## BIOGRAPHICAL SKETCH

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NAME: Joyce Besheer

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

POSITION TITLE: Professor of Psychiatry

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 |
|---|---|---|---|
| Indiana University, Bloomington, IN | B.S. | 12/1995 | Psychology |
| University of Nebraska, Lincoln, NE | M.A. | 5/1999 | Biopsychology |
| University of Nebraska, Lincoln, NE | Ph.D. | 5/2002 | Biopsychology |
| University of North Carolina, Chapel Hill, NC | Postdoctoral | 12/05 | Behavioral Pharmacology |

**A. Personal Statement**

Research in my laboratory is focused on understanding the neurobiology underlying behavioral pathologies of alcohol use disorder, with an emphasis on how stress impacts interoceptive and reinforcement processes. I have spent over 19 years examining the neurobiological mechanisms underlying alcohol self-administration, relapse-like behavior and sensitivity to the interoceptive effects of alcohol using drug discrimination methods and have extensive experience in these areas. In addition to my strengths in behavioral techniques, my lab also relies heavily on chemogenetic strategies, site-specific microinjections/viral injections, cannulae implantation to assess brain regional and circuitry regulation of behavior. We also utilize numerous molecular techniques such as immunohistochemistry, RT-PCR, western blot analyses, and microscopy to assess adaptive change in specific molecular targets. Together, these experiences have contributed to the multidisciplinary approach that I utilize in my projects.

I am committed to fostering a lab environment in which I can provide opportunities that will promote intellectual growth, confidence, independence, and promote diversity. I have a strong record of training postdoctoral, graduate, and undergraduate students and my lab regularly provides research opportunities for programs aimed at increasing diversity in science (i.e., PREP, SURF). My commitment to fostering a diverse scientific community and lab can also be demonstrated by my involvement at the university level. I am the Diversity Liaison for the Bowles Center for Alcohol Studies (BCAS) and the Chair of the BCAS DEI Committee. In the Department of Psychiatry, I also serve as a member on two DEI Committees. I am also heavily involved in leading science outreach programs as part of my role as an Investigator on the Information and Dissemination Component of the Bowles Center for Alcohol Studies P60 NIAAA grant.

**<u>Ongoing and recently completed projects that I would like to highlight include:</u>**

NIH/NIAAA R01AA028255 (MPI: Jin and Besheer) 10/1/2020 – 9/30/2023
Small molecule antagonist probes for the relaxin-3/RXFP3 system
The goal of this project is to develop compounds to target the relaxin-3 system and decrease alcohol drinking.
**Role: co-PI**

NIH/NINDS R01NS118563 (MPI: Linnstaedt and McLean) 10/1/2020 – 9/30/2025
*FKBP51 antagonism to prevent chronic pain: optimizing efficacy & evaluating safety and mechanisms*
This project will examine the therapeutic role of antagonizing FKBP51 for pain treatment.
**Role: Investigator**

NIH/NIAAA R01AA026820 (MPI: Jin and Kieffer) 9/1/18 – 8/31/23
*GPR88 Agonist for Alcoholism Treatment*
The goal of this project is to assess the efficacy of GPR88 compounds to reduce alcohol-related behaviors.
**Role: Investigator**

NIH/NIAAA P60 AA011605 (Kash) 12/1/22 – 11/30/27
*The contribution of neuronal and microglia proinflammatory signaling in insular cortex on escalated ethanol self-administration*
Component #2: The goal of this project is to examine the contribution of neuroimmune signaling to escalated alcohol self-administration, and the impact on molecular changes.
**Role: co-Project Lead with Dr. Leon Coleman**

NIH/NIAAA P60 AA011605 (Kash; Robinson/Faccidomo – Core PIs) 12/1/22 – 11/30/27
*Research Translation/Information Dissemination Component*
The function of this Core is 1) to disseminate information about alcohol abuse to healthcare professionals and 2) to reach out to youth/educators within the community to inform them of the dangers of alcohol misuse.
**Role: co-Investigator**

NIH/NIAAA R01AA026537 (Besheer) 9/12/17 – 9/30/22
*Characterization of alcohol self-administration following predator odor exposure: relevance to PTSD*
The goal of this project is to validate a preclinical model of PTSD and investigate the accompanying molecular and circuitry adaptations. **There is also a diversity supplement R01AA026537-S1 associated with this project.**
**Role: PI**

NIH/NIAAA R01AA024095 (MPI: Morrow and Besheer) 5/15/17 – 3/31/22
*Gene delivery of neuroactive steroids to modulate ethanol reinforcement/consumption*
The goal of this project is to examine the impact of the gene delivery of neuroactive steroids on alcohol self-administration and relapse-like drinking.
**Role: co-PI**

**<u>Completed Projects</u> (last 3 years)**
NIH/NIAAA P60 AA011605 (Kash; Robinson – Core PI) 12/1/17 – 11/30/22
*Research Translation/Information Dissemination Component*
The function of this Core is 1) to disseminate information about alcohol abuse to healthcare professionals and 2) to reach out to youth/educators within the community to inform them of the dangers of alcohol abuse.
**Role: Investigator**

NIH/NIAAA P60 AA011605 (Kash) 12/1/17 – 11/30/22
*Neuroimmune glutamatergic regulation of corticolimbic circuits in ethanol self-administration* - Component #2. There is also an Alzheimer's Disease supplement associated with this project.
**Role: Project Lead**

NIH/NIAAA R01AA025582 (MPI: Kash and Besheer) 9/1/16 – 8/31/22 (1 yr NCE)
*Unbiased analysis of molecular and circuit targets of low dose alcohol*
**Role: co-PI**

NIH/NIAAA R03AA026996 (MPI: Besheer and Parnell) 9/1/18 – 8/31/21 (1 year NCE)
*Consequences of prenatal alcohol and cannabinoid co-exposure on alcohol self-administration in adolescence*
**Role: co-PI**

NC TraCS 550KR211905 (Besheer and Blough) 7/1/19 – 2/1/21
*Developing anatabine analogs as novel therapeutics for alcohol use disorders*
**Role: co-PI**

R21DA039356 (Besheer and Bevins) 4/1/16 – 3/31/19 (1 yr NCE)
*Interplay between interoception, learning, and drug seeking*
**Role: co-PI**

**B. Positions, Scientific Appointments, and Honors**

**<u>Positions and Employment</u>**

| | |
|---|---|
| 10/2020-present | Professor, Department of Psychiatry, University of North Carolina-Chapel Hill |
| 2020-present | Associate Director for Translational Research Development, Bowles Center for Alcohol Studies, University of North Carolina-Chapel Hill |
| 2020-present | Chair, DEI Committee, Bowles Center for Alcohol Studies, University of North Carolina-Chapel Hill |
| 2020-present | Diversity Liaison, Bowles Center for Alcohol Studies, University of North Carolina-Chapel Hill |
| 2020-present | DEI Taskforce member, Department of Psychiatry, University of North Carolina-Chapel Hill |
| 2015-10/2020 | Associate Professor, Department of Psychiatry, University of North Carolina-Chapel Hill |
| 2017-present | Chair, Addiction Working Group UNC Department of Psychiatry |
| 2012-2015 | Assistant Professor, Department of Psychiatry, University of North Carolina-Chapel Hill |
| 2005-2012 | Research Assistant Professor, Department of Psychiatry, University of North Carolina-Chapel Hill |
| 2002-2005 | Postdoctoral Research Associate, University of North Carolina-Chapel Hill, Bowles Center for Alcohol Studies, Supervising P.I. - Dr. Clyde Hodge |
| 1997-2002 | Graduate Research Assistant, University of Nebraska-Lincoln<br>Department of Psychology, Supervising P.I. - Dr. Rick Bevins |
| 1996-1997 | Research Assistant, Indiana University-Bloomington<br>Department of Psychology/Program in Neural Science<br>Supervising P.I.- Dr. Preston Garraghty |
| 2022-present | co-Chair, Gordon Research Conference – Alcohol and the Nervous System – Feb 2024 meeting |
| 2021-present | Vice Chair, Gordon Research Conference – Alcohol and Nervous System – Oct 2022 meeting |
| 2022-present | Member of NIH study section AA-4 |
| 2022 | Reviewer, Biophysical, Physiological, Pharmacological and Bioengineering Neuroscience, F03B, NIH CSR Study Section, June 16 – 17 |
| 2021 | Reviewer, ZAA1 CC-(12) Integrative Neuroscience Initiative on Alcoholism (INIA) Consortia – Neuroimmune, October 19 |
| 2021 | Reviewer, ZGM1 TWD-5 (PR) S Review of NIGMS Postdoctoral Research Associate Training (PRAT), March 25 |
| 2020 | Reviewer and co-Chair, Biophysical, Physiological, Pharmacological and Bioengineering Neuroscience, F03B, NIH CSR Study Section, June 25 – 26 |
| 2020 | Reviewer, ZGM1 TWD-5 (PR) S Review of NIGMS Postdoctoral Research Associate Training (PRAT), March 16 |
| 2019 | Reviewer and co-Chair, Biophysical, Physiological, Pharmacological and Bioengineering Neuroscience, F03B, NIH CSR Study Section, Feb 28 – Mar 1; June 13 – 14 (co-Chair); October 24 – 25 (co-Chair) |
| 2018 | Reviewer, Special Emphasis Panel, ZRG1 BBBP-Y 02, NIH CSR Study Section, Mar and Nov |
| 2016-present | Review Editor, Frontiers in Pharmacology - Translational Pharmacology |
| 2015-present | Board of Editors, Journal of the Experimental Analysis of Behavior |
| 2013-present | International Society for Biomedical Research on Alcoholism |
| 2012 | Ad hoc member, Neurotoxicology and Alcoholism (NAL), NIH CSR Study Section, Jan 30 |
| 2009 | Reviewer, NC TraCS $10K Pilot Award Program |
| 2007 | Reviewer, Graduate Women in Science Fellowships |
| 2002-present | Research Society on Alcoholism |
| 1997-present | Society for Neuroscience |

**Selected Honors and Awards**

| | |
|---|---|
| 2022 | ACTeR (Advancing Collaborative Team Research) Phase I Project Award with Dr. Christian Hendershot |
| 2021 | HHMI Gilliam Fellow co-mentor |
| 2017 | Mentor of the Year, Curriculum of Neuroscience at UNC – Chapel Hill |
| 2004 | Enoch Gordis Research Recognition Award; Research Society on Alcoholism |
| 2000-2002 | National Research Service Award; National Institute on Drug Abuse (NIDA) |
| 2000-2001 | Fling Fellowship; University of Nebraska-Lincoln Graduate Studies Department |
| 1999-2000 | Wheeler Fellowship; University of Nebraska-Lincoln Graduate Studies Department |
| 1999 | Outstanding Graduate Research Assistant Award; University of Nebraska<br>University of Nebraska College of Arts and Sciences |

**C. Contribution to Science**

*Novelty seeking and reward*

My initial training and publications focused on the dopaminergic and cholinergic mechanisms underlying novelty seeking and reward. The interest in the behavioral and neurobiological underpinnings of novelty is related to personality constructs such as novelty and sensation seeking. Such behaviors are positively correlated with risk-taking behaviors such as drug use, high risk sexual behavior, and risky driving practices. Therefore, an underlying assumption is that engaging in novelty-related behaviors has some appetitive or rewarding component that maintains these risky behaviors. Our work focused on characterizing different behavioral models to measure novelty seeking and novelty conditioned reward in rat models. We showed that dopaminergic and cholinergic mechanisms were important for the detection of novelty and conditioned reward. Further, as part of my dissertation work, I was able to demonstrate that these behavioral assays were reliable tools for the measurement and characterization of nicotine withdrawal-induced anhedonia.

a) **Besheer J**, Short KR, & Bevins RA (2001) Dopaminergic and cholinergic antagonism in a novel-object detection task with rats. *Behavioural Brain Research*, 126, 211-217.
b) **Besheer J**, & Bevins RA (2003) The impact of nicotine withdrawal on novelty reward and related behaviors. *Behavioral Neuroscience,* 117: 327-40.
c) Bevins RA & **Besheer J** (2005) Novelty reward as a measure of anhedonia. *Neuroscience and Biobehavioral Reviews,* 29: 707-14.
d) Bevins RA, **Besheer J** (2006). Object recognition in rats and mice: A one-trial non-matching to sample learning task to study "recognition memory". *Nature Protocols*, 1: 1306-1311.

*Interoceptive drug conditioning*

The ability of stimuli associated with drugs to modulate behavior has been well established in the literature. Such stimuli can be both environmental/contextual or interoceptive (i.e., internal drug effects). Similar to environmental stimuli, interoceptive/internal stimuli can play a fundamental role in incentive motivational processing, as a consequence of being associated with other reinforcing events (e.g., peer-acceptance, work breaks). As such, these conditioned drug states have the potential to promote drug taking and relapse following periods of abstinence. Our publications show that a conditioned interoceptive drug state can rapidly come to gain control of goal-tracking behavior. Therefore, one of the advantages of these Pavlovian drug discrimination procedures is that they present to the literature additional tools by which to assess interoceptive drug effects, as there may be experimental situations in which short-term training procedures may be more suitable than longer-term operant drug discrimination procedures (e.g., adolescence).

a) Randall PA, Fortino B, Huynh YW, Thompson BM, Larsen CE, Callen MP, Barrett ST, Murray JE, Bevins RA, **Besheer J** (2019). Effects of nicotine conditioning history on alcohol and methamphetamine self-administration in rats. *Pharmacology, biochemistry, and behavior*, 179: 1-8.
b) Randall PA, McElligott ZA, **Besheer J** (2020) Role of mPFC and nucleus accumbens circuitry in modulation of a nicotine plus alcohol compound drug state. *Addiction Biology*. 25(4):e12782
c) Randall PA, Lovelock DF, VanVoorhies K, Agan VE, Kash TL, **Besheer J** (2021) Low-dose alcohol: Interoceptive and molecular effects and the role of dentate gyrus in rats. *Addiction Biology*. 26(3):e12965
d) Lovelock DF, Tyler RE, **Besheer J**. (2021) Interoception and alcohol: Mechanisms, networks, and implications. *Neuropharmacology*. 200:108807

*Preclinical evaluation of potential therapeutic targets for alcohol drinking*

Examination and identification of novel therapeutic targets for the treatment of alcohol use disorders is critical in order to broaden the availability of therapeutic options. Through the years, working in collaborations and as a PI, I have engaged in such preclinical studies investigating a diverse range of targets and their modulatory role in alcohol-related behaviors, with a focus on alcohol self-administration, relapse-like behavior and withdrawal.

a) Makhijani VH, Van Voorhies K, **Besheer J**. (2018) The mineralocorticoid receptor antagonist spironolactone reduces alcohol self-administration in female and male rats. *Pharmacology, Biochemistry, and Behavior*. 175: 10-18.
b) Makhijani VH, Irukulapati P, Van Voorhies K, Fortino B, **Besheer J**. (2020) Central amygdala mineralocorticoid receptors modulate alcohol self-administration. *Neuropharmacology*. 181:108337
c) Lovelock DF, Nguyen T, Van Voorhies K, Zhang Y*, **Besheer J***. (2022) RTICBM-74 Is a Brain-Penetrant Cannabinoid Receptor Subtype 1 Allosteric Modulator that Reduces Alcohol Intake in Rats. *J Pharmacol Exp Ther*. *co-corresponding authors
d) Gay EA, Guan D, Van Voorhies K, Vasukuttan V, Mathews KM, **Besheer J***, Jin C* (2022). Discovery and Characterization of the First Nonpeptide Antagonists for the Relaxin-3/RXFP3 System. *J Med Chem*.

65:7959-7974 *co-corresponding authors

*Impact of stress on sensitivity to alcohol interoceptive cues and self-administration/relapse.*
Stressful life events and chronic stressors have been associated with escalations in alcohol drinking. Altered sensitivity to the subjective/interoceptive effects of alcohol has been presented as a possible behavioral mechanism for escalated alcohol drinking during episodes of heightened elevations in glucocorticoid levels, such as stress. That is, during these episodes, an individual may consume more alcohol to achieve the desired interoceptive effects. Our publications show that following an episode of heightened elevations in stress hormone levels, rats are less sensitive to the interoceptive effects of alcohol and rats show transient increases in alcohol self-administration**.** Further, we show that adaptations in mGlu receptors, which may have a functional behavioral role in reducing stress-induced drinking and also may have functional relevance for populations that show reduced sensitivity to alcohol (e.g., individuals with a family history of an alcohol use disorder), who are at higher risk for developing alcohol use disorder. We have also transitioned to using exposure to a predator odor as a stressor in relation to alcohol self-administration with a focus on underlying gene expression changes in glutamate-related targets. I serve as the PI on these projects.

a) Tyler, RE, Weinberg B, Lovelock DF, Ornelas LC, **Besheer J** (2020) Exposure to the predator odor TMT induces early and late differential gene expression related to stress and excitatory synaptic function throughout the brain in male rats. *Genes, Brain and Behavior*. 19(8):e12684
b) Ornelas LC, Tyler RE, Irukulapati P, Paladugu S, **Besheer J** (2021) Increased alcohol self-administration following exposure to the predator odor TMT in active coping female rats. *Behavioural Brain Research*. 402:113068
c) Tyler RE, Bluitt MN, Engers JL, Lindsley CW, **Besheer J** (2022). The effects of predator odor (TMT) exposure and $mGlu_3$ NAM pretreatment on behavioral and NMDA receptor adaptations in the brain. *Neuropharmacology.* Apr 1;207:108943.
d) Tyler RE, Bluitt MN, Van Voorhies K, Ornelas LC, Weinberg BZS, **Besheer J** (2022) Predator odor (TMT) exposure potentiates interoceptive sensitivity to alcohol and increases GABAergic gene expression in the anterior insular cortex and nucleus accumbens in male rats. *Alcohol*. 104: 1-11.

*Interoceptive alcohol effects and alcohol self-administration/relapse: mechanisms and circuitry*
Drug taking and seeking behavior can be influenced by interoceptive drug effects. For example, the interoceptive cues that an individual experiences/attends to can prime further drug-taking (e.g., interoceptive effects of a low alcohol dose may prime more drinking) or signal satiety (e.g., interoceptive effects of a higher alcohol dose may limit further drinking). While it is experimentally difficult to determine the direct and specific contribution of the interoceptive effects of alcohol on self-administration/drinking in preclinical models, our research strategy has incorporated examining these behaviors in parallel, as changes to the interoceptive effects can inform and present important behavioral mechanisms for changes in drinking and relapse. To this end, our published studies have taken on multidisciplinary approaches and identified neural substrates and circuitry required for the expression of the interoceptive effects of alcohol. I served as the PI on these projects.

a) Jaramillo AA, Agan VE, Makhijani VH, Pedroza S, McElligott ZA, **Besheer J** (2017) Functional role for suppression of the insular-striatal circuit in modulating interoceptive effects of alcohol. *Addiction Biology*. 23(5):1020-1031
b) Jaramillo AA, Randall PA, Stewart S, Fortino B, VanVoorhies K, **Besheer J** (2018) Functional role for cortical-striatal circuitry in modulating alcohol self-administration. *Neuropharmacology*, 130:42-53.
c) Jaramillo AA, Van Voorhies K, Randall PA, **Besheer J** (2018) Silencing the insular-striatal circuit decreases alcohol self-administration and increases sensitivity to alcohol. *Behavioural Brain Research*, 348:74-81.
d) Randall PA, Lovelock DF, VanVoorhies K, Agan VE, Kash TL, **Besheer J** (2021) Low-dose alcohol: Interoceptive and molecular effects and the role of dentate gyrus in rats. *Addiction Biology*. 26(3):e12965

**Complete List of Published Work in MyBibliography**
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