

Genomic Psychiatry

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INNOVATORS & IDEAS: RESEARCH LEADER

Kerry J. Ressler: Exploring the translation of amygdala function at the cellular and genomic levels to understand stress, fear, and trauma disorders, such as post-traumatic stress disorder (PTSD)

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A pioneering force in psychiatric neuroscience, Dr. Kerry Ressler divides his time between serving as Chief Scientific Officer at McLean Hospital, Professor of Psychiatry at Harvard Medical School, and translational neuroscientist. Drawing from both molecular biology and human genetics, he has fundamentally changed how we understand fear and anxiety in the brain, especially through his innovative research on the amygdala. Throughout his remarkable career, which includes over 500 published papers, he has uncovered critical insights into the genetic and epigenetic basis of post-traumatic stress disorder (PTSD) and related anxiety disorders. His expertise has earned him membership in the National Academy of Medicine and a term as president of the Society for Biological Psychiatry. Dr. Ressler co-directs the Psychiatric Genomics Consortium PTSD Workgroup and founded the Grady Trauma Project in Atlanta before joining McLean Hospital. This Genomic Press Interview offers an intimate look at the path and perspectives of a scientist who has shaped modern psychiatric research and treatment.

Part 1: Kerry Ressler – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I grew up in the Deep South – southern Mississippi, Jackson, and then Ocean Springs, MS – first-generation college, an only child with an incredible single mom. I had a few fantastic teachers in high school, including a great science teacher and a math teacher, who helped me to understand there were options beyond the local or regional. I was a child of the early personal computer generation in the early '80s, enjoyed coding and the local (phone-based) tools and networks that were the predecessor to the internet.

With my science teacher's (Ms. Pat Dye) help, I was fortunate to be admitted to MIT in Cambridge, where I hoped to study computer science and artificial intelligence. Along the way, I was exposed to the molecular biology revolution (including having a small seminar class with Salvador Luria and other molecular biology gurus) and the early days of systems neuroscience – and my mind was blown. While in the '80s, artificial intelligence was merely a theory, it was very clear that the molecular neuroscience revolution was taking off – and I was more excited about understanding how brains create learning, memory, and emotion than I was about 'artificially' mimicking it.

I was fortunate to be able to attend Harvard's MD/PhD program in the early '90s. While there were not labs focused as much on my primary interest – learning, memory, and emotion – I had the serendipitous opportunity to hear Linda Buck give her excellent job talk about her discovery of the odorant receptor gene family in rats in Richard Axel's lab. I found out that it was a job presentation and that she would soon start her new



Figure 1. Kerry J. Ressler, MD, PhD. McLean Hospital, Harvard Medical School, USA.

lab at Harvard Medical School. I got the nerve up to call her and ask if I could work in her lab – she graciously welcomed me, and within a few weeks, we had cloned the mouse odorant receptor gene family based on the prior rat sequences. It was an extraordinary time to be in science – focused on a discovery that rapidly led to a new understanding of the molecular and anatomical logic of a previously mysterious sensory system based on genomics advances. In addition to the unbelievable opportunity to join Linda in Stockholm in 2004 for the Nobel Prize ceremony, this work inspired me to spend my career using molecular genomic tools to ask systems neuroscience questions related to Psychiatry.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

I went to Emory for residency in Psychiatry for several reasons: Charlie Nemeroff, the Emory Chair, was one of the most visionary and energetic leaders in biological psychiatry in the '90s; Tom Insel, who went on to be the next NIMH director, initiated the Center for Behavioral





Figure 2. Kerry Ressler and family enjoying a hike in the Colorado Rocky Mountains. They love to camp, off the grid, high up in the Rockies, to escape some of the chaos of the modern world, and enjoy the beauty and serenity of nature.

Neuroscience in Atlanta – one of the first and largest centers focused on neuroscience mechanisms of behavior which was a wonderful community to be a part of; and Mike Davis, one of the true leaders of our current understanding of Amygdala function, had been recruited by Charlie to move from Yale to Emory. After talking with Mike, his lab offered a unique opportunity for collaboration and training for us to work on the molecular mechanisms of amygdala function in fear, threat, and trauma-related disorders; this was in parallel with remarkable mentorship and collaboration with Barbara Rothbaum, a leader in anxiety-related disorders and PTSD.

As I grew my career at Emory, running a basic science lab focused on amygdala mechanisms of fear processing in mice, as well as a clinical lab focused on understanding the human biology of PTSD, I also served on admissions and executive committees for the Neuroscience Graduate Program and Medical School and MD/PhD programs, eventually becoming the director of the Emory Medical Scientist Training Program, and writing/leading Emory Psychiatry's NIMH R25 for a research residency track. After almost 20 years at Emory, I moved in 2015 to McLean Hospital / Harvard Medical School to 'trade in' my multiple administrative roles for one relatively focused on translating neuroscience to psychiatry in my current role as Chief Scientific Officer at McLean Hospital. McLean's breadth and depth of psychiatry clinical expertise with an enormous amount of preclinical and clinical research programs focused on psychiatric neuroscience – make it an almost unique and wonderful place for working on translational opportunities in psychiatry.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

Learning from Mike Davis and the broader amygdala field, including Joe LeDoux, Michael Fanselow, and their academic offspring, particularly at the preclinical level, how exciting and well-understood the amygdala, its connectivity, and its causal association with behavior. To me, this seemed the most tractable current circuit for understanding at a molecular and cellular level to address specific behaviors (e.g., fear/trauma) – I've been working on this general problem ever since.

What impact do you hope to achieve in your field by focusing on specific research topics?

Most proximally, I hope that our work may lead to novel approaches (pharmacological, neurostimulation, behavioral, etc.) to fear- and trauma-related disorders, perhaps even to prevent PTSD development in the first place, by better understanding the biological processes of fear- and trauma-memory consolidation and intervening in the emergency department, on the battlefield, or after mass disasters. Beyond our specific areas, the field of Psychiatry is in desperate need of early 'wins' demonstrating that a neurobiology and/or genomic understanding of any of our disorders are sufficiently mature to lead to science-driven rational intervention approaches to Psychiatric disease.

Please tell us more about your current scholarly focal points within your chosen field of science.

Our broader lab focuses on both top-down and bottom-up translational approaches to understanding fear- and trauma-related disorders. Specifically, at the human level, I am a co-PI of the Psychiatric Genomic Consortium – PTSD working group – working with Caroline Nievergelt, Karestan Koenen, Murray Stein, and our many excellent collaborators – we have recently published the largest GWAS to-date of PTSD – including > 1M subjects, with ~100 GWAS significant loci (Nievergelt et al., *Nature Genetics*, 2024) – so that we are indeed approaching a genetic architecture of PTSD. In parallel, we have recently published, with Nikos Daskalakis, Charlie Nemeroff, Joel Kleinman, and colleagues, among the largest postmortem brain multiomic (RNA, Protein, and epigenetic) along with snRNAseq datasets of PTSD and depression vs. controls (Daskalakis et al., *Science*, 2024). These data provide a 'ground truth' of the human brain in disease, complementary to the large-scale GWAS data, the extensive neuroimaging and physiology studies, and large prospective studies of PTSD following trauma – so that the field is developing true human biology to understand these disorders. In parallel, we continue to apply all the great 'new' circuit tools in mice, including, among others, cellular calcium imaging, single-cell sequencing, intersectional opto- and chemogenetics, to understand the mechanisms of these circuits, pathways, and molecules



in a model system (e.g., Hartmann et al., *PNAS*, 2024; Maddox et al., *Molecular Psychiatry*, 2024; Hisey et al., *Biol Psychiatry*, 2023; McCullough et al., *Nature Comm*, 2020; Maddox et al., *Neuron*, 20195).

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?

The gold-standard approaches of logic, precision, replication, testable hypotheses, and reductionistic questions hold up across multiple levels of analyses. Linda Buck and Michael Davis, my graduate and postdoc mentors, are remarkable, thoughtful, creative, and precise scientists who provided amazing examples and mentorship to me during my development. To this day, I try to think about complex problems in a reductive and logical way as best I can, based on observing their insightful, creative, and persistent approaches.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are particular cultural facets within the scientific community warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

My biggest concern regarding science and society at this point relates to the current sense of an anti-science movement, particularly in what we used to consider 'Western liberal democracies' that suggest tremendous skepticism of science and the scientific approach by the public. This is in part related to the exponential growth in social media, in which the loudest voice seems to be seen as the 'most true,' with a real dilution of fact- and data-based narratives – be it global warming, our fundamental understanding of communicable diseases, among others. The scientific community must find a better way to communicate, educate, and defend rational thought and data-driven decision-making in an increasingly unpredictable world.

What do you most enjoy in your capacity as an academic or research leader?

The ability to be an active member of one of the most exciting areas of science and discovery daily – it is an honor to be part of the worldwide community trying to understand how the brain creates behavior and is dysregulated in disease.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

Quiet time, as well as adventures, with family and loved ones.

Part 2: Kerry Ressler – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Relaxing at the beach or in the mountains, reading a book, being lost in the moment.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

What is your greatest fear?

Being a disappointment – not doing (or at least trying to do) my best.

Which living person do you most admire?

Barack Obama.

What are you most proud of?

My children and some amazing academic 'offspring'!

What is your greatest regret?

While I worry a lot about the future, I am fortunate to not regret too much about the past (for good or for bad!).

What is the quality you most admire in people?

Intelligence with generativity, grace, and humility.

What is the trait you most dislike in people?

Self-absorption and narcissism.

What do you consider the most overrated virtue?

Independence.

What is your favorite occupation (or activity)?

I enjoy beekeeping and hiking.

Where would you most like to live?

On a beach with a view of a mountain.

What is your current state of mind?

Peace, occasionally interrupted by angst about missing so many deadlines!

What is your most marked characteristic?

Easy to laugh, and (hopefully) slow to criticize.

Among your talents, which one(s) give(s) you a competitive edge?

Persistence, along with a flexible perspective.

What do you consider your greatest achievement?

Scientifically, it is a tie between my early contributions as a team member to the 2004 Nobel Prize for understanding olfaction and my work over the last twenty years helping the field of PTSD and fear/trauma achieve success in translation across genomics and circuits.

If you could change one thing about yourself, what would it be?

I would like to be less socially anxious.

What do you most value in your friends?

Kindness, grace, easy-going, and laughter.

What aphorism or motto best encapsulates your life philosophy?

'He tried his best to do good...'

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