



TAMING FEAR,
RISING CALM
—
A SOCIAL CONSCIENCE
ROOTED IN THE
DEEP SOUTH MOVES
KERRY RESSLER,
A PSYCHIATRIST
AND NEUROSCIENTIST,
TO TRY TO EASE THE
CONSEQUENCES
OF INNER
CITY TRAUMA.

—
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PHOTOGRAPHY BY
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hen Kerry Ressler walks briskly from his car to his laboratory on a steamy July morning, the rasp of cicadas fills the air. Inside, his fifth floor office at Emory University's Neuroscience Research Facility is quiet and overlooks the wooded grounds of the venerable Yerkes National Primate Research Center. The building is new, the atmosphere suburban; grad students tapping smartphones wait for a shuttle to the main campus.

The next morning, Ressler's in a different world. He stacks his car in a deck atop a McDonald's and lopes alongside the towering, tawny bulk of Grady Memorial Hospital. Perennially teetering on the edge of financial ruin, Grady remains the hospital of first and last resort for Atlanta's urban poor. Across from the main entrance, men leaning on "No Smoking" signs exhale plumes of smoke and raise their voices over the roar of the oppressively close Interstate. Although an architectural facelift has smoothed and tightened Grady's façade, look more closely and this massive, 21-story structure is marked by more than 50 years of hard use.

Ressler—a physician and a basic scientist—has been shaped by both places, and he's resolved not only to move what he learns from "bench to bedside" but to take it all the way to the violent and chaotic streets where Grady patients live.

"My scientific goal is understanding the biology of fear," says Ressler, a Harvard-educated M.D./Ph.D. who came to Emory University, in Atlanta, a dozen years ago to train in psychiatry. Now an associate professor of psychiatry and behavioral sciences, he is known for developing rodent models that help reveal what happens in the amygdala—the brain's command center for panic attacks and fight-or-flight responses—when fear is learned, remembered, and sometimes overcome.

Ressler was the lead author on a 2004 article reporting that a drug can boost the effectiveness of exposure therapy that uses virtual reality—a simulated glass elevator—to desensitize patients who have acrophobia, or fear of heights. These findings, which have been replicated in patients with social phobia, panic disorder, and obsessive compulsive disorder, are steps toward what he characterizes as his ultimate "social and political" goal: developing ways to lift weight off poor people who are worn down, held down, and made sick by post-traumatic stress disorder (PTSD) and other trauma-related disorders.

But that, he admits, may be a long time coming.

IT STARTS IN THE LAB

In late 2007, Ressler became the first psychiatrist named an HHMI investigator since Eric Kandel, who was selected in 1984. Kandel went on to win the Nobel Prize in 2000 for insights into learning and memory he acquired by studying *Aplysia*, a sea slug that looks like a cross between a tree fungus and a football.

"Kerry Ressler strikes me as a role model for the future of psychiatry," says Kandel, who is director of the Kavli Institute for Brain Science at Columbia University. He laments "disappointingly slow" progress in treating mental health disorders, which he blames on a shortfall of basic science and translational research in psychiatry. A new generation of scientists, he believes, can help close the gaps.

Ressler made his mark in translational research as a second-year resident, shortly after joining the Emory laboratory of renowned amygdala expert Michael Davis. In the almond-shaped amygdala, a structure found deep in the brain, the binding of the excitatory neurotransmitter glutamate to the N-methyl-D-aspartate (NMDA) receptor strengthens synaptic connections when fear is learned or extinguished. Ressler and Davis predicted they could speed the extinction of fear in rats by using an approved human tuberculosis drug, D-cycloserine, which binds and activates the NMDA receptor, thereby increasing glutamate binding in the amygdala. The experiment was a success.

"As soon as we knew it was working, I went to Barbara Rothbaum and asked if we could combine this with psychotherapy in people," Ressler recalls. Rothbaum is an Emory psychiatry professor who specializes in treating a spectrum of anxiety disorders. They launched a small study comparing the response of acrophobic patients to behavioral exposure therapy with or without a dose of D-cycloserine. Patients given the drug immediately before virtual or real exposure to heights clearly became less fearful than those not given the drug. Before the Emory team published these results in the November 2004 *Archives of General Psychiatry*, there was nothing in the literature about pharmacologic enhancement of fear extinction.

The idea that pharmacologic agents can alter brain plasticity, thereby mediating fear extinction, is no longer novel. Ressler's team is experimenting with other mediators of synaptic strength. In the July 2006 *Nature Neuroscience*, they reported that activation of the receptor for brain-derived neurotrophic factor is essential for extinguishing fear. His group has also determined that the protein β -catenin is essential for stabilizing synapses and forming fear memories, findings they reported in *Nature Neuroscience* in 2008.

In Ressler's neuroscience lab at Emory, nine graduate students and postdocs study fear with tools including small molecules and viral vectors that deliver modified genes to

specific brain regions in transgenic mice. By observing how mice react to environmental cues, such as a sudden noise or an elevated maze, researchers can tell whether genetic modifications have changed how animals handle fear. Meanwhile, at Grady Hospital, Ressler leads a massive search for genetic polymorphisms, or variations, that might predict which individuals who were abused as children will be especially vulnerable to PTSD as adults—and which ones will prove resilient.

A KNACK FOR CONNECTING

Growing up in Mississippi in the 1970s, Ressler had no clue he would become a behavioral neuroscientist with a social conscience. He certainly never thought Nobel laureates would know his name.

Ressler is an only child whose parents divorced when he was young. When he was 12, he and his mother relocated from Jackson to Ocean Springs, a small town between Biloxi and Pascagoula. “It was a wonderful place: you could bike to the Gulf and crab and fish and go canoeing in the bayou,” Ressler recalls with delight. Ocean Springs schools were also better than most in Mississippi.

When puberty hit, Ressler scored the geek trifecta. He had no gift for sports, he played tuba in the high school band, and he excelled at math and computers. About this time, his mother quit her office job to pursue her dream of becoming a nurse. “We both

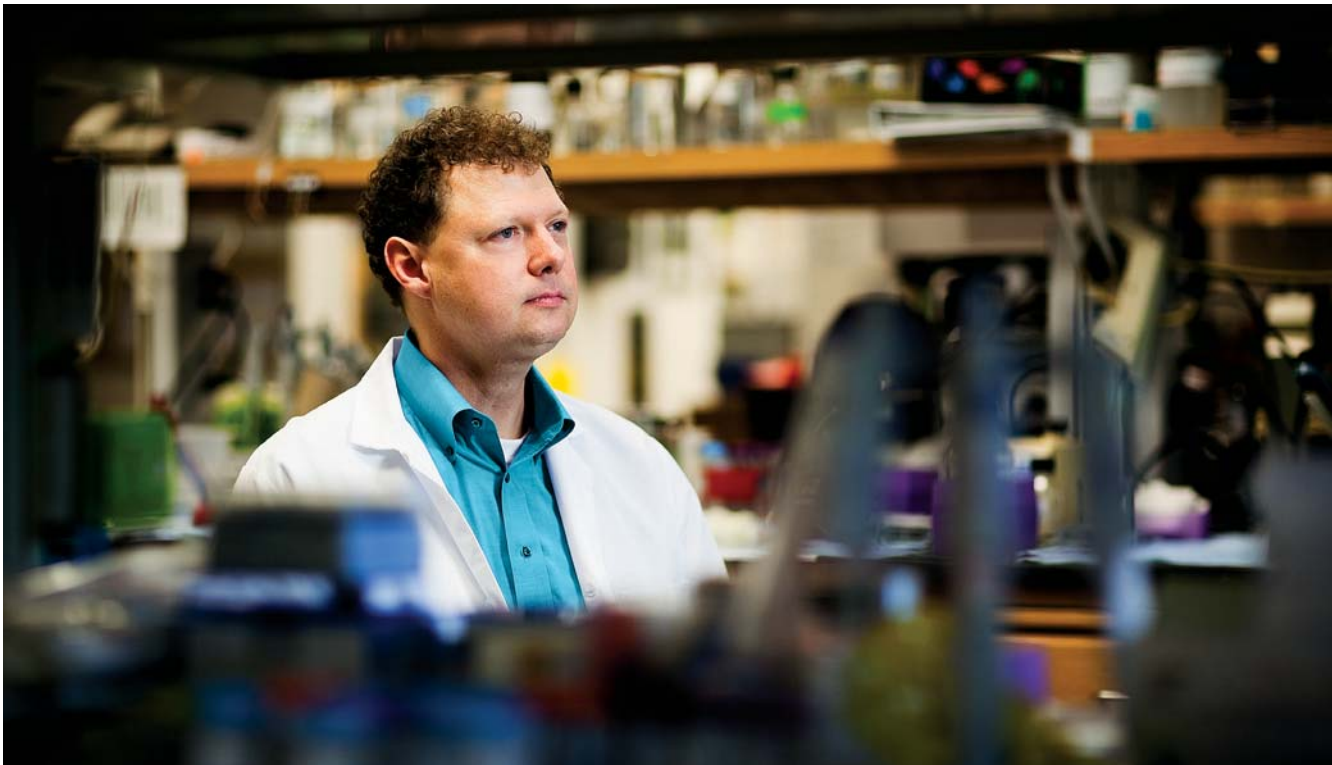
worked part-time to get her through college,” Ressler recalls. Some nights he helped her clean the doctors’ offices where she did desk work during the day. Finances eased when she graduated, got a nursing job, and remarried.

In the 1970s, “you could not grow up in Mississippi and not be extraordinarily aware of race,” Ressler says about his childhood. But his mother taught him that “people are often different because of what life has dealt them, not because of different abilities.” His mother’s lessons helped him at Grady Hospital, where patients have experienced oceans of disrespect.

“Using a lot of jargon and big words just doesn’t work around here,” says Grady chief psychologist and Emory psychiatry professor Nadine Kaslow, who supervised Ressler when he was a first-year resident in the hospital. From the start, Ressler had a knack for connecting with people of all descriptions: “Female patients see him as not sexist; male patients see him as someone they can bond with,” says Kaslow.

Besides his mother, the other influential woman in Ressler’s young life was his advanced placement math teacher, who encouraged him to excel in mathematics competitions and to apply to the Massachusetts Institute of Technology (MIT).

When the MIT acceptance packet arrived, Ressler had been working the night shift at Delchamp’s Superstore in Ocean



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Springs for several years. He swept and stocked shelves in the wee hours, when customers were rare. When he told his Delchamp's coworkers that he was quitting and heading for college, they were amazed he would leave such a good job. And when he said that his destination was MIT, the puzzled response was “MIT? That stands for Mississippi what?”

Ressler left Ocean Springs knowing that computer science was his destiny. Wasn't it obvious? “I enjoyed computers and I was going to MIT.” But he was nervous about moving to a strange city where he had no friends and might be a total misfit. He worried that MIT felt compelled to accept someone from Mississippi, and he was it.

His anxiety was short-lived. Within weeks he joined a fraternity, which was cheaper than living in a dorm because the residents did much of their own cooking rather than pay a chef. (“Many of our meals were pretty awful,” he admits.) He worked hard and played hard with 40 other guys at Phi Kappa Sigma in Boston's Back Bay.

He also discovered that biology was every bit as compelling as computer science and wondered if medicine—which his mother exposed him to—might be his calling. Then Ressler fell in love with an advanced genetics lab taught by *Drosophila* biologist Hermann Steller, now an HHMI investigator at Rockefeller University.

Steller had his students create transgenic fruit flies and observe phenotypic changes. “That's what really sold me on being a biologist and a scientist,” Ressler recalls. Polymerase chain reaction and other new techniques had slashed the time needed to identify and clone a gene, introduce it into an animal, and examine the results. Years' worth of work could be accomplished in a semester.

Ressler asked to stay on with Steller and remained in the fly lab until he graduated. Long hours earned him the nickname “the biologist.” When he wasn't at the lab or hanging out with the guys,

he was keeping company with Betsy Craig, a Wellesley student from Atlanta. The two are now married and have three sons.

As an MIT senior, Ressler was certain he and Craig belonged together and that he wanted to delve into the biology of thinking and learning. He was less sure about clinical medicine, but when he was accepted to the Medical Scientist Training Program at Harvard Medical School, he could not refuse.

DAZZLED BY SCIENCE

The first two years of medical school at Harvard went well, but Ressler still needed the right mentor for his Ph.D. work. He knew he wanted to use molecular biology and genetics to address a significant, clinically relevant problem in neurobiology—but what problem? At just this moment, a friend invited him to tag along to a lecture by Linda Buck, a Columbia University research associate being recruited by Harvard.

“I had never thought about smell a day in my life until I heard Linda give her talk,” Ressler says, still jazzed by the memory, “and I was absolutely blown away.” Buck had methodically identified about 1,000 odorant receptor (OR) genes and she outlined an orderly plan for decoding their function. Her work was “a beautiful example of using science to explain biology,” Ressler says.

He immediately wrote to Buck, asking for a research rotation in her lab if she did indeed join the Harvard faculty. Helping figure out how ORs are arrayed and how they integrate information to detect and identify smells—that was exactly the kind of difficult quest Ressler had been hoping for.

In early 1992, Buck, Ressler, and a truckload of equipment converged on the Harvard Medical School quadrangle. “My lab was full of boxes and crates of equipment when Kerry came in.

So I unpacked with him and we set up the lab in about a week,” says Buck.

She went to work writing grant proposals while Ressler set about creating a library of mouse OR genes and then determining where they are expressed in the lining of the nose. “That gave us the first inkling of how information from 1,000 different receptors is organized in the nose,” recalls Buck, an HHMI investigator now at the Fred Hutchinson Cancer Research Center.

Over the next three years, Ressler’s dissertation work contributed to the accomplishments that earned Buck the 2004 Nobel Prize in Physiology or Medicine, which she shared with HHMI investigator Richard Axel. Prominently displayed in Ressler’s Emory office is a framed picture of him with Buck at the Stockholm ceremony, both grinning broadly in formalwear. “I was in a numb fog the whole time,” Ressler says with the goofy laugh that is his signature.

The two have a mutual admiration society: Buck calls Ressler “a fantastic scientist and a wonderful, compassionate person.” For Ressler, Buck’s lab will always be where he initially experienced the joy of being the first to know something. Other epiphanies would come later, but in places nothing like the *beaux-arts* splendor of the Harvard Medical School quad. During his first weeks of clinical training at Grady Hospital, Ressler helped stabilize gunshot victims and debride wounds colonized by maggots.

URBAN WAR ZONE

Within weeks, Ressler was rotated to Grady’s psychiatric emergency room and from there to the hospital’s outpatient psych clinic, where the wounds were equally grim but less visible. None of the patients he evaluated matched the neat diagnostic checklists in DSM-IV, the standard reference for coding mental disorders. “Diagnostic messiness” is the norm, clinical veterans say, because Grady’s typical psychiatric patient is poor, black, uses drugs, and has multiple health problems.

As a fear biologist, Ressler saw something different. These patients carried “enormous amounts of trauma,” as a result of living in the urban equivalent of a war zone, and he reasoned that PTSD might be as common among them as among combat veterans. But PTSD was not high on the index of suspicion for Grady doctors because they don’t treat vets, who are cared for by private doctors or at the large VA Medical Center across town.

Ressler couldn’t shake the feeling that trauma was important here, and in 2003 he teamed with psychiatrist Ann Schwartz and psychologist Bekh Bradley to determine the prevalence of undiagnosed PTSD among mental health patients at Grady. Although PTSD was noted in only 6 percent of the charts, they found that 40 percent of patients met criteria for lifetime or current PTSD.

The three launched the Grady Trauma Project (GTP), today led by Ressler, which has been assessing environmental and genetic risk factors for PTSD in a broader sample of Grady patients since 2005. A team of trained interviewers, most of them students from Atlanta area colleges and universities, have collected saliva samples and conducted extensive interviews with more than 2,500 low-income, primarily African American, men and women waiting for primary care or ob-gyn appointments at the hospital.

Nearly 90 percent of GTP participants have been exposed to significant trauma, mostly interpersonal violence, at some point in their lives. Rates of emotional, sexual, or physical abuse during childhood are high; later in life, assaults by intimate partners or others are commonplace. The lifetime prevalence of PTSD is 46.2 percent among these Grady patients—as high as in combat veterans—Ressler’s team reports in the November 2009 *General Hospital Psychiatry*.

As these findings indicate, however, not every traumatized child or adult develops PTSD. With support from the National Institutes of Health, Ressler and his colleagues are searching for gene-environment interactions that may help explain why some suffer more than others. They started with some of the “usual suspects,” including genes involved in the glucocorticoid-mediated stress response. So far they’ve identified four single-nucleotide polymorphisms, tiny variations in the FKBP5 gene that appear to interact with severe child abuse trauma to predict adult PTSD symptoms. These findings were reported in *The Journal of the American Medical Association* in March 2008. Additional studies are under way to identify novel genes that affect who develops PTSD and who does not.

Although Ressler can offer no guarantees, he is hopeful that basic science findings—taken to the streets—could have an enormous public health impact. PTSD is associated with intergenerational violence, poverty, teen pregnancy, broken families, and a host of maladies both physical and mental. Therapies that unshackle people from some of their worst fears and help them establish new emotional habits might relieve some of the human misery that Ressler confronted as a resident in the Grady Hospital emergency room.

There’s little doubt that Ressler’s experiences at this battered landmark helped forge who he is today. As a raw newcomer, he began each shift “with a sense of dread, because there would be so much work to do and some of the stories would be so hopeless. But I always left in a really good mood, because we did help people and it was not all hopeless.”

Today, knowing what he knows, he still says “I am a pretty optimistic person.” ■