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: Benjamin Thomas Saunders

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

POSITION TITLE: Assistant Professor, University of Minnesota

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
West Virginia University	BS, BS	06/2007	Psychology, Biology
University of Michigan	PhD	06/2013	Biopsychology
Ernest Gallo Clinic and Research Center	Postdoc	2013	Behav. Neuroscience
University of California, San Francisco	Postdoc	2013-2014	Behav. Neuroscience
Johns Hopkins University	Postdoc	2015-2018	Behav. Neuroscience

A. Personal Statement

I am trained in biopsychology and behavioral and systems neuroscience, with an interest in the neurobiology of learning, motivation, and movement. I employ state-of-the-art neuroscience tools for circuit dissection and manipulation, coupled with sophisticated rodent behavior models. As a graduate student at the University of Michigan working with Terry Robinson, I investigated striatal mechanisms underlying trait variation in rodents as predictive indicators of drug seeking and relapse vulnerability in response to cues, using a variety of drug-seeking models. In my work as a postdoctoral fellow at the University of California, San Francisco and Johns Hopkins University, working with Patricia Janak, I employed *in vivo* optogenetics, fiber photometry, and deep brain calcium imaging methods to investigate functional and anatomical heterogeneity in mesostriatal circuits in Pavlovian reward processes. *As an early-stage investigator, I have an established record of integrating quantitative behavioral analysis approaches with powerful neuroscience tools for neural circuit dissection, a history of funding from NIH and private sources, and a productive publication record (23 works).* As an Assistant Professor, the goal of my research program is to produce innovative, translationally relevant research revealing how brain circuits orchestrate behavioral patterns in adaptive and maladaptive reward seeking and motor control, with the hope of identifying targets at the psychological, cellular, and neural circuit levels for intervention in psychiatric and neurological disease. I supervise a talented team of senior staff, graduate students, and research assistants. As a member of the Department of Neuroscience and Medical Discovery Team on Addiction at the University of Minnesota, my lab is positioned within an exceptional research environment, including a large number of new and established investigators using genetic, optical, and deep learning methods for *in vivo* neural activity and behavioral analyses, who further support my team and offer opportunities for powerful multidisciplinary collaborations.

Ongoing and completed projects I would like to highlight:

Active:
R01 MH129370
Saunders (PI)
12/01/2022 – 11/30/2027
Functional architecture of striatal networks in cue-reward learning

R01 MH129320

Saunders (MPI)
09/15/2022 – 07/30/2027
Circuit-level neurodevelopmental of decision-making computations across adolescence

Completed:
<u>R00 DA042895</u>
Saunders (PI)
08/01/2018 – 07/30/2022
Midbrain cellular and circuit dynamics of cocaine seeking

<u>NARSAD Young Investigator Award</u>
Saunders (PI)
01/01/2016 – 12/31/2017
Midbrain circuit dynamics of compulsive drug seeking and relapse

Relevant citations:

1. Engel L, Wolff AR, Blake M, Collins VL, Sinha S, & **Saunders BT**. VTA dopamine neurons engage spatiotemporally heterogenous striatal dopamine signals during learning. *bioRxiv,* 2023.07.01.547331: doi: https://doi.org/10.1101/2023.07.01.547331 (Under Review)
2. Collins V, Bornhoft KN, Wolff A, Sinha S, & **Saunders BT**. (2023). Hierarchical cue control of cocaine seeking in the face of cost. *Psychopharmacology,* 240(3), 461-476. PMCID: PMC10131580.
3. **Saunders BT**, Richard JM, Margolis EB, & Janak PH. (2018). Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties. *Nature Neuroscience*, 21(8), 1072-1083. PMCID: PMC6082399
4. **Saunders BT** & Robinson TE. (2012). The role of dopamine in the accumbens core in the performance of Pavlovian-conditioned responses. *European Journal of Neuroscience*, 36, 2521-2532. PMCID: PMC3424374

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2018-	Assistant Professor, Department of Neuroscience, University of Minnesota
2015-2018	Postdoctoral Fellow in Patricia Janak's laboratory, Johns Hopkins University
2013-2014	Postdoctoral Fellow in Patricia Janak's laboratory, University of California-San Francisco
2013	Postdoctoral Scholar in Patricia Janak's laboratory, Ernest Gallo Clinic and Research Center
2009-2011	Graduate Student Instructor, Department of Psychology, University of Michigan
2007-2013	Graduate Student in Terry Robinson's laboratory, University of Michigan
2005-2007	Undergraduate Research, West Virginia University

Honors

2021	Medical Discovery Team on Addiction Pilot Grant, University of Minnesota
2017	NIDA Pathway to Independence Award (K99/R00 DA042895)
2015	American College of Neuropsychopharmacology (ACNP) Travel Award
2015	NARSAD Young Investigator Award
2014	NIDA National Research Service Award Postdoctoral Fellowship (F32 DA036996)
2013	Winter Conference on Brain Research Travel Award
2013	Wyvell Award for Outstanding Dissertation in Biopsychology, University of Michigan
2011	NIDA National Research Service Predoctoral Fellowship (F31 DA030801)
2011	Rackham Graduate School Research Grant, University of Michigan: 2011-2012
2010	Pat Gurin Distinguished Lecture Award, University of Michigan
2009	NIDA Early Career Investigators Travel Award
2008	NSF Graduate Research Fellowship Program *Honorable Mention*
2007	NIDA Predoctoral Training Grant (T31 DA007281)

2005   Howard Hughes Medical Institute Summer Research Fellowship

Selected Talks

2023   American College of Neuropsychopharmacology meeting, Tampa, FL
2023   Pavlovian Society, Austin, TX
2023   Brain Resiliency Workshop, Simon Fraser University, Vancouver, Canada
2022   Brain Imaging in the Bay Symposium, University of California-Berkeley, CA
2022   Dopamine 2022 Meeting, Montreal, CA
2019   Osaka University, Osaka, Japan
2019   Japanese Neuroscience Society, Niigata, Japan
2019   Winter Conference on Brain Research, Snowmass, CO
2018   Itasca Biological Research Station, MN
2017   Gordon Research Conference on Catecholamines, Newry, ME
2015   National Institute on Drug Abuse, Baltimore, MD
2015   Professional Development Workshop, Society for Neuroscience, Chicago, IL
2015   Catecholamines Gordon Research Seminar, Newry, ME
2015   Winter Conference on Brain Research, Big Sky, MO
2014   Professional Development Workshop, Society for Neuroscience, Washington, DC
2014   Winter Conference on Brain Research, Steamboat Springs, CO
2012   University of Michigan, Ann Arbor, MI
2011   University of California-San Francisco, Gallo Center

C. Contributions to Science

Complete list of published work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/benjamin.saunders.1/bibliography/public/

1. Establishing individual vulnerability traits for drug "craving" and relapse in animal models

Addiction is characterized by a persistent threat of relapse, which is often spurred by drug-associated cues. As a graduate student working with Terry Robinson, I explored individual variability in relapse vulnerability using a variety of rodent drug seeking models. Faced with a behavioral context where a Pavlovian conditioned stimulus (i.e., a lever) is physically separated from the location of the reward (i.e., sucrose) it predicts, different individuals will learn different conditioned responses in response to the stimulus. Some individuals (sign trackers) develop robust approach and interaction with the Pavlovian cue, while others (goal trackers) approach the location of reward delivery. I found that this variation in the extent to which individuals find food cues attractive predicts relapse vulnerability in a number of settings. For instance, sign trackers are more likely to reinstate drug seeking when given the opportunity to work for presentations of a discrete cocaine-associated cue, compared to goal trackers (**Saunders & Robinson, Biological Psychiatry, 2010**). Moreover, sign trackers work harder to receive injections of cocaine, and a priming injection of cocaine reinstates drug seeking to a greater degree in these individuals, compared to goal trackers (Saunders & Robinson, 2011). I also found, using a novel behavioral model of relapse, that presentations of a discrete cocaine-associated cue will spur relapse behavior in sign trackers, despite the fact that negative consequences (i.e., footshock) much be endured to make a drug-seeking action (**Saunders, Yager, & Robinson, Journal of Neuroscience, 2013**). These studies illustrate the powerful motivational control drug cues can acquire over behavior and suggest that there is considerable individual variation in the extent to which they do so. Interestingly, when contextual information, rather than discrete stimuli, governs drug seeking, I discovered that goal trackers exhibit greater relapse, compared to sign trackers (**Saunders et al., Neuropsychopharmacology, 2014**). This final result suggests that there are multiple types of relapse vulnerability, and therefore consideration of the specific predisposing factors different individuals have is an important component of treatment for addiction and related disorders. ***Together, my research in this area was among the first to establish a trait (attributing motivational value to reward cues) that predicts drug seeking and relapse behavior prior to any drug use.*** These studies have since been cited over 1000 times. They have been extended by a number of laboratories, and neurobiological and behavioral correlates of sign and goal tracking are now being investigated in the context of human addiction, demonstrating their translational impact.

In my own lab at the University of Minnesota, we are expanding investigation of individual differences in reward learning and addiction-related behaviors. Making use of an intermittent access cocaine self-administration paradigm, we have shown (**Collins et al., Psychopharmacology, 2022**) that there are extensive individual differences in the extent to which different rats develop binge-like cocaine intake. This variability is associated with future cost-sensitivity during drug seeking. Furthermore, we find individualized vulnerabilities to relapse, that reflect bias in responsivity to state-level drug availability information, versus proximal drug-associated cues. These results suggest broad, fundamental variability in the type of cue information rats use to drive drug-seeking behavior, and point to a complex treatment landscape featuring multiple trajectories of addiction vulnerability.

1. **Saunders BT** & Robinson TE. (2010). A cocaine cue acts as an incentive stimulus in some but not others: Implications for addiction. *Biological Psychiatry*, 67, 730-736. PMCID: PMC2849872
2. **Saunders BT** & Robinson TE. (2011). Individual variation in the motivational properties of cocaine. *Neuropsychopharmacology*, 36, 1668-1676. PMCID: PMC3138662
3. **Saunders BT,** Yager LM**,** & Robinson TE. (2013). Cue-evoked cocaine "craving": role of dopamine in the accumbens core. *Journal of Neuroscience*, 33, 13989-14000. PMCID: PMC3756749
4. Collins V, Bornhoft KN, Wolff A, Sinha S, & **Saunders BT**. (2023). Hierarchical cue control of cocaine seeking in the face of cost. *Psychopharmacology,* 240(3), 461-476. PMCID: PMC10131580.

2. Nucleus accumbens dopamine signaling in cue-triggered motivation

Dopamine systems have long been studied for their role in reward, but the specific contribution of dopamine to Pavlovian learning, motivation, and reinforcement remains a matter of ongoing debate. The question of dopamine's role in these processes is fundamental to understanding both adaptive and, in disorders like addiction, maladaptive reward seeking. As such, while a graduate student, in parallel with the research I described in (1), I investigated the role of nucleus accumbens dopamine in Pavlovian motivation and cue-evoked drug seeking, by exploiting the behavioral variation seen in sign and goal trackers. I found that attraction and approach to Pavlovian food cues (sign tracking) is dependent on dopamine signaling in the nucleus accumbens core, while conditioned approach to the location of food delivery predicted by a Pavlovian cue (goal tracking) is expressed independent of core dopamine signaling (**Saunders & Robinson, 2012**). In a complementary finding, I discovered that dopamine signaling in the accumbens core was both necessary for the expression, and sufficient for the enhancement of cue-evoked motivation to relapse in the face of negative consequences (**Saunders, Yager, & Robinson, 2013**). ***Together, these results point to a critical role for nucleus accumbens dopamine in Pavlovian incentive motivation and drug "craving"; in particular, for the attribution and maintenance of incentive motivational value to reward-associated cues and suggest that individual variation in cue-spurred reward seeking is related to divergent dopamine function across individuals.*** My work in this area has generated a number of investigations into the dopamine system dynamics of Pavlovian learning and motivation. In the context of human drug addiction, my results suggest that dynamic fluctuations in dopamine signaling may drive powerful "craving"-like states that spur relapse when addicts encounter drug-related cues.

1. **Saunders BT** & Robinson TE. (2012). The role of dopamine in the accumbens core in the performance of Pavlovian-conditioned responses. *European Journal of Neuroscience*, 36, 2521-2532. PMCID: PMC3424374
2. **Saunders BT,** Yager LM**,** & Robinson TE. (2013). Cue-evoked cocaine "craving": role of dopamine in the accumbens core. *Journal of Neuroscience*, 33, 13989-14000. PMCID: PMC3756749
3. **Saunders BT** & Robinson TE. (2013)*.* Individual variation in resisting temptation: Implications for addiction. *Neuroscience and Biobehavioral Reviews*, 37, 1955-1975*.* PMCID: PMC3732519

3. Functional dissection of mesolimbic circuits in Pavlovian reward and reinforcement

As discussed in (2), dopamine systems play a complex role in reward. This is due in part to the anatomical, genetic, and physiological heterogeneity of dopamine neurons. Until recently, there was no feasible way to target manipulations to specific neuronal populations to isolate function. Joining Patricia Janak's laboratory as a postdoctoral fellow, my goal was to investigate functional heterogeneity in these systems in distinct reward processes. To this end, I employed state-of-the-art tools for circuit manipulation that allow for control of discrete

populations of genetically identified neurons in behaving animals (reviewed in **Saunders et al., 2015**). In one experiment conducted with my colleagues in the Janak laboratory, using optogenetics in transgenic Th-cre rats to selectively excite dopamine neurons at temporally precise intervals, we found that optogenetic stimulation of dopamine terminals specifically in the nucleus accumbens was sufficient to reinforce instrumental behavior (**Steinberg et al., 2014**). We also found that this reinforcement mechanism was dependent on coincident dopamine signaling from both D1- and D2-receptor expressing neurons in the nucleus accumbens. This finding built on classic literature that identified reinforcement circuitry using electrical stimulation of unidentified neuronal populations.

Moving past this finding and building on my interest in Pavlovian conditioned motivation described in (1) and (2), I observed that the majority of the studies of reward learning in neuroscience were focused on identifying functions for general populations of neurons, classed by their primary neurotransmitter content. In particular, dopamine research was dominated by a view that all populations of midbrain dopamine neurons more or less functioned the same in Pavlovian learning and reward seeking. I embarked on a project to interrogate this assumption, to assess functional heterogeneity in dopamine neuron function. This project led to a recent high-profile publication (**Saunders et al., Nature Neuroscience, 2018**) that _was the first to show_ systematic differences in the fundamental role of different dopamine neuron circuits, in the ventral tegmental area and substantia nigra, in Pavlovian cue conditioned behaviors, using fiber photometry and circuit-specific optogenetic methods. Optogenetic stimulation of dopamine neurons projecting to the nucleus accumbens core, but not the not nucleus accumbens shell or dorsal striatum, promote attraction and approach to associated cues, while stimulation of dorsal striatal projecting dopamine neurons promotes cue-evoked intense movement invigoration. **_These results are the first to demonstrate dopamine circuit-specific control of distinct components of Pavlovian learning and point to circuit-level "rules" by which distinct reward processes are orchestrated._** They challenge historical thinking about dopamine function and have a broad applicability to reward and movement neuroscience.

In my own lab, we have extended this work using dopamine biosensor recordings (**Engel, Wolff et al., 2023**), demonstrating the evolution of dopamine signals across striatal niches driven by dopamine neuron-mediated Pavlovian learning. In these studies, we show broad discussion in the fundamental prediction and reward-related information transmitted: dopamine signals in the nucleus accumbens core and the dorsomedial striatum are selectively engaged by Pavlovian cues and selectively sensitive to reward omission. Critically, despite the emergence of vigorous cue-evoked movement patterns late in learning, dorsal striatal dopamine signals do not develop, which stands in contrast to long-standing "ascending spiral" anatomical frameworks. **_Collectively this work deepens our understanding of functional heterogeneity in the dopamine system and motivates a reconceptualization of the functional architecture of striatal circuits._**

1. Poisson CL, Engel L, & **Saunders BT**. (2021). Dopamine circuit mechanisms of addiction-like behaviors. _Frontiers in Neural Circuits_, 15, 752420. PMCID: PMC8631198.
2. Collins AL & **Saunders BT**. (2020). Heterogeneity in striatal dopamine circuits: Form and function in dynamic reward seeking. _Journal of Neuroscience Methods_, 98, 1046-1069. PMCID: PMC7183907
3. **Saunders BT**, Richard JM, Margolis EB, & Janak PH. (2018). Dopamine neurons create Pavlovian conditioned stimuli with circuit-defined motivational properties. **_Nature Neuroscience_**, 21(8), 1072-1083. PMCID: PMC6082399
4. Engel L, Wolff AR, Blake M, Collins VL, Sinha S, & **Saunders BT**. VTA dopamine neurons engage spatiotemporally heterogenous striatal dopamine signals during learning. _bioRxiv,_ 2023.07.01.547331: doi: https://doi.org/10.1101/2023.07.01.547331