Fast track to the medial prefrontal cortex

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Studies of brain-damaged patients have provided remarkable insights into how our memories are organized (1). In particular, these studies have established that memory consolidation is a dynamic process involving gradual (but quite dramatic) reorganization of the circuits supporting memory over time (2, 3). A pioneer in this field was the French psychologist Theodule Ribot. In the late part of the 19th century, Ribot described how memory loss after brain insult tended to be related to the age of the memory: the effect on more recent memories was typically greater than that on older (or more remote) memories (4). Later studies established that damage to the medial temporal lobe (5), and more specifically the hippocampus (1), is responsible for this typical graded amnesia. This Ribot gradient has suggested that the hippocampus is only temporarily involved in the storage and recall of certain types of memory, and that these functions must be subsumed by extrahippocampal structures as memories mature (2, 6).

Hippocampal damage in experimental animals also preferentially disrupts recent memory. Such examples, from mice to monkeys, suggest that time-dependent memory reorganization is an evolutionarily conserved process for memory consolidation (3). However, differences do exist between human and experimental animal studies, and these differences have made it difficult to come up with a unified mechanistic account of memory consolidation. For example, the lengths of the gradients vary dramatically from days or weeks (for example, in rodents) to years (in humans), suggesting that the rate of reorganization may vary greatly across species. Second, although studies in experimental animals have begun to successfully identify extrahippocampal brain regions that support remote memory recall, the evidence from human studies of remote memory has been much less consistent, and it has even been suggested that autobiographical memories may never become truly independent of the hippocampus (7). A new functional imaging study by Takashima *et al*. in this issue of PNAS (8), however, appears to bring these two worlds a little closer together. Their data suggest that the rate of memory reorganization (at least for some types of material) may be much faster in humans than originally thought, occurring over months rather than years, and they identify the medial prefrontal cortex (mPFC) as playing a crucial role in "posthippocampal" recall.

In the experiment (8), subjects were asked to memorize a collection of photographs of various landscapes. In the initial study phase of the experiment, subjects viewed >900 of these photographs for 5.5 sec each. Recognition of these photographs was then probed during a test session conducted either the same day or 1 day, 1 month, or 3 months later. Patterns of brain activation were dramatically different at the different retention delays: whereas the confident recognition of these previous study items was associated with hippocampal activation at the short retention delays (1–2 days), confident recognition of these items was associated with activation of the mPFC at the longer retention delays (1 or 3 months). Therefore, similar to retrospective studies of brain-damaged patients, these data show that circuits supporting this type of recognition evolve in a time-dependent manner (albeit on a surprisingly accelerated time scale).

There is remarkable correspondence between these imaging data in humans and recent cellular imaging studies in mice. In these studies, mice were initially trained in a fear conditioning or spatial discrimination paradigm (9, 10). Then either 1 day (recent memory test) or 1 month (remote memory test) later, the mice were tested, and the expression of the activity-regulated genes *c-fos* and *zif268* induced by these tests was examined. Because the expression of these genes is tightly correlated with levels of neuronal activity, they can be used to track changes in memory organization over time. Regardless of the type of memory probed, a consistent pattern emerged: recall of the recent (day-old) memory was associated with activation of the hippocampus, whereas recall of the month-old (remote) memory was associated with activation of a number of different cortical regions (including the mPFC). And so, just like the new Takashima *et al.* (8) findings, these studies suggest that, within the space of 1 month, the circuits supporting memories undergo major reorganization, with activity shifting from the hippocampus to the mPFC. Although the new data in the Takashima *et al.* (8) study are consistent with these brain-mapping studies in mice, they also raise several new questions.

First, why so fast? The most striking feature of these new imaging data is that they suggest that memory reorganization occurs at a rapid pace, with recognition of the photographs seemingly independent of the hippocampus only 1 month after the initial study phase of the experiment. Most previous estimates of the time course of systems consolidation are based on retrospective studies of patients with damage to the medial temporal lobe, including the hippocampus (1). This raises the issue of whether retrospective neuropsychological and prospective neuroimaging approaches give different answers to the same question. For case studies, damage is rarely limited to the hippocampus. Therefore, when damage extends beyond the hippocampus, longer (or even flat) gradients may result, because sites for permanent memory storage are also affected (11). Although this may lead to overestimates of the length of the gradient in some instances, nonetheless, it is unlikely that extrahippocampal damage alone can account for the typically longer gradients observed in the retrospective patient studies.

Perhaps more important is the type of information encoded and the conditions of encoding. In retrospective studies of brain-damaged patients, autobiographical memories for the recent and remote past have typically been examined. It is likely that these rich detailed memories for specific events within a person's own life are encoded quite differently than the 960 photographs presented in a single study session in the Takashima *et al.* study (8), and these encoding differences may affect how these memories are consolidated. The consolidation of autobiographical memories may involve prolonged dialogue between the hippocampus and cortical structures (12) to slowly integrate these new memories into an existing knowledge base of related experiences in the cortex (6, 12, 13). By contrast, this dialogue may

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be much briefer for the large number of rapidly presented photographs, because it is hard to imagine such material forming richly detailed autobiographical memories of the kind examined in retrospective studies (14, 15). Indeed, it would be interesting to know whether subjects would still be able to recognize these photographs a few years later.

Second, are such dramatic changes in network organization possible on this time scale? The imaging data in the Takashima *et al.* article (8) provide evidence for large-scale network changes occurring within 24 h of initial encoding; for example, there is already a significant shift from hippocampal- to mPFC-dependent recognition in the test session conducted 1 day after the initial study session. What drives these rapid changes? In the Takashima *et al.* study (8), the subjects were instructed to take a nap after the initial study session. The amount of slow-wave sleep during this nap positively correlated with later recognition performance, suggesting that sleep-dependent processes may play a key role in memory reorganization. This is largely consistent with the view that memory reactivation during sleep promotes the gradual reorganization of hippocampal-cortical memory networks (16). Also consistent with this view, waking patterns of brain activity associated with earlier learning are selectively replayed during subsequent sleep in humans (17) and other species, including rodents (18). This coordinated replay occurs in hippocampal as well hippocampal-cortical and cortico-cortical networks and likely promotes gradual stabilization of memory traces in the cortex. Approximately 100 known genes (and ≈400 unidentified genes) have been shown to be up-regulated during sleep, independent of circadian time (19). It is likely that at least some of these genes are involved in stabilizing changes in synaptic strength and structure in reactivated memory circuits on the sort of time scale suggested by the Takashima *et al.* imaging data (8).

Third, what is the mPFC doing? The mPFC appears to play a crucial role in remote memory recall, because pharmacological inactivation or lesions of this region block recall of remote memories in mice, whether they be month-old fear conditioning (9), spatial discrimination (10), or trace eye-blink (20) memories. The mPFC consists of several highly interconnected regions, including the anterior cingulate, prelimbic, and infralimbic cortices. These regions are reciprocally connected to sensory, motor, and limbic cortices, and they are therefore ideally situated to integrate and synthesize information from a large number of different sources. This potential for integration has led to the hypothesis that the ability of the mPFC to process remote memories might mirror that of the hippocampus to process recent memories (3) (Fig. 1). Initially, the hippocampus is thought to integrate information from distributed but relatively independent cortical modules that represent the various features of an experience and then to rapidly fuse these various features into a coherent memory trace (12, 21). As memories mature, this integrative function might be transferred to the mPFC, allowing the cortical network to function independently of the hippocampus (22).

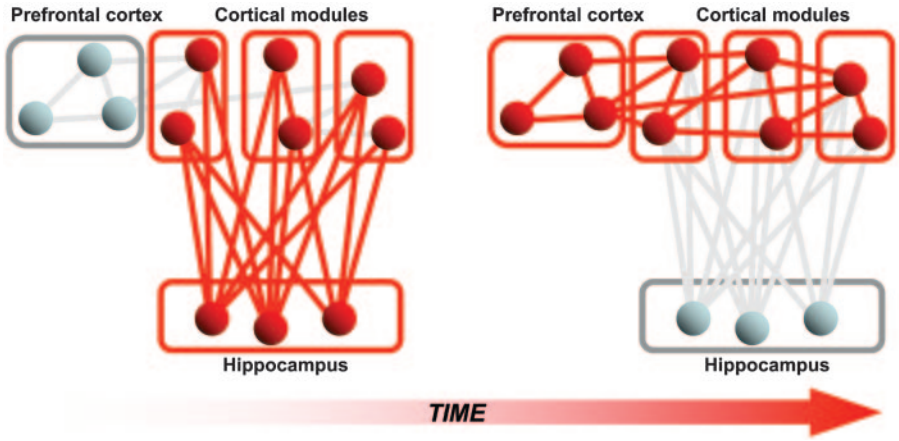

Fig. 1. Time-dependent memory reorganization. Memory recall depends on integration of information from a large number of cortical sources. The data from Takashima *et al.* (8) suggest that this function is initially carried out by the hippocampus, but with time, this integrative function is taken over by the mPFC.

Still, an alternative possibility is that the mPFC is required for more effortful recall (23). In the Takashima *et al.* study (8), response latencies increased as a function of remoteness, perhaps consistent with the idea that greater activation of the mPFC reflects the greater effort required to access a partially degraded memory trace. However, increased latencies at these more remote delays could simply reflect different temporal operating characteristics of the mPFC compared with the hippocampus. That is, mPFC-mediated retrieval could be slower compared with hippocampal-mediated retrieval. The difficulty in distinguishing between these two possibilities is that the age of the memory and the amount of effort required for recall tend to be related, because as memories age, they tend to weaken. To resolve this issue, future studies in human and experimental animal subjects need to dissociate these two variables. For example, this may involve creating conditions where it is possible to contrast recall of a weak recent memory with a strong remote memory.

These issues notwithstanding, the exciting new data presented by Takashima *et al.* in this issue of PNAS (8) suggest that a common conceptual framework may be used to describe memory consolidation processes in both mice and humans. We have highlighted some (of the many) key questions that still need to be addressed, but these data bring us a step closer to coming up with a unified mechanistic understanding of these processes.

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