BIOGRAPHICAL SKETCH
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NAME: Baram, Tallie Z.

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

POSITION TITLE: Distinguished Prof., Pediatrics, Anatomy/Neurobiology, Neurology, and Physiology/Biophysics D.D. Shepard Professor of Neurological Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date mm/yyyy	FIELD OF STUDY
Tel-Aviv University, Israel	BSc	1973	Biology
Weizmann Institute of Science, Rehovot, Israel	PhD	1978	Neuroscience
University of Miami School of Medicine, Florida	MD	1980	Medicine
Baylor College of Medicine, Houston, Texas	Residency	1982	Pediatrics
Baylor College of Medicine, Houston, Texas	Fellowship	1985	Child Neurology

A. Personal Statement

Tallie Z. Baram is the director of the Center. Baram is the Danette Shepard Professor of Neurological Sciences, and a Professor of Pediatrics, Anatomy & Neurobiology, Neurology, and Physiology/Biophysics at the University of California, Irvine. She has been studying the role of early-life experience in brain plasticity, supported by uninterrupted NIH funding, for over 25 years. Baram is trained as a developmental neuroscientist and child neurologist and is experienced in translational Neuroscience. She has focused her efforts on the influence of early-life experiences on the developing brain, and on the underlying mechanisms. She is studying this broad topic in two contexts: a) How early-life seizures, especially those associated with fever, can convert a normal brain into an epileptic one, and b) How early-life experiences including stress and maternal care influence resilience and vulnerability to cognitive and emotional disorders. She has used rodent models and cutting-edge molecular, cellular, epigenetic, and imaging methods to further the understanding of the effects of early-life experience on normal brain function and the contributions of early-life adversity and seizures to neuropsychiatric disorders. Her discoveries have been translational, providing the foundation for an FDA-approved therapy, and for novel clinical imaging approaches. Baram is an internationally recognized leader in studies of cognitive consequences of early-life and 'modern-life' stress and the underlying mechanisms, work that has appeared in high-impact journals (Nature Reviews Neurosci; PNAS; Trends Neurosci; J Neurosci; Molec. Psychiat; H factor=80; google scholar). Baram has contributed to NIMH panels and Symposia, chaired the Developmental Brain Disorders NIH study section. Her international reputation has led to presentations in numerous national and international conferences. Baram has the experience and administrative skills for leading funded multi-investigator projects, including the current Conte Center, where cutting-edge human and animal model studies are conducted in harmony.

Baram has a passion and commitment to mentoring including several funded NIH K awardees. Baram's prior students, from diverse countries and backgrounds, are now contributing independently to academic neuroscience.

B. Positions and Employment

1985-1987 Asst Prof, Neurology, Neuro-oncology & Pediatrics; Univ Texas & MD Anderson, Houston
1987-1992 Asst Prof, Neurology & Pediatrics; Univ of Southern California / Childrens Hospital, Los Angeles
1992-1995 Associate Professor, Neurology & Pediatrics; USC and CHLA
1995- Professor, Pediatrics, Anatomy / Neurobiology, Neurology; University of California at Irvine (UCI)
2002- Founder and Director, UCI Epilepsy Research Center (EpiCenter)
2010- Professor, Physiology & Biophysics, UCI
2013- Director, Conte Center @ UCI

Selected Honors

1978-1980 Kennedy Memorial Postdoctoral Award (highest Weizmann Institute Graduate Award)

1988-1993 NINDS: Career Development Research Award (KO8)
1991 American Epilepsy Society Young Investigator Research Award
1995- Danette D. Shepard Endowed Chair in Neurological Sciences: UC Irvine
1999 Athalie Clarke Excellence in Research Award, University of California-Irvine
2003 **American Epilepsy Society (AES) Research Initiative Award**
2004-2006 Elected, AES Executive Board
2005 **Research Recognition Award in Basic Science, the premier Epilepsy Research honor**
2006 **National Institute of Health NINDS Javits Merit award**.
2009 Distinguished Award for Research in Epilepsy, Am. Soc. Pharmacol & Exp. Therap (ASPET)
2010 Mentorship Award; UCI Alumni Association
2011 Soriano Lectureship Award, American Neurological Association
2013 **Bernard Sachs Distinguished Award for Research, Child Neurology Society**
2015 Elected member, American College of Neuropsychopharmacology
2018 **Cotzias lectureship, highest research honor of the American Academy of Neurology**

Professional Leadership and Contributions (partial)

Chair and member NIH NIMH Study Section for Conte Center Review, 2013, 2015 (Chair), 2016
Chair, NIH-CSR Developmental Brain Disorders (DBD) study section (Fall 2011-2013)
Executive Board, Hewitt Foundation for Biomedical Research 2014-
Chair, Executive Board of Trustees, American Epilepsy Lennox & Lombroso Research Trust (2010-)
NIH-NINDS Neuroscience (NST) study section, member (1998-2002)
NIH CSR and DoD Study Sections, ad hoc Member DBD, NNB, SRB-M, CNNT-SEP, others
Executive Board, American Epilepsy Society: (2004-2006);
Scientific Advisory Board, Epilepsy Foundation of America (2001-2015); Research Council (2006-2010)
Child Neurology Society committees: Science; Membership Chair, 93-95; Strategic Planning, 2008-2010

Editorial Boards (Current, partial)

Associate Editor, Journal of Neuroscience-2014-
Reviewing Editor, eNeuro, 2014-;
Annals of Neurology, 2005-2015; Neurobiology of Stress, 2014-; Experimental Neurology, 2012-

C. Contributions to Science

1. Early-life experience and cognitive and emotional consequences

Focusing on the study of chronic, early-life adversity, which affects >50% of the world's children, we created a novel naturalistic model of limited nesting-bedding. This mouse/rat paradigm of simulated poverty leads to fragmented, unpredictable maternal care and profound stress in pups. This model has now been adopted by >100 labs around the world. The use of this paradigm enabled detection of progressive cognitive consequences, specifically defects in hippocampal structure and function.

a. Avishai-Eliner S, Brunson KL, Sandman CA, Baram TZ. 'Stressed out?' Or *in (utero*). **Trends Neurosci,** 2002;25:518-24. PMC2930786.
b. Brunson KL, Kramár E, Lin B, Chen Y, Colgin LL, Yanagihara TL, Lynch G, Baram TZ. Mechanisms of late-onset cognitive decline after early life stress. **J Neurosci**, 2005; 25:9328-38. PMC3100717
c. Ivy A, Rex C, Chen Y, Dubé C, Maras P, Grigoriadis D, Gall C, Lynch G, Baram TZ. Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve activation of CRH receptors. **J Neurosci**, 2010;30:13005-15. PMC2991143.
d. Davis EP, Stout SA, Molet J, Vegetabile B, Glynn LM, Sandman CA, Heins K, Stern H, Baram TZ. Exposure to unpredictable maternal sensory signals influences cognitive development across species. **PNAS**. 2017;114(39):10390-10395. PMC5625898.

By contrast, we found that 'enhanced' early life experiences, via augmented maternal care and its predictability led to synaptic rewiring of stress-sensing hypothalamic neurons, reduced excitatory input to them and a resulting epigenetic 'reprogramming of gene expression patterns, mediated in part by the transcriptional repressor NRSF/REST.

a. Fenoglio KA, Chen Y, Baram TZ. Neuroplasticity of the hypothalamic-pituitary-adrenal (HPA) axis early in life requires recurrent recruitment of stress-regulating brain regions. **J Neurosci**. 2006;26:2434-42. PMC2408688.
b. Koorosi A, Shanabrough M, McClelland S, Liu ZW, Borok E, Gao XB, Horvath TL, Baram TZ. Early-life experience reduces excitation to stress-responsive hypothalamic neurons and re-programs the expression of corticotropin releasing hormone. **J Neurosci**. 2010;30:703-13. PMC2822406.
c. Singh-Taylor A, Molet J Jian S, Korosi A, Bolton JL, Noam Y, Simeone K, Cope J Chen Y, Mortazavi A, Baram TZ. NRSF-dependent epigenetic mechanisms contribute to programming of stress-sensitive neurons by neonatal experience, promoting resilience. **Molec Psychiat.** 2018;23:648-657. (IF= 15) PMC5503824.

2. Stress neurobiology is highly orchestrated by multiple local and global mediators

Most of the world's literature on stress and its profound effects on the brain has centered on the role of steroid hormones released by the adrenal gland. We reasoned that stress is a crucial biological phenomenon that permits adaptation of a changing environment. These changes promoted by stress take place at specific brain regions (e.g., hippocampus, amygdala), to alter cognitive or emotional response. They occur at timescales from millisecond to decades. These fine-tuned effects require multiple and local mediators. We established the presence of CRH and its receptors in hippocampus, showed that the peptide is released by stress. We demonstrated a role for the peptide in stress-induced memory deficits both acutely and after early-life stress. We are now working on the concerted interactive integrated effects of steroids and CRH.

a. Chen Y, Molet J, Lauterborn JC, Trieu BH, Bolton JL, Patterson KP, Gall CM, Lynch G, Baram TZ. Converging, synergistic actions of multiple stress hormones mediate enduring memory impairments after acute simultaneous stresses. **J Neurosci**, 2016; 36:11295-11307. PMC5148245
b. Joëls M, Baram TZ. The Neuro-symphony of Stress. **Nature Reviews Neuroscience.** 2009;10:459-66. PMC2844123.
c. Chen Y, Dubé C, Rice CJ, Baram TZ. Rapid loss of dendritic spines after stress involves derangement of spine dynamics by corticotropin-releasing hormone. **J Neurosci.** 2008;28:2903-11. PMC2409370
d. Maras PM, Molet J, Chen Y, Rice C, Ji SG, Solodkin A, Baram TZ. Preferential loss of dorsal-hippocampus synapses underlies memory impairments provoked by short, multimodal stress. **Mol Psychiatry**. 2014;19:811-22. PMC4074447

3. Stress and epilepsy throughout life

My single clinical study to date is a blinded comparison of high-dose ACTH and Prednisone for the therapy of infantile spasms, a devastating form of epilepsy in infants. ACTH in very high doses was highly efficacious (85-87%), and superior to lower dose ACTH and steroids. This study was the basis of FDA approval of ACTH for the treatment of IS. Embarking on understanding the basis of the efficacy of high dose ACTH for epilepsy using animal models, we found direct non-adrenal mediated actions of this stress hormone on the brain. Specifically, ACTH repressed the expression of the proconvulsant stress-activated peptide CRH in amygdala, a seizure-sensitive brain region. Our finding support the idea that the many different early-life insults that lead to IS do so by activating the brain's stress system including upregulation of CRH expression. ACTH reduces brain hyperexcitability and suppresses IS by repressing CRH levels. The hypothesis predicts that experimentally provoked early-life stress will cause IS and epilepsy, and this was recently found (2015).

a. Gunn BG, Baram TZ. Stress and Seizures: Space, Time and Hippocampal Circuits. **Trends Neurosci**. 2017; 40:667-679. PMC5660662
b. Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. **Pediatrics.** 1996:97:375-9. PMC3100715
This study is the basis of FDA approval for high-dose ACTH for infant epilepsy.
c. Baram TZ, Hatalski CG. Neuropeptide-mediated excitability: A key triggering mechanism for seizure generation in the developing brain. **Trends Neurosci.** 1998; 21:471-76. PMC3372323
d. Brunson KL, Khan N, Eghbal-Ahmadi, Baram TZ. ACTH acts directly on amygdala neurons to down-regulate corticotropin releasing hormone gene expression. **Ann Neurol**. 2001;49:304-13. PMC2849730.

4. Developmental epilepsies, including febrile seizures: mechanisms and consequences

We have focused on understanding developmental seizures including febrile seizures and their contribution to epilepsy, especially limbic (temporal lobe) epilepsy. We devised a successful model for long febrile seizures (febrile status epilepticus; FSE), and established the role of inflammatory cytokines in the generation of these seizures. We found that FSE is sufficient to generate epilepsy that highly resembles human TLE. We have uncovered the sequence of molecular and cellular events incited by the intense bout of neuronal activity (FSE) and leading to transcriptional and long-lasting epigenetic changes in the expression of crucial neuronal genes. These in turn, result in abnormal neuronal behavior and the formation of epileptic networks. We employed a 'marker gene' approach, teasing out the regulation of the HCN channels by epilepsy-inducing insults. We discovered a protean role for the neuronal transcriptional factor NRSF in orchestrating the large-scale changes in neuronal genes that lead to 'epileptic' neurons. More recently we have uncovered a non-invasive predictive surrogate marker on MRI that discriminates individuals that develop epilepsy after FSE from those that do not. We hope to take this marker to clinical studies.

a. Chen K, Baram TZ, Soltesz I. Febrile Seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits. **Nature Medicine.**, 1999;5:888-94. PMC3382971
b. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. **Nat Rev Neurol.** 2011;7:31-40.PMC3378051.
c. Brennan GP, Dey D, Chen Y, Patterson KP, Magnetta E, Hall AM, Dube CM, Mei Y-T, Baram TZ. Dual and opposing roles of microRNA-124 in the generation of epilepsy are mediated through inflammatory and NRSF-dependent gene networks. **Cell Reports.** 2016;14:2402-12. PMC4794429
d. Patterson KP, Barry JM, Curran MM, Singh-Taylor A, Brennan G, Rismanchi N, Page M, Noam Y, Holmes GL, Baram TZ. Enduring memory impairments provoked by developmental febrile seizures are mediated by functional and structural effects of neuronal restrictive silencing factor. **J Neurosci.** 2017;37:3799-3812. PMC5394897

Complete List of Published Work in MyBibliography
http://www.ncbi.nlm.nih.gov/sites/myncbi/tallie.baram.1/bibliography/40339658/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Active Research Support

NIH NIMH P50 MH 096889 (Conte center; PI: Baram) 06/17/2013 - 04/30/2019
Fragmented early life environment and emotional / cognitive vulnerabilities (NCE)

NIH NINDS, R01 NS35439, (PI: Baram) (Javits merit award renewed as RO1) 04/01/1997 - 07/31/2019
Epileptogenesis following FSE: mechanisms, biomarkers, prevention

NIH NINDS T32 NS 45540: (Baram, PI) 07/01/2003 - 06/30/2019
Training grant for pre/post-doctoral fellows focused on Epilepsy Research

NIH NIMH R01 MH 73136 (PI: Baram) 12/01/1999 - 05/31/2021
Effects of Early-life experience: Role of CRH

NIH NINDS RO1 NS108296 (MPI Holmes, Baram) (Pending; received 4%) 07/012018 - 6/30/ 2023
Cognitive deficits after early-life seizures: Neurobiology & Biomarkers

Mentor: (Current / recent funded grants):
D. Bota, MD, PhD: K08. Jack Lin, MD: K23. Katelin Patterson, EFA Predoctoral award;
Gary Brennan, PhD, Jessica Bolton, PhD, Hewitt Postdoctoral fellowship.

Completed Research Support

NIH NINDS NS 78279 (R01, Multiple PIs: Holmes & Baram) 07/01/2011 -06/30/ 2017
Cognitive deficits after experimental febrile seizures: neurobiology & biomarkers

NIH NINDS NS 28912 (R01, PI: Baram) 03/01/1992 – 06/30/2015
CRH in stress-induced hippocampus neuroplasticity

NIH NINDS P20 NS 80185 (PI: McNamara, Baram, investigator) 09/30/2012 – 06/302015
Prevention of Temporal Lobe Epilepsy

NIH NINDS P01 NS 45260 (Gall CM, PI, Baram, Project 4) 10/01/2011 - 08/31/2016
BDNF and Spine-Related Disorders of Memory and Cognition