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The day I told Karim Nader, "Don't do the study"

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ABSTRACT

Karim Nader changed the course of memory research by reviving interest in the mostly forgotten topic of post-retrieval manipulations of memory. In this paper I summarize the events leading up to his ground-breaking study in my lab on so-called memory reconsolidation, and the effects of that study on the field.

In the mid-1990s, the race was on to figure out the neural basis of memory consolidation. Several molecules had been implicated in studies of invertebrates, and vertebrate researchers were beginning to use these as clues in the vertebrate brain. The future had arrived in the form of techniques that could disrupt specific genes and assess their effects on learning and memory, presumably by affecting downstream proteins believed to underlie memory consolidation (Silva et al., 1998).

It had been known since the 1960s that disruption of protein synthesis prevented the conversion of short-term to long-term memory (Agranoff, 1967; McGaugh, 1966; Segal et al., 1971). This was most typically studied by giving animals systemic injections of a protein synthesis inhibitor. Ideally, the inhibitor should be injected into the brain area believed to be involved in memory consolidation. This would eliminate many of the confounding side effects that resulted from disrupting protein synthesis throughout the body, like lethargy and illness. But you would need know where to inject the drug.

Work by my lab and a couple of others were exploring the neural basis of so-called Pavlovian fear conditioning, and our findings all converged on the amygdala (LeDoux, 1996). My focus was not on the amygdala per se, but on mapping the circuits involved in the learning and control of the responses from sensory inputs to motor outputs. Because the amygdala turned out to be the interface between sensory and motor circuits, I got stuck there.

Our studies used a tone paired with a mild electric shock. After only one pairing, the tone alone would elicit freezing behavior. By following the tone to the amygdala, and the amygdala outputs that control freezing, we mapped the connections, and also demonstrated synaptic plasticity of neural activity in the amygdala (LeDoux, 1995, 1996; Quirk et al., 1996; Rogan and LeDoux, 1996). We could therefore use this knowledge to explore the molecular mechanism of emotional memory.

I didn't get involved in the knock-out mouse approach for two reasons. One was that I didn't have the expertise to do it. But the other was that the approach, at the time, affected genes throughout the body—in other works, though quite sophisticated and molecularly-specific, it had the same downside as systemic injections. Because we knew where to inject protein synthesis inhibitors, we could do the low-tech version to at least show that protein synthesis in the amygdala was required for memory consolidation. And that's what Glenn Schafe and I did (Schafe and LeDoux, 2000). Over the years, we did many other studies testing various molecules with this approach (summarized in Blair et al., 2001; Rodrigues et al., 2004; Johansen et al., 2011).

Karim Nader arrived in my lab in the late 1990s, right around the time when our molecular work was beginning. It was obvious from day one that he was force of nature. He quickly got involved in several projects that were related to his PhD work on motivation and learning, and published a couple of studies that got him adapted to our way of doing things (Nader and LeDoux, 1999a, 1999b; Amorapanth et al., 2000).

But Karim had a nose for where the action was, and he smelled it in Glenn Schafe's study. He dove into the memory consolidation research literature, going all the way back to the early studies in the 1960s. My lab was pretty large at the time, and I didn't monitor people's activities. So I only learned about what he had been spending his time on when he charged into my office with even more enthusiasm than usual.

Excitedly, Karim told me that we had the perfect brain and behavior model to test reconsolidation. I said, "what's that?" He said, if we block protein synthesis in the amygdala several days after learning, the next day the rats will not be able to remember and won't freeze. I said, there's no way that will work. He dejectedly walked out and said nothing about it for a month. Then he walked in grinning and said, "It worked." I said, "what worked?" He said that he and Glenn had blocked reconsolidation in the amygdala. I had to eat my words. Bravo Karim. We published the findings in Nature (Nader et al., 2000a).

What Karim had come up with was a body of research that had

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largely been swept under the rug for something like 30 years. Back in the 60s there were two competing ideas about memory. One was the traditional consolidation theory—the idea that memory is stored once, and each time you remember it you are retrieving the same memory (McGaugh, 1966). The other view was that each time a memory is retrieved it had to be restored to persist (Misanin et al., 1968; Riccio et al., 1968). The latter was known as post-retrieval memory manipulation effects, but came to be called the reconsolidation hypothesis (Przybyslawski and Sara, 1997).

Evidence for the consolidation hypothesis came from studies blocking protein synthesis systemically right after learning. When this was done, long-term memory did not form. For the sake of this discussion, I will explain the research approach to reconsolidation by describing the effects of systemic injection of protein synthesis inhibitors on fear conditioning. The actual procedures in the older studies were typically variants of avoidance conditioning and while some used systemic injections others used electroconvulsive shocks.

Rats that had been conditioned to a tone paired with a shock didn't freeze to the tone the next day. But if you waited several hours after learning to inject the drug, tone-elicited freezing was unaffected the next day.

Reconsolidation was supported by similar studies, but with the blocker injected at a different time. Specifically, several days were allowed to pass after conditioning before presenting the test tone, and then the blocker was injected systemically right after the tone was presented. When this was done, the rats froze to the tone, but didn't freeze to the it the next day. But if the blocker was injected several hours after test tone presentation, they did freeze the next day.

Both theories therefore had support—inhibition of protein synthesis right after learning disrupted memory, and inhibition of protein synthesis right after retrieval also disrupted memory. But one came to overshadow the other. Consolidation, being the choice of more influential scientists, made it, and reconsolidation largely faded away.

How do findings with momentum get lost? Actually, it's not that rare. In order for an idea to have legs in science it has to capture the imagination of the field, often by being touted by influential scientists. This was the case for consolidation. For example, consolidation theory was bolstered by work on memory storage in invertebrates by Eric Kandel, who was a particularly prominent neuroscientist (Bailey and Kandel, 1993). In the case of reconsolidation, there were attempts at revival over the years (Lewis et al., 1979; Rico and Richardson, 1984; Przybyslawski and Sara, 1997), but these didn't overcome the stronghold of consolidation theory on the field.

Karim's paper, however, broke through the barrier (Nader et al., 2000a). In part this was because we published it in Nature, one of the top journals in science. The consolidation theorists were not happy to see the reconsolidation monster raise its's head, as they thought their studies had effectively settled the issue decades earlier. It didn't help that Karim took a rather forward, take no prisoners, approach. As a result, he was criticized both for style and substance. But the findings were bigger than the controversy. And it wasn't long before other researchers got involved (Milekic and Alberini, 2002; Dudai and Eisenberg, 2004; Lee et al., 2004; Tronson and Taylor, 2007). Eventually reconsolidation became an active area of research that resulted in many important findings (Dudai, 2012; Alberini and LeDoux, 2013; Pine et al., 2014; Nader, 2015; Haubrich et al., 2018; Kida, 2019). Reconsolidation remained one of my lab's research topics for a for over a decade (Doyere et al., 2007; Monfils et al., 2010; Diaz-Mataix et al., 2011; Debiec et al., 2013; Schiller et al., 2010a.

One of the virtues of reconsolidation was that it meshed well with the classic idea that memory is a constructive process (Bartlett, 1932; Schacter and Addis, 2007). We do not store whole complex memories as unified entities, but instead we use bits and pieces to assemble a version of what happened in the past, and to predict what our future might be like.

A provocative possibility was raised early on by reconsolidation research. This was captured in a sentence in a review Karim, Glenn and I published later in the same year as the original study: "it might be possible to treat persons with post-traumatic stress disorder or other related anxiety conditions by reactivating traumatic memories under conditions that would prevent reconsolidation" (Nader et al., 2000b). This led to considerable enthusiasm in the therapeutic community, and reconsolidation researchers started being flooded with calls and emails from patients desperate for help. But ethicists were alarmed, arguing that memory is sacrosanct, and should not be manipulated (President's Council on Bioethics, 2003). The fact is, though, every interaction between two people, including patient and therapist, changes memory.

A key reason that reconsolidation was so exciting clinically was its contrast with consolidation. With consolidation manipulations, the only way to alter memory with medications is right after the experience; the window of treatment opportunity is very narrow. But if the reconsolidation hypothesis is correct, it might be possible to alter troubling memories any time after the experience by simply retrieving the memory. Human research began to take off (Hupbach et al., 2007; Brunet et al., 2008; Schiller et al., 2010b; Kindt et al., 2009). Reconsolidation came to be thought of in terms of 'memory erasure,' which captured the imagination of the lay press. But the therapeutic magic bullet did not materialize (Schiller and Phelps, 2011). Studies have continued to offer hope of a reconsolidation treatment (reviewed in Brunet et al., 2018), but there is still no reconsolidation therapy. The results are consistent with reconsolidation being the mechanism underlying the behavioral and physiological response changes, but the findings so far do not seem demonstrate that unequivocally.

I think that part of the problem was and is misplaced expectations. Most of the research done on reconsolidation involved simple conditioning tasks in which animals learned associations between specific stimuli or situations and aversive events. While this kind of learning certainly takes place in human trauma, much more is going on than conditioned responses elicited by trigger stimuli. We humans form complex memories about who we are, and what is happening to us, and what we might have done to avoid it, and what the consequence may be in the future.

Changing the behavioral, or in some cases physiological (e.g. heart rate), responses to a conditioned stimulus, or even a collection of such stimuli, is unlikely to be sufficient to ameliorate one's mental suffering (LeDoux, 2012, 2014, 2015, 2017; LeDoux and Pine, 2016; Taschereau-Dumouchel, 2022). It can be part of the solution, but ultimately the kinds of memories involved are conceptual, and because they are rehearsed and reconsolidated many times over, they come to be part of who one believes they are.

Yet, the misplaced expectations did not start with reconsolidation research. It was endemic to the field of behavioral neuroscience. Early neuroscientist interested in behavior were either behaviorists or were trained by behaviorists. Consequently, subjective experiences of fear or anxiety were viewed as ghostly fictions. For behavioral neuroscientists, objective behavioral responses were, and still are, the only appropriate measure of fear and anxiety (Fanselow and Pennington, 2017).

The behaviorist logic became the conceptual basis for efforts to use studies of animal behavior to find medications to treat mental disorders in the 1950s and 60s. I believe this is why the use of drugs to treat problems related to fear and anxiety fail so many people. Because defensive behavior (freezing, fleeing, or avoiding) and subjective experience occur in parallel in response to the same external threat, the assumption is that they reflect the same brain state, with behavior being the more objective way to measure that state. However, I have argued that these are different consequences in the brain of the same external event. Until we recognize that subjective well-being does not come for free by changing behavior, we will have inadequate treatments for mental problems (LeDoux and Pine, 2016; LeDoux, 2017; Taschereau-Dumouchel, 2022).

But regardless of its ultimate value as a therapeutic approach, the revival of reconsolidation was a crucial correction to the monolithic

consolidation model that dominated for so long. Reconsolidation is still a work in progress and still has the potential to be useful, especially in taming behavioral and physiological symptoms. If we recognize the distinction between behavior and physiology, on the one hand, and subjective experience, on the other, reconsolidation might even be useful for helping with complex conscious memories. Time will tell.

In the meantime, our understanding of memory would be worse off without reconsolidation in the picture. And without Karim Nader, reconsolidation likely would not have come to exist in modern neuroscience. We are fortunate that Karim ignored me and did the experiment.

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Data availability

No data was used for the research described in the article.

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