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Forever in fear

Unraveling the mysteries of PTSD

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Half of all women and 60% of all men will experience a traumatic event in their lifetimes. They will be raped, abused as children, assaulted, involved in a serious accident or witness a murder or attack. If they happen to serve in active military duty or live in an impoverished inner city, their odds of suffering such horrors go way up.

Most of these trauma victims will find a way to cope. They'll weep. They'll rage. They'll think about the event obsessively. And finally, they will put the tragedy behind them, not forgotten but relegated to a dark corner of their mind. For a small portion, however, the event will live on, forever current. They will struggle in the grip of nightmares, flashbacks and ceaseless anxiety, unable to distinguish between safe and dangerous

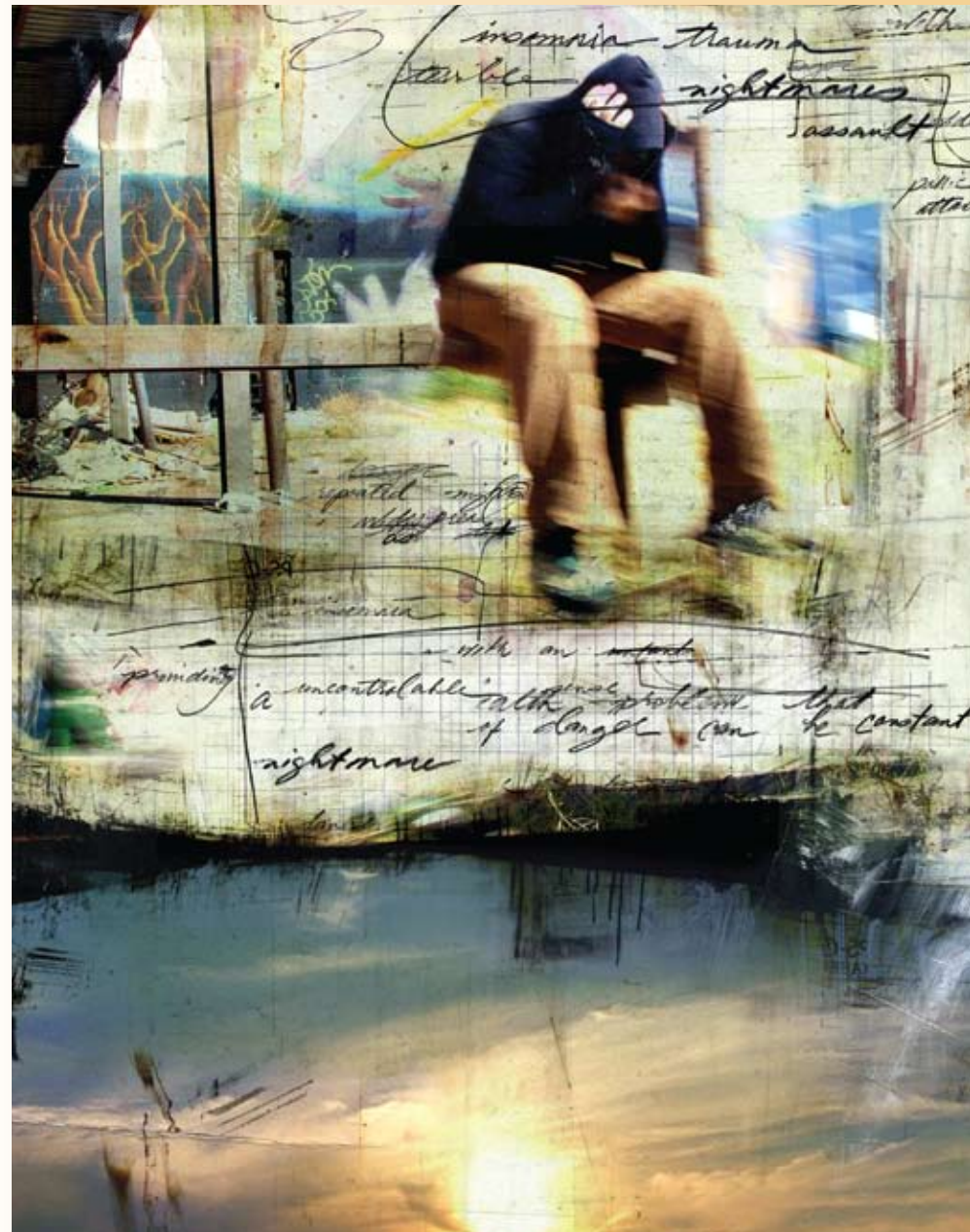
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assistant professor of psychiatry and a researcher at the Yerkes National Primate Research Center. "It's not simply a matter of having a bad experience and they grieve, but it seems to change the way the emotional part of their brain responds to the world so that they are not able to ever feel safe again."

Why do some people, after surviving a traumatic event, develop PTSD while others do not? That's the question that Emory researchers are trying to answer through a multitude of studies and clinical trials. From developing rat models of PTSD to treating returning Iraqi vets using virtual reality therapy, and from examining genetic, biological and psychosocial data from inner-city trauma victims to attempting to ward

situations. Their world will shrink as they try to avoid anything that might evoke painful memories. These victims suffer from Post Traumatic Stress Disorder (PTSD).

"Some people who have experienced a very severe trauma find that their life has changed forever after that," says Kerry Ressler, an Emory



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off the development of PTSD through immediate post-trauma intervention, Emory scientists from various disciplines are trying to unlock the mysteries of the disorder that will conservatively strike 10% of the general population.

"Our goal is to use the understanding – on a neuroscience level - of how we reduce these fears – a process known as 'extinction' - to develop new treatments that specifically target this memory process," says Ressler,

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who was recently named a Howard Hughes Medical Institute Investigator (see “Hughes Investigator,” page 4). “Instead of using a drug that just treats the symptoms, we want to find ways to combine new medications with the learning process that goes on with behavior exposure therapy to make a much more effective treatment.”

Forever in fear

Despite the debilitating effects of PTSD, relatively little is known about the disorder. By definition, it follows a traumatic event – a terrifying experience during which the victim may think his or another’s life is in danger. Symptoms, which can emerge months after the event include:

- Re-experience. A cue will remind the victim of the event and he will suddenly be reliving it in a flashback or nightmare.

- Avoidance and numbing. Victims avoid places and things that can remind them of the event. An often repeated example is a woman who was raped by a man whose hands smelled of oranges. Afterward, the taste of oranges made her nauseous. Then she found just seeing oranges in the produce section upset her, so she started avoiding that area of the grocery. Finally, she stopped going to the grocery altogether. Victims also experience a general numbing of emotions. “Feeling dead” is a common description.

- Sympathetic arousal. Victims tend to feel forever jumpy and on edge. They are constantly awash in adrenaline, trapped in a state of fight-or-flight. Exaggerated startle is one of the cardinal symptoms of PTSD.

“PTSD is something that haunts victims day and night,” says Barbara Rothbaum, an Emory psychiatry professor and director of the Trauma and Anxiety Recovery Program. “They don’t feel safe in their beds. They don’t feel safe anywhere.”

The primary treatment for PTSD is a combination of medications and talk therapy. All of the medications, however, merely target the symptoms. Victims are typically given antidepressants to combat depression, hyper-tensive drugs to ward off nightmares and/or anti-anxiety drugs to help calm them. “At this point, all the drugs we have for PTSD are just Band-aids,” says Ressler. “This is clearly a disorder of the memory, yet none of these drugs can target that.”

Talk therapy, on the other hand, can treat the root of the problem, not just the symptoms. “The Institute of Medicine recently reviewed all the studies of PTSD treatments – all the medications, all the forms of therapy – and it said the only treatment that had enough evidence to support it is exposure therapy,” says Rothbaum.

In imaginal exposure therapy, the therapist asks the victim to close his eyes and call up the memory of the trauma over and over again. “The idea is to only take people as far as they can go in a session, but to have them go to the point where they are quite upset and then keep talking, stay at

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that level of anxiety, fear and upset until it habituates down to a more normal level that they can handle,” says Ressler. “Then you can take them to the next step. By repeatedly exposing themselves to emotions

that are very difficult and that they typically avoid, they learn both cognitively and emotionally that they can, in fact, habituate to those emotions. When people habituate to those memories, then the strength those memories have over the rest of their lives diminishes.”

Virtual Iraq

To understand PTSD, scientists first have to understand how fear memories are formed and how they are extinguished. For that, Emory researchers turned to rats. A team led by Michael Davis, a professor of psychiatry,

and Ressler, conditioned rats to fear a cue – a light – by pairing it with a small shock. Then they tried to extinguish that fear by repeatedly exposing the rat to the light cue without the shock.

“This is not actually an end to the fear or an erasure of that fear memory,” says Davis. “Rather, it’s a new form of learning that actively suppresses the fear. This process is called extinction.”

Davis and his colleagues identified a particular protein in the amygdala – the fear center of the brain – that was critical to the extinction process. When he inactivated that protein – called NMDA receptor – he could present the light without the shock over and over again, but the rat never got over its fear of the cue.

Davis combined this discovery with the findings of other researchers that a tuberculosis drug called D-cycloserine (DCS) enhances NMDA receptor functioning to fashion his next experiment. “Since NMDA is critical for extinction, and DCS makes it work better, we reasoned that if we could give DCS when we were doing fear extinction training, perhaps the animal would get over its fear more quickly,” says Davis.

And that is what, in fact, happened. Davis injected DCS either systemically or directly into the rats’ amygdala immediately before extinction training, and they learned to inhibit their fear much more quickly. For



Michael Davis

Davis is trying to find out if a drug developed to treat tuberculosis can enhance the fear extinction process in rat models of PTSD.

example, in one experiment rats extinguished more than three times as rapidly as the rats that got the placebo.

The next step was to take these findings out of the lab and into a clinical study. “That’s the great thing about being at Emory,” says Davis. “Barbara Rothbaum pioneered the use of virtual reality in exposure therapy back in the early ‘90s. For me, it’s a perfect test procedure to use because everyone gets exactly the same treatment.”

Davis, Ressler, Rothbaum and other colleagues first paired DCS with virtual reality exposure therapy to treat patients with fear of heights and then retested them in the virtual environment either one week or three months later. The people given DCS got better about four times faster than the usual course of therapy. Their results were so encouraging that other researchers began studying the combination to treat other anxiety disorders, and positive results have already been shown from others at Harvard, Yale, and in Australia with social phobia and obsessive compulsive disorder. Additional, ongoing studies are combining DCS with a range of disorders from fear of public speaking (virtual audience) to addiction (virtual crack house). At Emory, Rothbaum is using a combination of DCS and a virtual Iraq setting to study PTSD in returning Iraq and Afghanistan veterans.

“It’s very likely to change the way we think about providing therapy,” says Dr. Farris Tuma, chief of the Traumatic Stress Disorders Program at the National Institute of Mental Health (NIMH), which is funding the Virtual Iraq study. “It’s setting the stage for dramatically more effective treatment.”

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In the Virtual Iraq study, participants are randomized into three groups – one receives DCS, one a placebo and one an anti-anxiety medication. “Many clinicians who do exposure therapy don’t want their patients on anti-anxiety drugs because they think it will interfere with the therapy,” says Rothbaum. “The patient has to become sufficiently anxious to begin to learn to overcome the fear. However, there is very little scientific data on this, so this will be one of the first studies to look at the use of anti-anxiety drugs and exposure therapy in a scientific way.”

All of the participants will receive the same therapy regimen – one introductory session and five sessions of virtual reality exposure therapy. “In the first session, we explain PTSD and the rationale for exposure therapy, since it’s counterintuitive to many people,” says Maryrose Gerardi, assistant professor of psychiatry. “They think, ‘This is so painful, why would I want to think about it?’ But that is exactly what they need to do in order to process it and move on.”

Gerardi also gets as many details as she can about the vet’s particular trauma so she can customize the virtual reality experience. She has two basic scenarios from which to choose – riding in a Humvee on a desert road or walking in a crowded street in Baghdad. From there, however, she can add cues specific to the vet’s story – a improvised explosive



Kerry Ressler

Ressler’s group found that low-income inner city residents suffer from PTSD at roughly the same rate as combat vets.

device (IED) exploding nearby, a roadside ambush or a comrade gunned down. “The goal is for them to have one foot there and one foot here,” says Gerardi. “With the head mask, they are seeing and hearing it. The platform they are sitting on vibrates, imitating the feel of driving in a Humvee, and I can add smells. In many ways, they really are back in Iraq, but I am talking to them the whole time, asking them what they are thinking and feeling, getting them to rate their anxiety level. They are able to process their feelings in a safe and controlled place.”

While nine to twelve sessions of imaginal exposure are generally needed to effectively treat PTSD, Rothbaum and her colleagues are hoping the combination of DCS and virtual therapy can cut that time in half, making therapy much more appealing to potential patients.

Stress in the city

Ressler and his colleagues are studying very different PTSD population in an effort to determine the genetic and environmental risk factors for developing the disorder. While many people equate PTSD with combat trauma, Ressler’s group found that low-income inner city residents suffer

at roughly the same rate as combat vets. Indeed, a pilot study of outpatients at Atlanta’s Grady Memorial Hospital showed that over 80% of this population has suffered a significant trauma and about 30% have PTSD.

“This population has experienced incredibly high rates of trauma,” says Ressler. “Something like two-thirds of the men have been attacked with a weapon and over one-third of the women have been sexually assaulted. More than half have known someone personally who has been murdered.”

Over the course of five years, Ressler, Rebekah Bradley, an assistant professor of psychiatry at Emory, and others will collect data on up to 4,000 subjects at Grady, having already interviewed over 1,500 subjects. Researchers conduct extensive interviews to gather information about any history of child abuse or trauma, demographic data, adult depression and PTSD symptoms. They also collect saliva and blood samples to gather genetic and biological data, along with measurements of startle response and heart rate.

“The overarching goal is to gather a large amount of psychological, biological and genetic data on people with civilian trauma and look at risk and resilience factors for predicting PTSD and depression,” says Bradley. “There’s a whole lot of resilient people out there, and we’d like to know what factors contribute to that resilience.”

Researchers already know there is a strong genetic component. The risk of PTSD given a severe trauma has been shown to have the same genetic heritability as depression and schizophrenia – on the order of 30%-40%. Researchers also have known that a history of child abuse or trauma puts a person at higher risk for developing PTSD as an adult, but they haven’t been sure why. “Our data suggests that, just as there is a critical period of development for sensory systems, there seems to be a critical period of development for emotional memory systems,” says Ressler. “So presumably stress during this time of emotional development alters the sensitivity of genes involved in the stress response, leading to an

altered stress sensitivity for the rest of the person’s life.”

To further probe this, Bradley is beginning to study inner city mothers and children, following them over time. “Almost all of the world’s literature on the effects of child abuse and PTSD are retrospective studies,” says Bradley. “In this study, I’ll gather psychological and, hopefully, imaging data on the children and mothers over time.

That way we’ll have a chance to look at children before they are exposed to trauma, and follow their development afterward.”

Ressler’s hope for these studies is nothing less than breaking the vicious cycle of inner city violence, “It makes intuitive sense that if you grow up in a violent atmosphere, you are more likely to be violent as an adult,” says Ressler, “But our hope is that by having a more medical model of understanding of how the intergenerational process works, we may be able to offer new policy and treatment options. I see that as critical, since our current social policy has left us with really no improvement in inner city rates of poverty and cycles of violence.”

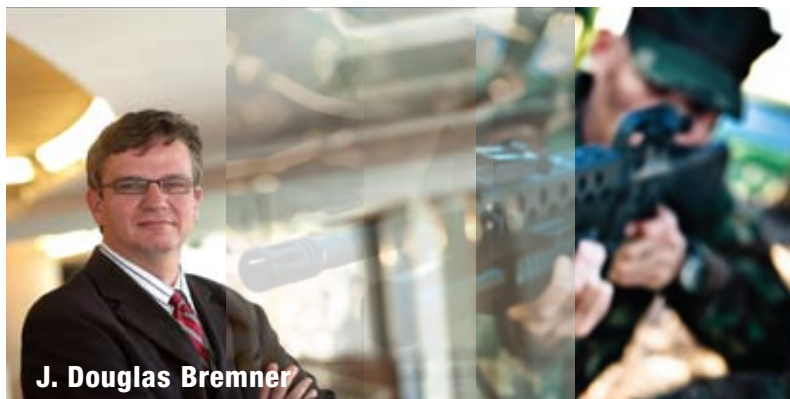
Hughes Investigator

Kerry Ressler, an Emory neuroscientist at the Yerkes National Primate Research Center, was named one of 15 new Howard Hughes Medical Institute (HHMI) Investigators. He is the first practicing physician to be appointed an HHMI investigator. HHMI, a nonprofit research organization, has been selecting investigators through national competitions since the 1990s. Rather than awarding research grants, HHMI selects highly creative, productive scientists and funds them. “The goal of HHMI is to increase the freedom of investigators to study the questions that they think are the most exciting,” says Ressler. “The area of research that I highlighted was the translational research between understanding fear in animals and treating fear in humans. This will allow us to strengthen the integration between the animal studies and the human pre-clinical studies.”

In blink of an eye

In another area of study, Emory researchers are trying to develop a reliable measure of the degree of PTSD for use in diagnosis and development of more effective treatments. Clinicians have typically assessed PTSD suffered based on their accounts of their symptoms. Erica Duncan, assistant professor of psychiatry at Emory, is looking at eye blinks as a means of objectively measuring the extent of the victim's fear control impairment.

Duncan divided combat vets at the Atlanta Veterans Affairs Medical



J. Douglas Bremner

Bremner is combining mindfulness meditation and yoga in an attempt to ground returning Iraqi vets in the present and to give them more control over their thoughts and memories.

Center into two groups – those with high-symptom PTSD and those with low-symptom. Both groups were trained to fear a particular visual stimuli – two lights appearing together, called for the sake of the study A and X. Anytime the subjects saw that combination, they got an unpleasant blast of air to their throat. Then the subjects were shown another visual stimuli – two lights, called B and X – with no air blast. Finally, the subjects were shown a novel combination of lights – A and B – with no airblast.

By measuring the startle response in each of the settings, Duncan could determine the subject's degree of reaction to the danger signal, the degree to which he was able to inhibit that reaction to the safety signal and his ability to transfer his knowledge of safety to a novel situation.

"The importance of this work is that it will allow us to measure the ability of an individual subject to inhibit fear to certain safety signals," says Duncan. "We're exploring whether we can use it as a test paradigm to do pharmacologic challenge studies to test medications that are being developed to treat fear symptoms in PTSD before all the hard work and expense of a large clinical trial. We're also looking at whether it will predict who will get better and who will not get better with treatment."

Nipping it in the bud

All the studies mentioned so far have focused on patients once they developed PTSD. Emory researchers also want to know if there is a way to prevent PTSD from developing in the first place. Once again, they turned to rats. "We have found that both the formation of a memory and the extinction of it seem to require new synapses to be formed," says Ressler. "A peptide – brain-derived neurotrophic factor (BDNF) – has long been studied with learning and memory. We found BDNF was increased after fear learning and after extinction learning, so it seems to be a neuroplasticity factor that is changed with both kinds of learning."

No drugs exist that specifically target BDNF receptors, so Ressler and his team created a genetically altered virus that would block BDNF in the rat brain. They injected the virus into the rat's amygdala either before the rat learned to be afraid of a stimulus or before it learned to extinguish that fear. If the rats were already afraid, and then the virus was put in, they could express the fear just fine. But if the virus was put in before they learned to be afraid, they could not learn a new fear memory. Also,

if they were already afraid and the virus was put in, they would not learn to extinguish the fear.

"This suggests the BDNF is required both to form fear memories and to inhibit them," says Ressler. "So new drugs that block BDNF function might be useful after a trauma to prevent the normal consolidation of that fear memory."

Emory scientists are also looking at the potential effectiveness of a therapeutic intervention immediately following a trauma in preventing PTSD from developing. "Dr. Davis and his group found that if you do extinction training almost immediately after you condition the fear, it nearly erases the rats' fear," says Rothbaum. "That suggests that while the memory is fresh, before it gets consolidated, it is malleable. So maybe if we can do an intervention right away, it won't be stored as a traumatic memory."

To test this theory, Debra Houry, an emergency room physician at Grady and director for the Center for Injury Control at Emory, is conducting a pilot study on ER patients at Grady. Houry and her colleagues will divide patients into two groups. One group will be guided through imaginal exposure therapy within 24 hours of their trauma, and the other group will merely get an assessment. Researchers will follow up with both groups up to 12 weeks afterward to see if they develop PTSD symptoms.

"I am not a psychiatrist," says Houry. "Dr. Rothbaum trained me and other non-psychiatric ER staff how to go through imaginal exposure therapy with a patient. If it is effective just using regular medical personnel, then it could be used in disaster settings and other ER departments more readily."

J. Douglas Bremner, director of mental health research at the Atlanta VA Medical Center and professor of psychiatry at Emory, is conducting a similar study with returning Iraqi vets. However, Bremner and his colleagues are using a technique called "mindful based stress reduction" rather than imaginal exposure. The technique combines mindfulness meditation with yoga to center the person in the present.

"The emphasis is on being in the here-and-now and not dwelling on things that happened in the past or might happen in the future," says Bremner. "But while we don't focus on the war trauma, the technique helps them deal with the trauma because it helps them have more control over their thoughts and memory."

Bremner and his colleagues are imaging the subjects' brains and measuring hormone response to stress before and after the study to detect any changes caused by the intervention. Bremner and his team were the first to apply brain imaging to the study of PTSD, finding altera-

Studies suggest that while a memory is fresh, it is malleable. That could mean an immediate intervention might keep an event from being stored as a traumatic memory.

tions in victims' brain circuits and systems. "This moved PTSD from being viewed as a psychological disorder to a brain-based disorder," says Bremner.

Emory scientists hope discoveries such as these will solve the mysteries of PTSD.

"I hope eventually that the biology of PTSD will lead to both increased predictability of who is at risk and more targeted drug therapeutics and psychotherapy approaches," says Ressler. "That would allow us, in the immediate aftermath of a trauma, to prevent the development of PTSD or help those with PTSD recover more quickly. From a social perspective, I hope these approaches can be taken in impoverished and traumatized communities and help decrease the cycle of violence that seems to be ongoing intergenerationally." ●