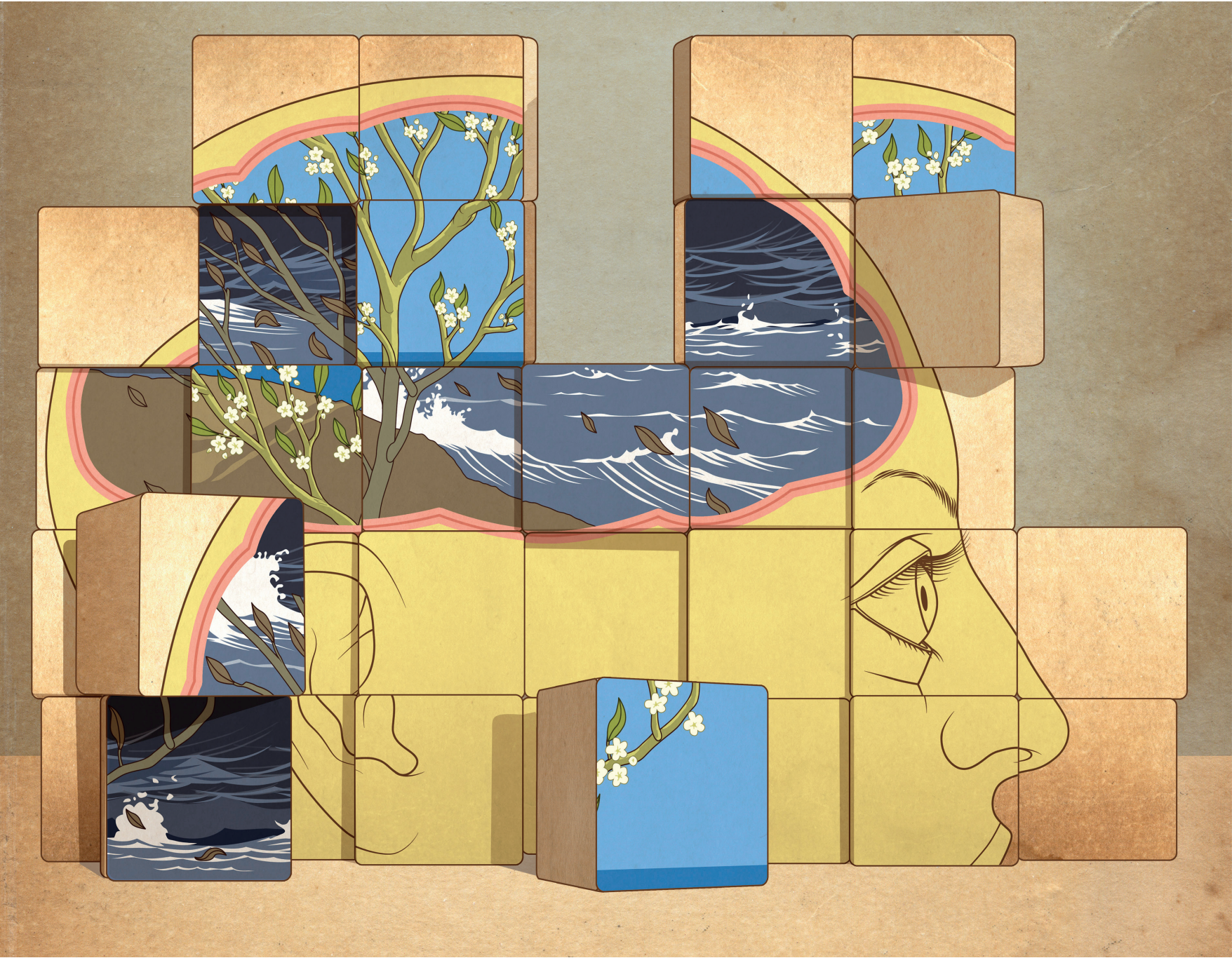


Mental blocks

We can rebuild memories to remove debilitating scars of past traumas – and perhaps more besides, finds Helen Phillips



LOUISE had been haunted by his face for 30 years. Racked with anxiety, she could barely sleep. When she did, horrific memories of being raped, aged 12, by her doctor spilled into nightmares. Then, after a single, experimental treatment, the haunting stopped.

Louise is one of an increasing number of people who have been helped by techniques that seem to free individuals from the torments of a traumatic memory. Those who have been raped are not the only ones to benefit. Soldiers haunted by visions of war and survivors of terror attacks and natural disasters are being helped by pills, electric shocks, even video games.

And as we continue to learn about how our brains form and maintain memories, far more might be possible. The focus until now has been on removing a memory's emotional sting, but we might also excise entire memories at will, or even recover ones wiped out by Alzheimer's disease. "We can break into the time machine and really reverse-engineer it, hijack it or jump-start it," says Steve Ramirez at Harvard University. "We can really try to fix memories."

Memories are physically imprinted on your brain. If you remember any of this article in a few days' time, it's down to changes in how your brain is wired. Over a number of hours or a night's sleep, your initial memory is consolidated for long-term storage by a suite of genes, which switch on to make the proteins that rework and reinforce neural connections. Only when this process is complete does a memory become permanent, like a book shelved in a vast library.

That, at least, is what we thought. But in 2000 Karim Nader, a neuroscientist then at New York University, showed something rather different. He had set out to test whether retrieving a memory, like its consolidation, required protein synthesis. He trained rats to associate a particular sound with a small electric shock, until they learned to fear the sound. When Nader then injected a drug known to block protein synthesis into the rat's brain as he played the sound, he found the

association was erased: the rats were no longer afraid. They could later relearn the association, however, and there was no effect on the rest of their memory.

Nader says he was blown away. The implication was that recalling a memory renders it unstable all over again, just as if it were a new memory being laid down. This means that memories are not permanent, but are built anew every time we recall them – a process now called reconsolidation.

That opens up new avenues to manipulating memories. "We normally think of memory as a tape recorder or like a video of the past, but it's actually very reconstructive in nature," says Ramirez. "It's becoming more obvious that memory is really dynamic and it's very easily modifiable when recalled."

An open window

Even before Nader's 2000 study, clinicians had had patchy success alleviating the terrifying flashbacks of post-traumatic stress disorder (PTSD) using cognitive behavioural therapies, and also a drug called propranolol that more typically treats high blood pressure, anxiety and migraine. The trouble was that people had to be treated within a few hours of a traumatic event, before the memory had consolidated.

Nader's insights brought the realisation that there was a window for treatment that could be gently eased open at any time. In the past few years, that's just what researchers have begun to do. In 2013, Marijn Kroes, a neuroscientist at New York University, succeeded in manipulating the memories of people with severe depression who were undergoing electroconvulsive therapy. First, he showed them two stories with unpleasant narratives – a car crash and an assault. A week later, just before their scheduled ECT session, the volunteers were given a brief reminder of one of the stories to reactivate the memory.

When asked to recall the stories 24 hours after their ECT – long enough for reconsolidation to have occurred – they could not do so for the memory that had

been reactivated. They remembered no better than chance, says Kroes; they might as well have been guessing. This confirmed that ECT had blocked reconsolidation, that remembered experiences can be lost – and that the effect is not limited to conditioned fear.

You don’t need shock therapy to achieve similar results, either. Alain Brunet, a clinical psychologist at McGill University in Montreal, Canada, works with those who experienced the April 2015 earthquakes in Nepal and the November 2015 terror attacks in Paris. Initially, he asks people to write about the worst aspects of their trauma in the first person. Then they take a dose of propranolol at weekly intervals over six weeks. On each occasion they reread what they wrote, thus reactivating the traumatic memory under the drug’s influence. “More or less two-thirds of people benefit from the treatment,” says Brunet. “Which is as good as it gets in psychiatry.”

Exorcising ghosts

It’s not clear exactly what propranolol’s mode of action is. Some researchers think it must interfere with protein synthesis directly. Others surmise that the benefits seen in PTSD are an indirect result of its calming effect on the physiological symptoms of stress or emotions through lowering blood pressure. Whatever the case, it seems to work. It was what helped Louise, who was tormented by memories of her rape. After treatment with propranolol her insomnia was gone, and her depression and nervousness of other people were a distant memory.

Encouraged by such successes, Brunet has recently begun trials with substance abusers to suppress memories that underlie cravings or cause relapse, as well as with people haunted by accidents and those struggling to recover from a romantic betrayal.



Phobias might be eliminated in the same way. In 2015 Merel Kindt at the University of Amsterdam in the Netherlands asked people with a lifelong fear of spiders to spend 2 minutes facing a tarantula in a terrarium. Many of them had trouble even entering the room. Immediately afterwards she gave them a dose of propranolol and asked them to return to the terrarium a day, a month or

Forgotten but not gone: new treatments can help retrieve hidden memories

even up to a year later. Despite some initially reporting that their horror of spiders was unchanged, all the volunteers who had taken the drug entered the room, and all were calmer and more confident than those who had taken a placebo. Most were even willing to touch or hold the spider.

If taking a drug to manipulate memories sounds sinister, it seems even playing a video game might do the trick. Emily Holmes at the Karolinska Institute in Stockholm, Sweden, and Ella James at the UK Medical Research Council’s Cognition and Brain Sciences Unit in Cambridge asked volunteers to watch videos of distressing events. A day later, they were shown images from the films to reactivate their memory and then asked to play *Tetris*. The game was chosen for the demands it makes on the brain’s visual and spatial processing. The idea was that it would compete with the largely visual flashback memories the participants would be

ANTI-MEMORIES

The progress in taming traumatic memories (see main story) raises a question: what makes them so persistent in the first place? We know that stress can make memories stronger – something that makes sense if improved recall of dangerous situations can help us survive and reproduce. But it’s far from helpful when our memory system causes terrifying flashbacks and panic attacks.

Normal brain functioning depends on a delicate balance of excitatory signals that stimulate an individual neuron’s activity and inhibitory processes that dampen activity. Too much excitation can lead to uncontrolled epilepsy, for example.

With that in mind, Helen Barron at the University of Oxford has proposed that inhibitory connections might also be stabilising the network of neurons during memory formation, perhaps to keep memories from being expressed at inappropriate times. She calls these inhibitory connections “anti-memories”.

Last year, she and her colleagues were able to show for the first time that inhibitory memories do indeed play a part in human memory formation and recall. She showed volunteers pairs of shapes and used functional brain imaging to

reveal the neural activity associated with the newly formed memory. Over time these memory traces seemed to fade – not, Barron surmised, because they were being lost, but because they were being masked by inhibitory anti-memories. Sure enough, by blocking the main inhibitory signal chemicals using an electric current applied near the scalp, she was able to reveal the memory, still present.

This suggests a new way to tackle unwanted or intrusive memories – as well as memories that fail to surface. “If a memory isn’t stored properly, that could be because the inhibitory part of the memory is not perfectly balancing the excitatory part,” says Barron.

It’s early days yet, but such insights raise the prospect of creating therapies for all kinds of memory-related conditions, not least Alzheimer’s disease, where memories may lie hidden – irretrievable, rather than lost entirely. Even conditions that don’t seem like memory problems, such as schizophrenia and autism, could come down to faulty anti-memory networks, Barron thinks, with the spontaneous activation of imagery and memories experienced as delusions or hallucinations.

vulnerable to during reconsolidation.

It worked. Playing *Tetris* seemed to reduce intrusive flashbacks without hindering intentional recall. The approach is now being tested in people who have experienced real trauma as a way to prevent harrowing memories taking hold. Lali Iyadurai at the University of Oxford, for example, has taken it into the emergency room, to help people who have been in road accidents. Antje Horsch at Lausanne University Hospital, Switzerland, is using the technique to help women who’ve had a bad experience during childbirth.

Nader argues that reconsolidation therapy, as it’s now called, has such striking benefits that there’s no reason it can’t be used to treat every kind of psychopathology, providing the timing and nature of the intervention is carefully controlled. As we delve deeper into the mechanics of memory consolidation and reconsolidation, there are even suggestions we might revive memories thought lost to degenerative brain conditions such as Alzheimer’s (see “Anti-memories”, above).

We might even soon develop drugs to delete problematic memories entirely. In 2006 Todd Sacktor, a neurologist at the State University of New York in Brooklyn, identified a molecule without which memories simply wither and die. The enzyme PKM ζ seems to linger and perhaps even replicate at synapses, the neural junctions that are rewired as memories form and strengthen. Mice with extra PKM ζ have

exceptional memories. Without it, they can’t remember a thing. Sacktor found he could delete a specific memory if, during its reconsolidation, he blocked PKM ζ using a chemical called ZIP. It even seemed to reduce the memories that create drug cravings in addicted rodents.

The idea suffered a wobble in 2013 when two groups showed that mice lacking the gene for PKM could still form long-term memories, and that ZIP could still wipe memories in those mice. But Sacktor and his colleagues recently showed that a molecule called PKM ι/λ takes over in the absence of PKM ζ .

Ethics warning

Even so, ZIP is toxic and too risky to test in humans. Nevertheless, Sacktor and Nader, who has also worked with ZIP, believe that eventually an alternative way to manipulate PKM ζ will be found. Chronic pain, in which pain signals are enhanced by a process in the brain that looks a lot like memory formation, is among the conditions Nader suggests as suitable targets.

But even if practical problems can be overcome, is it ethically right to meddle with memories? If you find the idea unsettling, you’re not alone. Questions were being raised almost as soon as Nader discovered how to soften up memories for reshaping. In 2003 the US President’s Council on Bioethics warned that using pharmacological agents to rewrite memories “risks making shameful acts seem less shameful or terrible acts less terrible than they really are”. Some have drawn parallels between the research and the 2004 film *Eternal Sunshine of the Spotless Mind*, in which scientists erase the shared memories of a couple who have been through a painful break-up.

The dystopian scenario is that these techniques might be used for military advantage, to wipe memories of genocide or other atrocities, for example. For that reason it is important to maintain a distinction between wiping memories and ridding them of their negative emotional associations, says Holmes. “Our ethical position is quite clear: we should not erase memories. We think it is irresponsible, and you don’t need to erase memory to treat trauma.” We devote a lot of resources to alleviating physical pain, after all. Why should we treat the psychological version any differently? ■

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