COLLEGE OF ARTS AND SCIENCE
VANDERBILT UNIVERSITY

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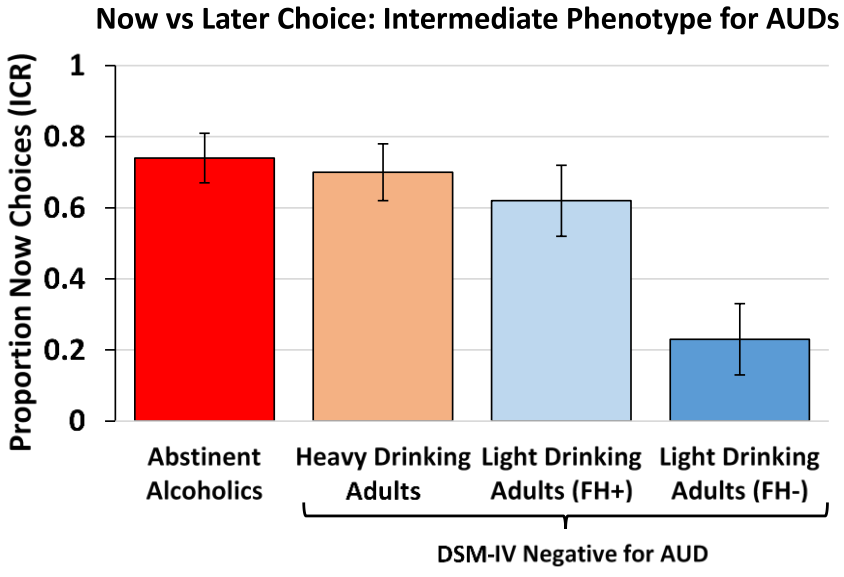
Members of the Search Committee:

I am excited to apply for the Assistant Professor position at **XXXX**. I received my PhD in Neurobiology from UNC Chapel Hill in 2014 (with Charlotte Boettiger) and am currently an NRSA postdoctoral fellow working with David Zald at Vanderbilt. Your **YYYY** initiative's research areas of interest closely align with the goals of my own research program: neuroimaging in populations with risk for substance use disorders, bioinformatics (genetics), and clinical trials evaluating promising approaches to treating substance use disorders.

Combining behavioral, genetic, and neuroimaging measures including functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET), I seek to better characterize individual differences in dopamine (DA) signaling and risk factors associated with drug abuse. At Albert Einstein, I plan to build off work showing that both cortical and striatal DA signaling are associated with risk behaviors for drug addiction in differential ways. Cortical DA effects on decision making behaviors such as *NOW vs LATER* choice often follows an inverted-U model while we have found striatal DA affects trait measures of impulsivity and subjective responses to drugs of abuse in a more linear manner. The next step is integrating this work into a comprehensive model of DA's role in complex behaviors that are also risk factors for substance abuse. Further characterization of both the biological bases and modulators of these risk factors **(*NOW choice bias, impulsivity, subjective experience*)** for substance use disorders will ultimately lead to improved intervention and treatment approaches. Furthermore, combining genetic and neuroimaging data with pharmacological studies can offer more thorough insights into how DA-targeted treatments may affect individuals differentially. This work may ultimately lead to more personalized and effective treatments for DA-related disorders including drug addiction, ADHD, schizophrenia, and Parkinson's disease.

Immediate Reward Selection Bias, Intermediate Phenotype for Alcohol Use Disorders

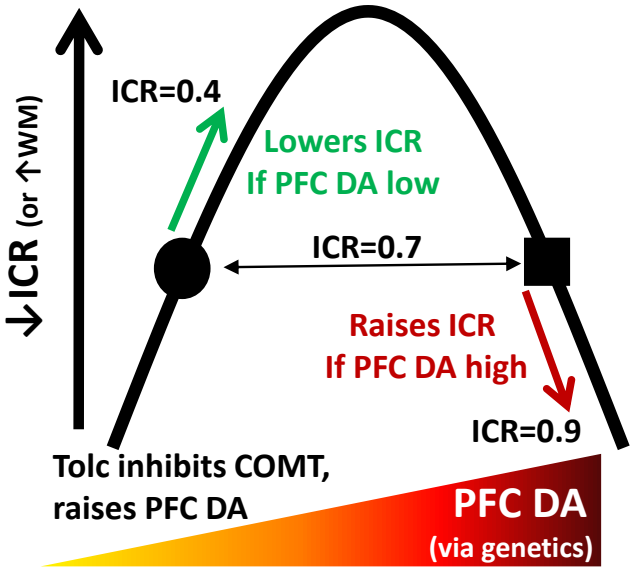
We (Smith et al., 2015 *Front Hum Neurosci*) have shown *NOW* choice bias (choosing a smaller, sooner reward over a larger, later reward; indexed by an **impulsive choice ratio, ICR**) displays many qualities of an intermediate phenotype for AUDs, including being elevated in heavy drinking adults without an AUD and in light drinking adults with a family history (FH+) of problematic alcohol use (**see Figure, right**). Furthermore, we observed that natural, age-related declines in *NOW* bias were not present in heavy drinkers suggesting heavy alcohol use may "lock in" a preference for *NOW*, potentially by affecting normal brain maturational processes. Importantly, we have also demonstrated this behavior is modulated by: 1) both age and putative prefrontal DA as assessed with the Val158Met *COMT* (catechol-*O*-methyltransferase, an enzyme critical



in metabolizing cortical DA) single nucleotide polymorphism (SNP rs4680; Smith & Boettiger, 2012 *Psychopharmacology*), 2) estradiol by *COMT* effects in naturally cycling female participants (Smith et al., 2014 *J Neurosci*), and 3) putamen DA synthesis capacity as assessed with FMT PET (Smith et al., 2016 *J Neurophys*). These data suggest means by which individual differences in DA signaling may modulate *NOW* bias and offer insights into potential treatments to reduce elevated *NOW* bias in drug abusers.

A goal for future work would be to further characterize the key neural and biological modulators of *NOW* bias. Our earlier findings (Smith & Boettiger, 2012 *Psychopharmacology*; Smith et al., 2014 *J Neurosci*) suggest *NOW* choice bias (**ICR**) follows an inverted U-shaped function of DA effects (intermediate DA levels lead to more optimal decisions, less *NOW* choice bias). This model has recently been extended to show inverted U-shaped effects on **ICR**, 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* choice bias. Tolcapone has been shown to modulate *NOW* bias and its neural underpinnings. However, no one has tested its potential to treat *NOW*-focused drug-addicted individuals. Tolcapone may assist in cognitive or motivational therapies used to reframe drug abusers' goals and priorities beyond immediate drug use toward more constructive endeavors (work, health, social relationships). My research suggests that tolcapone's effectiveness may depend on COMT genotype, age, and estradiol levels (**see Proposed Model, left**). Thus, I plan to work with collaborators at **XXXX** to examine tolcapone's effects on *NOW* bias in both healthy individuals stratified by some of these modulating variables (age, COMT genotype, estradiol levels) and ultimately test in a properly targeted (based on which groups show effects in healthy individuals) AUD population whether a tolcapone intervention in would be effective in improving their treatment outcomes.

Proposed effect of Tolcapone on ICR



PFC: prefrontal cortex; WM: working memory; ICR: impulsive choice ratio; DA: dopamine

Age, estradiol, COMT methylation, and striatal DA may also influence effects of DA treatments

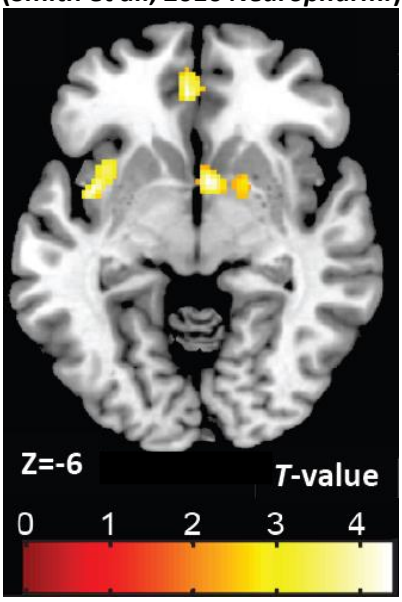
Furthermore, the *COMT* Val158Met SNP interacts with a SNP in *DARPP-32* (rs907094) to impact working memory (**WM**) performance (Smith et al., 2014 *JOCN*), a D1-mediated process. This supports the ability to use genetic polymorphisms to measure primarily D1 DA receptor signaling. This is important because good D1 receptor PET radiotracers are lacking. Work using tolcapone will allow for the hypothesis of *COMT* x *DARPP-32* genotype indexing D1 DA-related signaling to be tested by asking if tolcapone's effects modulate working memory according to an inverted-U pattern based on genetically determined D1 DA signaling. This work will offer greater insights into the key modulators of cortical DA signaling, which is thought to underlie psychiatric disorders like schizophrenia and may suggest that *COMT* x *DARPP-32* genotype serves as a biomarker for such disorders.

Variation in Subjective and Neural Signaling Responses to d-Amphetamine (dAMPH)

Using PET, we have shown relationships between Want More dAMPH ratings and dAMPH-induced DA release in vmPFC, insula, and ventral striatum (VS; Smith et al., 2016 *Neuropharmacology*; **see Figure, below**). We are now exploring the role of DA transporter (DAT) levels (measured via PET) in explaining differences in personality, dAMPH subjective effects, and DA release. We have recently found DAT levels

in VS are negatively related to trait impulsivity (**Smith et al., 2018**; in revision at *Translational Psychiatry*). This work has implications for understanding DA's role in traits present in both drug abusers and those with attention-deficit/hyperactivity disorder (ADHD). ***Future work*** that measures the neural correlates (fMRI BOLD activity, PET measures of DA release) of subjective responses to dAMPH and other drugs of abuse will allow for a more thorough characterization of brain areas and processes critical in these experiences. Furthermore, if early dAMPH subjective response is a marker of addiction risk, as we propose (Smith et al., 2016 *J Psychopharmacology*; it also correlates negatively with novelty seeking, a risk trait, in a small sample of subjects, data not published) we would expect individuals with a family history of drug abuse to be more likely to show an early dAMPH response. Identifying if early dAMPH response or DA signaling responsivity is associated with any genetic or neural markers may allow identification of at risk individuals. For instance, we have found that the C957T SNP (rs6277) in the DRD2 gene affects putamen and ventral striatum DA D2 receptor availability (Smith et al., 2017 *Translational Psychiatry*). We propose individuals with lower levels of D2 receptor availability (CC genotype) would be at increased risk for addiction based on previous PET studies but whether C957T confers addiction *risk* and/or differences in responsivity to drugs of abuse remains unknown. In addition, understanding the biological bases of why some individuals *don't respond* to dAMPH may offer insights into targets for ameliorating the positive subjective effects of abused drugs. Neuroimaging work investigating the structural and functional links between the vmPFC-insula-VS network nodes (associated with wanting more, **see Figure at right**) in response to dAMPH exposure in naïve individuals and at baseline in drug abusers with years of drug use and degrees of craving will offer greater insights into changes in this corticolimbic network over the course of drug use. Ultimately, this work will provide insights into critical biological nodes of change that could be targets for future treatments to reduce craving in substance abuse.

DA release in vmPFC, right VS, & left insula associate with wanting more dAMPH (Smith et al., 2016 *Neuropharm.*)



In addition, I plan to analyze a large collection of Fallypride PET data from Vanderbilt to identify genetic predictors of D2/3 receptor availability (n>200) and dAMPH-induced DA (n>80) release in the brain. The genetic variants we identify in the PET data could then serve as candidate polymorphisms to test in behavioral and fMRI data collected previously and to be collected at **XXXX**. I plan to build off this work by continuing to study the DA system with PET in the Radiology Department at **XXXX** Medical Center, ultimately combining this to-be-collected PET data with that previously collected to obtain better insight into robust predictors of individual variability in DA signaling.

My proposed research program is consistent with funding priorities at NIDA and NIAAA, which include the study of sex differences in drug abuse, neural changes associated with drug abuse/dependence, and potential genetic variants (*COMT, C957T*) associated with drug abuse risk.

In closing, as part of the **YYYY** initiative at **XXXX**, I envision combining my knowledge of genetics and neuroimaging to study individual differences in the DA system and their effects on behaviors associated with substance use disorder. This work also has relevance for a range of psychiatric disorders and ultimately I see findings from this work aiding in the identification and development of personalized treatments for these disorders.

Respectfully,

Christopher T. Smith