BIOGRAPHICAL SKETCH

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NAME: Downs, Anthony

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

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)	END DATE MM/YYYY	FIELD OF STUDY
Warren Wilson College, Swannanoa, North Carolina	BS	12/2012	Biology
Emory University, Atlanta, Georgia	PhD	01/2021	Pharmacology
University of North Carolina at Chapel Hill, Chapel Hill, North Carolina	Postdoctoral Fellow	10/2023	Neuropharmacology

A. Personal Statement

The overarching goal of my research is to investigate the neural circuitry that mediates stress, anxiety, and substance use disorder. I am particularly interested in investigating complex interactions and shared mechanisms between neuropsychiatric disorders, such as PTSD and Opioid Use Disorder. To accomplish these goals, I use mouse models and a combination of whole-cell electrophysiology, electrochemistry, viral strategies, immunohistochemistry, qPCR, and behavioral studies (avoidance, reward, opioid consumption and withdrawal) to study substance use disorder from genes to behavior. We recently developed a new model of oral fentanyl consumption in mice to model opioid use disorder. Studying the oral route of administration of fentanyl is especially important as the changing drug supply has changed how people administer unregulated fentanyl. We have found that long-term fentanyl consumption recapitulates many aspects associated with human opioid use disorder including withdrawal induced sleep disruptions and increased anxiety-like behaviors. We have also identified novel changes in fear extinction learning and basolateral amygdala physiology that may be relevant for understanding the link between opioid use disorder and other neuropsychiatric conditions like PTSD.

For my doctoral work, I studied the neurobiology of dystonia under the supervision of Dr. Ellen Hess at Emory University. I investigated deficits in striatal dopaminergic transmission in a mouse genetic model of DYT1 dystonia and found that the presence of the *TOR1A* mutation specifically in dopaminergic neurons was sufficient to reduce dopamine neurotransmission. I further investigated muscarinic antagonists as therapeutics for DYT1 dystonia and found that M4 muscarinic receptors on cholinergic interneurons were responsible for the dopamine-normalizing effects of muscarinic antagonists, such as trihexyphenidyl.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023 -	Assistant Professor, University of North Carolina at Chapel Hill, Chapel Hill, NC
2021 - 2023	Postdoctoral Research Fellow, University of North Carolina at Chapel Hill, Chapel Hill, NC
2015 - 2021	Graduate Student Researcher, Emory University, Atlanta, GA
2013 - 2015	Research Technician, East Tennessee State University, Johnson City, TN

Other Experience and Professional Memberships

Manuscript Review: *Neurobiology of Disease, Neuropharmacology, Journal of Pharmacology and Experimental Therapeutics, Neurobiology of Stress*

Honors

2025	Winter Conference on Brain Research Panel Travel Award
2017 - 2021	Predoctoral Individual National Research Service Award, NIH-NINDS
2016 - 2017	Pharmacological Sciences Training Grant, NIH-General Medical Sciences
2021 – 2023	Alcohol Studies Postdoctoral Training Grant, NIH-NIAAA

C. Contribution to Science

1. During my doctoral training, I studied defects in striatal dopamine neurotransmission in mouse models of dystonia. Mouse models of DYT1-TOR1A dystonia have significant reductions in striatal dopamine neurotransmission. While we did not find the precise mechanism for this reduction, we did find that the deficit in Dopamine release is due to the direct effects of the mutant TOR1A gene on midbrain dopamine neurons. Using a mouse model of DOPA-responsive dystonia, we uncovered changes in ERK signaling in both direct and indirect striatal projection neurons that underlie dystonia in this model.

    a. Roman KM, Briscione MA, Donsante Y, Ingram J, Fan X, Bernhard D, Campbell SA, Downs AM, Gutman D, Sardar TA, Bonno SQ, Sutcliffe DJ, Jinnah HA, Hess EJ. Striatal Subregion-selective Dysregulated Dopamine Receptor-mediated Intracellular Signaling in a Model of DOPA-responsive Dystonia. Neuroscience. 2023 May 1;517:37-49. PubMed Central PMCID: PMC10085842.

    b. Briscione MA, Dinasarapu AR, Bagchi P, Donsante Y, Roman KM, Downs AM, Fan X, Hoehner J, Jinnah HA, Hess EJ. Differential expression of striatal proteins in a mouse model of DOPA-responsive dystonia reveals shared mechanisms among dystonic disorders. Mol Genet Metab. 2021 Aug;133(4):352-361. PubMed Central PMCID: PMC8292208.

    c. Downs AM, Fan X, Kadakia RF, Donsante Y, Jinnah HA, Hess EJ. Cell-intrinsic effects of TorsinA(ΔE) disrupt dopamine release in a mouse model of TOR1A dystonia. Neurobiol Dis. 2021 Jul;155:105369. PubMed Central PMCID: PMC8327367.

2. One of the main therapeutics used to treat dystonia are muscarinic receptor antagonists. While these agents are effective, they are often poorly tolerated due to significant side effects. I investigated which muscarinic receptor subtypes mediate potential therapeutic mechanisms in a mouse model of DYT1-TOR1A dystonia, in the hope that this would lead to more specific therapeutics. I found that the non-selective muscarinic receptor antagonist normalizes striatal dopamine release in a mouse model of DYT1-TOR1A dystonia. Using a combination of newly developed subtype-specific muscarinic receptor antagonists and cell-type specific muscarinic receptor knockout mice, I determined that this dopamine enchanting effect was due to blockade of M4 muscarinic receptors on striatal cholinergic interneurons.

    a. Downs AM, Donsante Y, Jinnah HA, Hess EJ. Blockade of M4 muscarinic receptors on striatal cholinergic interneurons normalizes striatal dopamine release in a mouse model of TOR1A dystonia. Neurobiol Dis. 2022 Jun 15;168:105699. PubMed PMID: 35314320.

    b. Downs AM, Roman KM, Campbell SA, Pisani A, Hess EJ, Bonsi P. The neurobiological basis for novel experimental therapeutics in dystonia. Neurobiol Dis. 2019 Oct;130:104526. PubMed Central PMCID: PMC6885011.

    c. Downs AM, Fan X, Donsante C, Jinnah HA, Hess EJ. Trihexyphenidyl rescues the deficit in dopamine neurotransmission in a mouse model of DYT1 dystonia. Neurobiol Dis. 2019 May;125:115-122. PubMed Central PMCID: PMC6863078.

3. Epidemiological data suggests a link between life-long alcohol consumption and the later development of tauopathy disorders, including Alzheimer's disease and frontotemporal dementia. However, relatively little is known about interactions between alcohol and tauopathy in specific neuronal circuits. We investigated the effects of long-term intermittent access to alcohol on locus coeruleus function in the P301S mouse

model of tauopathy. We found significant changes to excitatory inputs to the LC following alcohol consumption, but this effect was absent in P301S mice. Alcohol consumption also enhanced excitability of locus coeruleus neurons, and this effect was enhanced in female P301S. Together this work demonstrates complex interactions between alcohol consumption, tau status, and sex on locus coeruleus function.

   a. **Downs AM, Catavero CM, Kasten MR, McElligott ZA. Tauopathy and alcohol consumption interact to alter locus coeruleus excitatory transmission and excitability in male and female mice. Alcohol. 2023 Mar;107:97-107. PubMed PMID: 36150608.**
   b. **Downs AM, Kmiec, G, Catavero, CM, McElligott ZA. Loss of excitatory inputs and decreased tonic and evoked activity of locus coeruleus neurons in aged P301S mice. *BioRxiv*. 2025. https://doi.org/10.1101/2025.01.17.63337**

4. Central noradrenergic signaling is known to play a significant role in multiple types of substance use disorder. Noradrenergic signaling modifies the rewarding properties of drugs, stress-induced reinstatement of drug seeking, and withdrawal states. Notably, drugs that reduce noradrenergic transmission are used clinically to reduce alcohol cravings and reduce the symptoms of both alcohol and opioid withdrawal. We hope to uncover changes in plasticity of noradrenergic neurons in the nucleus of the solitary tract, as this population has been implicated in both the rewarding properties and withdrawal symptoms of opioids. This could aid in the development of better therapeutics for opioid withdrawal.

   a. **Downs AM, McElligott ZA. Noradrenergic circuits and signaling in substance use disorders. Neuropharmacology. 2022 May 1;208:108997. PubMed Central PMCID: PMC9498225.**

5. The United States is experiencing an opioid epidemic due to the widespread availability of illicit fentanyl. Changes in the illicit drug supply has also changed how people choose to use drugs, and alternative routes of administration, like ingestion, have become more common. We have recently developed a mouse model of oral fentanyl consumption to model neurobiological and behavioral changes due to long-term fentanyl consumption. We found that fentanyl consumption increases anxiety-like behaviors. Fentanyl consumption also impaired normal fear extinction and enhanced basolateral amygdala neuron excitatory and inhibitory balance. Together this work begins to explore mechanisms by which long-term fentanyl use promotes anxiety-like and post-traumatic stress disorder-like behaviors in mice.

   a. **Downs, AM, Kmiec, G., McElligott, ZA. Oral fentanyl consumption impairs fear extinction learning and enhances basolateral amygdala excitatory/inhibitory balance in male and female mice. *Addiction Neuroscience. 2024.* 100182.**

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