BIOGRAPHICAL SKETCH

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NAME: Joyce Besheer

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

POSITION TITLE: Associate 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 disorders, with an emphasis on interoceptive cues (both alcohol and nicotine) and alcohol self-administration and relapse models. I have spent over 14 years examining the neurobiology underlying alcohol self-administration and relapse-like behavior as well as sensitivity to the interoceptive effects of alcohol and have extensive experience in these areas. Additionally, my lab routinely incorporates techniques such as immunohistochemistry, site specific brain injections/viral injections, cannulae implantations, into our studies allowing for examination of neuroadaptations and functional involvement of specific brain regions/circuits in various behaviors. Together, these experiences have contributed to the multidisciplinary approach that I utilize in my projects to examine different aspects of alcohol-related behaviors.

B. Position and Honors

Positions and Employment

1996-1997 Research Assistant, Indiana University-Bloomington
Department of Psychology/Program in Neural Science
Supervising P.I.- Dr. Preston Garraghty

1997-2002 Graduate Research Assistant, University of Nebraska-Lincoln
Department of Psychology, Supervising P.I. - Dr. Rick Bevins

2002-2005 Postdoctoral Research Associate, University of North Carolina-Chapel Hill
Bowles Center for Alcohol Studies, Supervising P.I. - Dr. Clyde Hodge

2005-2012 Research Assistant Professor, Department of Psychiatry, University of North Carolina-Chapel Hill

2012-2015 Assistant Professor, Department of Psychiatry, University of North Carolina-Chapel Hill

2015-present Associate Professor, Department of Psychiatry, University of North Carolina-Chapel Hill

Other Experience and Professional Memberships

1997-present Society for Neuroscience

2002-present Research Society on Alcoholism

2007 Reviewer, Graduate Women in Science Fellowships

2009 Reviewer, NC TraCS $10K Pilot Award Program

2012 Ad hoc member, Neurotoxicology and Alcoholism (NAL), NIH CSR Study Section, Jan 30

2013-present International Society for Biomedical Research on Alcoholism
2015-present Board of Editors, Journal of the Experimental Analysis of Behavior

Honors

1998 Scholastic Research Summer Fellowship
University of Nebraska-Lincoln Graduate Studies Department
1999 Outstanding Graduate Research Assistant Award
University of Nebraska Alumni Association
1999 Outstanding Graduate Research Assistant Award
University of Nebraska College of Arts and Sciences
1999-2000 Wheeler Fellowship
University of Nebraska-Lincoln Graduate Studies Department
2000-2001 Fling Fellowship
University of Nebraska-Lincoln Graduate Studies Department
2000-2002 National Research Service Award
National Institute on Drug Abuse (NIDA)
2004 Enoch Gordis Research Recognition Award
Research Society on Alcoholism

C. Contribution to Science

Novelty seeking and reward

My graduate training and related 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. Once optimal parameters were established, 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, such as evaluation of interoceptive drug effects during a brief developmental window (e.g., adolescence).

a) **Besheer J**, Palmatier MI, Metschke DM, & Bevins RA (2004) Nicotine as a signal for the presence or absence of sucrose reward: A Pavlovian drug appetitive conditioning preparation. *Psychopharmacology*, 172: 108-117.

b) **Besheer J**, Fisher KR, Durant B (2012) Assessment of the interoceptive effects of alcohol in rats using short-term training procedures. *Alcohol*, 46: 747-55.
c) Bevins RA and **Besheer J** (2014) Interoception and learning: Import to understanding and treating diseases and psychopathologies. *ACS Chemical Neuroscience*, 5: 624-31.
d) Randall PA, Cannady R, Besheer J (2016) The nicotine + alcohol interoceptive drug state: contribution of the components and effects of varenicline in rats. Psychopharmacology, 233:3061-74.

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) **Besheer J**, Lindsay TG, O'Buckley TK, Hodge CW, Morrow AL (2010) Pregnenolone and ganaxolone reduce operant ethanol self-administration in alcohol-preferring P rats. *Alcoholism: Clinical and Experimental Research*, 34: 2044-52.
b) Randall PA, Jaramillo AA, Frisbee S, & **Besheer J**. (2015) The role of varenicline on alcohol-primed self-administration and seeking behavior in rats. *Psychopharmacology*. 232: 2443-54.
c) **Besheer J**, Frisbee S, Randall PA, Jaramillo AA, Masciello M. (2015) Gabapentin potentiates sensitivity to the interoceptive effects of alcohol and increases alcohol self-administration in rats. *Neuropharmacology*. 101: 216-224.
d) Cannady R, Fisher KR, Graham C, Crayle J, **Besheer J**, Hodge CW (2016) Potentiation of amygdala AMPA receptor activity selectively promotes escalated alcohol self-administration in a CaMKII-dependent manner. *Addiction Biology*.

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 alcohol 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. For example, we have identified a functional role for metabotropic glutamate receptors (mGluRs) in relation to the expression of the interoceptive effects of alcohol and alcohol self-administration/reinforcement processes, as well as relapse-like behavior. I served as the PI or co-Investigator on these projects.

a) **Besheer J**, Grondin JJM, Salling MC, Spanos M, Stevenson RA, Hodge CW (2009) Interoceptive effects of alcohol require mGlu5 receptor activity in the nucleus accumbens. *Journal of Neuroscience,* 29:9582-91.
b) **Besheer J**, Grondin JJM, Cannady R, Sharko AC, Faccidomo S, Hodge CW (2010) Metabotropic glutamate receptor 5 activity in the nucleus accumbens is required for the maintenance of ethanol self-administration in a rat genetic model of high alcohol intake. *Biological Psychiatry*, 67:812-22.
c) Cannady, R., Grondin JJM, Fisher KR, Hodge CW, **Besheer J** (2011) Activation of Group II metabotropic glutamate receptors modulates the discriminative stimulus effects of alcohol via actions within the amygdala. *Neuropsychopharmacology*. 36: 2328-38.
d) Jaramillo AA, Randall PA, Frisbee S, Fisher KR, **Besheer J**. (in press) Modulation of sensitivity to alcohol by cortical and thalamic brain regions. *European Journal of Neuroscience*.

Impact of stress hormone exposure on sensitivity to alcohol interoceptive cues and self-administration.
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. While mimicking a “stressful episode” is difficult to do in an animal model, our lab implements a protocol in which we manipulate the physiological consequences of stress, in part, by administering the stress hormone corticosterone in the drinking water. 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 pharmacological manipulation of mGluR5 and mGluR2/3 can restore sensitivity to alcohol, 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 disorders. Understanding the functional impact of neuroadaptations that occur as a consequence of episodes of chronic elevations in glucocorticoid levels may enrich our understanding of altered subjective sensitivity and escalations in alcohol drinking during stressful episodes. I served as the PI on these projects.

a) **Besheer J**, Fisher, KR, Grondin JJM, Cannady R, Hodge CW (2012) The effects of repeated corticosterone exposure on the interoceptive effects of alcohol in rats. *Psychopharmacology*, 220: 809-22.
b) **Besheer J**, Fisher KR, Lindsay TG, Cannady R (2013) Transient increase in alcohol self-administration following a period of chronic exposure to corticosterone. *Neuropharmacology*, 72: 139-47.
c) **Besheer J**, Fisher KR, Jaramillo A, Frisbee S, Cannady R (2014). Stress hormone exposure reduces mGluR5 expression in the nucleus accumbens: Functional implications for interoceptive sensitivity to alcohol. *Neuropsychopharmacology*, 39: 2376-86.
d) Jaramillo AA, Randall PA, Frisbee S, Fisher KR, **Besheer J**. (2015) Activation of mGluR2/3 following stress hormone exposure restores sensitivity to alcohol in rats. *Alcohol.* 49: 525-32.

Complete List of Published Work in MyBibliography
http://www.ncbi.nlm.nih.gov/sites/myncbi/1feUvqnIycrA9/bibliography/48498294/public/?sort=date&direction=ascending

D. Research Support

1R01AA025582 (Besheer, Kash) 9/1/2016 – 8/31/2021
Unbiased analysis of molecular and circuit targets of low dose alcohol
The goal of this project is to identify and test the causal role of brain circuits and molecules that are activated by low dose alcohol.
Role: PI

R21DA039356 (Besheer; Bevins) 4/1/2016 – 3/31/2018
NIH/NIDA
Interplay between interoception, learning, and drug seeking
The goal of this project is to examine the impact of a drug conditioning history on relapse-like behavior.
Role: PI

R01 AA019682-S2 (Besheer) 7/1/15 – 6/30/17 – 1 year NCE
NIH/NIAAA/ORWH
The impact of HPA axis dysregulation on the interoceptive effects of alcohol – Administrative Supplement for Research on Sex/Gender Differences
The goal of this project is to examine sex differences as a consequence of corticosterone exposure on alcohol sensitivity and drinking behavior and neuroadaptations.
Role: PI

R01 AA019682-S1 (Besheer) 7/1/14 – 6/30/17 – 1 year NCE
NIH/NIAAA/NIDA
The impact of HPA axis dysregulation on the interoceptive effects of alcohol – Administrative Supplement to Promote Collaborative Research on Addiction at NIH (CRAN)
The goal of this project is to examine the consequence of corticosterone exposure on sensitivity to an alcohol + nicotine compound interoceptive cue.
Role: PI

R01 AA019682-01A1 (Besheer) 7/15/11 – 06/30/17 – 1 year NCE
NIH/NIAAA
The impact of HPA axis dysregulation on the interoceptive effects of alcohol
The goal of this project is to examine novel mechanisms of ethanol discrimination and self-administration involving interaction between stress hormone exposure and metabotropic glutamate receptor (mGluR5).
Role: PI

P60 AA011605 (Crews; Hodge, Component PI) 12/1/12 – 11/30/17
NIH/NIAAA
Molecular Mechanisms of Drinking and Relapse
The purpose of this Research Component of the NIAAA Center Grant is to examine the molecular mechanisms of alcohol self-administration and underlying neural circuitry.
Role: Investigator

P60 AA011605 (Crews) 12/1/12 – 11/30/17
NIH/NIAAA
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

Foundation of Hope (Besheer) 7/1/13 – 12/31/2017 – 1 year NCE
Adolescent depression: persistent behavioral and neuroadaptations in a rat model
The goal of this project is to characterize the persistence of depressive like behavior, specifically anhedonia, into adulthood and examine underlying glutamatergic mechanisms.

Completed Research Support (last 3 years)
R21 AA020914 (Besheer, PI) 12/1/12 – 11/30/15 (1 year NCE)
A Method to Assess Alcohol Discrimination in Adolescents

R01 AA014983 (Hodge, PI; Besheer, Investigator) 6/2011 – 2015
Molecular Mechanisms of Ethanol Reinforcement