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Shining a light on memory representations

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A recent study provides an exciting glimpse into the representations of events as they appear in the brain by showing that optogenetic activation of the neural representation of an environment can substitute for the actual experience and produce memories in a manner consistent with natural exposure to stimuli.

Memories of experiences are thought to be encoded in representations that consist of physical and chemical changes in neurons and the connections between them. A recent technological *tour de force* shows that artificial activation of the representation of an environmental context can substitute for the genuine experience of that context [1]. The 'false memory' induced by this artificial activation is similar to a natural memory in that it activates similar downstream regions and is able to drive a natural behavioural response.

Ramirez and colleagues [1] used optogenetics combined with contextual fear conditioning to induce what they refer to as a 'false memory' of an environmental context.

Optogenetics involves the insertion of genes that confer responsiveness to light into cells, which allows neurons subsequently to be turned on or off through exposure to light of a specific frequency. This method yields exquisite control of neuronal activity, with very high spatial and temporal resolution.

In contextual fear conditioning, an environmental context (the conditioned stimulus) is paired with an aversive stimulus such as a mild shock (the unconditioned stimulus). This pairing leads to the acquisition of a conditioned fear response, where an animal learns to produce freezing behaviour in response to the context in which the shock was presented. In this form of learning, the contextual representation is thought to be maintained in the hippocampus.

In a study published last year by the same group [2], a subpopulation of cells in the dentate gyrus (DG) subregion of the hippocampus that were active during exploration of a specific context were engineered to express the gene for the light-sensitive protein channelrhodopsin-2 (ChR2). Animals were given a mild foot shock when in the context and learned to produce the conditioned fear response of freezing when they were later exposed to the same context even in the absence of shock. Interestingly, however, subsequent optogenetic stimulation of the ChR2-expressing cells – comprising the putative representation of the training context – in a completely different context was sufficient to produce the conditioned freezing behaviour. These findings suggest that artificial activation of a specific group of DG neurons comprising at least a partial representation of a specific context is sufficient to produce recall of that context.

Ramirez and colleagues [1] take this work a step further by showing that optogenetically activating a previously formed representation of a context while delivering foot shocks can result in an association between shocks and a context in which they were never delivered. To do this, they placed mice in a chamber and allowed them to explore it, again engineering active neurons in the DG to express ChR2. The following day, the same mice were placed in a different chamber and, while they explored, they were given a mild footshock. At the same time, a blue light was shone down a fibreoptic cable implanted into the DG, in order to reactivate the neurons that had been active during exploration of the initial chamber on the previous day. Mice were later placed back into the first chamber and displayed conditioned freezing behaviour, even though they had never been shocked in that context. Activation of the amygdala, a structure downstream in the circuit supporting fear conditioning, was similar in this group of animals and a control group with fear memory induced by a genuine environmental context, providing further evidence that artificial stimulation of the representation was equivalent to natural exposure to a context.

This study uses cutting edge technology to demonstrate elegantly that it is possible to form an associative fear memory to a conditioned stimulus (the context) that was not naturally available at the time that the unconditioned stimulus (the footshock) was delivered. However, neuronal stimulation substituting for conditioned stimuli is not new. For example, early studies showed that microstimulation of the pontine nuclei or the middle cerebellar peduncle of the cerebellum can serve as a functional conditioned stimulus in the eyeblink conditioning paradigm (where a tone or light usually serves as the conditioned stimulus, and an airpuff serves as the unconditioned stimulus; e.g., [3]). Later work showed that high-frequency stimulation of the perforant path, an input to the DG, can also act as a conditioned stimulus [4]. It is also important to bear in mind that the experiment by Ramirez *et al.* involved the induction of a simple association between events that were actually experienced (albeit not at the same time), rather than the sort of complex, spurious episodic memory that is usually associated with false memory in humans (e.g., [5,6]).

Thus, the way in which Ramirez *et al.* [1] really move the field forward is with respect to the precision of the neuronal manipulation. The study is able to confirm a widely held notion – one with little direct supporting evidence – that

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the specific neurons that are active during encoding of a memory actually do form a representation that will also be active during retrieval of that memory [7]. Furthermore, controlled, artificial stimulation of the neurons that encode this representation leads to the formation of memories in a manner that is consistent with natural exposure to stimuli. The methodology therefore gives us an exciting glimpse into the representations of events as they appear in the brain and suggests that one can indeed point to an engram, or physical substrate, of specific memories. It will be fascinating to see how Ramirez and colleagues' results generalize to other forms of memory, as well as the extent to which this technology can be used further to understand the mechanisms of memory in the brain.

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Neural encoding of movement sequences in the human brain

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Humans learn and remember thousands of motor skills, but how these skills are represented in the brain is not well understood. A recent study by Wiestler and Diedrichsen demonstrates for the first time that individual motor sequences can be identified based on the pattern of neural activity in a distributed network of motor cortical regions.

A jazz pianist can perform dozens of pieces in a single evening. Playing *Take Five* requires thousands of identical finger movements, but Dave Brubeck, the famous American jazz pianist and composer, had no difficulty retrieving the correct sequence, never confusing it with *Bossa Nova USA*. Since the time of Lashley [1], a central issue in the neural control of movement has been to understand how unique sequences of actions are learned and represented in the brain. Neurophysiological studies in animals and brain imaging studies in humans have shown that sequence learning engages both cortical and sub-cortical motor regions, including primary motor (M1), premotor, and supplementary motor areas (PMC, SMA), the basal ganglia, and cerebellum [2–4] (Figure 1). Problematically, however, some studies show increased activity for well-learned items, whereas others show decreased activity [5,6]. One recent study showed global decreases in activity in M1 and the cerebellum, along with local increases in specific sub-regions of the same structures [7]. These results suggest that, with learning, the network of regions that represents a specific sequence becomes both more efficient and more specialized. They also indicate that detecting such specific changes is difficult using standard data analysis techniques.

To directly identify changes in specific neural representations of individual sequences with learning, Wiestler and Diedrichsen [5] used a very simple behavioral paradigm – learning of a five-finger key-press sequence – combined with a sophisticated data analysis technique – multivariate pattern classification (MVPA). MVPA allowed the authors to test whether there were unique patterns of neural activity associated with the performance of each sequence. Their results demonstrate that individual sequences are represented in a distributed network that includes M1, PMC, SMA and the intraparietal sulcus (IPS). Most importantly, they showed that these representations are multi-dimensional – that is, they do not represent simple dimensions of performance, such as difficulty, velocity, or force, but sequence-specific patterns of neural activity.

In the study, participants practiced four different key-press sequences for five days. They were then scanned using functional magnetic resonance imaging (fMRI) while performing the trained sequences compared with four untrained sequences matched for length and difficulty. Performance of both sequence types resulted in neural activity in motor cortical regions known to be involved in learning, including M1, PMC, SMA, and IPS. Compared to untrained sequences, trained sequences were performed more rapidly and with greater force. Despite this, performance did not produce greater brain activity, but rather

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