Memory Networks: Answering the Call of the Hippocampus

Without the hippocampus, experiences disappear without a memory trace. A recent study shows that changing synaptic strength within the hippocampus alters circuit function in widely distributed brain networks.

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Memories hold our personal histories; even a momentary experience can be remembered for a lifetime. I still remember the time an elephant tried to steal my peanut butter and banana sandwich during a visit to the Bronx zoo. I was two years old and sitting in a navy blue stroller watching the elephant reach its trunk past my head to grab the brown paper lunch bag. I smelled the hay, heard the sound of my mother and the elephant tugging on the paper bag, and the ultimate ripping sound - mother had won. How do we remember these events after many years? The hippocampus is implicated as, in the absence of a functional hippocampus, memories fade almost immediately. A recent study sheds new light on the underlying neural processes by showing that changing synaptic strength within the hippocampus alters widely distributed brain networks [1].

A generation of research has begun to reveal the brain mechanisms of memory. We know that encoding episodes depends upon brain structures in the medial temporal lobe (MTL), especially the hippocampus. After damage to the hippocampus people forget their experiences almost as soon as they occur. Like people, animals with hippocampal damage have impaired memory, and forget such things as where they recently found food [2]. The anatomy and physiology of the MTL reveals a system well-suited to encoding the multimodal information that comprises memory. Cortical regions relay highest order perceptual and motor information to the MTL, as do subcortical regions that support motivation and 'affect' (emotional responses), and this global, abstract record of neural coding converges on the MTL and ultimately the hippocampus.

Hippocampal circuits support rapidly induced, yet persistent, synaptic

plasticity that forms new associations among these different inputs, as revealed experimentally by long-term potentiation (LTP) and depression (LTD). LTP, an enduring increase in synaptic strength, can be induced in seconds by electrically stimulating hippocampal afferents with pulse trains that mimic spontaneous neuronal activity, and the potentiation can last for months. New learning induces detectable patterns of hippocampal LTP and LTD [3], and blocking LTP induction impairs learning in tasks that require the hippocampus and prevents the formation of stable neuronal firing patterns that correlate with new learning [4]. The converging inputs and remarkable plasticity may explain how single neurons in the human hippocampus come to fire selectively to highly abstract ideas, independently of how the ideas are brought to mind. For example, photographs, line drawings and caricatures of a familiar face will activate the same neuron that fires to the sound of the persons name or the same spelled in text [5]. Activity of the hippocampal neurons that respond selectively to specific video clips is triggered afterward during 'free recall', when people are asked to remember those recent experiences without further specification [6].

The mechanisms linking synaptic plasticity to encoding are better understood than those of memory consolidation, storage, or retrieval, which entail something like generating perception from the inside out. Remote memory deficits suggest that memory storage and retrieval engages the divergent, polysynaptic network of efferent fibers from the hippocampus that project back to the same brain regions that its inputs come from. MTL damage impairs the formation of new memories, and often debilitates remote memories - those acquired before the onset of brain damage [7]. The severity and extent of this

retrograde amnesia varies with the locus and amount of temporal lobe injury [8]. Damage restricted to the hippocampus proper seems to impair memory formation, but not older memories. More extensive damage to the temporal lobes can obliterate large portions of a persons autobiographical memory [9], but even the severest amnesia spares memories acquired long before the onset of the brain damage [10]. Consolidation theories propose that the hippocampus both rapidly encodes new information and more gradually establishes stable memories in widely distributed brain networks ([7]; compare [11]). The bidirectional interaction between the hippocampus and other brain circuits likely provides a crucial mechanism for consolidation and memory retrieval. Presumably the occurrence of synaptic plasticity in the hippocampus is coordinated with synaptic changes throughout this extended network.

Important functional interactions occur between the hippocampus and other brain structures, but their link to hippocampal synaptic plasticity is less clear. Classic experiments by Penfield and Gloor [12] demonstrated that electrical stimulation of the MTL in people (typically patients with epilepsy) elicited reports of vivid, multimodal imagery, sometimes described by patients as memories. Unilateral microstimulation of different parts of the rat hippocampus increased 2-deoxyglucose uptake (a metabolic marker of neuronal activity) in corresponding regions in the contralateral hippocampus, and if stimulation produced seizures, the increased metabolic activity spread to other connected brain regions, including the subiculum, perirhinal and entorhinal cortex, amygdala, diencephalic regions, and both olfactory and prefrontal cortices [13]. These results provide compelling evidence that hippocampal activity can spread throughout widespread brain networks, but the strongest effects were a consequence of pathological activity, such as seizures, or seemed to reflect pre-existing connectivity rather than the kind of plasticity that would be required for storage or consolidation.

More recent functional magnetic resonance imaging (fMRI) studies have revealed that coactivation of the hippocampus and, for example, the prefrontal cortex predict subsequent memory performance in people [14]. Single-unit recordings in behaving rats showed that spiking by prefrontal cortical neurons becomes phase locked with hippocampal units and slow waves when rats successfully use spatial memory [15,16]. These results again imply that synaptic plasticity in the hippocampus is somehow coordinated with more widespread network activity.

By combining fMRI and in vivo electrophysiology, Canals et al. [1] have now shown that inducing plasticity locally in hippocampal circuits simultaneously changes activity in widely distributed brain networks in the absence of pathology or detectable seizure activity. Using standard techniques to assess LTP, anesthetized rats were implanted with electrodes to stimulate the perforant path and record monosynaptic evoked potentials in the dentate gyrus of the hippocampus. High-frequency stimulation of the perforant path rapidly induces enduring potentiation of ipsilateral dentate granule cell synapses [17,18]. The new twist here was to perform this classic LTP experiment while whole-brain blood-oxygen-leveldependent (BOLD) signals were recorded in a 4.7 Tesla vertical MRI scanner. The results confirmed that the fMRI signals correspond with the evoked potentials recorded electrophysiologically: population excitatory post-synaptic potentials (EPSPs), spikes, and BOLD responses all covaried with stimulus intensity. Indeed, the EPSP slope correlated near perfectly with the percent increase in the BOLD response. As might be expected, LTP induction caused a persistent, correlated increase in each of these measures. Moreover, all of these changes were prevented by MK-801, a drug that permits excitatory neurotransmission but prevents LTP induction by blocking a crucial NMDA receptor-associated Ca²⁺ channel. (NMDA receptors are a class of glumate receptor strongly implicated in LTP and memory formation).

Although it is reassuring that fMRI detected changes in synaptic activity, the subsequent investigations of

more widespread network changes demonstrated the power of this new approach. After LTP induction, but not after control simulation, perforant path stimulation increased BOLD signals across broad and bilateral regions of the MTL, including the entorhinal cortex, subiculum, and the hippocampus. Moreover, in four of six rats, the activation spread more extensively and included the perirhinal cortex, the prefrontal cortex, the nucleus accumbens, and the anterior olfactory nucleus. In other words, stimulation patterns previously thought to primarily induce synaptic plasticity locally in the ipsilateral dentate gyrus, in fact altered subsequent BOLD activity across a wide network of interconnected brain regions. The results imply that hippocampal activity patterns that induce LTP locally also coordinate network synaptic changes more widely - precisely the kind of mechanism that could support memory consolidation.

This new work [1] provides an important approach for investigating the mechanisms linking circuit activity, synaptic plasticity, and the reorganization of distributed networks required for memory consolidation. Clear challenges remain. One is to determine if network changes engaged by learning and memory performance in behaving animals can be detected by these methods. Another is to determine if the particular stimulation patterns used in this experiment are unique, or if these findings generalize to other methods, perhaps, at the limit, chemically induced LTP. If indeed the brain answers the call of the hippocampus to change based on the induction of synaptic plasticity in hippocampal circuits, then local injections of NMDA receptor antagonists should block not only hippocampal LTP, but also the more widespread changes in network activity observed here. The new methods and results can address these issues to help reveal more precisely the changing patterns of activity across brain regions that may represent memories.

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DOI: 10.1016/j.cub.2009.03.020