# Long-term Memories: The Good, the Bad, and the Ugly

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*Editor's note: Traumatic memories haunt the lives of people suffering from post-traumatic stress disorder, or PTSD, and other illnesses. Fortunately, recent research into the changeability of long-term memories may someday develop into treatments for such individuals. But before this can happen, writes Cristina Alberini, Ph.D., of Mount Sinai School of Medicine, researchers must determine just how effectively the fear associated with older memories—especially those involved in PTSD—can be reduced and for how long. Researchers must also address the ethical issues that go hand in hand with modifying memory.*

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For more than a century, clinicians, psychologists, and biologists have worked to understand the mechanisms underlying the formation and storage of long-term memories. Recently, scientists found that when a stored memory is recalled, it becomes sensitive to disruption for a limited time.[1,2] This finding indicates that it might be possible to weaken or even erase memories of traumatic experiences that become uncontrollably intrusive in post-traumatic stress disorder (PTSD). This possibility has drawn great interest from scientific and clinical communities, as well as from nonscientists, who became interested in its potential clinical applications; furthermore, it raised ethical concerns.

Many ethical questions and debates about treatments designed to weaken memories may reflect the still poor understanding of how memory recall or reactivation results in memory fragility and the many unknowns surrounding its temporal boundaries. Whereas the study of animal models and healthy humans has provided some knowledge about post-recall memory disruption, data on the use of such disruption to treat PTSD symptoms are still conflicting. The strengthening of memory with the passage of time, the resilience of strong memories to disruption, and the specific aspects of memory that become sensitive to disruption raise questions about the limitations of this approach and warrant more research. Here, we will look at how we form memories of an emotional event and how these memories become fragile after recall. That will help us consider the potential, limitations, and ethics of disrupting memories of emotional or traumatic events as possible means of treating PTSD.

**Long-term Memory: The Important Experience is Stored**

We remember the facts important to our lives and the tasks that we repeat frequently. The rest of our daily experiences rarely become long-lasting memories. In fact, we retain most information for only a few minutes or hours before it fades away. As poet and novelist Cesare Pavese wrote in *Il mestiere di vivere* (*The Burning Brand: Diaries 1935-1950*), "We do not remember days, we remember moments. The richness of life lies in memories we have forgotten."[3] I would say rather that long-term memories are what lend richness to our lives.

Emotions or repetition turn an experience into a long-term memory. The memories of a single salient or traumatic event, such as the September 11 terrorist attacks, and those of something we do repeatedly, such as ride a bike, are very different. The former, which are memories of facts, people, events, and things, are

known as explicit or declarative. The latter, the memories of how to do things, are known as procedural or implicit: They are the things we do without having to think about them. I will focus on explicit or declarative memories (which I refer to as explicit memories from now on), those of the unique experiences that are stored for a long time.

An event's biological relevance makes it important: We remember painful, aversive events so that we can avoid repeating them; we remember happy, advantageous experiences because they represent our best biological fit (such as the best sources of food, sex, and abilities to adapt to changes). In other words, emotional events, whether bad or good, stay with us; the stronger the emotion, the longer-lasting the memory. With the exception of excessively traumatic experiences, which may actually cause amnesia, we can generally recall a painful fact or trauma in detail for a lifetime. Similarly, we long remember a very happy day.

We know more about how the brain forms painful and traumatic memories because they are easier to study in animal models. Additionally, traumas are relevant to the development of several psychiatric disorders, including anxiety, depression, borderline personality disorder, dissociative identity disorder, substance abuse, and PTSD. Obviously, a gradient of stress or traumatic response parallels the averseness of an experience. A memory of "I ran into that unpleasant person" is not the same as "A car hit me and I was almost killed."

More than 100 years of work in both humans and animals have shown that a newly formed explicit memory remains in a fragile state for quite some time. Indeed, if pharmacological or functional interferences of brain activity occur during or immediately after an event as a consequence of, for example, stroke, physical trauma, or behavioral interferences, a long-term memory of the event will not form. A typical example is a car accident: A person will not remember the details about what happened just before and around the time of the accident. The fragility of memory is greater right after the event, or learning phase). As time passes, the memory becomes more resistant to disruption.

The process that mediates this time-dependent stabilization of memory is known as consolidation.[4] The duration and anatomy of the consolidation process still is not fully understood. Clinical studies of people who have had brain traumas, stroke, seizure, or even removal of brain tissue because of untreatable pathological conditions have revealed that memory consolidation takes weeks to years and occurs while the

information is processed by the part of the brain known as the medial temporal lobe. However, once a memory has been consolidated, information storage seems to involve brain regions other than the temporal lobe, particularly cortical areas.

Research has shown that memory consolidation requires the activation of molecular and cellular pathways, including those involved in stress, cell survival, cell-to-cell communication, and the release of several neurotransmitters (chemicals released in the brain to transmit signals across cells).[4-7] These activations lead to various cellular and molecular modifications, including regulation of gene expression, changes in chromatin structure (the components that, with DNA, form chromosomes and control cell functions), and modifications of synapses, the physical contacts among brain cells. Interfering with these biological changes at the time of learning, or for some time thereafter, prevents memory consolidation. However, memory fragility in response to these biochemical interferences lasts only for about 24 hours, much shorter than the time frame of anatomical studies. We have yet to understand whether and how the biochemical and anatomical consolidations relate to each other.

For decades scientists believed that consolidation of explicit memories occurred through a single process of stabilization. They hypothesized that the process of memory consolidation involves critical molecular changes during the first 24 hours, significantly engages the hippocampus and related brain areas for a few weeks to months, and later involves different brain regions in the cortex, at which point memory was considered consolidated and insensitive to disruption.[8,9] Recent studies have challenged this hypothesis.

**Remembering and the Reconsolidation of Memory**

About 10 years ago, investigators revisited interesting discoveries made in the 1960s. They found that memories that were one day old or older, and thus resistant to biochemical interferences, became sensitive again to interference if and only if they were recalled. In short, recalling a memory makes it labile, or modifiable, for a few hours. During this time the memory restabilizes in much the way that a new memory consolidates after learning. Thus, a day after recall a memory is again stable and resistant to disruption. This post-recall process of restabilization has been termed reconsolidation.[1,2]

This discovery is of great clinical interest: If a memory becomes fragile and can be disrupted after recall, we may have an opportunity to weaken, even perhaps erase, painful memories, such as those that are so strong and intrusive in PTSD and addiction.

During the past decade, research in several laboratories, including mine, has focused on the process of memory reconsolidation. From this work, we now know that reconsolidation occurs with many different types of memories, not only those involving the medial temporal lobe.[10] Reconsolidation is not a faithful recapitulation of the initial consolidation, but instead often seems to recruit only a subset of the brain areas involved in consolidation. Interfering with reconsolidation selectively affects the recalled memory while leaving others intact.[2,10] Several studies, including some from my laboratory, indicate that one function of reconsolidation is to strengthen memories and prevent forgetting. In other words, we recall memories that are important, and by doing so we reconsolidate them to strengthen them and retain the information longer.

Another hypothesis holds that reconsolidation mediates the incorporation of new information into recalled memories—that it promotes memory updating. In testing this hypothesis, we and others have found that although recall is necessary for memory updating, reconsolidation is not the underlying process. Updating uses a new consolidation process that occurs in parallel with but independently from reconsolidation of a recalled memory.[11] Hence, it appears that two distinct processes occur when we recall a memory. The first is the reconsolidation of the original memory, which leads to memory strengthening. The second is the formation of new associations to connect past and present experiences. Thus, recalling the past does not merely transform our memories into different ones, losing the old information. Instead, by recalling a memory we can retain the old information, or at least part of it, but also process the recalled experience differently in light of new events, which ultimately will provide us with behavioral choices.

**Memory Reconsolidation and the Passage of Time**

One important feature of memory reconsolidation that has been found with different types of memories—aversive and not—is that in most cases, memories become stronger and more resistant to post-recall disruption as time passes.[10] Unlike the recall of memories that are only a few days old, the recall of stronger, older memories (weeks or months old in animals) does not result in memory fragility.[12] Some reports have suggested that the strength of the learning experience, the passage

of time, and the strength and type of recall all contribute to whether and to what extent a memory can become susceptible to disruption.[13]

Memory strengthening and the effects of the passage of time need further investigation to better determine the potential of using reconsolidation clinically. Painful memories such as those in PTSD usually are extremely strong. Also, affected subjects often seek treatment months or years after both the trauma itself and the onset of the disorder. If a memory is too old and too strong, can it still be modified after recall? Is there a restricted window of time that is optimal for intervention? Might other, more powerful types of treatments weaken stronger and older memories? Can some types of memories remain susceptible to reconsolidation at any time?[14] These questions still must be addressed.

Based on current results, I view reconsolidation as an integral part of a consolidation process that lingers for quite some time (weeks in animal models).[2] Thus, event-induced consolidation and recall-induced reconsolidation processes together contribute to the overall consolidation of the memory. After the learning experience, implicit reactivations seem to occur during sleep[15] or over circadian rhythmicity. Furthermore, aversive or traumatic events frequently replay in the brain, especially during the first days or weeks after their occurrence. These recalls or reactivations may serve the biologically important function of consolidating an aversive memory without repeating the aversive or traumatic experience. At each reactivation, the recalled memory also forms new associations and the memory network expands. It is tempting to speculate, but it remains to be demonstrated, that the ability to undergo memory reconsolidation reflects the temporal lobe–cortical reorganization of the consolidation process.

**Weakening Pathogenic Memories: Treating PTSD**

Can we disrupt the reconsolidation of traumatic memories that contribute to PTSD and bring relief to patients suffering from this disorder? PTSD can develop after someone experiences emotionally or physically traumatic events such as war, explosions, rape, accidents, earthquakes, attacks, and physical and psychological abuse. The person relives the trauma through repeated, intrusive memories of the traumatic experience and consequently may have difficulty sleeping and may feel detached or estranged. These symptoms are so severe and persistent that they

significantly impair normal functioning. The families of patients suffering from PTSD also are considerably affected.

*ReEntry*, a theater piece by Emily Ackerman and KJ Sanchez for the American Records Theater, highlights these effects of PTSD.[16] Ackerman and Sanchez interviewed and recorded the experiences of Marines returning from Afghanistan and Iraq and their families. These passages are taken directly from the interviews and describe how lives can fall apart with PTSD.

> **John (a Marine Corps officer early in his career):**
> It was really, like, it was kinda intense. It went from, like, zero to f----n' homicidal in about three seconds.
>
> **Liz (John's sister):**
> So he was back on the base and in a training op and he—you know, big loud noises, explosions …—and he had a flashback. He just froze, and people were yelling at him, and he was just like … gone. And that's a very big f-----g deal when you're a Marine—when they're like "go, go, go" and you don't do anything—you just freeze.
>
> . . .
>
> And he was sitting out on his balcony, and he realized how exposed he was out there. You know, he saw all the positions where a sniper could be. He's sitting on his balcony in San Diego, California, and he's looking around for snipers. And he became absolutely convinced that someone was gonna come into his house and kill him. So he got his guns out. He had a shotgun pointed at the door.

Recent studies report that 8 percent of Americans suffer from PTSD and about 15 percent of veterans experience multiple or all PTSD symptoms at some point after returning from combat. Available therapies rarely exceed 60 percent success rates, and no more than 20 to 30 percent of patients achieve full remission.[17,18] The need for more effective treatments is pressing.

Although no animal model that fully reproduces PTSD is yet available, it is possible to represent components of the disorder, such as the conditioned response to a fearful event. This is usually done via an experience that evokes fear. For example, an animal is exposed to a new place and given a small foot shock that causes the animal to

become fearful of that place. If re-exposed to the area, the animal will freeze, or, if given the choice to explore it again, will carefully avoid it. Using these techniques, several drugs have been tested to determine whether or not they can disrupt a recalled fear memory.

Another approach is a process called fear extinction. Recalling a fearful experience in a safe place brings the unpleasant event to mind but shows that the terrible event does not recur. Therefore, a new memory emerges, one of being safe from the bad experience. If this safe-recall experience is repeated many times, the subject will learn to extinguish the fear. Although treatments that enhance extinction are also clinically attractive, extinction and reconsolidation are very different processes. Interfering with reconsolidation aims to disrupt the associations to the trauma; promoting extinction aims to teach the subject a new memory that will help overcome the fear. Extinction is used in clinical treatments of phobia or obsessive-compulsive disorders. However, one drawback of extinction therapy is that the effect does not last; the original behavior usually re-emerges over time.

In principle, the pharmacological and behavioral interferences thus far found to be effective in disrupting fear memory reconsolidation in animals could be potentially useful in clinical settings. Propranolol, a blocker of the receptor for the stress hormone noradrenaline, has been explored at both the preclinical and clinical levels. Propranolol, which is most commonly used to treat hypertension, disrupts some but not all fear memories in both animals and humans.[19-21] Human studies have suggested the attractive hypothesis that propranolol targets the fear response but not its cognitive or explicit components.[21] This may be a great advantage in clinical applications, since only the associated fear, and not the memory content itself, would be disrupted by the treatment.

Another target that my co-workers and I have explored for the potential treatment of PTSD is the receptor for the stress hormone corticosterone (cortisol in humans). Corticosterone can enhance or decrease memory retention depending on the dose.[22] In smaller amounts, this hormone strengthens memory, while in high doses it disrupts both consolidation and recall. When we recall a trauma, we re-experience stress, and stress hormones including corticosterone are released; the corticosterone strengthens the memory.

We investigated whether we could disrupt reconsolidation and memory strengthening by blocking the action of this hormone. We administered mifepristone

(RU38486), which blocks receptors on cells that take up the corticosterone, after the recall of a fear memory in rats. We found that the treatment significantly weakened the original memory.[23,24] We also found that one or two treatments were sufficient to achieve maximal disruption of the fear memory, and that the treatment selectively targeted a memory without interfering with other, unrecalled memories.[24]

To examine whether the efficacy of treatment changes with the intensity of a traumatic experience, we tested the effects of mifepristone in rats on memories evoked by shocks of different intensities. We found that mild fear memories could be easily weakened but that strongly traumatic memories were significantly less susceptible to disruption. However, we found that we could weaken these memories if we administered the recall and treatment a week or so after the learning and if we increased the number of interventions. In light of these results, the stress hormone cortisol and its receptors appear to be a promising target for pharmacologic intervention in trauma-related pathologies, including PTSD.

However, in order to see what these important findings on propranolol and mifepristone might mean for how we treat people with PTSD, we need to find the answers to at least two important questions. First, is there an optimal time window for the treatments? Second, do these drugs disrupt strongly traumatic memories? We also need to understand why only a fraction of people who experience a trauma develop PTSD, and why the disorder surfaces over time, often months, after a trauma. Are the storage mechanisms for recurrent, intrusive memories that affect people with PTSD different from the storage mechanisms for traumatic memories in people who don't develop the disorder?

An alternative possibility would be to use the reconsolidation approach to prevent trauma-induced pathologies including PTSD. Weakening the intensity of traumatic memories during the first few weeks or months of the consolidation phase may be useful in impeding the development of PTSD or other disorders, including borderline personality disorder, dissociative identity disorder, substance abuse, anxiety, and depression.

Another interesting behavioral approach that has been identified recently by studies in both animals and humans is based on a sequential retrieval (reconsolidation) and extinction protocol. Extinction after fear memory recall leads to a permanent loss of the fear association if the extinction is conducted within reconsolidation's temporal

window.[25,26] Further studies need to investigate whether this approach is effective in old and strong memories and to determine how it works.

**Ethical Issues**

Reconsolidation studies raise the question of whether it is ethical to use approaches that could someday be used to erase memories and thereby potentially change people's identities. Can these methods be used to control people's minds and behaviors? Will reconsolidation research, as portrayed in the movie *Eternal Sunshine of the Spotless Mind*, lead to firms like the fictional Lacuna, where unhappy people go to have their disappointments erased? Will people be able to decide whether to erase memories? Any discovery has the potential for misuse. Regulations are important, and treatments should be given only when medical conditions require them. However, concern about logical extremes should not stop research that could lead to disease treatments.

As noted earlier, research on fear memories suggests that some pharmacological treatments may be able to target the emotional and fear response but not the memory content; more investigations are necessary.[21] We also should remember that our long-term memories of a given experience are the result of distributed representations and relative connections with many other memories. Thus, any treatment is unlikely to eliminate significant portions of patients' overall memory content and with it their sense of self or identity.

Although any treatment that targets the brain and mind is daunting, mental disorders themselves change people's feelings and behavior and, in the end, personality. In severe cases, depression, anxiety, panic, borderline personality disorder, dissociative identity disorder, and PTSD *all* lead to a loss of self and identity. Those who suffer from these pathologies cannot function normally and instead live with profound, sometimes unbearable, suffering.

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