NEUROSCIENCE

Forgetfulness illuminated

Memories are stored in the complex network of neurons in the brain. With the help of innovative tools to manipulate the connections between neurons, memories in mice can now be erased with a beam of light. SEE ARTICLE P.333

JU LU & YI ZUO

More than a century ago, the German biologist Richard Semon proposed that memories leave physical traces in the brain, and coined the term 'engram' to describe such traces[1]. Although the concept has gained general recognition, the search for the engram is ongoing. In this regard, the synapse — a specialized connecting region between neurons — has received much attention, but there is still no direct evidence of a causal link between synaptic changes and memory formation. In this issue, Hayashi-Takagi *et al.*[2] (page 333) fill this gap. Using ingenious protein engineering and live imaging, the authors identify which synapses are activated when a mouse learns a motor skill, and then weaken these synapses to erase motor memory.

Most synapses in the brain form between axons (neuronal 'output cables') and dendrites (input cables). Signals to excitatory synapses are usually received by micrometre-sized protrusions called spines that emanate from dendrites. The size of the spine head correlates with the strength of the synapse[3]. Spines may emerge, disappear or change in size during learning and memory formation, reflecting changes in the wiring of neuronal circuits[3].

To investigate the causal relationship between the formation of motor memories and the structural potentiation of spines (spine formation or enlargement), Hayashi-Takagi *et al.* developed an 'optoprobe' called AS-PaRac1 that manipulates potentiated spines in response to light. The DNA construct for AS-PaRac1 encodes a light-activatable version of the small signalling protein Rac1, whose prolonged activity induces spines to shrink. The construct also incorporates the dendrite-targeting sequence of the gene *Arc*, which is expressed rapidly and transiently in response to neuronal activity, ensuring that the probe moves to dendritic spines that are undergoing structural potentiation. The AS-PaRac1 optoprobe is the first optogenetic tool to enable the manipulation of potentiated spines.

Hayashi-Takagi and colleagues expressed AS-PaRac1 in the motor cortex of mice and trained the animals to run on an accelerating rotating rod known as a rotarod. Light activation of AS-PaRac1 in potentiated spines after learning caused the spines to shrink, disrupting the animals' ability to run on the rotarod. This demonstrates the causal relationship between synaptic strength and motor memory in this context (Fig. 1).

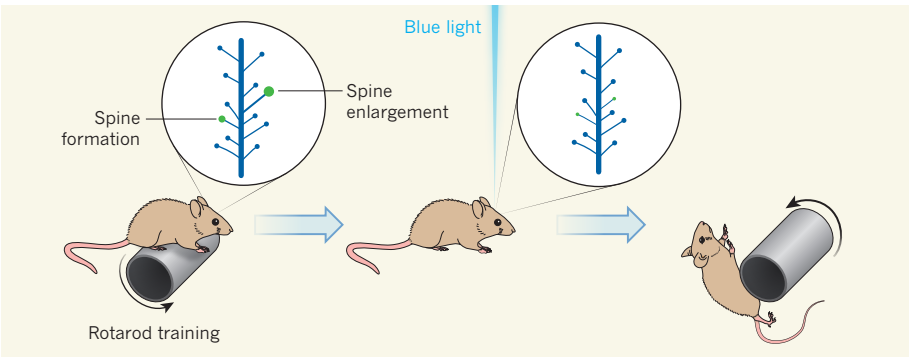

Figure 1 | Inducing forgetting. A neuron receives excitatory signals from other neurons through dendritic spines. When a mouse learns a new task, such as running on an accelerating rotating rod (a rotarod), spines involved in learning this task become potentiated (new spines form and existing spines increase in size). Hayashi-Takagi *et al.*[2] developed an 'optogenetic construct' based on a light-activatable form of the small signalling protein Rac1, which targets recently potentiated dendritic spines. Blue light activates the modified Rac1, which induces shrinkage of the spines. The authors found that spine shrinkage caused the mouse to forget the skill it had learnt, so it soon fell off the rotating rod.

Next, the authors showed that the effect of the probe is task-specific. When mice learnt to run on the rotarod and then learnt to walk on a thin beam, disrupting the spines that were potentiated during beam walking did not affect performance on the rotarod. Furthermore, AS-PaRac1 activation in spines that spontaneously potentiated two days after learning (presumably because of unrelated motor tasks) did not affect motor performance. Finally, when the authors retrained mice on the same task for which spine potentiation had been disrupted, most of the optically shrunken spines reverted to their original potentiated sizes. Together, these results suggest that distinct subsets of synapses are altered in a task-specific way during motor learning and memory formation.

In the long quest for the engram, neuroscientists have reached the consensus that the mammalian brain stores different memory traces in different subsets of neurons in specific regions. Methods for labelling, imaging, activating and silencing neurons in animals have enabled researchers to map the ensemble of neurons that correlates with a particular learning task, to manipulate their activities, and even to generate artificial memory traces[4–6]. However, a single neuron may participate in the processing and storage of more than one distinct piece of information[7]. Therefore, the engram of a particular memory involves not only the identity of the constituent neurons, but also the entire set of synaptic connections between these neurons. How memory is allocated at this synaptic level remains unclear.

To qualify as an engram, a synaptic circuit should satisfy several criteria. First, changes in synaptic structures and function should correlate with learning. Second, blocking such synaptic modifications should prevent memory formation, demonstrating the need for these changes. And third, artificially inducing synaptic changes should be sufficient to produce a memory without the need for behavioural training. Over the past decade, *in vivo* imaging has revealed[8] that the dynamic formation and elimination of dendritic spines correlates with motor-skill learning and memory. Now, Hayashi-Takagi and colleagues have taken the next step, by establishing necessity — they show that undoing the synaptic changes that accompany motor learning does indeed disrupt the memory.

The development of genetic and optical tools such as AS-PaRac1 promises to enable

dissection of the finer details of the engram. The use of promoter sequences that drive the expression of target genes in a cell-type-specific manner, as well as connectivity-specific labelling methods[9], can help to unravel the roles in learning and memory of synaptic circuits formed by different types of neuron — revealing, for example, the relative contributions of excitatory and inhibitory neurons, or of neurons in different layers of the brain's cortex. When we have a deeper understanding of the molecular signalling events that occur at synapses during memory formation[10], tools similar to AS-PaRac1 can be devised to modulate other components of the molecular machinery. Improved microscopy techniques can already target individual neurons or synapses[11], rather than manipulating a population of neurons as a whole.

When used together, such technical advances will enable us to strengthen existing engrams, to facilitate the formation of new ones, and to generate synthetic memory traces at the synaptic level. We will then be able to study the interaction between different memory traces, as well as the mechanisms that translate an engram into behavioural outputs. These efforts should allow us to gain an understanding of the intriguing phenomenon of memory simply by shining a light on its physical basis. ■

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CATALYSIS

Tens of thousands of atoms replaced by one

Many catalysts comprise metal nanoparticles on solid supports. The discovery that single atoms of palladium anchored to a solid support also exhibit high catalytic activity might help to conserve the supply of this and related rare metals.

JOHN MEURIG THOMAS

The platinum-group metals — ruthenium, rhodium, palladium, osmium, iridium and platinum — are extensively used as catalysts in industries that produce compounds such as agrochemicals, dyestuffs and pharmaceuticals, and several of them are crucial components of catalytic converters in cars. But as demand for these relatively scarce metals increases, their future availability is a cause for concern. This would be dispelled if the metals could be used in an atomically dispersed state, rather than as nanoparticles containing up to 100,000 atoms, as is conventional. Writing in *Angewandte Chemie*, Vilé *et al.*[1] report that individual atoms of palladium can be anchored to carbon nitride (C_3N_4), an easily prepared nanoporous solid[2]. The resulting materials are excellent, thermally stable catalysts for selective hydrogenation reactions, which facilitate the production of many organic substances, including polymers and biologically important compounds[3].

There are many examples of catalysts in which the active components are supported nanoparticles of platinum-group metals (PGMs) or gold (see refs 4–6, for example). But in several cases, it has long been suspected[7–9] that the nanoparticles are unimportant, and that catalysis occurs at single-atom sites. Indeed, isolated metal atoms have previously been manipulated as a strategy for enabling selective catalytic hydrogenations[10]: atomically dispersed palladium atoms on the surfaces of a copper crystal stimulate local breaking of the bonds in hydrogen molecules, and the resulting hydrogen atoms become mobile on the copper surface, readily reacting with unsaturated molecules such as acetylene and styrene. However, in that system, the single atoms are laid down on the copper by heating a palladium source in a high-vacuum chamber using an electron beam. This method is suitable for preparing single-atom catalysts of other PGMs, but does not readily translate to the production of industrial-scale quantities of catalysts.

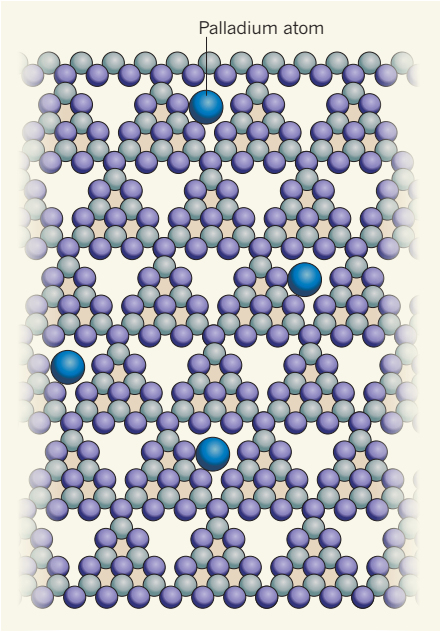

Figure 1 | A single-atom palladium catalyst. Vilé *et al.*[1] report that isolated palladium atoms on a solid support of carbon nitride (C_3N_4; carbon atoms, grey; nitrogen atoms, purple) act as catalysts for hydrogenation reactions. Strong bonds to the nitrogen atoms firmly anchor the palladium atoms in roughly triangular pores in the stacked, two-dimensional layers of the support. Only one layer is depicted, for simplicity. (Adapted from ref. 1.)

In their study, Vilé and colleagues propose that the catalytically active individual palladium atoms are tenaciously attached to the nitrogen atoms of the C_3N_4 support (Fig. 1), owing to the lone pair of electrons that each nitrogen atom has[11]. The authors' X-ray-absorption studies found no evidence of palladium–palladium bonds, indicating that the atoms are indeed separate from each other. The researchers also studied their samples using a technique called annular dark-field electron microscopy[12], which takes advantage of the Rutherford scattering of electrons[13] (scattering at large angles) to detect heavy atoms of PGMs on the light elements of C_3N_4. These experiments identified only single palladium atoms in the active catalyst.

Vilé and co-workers' catalysts are particularly notable because reproducible, thermally stable single-atom preparations can be readily made, provided that care is taken to incorporate only small amounts of the palladium on the nanoporous support. Moreover, C_3N_4 is inexpensive and may be routinely prepared in a graphite-like form[2,14] that has relatively widely separated layers, thereby increasing the accessibility of the anchored palladium atoms to reactants. The authors report that it also has the merit of a high surface area