BIOGRAPHICAL SKETCH

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NAME: Lewis, Alan

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

POSITION TITLE: Assistant Professor of Psychiatry and Behavioral Sciences and Neurology

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)	END 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

A. Personal Statement

I am a neuroscientist and board-certified psychiatrist interested in understanding how neuropsychiatric disorders predispose to impaired forms of social interaction, especially impulsive aggressive behavior. Disruption of social behavior is observed in a wide variety of neurological conditions with genetic and acquired etiologies, including epilepsy, neurodevelopmental disorders, and traumatic brain injury. Social and behavioral aspects of these disorders are significant drivers of morbidity for patients, yet limited effective treatments exist. During my post-doctoral research at Yale University, I conducted both basic and translational research identifying the alpha-7 nicotinic acetylcholine receptor (nAChR) as a potential regulator of aggressive behavior through its effects on hippocampal excitatory/inhibitory balance. We found that transdermal nicotine, a pan-nicotinic agonist, reduced aggression and irritability in young adults with autism spectrum disorder in a double-blind, placebo controlled exploratory trial. Interestingly, alpha-7 nAChRs may represent a key biological node linking altered neuronal excitability with aberrant social behaviors, as demonstrated by the 15q13.3 microdeletion syndrome. This syndrome results from the deletion of a portion of chromosome 15, including *CHRNA7*, the gene coding for the alpha-7 nAChR, and patients with this condition demonstrate a heterogeneous phenotype frequently involving epilepsy and aggressive behaviors. Encouragingly, oral agents to selectively target the alpha-7 nAChR in previous trials to improve cognition in schizophrenia have been shown to be safe and highly tolerable in humans. These studies suggest such agents might be repurposed for alternative, mechanism-driven treatments. Future basic research objectives to understand the regulation of excitation/inhibition in the hippocampus and other limbic structures by alpha-7 nAChRs will lay the foundation to support clinical studies to test whether alpha-7 nAChR modulation might be beneficial for individuals with specific forms of epilepsy or impulsive aggressive behaviors.

1. 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.
2. 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.

3. Lewis AS, Mineur YS, Smith PH, Cahuzac ELM, Picciotto MR. Modulation of aggressive behavior in mice by nicotinic receptor subtypes. Biochem Pharmacol. 2015 Oct 15;97(4):488-497. PubMed PMID: 26212554; PubMed Central PMCID: PMC4600457.
4. Van Schalkwyk GI, Lewis AS, Qayyum Z, Koslosky K, Picciotto MR, Volkmar FR. Reduction of Aggressive Episodes After Repeated Transdermal Nicotine Administration in a Hospitalized Adolescent with Autism Spectrum Disorder. J Autism Dev Disord. 2015 Sep;45(9):3061-6. PubMed PMID: 25982311; PubMed Central PMCID: PMC4755349.

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, 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 - Member, Vanderbilt Kennedy Center, Vanderbilt University Medical Center, Nashville, TN

Other Experience and Professional Memberships

2008 - Member, Society for Neuroscience
2011 - Member, American Psychiatric Association
2012 - 2018 Member, Connecticut Psychiatric Society
2012 - 2018 Member, Connecticut State Medical Society
2016 - Diplomate in Psychiatry, American Board of Psychiatry and Neurology

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

C. Contribution to Science

1. **Understand the pharmacological basis of nicotine's serenic effects in animal models.**

   My interest in understanding the relationship between nicotine, tobacco, and impulsive aggression began from my clinical experiences at Yale. I was struck by the degree of irritability and even physical aggression demonstrated by some patients who were denied the opportunity to smoke cigarettes, even when their last cigarette was smoked only moments earlier. This led me to wonder whether nicotine had anti-aggressive, or "serenic" properties independent of nicotine withdrawal. I was intrigued to find in the literature that acute administration of purified nicotine was consistently serenic in animal models across diverse species, including humans. However, the nicotinic receptors mediating this effect and the brain regions involved were unknown, which I reasoned might serve to support future research to identify novel treatments for impulsive aggression. In Dr. Marina Picciotto's lab at Yale, I found that nicotine administration was serenic across multiple strains of mice. Antagonism of the α7 nicotinic acetylcholine receptor (nAChR), but not β2-containing nAChRs, blocked this effect, and the α7 partial agonist GTS-21/DMXB-A recapitulated nicotine's serenic effects. Finally, we identified α7nAChRs in the dentate gyrus of the hippocampus as both necessary and sufficient to limit aggression in mice. These data support the α7 nAChR as a critical target for reducing aggressive behavior, and serve as the mechanistic basis for future translational studies.

   a. Lewis AS, Mineur YS, Smith PH, Cahuzac ELM, Picciotto MR. Modulation of aggressive behavior in mice by nicotinic receptor subtypes. Biochem Pharmacol. 2015 Oct 15;97(4):488-497. PubMed PMID: 26212554; PubMed Central PMCID: PMC4600457.
   b. 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.
   c. Picciotto MR, Lewis AS, van Schalkwyk GI, Mineur YS. Mood and anxiety regulation by nicotinic acetylcholine receptors: A potential pathway to modulate aggression and related behavioral states. Neuropharmacology. 2015 Sep;96(Pt B):235-43. PubMed PMID: 25582289; PubMed Central PMCID: PMC4486625.

2. **Translate nicotinic receptor approaches to treat impulsive aggression into human clinical populations.**

   In collaboration with researchers and clinicians in the Department of Psychiatry and the Yale Child Study Center, we trialed transdermal nicotine as an adjunct treatment for a hospitalized adolescent male with severe autism and aggression refractory to pharmacological and non-pharmacological treatments after obtaining informed consent from his guardian. We found that transdermal nicotine reduced his need for chemical and physical restraints due to aggression without significant side effects and facilitated his discharge from the hospital. Similar results in other treatment-refractory patients inspired initiation of a pilot clinical trial to test transdermal nicotine in adults with autism and aggression (NCT02552147). This randomized, double blind, placebo-controlled crossover study enrolled seven subjects with severe autism and moderate levels of aggression, and found that transdermal nicotine use was feasible, well tolerated, and in a majority of patients efficacious to reduce aggression and irritability. The results of this pilot study, in conjunction with the preclinical studies described above, form the basis for future studies of the use of pharmacological agents with greater specificity for the a7 nAChR such as GTS-21, supported by K23 funding. Performing clinical studies based on preclinical mechanistic experiments to is a major career goal, and as such I have sought to understand the barriers to translating a7 nAChR agonists from rodent models into human treatments. I have approached this challenge recently using meta-analytic methods to compare the effect sizes of specific cognitive outcomes in clinical trials with those from rodent cognitive tasks. These studies identified important considerations for future translational endeavors, and illustrate my consistent

interest in translational research to identify novel treatment approaches for impulsive aggression arising within severe neuropsychiatric disorders.

a. 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.
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.
c. Lewis AS, van Schalkwyk GI, Bloch MH. Alpha-7 nicotinic agonists for cognitive deficits in neuropsychiatric disorders: A translational meta-analysis of rodent and human studies. Prog Neuropsychopharmacol Biol Psychiatry. 2017 Apr 3;75:45-53. PubMed PMID: 28065843; PubMed Central PMCID: PMC5446073.
d. Van Schalkwyk GI, Lewis AS, Qayyum Z, Koslosky K, Picciotto MR, Volkmar FR. Reduction of Aggressive Episodes After Repeated Transdermal Nicotine Administration in a Hospitalized Adolescent with Autism Spectrum Disorder. J Autism Dev Disord. 2015 Sep;45(9):3061-6. PubMed PMID: 25982311; PubMed Central PMCID: PMC4755349.

3. **Identify the role of the auxiliary subunit TRIP8b in HCN channel trafficking and function.**

My doctoral thesis research in the lab of Dr. Dane Chetkovich at Northwestern University sought to understand the mechanism underlying the striking distal dendritic enrichment of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel in hippocampal area 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. My research was inspired by previous findings that a protein called TRIP8b interacted and colocalized with HCN channels in vivo, however, the role of TRIP8b on channel trafficking was poorly understood. I designed, conducted, and analyzed experiments using techniques in biochemistry, molecular biology, and confocal and electron microscopy to demonstrate that the N-terminus of TRIP8b was highly alternatively spliced, with individual splice isoforms differentially regulating surface trafficking of HCN channels in hippocampal neurons. Furthermore, we demonstrated using TRIP8b knockout mice that TRIP8b was necessary for distal dendritic enrichment of HCN channels and that mice lacking TRIP8b demonstrated antidepressant-like behavior. Finally, we mapped the interaction sites between TRIP8b and HCN channels to dissociate TRIP8b's effects on HCN channel trafficking from its effects on HCN channel biophysical properties. These studies were generative of multiple collaborations at Northwestern, nationally, and internationally to further investigate the basic biology of HCN channels as well as understand their potential role in human disease. The Chetkovich Laboratory is currently investigating the interaction of HCN/TRIP8b as a novel treatment target for depression.

a. Han Y, Noam Y, Lewis AS, Gallagher JJ, Wadman WJ, Baram TZ, Chetkovich DM. Trafficking and gating of hyperpolarization-activated cyclic nucleotide-gated channels are regulated by interaction with tetratricopeptide repeat-containing Rab8b-interacting protein (TRIP8b) and cyclic AMP at distinct sites. J Biol Chem. 2011 Jun 10;286(23):20823-34. PubMed PMID: 21504900; PubMed Central PMCID: PMC3121500.
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 Ih 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. 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.

d. 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.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/alan.lewis.2/bibliography/42529213/public/

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

Ongoing Research Support

K23MH116339, NIH/NIMH
Lewis, Alan (PI)
04/13/18-04/01/23
A translational approach to understand hippocampal neural circuitry regulating impulsive aggression
This career development award will study both mice and humans to understand how the balance between excitation and inhibition in the hippocampus influences aggressive behavior, with the goal of developing more specific and effective therapeutic interventions that target neuronal circuits regulating aggression.
Role: PI

Completed Research Support

9699, Autism Speaks
Lewis, Alan (PI)
12/01/15-04/30/18
Nicotinic cholinergic modulation as a novel treatment strategy for aggression associated with autism
This Meixner Postdoctoral Fellowship in Translational Autism Research supports training and research experiences in both clinical and basic research related to aggression in autism. Research includes a pilot clinical trial to study transdermal nicotine to treat aggression in adults with autism, as well as preclinical studies to understand the anti-aggressive effects of nicotine in mouse models of aggression.
Role: PI

F30 NS064757-01
Lewis, Alan Seth (PI)
01/05/09-05/31/12
The Role of TRIP8b in Neuronal HCN Channel Trafficking
This F30 fellowship award supported my predoctoral work with Dr. Dane Chetkovich at Northwestern. This research identified how TRIP8b, an auxiliary subunit of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, regulates HCN channel trafficking and function in the hippocampus.
Role: PI