Toying with memory in the hippocampus

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Mice lacking NMDA receptors in hippocampal area CA1 are deficient in spatial memory. They also have nonspatial memory deficits, which are overcome by environmental enrichment.

> "Memory being... altogether conditioned on [the ability to excite] brain-paths, its excellence in a given individual will depend partly on the number and partly on the persistence of these paths." (William James[1], p. 659)

In this two-factor view of the biological basis of memory, James characterized the "persistence" factor as a physiological property of one's brain tissue. He envisioned persistence as a "native tenacity," except for natural variability among individuals and decline with illness or aging. By contrast, James characterized the "number of paths" factor as very much modifiable with experience. He argued that memory could be improved substantially by establishing a large network of linkages through which one could readily associate, and later access, a new memory. As an example, James described the college athlete who was a "dunce at his books" but could astonish with his ability to remember sports statistics precisely because he had worked at creating a rich knowledge framework for this kind of information. James may have been prescient in proposing that enriching one's memory network can make up for a lesser native persistence, as in findings from Joe Tsien and colleagues[2] in the current issue of *Nature Neuroscience*.

This report extends a recent study that used state-of-the-art molecular genetics to knock out the N-methyl-D-aspartate (NMDA) receptor beginning at postnatal weeks three and four selectively within the CA1 region of the hippocampus[3]. These mutant mice lack NMDA-receptor-dependent long-term potentiation (LTP), a type of physiological plasticity thought to be a cellular substrate of memory. Correspondingly, they have severely impaired spatial learning and memory[4]. Now Tsien and colleagues[2] show that mice with the same mutation are severely impaired across a broad range of nonspatial learning tests. The authors also address James's "number of paths" factor by exposing these mice to a complex 'enriched' environment, in which they could presumably establish many diverse associations through exploration. By electron microscopy, environmental enrichment was shown to increase the number of synaptic connections within hippocampal area CA1 in normal mice, and surprisingly also in the mutant mice, even without NMDA receptors. Furthermore, enrichment improved learning performance in control mice and almost eliminated the memory deficits observed in the CA1 NMDA receptor-knockout mice.

How is it possible that enriched experience can support new memory even without NMDA-receptor-dependent LTP? Does the observed anatomical plasticity compensate for the impaired functional plasticity, and if so, how? Here we consider two interpretations of Tsien and colleagues[2] that differ in the critical locus where increased connectivity ameliorates the loss of NMDA-receptor-dependent LTP in area CA1. First, enhanced intrinsic hippocampal connectivity might compensate for the loss of LTP through NMDA-receptor-independent processes. Second, enhanced connectivity outside the hippocampus, specifically within the neocortex where NMDA-receptor-dependent plasticity is intact, might compensate for a dysfunctional hippocampus.

According to the first possibility, the hippocampus might use processes that do not require NMDA receptors after exposure to environmental enrichment. In CA1, LTP can be induced by strong patterned stimulation, even when NMDA receptors are pharmacologically blocked[5]. This form of LTP is NMDA receptor independent. Tsien and colleagues[2] show that many new dendritic spines form, and robust synaptogenesis occurs within CA1 after enrichment experience (**Fig. 1b**) in both mutant and control mice. This synaptogenesis does not depend on NMDA receptors because an equal number of new dendritic spines and synapses formed in mutant and con-

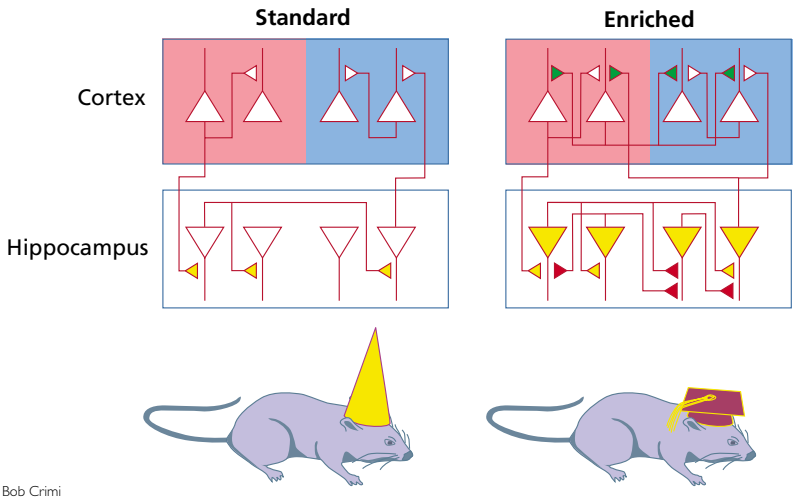

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Fig. 1. Environmental enrichment increases the connections within the hippocampus and neocortex. (**a**) Under control conditions, there are fewer synapses within both the hippocampus and cortex, as well as between these areas. The pathway through the hippocampus could be required to connect distinct representations in the neocortex (red and blue), and this capacity could be mediated by strengthening the existing connections within the hippocampus using NMDA receptors (yellow). (**b**) After exposure to an enriched environment, more connections are formed within both the hippocampus and neocortex, and perhaps between these areas. Strengthening of additional non-NMDA receptor connections (orange) within the hippocampus, or between the hippocampus and cortex, may suffice to improve memory. Alternatively, the additional connections within the neocortex (green) may suffice to link distinct neocortical representations and thereby 'short circuit' the hippocampal contribution.

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trol mice following environmental enrichment. Other studies have shown robust synaptogenesis in the adult brain when synaptic activity is silenced pharmacologically[6,7]. The new spines form either when presynaptic release of neurotransmitter is blocked or when postsynaptic glutamate receptors are blocked, and new spines can last for at least eight hours without subsequent activation. Furthermore, induction of NMDA-receptor-dependent LTP in hippocampal area CA1 does not require the formation of new synapses[8,9]. Together with the findings from Tsien and colleagues, these studies show that dendritic spines can form in the mature brain without NMDA-receptor-dependent processes like LTP, and even without synaptic activity. Perhaps the new spine synapses can facilitate NMDA-receptor-independent processes within the hippocampus to enhance subsequent learning and memory in CA1-NMDA knockout mice.

How might the enrichment-induced dendritic spines within the hippocampus facilitate learning and memory? Hebb[10] originally suggested that learning and memory occurs by strengthening some connections and weakening other, inappropriate connections. Tsien and collegues show that the enrichment effects are specific to a particular type of spine synapse, causing an increase only in those with a continuous (that is, 'non-perforated') postsynaptic surface. There was no change in the frequency of large irregularly shaped synapses, those with 'perforated' postsynaptic surfaces. Thus, the non-perforated synapses might enhance some forms of learning and memory via NMDA-receptor-independent mechanisms. Other studies have shown a transient elaboration of a subset of perforated synapses with NMDA-receptor-dependent LTP[11]. An open question is whether NMDA-receptor-dependent changes at perforated synapses might be involved in refinement of synaptic connections during more complex learning protocols than those tested by Tsien and colleagues[2]. Either way, these findings are among the first to demonstrate a possible role for non-perforated synapses in learning and memory. Understanding the function of the small non-perforated synapses is especially important because these are normally the most abundant synapse type (> 75%) in both hippocampus and neocortex.

The second possible explanation for the findings of Tsien and colleagues[2] is that the hippocampus can be short-circuited altogether during learning and memory if environmental enrichment can induce enough connectivity outside the hippocampus, specifically within the neocortex. Tsien and colleagues did not examine the cortex, but previous evidence indicates that enriched experience increases intrinsic connectivity within the neocortex[12]. It is clear that memory is not mediated solely by CA1, or even by the entire hippocampus alone. Rather, the hippocampus is part of a memory system that prominently involves its bidirectional connections with diverse and interconnected regions of the cerebral cortex[13] (**Fig. 1**). Within this system, memories are likely 'stored' among large cell assemblies widespread across the cortex, and the organization of associations is mediated by the formation of links between the cell assemblies[10]. The role of the hippocampus may be to facilitate the consolidation of these cortical linkages by storing aspects of new information, or indices pointing to cortical loci of new representations, and using these to temporarily link otherwise separated cortical memories (**Fig. 1a**). We know that the role of the hippocampus is temporary because it is not necessary for the recall of long-established memories, suggesting that eventually new intracortical connections form to mediate permanent links[14]. The increase in synaptic connectivity in neocortex, likely to have occurred as a result of enriched training experience[12], might be so effective that lasting plasticity within the hippocampus is not required (**Fig. 1b**), at least for the relatively simple types of learning examined by Tsien and colleagues[2].

One way to distinguish the 'cortical hypothesis' from the 'hippocampal hypothesis' discussed above would be to determine whether the CA1-NMDA knockout mice after enrichment can tolerate loss of hippocampal area CA1 and still enjoy improved learning and memory. An early study[15] found that enriched experience reduced, but did not eliminate, the effects of hippocampal damage on spatial learning. These findings are consistent with the possibility that both putative mechanisms contribute to the effects of enrichment.

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Attention - brains at work!

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Two new studies use event-related fMRI to reveal a network of brain regions that are activated during different steps in the control of visual spatial attention.

The amount of information that is potentially available through our sense organs is far greater than our brains can handle. Much of this information must therefore be discarded, and the brain must select only those stimuli that are of greatest relevance for further processing. Understanding how this occurs is a major challenge for cognitive neuroscience, and two papers[1,2] in the current issue of *Nature Neuroscience* provide the most detailed spatio-tem-

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