



Toward a New Treatment for Traumatic Memories

Whether the result of violence, war, or disaster, the intrusive memories that haunt people with post-traumatic stress disorder (PTSD) cannot always be healed through psychotherapy or current medications. Now research on the biological basis of memory offers the hope of new drug treatments that may be able to lessen the disabling fear associated with traumatic memories and perhaps even fundamentally alter them. Neuroscientists Jacek Dębiec, M.D., Ph.D., and Margaret Altemus, M.D., argue that this possibility raises profound ethical and philosophical questions that must be examined even as researchers work to relieve the suffering of PTSD.



About the Authors:

Margaret Altemus, M.D., is an associate professor of psychiatry at Weill Medical College, Cornell University, and a board-certified psychiatrist. Her research focuses on the role of the endocrine system in affective disorders and the physiology of the stress response in humans. She can be reached at maltemus@med.cornell.edu.



Jacek Dębiec, M.D., Ph.D., is a psychiatrist, neuroscientist, and philosopher. He is a research scientist at the New York University Center for Neural Science, where he studies the neural mechanisms of emotional learning and memory. He is the coauthor with Joseph LeDoux and Henry Moss of *The Self: From Soul to Brain* (New York Academy of Sciences, 2003). He can be reached at jd86@nyu.edu.

*by Jacek Dębiec, M.D., Ph.D.,
and Margaret Altemus, M.D.*

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The titles of stories for non-scientists about research on altering traumatic memories express the hopes and fears of our society:

- “Studies say old memories can be lost” (Carey Goldberg, *Boston Globe*, 2003)
- “Blank for the memories: Someday you may be able to take a pill to forget painful recollections” (Scott LaFee, *San Diego Tribune*, 2004)
- “Is every memory worth keeping? Controversy over pills to reduce mental trauma” (Rob Stein, *Washington Post*, 2004)
- “When remembering might mean forgetting” (Douglas Steinberg, *The Scientist*, 2004)
- “Rewriting your past: Drugs that rid people of terrifying memories could be a lifeline for many. But could they have a sinister side too?” (Gaia Vince, *New Scientist*, 2005).

Some of these stories' authors, or at least the headline writers, have stretched the current science a bit. Forgetting, for example, is an active psychological process, not a simple memory erasure; and none of the studies so far has demonstrated a complete blockade of a targeted memory. But these writers are raising some of the right questions.

Scientists have made great progress in understanding the neural basis of learning and memory, and their discoveries suggest it might be possible to use drugs to relieve the distress of traumatic memories. For those who carry memories too painful to bear, such as people who suffer the nightmares and intense flashbacks that characterize post-traumatic stress disorder (PTSD), a method to block oppressive

recollections is well worth the effort. The National Center for PTSD estimates that, over a lifetime, 7.8 percent of adult Americans will suffer from intrusive, often disabling memories associated with PTSD. Those with PTSD often relentlessly avoid anything that might trigger memories of a trauma.

Why not help them?

But as the headlines suggest, there are ethical implications to altering one's consciousness through drugs. Which memories

should be clouded? Whose? How much? Such public attention also has spurred debate among scientists, philosophers, ethicists, lawyers, and lawmakers about how and when one might use drugs to alter memories. As practitioners and as a society, we need to ask: What should the limits be?

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HOW MEMORIES FORM

All memories are made in stages. The initial phase of new learning is often known as short-term memory. In this stage, newly acquired information is unstable and susceptible to interference, such as when a brief distraction makes us instantly forget the phone number we have just learned. If undisturbed, new learning becomes consolidated within a few hours into a long-term memory that is much more resistant to interference.

Research in animals has shown that the development of long-term memories involves activation of molecules at the synapses between nerves. This initiates cascades of intracellular reactions that modify the synaptic connections. Drugs that disrupt any aspect of consolidation prevent stable, enduring memories from forming, yet once the window of consolidation

is closed, the same drugs do not have any effect on the memory. Similarly, drugs that enhance memory consolidation do not have the same result if they are administered more than a few hours after the new experience.

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of norepinephrine (also known as noradrenaline). The main source of norepinephrine in the brain is the locus coeruleus (in Latin, “blue spot”). The locus coeruleus, located in the brain stem, sends abundant projections to other parts of the brain, including the amygdala, the hippocampus, and the

prefrontal cortex, all of which play important roles in memory formation. From animal studies, we know that stimulating one type of norepinephrine receptor at nerve synapses—the beta-adrenergic receptor—enhances the intracellular processes that contribute to memory consolidation and thus strengthens memories, and that blocking it during stress or arousal prevents its augmenting effects on memory.

Norepinephrine acts in several brain sites to strengthen memory formation. The release of more brain norepinephrine or more intense activation of the locus coeruleus inhibits performance of the prefrontal cortex, which plays a role in emotional control and extinction or suppression of memories. This stimulation also excites the amygdala, the key part of the brain in generating fear behaviors. The combined effects of norepinephrine on the prefrontal cortex and the amygdala may explain why we sometimes acquire habitual reactions that are difficult to control.

A trauma, by definition, is associated with high levels of arousal and activation of stress hormones. Many scientists interpret the clinical symptoms of PTSD, such as nightmares, flashbacks, and increased arousal in response to trauma-related cues, as an exaggeration or disturbance of the normal processes of emotional learning and memory. In this view, PTSD may be understood as a consequence of overconsolidation of the traumatic memory caused by increased activity of stress hormones and other biochemicals. In a 2002 clinical study, Roger Pitman, M.D., and his colleagues from Harvard University first applied this idea to people who had experienced a trauma. They administered propranolol (a beta-adrenergic receptor antagonist commonly used for treating hypertension and cardiac arrhythmias) to people who came to an emergency room

after experiencing a trauma and continued the drug treatment for 10 days. When they tested these study participants three months later, they found that the propranolol had lowered the risk of developing hyperarousal in response to cues that reminded participants of their particular trauma. This approach has limits, though: The risk of developing PTSD after most types of trauma is relatively low, and many people who have experienced a trauma do not immediately seek medical treatment.

To create treatment strategies that can be used long after PTSD has developed, researchers are now turning to what has been learned about the biological underpinnings of processes known as memory reconsolidation and extinction.

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HOW MEMORIES RECONSOLIDATE

Until very recently, most brain scientists believed that memories were completely immune to pharmacological alterations once they were consolidated. But there were a few animal studies in the late 1960s and early 1970s that suggested otherwise, reporting that administering a consolidation-blocking drug shortly after a reminder of a long-term memory

impaired the subsequent strength of that memory. In 1979, Donald J. Lewis, Ph.D., from the University of Southern California, proposed a distinction between active and inactive states of memory, based on the earlier reports. Perhaps retrieving well-established memories activates them in a way that renders these memories vulnerable to either disruption or strengthening by drugs that act on the underlying neurobiological systems.

Two decades later, Susan Sara, Ph.D., from Centre National de la Recherche Scientifique in Paris, built on Lewis's ideas. To explain how drugs might cause deficits in a previously well-established memory, she suggested that reactivating a memory by recalling it triggers another round of consolidation, which she labeled reconsolidation. This reconsolidation might enable the memory to be updated, incorporating new experience.

To test this notion, Karim Nader, Ph.D., Glenn Schafe, Ph.D., and Joseph E. LeDoux, Ph.D., from New York University, investigated fear memories in rats, using a common experimental learning model called auditory fear conditioning and what they knew about where in

the brain such memories are formed. In this model, animals hear a tone—the conditioned stimulus—then feel a mild electric foot shock—the unconditioned stimulus. Animals learn that the tone precedes the shock, and when researchers subsequently play the tone alone, the animals freeze out of fear. By measuring how long the animals freeze, researchers estimate the strength of their fear memory. In auditory fear learning, the amygdala is a key brain structure. Previous studies had shown that infusing the amygdala with consolidation blockers, including the protein synthesis inhibitor anisomycin, disrupts formation of long-term auditory fear memories.

Using this model, Nader and his colleagues trained their rats to be scared of a tone. After enough time had passed that the fear memories

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had consolidated, they sounded the tone again without the shock and immediately infused anisomycin straight into the rats' amygdalas. The next time they heard the tone, rats that received the anisomycin froze for a much shorter time, expressing less fear. Interestingly, the drug caused this apparent amnesia only if it was infused immediately after the tone; it had no effect when administered a few hours later or when not preceded

by the tone that reactivated the rat's memory.

Since 2000, when Nader and his colleagues published their findings in the journal *Nature*, other scientists have published studies showing that reconsolidation occurs in a variety of species, including the snail, sea slug, crab, honeybee, mouse, as well as the rat. Recent studies also suggest that, although reconsolidation and consolidation share similar mechanisms, they are distinct molecular processes. Both may be altered, though, for better or worse, by administering a drug.

In the first human-based study, published in 2003, Matthew Walker, Ph.D., and his colleagues from Harvard University trained participants in the study to perform a short sequence of finger movements. Once the learning had consolidated, they asked participants to repeat the sequence and then immediately instructed them to perform a different manual task (called the interference task). Walker and his colleagues observed that interfering with the reactivated memory of the finger sequence profoundly impaired people's future performance of that sequence. No drugs were used; instead memory was altered by a behavior that interfered with the same neurobiological processes.

FROM ANIMALS TO HUMANS

Scientists are eager to apply these discoveries to develop new treatments for PTSD and other forms of disabling fear, but the studies so far are not a one-to-one match. The demonstration by Walker and his colleagues that a consolidated, long-term human memory can be disrupted is exciting, for example, but the finger-sequencing task may not involve the memory systems that are crucial to traumatic memory. A difference may well exist between how conscious declarative memories are formed and re-formed and procedural forms of learning, such as the finger task. In addition, the finger-sequencing task does not result in an emotional memory that would be associated with releasing stress hormones, let alone with traumatic, intrusive features.

Researchers are now focusing on translating to humans the animal studies that used drugs to lessen the intensity of fear memories. Some reconsolidation blockers, such as protein synthesis inhibitors, are very

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toxic, but other drugs can be safely used in humans. In 2004, Jacek Dębiec and Joseph E. LeDoux showed that propranolol can block reactivated conditioned fear responses in rats. It was effective in disrupting reconsolidation even a few months after the rats had first learned the fear response. Recently, Melinda Miller, Margaret Altemus, and

their collaborators reported an as yet unpublished human-based study that suggests propranolol may also impair reconsolidation of conditioned fear responses in people who do not have any neuropsychiatric disorder. Trials are now under way to investigate the effects of propranolol on reactivated trauma memories in people who are diagnosed with PTSD.

Another approach is to enhance the process of memory extinction, which in certain ways is the opposite of memory reconsolidation. While reconsolidation updates and strengthens learning, memory extinction reduces the strength of a memory by repeated exposure to information that conflicts with the original memory. One could also say that extinction is a form of new learning, in which an organism comes to know that a cue originally associated with a traumatic experience no longer precedes trauma. For example, if rats are continually exposed to the same tone, but it is no longer paired with a shock, the length of time they freeze in response will progressively shrink. This approach is

the basis of exposure therapy, which is the type of psychotherapy that is most effective for treating PTSD and phobias. People are guided to recall their traumatic experiences, or are exposed to phobic cues such as heights, spiders, or public speaking under controlled, safe conditions so that they can learn to tolerate the cues without having explosive anxiety reactions or using defense mechanisms such as dissociation, which leads to disconnection from reality.

Many researchers are studying the psychological and neurobiological processes involved in memory extinction, and the possibility of using drugs to facilitate extinction, especially of traumatic memories. Michael Davis, Ph.D., and his colleagues at Emory University showed that seromycin—an antibiotic, also known as cycloserine, used to treat tuberculosis—can enhance memory extinction in animals. Seromycin activates

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NMDA receptors, a type of receptor for the amino acid glutamate, which is known to enhance learning. Davis and colleagues reported this year that they have extended their research to humans, demonstrating that people recover from a fear of heights more quickly if doctors give them seromycin immediately before exposure therapy sessions. In a separate study by

Stefan Hofmann, Ph.D., and his colleagues at Boston University, exposure treatment for anxiety about public speaking was enhanced by giving seromycin before each psychotherapy session.

Since both propranolol and seromycin are widely used to treat other medical disorders, one might wonder whether they alter memory when used to treat those disorders. But animal studies suggest that taking the medications repeatedly may not affect memory in the way it does when they are taken in single doses in immediate association with memory recall. Further research is needed.

Another big caveat in assuming these animal memory advances will translate smoothly to human breakthroughs is the communication barrier—we really don't know what animals are thinking. One major problem with animal models of human mental illness is that the core features of the disorders are subjective experiences, rather than observable behaviors. In the case of fear memories, for example, researchers study freezing, startle, and approach/avoidance behaviors in animals. Although they can observe these behaviors, they have no way to access

the emotional experience of the animals. When a propranolol-treated rat shows a reduction in freezing behavior in response to a tone that had been previously paired with shock, some scientists interpret that response as meaning that the rats have forgotten the memory that the tone is followed by a shock. But at this point we have no way of knowing whether the memory is actually erased, or has become inaccessible, or whether only the fear associated with the memory is reduced.

WHERE SHOULD THE LIMITS BE?

Memory has a fundamental role in human life; in some ways, it defines us. As the President's Council on Bioethics, in its report *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, points out: "Memory is central to human flourishing . . . because we pursue happiness in time, as time-bound beings. . . . If we are to flourish as ourselves, we must do so without abandoning or forgetting who we are or once were."

The members of the Council acknowledged that some memories, such as traumatic memories of violence, war, or disaster, constrain and distort our human experience. People with PTSD and phobias are disabled by their symptoms. The extreme fear and arousal associated with remembering a trauma makes it difficult for people with PTSD to integrate these memories into the rest of their experience and to react in a deliberate, intentional way. Women

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who have been sexually assaulted, for example, often avoid all relationships with men. In addition, because some victims dissociate, distancing themselves from the situation when danger cues trigger trauma memories, they may lose their ability to properly evaluate dangerous situations. This can make them vulnerable to further assault. A person who developed PTSD after surviving a terrible car accident may react to the sound of a car braking with a racing heart, sweating, and inability to take a step for several minutes. Such problems eventually cause many people with PTSD to avoid situations that might bring back the memory of trauma, sometimes to the extent that they become housebound. Traumatized war veterans often isolate themselves, both to prevent their irritability and hyperarousal from disrupting social interactions and because their hypervigilance makes them experience innocuous situations as threatening.

A treatment that reduced the associated fear could get them out of the house and out into the world, helping them gather the new experiences and memories that are part of the lifelong process of defining and developing a strong sense of self and identity. In the case of a phobia, such as excessive fear of heights or snakes, it is hard to see how lessening a reaction of explosive fear would harm the person with the phobia or change his identity.

Although current research is focused on alleviating emotional and physiological aspects of traumatic memories, such as hyperarousal, we do not know how interfering with the emotional coloring of memory

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would affect the way we remember and thus how we relate to our past. The potential for relieving human suffering is great, but these pharmacological “tools of interference” with human memories could also be misused. Once memory-blunting drugs are readily available, they may be used not only by trauma victims

but also by offenders who cause trauma, as well by witnesses to crimes or accidents. The authors of *Beyond Therapy* hypothesize that blunting emotional responses in those who have committed crimes may also result in diminishing any feeling of guilt, “the psychic pain that should accompany their commission of cruel, brutal and shameful deeds.”

At this point, we do not know what aspects of memory can be altered by the drug treatments now being developed for PTSD and other anxiety disorders. Ideally, the disabling fear and autonomic arousal will be reduced, but the memory of a traumatic event might remain intact, and perhaps even become clearer, since intense emotions disturb cognitive processes and impair recall. When patients with PTSD undergo psychotherapy, their memory of the traumatic event often improves. If the treatments also reduce their fear and dissociation, they will have the opportunity to create more complex, and more integrated, personal responses to the trauma, such as sadness, anger, outrage, or remorse. Carefully focused future research will continue to help answer questions about the effects of drug treatments; researchers and society as a whole have this window of time to consider the ethical issues.

If it is possible to erase essential aspects of a memory, the cure for one person may become a way to escape justice and responsibility for others. Before we start using drugs to treat traumatic memories, we must

address many ethical as well as scientific questions, a task that can be accomplished only through meticulous research and an intense multidisciplinary dialogue. ■

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