BIOGRAPHICAL SKETCH

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

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

POSITION TITLE: Professor of Psychiatry, Harvard Medical School
Chief Scientific Officer and Chief, Division of Depression & Anxiety, McLean Hospital
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 lab studies the neurobiology of fear, threat, and stress, and the translation of these findings to human disorders. I bring recent experiences involved in both mentorship and research, including: McLean Hospital Chief Scientific Officer and Harvard Program In Neuroscience Committee Member (2016-present); Emory University MD/PhD program Co-director 2005-2014, Director 2014-2015; Emory Psychiatry Resident Research Director, 2013-2015; HHMI Investigator 2008-'15, and lecturer in Residency and Graduate education. I have directly mentored over 75 undergraduates, 14 PhD graduate students, 20 postdocs, and many Psychiatry Residents. Those who have completed their training have gone onto academic postdoctoral or faculty positions in neuroscience, psychiatry and psychology.

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 national research awards for research including: member of the National Academy of Medicine, prior HHMI Investigator, recipient of the Freedman Award from NARSAD and the Clinical Scientist Award in Translational Research from the Burroughs Wellcome Fund; 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 Chair of the SAB for the Army STARRS project, and on the SAB for the National Center for PTSD, the Past-President of the Society for Biological Psychiatry and a Council member of the American College of Neuropsychopharmacology.

I am currently PI on several R01 grants to understand translational, physiological and genetic 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 was on the NIMH Board of Scientific Counselors. These experiences and our labs' expertise provide for a powerful combination of sophisticated approaches to understand the physiological and (epi)genetic risk for PTSD and stress-related disorders. Prior, particularly relevant, publications from our group related to translational understanding of fear and anxiety-related disorders are outlined below:

- Maddox SA, Hartmann J, Ross RA, and **Ressler KJ** (2019) Mechanisms of Fear and Trauma Memory Encoding: Deconstructing the Gestalt. *Neuron.* 2019, 102(1):60-74. PMID: 30946827.
- **Ressler KJ.** (2018) Alpha-Adrenergic Receptors in PTSD - Failure or Time for Precision Medicine? *New England Journal of Medicine*. 378(6):575-576. PMID: 29414268.
- Dedic N, Kühne C, .. **Ressler KJ**, Wotjak CT, ... Deussing JM. (2018) Chronic CRH depletion from GABAergic, long-range projection neurons in the extended amygdala reduces dopamine release and increases anxiety. *Nature Neuroscience.* 21(6):803-807. PMID: 29786085.
- McCullough KM, Choi D, Guo J, Zimmerman K, Walton J, Rainnie DG, **Ressler KJ**. (2016) Molecular characterization of Thy1 expressing fear-inhibiting neurons within the basolateral amygdala. *Nature Communications*. 7:13149. PMID: 27767183.
- **Ressler KJ**, Mercer KB, Bradley B, Jovanovic T, Mahan A, …Binder EB, and May V (2011) PTSD is associated with PACAP and the PAC1 receptor, *Nature*, *470: 492-497.* PMID: 21350482.

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.
2016-'17 President, *Society of Biological Psychiatry*
2017- Member, *Society of Biological Psychiatry* and *ACNP* Councils

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
2017 NARSAD / Brain & Behavior Research Foundation - Distinguished Investigator Award
2019 American Psychiatric Association - Judd Marmor Award
2019 University of Michigan - Eisenberg Translational Research Prize

C. Contributions to Science

Genetic risk for Trauma, Fear and Stress Disorders and 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. 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. Koenen KC, Duncan LE, Liberzon I, **Ressler KJ.** (2013) From candidate genes to genome-wide association: the challenges and promise of posttraumatic stress disorder genetic studies. *Biological Psychiatry*, 74(9):634-6. PMID: 24120289.
3. 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) PACAP receptor gene polymorphism impacts fear responses in the amygdala and hippocampus. *PNAS.* 111(8):3158-63. PMID: 24516127.
4. 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 a genetic variant and a role for microRNAs. *Molecular Psychiatry*. 2016 Sep 6. PMID: 27595594.

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 Fear 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. We also 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.*

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. Kilaru V, Iyer SV, Almli LM, Stevens JS, Lori A, Jovanovic T, Ely TD, Bradley B, Binder EB, Koen N, Stein DJ, Conneely KN, Wingo AP, Smith AK, **Ressler KJ**. (2016) Genome-wide gene-based analysis suggests an association between Neuroligin 1 (NLGN1) and post-traumatic stress disorder. *Translational Psychiatry*. 6:e820. PMID: 27219346.
4. Banerjee SB, Gutzeit VA, Baman J, Aoued HS, Doshi NK, Liu RC, **Ressler KJ.** (2017) Perineuronal Nets in the Adult Sensory Cortex Are Necessary for Fear Learning. *Neuron*. 2017 Jul 5;95(1):169-179.e3.

Molecular Mechanisms of Olfaction and Olfactory Fear-related 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. 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. 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*.112(41):12846-51. PMID: 26420875.
4. 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.*
Also see *Aoued HS, … **Ressler KJ**, Dias BG (2018) Biological Psychiatry, 85(3):248-256.*

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. 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.
3. McCullough KM, Choi D, Guo J, Zimmerman K, Walton J, Rainnie DG, and **Ressler KJ** (2016) Molecular Characterization of a 'Fear-Off' Neuronal Population in the Basolateral Amygdala. *Nature Communications*, 7:13149. PMID: 27767183
4. Fenster RJ, Lebois LAM, **Ressler KJ,** Suh J. (2018) Brain circuit dysfunction in post-traumatic stress disorder: from mouse to man. *Nature Reviews Neurosci*. 19(9):535-551. PMID: 30054570.

Complete List of Published Work:*(Google Scholar: H-index = 91, total publications>350, citations >33,000)*
http://www.ncbi.nlm.nih.gov/sites/myncbi/kerry.ressler.1/bibliography/41158960/public/?sort=date&direction=ascending

D. Selection of Current Research Support

NIH, NIMH, U01 MH110925 (McLean, UNC Chapel Hill; sub-award PI Ressler) 09/23/2016- 07/31/2021
"Longitudinal Assessment of Post-traumatic Syndromes" - Sub Award
This is a very large multi-site study (target enrollment = 5000) examining the biological, physiological, and psychological development of symptoms and syndromes in the aftermath of Trauma.

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.
This is a double-blinded, multi-site, randomized controlled trial of an angiotensin receptor blocker for the treatment of PTSD, based on clinical and preclinical work identifying angiotensin as a target in PTSD.

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 improved understanding.

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"
This grant will 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, NIMH, R01 MH117292 - 01 (McLean Hospital, Ressler, Kerry J) 07/01/2018 - 06/30/2023
"Understanding PTSD through Postmortem Targeted Brain Multi-omics, Site 3/3"
This proposal utilizes a Linked R01 mechanism across 3-sites to perform a postmortem, multi-omic study of brains from 300 total subjects with PTSD, mood disorder non-PTSD psychiatric controls, and normal controls. These data will allow an understanding of the region-specific genotype-dependent transcriptional and translational profiles, and findings will be integrated with detailed multi-omic data from other studies to further our understanding of PTSD and advance future treatment and diagnostic biological targets

NIH, NIMH, P50 MH115874-01 04/01/2019-03/31/2024
(Carlezon, Overall PI; Ressler, Co-Director Admin Core; Ressler, Project 1 Project Lead)
"Silvio O. Conte Center for Stress Peptide Advanced Research, Education, & Dissemination"
Admin Core: SPARED Center: The Administrative Core will support and complement the comprehensive qualities of the science and will also support a broad range of training and educational activities, including expansion of already piloted outreach programs and new approaches to both scientists and lay-persons.
Project 1/5: CRF-PACAP effects in mice: The major goals of SPARED Project 1 are to perform mechanistic studies in mice to understand the role of cell-type specific CRF- and PACAP-expressing neuron populations within central amygdala (CeA), BNST, mPFC, and PBN areas of the brain.