MANIPULATING MEMORY

Insights into the cellular and molecular basis of emotion and memory could help patients with post traumatic stress disorder.

By Joseph LeDoux (published in *The Scientist* March 2009)

In 1999 a postdoc in my lab, Karim Nader, walked into my office with an idea for a new experiment. He outlined his plan to test a controversial theory in neuroscience called memory reconsolidation that contradicted what we had learned as a field about how memories were stored. The experiment he proposed seemed like such a reach that I told him not to bother doing it. As luck would have it, Nader wasn't a particularly obedient postdoc.

A month later, Nader came back into my office and said, "It worked." I looked at him surprised. "What worked?" I asked. "The reconsolidation experiment," he told me. I was amazed. Most neuroscientists, myself included, believed that a new memory, once consolidated into long-term storage, is stable. It's as if every long-term memory had its own connections in the brain. Each time you retrieve the memory, or remembered, you retrieved that original memory, and then returned it. Reconsolidation theory proposed a radically different idea—that the very act of remembering could change the memory. Therefore, every time you remembered, you'd recall the memory as it was the very last time you remembered it, rather than the memory that was created the first time. And it would be replaced as a new representation. This theory suggested that the very act of remembering might render memories fragile, subject to change or perhaps erasure. If Nader's pilot findings were correct, it might have huge implications in treatments for soldiers and other patients with posttraumatic stress disorder (PTSD): Could traumatic memories be dampened or erased by simply remembering? Nader's pilot data convinced me to focus my attention and lab resources on studies of reconsolidation, and many other labs soon followed. Reconsolidation took off like wildfire. [The field of reconsolidation blossomed. Hundreds of studies have been done since.]

I have spent 25 years or so working out the neural basis of emotion, with a number of successes along the way. But I had never experienced anything quite like this. It wasn't that everyone accepted the idea. In fact, it is still quite controversial. It's sometimes said that the success of a scientific publication is based on how many other publications result. By that measure, reconsolidation has been a whopping success story, and one I might have easily missed.

The people who knew me as a boy would never have predicted that I would have become a neuroscientist. I grew up in Euncie, Louisiana, a typical small town that I longed to leave. My parents, however, wanted me to stay in Eunice and attend the new junior college that had just opened up there. I was resistant to the idea, so they put a deal on the table. They'd let me leave Eunice and go to college in Baton Rouge if I became a business major and came back to town to be a banker. People will say anything under duress: I told them they had a deal.

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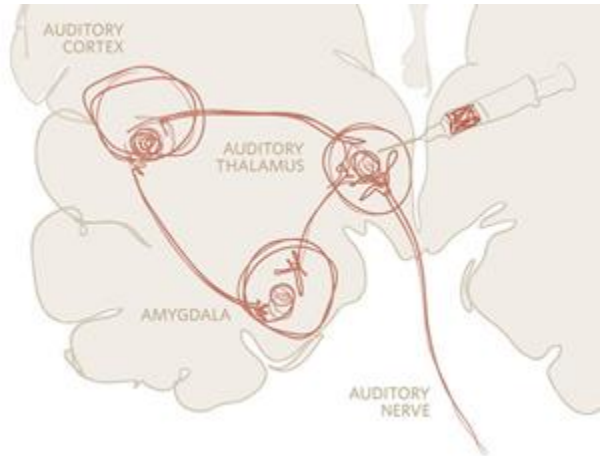
Unfortunately for my parents, the business courses bored me to tears. As part of the

requirements, I took classes in consumer psychology that investigated the reasons people buy the stuff they buy. It was the late 1960s and I wanted to be a "Nader's Raider,"—a consumer advocacy group led by Ralph Nader to investigate the role of corporations in public life and to protect consumers. That was before I took a class with Robert Thompson on the brain mechanisms of memory and motivation. I became fascinated by the idea that the driving mechanisms behind memory and motivation were so fundamental that they could be studied in the brains of rats. I began working in his lab as a volunteer. The work was, as we said at the time, "far out."

I fell in love with the brain and decided to apply to graduate school for a PhD in my newly found passion. With no coursework in science to speak of, except for a psychology class here and there, I was rejected by all of the schools I applied to; all but one—the State University of New York at Stony Brook, where a colleague of Thompson's worked. There, I joined Mike Gazzaniga's lab and did my PhD studying epilepsy patients who had undergone split-brain surgery. Through my work with Gazzaniga I became interested in the topic of emotion. I then moved to Cornell Medical School in 1978, and, after a short stint studying language disorders in brain injured patients, joined Donald Reis' laboratory so that I could explore the brain mechanisms of emotion in rats.

It was in the Reis laboratory that I learned to be a laboratory neuroscientist. At the time, neuroscience was a young discipline with new methods emerging all the time. The Reis lab seemed to acquire them just as soon as they emerged. Whenever I ran into a wall with my own research, I simply walked down the hall and asked a colleague to train me in a technique that could approach the question from a new angle. It was an immensely collaborative environment.

Gazzaniga had pointed out that no one was working on the emotional brain. So I decided to take this on in the Reis lab. My split-brain research had forced me to think about brain processing in terms of specific pathways that transmit information from one area to another. Mort Mishkin at the National Institute of Mental Health (one of my other heroes) had also used this approach in trying to understand the brain mechanisms of perception and memory. The same logic had been applied by Eric Kandel and his colleagues in studies of learning in the sea slug Aplysia californica.[2] I put together the techniques of all the researchers I admired and came up with an approach to better understand emotion in the brain (click here to learn about [3]



Fear Circuitry: In the 1980s most researchers thought that memories involving sounds required the auditory cortex—the area in the brain that attaches meaning to sound. By performing brain

lesions, we showed that the auditory cortex was not necessary in creating fear memories associated with sound. The auditory thalamus, however, was necessary. By tracing connections between neurons using an injectable stain, we showed that the auditory thalamus connects directly with the amygdala, an area that had previously been implicated in fear. The auditory cortex also connects with the amygdala, and is probably involved when fear is based on more complex auditory stimuli.

If rats without an auditory cortex could learn to be afraid, perhaps it was the thalamic rather than the cortical input to the amygdala that processed sounds associated with fear. To test that hypothesis, we lesioned the auditory thalamus, and noted that the rat was unable to learn. And when we lesioned the amygdala fear learning was also disrupted. But when we cut the connections from the thalamus to the amygdala, to our surprise, fear learning was not disrupted. It turned out that fear memories could be routed via the auditory cortex to the amygdala when the direct connection to the amygdala was not available. For simple sounds like the ones we were using, either pathway could provide the amygdala with the auditory information. The results suggested that for more complex sounds the auditory cortex is required.

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Since the cortex is required for conscious processing of stimuli, the results showed for the first time that the brain could create emotional memories without awareness. It's important to realize that although both pathways process and are equivalent for the simple sounds we use in the lab, in real life it is likely that the two pathways learn and store different aspects of a stimulus situation. This has tremendous implications for psychiatry and PTSD since it means that the things we fear are not necessarily available to our conscious minds and the fear response we express is not necessarily controlled by triggers we are aware of.

Understanding the general location where fear memories were processed was a great first step, but I didn't feel that we had the full picture yet. With further studies, we could see that the particular region of the amygdala involved in fear learning and memory was the lateral nucleus.[4] This is where the tone and shock are integrated and thus where the association that constitutes the memory is formed and stored. Knowing the location of the cells that stored the memory allowed us to turn to much more detailed studies of the cellular and molecular mechanisms that actually create memory storage.

Studies by my and other labs revealed which neurotransmitters bring information in and out of these circuits and modulate the circuit activity, and what goes on at the molecular level inside cells when memories are formed. We learned that the amino acid glutamate is responsible for the transmission of the sound from the auditory system to the lateral nucleus of amygdala. During memory formation, glutamate binds to NMDA receptors which in turn activate gene expression and protein synthesis via protein kinases such as MAPK and PKA. Kandel's work in the 1980s had strongly suggested that long term memory formation involves structural changes in neural connections via protein synthesis (short term memories simply required modification of existing proteins). These proteins generated during the consolidation into long-term memory may be involved in restructuring the shape of the axon, others may increase the number of receptors on the receiving dendrite to lower the threshold needed to fire across the synapse.

In 2000, Glenn Schafe who was working in my lab, extended our understanding by showing that protein synthesis that occurred specifically in the lateral amygdala was required for consolidating fear memories into long term storage.[5] With protein production blocked, the memory would only exist for a short while before it was forgotten—creating amnesia of the event.

It was these studies that I thought of when Nader came to me with his proposal for a reconsolidation study. I couldn't envision how reconsolidation could be involved in memory. Once the cells had built the structures necessary for long-term storage, how could those structures be so easily disrupted simply by retrieving the memory?

When Nader started thinking about reconsolidation, he started from Schafe's consolidation studies. Schafe had shown that we could artificially create amnesia for a fearful experience by blocking protein-synthesis in the amygdala with the drug anisomycin right after the tone-shock training. So Nader modified the Schafe study and instead administered the protein-blockers to the lateral amygdala of rats right after they retrieved a previously trained memory. (In our rat model, we knew a rat had retrieved a memory, or "remembered," when it reacted with fear to the tone by itself.) Contrary to what the consolidation theory predicted, the next time Nader tested the memory by giving the tone, the rat reacted calmly without fear—it had forgotten the memory.

In short, once recalled, a memory is in a fragile state and susceptible to disruption. This had profound implications in PTSD research. If we could bring up traumatic memories, associated with certain triggers, and then administer a drug that blocks protein synthesis, thus blocking reconsolidation, we might improve the psychological outcome of thousands of returning veterans. The drugs that could do this are already on the market and approved for other uses. The clinical applications of reconsolidation are exciting, but not entirely proven yet. Nader has gone on to continue his research at McGill University with PTSD patients with some success. When he administered a drug that blocks reconsolidation, triggers that would normally elicit fear and anxiety in the patients, were less potent.

Why would memory work like this? Very likely, reconsolidation is an adaptive process, a means by which memories can be updated and influenced by new information. Reconsolidation is not simply a process by which memory is disrupted. Indeed, we and others have found that you can also enhance memory in the time after retrieval. It all depends on the drug you use. For example, the beta adrenergic antagonist propranolol is the drug of choice for weakening memory in people (it's safe to use in people). In rat studies it works a as protein synthesis blockade to dampen memory. On the other hand, also in rats, a beta agonist enhances memory. Memory reconsolidation is a process by which memory is regulated, and can involve either disruption or facilitation, depending on what treatment you give.

While many worry about the idea of altering memories with drugs, patients who suffer from reactions to memories they can't control have said that they would rather risk losing a memory or two if it meant being able to remove the debilitating ones. However, in the late 1990s the President's Council of Bioethics said that it would be unethical to alter memories, which caused some controversy and perhaps temporarily dampened efforts to bring this to patients. The reality of cognitive function is that memories are altered every day when we learn, and every time we remember. In a sense, therapy is way of rerouting memories, by interpreting them differently. It is clear that careful clinical studies need to be done to understand whether other memory

functions could be affected, yet the promise of alleviating debilitating fear is clearly worth the effort.

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