

When remembering runs amok, past pain can disrupt someone's present. New drugs, psychotherapeutic approaches, and other strategies might temper traumatic memories

## Learning to Forget

Memory lends our lives a sense of continuity, enabling us to learn from experience, nurture lasting relationships, and keep good times from vanishing into the past. But memory also brings pain. A humiliating failure, a gruesome accident scene, or the death of a parent can torment the mind long after the event. In extreme cases, bad memories unravel lives, as they do for people with posttraumatic stress disorder (PTSD) and other anxiety conditions. Remembering the good times is nice, but forgetting the really awful times—or at least keeping those memories in check—may matter more for quality of life.

After decades of intense and fruitful research on how the brain encodes new memories, many neurobiologists are now turning their attention to how the brain keeps unwanted memories at bay. Recent work has identified key brain regions involved in suppressing memories and fingered some of the chemical messengers involved. Applying their work to the clinic, some researchers have seen promising preliminary results with drugs that either weaken the emotional hold of traumatic memories or prevent newly formed memories from becoming destructive in the first place. These studies may open the way to treatments that return normalcy to the lives of millions of people hamstrung by anxiety disorders.

But this work makes some bioethicists—including those on President George W. Bush's Council on Bioethics—squirm. They foresee a not-so-brave new world in which the cares and fears of everyday life can be erased by tossing back a pill—much to society's detriment.

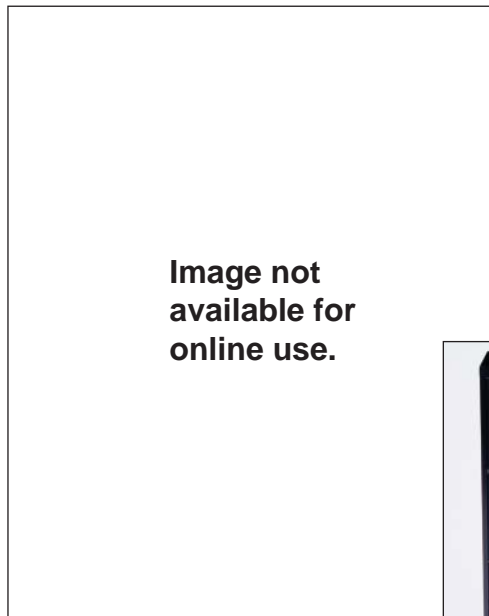
### Persistence of memory

Memories of traumatic events tend to endure, says Roger Pitman, a psychiatrist at Harvard Medical School in Boston, because “evolution has found a way to make us remember things that are important for our survival.” A caveman who encounters a vicious animal while taking a shortcut to the water hole will likely remember the experience and avoid that route in the future.

Circuits in the amygdala and other brain

regions specialize in cementing associations like the one between the shortcut and the animal, which are bolstered by hormones pumped out in times of stress. “The same adrenaline that's making you run from the animal is working in your brain to strengthen associations between the route and the animal,” says Pitman.

But traumatic memories that are too powerful can be detrimental. If the caveman lies



**Distress control.** When subjects “reappraise” a disturbing image such as a blood-spattered toilet with a less disconcerting explanation, their amygdala activity is similar to that evoked by a neutral image such as a file cabinet.

awake night after night reliving the attack, he may lose his effectiveness as a hunter.

Nearly a century ago, Sigmund Freud proposed that repression—“turning something away and keeping it at a distance from the conscious”—is a basic psychological defense mechanism. The authors of a recent brain-imaging study claim to have found something like what Freud described (*Science*, 9 January, p. 232). They identified a network of brain regions that keeps unwanted memories below the surface of consciousness.

Michael Anderson of the University of

Oregon in Eugene and colleagues at Stanford University used functional magnetic resonance imaging (fMRI) to monitor the brain activity of volunteers trained to suppress memories—not bad ones in this case, but bland associations. Volunteers memorized pairs of words, such as “ordeal” and “roach.” Then, inside the scanner, single words flashed on a screen in either green or red letters. If “ordeal” appeared in green, subjects were instructed to recall “roach.” But if “ordeal” was written in red, they were to avoid thinking “roach.”

On a paper-and-pencil test taken after the scanning session, subjects were about 10% worse at remembering word pairs they'd suppressed compared to ones they'd recalled. The brain scans hint at why. When subjects suppressed a memory, their dorso-lateral prefrontal cortex was active. This area has been linked frequently to what cognitive neuroscientists call executive control;

it is active, for example, when subjects consciously suppress a particular movement or emotion. At the same time, activity in the hippocampus—a key memory center—decreased. “What this shows is that when people are trying to suppress a memory, they're doing something very active that involves a distinct network of [brain] regions,” Anderson says.

“It's a very interesting paper on a really underexplored topic,” says Elizabeth Phelps, a cognitive neuroscientist at New York University. “How we forget, or

inhibit, or do away with a memory [has] always been a big part of the story, but it's one we haven't really focused on.”

Anderson plans to repeat the experiment in people who have trouble forgetting, such as those with PTSD. “We might find that people with PTSD are deficient in their ability to recruit this network,” he hypothesizes.

There are at least two lines of defense when faced with a traumatic experience, says Kevin Ochsner, now at Columbia University in New York City, who collaborated with Anderson on the *Science* study: Don't remember



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it happened, or given that it happened, reinterpret it in a more positive light. Just as the dorsolateral prefrontal cortex may dampen activity in the hippocampus to manage memory, it may play an analogous role in managing emotions. It dampens activity in the amygdala when people try to put a positive spin on a bad situation, Ochsner claims.

He and colleagues showed volunteers a set of disturbing photos—a burned body, a gunshot wound, a toilet splattered with blood or vomit—and asked them to concoct a story in their mind that made the situation less negative. In fMRI scans, the prefrontal cortex lit up when subjects “reappraised,” and the amygdala grew quieter. In fact, subjects’ amygdala activity during reappraisal of negative images was similar to that during passive viewing of neutral images such as a file cabinet.

Both Anderson and Ochsner see their findings as illustrating everyday cognitive processes. “There’s this spin control we’re doing all the time,” says Ochsner, whether we’re dealing with a bad review on a journal article or rehashing an argument with a friend. But the work may shed light on psychiatric disorders as well.

“We know a lot about the pathophysiology” of depression, Ochsner says, “but we don’t know what the pathophysiology reveals.” For example, some studies have found heightened amygdala activity and decreased prefrontal cortex activity in depressed people. That might mean people with depression are less able to tap into the neural networks for reappraisal, Ochsner speculates.

Stimulating sluggish frontal regions, perhaps with drugs or transcranial magnetic stimulation (TMS) (*Science*, 18 May 2001, p. 1284), might improve people’s ability to place painful memories in context. A study published in the March issue of the *American Journal of Psychiatry* found that 10 daily sessions of TMS focused on the right dorsolateral prefrontal cortex had a therapeutic effect on 10 PTSD patients.

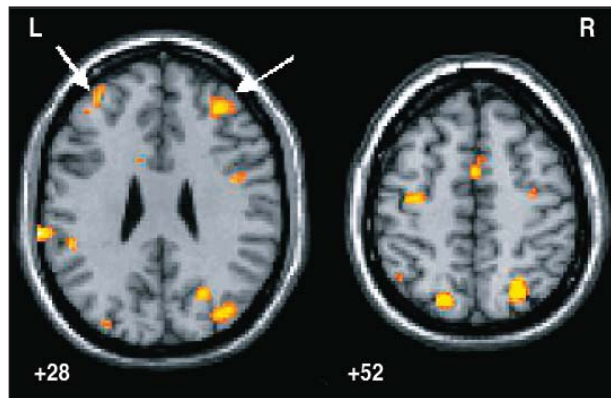
#### Promoting extinction

Clinical payoffs might also come from research on the signaling molecules involved in learning—and unlearning—fear. Much of this work involves a behavioral training regime called fear conditioning. Typically, researchers present a lab rat with a flash of light followed by a mild shock. After a few repetitions, the rat exhibits a “fear response,” freezing when it sees a flash. If researchers cease pairing each flash with a shock, the rat eventually stops freezing—a process called extinction.

Although extinction may seem like a

simple matter of forgetting, it is not. In a rat that has seemingly lost its fear of light flashes through extinction, the fear response comes back with a vengeance when the light is once again followed by a shock. Many researchers see in extinction a parallel to psychiatric therapy: Both involve a special kind of learning that is prone to relapse.

Drugs that hasten or fortify extinction, some researchers reason, might be useful for therapies that help people overcome fearful associations. One compound, D-cycloserine, has already shown promise in a clinical trial. The drug enhances the function of a particu-



**Suppress that thought.** Activity in the dorsolateral prefrontal cortex (arrows) puts a damper on unwanted memories.

lar receptor for the neurotransmitter glutamate—the so-called NMDA receptor—that earlier work has shown to be critical for extinction. Michael Davis and colleagues at Emory University in Atlanta, Georgia, found that administering the drug to acrophobic patients during therapy—playing a virtual reality game that simulates riding a glass elevator—helps ease their fear of heights in real life (*Science*, 21 November 2003, p. 1321).

Other groups have identified additional candidate extinction promoters. Mark Barad, a psychiatrist at the University of California (UC), Los Angeles, says his team is organizing a clinical trial of yohimbine, a drug that stimulates activity of the neurotransmitter norepinephrine and provides an “enormous boost” to extinction in rats. Cannabinoids—the psychoactive ingredients in marijuana—may also have potential. In 2002, Beat Lutz and colleagues at the Max Planck Institute of Psychiatry in Munich, Germany, reported in *Nature Neuroscience* that mice lacking cannabinoid receptors are impaired in extinction but not other types of learning. Since then his group has been screening cannabinoids and related compounds for ones that aid extinction. The list of candidates also includes drugs that enhance the activity of certain calcium channels or the inhibitory neurotransmitter GABA. Researchers have yet to form a clear picture of how all these signaling

molecules fit together.

It may also be possible to make extinction—and potentially therapy—more effective without drugs. Barad’s group reported in the *Journal of Experimental Psychology: Animal Behavior Processes* last October that the timing of extinction training has a big influence on its effectiveness. Rats get over their trained fear of light flashes more quickly when exposure to the flash alone is delivered in clusters than when the flashes are evenly spread out.

Subsequent experiments hint that continuous exposure to the feared stimulus is even better than clusters, Barad says. He sees parallels in his psychiatric practice. One patient with obsessive-compulsive disorder had an irrational fear of catching cancer from people who have cancer, including her mother. Barad convinced her to wear a scarf that belonged to her mother continuously, and over time her fear disappeared.

“We learn fear very easily,” Barad says, and extinction is the brain’s way of weeding out maladaptive associations. Tapping into this natural learning process—whether through drugs or therapy or both—could help patients with a variety of disorders conquer bad associations. Extinction exper-

iments can teach therapists how to expose people more effectively to feared cues and prevent them from expressing inappropriate behaviors in response, Barad says.

#### It never happened

While some researchers work on aids to unlearning, another set of recent studies suggests that it may be possible to prevent newly formed memories of traumatic events from becoming disruptive. Techniques could weaken both the memories themselves and their emotional associations.

Memories of emotionally significant events are strengthened by stress hormones such as adrenaline. A classic study by Larry Cahill and James McGaugh of UC Irvine published a decade ago showed that blunting the effects of stress hormones in the brain can negate this strengthening effect. Volunteers viewed a slide show and listened to a narrative about the slides—either a tame one about a boy visiting his father at work or a tragic version of the same story. A week later, subjects remembered the emotional story much better. But subjects who received propranolol—a beta-blocker drug, named for the subtype of adrenergic receptor it blocks—remembered the emotional story no better than the neutral one. Propranolol blocks the effects of the neurotransmitter norepinephrine, levels of which rise in the brain in response to adrena-

line. The researchers concluded that adrenergic activity—brain signals transmitted by members of the adrenaline family—is essential for the enhancement of emotional memories.

Subsequent research has hinted that adrenergic activation plays a role in the development of PTSD. People who show greater signs of adrenergic activation, such as a racing heart rate and panicky behavior, immediately after a traumatic event are more likely to exhibit symptoms of PTSD later, says Charles Marmar, a

**Problematic.** The President's Council on Bioethics warns against manipulating memories.

psychiatrist at UC San Francisco.

Together with colleagues in France, Marmar recently gave propranolol to 11 people admitted to French hospitals following a motor vehicle accident or physical assault. The patients, who did not have serious physical injuries, took the drug within a few hours of the incident in most cases and continued to take it for 2 to 3 weeks. Two months later, this group had fewer symptoms of posttraumatic stress than a similar group of patients that didn't take the drug. A previous pilot study by Pitman and colleagues, published in 2002, found similar results.

Both Pitman and Marmar say the findings are encouraging but preliminary. "You can't take this to the bank," Marmar says of the combined results, "but I think it's enough to justify a large-scale trial." Indeed, both groups learned late last year that they will receive funding for larger, blinded, placebo-controlled trials. "If this is all correct, it means that PTSD, which affects close to 8% of the American population at some point in their life, might be predictable at the time of the event and may even be preventable ... with a course of medication that costs \$15," Marmar says.

#### Medicating away morality?

But that doesn't sound like a bargain to the President's Council on Bioethics. In a report\* released last October, the panel opined that "the prospect of preventing (even) PTSD with beta-blockers or other memory-blunting agents seems to be, for several reasons, problematic."

Among practical problems, the report

says, is knowing whom to treat. Victims don't exhibit symptoms of PTSD, by definition, at the time of the event. Accident witnesses might start demanding prescriptions, imperiling their future testimony. In the future foreseen by the council, doctors could "give beta-blockers liberally to soldiers on the eve of combat, to emergency workers en route to a disaster site, or even to individuals requesting prophylaxis against the shame or guilt they might incur from future misdeeds." The potential for misuse, they claim, abounds.

Moreover, the report continues, bearing traumatic memories is the moral obligation of those who witness atrocities. Even if individual Holocaust survivors were to benefit from treatments that weakened the memories of their experiences, the council writes, society as a whole might be badly served by having no witnesses whose memories are unadulterated. "Our memory is not merely our own; it is part of the fabric of the society in which we live."

The council's report largely misses the mark, says Arthur Caplan, a bioethicist at the University of Pennsylvania in Philadelphia. Certainly society must preserve the

record of atrocities such as the Holocaust, he says, but doing so doesn't require denying individuals the benefits of therapeutic drugs: "The notion that we need to have suffering martyrs among us is cruel and exploitative."

The subtext of the council's argument, says Caplan, seems to be that using drugs to manipulate memories—whatever the content of the memories—is unnatural and therefore morally suspect. "I don't accept that at all," he says. For one, it obliterates the line between treating memory and mood disorders and using drugs for the selfish pursuit of self-improvement. And if treating an infection with antibiotics is OK, he asks rhetorically, why shouldn't it be OK to use drugs to correct a problem with memory or cognition? "It's a moral argument that, if turned in in my undergraduate bioethics class, would pull a C."

Selectively erasing memories does indeed raise ethical questions, says Joseph LeDoux, director of the Center for the Neuroscience of Fear and Anxiety in New York City. But that's always true of science that pushes the bounds, he says: "If we're successful in doing these sorts of things, it will raise a societal debate about how far we want to go." —GREG MILLER

## A Star-Studded Search for Memory-Enhancing Drugs

An eager market—from Alzheimer's patients to aging overachievers—awaits the first memory-enhancing drugs. High-profile neuroscientists are racing to provide the goods

Forgetfulness is a common failing of old age that patent medicines once promised to cure. But rescuing memory has now moved from snake oils and placebo effects

into the scientific mainstream. There's been an explosion of new drug candidates designed to boost memory in recent years, and many are entering clinical trials. Although a few elixirs have already fallen by the wayside, observers see encouraging signs in the breadth and depth of clinical experimentation.

Although big pharmaceutical firms are heavily involved, some of the most ambitious efforts are led by small companies, each tied to a prominent academic scientist and backed by a famous institution. And star scientists are drawing media attention and giving the enterprise a dash of glamour.

The commercial potential for memory enhancers is immense. Some drugs in development are designed to help people with Alzheimer's disease or other brain disorders, whose number is in-

**Early start.** Gary Lynch of UC Irvine helped launch Cortex more than a decade ago; in the 1990s the firm began to develop drugs called ampakines to boost memory.



\* *Beyond Therapy: Biotechnology and the Pursuit of Happiness*