How do memories leave their mark?

Mark F. Bear

We remember some events while others slip from our minds. The results of a new study indicate how records of sensory experiences might be consolidated into long-term memory.

Sensory experiences leave their mark on the brain by altering the effectiveness of synapses between neurons. Based on how active they are during a sensory experience, some synapses on a neuron grow stronger, while others grow weaker; and the pattern of synaptic change represents a memory of the experience. Changes in synaptic strength are due to modifications of existing synaptic proteins, by phosphorylation and dephosphorylation, for example. However, unless these modifications are consolidated, the synaptic strengths decay back to their original values and the memory is lost.

Consolidation requires protein synthesis[1]. Presumably, the newly made proteins are transported to the modified synapses where they make the temporary changes permanent. But how do they find the correct synaptic address? The results of a clever new study have led Frey and Morris[2] (on page 533) to suggest an answer.

Frey and Morris used a popular synaptic model for memory: hippocampal long-term potentiation (LTP). LTP is a prolonged increase in the strength of synapses that have been stimulated repetitively at high frequencies (for example, 100 Hz; Fig. 1a). The duration of the change depends on how much of this rapidly repeated ('tetanic') stimulation is given. A single, brief tetanus produces a large increase in synaptic strength, but this decays back to baseline values within a few hours (Fig. 1b, single upward arrow). Repeated, longer tetani produce about the same change in synaptic strength, but the change persists for longer than 8 hours (Fig. 1b, three upward arrows). LTP that lasts for longer than 3 hours is termed late LTP.

The main difference between single and repeated tetani is revealed by the effect of agents that inhibit protein synthesis. Such agents lead to a reduction in the time course of LTP that is caused by repeated tetani, so that it resembles the decaying LTP that is caused by a single, brief tetanus (Fig. 1b, dashed line). Along with other observations, this has led to the idea that not only do repeated tetani produce post-translational modifications in the existing synaptic proteins that cause the initial potentiation, but they also trigger a wave of protein synthesis that causes the LTP to become consolidated[3].

Frey and Morris set out to determine whether the newly made proteins would act only on those synapses whose stimulation had triggered their synthesis. To do this, they took advantage of another property of LTP called 'input specificity', which means that potentiation occurs only at (or near[4]) synapses that are stimulated during the tetanus. So if a tetanus was delivered to the first synapse in Fig. 1, only that synapse would be potentiated — the second synapse would be unchanged.

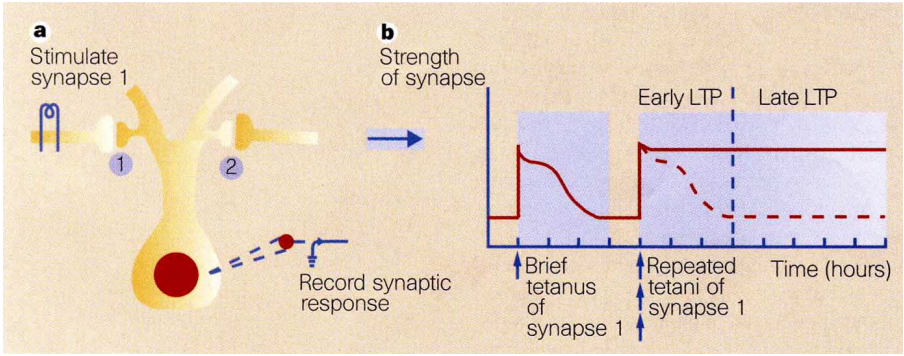

Figure 1 **The memory of a sensory experience is formed by a pattern of changes in the strength of synapses.** a, **Individual synapses can be stimulated repetitively at high frequency ('tetanic stimulation').** b, **The resulting increase in the strength of the synapse can be recorded. A brief tetanus (single upward arrow) produces LTP which lasts about 3 hours. Repeated tetani (three upward arrows) produce a change in synaptic strength that lasts longer than 8 hours. If a protein-synthesis inhibitor is added during, and immediately after, the repeated tetanization, the duration of LTP is much less (dashed line). The protein-synthesis-dependent LTP that lasts longer than 3 hours is known as late LTP.**

The idea behind the experiment was to stimulate the first synapse with repeated tetani to trigger the wave of protein synthesis, and then ask if these proteins would consolidate LTP induced by a single tetanus at the second synapse some time later (Fig. 2, overleaf). They found that the wave of protein synthesis that is triggered by repeated tetani at the first synapse does lead to consolidation of LTP at the second synapse — but only if the single tetanus to the second synapse is delivered within 90 minutes of the initial repeated tetanization. So the new proteins are not targeted specifically to the synapses whose activity triggered their synthesis; they are available to all the synapses on the neuron. However, only the synapses that are tetanized within the 90-minute time-window can use this new resource.

This work has several implications. The involvement of gene expression in establishing long-term memory had suggested that memories may actually reside in the nucleus, and that they are maintained by self-sustaining changes in gene transcription. But the new results indicate that all that may be necessary is a transient change in gene expression, to provide a resource that can prolong an otherwise temporary change in synaptic strength[5]. Another implication is that the induction of LTP creates a synapse-specific receptor — or tag — that accepts the resource provided by gene expression. If the resource is available and the tag is present, the synaptic enhancement is consolidated.

Two obvious questions remain: what is the resource, and what is the synapse-specific tag? The resource, which could be one or several proteins, is likely to be the product of immediate–early gene expression, which is under the control of the cyclic-AMP-response element (CRE).

The reasons to suspect the involvement of immediate–early genes are the rapid onset and brief duration of the essential wave of protein synthesis, and the fact that these genes are turned on by strong synaptic stimulation[6]. There are several reasons to suspect that expression of the resource is controlled by CRE: CRE-mediated gene expression occurs in hippocampal neurons following repeated, but not single, tetani[7]; and disruption of CRE regulation prevents the induction of late LTP with repeated tetani[8].

A good guess as to the identity of the synapse-specific tag would be a synaptic phosphoprotein. One intriguing possibility is that the tag is a substrate for cAMP-dependent protein kinase, as there is evidence that cAMP is generated at tetanized synapses[9]. This could explain why the addition of cell-permeable analogues of cAMP to hippocampal slices produces a nonspecific

synaptic strengthening that resembles late LTP[10]. Treatment with cAMP could therefore potentially both tag the synapses and stimulate production of the resource.

The story holds together nicely for the LTP model, but what about real-life memories? One of the most exciting developments in neurobiology over the past few years has been the discovery that CRE-mediated gene expression is required for the establishment of long-term memory in species ranging from fruitflies to mice[11]. The new results indicate that these CRE-dependent proteins will consolidate (into long-term memory) events over and above those that triggered the gene expression in the first place. Where were you when Kennedy was shot? If you remember, Frey and Morris would suggest that the synapses in your brain that were transiently tagged by the experience of your location were consolidated by the wave of protein synthesis that was triggered by the news of the assassination.

Because the consolidation process is not restricted to the synapse by which it was triggered, it could be subject to modulation by other signals. Interestingly, the profound amnesia that is produced by lesions of the medial temporal lobes is qualitatively similar to that produced by protein-synthesis inhibitors. Perhaps the medial temporal lobes exert their effects on memory consolidation by chemically modulating gene expression in neurons throughout the cerebral cortex. Understanding such modulation could open new avenues for the treatment of the memory loss that often accompanies traumatic brain injury, stroke, Alzheimer's disease and normal ageing. □

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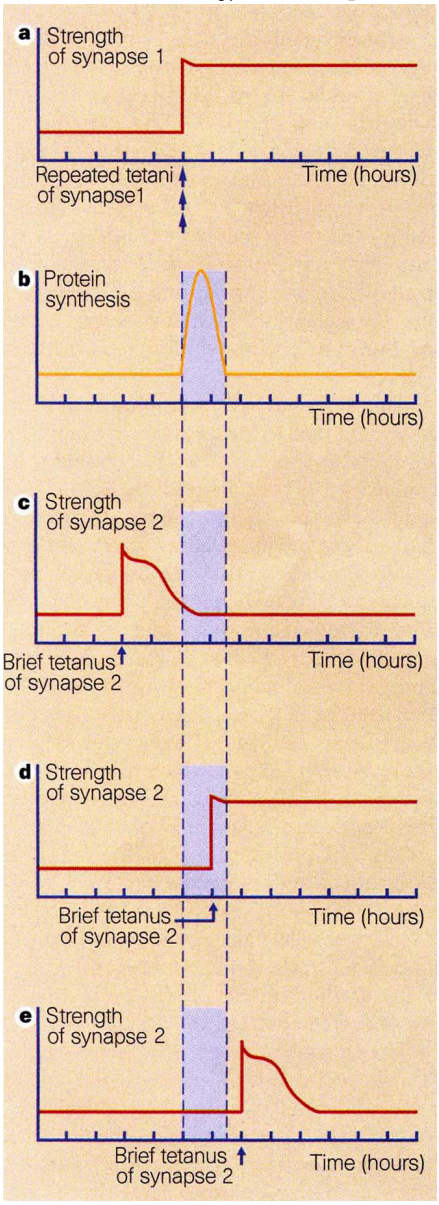

Figure 2 **Measurements made by Frey and Morris[2] to determine whether the proteins induced by repeated tetanization of synapse 1 allow consolidation of a single tetanus at synapse 2.** a, **Repeated tetani are delivered to synapse 1 to trigger a wave of protein synthesis.** b, **Time course of the presumptive increase in protein synthesis required for consolidation of LTP.** c, **Effect on synapse 2 of a single tetanus delivered before the wave of protein synthesis is triggered; no late LTP is produced.** d, **Effect of a single tetanus delivered to synapse 2 during the wave of protein synthesis; late LTP is produced.** e, **Effect of a single tetanus at synapse 2 after the wave of protein synthesis; no late LTP is produced.**

Quantum optics

The amazing atom laser

Keith Burnett

The word laser now has a strong emotional impact, conjuring up images of space-battles and high-tech surgery. There was a time when this strange acronym, as yet unloved by science-fiction writers, conjured up nothing at all to a general audience. What is more, scientists thought of the laser as nothing more than a curiosity brought forth by optical physicists and engineers, fascinating perhaps, but little more. It was termed, admittedly by the unkind, 'a solution in search of a problem'.

We now have the beginnings of a new type of solution — a new type of laser. This is not a source of light but of matter, in the form of alkali atoms. In the 27 January issue of *Physical Review Letters*[1], a group at MIT led by Wolfgang Ketterle describe an 'output coupler' that allows pulses of matter to escape in a narrow beam from a trapped Bose–Einstein condensate (Figs 1 and 2). In the 31 January edition of *Science*[2], the same group show that this beam is coherent, an essential test of laser behaviour.

The possibility of an atom laser should not be such a shock if we recall that all matter has a wave-like nature, just like light, with each particle's de Broglie wavelength determined by its momentum. So if light is made of waves and can be produced in laser form, why not a laser-like source of matter waves?

The problem is how to do it. In the case of light, we rely on a very important property of photons. Energy is first put into a material form — the excited states of atoms or molecules — and then re-emitted in the form of photon energy packets; lasers are possible because photons can be created with exactly the same direction and speed as those that are already travelling through the medium. This means that the number of photons travelling through a laser medium can become enormously amplified. This property was elucidated first by Einstein and Bose in their studies of the implications of wave mechanics for the theory of radiation.

So can this idea be extended from photons to other particles, such as atoms?

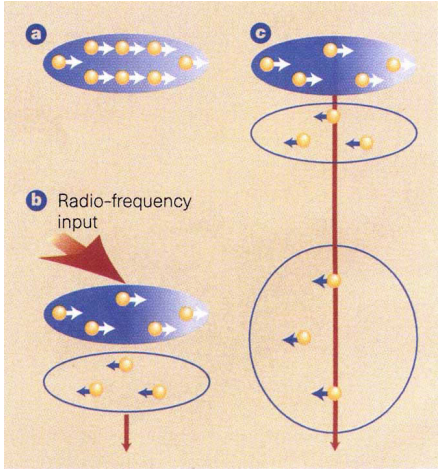

Figure 1 **Radio leakage. The magnetically trapped Bose–Einstein condensate** (a) **is separated into two states with opposing spins by a radio-frequency input** (b)**. The state with flipped spin is no longer held by the magnetic trap, and so falls out** (c).