BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Jessica Jillian Walsh

eRA COMMONS USER NAME (credential, e.g., agency login): WALSH86

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
Columbia College of Columbia University, New York, New York	B.A.	05/2008	Neuroscience & Behavior
Icahn School of Medicine at Mount Sinai Medical Center, New York, New York	M.S.	05/2010	Biomedical Sciences
Icahn School of Medicine at Mount Sinai Medical Center, New York, New York	Ph.D.	08/2013	Neuroscience
Stanford University, Palo Alto, California	Postdoctoral	06/2021	Neuroscience

A. Personal Statement

The mission of my research program at the University of North Carolina at Chapel Hill is to elucidate the brain circuits and molecular mechanisms underlying motivated behavior. One of the major focuses is to understand how genetic mutations, as well as experience, lead to circuit adaptations that govern impaired behavior seen in mouse models for autism spectrum disorders (ASD). Utilizing a systems levels approach, I aim to: 1) model these disorders with well described genetic and environmental markers, 2) define causal relationships between activity within discrete anatomical structures in the brain that are critical to the physiology of the symptom under investigation (e.g. sociability), 3) perform deep characterization of the physiological profiles of these circuits and using that information, target specific receptors or molecules that may not have been considered for the treatment of specific ASD symptoms. My prior training has equipped me to pursue these topics and make me particularly well-suited for achieving these goals.

As an independent investigator, I aim to support and encourage inclusion and equality for all. I believe that if young women have role models with whom they can self-identify it will help them to see their own potential. Further, through both education and outreach, we can encourage individuals from a variety of backgrounds to pursue careers in STEM. I believe it is my responsibility, especially as a woman in science, to encourage others to push boundaries and provide platforms for them to succeed. Additionally, through outreach we may help fight stereotypes and bridge the gaps that exist between the scientific and lay communities.

I have had the distinct privilege to be mentored by many amazing neuroscientists. I began my career volunteering in Dr. Gerald Fischbach's laboratory when I was a high school student. More than simply learning many techniques, I began to understand how to develop hypotheses and ask scientific questions. I worked in Dr. Fischbach's laboratory throughout college. I began my master's degree at the Icahn School of Medicine at Mount Sinai, investigating changes in neuronal morphology in select brain regions implicated in Alzheimer's

disease through the use of a knockout mouse model. Following this, I pursued my PhD in Dr. Ming-Hu Han's laboratory investigating the circuitry underlying a mouse model for major depressive disorder. During my postdoctoral fellow, I built on my previous training combining optogenetics and behavior with transgenic mouse models for ASD and slice electrophysiology. These have allowed me to precisely identify a circuit and molecular mechanism important in social deficits present in a mouse model with a *16p11.2* deletion and extend these findings to demonstrate that enhanced 5-HT signaling is therapeutically efficacious across multiple mouse models for ASD.

Overall, my research aims to fill a critical gap in our knowledge of molecular, cellular and circuit level mechanisms within the brain underlying discrete behaviors both in normative and perturbed states. My goal and hope is that this research will help inform the development of novel, more targeted pharmacological interventions for members of vulnerable populations.

Ongoing and completed projects I would like to highlight include:

F32 MH 103949 Walsh (PI) 07/01/14-11/30/16
Systems level investigation of di-synaptic circuit involved in panic disorder (National Institute of Mental Health)
This project sought to employ a systems-level neurobiological strategy to parse out the specific sub-population of LH and A2 neurons that underlie anxiety-like behaviors. However, several challenges lead to unclear and inconsistent results, ultimately resulting in the unfeasibility of the proposed project. Therefore, I decided on an alternative approach that still addressed the neural circuit basis of behaviors that are of great relevance to mental illnesses, such as social deficits seen in autism spectrum disorder. The major goal of the proposal was to investigate the role of specific sub-population of DR neurons that underlie autism-like behaviors with a focus in social behaviors, in addition to parsing out the contribution of specific inputs and outputs to this brain region through both behavioral and physiological techniques.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

07/2021-present	Assistant Professor of Pharmacology, The University of North Carolina at Chapel Hill, Chapel Hill, NC
10/2013-06/2021	Postdoctoral Fellow of Neuroscience, Stanford University, Stanford, CA
08/2010-10/2013	Pre-doctoral Fellow of Neuroscience, Icahn School of Medicine at Mount Sinai Medical Center, New York City, NY
05/2010-08/2010	Research Coordinator in Department of Neuroscience, Icahn School of Medicine at Mount Sinai Medical Center, New York City, NY
05/2008-08/2008	Research Coordinator in Department of Pharmacology, Columbia University, New York City, NY

Academic and Professional Honors

2018	Sammy Kuo Award in Neuroscience (Stanford University), Best publication of the year authored by a Stanford postdoctoral fellow
2018	11th Annual Autism Spectrum Disorders Update, Scholarship, Stanford University
2016	FENS/IBRO-PERC Travel Grant, Copenhagen, Denmark
2014	Ruth L. Kirschstein National Research Award (F32), National Institute of Mental Health
2014	A.P. Giannini Foundation Postdoctoral Research Fellowship, Declined, San Francisco, California
2013	Society for Neuroscience, Organizer, Chair and Speaker of a Nanosymposium, San Diego, California
2012	Hausfeld Award in Neuroscience (Mount Sinai School of Medicine), Endowment award for the most outstanding senior graduate student
2012	Society for Neuroscience, Organizer, Chair and Speaker of a Nanosymposium, New Orleans, Louisiana
2012	Ruth L. Kirschstein National Research Award (F31), National Institute of Mental Health

2012 Mount Sinai School of Medicine Neuroscience Retreat, Speaker
2012 Travel Award, Society for Neuroscience Conference, New Orleans, Louisiana
2011 Travel Award, Society for Neuroscience Conference, Washington, D.C.
2011 SfN Travel Fellowship to IBRO World Congress, Florence, Italy
2011 First Place Poster Award at Mount Sinai Neuroscience Retreat
2010 Travel Award, International Conference on Alzheimer's Disease, ISTAART, Honolulu, Hawaii
2009 Second Place Poster Award at Mount Sinai Neuroscience Retreat
2007 The New York Academy of Science, 4th Annual President's Reception, Presenter

C. Contributions to Science

1. Investigation of the role of serotonin (5-HT) signaling in social behavior:
Social interactions are fundamental to survival. Dysfunction of the 5-HTnergic system has been long associated with deficits in sociability present in neurodevelopmental and psychiatric disorders. My research has found that enhanced 5-HT release in the nucleus accumbens (NAc) increases sociability, either pharmacologically with MDMA or via optogenetic stimulation. To examine the therapeutic potential of enhanced 5-HT, I utilized a *16p11.2* deletion mouse model for autism spectrum disorder (ASD), where selective deletion of the syntenic chromosomal region in 5-HT neurons decreases DR 5-HT neuronal activity and induces social deficits. These deficits were rescued by increasing 5-HT activity in the NAc. I next investigated if enhancing 5-HTergic tone in six etiologically distinct mouse models for ASD with distinct types of mutations, is sufficient to ameliorate social deficits. I found that systemic administration of MDMA acutely rescued social deficits in 4 models and that systemic administration of a specific 5-HT1b receptor agonist acutely normalized the behavioral profile of all 6 models. These findings suggest that robust enhancement of 5-HT or selectively targeting the 5-HT1b receptor might be more therapeutically efficacious in the treatment of social deficits present in ASD.

a. **Walsh JJ**, Christoffel DJ, Ben-Dor GA, Selimbeyoglu A, Taylor M, Hung LW, Deisseroth K, Malenka RC. (2018) 5-HT release in nucleus accumbens rescues social deficits in mouse autism model. *Nature*. 560. 589-594.
b. Heifets BD, Salgodo JS, Taylor MD, Hoerbelt P, Cardozo Pinto DF, **Walsh JJ**, Steinberg EE, Sze JY, Malenka RC. (2019) Distinct neural mechanisms for prosocial and rewarding properties of MDMA. *Science Translational Medicine.* 522. eaaw6435.
c. **Walsh JJ**, Llorach P, Cardozo Pinto DF, Wenderski W, Christoffel DJ, Salgodo JS, Heifets BD, Crabtree GR, Malenka RC. (2021) Systemic enhancement of serotonin signaling reverses social deficits in multiple mouse models for ASD. *Neuropsychopharmacology*. 46. 2000-2010.
d. **Walsh JJ**, Christoffel DJ, Wu X, Pomrenze M, Malenka RC. (2021) Dissecting neural mechanisms of prosocial behaviors. *Current opinion in neurobiology*. 68, 9-14.

2. Neural circuit mechanisms in the nucleus accumbens (NAc) that influence motivated behaviors:
The NAc is a primary hub of the circuitry regulating motivation for natural rewards, such as sociability as well as in impulse control disorders. To begin identifying the mechanism regulating enhanced sociability, I worked in collaboration with others to examine the effects of 5-HT and MDMA on excitatory synaptic transmission in the NAc and found that bath application of both 5-HT and MDMA elicits long-term depression (LTD) at specific excitatory NAc inputs. Additionally, activity of the medial prefrontal cortex is necessary for the prosocial effects of MDMA. Given that the consumption of palatable foods is highly rewarding, in a separate study, modulation of prefrontal cortex versus anterior paraventricular thalamus excitatory inputs to the NAc had opposing effects on high fat intake.

a. Christoffel DJ*, **Walsh JJ***, Hoerbelt P*, Heifets BD, Llorach P, Lopez RC, Ramakrishnan C, Deisseroth K, Malenka RC. (2021) Selective filtering of excitatory inputs to nucleus accumbens by dopamine and serotonin. *Proceedings of the National Academy of Sciences*. 118. e2106648118. *Co-first authors.
b. Christoffel DJ, **Walsh JJ**, Heifets BD, Hoerbelt P, Neuner S, Sun G, Ravikumar V K, Wu H, Halpern CH, Malenka RC. (2021) Input-specific modulation of murine nucleus accumbens differentially regulates hedonic feeding. *Nature Communications*. 12. 2135.

3. Molecular mechanisms and circuit function of midbrain dopamine (DA) neurons in social defeat stress:
I was one of the first to report on the contribution of DA neurons of the ventral tegmental area (VTA) that selectively project to the nucleus accumbens and prefrontal cortex to regulation of stress response. Specifically, I utilized the social defeat stress mouse model in combination with optogenetics to explore the neural circuit mechanisms underling susceptibility and resilience to this stress. These initial findings were followed up by examining the ionic mechanisms underlying the differential physiological properties of VTA DA neurons in these two phenotypes and identified the KCNQ channel as a critical mediator of the development of resilience to social defeat stress. Finally, I published a review on the role of the neurons in the VTA and their projections in a number of mood-related dysfunctions, including depression.

a. Chaudhury D*, **Walsh JJ***, Friedman AK, Juarez B, Ku SM, Koo JW, Ferguson D, Tsai HC, Pomeranz L, Christoffel DJ, Nectow AR, Ekstrand M, Domingos A, Mazei-Robison M, Mouzon E, Lobo MK, Neve RL, Russo SJ, Deisseroth K, Nestler EJ, and Han MH. (2013) Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature*. 493. 532-536. *Co-first authors
b. Friedman AK, **Walsh JJ**, Juarez B, Chaudhury C, Ku SM, Wang J, Li X, Dietz DM, Vialou VF, Neve RL, Yue Z, Deisseroth K, Han MH. (2014) Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. *Science*. 344. 313-319.
c. Friedman AK, Juarez B, Ku SM, Zhang H, **Walsh JJ**, Chaudhury C, Hawkins A, Zhang S, Calizo R, Dietz D, Murrough J, Ribadeneira M, Wong E, Neve R, Han MH. (2016) KCNQ channel openers reverse depressive symptoms via an active resilience mechanism. *Nature Communication*. 7. 11671-11678.
d. **Walsh JJ***, Han MH. (2014) The heterogeneity of ventral tegmental area neurons: projection functions in a mood-related context. *Neuroscience*. 282C. 101-108.

4. BDNF mechanisms in midbrain dopamine (DA) neurons and social defeat stress:
After establishing the critical importance of VTA DA to NAc circuit in the development of susceptibility, I sought to understand the specific molecular underpinnings of this development. I utilized optogenetic and viral-mediated gene transfer approaches, in combination with molecular techniques and found that phasic activation of the neurons in this pathway increased BDNF levels in the NAc, which was blocked by knocking down BDNF in the projection and was dependent on the context of stress. Follow up studies identified BDNF, but not DA as the mediator of the depressive symptoms seen in the social defeat model.

a. **Walsh JJ***, Friedman AK, Sun H, Ku SM, Heller EA, Juarez B, Burnham VL, Mazei-Robison MS, Ferguson D, Golden SA, Koo JW, Chaudhury D, Christoffel DJ, Pomeranz L, Friedman JM, Russo SJ, Nestler EJ, Han MH. (2014) Stress and CRF gate neural activation of BDNF in the mesolimbic reward pathway. *Nature Neuroscience*. 17. 27-29.
b. Wook Koo J, Labonté B, Engmann O, Calipari ES, Juarez B, Lorsch Z, **Walsh JJ**, Friedman AK, Yorgason JT, Han MH, Nestler EJ. (2016) Essential Role of Mesolimbic Brain-Derived Neurotrophic Factor in Chronic Social Stress-Induced Depressive Behaviors. *Biological Psychiatry*. 80. 469-478.

5. Optogenetic modulation of projection-specific pathways in social behavior
In addition to the conceptual findings of DA neuron function in social defeat, I played a critical role in the development of techniques to identify projection specific neuronal populations. I published two protocol papers detailing these techniques, as well as being an important collaborator in future studies examining projection-specific circuits in social behavior.

a. **Walsh JJ***, AK Friedman*, Chaudhury D*, Juarez B, Ku SM, and Han MH. (2012). Injection of Retrograde Beads into the Nucleus Accumbens (NAc) and Medial Prefrontal Cortex (mPFC) to Isolate Projection-Specific Neurons in the Ventral Tegmental Area (VTA). *Protocol Exchange* DOI:10.1038/protex.2012.050
b. **Walsh JJ***, Chaudhury D*, Friedman AK, Juarez B, Ku SM, Lobo MK, and Han MH. (2012). Optogenetic Manipulation of Ventral Tegmental Area (VTA) Neurons that project to the Nucleus Accumbens (NAc) and medial Prefrontal Cortex (mPFC). *Protocol Exchange* DOI:10.1038/protex.2012.049
c. Golden SA, Heshmati M, Flanigan M, Christoffel DJ, Guise K, Pfau ML, Aleyasin H, Menard C, Zhang H, Hodes GE, Bregman D, Khibnik L, Tai J, Rebusi N, Krawitz B, Chaudhury D, **Walsh JJ**, Han MH,

Shapiro ML, Russo SJ. (2016) Basal forebrain projections to the lateral habenula modulate aggression reward. *Nature*. 534. 688-692.

d. Christoffel DJ, Golden S, **Walsh JJ**, Guise KG, Heshmati M, Friedman AK, Dey A, Smith M, Rebusi N, Pfau M, Ables J, Aleyasin H, Khibnik LA, Hodes G, Ben-Dor GA, Deisseroth K, Shapiro ML, Malenka RC, Tallon-Ibanez I, Han MH, Russo SJ. (2015) Excitatory transmission at thalamo-striatal synapses mediates susceptibility to social stress. *Nature Neuroscience*. 18. 962-964.

A complete list of my publications: https://www.ncbi.nlm.nih.gov/myncbi/jessica.walsh.1/bibliography/public/