BIOGRAPHICAL SKETCH

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NAME: **Kerry James Ressler, MD, PhD**

eRA COMMONS USER NAME (credential, e.g., agency login): KRESSLER1

POSITION TITLE: Chief Scientific Officer, Chief Division Depression & Anxiety, McLean Hospital,
Professor of Psychiatry, Harvard Medical School;
Visiting Professor, Emory University

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Massachusetts Institute of Technology, Cambridge,MA	B.S.	1986-1990	Molecular Biology
Harvard University, Cambridge, MA	Ph.D.	1990-1995	Neurobiology
Harvard University School of Medicine, Boston, MA	M.D.	1990-1997	Medicine
Emory University School of Medicine, Atlanta, GA	Residency	1997-2001	Psychiatry

A. Personal Statement

My expertise is in Genomics, Neurobiology, and Clinical Psychiatry and Translational Neuroscience, specifically focused on biological mechanisms of trauma-related disorders. My overall program is to understand the risks for psychopathology that include developmental, genetic and environmental risk factors of PTSD and fear-related disorders. I also have over a decade of leadership roles locally and nationally across the neuroscience and psychiatry disciplines. I have received international research awards for basic and translational research on fear in animals and humans including being named an HHMI Investigator, a member National Academy of Medicine; the Freedman Award in Basic Science from NARSAD and the Clinical Scientist Award in Translational Research from the Burroughs Wellcome Fund; and previously, the Pfizer Fellowship in Biological Psychiatry, the Anxiety Disorders Association of America Junior Faculty Award, two NARSAD young investigator awards, a Rockefeller Brother's Fund Young Investigator Scholarship, and K01 from the National Institutes of Health. I am also the current President of the Society for Biological Psychiatry.

I am currently Principal Investigator (PI) on several R01 grants to understand translational, genetic and psychological risk factors for PTSD. I have served on VA and NIMH standing study sections, was on the NIMH RDOC committee for fear-related disorders, and I am on the NIMH Board of Scientific Counselors. These experiences and our labs' expertise provide for a powerful combination of sophisticated behavioral, genetic and epigenetic approaches to understand the genetic and epigenetic risk for developmental stress- and trauma-related disorders. Some prior work that is particularly relevant is outlined below:

1. Wingo AP, Almli LM, Stevens JS, Jovanovic T, Wingo TS, Tharp G, Li Y, Lori A, Briscione M, Jin P, Binder EB, Bradley B, Gibson G, **Ressler KJ.** (2016) Genome-wide association study of positive emotion identifies genetic variant & role for microRNAs. *Molecular Psychiatry*. Sep 6. PMID: 27595594.
2. Wingo AP, Almli LM, Stevens JJ, Klengel T, Uddin M, Li Y, Bustamante AC, Lori A, Koen N, Stein DJ, Smith AK, Aiello A, Koenen KC, …Gibson G, and **Ressler KJ** (2015) *DICER1* and microRNA regulation in Post-Traumatic Stress Disorder, *Nature Communications,* 2015 Dec 3;6:10106. PMID: 26632874
3. Michopoulos V, Rothbaum AO, Jovanovic T, …Gillespie CF, **Ressler KJ.** (2015) Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. *Am. J.Psychiatry.* 172(4):353-62. PMID: 25827033.
4. Stevens JS, Almli LM, Fani N, Gutman DA, Bradley B, Norrholm SD, Reiser E, Ely TD, Dhanani R, Glover EM, Jovanovic T, **Ressler KJ.** (2014) PAC1R gene polymorphism impacts fear responses in the amygdala and hippocampus. *PNAS.* 111(8):3158-63. PMID: 24516127.
5. **Ressler KJ**, Mercer KB, Bradley B, Jovanovic T, Mahan A, Kerley K, Norrholm SD, Kilaru V, Smith AK, Myers A, Ramirez M, Engel A, Hammack SE, Toufexis D, Braas KM, Binder EB, and May V (2011) PTSD is associated with PACAP and the PAC1 receptor, *Nature*, *470: 492-497.* PMID: 21350482.
6. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, Tang Y, Gillespie CF, Heim CM, Nemeroff CB, Schwartz AC, Cubells JF, **Ressler KJ**. (2008) Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA*. 299(11):1291-305. PMID: 18349090

B. Positions and Honors

Professional Experience:

1987-'91 Undergrad. Research: M.I.T., Hermann Steller, PhD; Richard Wurtman, MD; Ann Graybiel, PhD
1990-'97 MD/PhD Student: Harvard Longwood, Cambridge Hospital, Massachusetts General Hospital
1992-'95 Graduate Thesis Laboratory: Harvard University, Mentor: Linda Buck, PhD
2000-'01 Psychiatry Resid. Fellowship: Neurobiology of Fear, Emory University, Mentor: Michael Davis, PhD
2001-'07 Assistant Professor: Department of Psychiatry and Behavioral Sciences, Emory University
2001- Co-Director: Post-traumatic Stress Disorders Clinic, Grady Memorial Hospital, Atlanta, GA
2004, 2012- *Member,* Learning and Memory Study Section (LAM), Center for Sci. Review, NIH
2006-'10 *Member*, VA Merit Review Subcommittee: PTSD, stress and anxiety related grants.
2007- *Scientific Advisory Boards:* American Foundation for Suicide Prevention; Anxiety Disorders Association; Simons Foundation; NARSAD; DANA Alliance for Brain Research
2007-'14 Co-Director, Emory MD,PhD Medical Scientist Training Program
2007- Director, Emory NINDS-funded Transgenic Viral Vector Core
2008-'15 Investigator, Howard Hughes Medical Institute; Associate Professor, Emory University
2011- NIMH, NIH Committee Member, Research on Domain Criteria (RDOC), 'Negative Affect Domain'
2011- Chairman, Sci. Adv. Board, Army STARRS (Study To Assess Risk/ Resilience in Servicemembers)
2013- Professor with Tenure, Department of Psychiatry and Behavioral Sciences, Emory University
2013- Co-Director, PTSD Subgroup, *International Psychiatric GWAS Consortium*
2013-'18 Member, *NIMH Intramural Board of Scientific Counselors*
2014-'15 Director, Interim, Emory MD,PhD Medical Scientist Training Program
2014-'15 Chair, Scientific Advisory Council, *Anxiety and Depression Association of America*
8/2015- Chief Scientific Officer / Chief, Division of Depression & Anxiety, McLean Hospital, Harvard Med. Sch.
5/2016- President, *Society for Biological Psychiatry*

Editorial Service:

Editorial Boards: *Neuron, Biological Psychiatry, Neuropsychopharmacology.; Depression & Anxiety; Personalized Medicine in Psychiatry; Harvard Review of Psychiatry*
Editor/Co-Ed: *Principles of Molecular Medicine; Neurobiology of Mental Illness; Neurobiology of PTSD; Anxiety Disorders: A Primer;*
Peer Reviewer: *Journal of Neuroscience, Neuron, Neuropsychopharmacology, Neuroscience, Archives General Psychiatry, J Trauma Stress, Biological Psych., Am J Psychiatry, Nature Neuroscience, European J Neuroscience, Brain Research, Science, Nature*

Honors and Awards:

1990-'97 NIH, MD / PhD Scholar, Medical Scientist Training Program
1992-'95 Sackler Scholar in Psychobiology, and Quan Fellowship in Neurobiology, Harvard Med. School
1999 Resident Teaching Award, Emory School of Medicine; NIMH Outstanding Psych. Resident Award
2000 Laughlin Fellow, American College of Psychiatry; Lilly Fellow, Society for Biological Psychiatry
2000-'03 Pfizer Postdoctoral Fellowship Award in Biological Psychiatry
2001-'04 Culpeper Medical Scholarship, Rockefeller Brothers Fund & Goldman Philanthropic Partners
2002-'03 Travel Fellow, ACNP; Jr. Faculty Research Award, Anxiety Disorders Assoc.
2004 Graduate advisor, Linda Buck, 2004 Nobel Prize for characterization of odorant receptor genes
2002 & '05 Young Investigator Award, National Alliance for Research on Schizophrenia and Depression
2006 Burroughs Wellcome Foundation, "Translational Clinical Scientist Award"
2008-2015 *Investigator*, Howard Hughes Medical Institute; *Member*, Dana Foundation for Brain Research
2008 Member, American College of Neuropsychopharmacology; *2011-2013 Program Committee*
2009 Freedman Award for Outstanding Basic Science Research, NARSAD
2011 Emil Kraepelin Guest Professorship, Max Planck Institute for Psychiatry, Munich, Germany
2011 Laufer Award for Outstanding Scientific Achievement, International Soc. Traumatic Stress Studies
2011 Eva King Killam Award, Outstanding Translational Research (inaugural award), ACNP
2012 Outstanding Postdoctoral Mentor Award, Emory School of Medicine, Laney Graduate School

2012 *Fellow*, American College of Neuropsychopharmacology
2012 Elected *Member* of the **Institute of Medicine** of the National Academies
2014 Awarded Annual Dean's Distinguished Faculty Lecture and Award, Emory School of Medicine
2015 Gerald Klerman Award, Cornell University School of Medicine
2015 Yale "Flynn" Lecture for outstanding contribution to Psychiatry, Yale University

C. Contributions to Science

Genetic risk for PTSD. Post-traumatic stress disorder (PTSD) occurs only in vulnerable individuals after exposure to severe traumatic events. This differential risk is due in part to vulnerability and resilience that is 30-40% heritable. Thus, PTSD is among the most likely of psychiatric disorders to be understood from the perspective of environmental influences interacting with genetic vulnerability, since diagnosis requires a specific, highly traumatizing experience. Over the past 10 years, our group has collected a large, invaluable sample cohort and demonstrated significant gene-environment interactions in PTSD through our hypothesis-driven efforts in a highly traumatized population. We are currently using state-of-the-art genetic approaches to identify, in an hypothesis-neutral fashion, which genes are the most likely to contribute to PTSD, using a GWAS approach involving N=8,000 subjects. Focusing on subjects from a population with similar environmental exposure to a high trauma burden (4000 affected, 4000 unaffected) will allow us to identify a set of genetic variants (SNPs and CNVs) associated with the presence or absence of PTSD symptoms in subjects with a common environmental background.

Notably, I am also taking a lead nationally in forming the Psychiatric GWAS Consortia – PTSD subgroup, which we hope will contain ~100,000 samples and controls within the next ~5 years. We hypothesize that by focusing on genes and markers that are associated with the presence vs. absence of PTSD within a highly-traumatized population, we will have the greatest likelihood for prioritizing and replicating genetic variants involved in the etiology of PTSD.

1. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, Pace TW, Mercer KB, Mayberg HS, Bradley B, Nemeroff CB, Holsboer F, Heim CM, **Ressler KJ**, Rein T, Binder EB. (2013) Allele-specific *FKBP5* DNA demethylation mediates gene-childhood trauma interactions. *Nature Neuroscience* 16(1):33-41. PMID: 23201972.
2. Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, Pace TW, Rex-Haffner M, Loeschner A, Gonik M, Mercer KB, Bradley B, Müller-Myhsok B, **Ressler KJ**, Binder EB. (2013) Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proceedings of the National Academy of Sciences* 110(20):8302-7. PMID: 23630272.
3. Jovanovic T, Norrholm SD, Davis J, Mercer KB, Almli L, Nelson A, Cross D, Smith A, **Ressler KJ,** Bradley B.(2013) PAC1 receptor (*ADCYAP1R1*) genotype is associated with dark-enhanced startle in children. *Molecular Psychiatry*. 2013 Jul;18(7):742-3. PMID: 22776899.
4. Mercer KB, Dias B, Shafer D, Maddox SA, Mulle JG, Hu P, Walton J, **Ressler KJ.** (2016) Functional evaluation of a PTSD-associated genetic variant: estradiol regulation and ADCYAP1R1. *Transl Psychiatry.* 2016 Dec 13;6(12):e978. PMID: 27959335.

Molecular correlates of fear memory consolidation. Understanding mechanisms of fear consolidation is both a tractable problem as well as an imminently important one for preventing the development of trauma-related disorders such as PTSD. Furthermore, the methods by which neuronal connections shift from stable to transiently unstable, allowing the formation of new synapses and postsynaptic spine structures, is a fascinating biological process.

Along these lines, we have been the first to demonstrate these points in amygdala-dependent memory formation, particularly related to the role of growth factors (e.g. BDNF). Current work utilizing hypothesis-neutral genetic screening approaches have identified pathways in both the Notch and Nogo signaling pathways, among others, that we are actively examining with regards to memory formation.

1. Chhatwal, J., Stanek-Rattiner, L, Davis, M., and **Ressler, KJ** (2006) Amygdala BDNF signaling is required for consolidation but not encoding of extinction. *Nature Neuroscience*, 9(7):870-872. PMID: 16783370
2. Heldt S.A., Chhatwal, J., Stanek-Rattiner, L, and **Ressler KJ** (2007) Hippocampal-specific deletion of the BDNF gene impairs spatial learning tasks and normal extinction of cued fear. *Mol. Psychiatry,12(7):656-70.*
3. Andero R, Dias BG, and **Ressler KJ** (2014) A role for *Tac2*, NkB and Nk3 receptor in normal and dysregulated fear memory consolidation. *Neuron,* 83(2):444-54. PMID: 24976214.
4. Dias BG, Goodman JV, Ahluwalia R, Easton AE, Andero R, and **Ressler KJ** (2014) Amygdala-dependent fear memory consolidation via miR-34a and Notch signaling. *Neuron*, 83(4):906-18. PMID: 25123309.

Developmental genes are activated during learning: In addition to its role in cellular development and proliferation, there are emerging *in vitro* data implicating the Wnt/β-catenin pathway in synaptic plasticity. Yet *in vivo* studies had not examined whether Wnt activity is required for learning and memory in adults. In the amygdala, we found that many Wnt-signaling genes were dynamically regulated, with an immediate decrease, followed by an eventual normalization during fear memory consolidation. This rapid, consolidation-dependent, decrease in Wnt mRNA was confirmed with individual qPCR and *in situ* hybridization. While manipulating Wnt signaling with Dkk-1 or Wnt1 infused directly into amygdala had no effect on control behaviors but prevented long-term fear memory consolidation. Dkk-1 and Wnt infusions had destabilizing, but opposite, effects on the requisite β-catenin/cadherin dynamic interactions that occur during consolidation. We then examined β-cat expression and function in the adult amygdala[7]. We found alterations in β-cat mRNA and protein phosphorylation during fear-memory consolidation. Such alterations correlated with a change in the association of β-cat with cadherin. Furthermore, amygdala-specific deletion of β-cat prevented the normal transfer of newly formed fear learning into long-term memory. Overall, these data suggest that dynamic modulation of Wnt/β-catenin signaling during consolidation is critical for the structural basis of long-term memory formation.

Intriguingly, these data suggest that gene pathway patterns which underlie developmental processes are also reactivated transiently during synaptic plasticity in adult neurons. This is very intriguing because it suggests that mechanisms for forming neuronal connections are shared from development to adult plasticity.

1. Maguschak K. & **Ressler KJ** (2008) *β-catenin* is required for fear memory consolidation. *Nature Neuroscience, 11(11):1319-26.* PMID: 18820693.
2. Maguschak KA and **Ressler KJ** (2011) Wnt Signaling in Amygdala-Dependent Learning and Memory. *Journal of Neuroscience.* 31 (37): 13057-67. PMID: 21917789.
3. Mahan AL, **Ressler KJ.** (2012) Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. *Trends in Neuroscience* 35(1):24-35. PMID: 21798604.
4. Parsons R and **Ressler KJ** (2013) Implications of memory modulation for post-traumatic stress and fear disorders. *Nature Neuroscience, 16(2):146-53.* PMID 23354388.

Molecular mechanisms of Olfactory Learned and Inherited Behavior. I was the first graduate student of Linda Buck, PhD (Nobel Prize, 2004), and in her lab I cloned and characterized the first mouse odorant receptor genes. More recently we were the first to show that the olfactory receptor population is plastic in adult mice, and that olfactory fear conditioning leads to specific increases in olfactory sensory neurons (OSNs) and the size of their specific glomeruli in the bulb, corresponding to their increased sensitivity to the trained odorants. To begin to address intergenerational transmission in a very reduced and mechanistic way, we have developed a paradigm to follow the structural representation underlying olfactory cue processing across generations. We found that olfactory fear conditioning in adult mice (F0 generation) causes subsequently conceived generations (F1, F2) to display sensitivity to the paternally-conditioned odor. Odorant-receptor-specific neuroanatomical changes in the olfactory system of the F1, F2, and IVF generations accompany this behavioral sensitivity including enhanced olfactory-potentiated startle. Epigenetic analyses in the olfactory epithelium of the F0, F1, F2, and IVF generations indicate that these neuroanatomical changes may result from increased transcription of the specific receptor gene that detects the conditioned odor. Together, these studies involving IVF, F2 generations, and cross-fostering all suggest that the transgenerational effects are inherited via the gametes. We conclude that parental olfactory experience before conception can be inherited at the level of structure and function in the nervous system.

1. **Ressler, KJ**, Sullivan, SL, and Buck, LB (1993) A Zonal Organization of Odorant Receptor Gene Expression in the Olfactory Epithelium. *Cell 73,* 597-609. PMID: 7683976
2. **Ressler, KJ**, Sullivan, SL, and Buck, LB (1994) Information Coding in the Olfactory System: Evidence for a Stereotyped and Highly Organized Epitope Map in the Olfactory Bulb. *Cell 79*, 1245-55. PMID: 7528109
3. Dias BG and **Ressler KJ** (2014) Parental olfactory experience influences behavior and neural structure in subsequent generations. *Nature Neuroscience*, 17(1):89-96. PMID: 24292232. *Featured in News & Views.*
4. Morrison FG, Dias BG, Ressler KJ. (2015) Extinction reverses olfactory fear-conditioned increases in neuron number and glomerular size. *Proc Natl Acad Sci U S A*. 12(41):12846-51. PMID: 26420875

Cell Type Specific Regulation of Amygdala Mediated Fear and Extinction. For progress to occur with targeted rationally-designed therapies for fear-related disorders, a greater understanding of the neural circuitry mediating fear inhibition and extinction is needed. It is critical that we understand the role of specific cell types within the amygdala supporting fear inhibition and fear extinction learning. It is known that the Basolateral Amygdala (BLA) modulates fear expression via projections to the medial (CeM) and lateral division (CeL) of the central amygdala. In mice, the Intercalated Cell Nuclei of the Amygdala (ITC) consist of islands

between the BLA and CeL, and the ITC receive inputs from medial prefrontal cortex (mPFC) and act as an inhibitory gate to the CeL. We have targeted specific cell-types within the BLA, ITC, CeL and CeM which are involved in inhibiting the fear response, including the *Thy1*, *CRH, Tac2, Oprl1* populations, with ongoing work targeting *FoxP2,* and *PKCδ* subpopulations within the ITC and CeL. *Through cell-type specific RNA profiling, epigenetic analyses, electrophysiology, and optogenetic and Designer Receptors Exclusively Activated by Designer Drug (DREADD) regulation*, *we will determine the activity-dependent molecular events underlying the inhibition of fear within the amygdala.*

1. Gafford G., Guo JD, Flandreau EI, Hazra R, Rainnie DG, and **Ressler KJ.** (2012) Cell type specific deletion of GABA(A)α1 in CRF-containing neurons enhances anxiety and disrupts fear extinction. *Proceedings of the National Academy of Sciences, 109(40):16330-5.* PMID: 22992651.
2. Jasnow AM, Ehrlich DE, Choi DC, Dabrowska J, Bowers ME, McCullough KM, Rainnie DG, **Ressler KJ**. (2013) Optogenetic activation of Thy1-expressing neurons in the basolateral amygdala mediates fear inhibition. *Journal of Neuroscience* 33(25):10396-404. PMID: 23785152
3. Andero R, Brothers SP, Jovanovic T, Chen YT, Salah-Uddin H, Cameron M, Bannister TD, Almli L, Stevens JS, Bradley B, Binder EB, Wahlestedt C, and **Ressler KJ** (2013) Amygdala-dependent fear is regulated by Oprl1 in mice and humans with PTSD. *Science Trans. Med.* 5, 188ra73. PMID: 23740899.
4. McCullough KM, Choi D, Guo J, Zimmerman K, Walton J, Rainnie DG, and **Ressler KJ** (2016) Molecular Characterization of a 'Fear-Off' Neuronal Population within the Basolateral Amygdala. *Nature Communications,* Oct 21;7:13149. doi: 10.1038/ncomms13149.PMID: 27767183

Complete List of Published Work in MyBibliography: *(H-index (Google) = 68, total publications>275)*
https://www.ncbi.nlm.nih.gov/pubmed/?term=ressler+k http://scholar.google.com/citations?user=pS2_3lIAAAAJ&hl=en

D. Current Research Support

NIH, NIMH, R01 MH096764 (Ressler, PI) 04/01/2012 – 03/31/2017
"Genetic and estrogen-dependent regulation of the human PAC1R receptor and PTSD" This grant will extend our findings that the PACAP/PAC1 receptor pathway is associated with PTSD and with dysregulation of fear in humans by examining the mechanisms by which estrogen, epigenetic modulation, and genetic polymorphisms differentially modulate PAC1 gene expression in humans.

NIH, NIMH, U01 5U01MH110925-02 (McLean, PI; Ressler, co-PI) 08/01/2017 – 07/31/2022
"Longitudinal Assessment of Post-traumatic Syndromes"
This large, multisite study aims to examine a full range of biomarkers and digital phenotypes leading to a comprehensive model of PTSD development over time in Civilians.

NIH, NIMH, R01 MH094757 (Ressler, PI) 04/01/2012 – 03/31/2017
"Prospective Determination of Psychobiological Risk Factors for PTSD"
This grant examines genetic, epigenetic, and hormonal biomarkers in the hours after a trauma occurs, combined with 6-12 month followup to identify biomarkers of PTSD in civilians.

NIH, NIMH, R01 MH100122 (Jovanovic, PI, Ressler, Co-I) 07/01/2013 – 06/30/2018
"DEVELOPMENT, TRAUMA, AND GENOTYPE BIOMARKERS OF ANXIETY IN CHILDREN"
The proposed study will target the ADCYAP1R1 gene in children at risk for trauma and PTSD, using psychophysiological biomarkers of anxiety, to examine the emergence of sex differences in PTSD.

Usamraa W81XWH-15-2-0090; Co-PI (PI Stein, co-PI Ressler) 09/30/2015 - 09/29/2019
Enhancing Fear Extinction via Angiotensin1 Rec Inhibition: A Randomized Controlled Trial in PTSD.
The purpose of this work is to perform a double-blinded, multi-site, randomized controlled trial of an angiotensin receptor blocker for the treatment of PTSD. This work is based on clinical and preclinical work from the Ressler lab identifying the angiotensin receptor as a robust target in mediating PTSD symptoms.

NIH R01 MH108665-01A1 PI(co-PI, Bolshakov) 07/01/2016 - 06/30/2021
"Cell Type Specific Genomic and Functional Dissection of Fear Off Amygdala Pathways"
The purpose of this grant is to use cell-type specific modulation of cells within the amygdala to understand the neural circuitry of BLA and CeA amygdala subdivisions underlying fear behavior and potential therapeutics.

NIH R01 MH106595-01A1 co-PI ((Neivergelt, UCSD, co-PI, Ressler)
"PSYCHIATRIC GENOMICS CONSORTIUM FOR PTSD" 08/01/2016 - 07/30/2019
The primary aim of this study is to detect novel genetic variants that predict the development of PTSD following trauma. Identifying the genetic pathways underlying PTSD will lead to an improved neurobiological understanding, enhanced prevention, and improved treatment of this debilitating syndrome.