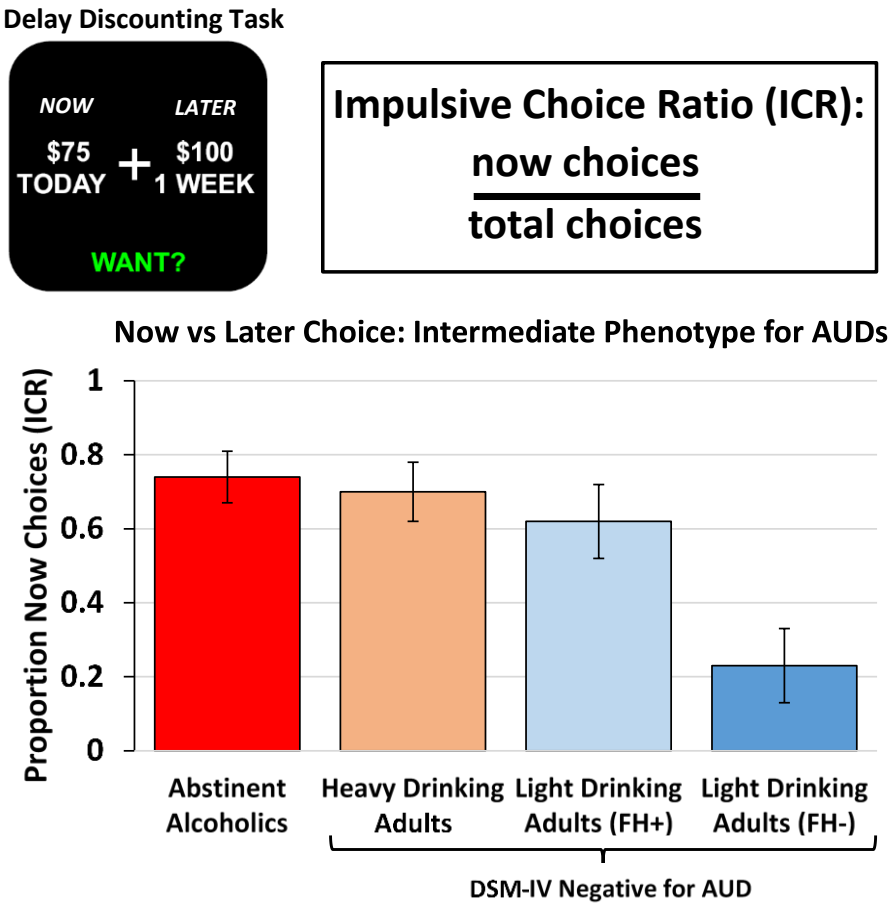
Drugs of abuse release dopamine (DA) in the brain. This fact suggests that individual differences in DA signaling may explain variation in risk for developing drug abuse. My research has involved combining behavioral, genetic, and neuroimaging measures including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to better characterize risk factors associated with drug abuse. In addition, I have used behavioral genetics to begin to study the role of cortical DA signaling in the cognitive process of working memory as well has how estradiol may modulate decision-making processes via cortical DA signaling. I plan to continue my behavioral genetic work at **XXXX** University in addition to teaching students about neuroimaging data and analysis techniques.

Immediate Reward Selection Bias, Intermediate Phenotype for Alcohol Use Disorders

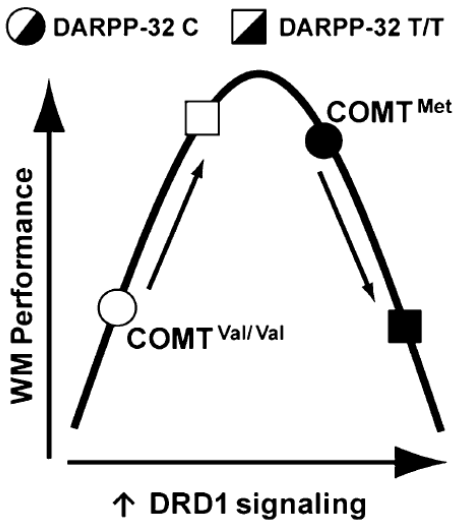


While work has demonstrated immediate reward selection bias (choosing a smaller, sooner reward (*NOW*) over a larger, later reward (*LATER*)) is elevated in individuals with substance use disorders, whether increased *NOW* choice bias is a cause or consequence of drug use remains unclear. We (Smith et al., 2015 *Frontiers in Human Neuroscience*) have shown *NOW* choice bias (indexed by an **impulsive choice ratio, ICR; see Figure for task example and ICR calculation details**) displays many qualities of an intermediate phenotype for alcohol use disorders (AUDs), including being elevated in heavy drinking adults without an AUD and in light drinking adults with a first degree relative with problematic alcohol use (family history (FH)+, **see Figure**). 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* (rs4680) single nucleotide polymorphism (SNP; Smith and 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.

Future longitudinal work that investigates initial *NOW* bias level before alcohol use initiation and changes in *NOW* bias as a result of natural exposure to alcohol in college-aged individuals will offer greater insights into *NOW* bias as a potential risk factor for and/or cause of excessive alcohol use. At **XXXX**, this work could involve assessing ICR either in newly-enrolled freshman or community members of a similar age and then conducting follow-up tests at multiple time points in the future. This would be coupled with collection of alcohol and drug use measures in these individuals, which could be collected online via a system that de-identifies their responses and then links them to their ICR data collected in the lab. This study would offer powerful information on ICR as a potential risk factor for drug use. Furthermore, assessing state affect and stress at the time of assessments, which could be accomplished electronically via mobile applications or text message systems, could add valuable information on individual variability measures that may affect choice behavior.

Genetic Measures of Dopamine System Function: Investigating the Inverted-U Relationship

DA has been linked to the executive process of working memory (WM). Specifically, D1 DA receptor signaling in the prefrontal cortex (PFC) is associated increased activity during the delay period of a visual working memory task on correctly performed trials in monkeys. This work, and others, has suggested that DA increases the signal-to-noise in PFC representations of stimuli and/or goals.



We have demonstrated that SNPs in the *COMT* and *DARPP-32* genes interact to affect WM performance (**see Figure**), presumably by indexing D1 DA-related signaling (Smith et al., 2014 *J Cogn Neurosci*). We have tested this via an n-back task of WM using letter stimuli and a 0, 2, and 3-back condition and found a stronger relationship between putative frontal cortical DA signaling when comparing target detection at high WM load (3-back). Importantly, our data fit with pharmacological work in humans suggesting an inverted-U relationship between PFC DA and optimum performance on a WM task (**see Figure**).

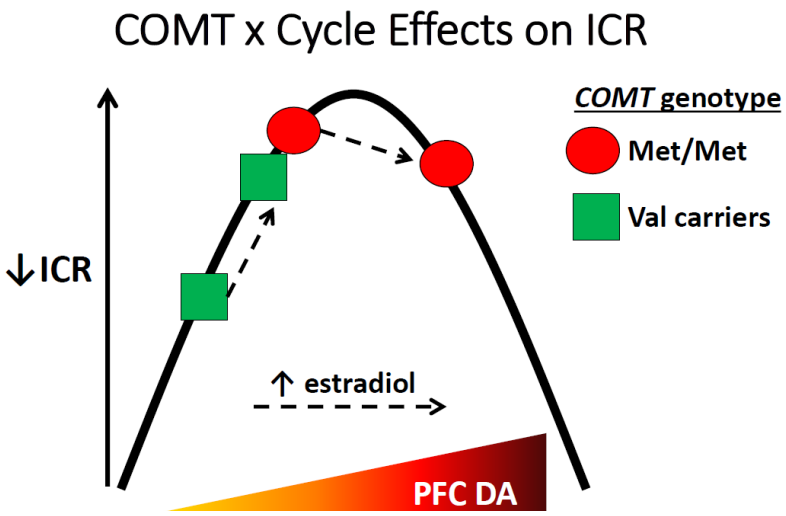
In future work, I plan to further probe this relationship as there are several WM-related processes that could be affected by these SNPs, including WM updating and maintenance. The question of whether these SNPs support increased signal-to-noise in PFC could be assessed by increasing the noise in the stimuli (visually degrading them). Finally, this work was performed in healthy young adults and my other work (Smith and Boettiger, 2012 *Psychopharmacology*) suggest that *COMT* effects may vary by age. If this is true, we would expect the WM performance curve to shift to the left in older adults as DA signaling declines with age. I plan to test this hypothesis to further support the importance of considering age effects on DA-modulation of task performance.

I have worked with undergraduate students at UNC to collect DNA via a simple saliva collection kit, extract DNA, run PCR, and prepare samples for genotyping. This could be continued in house at **XXXX** with minimal cost (-80° freezer, thermocycler for PCR, pipettes, centrifuge (x2)). There are several companies recommended by ThermoFisher that will genotype raw or extracted DNA samples.

Role of Hormones in Modulating Value, Choice, and Dopamine-Dependent Processes

Many psychiatric disorders including schizophrenia, depression, attention-deficit hyperactivity disorder (ADHD), and drug addiction are known to exhibit considerable sex differences in terms of onset, prevalence, severity, and treatment outcomes. However, our understanding of mechanistic neurobiological differences between males and females is limited. In response to this, the National Institutes of Health has recently taken steps to emphasize the importance of sex as a biological variable. As a researcher interested in studying the role of DA in human behavior, the female sex-linked hormone estradiol is particularly interesting to study as it has been shown in rats to increase striatal DA synthesis and levels of tyrosine hydroxylase, the rate limiting enzyme in the DA biosynthetic pathway. Estradiol administration to ovariectomized rats increases drug-seeking behavior and self-administration rates of cocaine. Furthermore, estradiol has been associated with increased DA release in response to d-amphetamine (dAMPH) in rats and, along with progesterone, differential subjective responses to dAMPH in humans. Thus, there is strong evidence that female hormones can modulate the pleasurable effects of drugs of abuse in the brain. Indeed, stress- and cue-induced craving for cocaine in women are affected by progesterone and estradiol.

Related to my research program, fluctuations in estradiol over the female menstrual cycle have been linked to changes ICR (Smith et al., 2014 *J Neurosci*; **see Figure**) and WM (Jacobs and D'Esposito, 2011 *J Neurosci*) in a *COMT*-dependent fashion. Further work is needed, however, to determine how estradiol *and progesterone* are associated with decision making and affective processes, especially in relation to the use of birth control products that often affect these hormones.



Future work will continue to investigate the role of female hormones on cognitive, motivational, and affective processes. Making use of natural fluctuations in female hormones over the menstrual cycle, we will investigate how not only *Now* Choice (ICR) and WM change over the cycle (to replicate and build off previous reports) but also explore the effects of hormonal fluctuation on effort-based decision making using the EEfRT task developed in my postdoctoral lab at Vanderbilt. As ICR, WM, and EEfRT are modulated by DA signaling, we will be able to probe the effects of estradiol and progesterone in modulating these processes by measuring these tasks at multiple points in the cycle when each hormone is relatively low and high. Coupling these measurements with genetic measures of putative DA signaling (*COMT*, *DARPP-32*, *DRD2*, *DAT1*) will allow us to investigate whether the inverted-U model applies to estradiol's effects on effort-based decision making.

Furthermore, birth control affects estradiol and progesterone levels which can affect components of the DA system and thus, DA-dependent processes. However, little work has systematically investigated the effects of birth control on decision making processes. Thus, my lab will embark on an ambitious study to categorize the effects of the most common forms of birth control (combination estrogen+progestin pill, progestin only pill, combination extend-cycle pill, progestin injection) on decision making behavior by assessing ICR, WM, and EEfRT performance of females on and off birth control as well as age-matched males (between-subjects design), controlling for *COMT* genotype. This work has implications for treating a variety of DA-related disorders in female patients.

I have successfully measured estradiol from saliva with undergraduate UNC students who served as co-authors on the paper. A simple ELISA assay, plate shaker, and plate reader are needed to collect this data and assays exist for progesterone and cortisol, which my lab will also investigate.

Working with Publically Available Neuroimaging Data:
A Great Hands-On Experience for Undergraduate Students

Publically available neuroimaging data exists in a variety of repositories including the Human Connectome Project, OpenNEURO, and, most important to my research interests, the Adolescent Brain Cognitive Development (ABCD) study. The ongoing ABCD study will be particularly powerful as it has the goal of discovering risk and resilience factors for drug use initiation as well as the development of substance use disorders during the transition from adolescence to young adulthood. Currently, data from the first 4,500 ABCD participants is available online with more to be released and updates on the participants to follow in the months and years to come. This dataset is particularly powerful as it will be longitudinally following its participants over a 10 year time period with annual and biannual assessments of behavior, imaging, and bioassay measures.

These publically available neuroimaging datasets will allow undergraduate students at **XXXX** to learn how to process and analyze both structural and functional brain imaging data. Developing these skills will make **XXXX** students uniquely prepared for pursuing graduate work in neuroscience or cognitive neuroscience and would also be helpful for those interested in going into medical fields like radiology, neurology, and psychiatry. I have 10+ years' experience working with neuroimaging data across a variety of modalities and have successfully taught undergraduate students how to use neuroimaging analysis programs. This has resulted in publications that are either in revision or published with undergraduate co-authors.

The key requirement for this type of work are a few computers capable of running the analysis software. The decreased cost of RAM and data storage makes purchasing a few computers capable of running these analyses feasible at **XXXX**. Furthermore, these computers could be shared across the Psychology Department and Neuroscience program for research taking place in other labs or for hands-on lab instruction as part of a course/seminar in Brain Imaging (PSY-416).

In closing, my research interests are capable of being performed successfully (leading to co-authored publications) with undergraduates and offer them a unique ability to understand how genetic and hormonal variation affect human behavior. In addition, I possess a unique set of skills that will allow me to instruct students in the processing and analysis of neuroimaging data. The ability to access these data via online repositories makes working with neuroimaging data feasible at **XXXX** and will lead to a unique learning opportunity for students in the Neuroscience Program.