COLLEGE OF ARTS AND SCIENCE
VANDERBILT UNIVERSITY

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Members of the Search Committee:

I am excited to apply for the Assistant Professor position the Department of Psychology **XXXX**. I received my PhD in Neurobiology from the University of North Carolina at Chapel Hill in 2014 (with Charlotte Boettiger). Currently, I am an NRSA postdoctoral fellow working with David Zald at Vanderbilt University. My broad research interests lie in the area of individual differences in dopamine (DA) signaling as it relates to risk for substance abuse including subjective rating differences to d-amphetamine, decision making behavior, and neural differences assessed with both functional magnetic resonance imaging (fMRI) and Positron Emission Tomography (PET).

My program of research uses behavioral genetic and neuroimaging approaches to understand the neurocognitive bases of initial subjective responses to drugs of abuse (affect) and decision processes (immediate reward selection or *Now* bias) that associate with drug abuse risk. *Now* bias has the hallmarks of an intermediate phenotype for alcohol use disorders (AUDs; **Smith** et al., 2015 *Front Hum Neurosci*) but further work on its biological and neural bases as well as approaches that can be used to modulate it is needed. One intriguing finding from our 2015 study is that age and alcohol use interact to affect *Now* bias. This suggests that problematic drinking could "lock in" a more immature brain state that is prone to valuing the present over the future. I plan to pursue this line of research further at **XXXX**, including asking whether elevated *Now* bias predicts subsequent drug use and whether genetic variation mediates this effect.

In regards to genetics, we have found that a single nucleotide polymorphism (SNP) in the gene that encodes the prefrontal cortical DA regulatory enzyme catechol-*O*-methlytransferase (COMT) interacts with age to affect *NOW* bias (**Smith** & Boettiger, 2012 *Psychopharmacology*) and interacts with estradiol to explain changes in *NOW* bias over the menstrual cycle (**Smith** et al., 2014 *J Neurosci*). Both these findings suggest *NOW* bias follows an inverted U-shaped function of DA effects (intermediate DA levels lead to more optimal decisions, less *NOW* bias). This model has recently been extended to show inverted U-shaped effects on *NOW* bias, neural activation during choice, and resting state functional connectivity in an fMRI study by our group (Elton, **Smith** et al., 2017 *Front in Hum Neurosci*). Based on this inverted U-shaped model, individuals can be impulsive from either too little or too much DA. Thus, understanding these individuals' endogenous DA levels via genetic markers will be critical in implementing the correct treatment (DA agonists versus antagonists or COMT inhibitors such as tolcapone) to reduce their *NOW* bias. Since stress has been shown to increase DA and other catecholamine levels in the brain, individual differences in trait DA based on genetics, age, and sex hormones may ultimately affect individual responses to acute stress. Based on the inverted U-shaped model, individuals with low trait level cortical DA would get a DA boost from stress that may improve cognitive processing while those with high levels of trait cortical DA may become overdosed for DA signaling when under stress and more likely to make poor decisions. **By understanding the key modulators of this U-shaped model, we can ultimately develop more personalized interventions to lower *NOW* bias and reduce its effects on promoting or perpetuating substance used disorders.**

I have also utilized PET to understand individual differences in DA signaling (**Smith** et al., 2017 *Translational Psychiatry*) and how this may affect subjective value (specifically the relationship between DA release and drug wanting; **Smith** et al., 2016 *Neuropharmacology*) and choice processing (**Smith** et al., 2016 *J Neurophysiology*). My work suggests a vmPFC-insula-ventral striatal

circuit may be particularly sensitive to drugs of abuse and whose connectivity (measured with fMRI) I propose could change as individuals transition to drug abuse and dependence. I will investigate the neural connectivity of this circuit in individuals with and without family history of drug abuse as well as drug abusers to identify if and how the circuit may be modified by genetics and environment (stress, drug use). Understanding this circuit and dopamine's role in its modulation may offers insights into potential mechanisms for treatment of drug addiction.

During my 10+ years of graduate and postdoctoral work, I have mentored over 20 undergraduate students, including 3 honors theses, served as an instructional assistant for Introductory Psychology at UNC Chapel Hill, given guest lectures (n=3), and obtained a Certificate in College Teaching at Vanderbilt. I take great pride in mentoring and developing students as evident in my mentees receiving an NSF Graduate Research Fellowship, being selected as best UNC Psychology honors thesis in 2014, and advancing on to PhD programs (n=2), medical school (n=1), and a joint DVM-PhD program (n=1). I look forward to teaching, mentoring, and training the talented graduate and undergraduate students that attend **XXXX**. After examining the courses offered in the Psychology Department, I think my broad training background would allow me to teach Mind, Brain and Behavior, Cognitive Neuroscience, Drugs & Behavior, and Thinking & Decision-making.

At **XXXX**, I envision combining my knowledge of genetics and neuroimaging to study behavioral risk factors (*Now* bias; risk taking; initial subjective responses to drugs, **Smith** et al., 2016 *J Psychopharmcol*) for substance abuse, their neural bases, and factors that may modulate them (age, sex, genetics). **XXXX** has a wealth of resources available for neuroimaging, including the ability for me to continue working on PET imaging. Furthermore, **XXXX** has expertise in genomic research available through the **XXXX** Genome Center & Institute for Genomic Medicine and the ability to perform hormone analyses via the Biomarkers Core Lab within the **XXXX** Institute for Clinical & Translational Research. The ability to leverage **XXXX**'s research expertise in these areas will accelerate the speed with which insights can be extracted from data I plan to collect in my lab.

There are several faculty in your department whom I could see collaborating with on projects related to decision making, executive function, brain development, motivation, reward processing, and assessing and modeling their neural bases including Drs **AAA, BBB, & CCC**.

Utilizing the abundant resources at **XXXX** and building collaborations within and outside the university, I think I can contribute to exciting discoveries in identifying risk for drug abuse and, ultimately, in the development of successful, personalized interventions.

In closing, I think I offer a unique set of research skills in neuroimaging, pharmacology, and genetics and a strong training background in neuroscience and psychological research that would bring an additional but complementary perspective to the work being conducted in your department.

Thank you for your consideration,