Total recall

Reconsolidation theory unifies cognitive psychology and neuroscience and creates new therapeutic options for memory-related disorders

Philip Hunter

There are many popular ideas about human memory serving as the repository of experiences etched into the substance of our brains until they are wiped out through death or disease. As the British writer Oscar Wilde put it, "Memory [...] is the diary that we all carry about with us." And even if we sometimes cannot remember a particular event or person, we rarely doubt our memories. Friedrich Nietzsche, the German philosopher, placed great faith in memory, noting that, "The existence of forgetting has never been proved: we only know that some things don't come to mind when we want them."

Despite these popular notions of infallible human memories, our understanding of how long-term memory works has changed dramatically during the past decade: it seems that our memories are not as permanent as we once thought. This has profound implications for both neuroscience and for treating a range of cognitive disorders including PTSD (post-traumatic stress disorder), drug addiction, chronic pain and even possibly Alzheimer disease.

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For a long time, neurologists and psychiatrists had assumed that after an initial period of consolidation, during which memories are liable to change or be erased, memories eventually become enshrined and immune to alteration. But since 2000, this memory consolidation theory has gradually been replaced by a new one called reconsolidation, which posits that long-term memories can, at least in some circumstances, be changed. On activation or recall, the memory of an object or event enters an update process during which it can be strengthened, weakened or modified, just as short-term memories can be during the initial consolidation phase. The new reconsolidation theory has created great excitement

among cognitive disorder researchers and practitioners. As many disorders are associated with some form of long-term memory malfunction or impairment, a reliable method that can reactivate and amend these memories would have great potential as a treatment; indeed a number of clinical trials to treat PTSD are currently testing this new understanding of memories.

As happens so often in science, reconsolidation is actually an old idea that has been reincarnated. The theory first emerged in the 1960s when neurologists found that fear memories in rats could be greatly weakened if they were reactivated on recall (Misanin *et al*, 1968). Before then, it had been assumed that retrograde amnesia—the inability to access memories formed during or just before a traumatic event or illness—worked backwards in time to affect recently acquired memories. Retrograde amnesia also occurs in humans as a result of head injuries or, sometimes, extreme trauma. The experiments in rats, however, showed that even older memories might be vulnerable if they were in an active state of recall at the time of the trauma, but interest in the research waned because of the lack of any neurological or molecular basis for the theory. This all changed with the publication of a seminal paper in 2000 by Karim Nader at McGill University in Montreal, Canada, who demonstrated the reconsolidation of a fear memory in the lateral amygdala (Nader *et al*, 2000). This walnut-sized region in the medial temporal lobe of the brain has a key role in emotional memory in that it orchestrates the production of hormones

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or neurotransmitters such as dopamine, noradrenaline and adrenaline.

The work by Nader and Joseph LeDoux at New York University, USA, heralded the beginning of a unification between the previously largely distinct fields of neuroscience and cognitive psychology. Neuroscience had been driven chiefly by animal research to identify the underlying molecular, genetic and neurochemical basis of behaviour, emotion and memory. Cognitive psychology had been based almost entirely on behavioural experiments in humans. This unification process is still in its infancy, but advances in imaging techniques, particularly functional magnetic resonance imaging, promises to combine behavioural experiments in humans with observing changes in brain activity. According to Valérie Doyère, from the Centre of Neurosciences at Paris-Sud University in France, it will help resolve questions about how different regions of the brain interact during memory recall and reconsolidation. "I think the next step is to do neural imaging, as this would help detect at which step in the network the system has been modified or blocked," Doyère, a pioneer of reconsolidation theory and collaborator of LeDoux and Nader, explained. "That is difficult to know unless you do have some way of analysing the neural network activity to try and see what you update and where."

Even without this insight, a lot of progress has been made in linking molecular events at the neuron level with the reconsolidation process—at least in animals. The starting point was the discovery by Nader and colleagues that reconsolidation in rats involved protein synthesis. They noted from other work that the initial consolidation of fear memories in rats could be inhibited by infusion of the protein synthesis inhibitor anisomycin into the amygdala, shortly after fear training. Such training typically involves traditional methods first used by the Russian physiologist Ivan Pavlov (1849–1936) in which an animal is given a so-called conditional stimulus (CS), such as a particular sound, followed shortly by an unconditional stimulus (US), such as an electric shock. The animal learns to associate the two so that exposure to the sound triggers fear: it begins with the activation of the amygdala, which is followed by a signalling cascade that leads to elevated heart and respiratory rates, with an associated increase

in glucose production in preparation for the 'fight or flight' response. The administration of anisomycin shortly after this training process blocks consolidation and prevents the animal from associating the CS signal with the US response.

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Similarly, Nader found that if the rats were exposed to the CS some days after the initial conditioning, to recall the association between the sound and the electric shock, anisomycin blocked reconsolidation and generated amnesia: the rats 'forgot' the association between CS and US and had a greatly reduced fear response on exposure to the CS. Nader argued that this must mean the reconsolidation of the memory had been interrupted, because if the rats were given anisomycin after the initial training, but without exposure to the CS sound, they retained their fear conditioning. This link between memory reconsolidation and protein synthesis has also been demonstrated in other animals, including primitive

invertebrates such as worms, suggesting that this is an evolutionarily conserved adaptation (Rose & Rankin, 2006).

Attempts to observe this link between reconsolidation and protein synthesis in humans, however, have remained elusive. "We can't test whether the mechanisms in humans are mediated by protein synthesis because those drugs would not be approved for human use," Nader said. "Usually, rodent preps are used to understand the molecular mechanisms, and these seem to generalize to humans."

Indeed, Nader argues that evidence for reconsolidation in humans is now very strong in the light of recent work by LeDoux, demonstrating that the principles of fear extinction training in rats could be applied to humans to weaken the association between a CS trigger and memory of the US (Schiller *et al*, 2010). Human participants were shown an object and then given a mild electric shock in classical Pavlovian conditioning—the authors tested for the presence of the fear memory by measuring the change in skin electrical conductance in response to seeing the object. Once this fear memory was established, the authors reminded the participants of the object a

day later to initiate the reconsolidation process, but then provided information that the same object was now 'safe'—this being called 'extinction training'. A day later, the participants were tested again to see whether the object elicited a fear response.

The key point is that extinction training had to be conducted within the reconsolidation window, when the memory was temporarily unstable, to eliminate the fear response. The researchers also showed that rewriting the fear memory was specific to the CS object that was reactivated. If participants had been conditioned to associate several different objects with fear, then extinction training would only work on the specific object used during the training. Participants would continue to associate the other objects with fear, indicating that extinction training is selective.

Various forms of extinction training have long been applied to some disorders, notably PTSD—an anxiety disorder that occurs in the aftermath of exposure to a traumatic experience involving death or the threat of death. The victim ingests a trauma memory that is emotionally overwhelming and cannot be resolved in

the normal way, often intruding spontaneously into consciousness with a continued state of hypervigilance. The idea of extinction training is to force sufferers to actively recall memories frequently, but success has so far been mixed.

Although anisomycin cannot be given to PTSD sufferers to edit long-term memories, propranolol is an alternative. It has already been approved to treat hypertension as a so-called beta blocker that blocks the beta adrenergic receptor and diminishes the effect of stress hormones. Having been largely replaced by other drugs for treating high blood pressure, interest in propranolol was revived by its potential for treating PTSD in association with psychotherapy (Brunet *et al*, 2007). It also triggered research into the role of beta adrenergic receptors in PTSD, notably by Jacek Debiec and colleagues at New York University, who found that adrenergic signalling in the amygdala is involved in the memory consolidation process (Debiec *et al*, 2011).

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Drugs such as propranolol seem to suppress memory reconsolidation and thereby weaken the emotions associated with trauma memories. This is the theory, and early evidence of success has attracted significant interest in the USA, where PTSD is a particular problem given the country's long-standing involvement in armed conflicts and the resulting large number of former soldiers suffering from the syndrome.

The US Department of Defense's standard treatment for PTSD has been cognitive behavioural therapy, in which individuals learn to identify thoughts that make them feel afraid or upset and then try to replace them with less distressing thoughts. But the potential of propranolol to replace or enhance cognitive behavioural therapy has prompted the US National Institutes of Health to conduct a phase II clinical trial, for which it is currently recruiting volunteers.

The urgency of finding a more complete cure for PTSD has been increased by recent indications that the disorder not only diminishes quality of life for sufferers and their

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families, but also has serious long-term effects on physical as well as mental health, including premature ageing and a heightened risk of dementia. This link was confirmed by a recent retrospective study of 181,093 US war veterans aged 55 years or older, 53,155 of whom had PTSD (Yaffe *et al*, 2010). Kristine Yaffe (University of California, San Francisco and the San Francisco Veterans Affairs Medical Center) and her colleagues found that veterans with PTSD had a 10.6% risk of developing dementia compared with 6.6% among the general elderly population without PTSD. Although this result was statistically significant given that the study was adjusted for other factors such as demographic variation and psychiatric illnesses, it did not entirely preclude other risk factors. The causes of the higher risk of dementia were related to either the physiological stress on the brain with associated inflammation, or the systemic effect of long-term disruption to memory functioning, or probably a combination of both.

The emphasis in treating PTSD and addictive disorders is on weakening aspects of long-term memory, but the emerging reconsolidation theory can equally provide clinical benefits by strengthening connections, as LeDoux pointed out. "Memory reconsolidation is not a process of weakening memory from the evolutionary point of view. It is an update mechanism. It allows memories to be changed when new information is available," he said. "An extreme example from our work is that fear memory can be increased or decreased, depending on how you activate beta-adrenergic receptors. Block these during retrieval and you get a weakening of memory; stimulate these and you get an enhancement."

The ability to stimulate memory could inspire new treatments for sufferers from memory loss, according to Doyère. "In the case of a disease like Alzheimer's, it may be possible to reincorporate some elements and recover memory that has been lost. At least it may be possible to delay some of the symptoms," she explained.

Yet, more work is needed to expand on the emerging theory of reconsolidation, particularly in humans, because human memory recall goes beyond what happens in most animals. "Humans have the knowledge of a memory association and that may reactivate the emotional value," Doyère commented. In other words, humans can better exploit their associated knowledge of events that they recall either wittingly or possibly in dreams, and this can affect the reconsolidation process. Moreover, there is also the role of sleep and dreaming in long-term memory recall and reconsolidation. In any case, it seems that reconsolidation as a unifying theory has both great therapeutic and scientific potential to explore human memory.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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