

BIOGRAPHICAL SKETCH

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NAME: Lewis, Alan

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

POSITION TITLE: Assistant Professor

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
University of Pennsylvania, Philadelphia, PA	BA	05/2005	Chemistry
Northwestern University Feinberg School of Medicine, Chicago, IL	PHD	12/2010	Neuroscience
Northwestern University Feinberg School of Medicine, Chicago, IL	MD	05/2012	Medicine
Yale University School of Medicine, New Haven, CT	Resident	06/2016	Psychiatry
Yale University School of Medicine, New Haven, CT	Fellow	04/2018	Neuroscience research, Picciotto Lab

A. Personal Statement

I am a neuroscientist and board-certified psychiatrist. The goal of our research is to use model systems to develop a mechanistic understanding of molecular and circuit abnormalities observed in humans with schizophrenia, autism, and related neurodevelopmental disorders. Our research focus is on circuitry of the hippocampus and dentate gyrus. We are interested in how information transmission along the hippocampal longitudinal axis influences learning, memory, and social behaviors. To this end, we are focused on how long-distance projections from mossy cells in the ventral dentate gyrus interact with cortical inputs to influence spatial memory encoding and novelty signaling. Because ventral hippocampal hyperactivity is detected in patients with disorders of neural development and in animal models, these studies may help identify how ventral hyperactivity can contribute to cognitive dysfunction. We ultimately hope to integrate these basic neuroscientific studies with other levels of information using data from human genetics, behavior, and clinical psychopharmacology to develop novel treatments to improve function and quality of life for people with neurodevelopmental disorders.

1. Kim A, Rader SL, Fernandez TV, Vandekar SN, **Lewis AS** (2020) Leveraging aggression risk gene expression in the developing and adult human brain to guide future precision interventions. **Molecular Psychiatry**. In press. PubMed PMID: [33046832](#).
2. **Lewis AS**, Pittenger ST, Mineur YS, Stout D, Smith PH, Picciotto MR. Bidirectional Regulation of Aggression in Mice by Hippocampal Alpha-7 Nicotinic Acetylcholine Receptors. **Neuropsychopharmacology**. 2018 May;43(6):1267-1275. PubMed PMID: [29114104](#); PubMed Central PMCID: [PMC5916354](#).
3. **Lewis AS**, van Schalkwyk GI, Lopez MO, Volkmar FR, Picciotto MR, Sukhodolsky DG. An Exploratory Trial of Transdermal Nicotine for Aggression and Irritability in Adults with Autism Spectrum Disorder. **J Autism Dev Disord**. 2018 Aug;48(8):2748-2757. PubMed PMID: [29536216](#); PubMed Central PMCID: [PMC6394231](#).

4. Roeske MJ, Konradi C, Heckers S, **Lewis AS**. Hippocampal volume and hippocampal neuron density, number and size in schizophrenia: a systematic review and meta-analysis of postmortem studies. **Mol Psychiatry**. 2020 Jul 28;PubMed PMID: [32724199](https://pubmed.ncbi.nlm.nih.gov/32724199/).

B. Positions and Honors

Positions and Employment

- 2012 - 2016 Resident Physician in Psychiatry, Department of Psychiatry, Yale School of Medicine, New Haven, CT
- 2015 - 2016 Chief Resident, Clinical Neurosciences Research Unit, Department of Psychiatry, Yale School of Medicine, New Haven, CT
- 2015 - 2017 Chief Resident, Neuroscience Research Training Program, Department of Psychiatry, Yale School of Medicine, New Haven, CT
- 2016 - 2018 Neuroscience Research Training Program Research Fellow, Department of Psychiatry, Yale School of Medicine, New Haven, CT
- 2017 - 2018 Lecturer in Psychiatry, Department of Psychiatry, Yale School of Medicine, New Haven, CT
- 2018 - 2018 Instructor in Psychiatry, Department of Psychiatry, Yale School of Medicine, New Haven, CT
- 2018 - Assistant Professor, Departments of Psychiatry and Behavioral Sciences and Neurology (secondary), Vanderbilt University Medical Center, Nashville, TN
- 2018 - Investigator, Vanderbilt Kennedy Center, Vanderbilt University Medical Center, Nashville, TN
- 2018 - Member, Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN
- 2018 - Training Faculty, Vanderbilt Brain Institute, Vanderbilt University, Nashville, TN

Other Experience and Professional Memberships

- 2008 - Member, Society for Neuroscience
- 2010 - Ad hoc reviewer: *Schizophrenia Research*, *Neuroscience Letters*, *Journal of Neurophysiology*, *Journal of Autism and Developmental Disorders*, *The Primary Care Companion for CNS Disorders*, *Journal of Child and Adolescent Psychopharmacology*, *Psychopharmacology*, *Frontiers in Molecular Neuroscience*, *Cognitive and Behavioral Neurology*, *SAGE Open Medical Case Reports*, *Behavioral Brain Research*, *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *World Journal of Biological Psychiatry*, *European Journal of Neuroscience*
- 2011 - Member, American Psychiatric Association
- 2012 - 2018 Member, Connecticut Psychiatric Society and Connecticut State Medical Society
- 2014 - 2018 Connecticut medical license number 53231
- 2016 - Diplomate in Psychiatry, American Board of Psychiatry and Neurology
- 2018 - Tennessee medical license number 57846
- 2018 - Member, Society of Biological Psychiatry
- 2018 - Member, Elliot Newman Society, Vanderbilt University Medical Center
- 2019 - Editorial Board Member, *Journal of Autism and Developmental Disorders*
- 2020 - Member, Pavlovian Society; Member, International Society for Research on Aggression

Honors

- 2005 Phi Beta Kappa, University of Pennsylvania
- 2005 Summa cum laude, University of Pennsylvania
- 2009 Ruth L. Kirschstein National Research Service Award for Individual Predoctoral MD/PhD Fellows, NIH/NINDS
- 2009 Morton Heller Award for Exemplary Research, Northwestern University Medical Scientist Training Program
- 2010 Best oral presentation, Northwestern University Medical Scientist Training Program
- 2013 McNeil Research Award, Department of Psychiatry, Yale University School of Medicine
- 2014 Research Colloquium for Junior Investigators, American Psychiatric Association

2015	Meixner Postdoctoral Fellowship in Translational Research, Autism Speaks
2015	Travel Fellowship Award, Society of Biological Psychiatry
2015	Seymour L. Lustman Resident Research Award in Psychiatry, Department of Psychiatry, Yale University School of Medicine
2016	Laughlin Foundation Merit Award, Department of Psychiatry, Yale University School of Medicine
2017	Career Development Institute for Psychiatry, University of Pittsburgh, Stanford University, NIMH
2017	Travel Award, American College of Neuropsychopharmacology
2018	Annual Meeting Senior Researcher Award, American Academy of Child and Adolescent Psychiatry
2020	Young Physician Scientist Award, American Society for Clinical Investigation

C. Contributions to Science

1. Understand how voltage-gated ion channels in the hippocampus regulate behaviors relevant for learning, memory, and depression.

My doctoral research in the lab of Dr. Dane Chetkovich at Northwestern University sought to understand the mechanism underlying the distal dendritic enrichment of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel in hippocampal CA1 pyramidal neurons. The distribution of CA1 HCN channels and their biophysical properties play a key regulatory role in the output properties of neurons, which in turn contribute to aspects of learning and memory. I tested how an auxiliary subunit of HCN channels, called TRIP8b, contributed to HCN channel trafficking using biochemistry, molecular biology, and confocal and electron microscopy. In multiple publications, we reported that alternative splicing of TRIP8b differentially regulates HCN surface trafficking, that TRIP8b is necessary for distal dendritic enrichment of HCN in CA1, and that mice lacking TRIP8b show antidepressant-like behavior and impaired motor learning. These studies were generative of multiple collaborative projects at Northwestern, nationally, and internationally to further investigate the basic biology of HCN channels and understand their role in human disease. The interaction of HCN/TRIP8b remains an active area of study as a novel treatment target for depression.

- a. **Lewis AS**, Schwartz E, Chan CS, Noam Y, Shin M, Wadman WJ, Surmeier DJ, Baram TZ, Macdonald RL, Chetkovich DM. Alternatively spliced isoforms of TRIP8b differentially control h channel trafficking and function. **J Neurosci**. 2009 May 13;29(19):6250-65. PubMed PMID: [19439603](#); PubMed Central PMCID: [PMC2730639](#).
- b. **Lewis AS**, Vaidya SP, Blaiss CA, Liu Z, Stoub TR, Brager DH, Chen X, Bender RA, Estep CM, Popov AB, Kang CE, Van Veldhoven PP, Bayliss DA, Nicholson DA, Powell CM, Johnston D, Chetkovich DM. Deletion of the hyperpolarization-activated cyclic nucleotide-gated channel auxiliary subunit TRIP8b impairs hippocampal lh localization and function and promotes antidepressant behavior in mice. **J Neurosci**. 2011 May 18;31(20):7424-40. PubMed PMID: [21593326](#); PubMed Central PMCID: [PMC3169171](#).
- c. Bankston JR, Camp SS, DiMaio F, **Lewis AS**, Chetkovich DM, Zagotta WN. Structure and stoichiometry of an accessory subunit TRIP8b interaction with hyperpolarization-activated cyclic nucleotide-gated channels. **Proc Natl Acad Sci U S A**. 2012 May 15;109(20):7899-904. PubMed PMID: [22550182](#); PubMed Central PMCID: [PMC3356637](#).
- d. Chan CS, Glajch KE, Gertler TS, Guzman JN, Mercer JN, **Lewis AS**, Goldberg AB, Tkatch T, Shigemoto R, Fleming SM, Chetkovich DM, Osten P, Kita H, Surmeier DJ. HCN channelopathy in external globus pallidus neurons in models of Parkinson's disease. **Nat Neurosci**. 2011 Jan;14(1):85-92. PubMed PMID: [21076425](#); PubMed Central PMCID: [PMC3058391](#).

2. Understand hippocampal pharmacological and circuit basis of behaviors relevant to cognitive and social dysfunction in neuropsychiatric disorders.

As a psychiatry resident and postdoctoral research fellow in the lab of Dr. Marina Picciotto at Yale, I furthered my interest in studying the hippocampus, an area of concentration that originated from my doctoral studies. During my clinical work I was struck by the intersection between nicotine use, impulsivity, and even physical aggression in patients with schizophrenia. I was intrigued to find a large literature on nicotine's effects on social and aggressive behaviors, which we reviewed in several publications (Lewis and Picciotto, 2020; Picciotto et al. 2015). However, neither a detailed pharmacological nor neuronal basis of these effects was known. We studied this question in mouse models and found that $\alpha 7$ nicotinic acetylcholine receptors in the dentate gyrus bidirectionally influence offensive aggression, likely via effects on local inhibitory interneurons where $\alpha 7$ is strongly expressed. In other work, we developed a novel paradigm using olfactory conditioning to bias social approach toward a conspecific, which can be used in future mechanistic studies to explore the intersection of cognition and social neuroscience. Finally, we recently published the first large meta-analysis of postmortem studies in patients with schizophrenia showing striking lateralized reduction in hippocampal subfield volumes and neuron numbers. Together, these studies exemplify my commitment to both primary investigations of hippocampal physiology and its relationships to behavioral abnormalities in neuropsychiatric disorders, as well as quantitative analysis of human data that enable focused future mechanistic investigations in animal models.

- a. **Lewis AS**, Pittenger ST, Mineur YS, Stout D, Smith PH, Picciotto MR. Bidirectional Regulation of Aggression in Mice by Hippocampal Alpha-7 Nicotinic Acetylcholine Receptors. **Neuropsychopharmacology**. 2018 May;43(6):1267-1275. PubMed PMID: [29114104](#); PubMed Central PMCID: [PMC5916354](#).
- b. Chan J, Stout D, Pittenger ST, Picciotto MR, **Lewis AS**. Induction of reversible bidirectional social approach bias by olfactory conditioning in male mice. **Social Neuroscience**. 2020 Feb;15(1):25-35. PubMed PMID: [31303111](#); PubMed Central PMCID: [PMC6980898](#).
- c. Roeske MJ, Konradi C, Heckers S, **Lewis AS**. Hippocampal volume and hippocampal neuron density, number and size in schizophrenia: a systematic review and meta-analysis of postmortem studies. **Mol Psychiatry**. 2020 Jul 28;PubMed PMID: [32724199](#).

3. Bridge basic and clinical research of hippocampal mechanisms for learning, memory, and social behavior to investigate novel treatments in patients with schizophrenia or autism.

As a physician-scientist committed to translating basic research findings into novel treatment avenues, we built on our findings from animal models to test whether nicotinic agonists were a feasible, safe, and efficacious adjunct treatment for refractory aggression in young adults with severe autism spectrum disorder. We found in both a single case study and a pilot randomized, double blind, placebo-controlled crossover study (clinicaltrials.gov study NCT02552147) that transdermal nicotine was well tolerated and, in most patients, efficacious to reduce aggression and irritability. As developing new ways to improve function in patients with autism and schizophrenia is a major career focus, I have sought to understand the barriers to translating highly replicable animal model findings of cognitive and social behavioral effects into effective clinical treatments. I have approached this challenge using a variety of methods, including the use of large human genetic datasets and secondary analysis of clinical trials.

- a. Kim A, Rader SL, Fernandez TV, Vandekar SN, **Lewis AS** (2020) Leveraging aggression risk gene expression in the developing and adult human brain to guide future precision interventions. **Molecular Psychiatry**. In press.
- b. **Lewis AS**, van Schalkwyk GI, Lopez MO, Volkmar FR, Picciotto MR, Sukhodolsky DG. An Exploratory Trial of Transdermal Nicotine for Aggression and Irritability in Adults with Autism Spectrum Disorder. **J Autism Dev Disord**. 2018 Aug;48(8):2748-2757. PubMed PMID: [29536216](#); PubMed Central PMCID: [PMC6394231](#).
- c. **Lewis AS**, Olincy A, Buchanan RW, Kem WR, Picciotto MR, Freedman R. Effects of a nicotinic agonist on the Brief Psychiatric Rating Scale five-factor subscale model in schizophrenia. **Schizophr Res**. 2018 May;195:568-569. PubMed PMID: [29050790](#); PubMed Central PMCID: [PMC6476180](#).

