

Building a Fearless Mind

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In the late 1960s, in an animal lab at Rutgers University, psychological science gave an unexpected boost to the timeless hope of conquering our fears. Researchers James R. Misanin, APS Fellow Ralph R. Miller, and Donald J. Lewis taught some rats to fear white noise by delivering a little foot-shock along with the sound. Afterward, the animals returned to their cages while the researchers waited for the scary new memory to sink in deeper.

At the time, most psychologists believed that a fresh memory quickly hardened into permanent form. They called this process *consolidation*. You could disrupt consolidation and fend off a budding fear memory — say, by issuing an electroconvulsive jolt to the head immediately after a scary episode — but you had to act extremely fast. If you missed that small window to interfere with consolidation, the memory was fixed into place forever. So the thinking went.

What Misanin and colleagues discovered upon returning to the lab challenged that conventional theory to its core. Their study involved five groups of rats, but the key revelation emerged from two in particular. One of these key groups received an electroconvulsive shock a full day after learning to fear the white noise. The other key group received the same shock — but first received a brief reminder of the noise they found so scary.

That slight twist made all the difference. One day later, the shock-only group remained scared of the white noise, as measured by their decreased drinking rate. Their fear memories had consolidated beyond

manipulation. But the group that was briefly reminded of its fear before the shock behaved as if they weren't afraid at all. These rats drank at the same rate as a control group whose fear had been disrupted before it ever consolidated in the first place.

The implication was enormous: When an older fear memory was retrieved for a moment, it was just as malleable as a brand new memory that had yet to stabilize. "This outcome is not predicted by consolidation theory in its present formulation," wrote Misanin and colleagues in a 1968 issue of *Science*. Instead, a new theory was needed to explain the finding: *reconsolidation*. The idea that a stale memory, made active again, enters the consolidation process all over.

In recent years, spurred by rising rates of anxiety disorders, psychological scientists have shown a renewed interest in reconsolidation as a way to give therapists another chance to dampen — or perhaps even erase — the memory of a traumatic moment. So far, both drugs and behavioral interventions targeting fear during reconsolidation have shown promise. The science remains a bit mixed, but the potential clinical impact has given the field a new level of urgency.

"In the past 10 to 15 years, a lot has happened," says Marie-H. Monfils of the University of Texas at Austin. "I think it's a really exciting time, and also it's a very important time, to come up with tools to modify memories."

When Fear Is "Subject to Disruption"

In 2000, the research community rediscovered the 1960s Rutgers breakthrough with a passion. That year, a study group led by Karim Nader (then at New York University, now at McGill University) reported that rats lost their fear when injected with the drug anisomycin during the reconsolidation phase. Anisomycin blocks the protein synthesis required for memory formation; it was the Nader team's modern substitute for an electroconvulsive shock, and it worked just as well.

In a paper published in *Nature*, Nader and collaborators concluded that all "active" memories, as opposed to only "new" memories, should be considered "subject to disruption."

Before long, hundreds of related publications were appearing from labs all over the world. Soon psychological scientists were using reconsolidation to disrupt old memories in everything from roundworms to people. But the progress carried with it a concern: drug injection (to say nothing of electroconvulsive shock) was a rather invasive and risky form of neural intervention. Some researchers wondered if scary memories could be erased in more natural ways.

This hope had plenty of history behind it. Clinicians had long helped people confront their anxieties with "exposure" therapy: reminding patients of their fears in a safe setting until the frightening association diminished. (Research scientists refer to this same process as "extinction training.") The approach worked well for some people, but others experienced frustrating bouts of fear recovery. If clinicians could perform extinction training during reconsolidation, the effect might prove more lasting.

Early signs in animals were encouraging. In work published in a 2009 issue of *Science*, led by Monfils, rats indeed lost their fear through extinction training delivered during reconsolidation. The big challenge, of course, would be repeating the finding in people. That task was taken up by a research

team led by Daniela Schiller and APS President Elizabeth A. Phelps of New York University. (Monfils joined the Schiller group as a collaborator.)

To begin, Schiller and company trained study participants to fear a colored square by pairing it with an occasional shock to the wrist. A day later the researchers tried to erase this fear three different ways. One group of participants received basic extinction training, which consisted of seeing the scary colored square without getting a shock. Another group received the same training six hours after its fear was reactivated (or “retrieved”). A third group received the same training a mere 10 minutes after fear retrieval.

The following day all the groups returned to the lab yet again and took a look at the colored square. The first and second groups were scared of it; extinction training had done little to quell their consolidated fears. But the third group was fine, Schiller and company reported in a 2010 issue of *Nature*. And the effect was remarkably durable: when the researchers brought study participants back into the lab a full year later, they found similar results.

By treating fear with extinction training during the window of reconsolidation, the researchers had prevented its return — evidently for keeps.

“I think the major impact is the relevancy for clinical therapy,” says Schiller, now at Mount Sinai School of Medicine, of this pioneer study. “It created a dialogue between neuroscientists and therapists, which is ongoing and developing.”

Sorting Through a “Mixed Literature”

The clinical community welcomed the idea of erasing fear through extinction training with excitement, but much of the scientific community greeted it with skepticism. Multiple labs have since failed to replicate the findings in animals despite using very similar methods. In 2009, researchers at the University of New South Wales in Australia reached the *opposite* conclusion; their work with rats found that extinction training actually made fear memories worse.

“It’s a really mixed literature right now,” says APS Fellow Stephen Maren of Texas A&M University, whose 2011 review of fear-blocking research in *Neuron* may be the most comprehensive on the subject. “Some people find the effect. Many, many others don’t.”

A more recent attempt to replicate the work in people fell short, too. For that study, Merel Kindt and Marieke Soeter of the University of Amsterdam recruited 40 undergraduate participants and trained them to fear pictures of spiders by delivering a simultaneous shock to the wrist. A day later, some participants received only extinction training, while others received extinction training 10 minutes after fear retrieval — smack dab in the middle of reconsolidation.

Neither therapy worked better than the other, Kindt and Soeter reported earlier this year in *Biological Psychology*. On three different measures of fear — startle response, skin conductance tests, and fear expectancy ratings — the participants showed no difference regardless of when they’d received the extinction training. Slight methodological variations aside, the results suggest that there’s a lot about behavioral fear interventions that researchers still don’t understand.

“We all discuss and struggle with that,” says Schiller of the conflicting reports that have emerged over the years. “There are definitely boundary conditions as to where reconsolidation happens or not.”

In his literature review, Maren highlighted a number of key variables that might influence efforts to eliminate fear in lab and clinic alike. One of the biggest is context.

If an animal loses fear of a noise in one cage, he says, that’s no guarantee the same noise won’t produce the old fear in another. What this suggests to Maren and others is that the original fear memory has not been rewired at all. Rather, the brain has stored a safe new memory capable of overriding the bad one in some circumstances.

“What the animal has done is learn something new — the safety memory — and applies that memory in certain situations but not others,” says Maren. “So that illustrates that brains can actually acquire multiple meanings of a particular stimulus and retrieve those depending on the context the animal is in.”

Other variables that could have an impact on fear intervention are the timing of the treatment and the severity of the fear itself. Maren’s own research in rats (especially a study published in a 2006 issue of *Proceedings of the National Academy of Sciences*) has found that some episodes can be so traumatic that even very fresh fear memories prove resistant to interference. He believes reconciling all these factors will require a better understanding of the basic neural mechanisms at work.

“This is a very dynamic state of affairs at this moment in time,” says Maren. “The question of whether memories can be erased is still really an open question.”

A “Huge” Gap Between Lab and Clinic

These lingering doubts about blocking fear during reconsolidation may explain why transferring the technique from participant to patient has been a slow process. In a 2011 essay on reconsolidation therapy for *Frontiers in Behavioral Neuroscience*, Roger K. Pitman of Harvard Medical School described the gap between lab and clinic as “huge.” If erasing day-old fear memories were like a firecracker, wrote Pitman, then erasing something as complex as PTSD was more like an atomic bomb.

To date, only one published research study has tried to dampen fear during reconsolidation in a clinical population. That work, which involved both Nader and Pitman as collaborators, was led by Alain Brunet of McGill University. The researchers recruited 19 people suffering from PTSD and asked them to describe the event that had triggered their illness. Doing so reactivated the fear — sparking the reconsolidation process along with it.

Afterward, some patients received propranolol (a drug found to attenuate fear conditioning) while others received a placebo pill. A week later all the patients listened to a tape-recorded description of their personal trauma. Those who’d received propranolol during reconsolidation showed less physiologic distress, as measured by heart rate and skin conductance, than those who’d taken the placebo. Their fear wasn’t gone, but it now lacked the power that defined a clinical disorder.

“In the present study, the PTSD subjects who received post-retrieval placebo showed physiologic responses typical of trauma victims with PTSD,” reported Brunet and coauthors in a 2008 issue of the *Journal of Psychiatric Research*, “whereas the PTSD subjects who received post-retrieval propranolol

showed physiologic responses typical of trauma victims without PTSD.”

Monfils says it’s only natural for the transition from theory into therapy to “proceed with caution” when patient health is on the line. Still, if her own experience is any indication, that shift may be on the verge of a tipping point. Since the publication of her extinction training studies, a number of clinicians have approached her for a collaboration. Her work with one group has been presented at conferences and will soon be submitted to journals, she says. Other labs may be on a similar course.

“When we have this dialogue between clinicians and basic researchers, I think we enhance both the therapeutic applications but also the basic research,” says Monfils. “In the long run this promotes faster translation, which ultimately is better for everyone.”

The big challenge, she says, may be identifying which patients will benefit more from reconsolidation therapy — drug, behavioral, or otherwise — than their current treatment. Exposure therapy applied outside reconsolidation windows has its limitations, but still works well for many people. Determining what makes one patient population receptive to one therapy instead of another will be an ongoing challenge. In the end, though, it could mean better options for everyone.

“We’re going to start having more uniquely crafted tools to help people with anxiety-related disorders,” says Monfils. “I think it will really change the clinical field in some ways.”

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