retrograde memory loss for episodic and semantic as well as spatial and nonspatial information, consistent with the classic view. Also, in animal studies, temporally graded retrograde amnesia has been reported across a variety of memory tests, from eye-blink conditioning to socially acquired food preferences to learning the spatial context of a fearful event. In some of these studies, remote memories survived despite the complete destruction of the hippocampus⁸. In work on both animals and humans, a central issue is whether the damage is truly confined to the hippocampal region. By the classic view, incidental damage to the neocortex would be expected to affect the permanent memory store, resulting in a time-invariant retrograde impairment. This problem reveals an inherent limitation in the lesion

approach. Fully complete and fully selective damage to the hippocampal region is never observed in clinical cases. Even in animal models, this ideal cannot be realized because direct hippocampal damage necessarily involves destruction of major afferent and efferent fibers or their synaptic targets in immediately connected neocortical areas, making it unlikely these areas could function normally.

Can we gain insights into consolidation using other experimental strategies? One fruitful approach has been functional brain imaging, which can inform us on what brain areas are activated during recollection in humans. According to the classic view, one might expect the hippocampal region to be activated more during recollection of recent than remote memories, whereas the neocortex would be activated equally regardless of the age of a memory. Using this logic, two groups scanned subjects during prompted recollection of personal episodes from different periods in life^{9,10}. Both studies found equivalent hippocampal activation for remote and recent memories, and concluded in favor of lasting hippocampal involvement. However, the consolidation hypothesis makes predictions only about when the hippocampal region is required, not about when it is activated. It is entirely possible that the hippocampus is normally activated during any retrieval search, especially if the search is effortful, but that for remote memories, success may be accomplished within the neocortex and not require the hippocampal activation. A lesser hippocampal activation for remote memories may be observed only when a consolidated memory can be retrieved rapidly within the neocortex, calling on minimal, non-requisite hippocampal region engagement.

The study by Haist and colleagues⁴ in this issue used such an approach, and a pattern of brain activations consistent with the classic view emerged. Instead of prompting subjects to retrieve detailed experiences, Haist and colleagues asked subjects to identify faces of famous people. The subjects were scanned during the presentation of faces of people who were famous primarily within a particular decade, as well as faces of non-famous people (Fig. 1). Selective activation for famous faces was observed in the hippocampus robustly only when fame was achieved within the 1990s. In the entorhinal cortex, a part of the hippocampal region that links the hippocampus to widespread neocortical areas, activation was most prominent for

The author is in the Laboratory of Cognitive Neurobiology, Department of Psychology, Boston University, 64 Cummington Street, Boston, Massachusetts 02215, USA.
e-mail: hbe@bu.edu

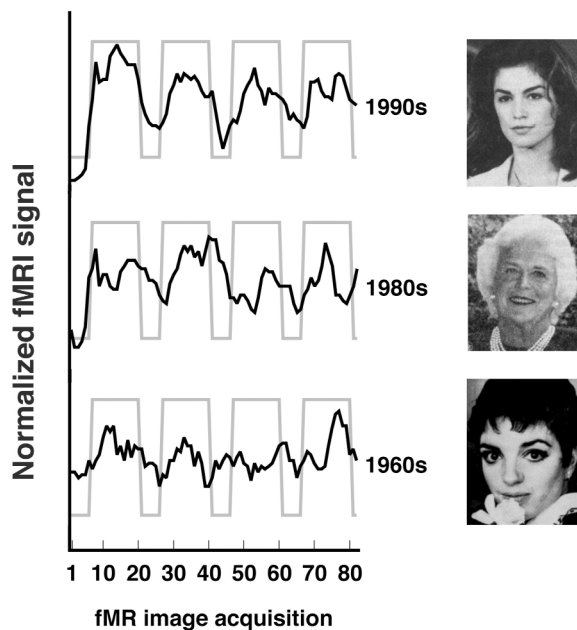


Fig 1. Mean fMRI time series data from the entorhinal cortex (right hemisphere) in eight subjects from the famous faces remote memory test. The upward and downward deflections represent face presentation and rest periods, respectively. Note the stronger signal and higher correlation to the time series for the more recent famous faces (such as Cindy Crawford and Barbara Bush); signal and correlation are reduced in the recall of a more remote decade condition (Liza Minelli). Data courtesy of Frank Haist.

faces that became famous in the 1990s, less prominent for faces famous in the 1980s, and absent for older memories. In contrast, in a neocortical area involved in face recognition, differential activation for famous faces was time-invariant. These results are consistent with the classic view of the prolonged consolidation period.

These findings are also consistent with data from other neurobiological approaches. In a study on rodents, the hippocampus and entorhinal cortex were highly activated during retrieval of a recently acquired spatial memory task, but less activated if the task was acquired remotely¹¹. The opposite pattern, greater activation for remote than for recently acquired memory, was observed in areas of the neocortex, suggesting that primary involvement switches from the hippocampal region to the cerebral cortex as the memory ages. Also, Frankland and colleagues¹² reported that a genetic alteration that selectively blocks lasting

synaptic plasticity in the neocortex (but does not affect hippocampal plasticity) spared memory over 1–3 days, but resulted in memory loss afterward. This finding contrasts with the typical memory loss within a day following damage to or blockade of synaptic plasticity within the hippocampus itself. These findings are consistent with the view that the neocortex gradually acquires a spatial memory trace that only initially depends on plasticity within the hippocampal region.

Finally, although confirming the classic view of the prolonged phase of consolidation, Haist and colleagues' findings suggest this process occurs in two stages, an initial, relatively brief stage mediated by the hippocampus and a more lasting stage mediated by the adjacent entorhinal cortex. These

findings are consistent with the observation that more extended retrograde amnesia takes place in cases where the damage occurs in entorhinal cortex, and not only in the hippocampus¹³. Parallel considerations of the firing properties of neurons in the hippocampal region suggest the same notion of stage-wise consolidation, and also suggest a mechanism¹⁴. Hippocampal neurons rapidly encode a series of events that are specific to a distinct type of behavioral episode, and encode features that are common to related types of episodes. Thus, the hippocampus may contain a network of episodic memories linked by their common features. It is unlikely that hippocampal networks contain many details of episodes, but rather, they may connect areas of the entorhinal cortex encoding more detailed information. Repetitive interactions between the hippocampus and entorhinal cortex could fix episodic representations and their links in the entorhinal area. In turn, it is expected that the greatest level of detail about

episodes is contained in the neocortex, and that networks in entorhinal area connect these neocortical representations. Therefore, the second stage involves repetitive interactions between the entorhinal area and directly connected widespread neocortical areas, leading to a fixation of links between the neocortical representations. Such a staging of consolidation is slow, but has the major advantage of allowing new memories to be interleaved with the pre-existing organization of knowledge in the neocortex, a process critical in theoretical models of memory¹⁵. In addition, this slow reorganization is advantageous for as long as new experiences can shape our pre-existing view of the world. It might be completed within several days, if the pre-existing knowledge is limited and not subsequently changed, such as in the animal models. But, when the body of relevant knowledge is large and frequently supplemented by new information, as in humans, consolidation can go on for decades.

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