My program of research seeks to provide a comprehensive account of the etiology of alcohol and other drug addiction in humans to bolster early identification and prevention efforts. In pursuit of this goal, I employ a variety of methodologies needed to advance a comprehensive understanding of the phenomenon of addiction, including human neuroscientific methods (electroencephalogram [EEG] and neuroimaging), ambulatory assessment techniques (ecological momentary assessment), and biometric (behavioral genetic) analyses. Much of my work includes a strong quantitative component, harnessing innovative statistical modeling approaches to effectively test nuanced hypotheses. My work is inherently developmental in its focus on disturbances in cognitive-affective processes across time that give rise to the emergence of substance use disorders (SUDs) and other forms of externalizing psychopathology. Specifically, I focus on three complementary substantive areas in pursuit of the *mechanisms of risk* for addiction: (1) Understanding *dispositional trait liabilities* promotive of addiction, particularly as concerns the interplay between cognitive control and reward sensitivity, (2) leveraging *behavioral economic paradigms* to characterize *proximal risk and maintenance* processes implicated in SUD, and (3) bridging *between-* and *within-subject mechanisms* of risk for problematic consumption through use of *ecological momentary assessment*.

Identifying Dispositional Trait Liabilities

In conceptualizing the etiology of addiction, my research program focuses on two broad (and in some cases overlapping) categories of '*trait liabilities*' and '*proximal*' psychological processes implicated in the development and maintenance of disordered substance use. I articulated this programmatic approach extensively in a recent co-first-authored theoretical article (Perkins, Joyner, et al., 2020, *Dialogues in Clinical Neuroscience*), written in collaboration with the Neurobiology workgroup of the Hierarchical Taxonomy of Psychopathology (HiTOP) .[1] In this article, I conceptualize trait liabilities as "distal" processes that are largely heritable, relatively stable, and confer prospective risk for problematic substance use. Through this lens, my work to date has focused on operationalizing and advancing study of a trait-dispositional factor rooted in weak cognitive control — termed "disinhibition" — as the main distal risk factor for addiction.

To address the fact that disinhibitory liability is often used interchangeably with 'impulsivity' (a case of the jangle fallacy), some of my recent work has sought to show how these constructs and their common operationalizations differ empirically. In one such study (Joyner et al., in press, *Psychological Assessment*),[2] I used structural equation modeling to demonstrate that disinhibition relates selectively to externalizing psychopathology, whereas impulsivity as assessed by a widely used inventory show associations with internalizing as well as externalizing psychopathology. Using dominance analyses, I further showed that disinhibition is a *better* predictor – in quantitative terms – of externalizing problems, including substance use. In another study, I used a *co-twin control design* (Joyner et al., 2020, *International Journal of Psychophysiology*)[3] to show that disinhibition operates largely as a *liability* for SUD, whereas another impulsivity-related trait, conscientiousness, does not. In other words, the heritable factor underlying SUD converged with that of disinhibition, whereas it did not for conscientiousness. In this study, I also operationalized disinhibition as a *cross-domain* construct – as a latent variable defined by indicators from both self-report (trait scale) and neural (P3 brain response) domains of measurement – and showed that the proportion of heritable variance shared between this cross-domain disinhibition variable and SUD symptomatology was significantly higher than for self-report assessed disinhibition. That is, when quantified through use of measures from different modalities, disinhibition showed a stronger heritable-dispositional 'signal' in common

with substance problems. This study highlights an aspect of my research program I intend to continue in the future: leveraging neuroscientific measures to "purify" operationalizations of trait constructs in a way that enhances their effectiveness as liability indicators.

Although disinhibition — particularly when defined as a cross-domain construct — confers risk for SUD, it appears to operate multifinally as a liability for disorders spanning the externalizing spectrum. My work suggests that a second trait, reward sensitivity, may guide the expression of disinhibitory liability in the specific direction of disordered substance use. Reward sensitivity can be measured neurophysiologically using the Reward Positivity (RewP), an event-related potential (ERP) generated by reward-related regions of the brain. In support of the view that this ERP measure indexes reward sensitivity, recent research on which I collaborated (Bowyer, Joyner et al., 2019, *Psychophysiology*)[4] showed that reduced RewP selectively relates to persistent, trait-like depression rather than internalizing problems more broadly. Drawing on this work, I conducted a study that examined whether reduced reward sensitivity as indexed by RewP might contribute to substance problems – in itself, and perhaps in conjunction with disinhibitory liability. I found that blunting of the RewP was associated with greater SUD severity, suggesting a *reward hyposensitivity* process implicated in addiction (Joyner et al., 2019, *Clinical Psychological Science*).[5] Further, there was an interactive effect with disinhibition, such that individuals at high risk (high disinhibition) for addiction showed increasing SUD symptomatology as reward sensitivity decreased, whereas individuals at low risk (low disinhibition) showed no association between reward sensitivity and SUD symptom severity. These findings suggest that the combination of high disinhibition and low reward sensitivity may confer enhanced liability for SUDs. Consistent with my developmental interests and the ontogenetic model described above, I have conducted a successful "close-replication" of this interaction in a large longitudinal study of adolescents using functional neuroimaging (Joyner et al., in prep), and plan to continue this line of work in the future.

Behavioral Economics Approaches

I conceptualize proximal processes implicated in SUD as those that are "near" to the phenotype of interest, potentially operating as mediating factors between the distal processes and psychopathology outcome of interest. More so than dispositional liabilities, these proximal processes are likely to show a dynamic relationship with psychopathology, arising alongside and possibly as a result of active symptomatology (Perkins, Joyner, et al., 2020).[1] Some proximal processes may operate as mechanisms of change in treatment contexts, such that targeting the processes themselves could facilitate symptom reduction. Through this lens, another line of my research has focused on behavioral economic measures of reward valuation and substance-free reward engagement as proximal factors for addiction. Behavioral economic theory conceptualizes substance use in terms of reinforcer pathology — that is, when the relative *reinforcing value* of the drug exceeds that of available alternative (i.e., "substance-free") rewards, the individual preferentially engages in substance-related activities. One measure of substance reward valuation I have utilized is that of *demand*. Behavioral economic demand can be operationalized in a substance purchase task, in which participants indicate the amount of substance to be consumed across a range of escalating prices, and yields economic metrics interpreted as indicators of reward value. My work has demonstrated these demand factors to be sensitive to behavioral contingencies, such that having other responsibilities (e.g., preparing for a major exam) reduces demand for the substance (Joyner et al., 2019b, *Alcoholism: Clinical and Experimental Research*).[6] Additionally, I have found that individuals who appear least sensitive to these contingencies display the most severe types of alcohol problems, as defined through use

of item response theory (IRT) analyses. Another study I will soon submit for publication tracked the dynamic interrelations among alcohol demand and alcohol problems across a critical period of drinking development, from age 19 to 21, across six waves of data collection. A random intercept, cross-lagged panel model suggested that specific demand facets (intensity, breakpoint, and O_{max}) operated as lagging indicators of alcohol problems (i.e., potential consequences of increasingly disordered use), whereas demand elasticity operated as a pre-existing liability for subsequent problems.

Another important concept in behavioral economic theory is substance-free reward, which refers to normatively pleasurable activities and stimuli not inherently tied to drug-seeking behavior (e.g., dating, sports, other recreational activities). My work has found multiple aspects of decreased substance-free reward to be linked to more severe SUD, including difficulty accessing sources of reward (Joyner et al., 2016,[7] *Alcoholism: Clinical and Experimental Research*, and replicated in a co-authored paper[8]) and lower frequency of engagement in substance-free activities (Joyner et al., 2018, *Experimental and Clinical Psychopharmacology*).[9] Interestingly, this last paper[9] also evidenced a moderating effect of positive family history of alcohol problems (FH+) on the association between substance-free reward and alcohol problems, such that the negative correlation between the two is observed only among FH+ individuals. This finding dovetails nicely with my aforementioned paper[5] showing that disinhibition, which other work has identified as the primary trait disposition conferred by FH+ status, interacts with low reward sensitivity to amplify the propensity toward substance problems.

Current and Future Work – Bridging Between- and Within-Subject Models of Risk

My current work integrates my research on traits and behavioral economics as described above with the aim of establishing a unifying account of addiction etiology at both the between- and within-subject levels. To bridge to this new area of my work, I successfully obtained research funding from the National Institute on Drug Abuse (NIDA), in the form of an R36 grant ($100,000 in direct costs) that started in August 2020. My grant project, currently in the data collection phase, uses 1) an ecological momentary assessment protocol measuring engagement in substance-free pleasurable activities as well as alcohol, tobacco, and marijuana-related reward, use, and consequences, with mobile surveys administered five times per day, and 2) a multi-method lab-experimental protocol that characterizes substance-related versus substance-free reward through both self-report questionnaires and brain (EEG) responses to reward cues. My major hypothesis is that if an individual possesses limited neurobiological capacity to process natural rewards (e.g., is hyposensitive to rewards), then the behavioral act of engaging in substance-free rewards is unlikely to protect against substance misuse, as substances comparatively provide a source of direct, intense reward delivery. I plan to extend this line of research in my future work to understand personalized models of addiction risk using ecological momentary assessment methods, parsing between- from within-subject mechanisms across self-report, behavioral, and neural measurement modalities. In addition to yielding greater understanding about unique and important research questions, this current grant will serve as an excellent source of preliminary data for future grant applications, increasing the feasibility of translation to a fully independent research program.

A second line of my current and future planned work uses advanced quantitative methods to aid in causal inference using biometrically-informed designs. My dissertation builds on a behavioral genetics approach called the co-twin control model, in which one member of a twin pair serves as the ‘counterfactual’ to the other twin, allowing for estimation of the quasi-causal

effect of one variable on a clinical outcome of interest. Although this innovative modeling method has yielded important insights into the nature and magnitude of potentially causal effects, all current implementations of the co-twin control method dictate effects to be invariant across participants. However, this need not be the case. My dissertation extends this analytic approach to the case of the co-twin control model through the use of *quantile multilevel modeling*. This new quantile co-twin control ("qCTC") modeling method that I've created enables inferences regarding the causal effects of substance use on outcomes, *at different levels of the outcome variable*. For example, in studying brain dysfunction due to the neurotoxic effects of alcohol, one could test whether alcohol played a potentially causal role in brain dysfunction *only at high levels of brain dysfunction*. As a new PI, I intend to apply for NIH funding to comprehensively develop this methodology, including both simulation and applied work, and demonstrate its value in established twin datasets (e.g., Adolescent Brain and Cognitive Development [ABCD]).

In sum, I have established a comprehensive, multi-domain investigative framework for understanding the etiology of addiction that focuses on (1) broad trait dispositions that are heritable but not specific to SUD, and neural processes, rooted in reward sensitivity, that facilitate the expression of SUD rather than other forms of externalizing, (2) proximal risk and maintenance factors for SUD rooted in behavioral economic theory, and (3) between- and within-subject models of risk using ambulatory assessment approaches. It is my sincere belief that research of this type will be instrumental in the development of useful, precise, and scalable early assessment and prevention tools to lessen the impact of addiction on our communities.

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