

Post-traumatic Stress Disorder and Traumatic Brain Injury Healing the Battered Brain

By Kayt Sukel

For decades, researchers have hoped to uncover the biological mechanisms behind post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI), increasingly common afflictions among both soldiers and civilians. In 2008, researchers renewed their focus on these conditions and sought to identify the processes that will provide new avenues for prevention and treatment.

The findings include a study that shows that damage to certain areas of the brain may actually protect against the development of PTSD. Coupled with other neuroimaging studies, these results provide a probable neural circuit for the disorder that may yield new discoveries about who may be more susceptible to it as well as new targets for treatment. By targeting fear extinction at the neural level, two new compounds are showing promise in both the prevention and treatment of PTSD. And finally, scientists have discovered that progesterone is no mere sex hormone. Preliminary studies suggest that the sex steroid may help protect the brain from the “cytotoxic cascade” of TBI.

Post-traumatic Stress Disorder

Researchers investigating the neural mechanisms of PTSD want to understand why one soldier develops the disorder while the soldier’s immediate comrades do not and why certain treatments may work for one individual but not another.

Steve Centore was the leader of a Department of Energy Hazardous Materials Response Team when he first set foot in Ground Zero after the September 11, 2001, attacks. He was testing for potential contaminants in the debris or air that might be dangerous to people working within the perimeter. While running test protocols, Centore and his team were in plain sight of the “bucket brigades,” rescue workers moving debris away in five-gallon buckets in hopes of discovering survivors. “We would walk around the pile and do our tests,” he said. “While you were doing them, you’d look down. And what you thought was a rubber hose, just something peculiar that caught your eye, would instead be a severed arm.”

Centore said that you couldn’t help but see these gruesome artifacts while working at Ground Zero. Years later, he still sees them. In 2005, after suffering from flashbacks and panic attacks so severe that he became afraid to leave his home, Centore was diagnosed with PTSD. The disorder, often referred to in the past as “shell shock” or “battle fatigue,” has dramatically changed his life, rendering him unable to work, afraid to sleep, and reluctant to venture out of his house.

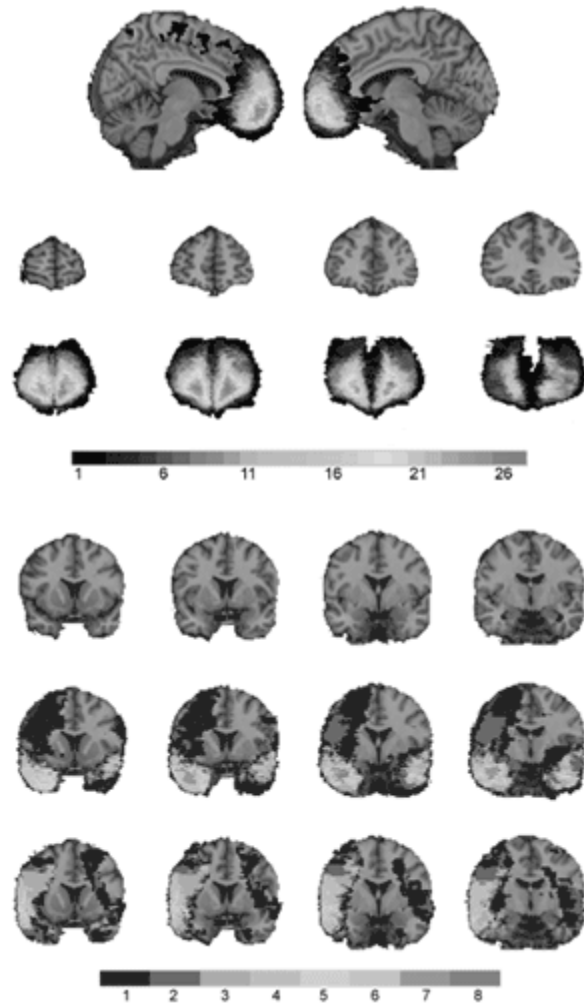
According to the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, the standard handbook for mental health professionals, PTSD is the development of characteristic symptoms after experiencing an extreme traumatic event that threatens death or bodily harm. Those symptoms include reexperiencing the event over time (i.e., flashbacks), persistent avoidance of stimuli that remind individuals of the event, hypervigilance, difficulty controlling emotions, sleep disturbances, and social avoidance behaviors. The disorder can be debilitating, wreaking havoc with work and social lives.

PTSD is not a new phenomenon. Greek historian Herodotus made mention of battle-related stress symptoms after the Battle of Marathon in 490 B.C. But until the Vietnam War, many viewed “shell shock” more as a sign of cowardice than as a true psychological disorder. Soldiers from conflicts such as the Civil War and World Wars I and II were often stigmatized for “battle fatigue” and, when compassionately diagnosed, treated with bed rest, isolation, or early versions of talk therapy. The Vietnam War was a turning point. With the influx of returning veterans, many of whom had difficulty adjusting to the civilian world, “shell shock” gained new respect as a true psychological disorder (as did its new moniker, PTSD). Since health professionals did not understand the underlying neuropathology of the disorder, they most often treated patients with counseling, exposure therapy, and anti-anxiety medications.

Looking to the Past to See the Future

In a novel approach to studying PTSD and the brain, Judith Pizarro Andersen and colleagues at the University of California, Irvine, looked to old paper medical records instead of genetic studies or neuroimaging protocols. Mining Civil War files, the researchers were able to extrapolate the long-term health effects of traumatic war experiences on thousands of Civil War vets. Their research, published in the February 2006 *Archives of General Psychiatry*, revealed that being a prisoner of war, being wounded, or witnessing the deaths of a large number of fellow soldiers was linked to higher incidence of cardiac, gastrointestinal, and nervous disease later in life.¹

Andersen said that the most surprising finding was that veterans who entered service when they were younger than twenty were more susceptible to later health problems. “That age was a powerful predictor [of] whether the soldiers would get chronic diseases earlier in life,” she said. “And it also influenced if they would die earlier— their actual survival.”



A study examined Vietnam veterans who both sustained brain damage and experienced war trauma. The subjects were grouped according to the site of the injury, into the ventromedial prefrontal cortex group (top) or the amygdala and temporal lobe comparison group (bottom). In the images, the shade of the brain area corresponds to a scale at bottom indicating the number of veterans who exhibited brain damage there. (Jordan Grafman, Ph.D. / National Institute of Neurological Disorders and Stroke)

In the same issue of the journal, Roger Pitman commented in his own review that pathways that process fear and fear extinction—an inhibitory learning process that allows a fearful memory to lose its potency over time—may not have fully matured until the age of twenty.² “We need to really think about what age means in a neurological way,” said Andersen. “The idea that some of those neurobiological pathways aren’t developed yet to handle these events makes sense. But it needs to be better understood.”

Brain Differences in PTSD

Although PTSD has been classified as a psychiatric illness for nearly a century, only in recent years has research given us greater understanding of the neurobiological basis of the disorder. Lisa Shin, a researcher at Tufts University, has been studying brain activation differences in PTSD patients for more than a decade. Her work, using positron-emission tomography and functional magnetic resonance imaging (fMRI), has found significant differences in brain areas linked to memory and emotion in patients with PTSD.³

The amygdala, part of the limbic system and implicated in both memory and fear processing, is one such area. “In PTSD, the amygdala is hyper-activated,” said Shin. “When you scan people as they remember traumatic events or look at fearful faces, the amygdala is responsive to that. And many studies with PTSD patients have found exaggerated responsivity to those kinds of stimuli.”

Just as important, the medial prefrontal cortex (PFC) is underresponsive to fearful stimuli, Shin said. “Perhaps the medial prefrontal cortex can’t inhibit the amygdala. It’s a nice circuit to look at, considering that it is the same circuit involved with fear conditioning and extinction.” Shin’s lab is currently looking at brain activation patterns as a way of predicting response to treatment.

Research by Jordan Grafman, a senior investigator at the National Institute of Neurological Disorders and Stroke, and colleagues suggests that focal brain damage in the amygdala and the ventromedial PFC may actually protect the brain from PTSD. In a study published in the February 2008 issue of *Nature Neuroscience*, Grafman and his collaborators looked at Vietnam veterans who had both brain injury and exposure to war trauma.⁴

“When people have a brain injury, you generally don’t expect it to be helpful,” said Grafman. “But in this case, when the injury was in the amygdala or ventromedial prefrontal cortex, it did protect against the constellation of impairments that result in PTSD.” The finding implies that these areas play a key role in the development of PTSD and offers future researchers a good place to focus, Grafman argues.

The thalamus is also of interest in PTSD. Keith Young, a researcher at the Center of Excellence for Research on Returning War Veterans, part of the Central Texas Veterans Healthcare System in Waco, focuses on alterations in brain anatomy that may predispose individuals to stress disorders.

“Many studies focus on the frontal cortex, where fear memories are formed and then go on to influence emotion,” said Young. “The thalamus is an input to these areas. Both vision and hearing go through the thalamus before getting repackaged, so to speak, and sent to the frontal cortex and limbic system.”

In a paper published in the June 2008 *British Journal of Psychiatry*, Young and colleagues link a certain genotype in humans—one that underlies serotonin transport function—to the development of PTSD. This particular genotype results in an increased number of neurons in the thalamus. And that, in turn, can make those individuals more susceptible to the development of major depression and PTSD.⁵ Young hypothesizes that this enlarged thalamus may amplify fearful memories, making people more susceptible to these disorders. “When people have this enlarged thalamus, they are able to shift more of the sensory input to the limbic system,” he said. “So these people are basically capable of producing more and stronger fears that can lead to PTSD.”

Young believes that this genotype could help doctors identify individuals who are more vulnerable to PTSD before they are exposed to trauma as well as help generate new treatments.

Fear Conditioning and Extinction

Many people live through traumatic situations, but most of them do not develop debilitating psychiatric disorders. Michael Davis, a neurobiologist at Emory University, studies the cellular mechanisms underlying fear extinction. He argues that the symptoms of a disorder such as PTSD, particularly the vivid flashbacks, are a powerful type of fear conditioning that can train the mind to remain anxious even when there is no longer any danger.

“The memories are hard to get out of the mind,” Davis said. “The condition can be triggered by signals in the environment that remind people of the trauma. Vietnam veterans may smell Asian food, experience a warm, muggy night, smell sulphur, and that triggers the flashbacks.” The flashbacks, in turn, strengthen the body’s response.

But many PTSD patients can be successfully treated with techniques that promote extinction of the fearful memory. “If you can remind people with PTSD of the bad things that happen to them and explain that they won’t happen again, do that again and again, so that they learn that if they face these fearful things nothing bad will happen, they will eventually get over that fear,” said Davis. But despite knowing exquisite detail about how animals learn to fear initially, researchers still have much to learn about how to extinguish that fear.⁶

For some individuals with PTSD, fears either are not extinguished or are only temporarily quieted. “It’s a big question—why is it that some patients continue to exhibit high fear and anxiety when there is no longer any danger present?” asks Mohammed Milad, a researcher at Massachusetts General Hospital. In a study published in the June 2008 *Journal of Psychiatric Research*, Milad and colleagues examined fourteen pairs of identical twins in which one had PTSD. The researchers assessed extinction learning and found that the retention of the extinction memory was deficient in those with PTSD. Just as important, the nature of the twin studies suggests that the deficit was acquired with the trauma as opposed to being a predisposing factor.⁷

Milad hypothesizes that a faulty ventromedial PFC makes it difficult for individuals to recall prior inhibitive learning. “The idea is that if you have a healthy ventromedial prefrontal cortex, you can convert inhibitive learning to long-term memory. If [the ventromedial PFC] is not healthy, presumably you can learn not to fear in the short term but that fear will come back over time.” He is continuing to study pathologies in the PFC that may result in anxiety disorders.

Enhancing Fear Extinction

Davis’s past work has demonstrated that the fear circuit in the brain, involving areas such as the amygdala, has to actively work to extinguish fearful memories. Part of that process involves the activation of N-methyl-D-aspartate acid (NMDA) receptors in those areas. Using rat models, they found that a drug called D-cycloserine facilitates NMDA receptor function, in turn promoting fear extinction. Davis and colleagues are now testing the use of D-cycloserine in humans.

“The drug sticks to receptors in the amygdala neurons, changing their shape,” Davis said. “This change seems to help lay down that inhibitory memory we call extinction.” But he asserts that much about how the extinction process is initiated and carried out remains a mystery.⁸

Propranolol, another drug that may help promote fear extinction, has historically been used to treat hypertension and migraine headaches. Karim Nader and collaborators at McGill University found that the drug helped to stop the reconsolidation of fear memories in humans. When an individual learns something, he must consolidate the memory in the brain in order to access it later. But over time, some memories may grow unstable and need to be reconsolidated.

“Reconsolidation is a new process that uses some of the same mechanisms as consolidation,” Nader said. “And with fear memories, even very old ones, you can essentially get rid of them by blocking this reconsolidation process.”

In a study published in the May 2008 *Journal of Psychiatric Research*, Nader’s group gave PTSD patients propranolol and then asked them to recount their traumatic memory.⁹ “The idea is that if you ask people to remember that traumatic memory then maybe it goes back to a more unstable state,” said Nader. “That gives us a window to use propranolol to reduce the strength of the memory.”

When speaking of the traumatic events, study participants who received the drug showed a lower fear response as gauged by metrics such as heart rate and the skin’s electrical resistance. The researchers hypothesize that propranolol somehow interferes with the emotional reconsolidation of the memories as the situational details remain intact. “If you give them propranolol, they remember the information, but they just don’t get the same emotional boost from the event that they got before,” said Nader.

Reliving Traumatic Memories

Past clinical and neuropsychological studies have indicated that the path to extinction involves confronting traumatic memories head-on. But is it enough just to recall a memory? Could extinction perhaps happen faster or last longer if a person with PTSD could somehow relive the past trauma in a more tangible manner?

Skip Rizzo, codirector of the Laboratory for Virtual Reality, Psychology, Rehabilitation, and Social Neuroscience at the University of Southern California's Institute for Creative Technologies, helps develop virtual reality (VR) applications that help clinicians reimpose patients into a past trauma.

“Over the last twenty to twenty-five years, we’ve found that exposure therapy is one of the most effective to treat PTSD. But we don’t know what’s going on in the hidden world of imagination,” said Rizzo. “VR is a tool that can deliver that exposure therapy in a more controlled environment. Patients are immersed in a virtual world that can systematically deliver elements that they may be fearful of.”



Skip Rizzo’s virtual Iraq application allows patients to confront their memories of traumatic events, such as an attack on a convoy. (Skip Rizzo, Ph.D. / USC Institute for Creative Technologies)

Rizzo’s group has designed applications for fear of flying and fear of heights. But the researchers have received recent attention for their virtual Iraq system, which allows Operation Iraqi Freedom veterans with PTSD to virtually return to the scene of the emotional trauma.¹⁰

“A patient’s worst event may be a convoy being blown up with an improvised explosive device,” said Rizzo. “With the VR system, a therapist might start off having the patient just sit in a Humvee, look around a little. Once he gets comfortable with that, the therapist can add a little more at a time, gradually approaching those elements that the patient recalled as the seminal event.”

Rizzo said that a virtual environment allows the patient to process the fearful memories, eventually habituating to them. And at one therapy site, Rizzo reports that eighteen individuals progressed enough after three months of therapy to no longer meet the case definition for PTSD. Rizzo plans to look more closely at what is happening in the brain during VR therapy in future work.

Hormone Treats Traumatic Brain Injury

Another artifact of war is an increase in blunt head traumas and traumatic brain injury (TBI). The effects of TBI range from mild to severe, but in all cases a blow to the head causes damage to the brain. That damage can trigger problems that extend injury beyond the area of impact.

“The injury sets off what is called a cytotoxic cascade of events,” said David W. Wright, a researcher at Emory University’s Emergency Medicine Research Center. At the point of injury, neurons may die off simply from the trauma. And as those neurons die, they release chemicals that are toxic to surrounding cells, perpetuating through the network. The body’s natural response to this is edema, or swelling, which in the enclosed skull can result in further cell death.

“These cascades can continue for days, weeks, even up to years,” said Wright. “It’s a cyclic path to more cell death across the brain.” And the results can be severe. Patients with a mild form of injury may have symptoms such as slurred speech, loss of coordination, and weakness in the extremities. Those with more severe injuries can suffer from permanent neurological impairment. Patients with TBI-related injury caused by the improvised explosive devices (IEDs) common to the Iraq conflict may have even more formidable damage to the brain. In 2008, the U.S. Department of Veterans Affairs proposed that blast-related TBIs be considered a special neurological condition.

“With an IED, you get a shock wave that is transmitted through the abdomen up to the brain, compressing the blood,” said Joseph Coyle, a researcher at Harvard Medical School. “This causes damage in the deep brain structures as well as shearing that damages the neuronal connections in the brain.” Some hypothesize that the damage to these primitive brain structures may result in a higher susceptibility to PTSD as well as a slower appearance of neurological symptoms.¹¹ However, a thorough study of these hypotheses has yet to be conducted.

For decades, researchers believed that nothing could be done to alleviate the brain damage that follows TBI. Wright has initial results that suggest that progesterone, commonly thought of as a “female” hormone, may limit these cytotoxic effects, reducing the amount of damage when artificially introduced immediately after a blunt head injury. In a study published in the February 2008 issue of *Brain Injury*, Wright and colleagues showed that application of progesterone reduced cerebral swelling and helped rats with a model of traumatic brain injury recover.¹²

Wright has also successfully used progesterone with human patients. A small pilot study of one hundred patients resulted in a 50 percent reduction in mortality compared with a control group that received a placebo, as well as improved neurological function after thirty days in patients with moderate TBI.¹³ His research group will soon start a four-year study of more than 1,000 patients at seventeen trauma centers nationwide.

Wright's work addresses a method of minimizing injury. Gary Strangman, another researcher at Massachusetts General Hospital, is using fMRI scans to try to predict which TBI patients will respond to a language rehabilitation protocol after the damage has been done.

Though two patients may both be classified as mild cases, the injuries both occur and manifest themselves in different ways with different symptoms. But even with that kind of dissimilar damage among participants, Strangman and colleagues found that patterns of activity in the left lateral PFC could help predict how well patients responded to a semantics-based list-learning strategy, a method of remembering a list of words after grouping them into meaningful categories that would help cue recall. The results were published in the May 2008 issue of the *Archives of Physical Medicine and Rehabilitation*.¹⁴

"Our purpose was to see whether we could use fMRI information to predict outcomes," Strangman said. "This kind of strategy could help us better tailor rehabilitation strategies to individuals in, say, five to ten years."

Strangman's group plans to do further studies to see if fMRI activation in the brain can help predict response to other rehabilitation strategies.

Notes

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