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Evaluation of Neurobiological Risk Factors for Alcohol Consumption; Convergent Evidence for Predispositional Effects of Brain Volume

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Evaluation of Neurobiological Risk Factors for Alcohol Consumption; Convergent Evidence for Predispositional Effects of Brain Volume

by
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David Antoine Anderson Baranger

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Dedicated to my family,
whose support brought me here

Abstract of the Dissertation

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Alcohol is one of the most widely used psychoactive substances and accounts for 5% of global disease burden. The goal of the present work is to help advance efforts to both identify prognostic markers of risk, and to understand the mechanisms by which alcohol consumption impacts health. Early life stress is one of the strongest predictors of mental illness, including alcohol dependence, and has been hypothesized to impact risk via modulation of striatal reward functions and reward learning. Studies examined the effect of stress on reward learning and processing, and tested for moderation by genetic and environmental risk. Results were largely null showing no impact of early life stress or acute laboratory manipulated stress on behavioral or neural indices of reward learning. There were also suggestive results indicating that genetic risk may moderate the effects of early life stress. These findings challenge suggestions that stress-induced anhedonia may underlie the pathogenic effects of stress, but must also be considered in the context of study design differences (timing of stress manipulation and magnitude of rewards used). The final study in this work took the opposite approach, identifying replicable and genetically-conferred reductions in gray matter volume of frontal gyri, which prospectively predicted alcohol use. Further, gene expression analyses in the post-mortem human frontal cortex identified replicable

associations with genetic risk for alcohol consumption, which implicated changes in spliceosomal and endocytotic pathway components. These results suggest that alcohol consumption does not drive reduced brain volume, but rather that these associations are attributable to shared genetic factors.

Chapter 1: Introduction

1.1 Why study alcohol consumption?

Alcohol use and its associated negative outcomes are ubiquitous international public health concerns. Alcohol is one of the most widely used psychoactive substances (82% of the U.S. population reports lifetime use), is one of the earliest used (29.6% of children aged 12-17 report lifetime use) (Substance Use and Mental Health Administration, 2015), and use is frequently initiated prior to other substances of abuse (Barry et al., 2016). The consequences of alcohol use are substantial; it accounts for 6% of deaths globally, 5% of the global disease burden (World Health Organization, 2014), and costs associated with alcohol use amount to more than 1% of the gross national product in high-and-middle-income-countries (Rehm et al., 2009). Moreover, alcohol use is associated with a host of physical and mental health conditions, including numerous forms of cancer and depression (Kessler et al., 1996; Rehm et al., 2010), further compounding the negative impact of alcohol on public health and the global economy. It is thus critical to advance efforts to both identify prognostic markers of risk, and to understand the mechanisms by which alcohol consumption impacts health.

1.2 Consequences and correlates of alcohol consumption

1.2.1 Comorbidities

Alcohol dependence is frequently observed to be co-morbid with a wide array of other psychiatric disorders, including abuse of other substances, depression, anxiety, post-traumatic stress disorder (PTSD), bipolar disorder, as well as borderline and antisocial personality disorders (Bierut et al., 1998; Conditions & Conditions, 2004; Grant et al., 2008; Kessler et al., 1996). The

associations between alcohol dependence and its comorbidities are complex, as there is evidence for bi-directional risk with several disorders (i.e. depression, anxiety, PTSD, and several personality disorders; see 'Mechanisms of Risk' below). Of these comorbidities, there is evidence that alcohol dependence increases risk for depression, anxiety, and cannabis dependence (Barry et al., 2016; Boden & Fergusson, 2011; Jeanblanc, 2015; Schlossarek et al., 2016). Moderate alcohol consumption has been observed to be associated with reduced risk for depression and anxiety (Bellos et al., 2013), while abstinence has been observed to be associated with increased risk, though this may be attributable to confounds with abstinence, such as the inclusion of former-drinkers (Bell et al., 2014).

1.2.2 Cognition

Chronic alcohol abuse and dependence are associated with accelerated cognitive decline and increased risk for dementia (Topiwala & Ebmeier, 2017). There is some evidence, from large longitudinal epidemiological studies, that moderate alcohol consumption (i.e. 1-2 drinks per day) is associated with improved cognition (Piumatti et al., 2018), though these associations are not consistently observed (Topiwala & Ebmeier, 2017). The context in which alcohol is consumed may also be important, with some data suggesting that the benefits of moderate consumption in older adults are mediated by social-drinking (i.e. maintaining an active social life into old age) (Dunbar et al., 2017), and concerns remain that confounds such as socioeconomic status and intelligence are driving the purported health benefits (Topiwala & Ebmeier, 2017).

Alcohol use in adolescence and young adulthood has been associated with lower performance across a variety of neuropsychological tasks, including attention, verbal memory, visuospatial functioning, processing speed, and executive functioning (Jacobus & Tapert, 2013). While these associations appear to be largely driven by heavy drinkers (Brown et al., 2000;

Squeglia et al., 2010), there is also some evidence of a dose-dependent relationship (Squeglia et al., 2010). Taken together with evidence that an earlier age of initiating alcohol consumption is associated with increased risk for an alcohol use disorder later in life (Aiken et al., 2018; Hingson et al., 2010), these results emphasize that alcohol consumption during adolescence and young adulthood may be detrimental to long-term cognitive health.

Beyond executive functioning and related processes, impulsivity-related constructs are among the most frequently observed correlates of alcohol use and dependence, across both adolescence and adulthood (Heinrich et al., 2016; Jonker et al., 2014; Loxton & Dawe, 2001; Stautz & Cooper, 2013; Tapper et al., 2015). This includes reward sensitivity, behavioral impulsivity, negative urgency, and risk sensitivity (Jentsch et al., 2014), where alcohol use and dependence have been found to be associated with increased impulsivity. In addition to associations with current drug use, executive functioning deficits and increased impulsivity/reward sensitivity may contribute to future risk (see 'Mechanisms of Risk', below) (Coskunpinar & Cyders, 2013).

1.2.3 Brain function and structure

In line with its effects on cognition, alcohol dependence is associated with widespread reductions in brain volume of regions known to be important for executive functioning, long term memory, and reward processes. This includes the dorsal lateral prefrontal cortex, middle frontal cortex, anterior cingulate cortex, insula, superior temporal cortex, precentral gyrus, thalamus, hippocampus, striatum, and cerebellum (Spear, 2018; Yang et al., 2016). While only a limited number of longitudinal studies have been conducted in adults, there is evidence that alcohol dependence is associated with accelerated age-related shrinkage of the frontal cortex (Sullivan et al., 2018). Alcohol consumption has also been reported to be associated with lower intracranial

volume (ICV) (Paul et al., 2008) and hippocampal volume (Sullivan et al., 2018; Topiwala et al., 2017), lower volume of the cerebellum, insula, caudate and operculum (Thayer et al., 2017), and in a sample with comorbid psychiatric disorders (i.e. schizophrenia and bipolar disorder), wide-spread cortical thinning, particularly in the frontal cortex and insula (Lange et al., 2017).

In adolescents, heavy drinking is correlated with lower volume and thickness in the frontal and temporal cortices (Pfefferbaum et al., 2016; Whelan et al., 2014), as well as lower volume of the hippocampus, cerebellum, insula, cingulate, cuneus, and striatum (Heikkinen et al., 2016; Lisdahl et al., 2013; Nagel et al., 2005; Squeglia et al., 2014; Thayer et al., 2017). Longitudinal studies have found that the initiation of heavy drinking in adolescence is associated with accelerated age-related shrinkage of the frontal and temporal cortices (Luciana et al., 2013; Pfefferbaum et al., 2017; Squeglia et al., 2015). Twin analyses have also found some evidence for putatively causal effects of heavy alcohol consumption on reduced volume of the hippocampus and temporal cortex (Wilson et al., 2017, 2015). Notably, the one longitudinal study to report also examining moderate alcohol use did not find any associations (Pfefferbaum et al., 2017).

Rodent models have strongly implicated striatal dopamine neurotransmission, particularly in the context of reward paradigms, in the etiology of addiction (Spoelder et al., 2017; Wang et al., 2015). Thus, a large body of work has focused on the effects of alcohol addiction and dependence in humans on reward task-related brain activity via functional magnetic resonance imaging (fMRI) (Balodis & Potenza, 2015). Studies using drug-associated cues have largely found evidence for increased activation at the time of cue receipt in an extended network of reward-associated regions, including the caudate, insula, amygdala, anterior cingulate, and orbitofrontal cortex (Diekhof et al., 2008; Geyer et al., 2010). In contrast, studies using monetary rewards have largely found evidence for reduced activation of the striatum during reward anticipation, though this evidence is more mixed (Balodis & Potenza, 2015). Differences in findings across studies

have been attributed to differences in duration of illness, as well as potential moderating effects of socioeconomic status (Balodis & Potenza, 2015; Hommer et al., 2011).

The largest functional neuroimaging study to specifically examine adolescent drinking behavior to date (n=692), found that binge drinking was associated with reduced prefrontal and inferior frontal activation during reward anticipation, as well as increased activation of the hippocampus and caudate (Whelan et al., 2014). A later study that included the same sample (N=1,544) found that alcohol consumption was positively correlated with caudate activity during reward anticipation (Jia et al., 2016). Beyond reward processing, and in line with data supporting an effect of alcohol abuse on executive functions, heavy drinking or binge drinking in adolescence has been associated with differences in frontal and parietal activation during working memory and cognitive control tasks across several studies, though the direction of effect is not always consistent (Feldstein Ewing et al., 2014). Some have proposed that this might be interpreted with a shifted “inverted-U” model (Squeglia et al., 2014), where initial damage to the system (i.e. 1-2 years of binge drinking) requires compensatory activity to maintain performance (i.e. greater activity), but after several years of damage it’s too difficult to maintain performance, resulting in reduced activation.

1.3 Risk for alcohol consumption

1.3.1 Environmental risk

Early life stress (ELS) is arguably the single strongest environmental predictor of risk for psychopathology, including alcohol dependence (Enoch, 2011). Model simulations from a large cross-sectional survey found that as much as 21% of the population risk for substance use may be attributable to ELS (Green et al., 2013). Beyond the abundant cross-sectional evidence,

longitudinal prospective studies have also repeatedly found that ELS predicts the future onset and severity of alcohol use (Cornelius et al., 2016; Harrington et al., 2011; Mersky et al., 2013; Ramos-Olazagasti et al., 2017). Recent and acute stress are also associated with increased alcohol consumption (Casement et al., 2013; Magrys & Olmstead, 2015; McGrath et al., 2016) possibly as a coping mechanism (Park et al., 2004), and there is some evidence that the effect of recent stress may be stronger in people who also experienced ELS (Young-Wolff et al., 2012).

In addition to stress, circadian disruption is also associated with increased risk for alcohol dependence (Hasler et al., 2012), and circadian disruption is hypothesized to be one of the mechanisms by which stress impacts health outcomes (Sarkar, 2012). There is a bi-directional relationship between alcohol use and the circadian system. Moderate alcohol consumption induces sleepiness (Roehrs & Roth, 2001), while binge drinking and alcohol dependence are associated with disrupted sleep homeostasis, reduced sleep quality, and disrupted biological and cellular rhythmicity (Huang et al., 2010; Roehrs & Roth, 2001; Thakkar et al., 2015). Conversely, chronotype and sleep quality are associated with future risk for alcohol dependence (Hasler et al., 2017; Logan et al., 2017; Wong et al., 2018), and shift work is associated with sleep disruption and increased alcohol consumption (Morikawa et al., 2013). The circadian system has also been proposed to mediate some of the effects of stress on risk for alcoholism, as the major stress system hormones are regulated via circadian mechanisms (Nader et al., 2010).

1.3.2 Genetic risk

Twin studies indicate that both alcohol dependence and consumption are moderately heriTable 2.(dependence: 49% (Verhulst et al., 2015); consumption: 33% (Mbarek et al., 2015)). Moreover, cross-sectional genome-wide association studies (GWAS) have found that a substantial portion of the heritability is captured by common single nucleotide polymorphisms

(SNPs; dependence: 10-30% (Palmer et al., 2015; Walters et al., 2018); consumption: 13% (Clarke et al., 2017)). These results indicate that, as with most human traits, both genetic and environmental factors influence risk. Perhaps the best-known single variant which predicts alcohol dependence and consumption is rs671 in the aldehyde dehydrogenase (*ALDH2*) gene, the A-allele of which results in a catalytically inactive version of the protein (Edenberg, 2007), and in turn slows metabolism of acetaldehyde (the second step in the alcohol metabolism pathway). This allele, which is most common in East-Asian populations, results in the well-known flushing of the face, in addition to significant discomfort, thereby resulting in reduced risk for alcohol dependence (Jorgenson et al., 2017).

Thanks to relatively recent large-scale collaborations, such as the Psychiatric Genetics Consortium (PGC), large nation-wide studies like the UK Biobank, and the increase in public-interest in personal health technologies like the company 23andMe, there has been a surge of extremely large-sample GWAS (i.e. N = 50k–120k) for numerous phenotypes, including several alcohol use and dependence phenotypes (Clarke et al., 2017; Crist et al., 2018; Jorgenson et al., 2017; Sanchez-Roige et al., 2017; Schumann et al., 2016; Walters et al., 2018). These studies have finally reached the sample-size threshold necessary to identify dozens of loci that survive statistical correction for multiple comparisons (i.e. correcting for an estimated effective 1 million independent comparisons at $p<5x10^{-8}$). Some findings recapitulate what was already known about the etiology of alcohol use and dependence, including several associations in alcohol dehydrogenase genes expressed in the liver (i.e. *ALDH2*, *ADH1B*, *ADH1C*, and *ADH5*).

Other associations from GWAS provide new and complimentary insights. Loci near the autism candidate susceptibility gene *AUTS2* have been associated with both alcohol phenotypes and insomnia (Jorgenson et al., 2017; Schumann et al., 2016; Stein et al., 2018), highlighting the reciprocal relationship of these phenotypes. Recent as-yet unpublished work has found an association between alcohol consumption and a locus spanning the Corticotropin Releasing

Hormone Receptor 1 (*CRHR1*), one of the primary receptors for CRF, which regulates the HPA axis and the stress response (Crist et al., 2018; Sean M. Smith & Vale, 2006). In addition to these, several associations with genes that are known to play important roles in brain function and development have been found. These include *AUTS2* (Schumann et al., 2016), which has been implicated in human-specific evolution and neuronal development (Oksenberg & Ahituv, 2013). Variants in *CADM2* have been identified (Clarke et al., 2017; Crist et al., 2018) - a brain-enriched cellular adhesion protein also associated in GWAS of executive functioning and risk-taking (Ibrahim-Verbaas et al., 2016; Strawbridge et al., 2017). Variants in a more well-known gene, *DRD2*, have also been found (Clarke et al., 2017; Crist et al., 2018). *DRD2* is the dopamine D2 receptor, a classic schizophrenia candidate-gene, which is well-known to play a role in striatal functioning and has also been found in recent GWAS of schizophrenia and sleep duration (Cade et al., 2016; Ripke et al., 2014). Replicable associations with *KLB*,, a gene encoding a protein which binds the liver enzyme FGF21, have been found (Clarke et al., 2017; Schumann et al., 2016), though intriguingly it has been demonstrated that *KLB* may exert its influence on alcohol consumption via a neuronal mechanism (Schumann et al., 2016).

Another confirmation that GWAS of alcohol use and dependence have identified replicable genetic predictors of alcohol phenotypes come from studies of polygenic risk scores. A polygenic risk score (PRS) is a metric reflecting an individual's genetic burden for a disease of interest. PRS are typically calculated by averaging the number of disease-associated alleles, weighted by their effect-size, from independent samples (Bogdan et al., 2018). While PRS do not capture the total amount variance attributable to genetics, they do replicably predict risk. Initial PRS analyses have found that a PRS for alcohol dependence and consumption replicably predict these same phenotypes in independent samples (Clarke et al., 2016, 2017; Kapoor et al., 2016; Li et al., 2017; Savage et al., 2018; Taylor et al., 2016). Though the effect sizes of PRS analyses are small (typically <0.5%), recently developed methods (Turley et al., 2018) can be used to generate

modest improvements (>2%; Baranger, unpublished data). Thus, further work is needed before the association between polygenic risk scores for alcohol phenotypes and other traits can be reliably examined.

In addition to the identification of genetic associations, recently developed methods permit GWAS researchers to examine the extent to which genetic associations may correlate across disorders - using only the statistical associations with each phenotype - even in samples that are only partially overlapping or fully independent (i.e. LD-Score regression (Bulik-Sullivan et al., 2015)). This approach can help to establish whether it is plausible that two traits share causal genetic risk factors, as two traits will show a higher genetic correlation if they share more causal variants. It should be noted that this method is not a test for causality *per se*, as it is correlation-based. For instance, smoking and lung cancer have a high genetic correlation (Bulik-Sullivan et al., 2015) in large part because smoking causes lung cancer, not simply because genetic variants associated with smoking independently increase risk for lung cancer (though this may also be true). As expected, alcohol use and dependence show genetic correlations with the use of other addictive and psychoactive substances, namely tobacco and cannabis use (Clarke et al., 2017; Walters et al., 2018). Alcohol dependence is also consistently associated with other psychiatric disorders, including depression, schizophrenia, and ADHD, echoing the epidemiological literature on the consistent comorbidities of psychiatric disorders (Crist et al., 2018; Walters et al., 2018). These patterns of genetic correlations suggest that many of the risk associations are not specific to any one disorder, but rather that they indicate a general increased genetic vulnerability to many psychiatric disorders (i.e. the omnigenic model (Boyle et al., 2017)).

Interestingly, alcohol consumption and dependence show divergent genetic correlations with other health outcomes. Alcohol consumption is positively correlated with education and HDL cholesterol, and negatively correlated with BMI, obesity, and related health outcomes (Clarke et al., 2017; Sanchez-Roige et al., 2017). In contrast, alcohol dependence is not associated with

these health outcomes, and is *negatively* correlated with education (Crist et al., 2018; Walters et al., 2018). These divergent results may be driven by differences in the socioeconomic (SES) distribution of alcohol dependence, where dependence and binge-drinking are more prevalent in low SES populations, and consumption without dependence is more prevalent in high SES populations (Crist et al., 2018). However, these correlations also echo the somewhat controversial observations of putative cardiovascular health-benefits associated with moderate alcohol consumption (Roerecke et al., 2014), and suggest that alternative explanations for those findings, such as more alcohol consumption among individuals genetically predisposed towards increased cardiovascular health (e.g. the "sick quitter" hypothesis and survivor bias (Shaper et al., 1988)), bear further consideration.

1.3.3 Genetic-by-environmental risk

Genes and the environment can impact risk independently, but there is growing evidence that they also interact with one another to increase or decrease risk for alcohol phenotypes. There is a large amount of evidence from twin studies for gene-by-environment (GxE) effects – comparisons of heritability between families with different environmental exposures, or within twins across time, may indicate the presence of a GxE effect if the heritability estimate differs depending on the environmental background. Broadly, results indicate that a permissive environment (e.g. low parental knowledge or wider availability) magnifies the effects of genetic risk for alcohol consumption (Young-Wolff et al., 2011). For instance, heritability for alcohol use is higher in twins who report that more of their friends drink (Dick et al., 2007), and heritability is higher in young adults who live in areas with more businesses selling alcohol (Slutske et al., 2018). Similarly, a study using polygenic risk scores found that high genetic risk was predictive of increased alcohol problems in adolescents in permissive environments, but were not predictive

of use in adolescents in non-permissive environments (Salvatore et al., 2014). Finally, there is growing evidence that environmental stressors moderate genetic risk. A recent GxE GWAS identified a variant that was associated with increased risk for alcohol misuse in African American participants who were trauma-exposed, and decreased risk in trauma-free controls (Polimanti et al., 2018). Notably, this variant was in the gene *PRKG1*, which has been implicated in learning, memory, and circadian processes.

1.4 Predicting risk

1.4.1 Alcohol use and mental illness

Several psychiatric disorders are associated with increased risk of alcohol consumption, problematic drinking, and alcohol dependence. Longitudinal studies have found that both depression and anxiety predict future risk in adults (Crum et al., 2001; Kushner et al., 2000; Prisciandaro et al., 2012) as well as in adolescents and young adults (Aalto-Setälä et al., 2002; Webster-Stratton, 2001; King et al., 2004; Kumpulainen, 2000; Marmorstein et al., 2010; Nichter & Chassin, 2015), and there is some evidence that these effects may be moderated by sex (DeMartini & Carey, 2011; JianLi Wang & Patten, 2001). In line with the large body of evidence that early life stress increases risk for alcohol use and dependence (see 'Environmental Risk' above), post-traumatic stress disorder (PTSD) has also been observed to prospectively predict alcohol use, both in college (Read et al., 2013) and combat veteran (Black et al., 2018; Gaher et al., 2014; Possemato et al., 2015) samples. Similarly, borderline and antisocial personality disorders have both been observed to be predictive of future alcohol use problems (Rosenström et al., 2018; Stepp et al., 2005), as have externalizing disorders (e.g. ADHD and conduct disorder) (Farmer et al., 2016; Wilens et al., 2011).

Recent genetic studies have also observed that genetic risk (ascertained via polygenic risk score) for some disorders is correlated with, and predictive of, substance and alcohol use. Genetic risk for depression, bipolar disorder, schizophrenia, and ADHD have been observed to be correlated with alcohol use and dependence (Andersen et al., 2017; Carey et al., 2016, 2017; Du Rietz et al., 2018), though the associations with schizophrenia may not be specific to alcohol dependence (Hartz et al., 2017). This work builds on evidence from genetic correlation analyses (see 'Genetic Risk' above) by providing further evidence that the associations between alcohol phenotypes and other psychiatric disorders can at least partially be attributable to shared genetic risk factors.

1.4.2 Cognition

Several cognitive phenotypes are predictive of future alcohol use. While there is abundant evidence that chronic alcoholism impairs executive functions (see 'Consequences and Correlates' above), there is also some evidence that poor working memory precedes the initiation of alcohol use (Khurana et al., 2013; Peeters et al., 2015). Beyond these, impulsivity and related externalizing constructs (e.g. risk taking) are strongly implicated in the etiology of alcohol use and dependence (Dick et al., 2010). Several longitudinal studies of adolescents have found that behavioral and self-report measures of impulsivity and reward sensitivity predict future alcohol use (Fernie et al., 2013; Nigg et al., 2006; Stautz et al., 2016; Tapert et al., 2014). Additional distinct pathways leading to alcohol use have been observed, particularly drinking to cope with negative affect (Verheul et al., 1999). However, this pathway is suggested to have largely divergent neural and cognitive underpinnings (Nikolova et al., 2015), and as such will not be discussed in detail here.

Differences in impulsivity and reward phenotypes are related to environmental risk factors like stress and sleep, and there is some evidence from longitudinal studies that impulsivity partially mediates the effects of early life stress (Oshri et al., 2017) and sleep problems (Wong et al., 2010) on risk for later alcohol use. Indeed, impulsivity and reward learning behaviors have been observed to vary diurnally (Byrne & Murray, 2017; Whitton et al., 2018), and sleep quality and chronotype correlate with impulsivity measures (Kandeger et al., 2018; McGowan et al., 2016). Similarly, early life stress is associated with differences in impulsivity and reward sensitivity (Birn et al., 2017; Kamkar et al., 2017; Kim et al., 2018), and acute stress manipulations have also found that stress can modify reward sensitivity and learning (Bogdan et al., 2010; Bogdan & Pizzagalli, 2006; Bogdan et al., 2011; Corral-Frías et al., 2016).

Impulsivity and other externalizing behaviors also likely predict future alcohol use and dependence because, in part, they share some underlying genetic risk factors. Building on evidence from twin studies showing a genetic overlap of ADHD and alcohol dependence (Edwards et al., 2012; Quinn et al., 2016), twin studies have also shown genetic overlap of impulsivity measures and alcohol outcomes (Khemiri et al., 2016; Rosenström et al., 2018). Similarly, a family history of alcoholism is associated with increased impulsivity in non-alcoholic adolescents and adults (Acheson et al., 2011; Andrews et al., 2011; Jones et al., 2017; Sanchez-Roige et al., 2016; Sugaparaneetharan et al., 2016). Recently, a GWAS of self-reported risk-taking found that risk taking has a positive genetic correlation with alcohol consumption (Jones et al., 2017), and polygenic risk for alcohol use has been found to be associated with sensation seeking (seeking out novel or exciting experiences) (Li et al., 2017).

1.4.3 Brain function and structure

Differences in brain function and structure are proposed to mediate the effects of risk factors on future impulsivity, risk behavior, and reward learning, which in turn lead to increased

risk for alcohol use and dependence. Activation of the striatum, prefrontal cortex, insula, and cingulate correlate with risk taking, reward processing, and impulsivity in adolescents (Blankenstein et al., 2018; Braams et al., 2015; Schreuders et al., 2018; Silverman et al., 2015) and young adults (Chase et al., 2017; Hariri et al., 2006). Striatal reward activation has also been found to be predictive of future impulsivity behavior in a small sample of adolescents (van Duijvenvoorde et al., 2014). Reduced volume and thickness of many of these same regions, particularly the frontal cortex, insula, and cingulate, have been associated with both self-report and behavioral impulsivity in adults and adolescents (Bjork et al., 2009; Holmes et al., 2016; Pehlivanova et al., 2018; Tschernegg et al., 2015).

There is also evidence that activity and structure of these regions is predictive of future alcohol use in adolescents. Three studies have combined brain function and structure in machine learning analyses predicting future adolescent drinking behavior. Whelan et al., 2014 found that increased volume of the precentral gyrus, reduced volume of superior frontal gyrus, and increased reward and inhibition-related activity of these regions at age 14, contributed to the model prediction of age 16 binge drinking behavior. Squeglia et al., 2016 found that a thinner cortex and reduced working memory activation, particularly of frontal and temporal regions, in drug-naive adolescents ages 12-14 contributed to the model prediction of moderate-to-heavy drinking at age 18. Bertocci et al., 2017 found that in adolescents ages 10-17, increased reward-related prefrontal activity, decreased insula activity, and a thicker cingulate contributed to the prediction of initiation of substance and alcohol use 2 years later.

Studies focusing on brain structure in adolescence have been less successful. One study has found that reduced volume of the nucleus accumbens was predictive of future initiation of regular alcohol and substance use (Urošević et al., 2015). Lower baseline volume of the cingulate and pars triangularis has also been reported to predict future heavy drinking in a small study of adolescents (Squeglia, et al., 2014). However, these results were not replicated in two recent

larger analyses (Pfefferbaum et al., 2017; Seo et al., 2018) which have found that baseline gray matter volume in adolescents was not predictive of who later made the transition to heavy drinking. It is difficult to say why this literature is mixed. One possible reason is that studies focusing on initiation or level of use report relatively more statistically significant associations than those testing whether a threshold of alcohol consumption is surpassed - dichotomizing behavior in this way may mask effects (Altman, 2006). Another potential reason is that studies of heavy drinking adolescents often combine low and non-drinking participants in the control group (Pfefferbaum et al., 2017; Seo et al., 2018). This approach helps attain a sufficiently large sample size; however, it is likely that some of the non-drinkers have never exposed to alcohol, and as such may actually be predisposed towards heavy drinking.

Studies of reward-related activity in adolescence have generally met with more success. Heightened activity of reward regions during risky decision making is predictive of future binge drinking (Morales et al., 2018), and future onset of substance and alcohol use is predicted by heighten striatal activation to monetary rewards (Stice et al., 2013). Blunted striatal anticipatory activity has also been found to predict future problematic alcohol and drug use in adolescents (Büchel et al., 2017), though the opposite direction of effect (i.e. heightened anticipatory activity) has also been reported (Heinrich et al., 2016; Heitzeg et al., 2014). There is some evidence that this effect may be moderated by the age of initiation - heightened anticipatory activity is predictive of initiation at age 14, but not age 16 in one study (Heinrich et al., 2016), which might explain these divergent findings.

There is additionally evidence that genetic risk for alcohol use influences the structure and function of regions implicated in alcohol use. The effects of alcohol use on accelerated gray-matter shrinkage have been found to be moderated by a family history of alcoholism, wherein adolescents with a family history show a steeper decline across the brain (Pfefferbaum et al., 2017), though it was not tested whether family history predicted baseline volume. Non-drinking

adolescents with a family history of alcohol dependence have also been observed to have thinner frontal and parietal cortices (Henderson et al., 2018). A study of female adolescent twins found evidence that the majority of volumetric reductions (amygdala, and frontal and temporal cortex) were attributable to genetic vulnerability (Wilson et al., 2015). Few studies have examined possible genetic effects in adults – there is one report of reduced amygdala volume associated with alcoholism, which was fully attributable to familial risk (Dager et al., 2015).

Studies of reward related activity have also found evidence for an influence of alcohol-related genetic risk. Blunted striatal response to reward anticipation has been reported in young adults with a family history of alcoholism (Andrews et al., 2011; Yau et al., 2012). The direction of this association appears to be flipped in adolescence, with increased striatal response to reward anticipation and alcohol cues in adolescents with a family history of alcohol use (Nguyen-Louie et al., 2017; Stice & Yokum, 2014). Further evidence comes from the largest GWAS of reward-related brain activity to date (reward anticipation), which was conducted in a sample of adolescents (Jia et al., 2016). They identified a variant associated with reward anticipation in *VSP4*, a gene which has been shown to influence alcohol reward sensitivity in rodents.

There is abundant evidence that brain structure and function are influenced by environmental risk factors for alcohol use, including stress and circadian variables. Research on the effects of stress on brain structure has largely focused on corticolimbic circuitry implicated in the stress response itself – namely the amygdala, hippocampus, and frontal cortex (Bogdan et al., 2015). Reduced volume of the hippocampus has been observed in PTSD (Logue et al., 2018) and with childhood stress (Dahmen et al., 2018; Whittle et al., 2017), though notably the association with childhood stress is not consistently observed (Marečková et al., 2018). There is also some evidence that the effect may be moderated by genetic risk (Pagliaccio et al., 2014) or the subtype of early adversity (King et al., 2018). In contrast, while largely negative associations between PTSD and amygdala volume have been reported (Logue et al., 2018), studies in children

have reported positive associations (Evans et al., 2016; Tottenham et al., 2010), though again this is an inconsistent association (Pagliaccio et al., 2014). It should be noted that for both the amygdala and hippocampus, there is some evidence that the method of delineating the boundaries of the structures influences whether positive or negative associations are observed (Lyden et al., 2016). Associations between stress and structure of the frontal cortex are similarly inconsistent, with both negative (Besteher et al., 2017; Haddad et al., 2015; Savic, 2015) and positive associations (Evans et al., 2016; Michalski et al., 2017) reported, for both early life and recent stress.

Associations between stress and reward-related activity of the brain are largely more consistent than structural associations. Early life stress has been widely reported to be associated with reduced striatal activity at reward anticipation (Boecker et al., 2014; Goff & Tottenham, 2014; Hanson et al., 2015; Novick et al., 2018; Teicher et al., 2016), though there are also reports of positive associations at reward receipt (Kamkar et al., 2017). Acute stress manipulations have similarly been associated with blunted striatal activity, particularly at reward receipt (Bogdan et al., 2011; Kumar et al., 2014; Lewis et al., 2014; Montoya et al., 2014; Porcelli et al., 2012).

There is a growing body of work indicating that circadian variables are associated with brain structure and function. Sleep disturbances in early childhood have been associated with reduced brain volume, particularly of the prefrontal cortex (Kocevska et al., 2016) and an evening chronotype has been associated with reduced gray matter in the orbitofrontal cortex (Takeuchi et al., 2015). There is more evidence implicating the circadian system in reward related brain activity. Striatal activation to reward receipt has been observed to vary diurnally, though evidence is conflicting as to whether its minimum is in the evening (Hasler et al., 2014) or afternoon (Byrne et al., 2017). An evening chronotype has been associated with elevated striatal and frontal activation to reward receipt (Hasler et al., 2017, 2013), and a variety of phenotypes related to a lack of sleep,

including sleep deprivation and insomnia, are associated with blunted prefrontal activation to reward receipt (Casement et al., 2016; Hasler, Dahl, et al., 2012; Mullin et al., 2013).

1.5 Aims of the current work

The research highlighted in this Introduction suggests a mechanistic path leading from risk factors to alcohol use and dependence. These effects are likely mediated via brain structure and function, which subsequently drive differences in behavior that increase risk. The following studies were designed to further examine, replicate, and expand on this work. Building on links between early life stress, striatal reward activity, and alcohol dependence, the first study (Chapter 2) examined whether a previously identified interaction between a circadian genetic risk variant and stress, which predicted alcohol consumption, replicates in an independent sample and is mediated by striatal reward activity. The subsequent study (Chapter 3) examined the interaction between different forms of stress – early life and acute – and how these risk factors impact reward learning behavior and reward processing. The final study in this work (Chapter 4) took a different approach, focusing on the associations between non-disordered alcohol consumption and brain structure. While correlations between alcohol use and brain structure in adults have been widely reported in the literature, the causal nature of this relationship remains unknown, as the majority of reports are correlational. I hypothesized that structural associations are primarily attributable to shared genetic factors, and thus would be predictive of future alcohol-related behaviors.

Chapter 2: PER1 rs3027172 genotype interacts with early life stress to predict problematic alcohol use, but not reward-related ventral striatum activity

Baranger DAA, Ifrah C, Prather AA, Carey CE, Corral- Frías NS, Conley ED, Hariri AR, Bogdan R. PER1 rs3027172 Genotype Interacts with Early Life Stress to Predict Problematic Alcohol Use, but Not Reward-Related Ventral Striatum Activity. *Frontiers in Psychology*, (2016) 7(3), 1–10. doi:10.3389/fpsyg.2016.00464

2.1 Abstract

Increasing evidence suggests that the circadian and stress regulatory systems contribute to alcohol use disorder (AUD) risk, which may partially arise through effects on reward-related neural function. The C allele of the *PER1* rs3027172 single nucleotide polymorphism reduces *PER1* expression in cells incubated with cortisol and has been associated with increased risk for adult AUD and problematic drinking among adolescents exposed to high levels of familial psychosocial adversity. Using data from undergraduate students who completed the ongoing Duke Neurogenetics Study (n=665), we tested whether exposure to early life stress (ELS; Childhood Trauma Questionnaire) moderates the association between rs3027172 genotype and later problematic alcohol use (Alcohol Use Disorders Identification Test) and ventral striatum (VS) reactivity to reward (card-guessing task while functional magnetic resonance imaging data were acquired). Initial analyses found that *PER1* rs3027172 genotype interacted with ELS to predict both problematic drinking and VS reactivity; minor C allele carriers, who were also exposed to elevated ELS reported greater problematic drinking and exhibited greater ventral striatum reactivity to reward-related stimuli. When gene x covariate and environment x covariate interactions were controlled for, the interaction predicting problematic alcohol use remained significant ($p<0.05$, corrected) while the interaction predicting VS reactivity was no longer significant. These results extend our understanding of relationships between *PER1* genotype, early life stress, and problematic alcohol use, and serve as a cautionary tale on the importance of controlling for potential confounders in studies of moderation including gene x environment interactions.

2.2 Introduction

Observable psychiatric symptoms (e.g., insomnia/hypersomnia) and biological rhythm perturbation (e.g., dysregulated diurnal cortisol) have been linked to variability in circadian rhythm function (Chong et al., 2012; Nader et al., 2009; Wirth et al., 2013; Wulff et al., 2009). Accumulating cross-species evidence highlights a bidirectional relationship between the circadian system and alcohol consumption; circadian manipulations induce changes in alcohol consumption while alcohol intake impacts circadian rhythm-related gene expression (Gamsby et al., 2013; Kovanen et al., 2010; McCarthy et al., 2013; Spanagel et al., 2005). Further evidence suggests that stress, one of the most potent provocateurs of alcohol use (Enoch, 2011), may play an important role in links between alcohol use and circadian rhythm dysregulation, through interaction with the stress-regulatory neuroendocrine hypothalamic pituitary adrenal (HPA) axis (Sarkar, 2012).

The circadian system is governed by a system of transcriptional repressors (i.e., Period genes: *PER1, PER2, PER3*; Cryptochrome genes: *CRY1, CRY2*) and enhancers (i.e., *CLOCK* and *BMAL1*) that influence numerous downstream clock-responsive genes to maintain a 24-hour biochemical (e.g., hormone production), physiological (e.g., brain function, body temperature), and behavioral (e.g., sleep. eating) cycle (Sarkar, 2012). The maintenance of this daily oscillation is disrupted by stress (Meerlo et al., 2002) with intriguing evidence that mutual interactions among the circadian system and HPA axis may mediate these effects (Nader et al., 2010) and importantly contribute to problematic alcohol use (Blomeyer et al., 2013; Dong & Bilbao, 2011). The period 1 gene (*PER1*) plays a prominent role integrating the circadian system and HPA axis, with recent evidence that it may be critical for understanding problematic drinking behavior. *mPer1* null mutant mice (*mPer1*^{Brdm1}) have increased ethanol intake and conditioned place preference (Gamsby et al., 2013). Moreover, highlighting the potential etiologic role of stress and the HPA axis in this relationship, these mice display stress-induced (social defeat, swim stress, or foot

shock) increases in ethanol consumption (Dong & Bilbao, 2011) and impaired glucocorticoid rhythmicity (Dallmann et al., 2006).

While the specific mechanisms by which stress and circadian disruption modulate alcohol consumption remain to be elucidated, evidence suggests that altered neural processing of rewards may play a mediating role. Indeed, it has be shown that that individuals with alcohol use disorders and those at genetic risk for their development have differential ventral striatum responses to non-alcohol rewards (Beck et al., 2009; Yau et al., 2012). Further, knocking out *mPer1* or reducing its expression in rodents abolishes conditioned place preference to drug reward (Abarca et al., 2002; Y. Liu et al., 2007), and sleep deprivation is associated with enhanced striatal reactivity to rewards in humans (Mullin et al., 2013; Venkatraman et al., 2011). Moreover, early life stress (ELS) is associated with reduced D2 dopamine receptor positive cells in the striatum of rodents (Li et al., 2013) and reduced ventral striatal activation to rewards in human participants (Boecker et al., 2014; Dillon et al., 2009).

In humans, a single nucleotide polymorphism (SNP) within *PER1*, rs3027172, has been associated with individual differences in cortisol-dependent gene expression as well as problematic drinking in the context of environmental adversity (Dong & Bilbao, 2011). Specifically, the minor C allele at rs3027172, which leads to reduced *PER1* expression in B-lymphoblastoid cell lines incubated with cortisol, predicts elevated rates of alcohol dependence among adults and problematic drinking among adolescents exposed to prenatal familial psychosocial adversity. Using data from the ongoing Duke Neurogenetics Study (n=665), which assesses a wide range of behavioral, experiential, and biological phenotypes in university students, the present study examined whether *PER1* rs3027172 genotype and ELS interact to predict problematic alcohol use. We further examined whether *PER1* rs3027172 genotype and ELS predict variability in reward-related ventral striatum reactivity, which may play a mediating role linking *PER1* rs3027172 genotype and ELS to problematic alcohol use.

2.3 Materials and Methods

2.3.1 Participants

Overlapping neuroimaging and genetic data that were fully processed by January 6th 2014 were available from 727 participants who completed the Duke Neurogenetics Study (DNS). The DNS assesses a wide range of behavioral, experiential, and biological phenotypes among young-adult (i.e., 18-22 year-old) college students. Each participant provided informed written consent prior to participation in accord with the Declaration of Helsinki and guidelines of the Duke University Medical Center Institutional Review Board. Participants received $120 remuneration. All participants were in good general health and free of DNS exclusion criteria: (1) medical diagnosis of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease or lifetime psychotic symptoms; (2) use of psychotropic, glucocorticoid or hypolipidemic medication, and (3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension). Current DSM-IV Axis I and select Axis II disorders (Antisocial Personality Disorder and Borderline Personality Disorder) were assessed with the electronic Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and Structured Clinical Interview for the DSM-IV Axis II (SCID-II) (First et al., 1996). These disorders are not exclusionary as the DNS seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology.

The final sample consisted of 665 participants after quality assurance (age=19.64±1.24; 294 males; 123 with a DSM-IV Axis I disorder; 305 European Americans, 73 African Americans, 187 Asians, 39 Latinos, and 61 of Other/Multiple racial origins according to self-reported ethnicity). Participants were excluded (n=62) for scanner-related artifacts in fMRI data (n=5), incidental structural brain abnormalities (n=2), a large number of movement outliers in fMRI data (n=31; see ART below), poor behavioral performance or an inadequate feedback schedule (n=11), outlier status according to ancestrally-informative principal components (n=6), scanner malfunction

(n=2), incomplete fMRI data collection (n=1), missing or uncollected task behavioral data (n=1), and subjects falling asleep (n=2). An additional participant was excluded as they did not complete the questionnaires used for these analyses (n=1). Comparison of participants excluded due to lack of neuroimaging data to those included found no significant differences (**Supplemental Table 2.1**).

2.3.2 Self-report Questionnaires

Participants completed a battery of self-report questionnaires to assess past and current experiences and behavior. The Childhood Trauma Questionnaire (CTQ; (Bernstein et al., 2003), the Alcohol Use Disorders Identification Test (AUDIT; (Saunders et al., 1993), and the Pittsburgh Sleep Quality Inventory (PSQI; (Buysse et al., 1989)) were used for the present study. The CTQ is a 28-item, retrospective screening tool used to detect the occurrence and frequency of emotional, physical, and sexual abuse as well as emotional and physical neglect before the age of 17 ($\alpha = 0.654$). The instrument's five subscales, each representing one type of abuse or neglect, have robust internal consistency and convergent validity with a clinician-rated interviews of childhood abuse (Scher et al., 2001). The AUDIT is a 10-item scale developed by the World Health Organization to screen for hazardous or dependent alcohol use patterns by assessing the frequency and nature of consumption ($\alpha = 0.799$); a score of 8 or greater is considered indicative of hazardous or harmful use (Saunders et al., 1993). While the AUDIT was originally developed to screen for alcohol use problems and high-risk drinking in primary care settings, evidence suggests that it is a valid assessment for college student populations as well (Kokotailo et al., 2004). The PSQI is a 19-item scale that is widely used and considered a reliable measure of global sleep quality and sleep-related symptoms over the past 1 month ($\alpha = 0.727$). Scores range from 0 to 21, with poorer sleep quality associated with a higher score.

2.3.3 Genotyping

DNA was isolated from saliva derived from Oragene DNA self-collection kits (DNA Genotek) customized for 23andMe (www.23andme.com). DNA extraction and genotyping were performed through 23andMe by the National Genetics Institute (NGI), a CLIA-certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of two different Illumina arrays with custom content was used to provide genome-wide SNP data, the HumanOmniExpress or HumanOmniExpress-24 (Do et al., 2011; Eriksson et al., 2010; Hu et al., 2016; Tung et al., 2011).

PER1 rs3027172 was directly genotyped for 324 participants. It was imputed for the remaining 403. Imputation was run separately for participants genotyped on the Illumina HumanOmniExpress and the Illumina HumanOmniExpress-24 arrays using bi-allelic SNPs only, the default value for effective size of the population (20,000), and chunk sizes of 3Mb and 5Mb for the respective arrays. Within each array batch, genotyped SNPs used for imputation were required to have missingness < 0.02, Hardy-Weinberg equilibrium $P > 10^{-6}$, and MAF > 0.01. The imputation reference set consisted of 2,504 phased haplotypes from the full 1000 Genomes Project Phase 3 dataset (May 2013, over 70 million variants, release "v5a"). Imputed SNPs were retained if they had high imputation quality (INFO >0.9), low missingness (<5%), and MAF > 0.01. *PER1* rs3027172 had excellent imputation metrics (INFO=0.997, Certainty=0.999). Genotype frequencies did not deviate from Hardy-Weinberg Equilibrium across any ancestral group (HWE: $\chi^2 = 1.97$, p = 0.85; HWE Caucasian: $\chi^2 = 1.03$, p = 0.78; African-American: $\chi^2 = 0.96$, p = 0.90; Asian1: $\chi^2 = 0.24$, p = 0.93; Asian2: $\chi^2 = 0.38$, p = 0.95; Hispanic: $\chi^2 = 0.65$, p = 0.82; Other $\chi^2 = 1.83$, p = 0.85).

To account for differences in ancestral background in the full sample, we used EIGENSTRAT (v. 5.0.1) (Price et al., 2006) to generate principal components; k-means cluster plotting and visual inspection of the top 10 components revealed that the top 5 principal components account for divergent ancestral groups within the population (**Supplemental Fig. 1**).

Six participants were identified as outliers, as they were more than 6 standard deviations from the mean on these top 5 components, and were excluded from analyses. Ancestral subsamples were determined based on self-report (Caucasian, African American, Hispanic, Asian, or Other), except in the case of the Asian sample, which, based on visual inspection of the principal components produced by EIGENSTRAT, was composed of two genetically distinct subsamples. Self-reported Asians were thus further divided into two subsamples (Asian1: n=47; Asian2: n=147) based on k-means clustering of the first two principal components.

2.3.4 BOLD fMRI paradigm

A number guessing paradigm (Delgado et al., 2000) was used to probe reward-related VS activity. Our blocked design consisted of a pseudorandom presentation of 3 blocks each of predominantly positive (80% correct guess) and negative (20% correct guess) feedback. There are 5 trials during each block. During each task trial, subjects had 3s to guess, via button press, whether the value of an upcoming visually presented card would be < or > 5 (index and middle finger, respectively). The numerical value of the card was presented for 500ms followed by appropriate feedback (i.e., green “up” arrow for positive feedback on a correct trial; red “down” arrow for negative feedback on an incorrect trial) for an additional 500ms. A crosshair focus point was then presented for 3s for a total trial length of 7s. One incongruent trial type was included within each task block to prevent subjects from anticipating the feedback for each trial and maintain subject’s engagement and motivation to perform well. The six task blocks were interleaved with three control blocks. During control blocks, subjects were instructed to make button presses during the presentation of an “x” (3s), which was followed by an asterisk (500ms) and a yellow circle (500ms). Each block was preceded by a 2s instruction of “Guess Number” (for task) or “Press button” (for control), resulting in a total block length of 38s and a total task length of 342s. Subjects were unaware of the fixed outcome probabilities associated with each block and were led to believe that their

performance would determine their net monetary gain, although all subjects received $10 upon completion of the task.

2.3.5 BOLD fMRI acquisition

Participants were scanned using a research-dedicated GE MR750 3T scanner equipped with high-power high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high bandwidth up to 1MHz at the Duke-UNC Brain Imaging and Analysis Center. A semi-automated high-order shimming program was used to ensure global field homogeneity. A series of 34 interleaved axial functional slices aligned with the anterior commissure-posterior commissure (AC-PC) plane were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artifact [TR/TE/flip angle=2000 ms/30 ms/60; FOV=240 mm; 3.75×3.75×4 mm voxels (selected to provide whole brain coverage while maintaining adequate signal-to-noise and optimizing acquisition times); interslice skip=0]. Four initial RF excitations were performed (and discarded) to achieve steady-state equilibrium. To allow for spatial registration of each participant's data to a standard coordinate system, high-resolution three-dimensional structural images were acquired in 34 axial slices co-planar with the functional scans (TR/TE/flip angle=7.7 s/3.0 ms/12; voxel size=0.9×0.9×4 mm; FOV=240 mm, interslice skip=0).

2.3.6 BOLD fMRI data analysis

The general linear model of Statistical Parametric Mapping 8 (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) was used for whole-brain image analysis. Individual subject data were first realigned to the first volume in the time series to correct for head motion before being spatially normalized into the standard stereotactic space of the Montreal Neurological Institute

(MNI) template using a 12-parameter affine model. Next, data were smoothed to minimize noise and residual differences in individual anatomy with a 6mm FWHM Gaussian filter. Voxel-wise signal intensities were ratio normalized to the whole-brain global mean. Then the ARTifact Detection Tool (ART) (http://www.nitrc.org/projects/artifact_detect/) was used to generate regressors accounting for images due to large motion (i.e., >0.6mm relative to the previous time frame) or spikes (i.e., global mean intensity 2.5 standard deviations from the entire time series). Participants for whom more than 5% of acquisition volumes were flagged by ART (n = 30) were removed from analyses. A 5mm sphere based on the maximum voxels from Hariri et al. (Hariri et al., 2006) was used to ensure adequate ventral striatal coverage; no subjects had <90% coverage of the region.

Following preprocessing steps outlined above, linear contrasts employing canonical hemodynamic response functions were used to estimate task-specific BOLD responses for each individual using a “Positive Feedback > Negative Feedback” contrast. Individual contrast images (i.e., weighted sum of the beta images) were used in second-level random effects models accounting for scan-to-scan and participant-to-participant variability to determine mean contrast-specific responses using one-sample t-tests. A voxel-level statistical threshold of $P < 0.05$, family wise error corrected for multiple comparisons across the bilateral ventral striatal region of interest, and a cluster-level extent threshold of 10 contiguous voxels was applied to these analyses. The bilateral ventral striatal region of interest (ROI) was defined by a 5mm sphere based on the maximum voxels from Hariri et al. (2006), created with the Wake Forest University PickAtlas (Lancaster et al., 2000; Maldjian et al., 2003) (**Supplemental Figure 2.2**)

BOLD parameter estimates from clusters within the left and right ventral striatal ROIs exhibiting a main effect for the “Positive Feedback > Negative Feedback” contrast were extracted using the VOI tool in SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and exported for regression analyses. Bilateral ROI values were calculated by weighting mean activity in each hemisphere by cluster size and then averaging across the hemispheres. Extracting parameter estimates from

clusters activated by our fMRI paradigm, rather than those specifically correlated with our independent variables of interest, precludes the possibility of any correlation coefficient inflation that may result when an explanatory covariate is used to select a region of interest. We have successfully used this strategy in prior studies (Carré et al., 2012; Corral-Fríasa et al., 2015).

2.3.7 Statistical Analyses

Extracted neuroimaging data values were winsorized (to ±3 SDs; n=11) to maintain variability while limiting the influence of extreme outliers before being analyzed in PASW Statistics (Version 19; SPSS Inc.; Chicago, IL). A regression-based moderation model was tested using the PROCESS macro for SPSS (Hayes, 2013) to examine the independent and interactive effects of early life stress (i.e., CTQ score) and *PER1* rs3027160 genotype on problematic alcohol use (i.e., AUDIT score) and reward-related ventral striatum reactivity (i.e., positive reward > negative loss). CTQ scores were log-transformed for all analyses, as they had a high positive skew (**Supplemental Table 2.2.**) As there were only 20 *PER1* rs30271672 minor allele (C) homozygotes in the sample (3.0%), and 162 *PER1* rs30271672 heterozygotes, *PER1* genotype was coded as the presence or absence of the minor-allele, consistent with prior studies (Dong & Bilbao, 2011). A power analysis conducted with Quanto (v.1.2.4) using the effect size previously observed by Dong and colleagues, and our observed genotype frequency and CTQ distribution, revealed that the current sample has 80% power to detect GxE interaction effects greater than β=0.119 (Gauderman, 2002a, 2002b). Initial moderation analyses were conducted using sex, age (i.e., above or under 21; the legal drinking age in North Carolina), sleep quality (PSQI score), the presence of a psychiatric diagnosis, and the top 5 principal components accounting for divergent ancestral groups within the population (**Supplemental Figure 2.1**). Sleep quality was included as a covariate as sleep disruption is associated with increased risk for drug problems (Wong et al., 2010), and variants within other circadian genes have been associated with sleep phenotypes

(Hu et al., 2016). Controlling for sleep quality thus permits examination of the effects of PER1 rs3027160 independent of any potential associations of sleep quality. Consistent with recommendations (Keller, 2014), additional follow-up moderation analyses included 18 additional terms for gene x covariate and environment x covariate interactions to better account for potential confounds to GxE research (e.g. *PER1* rs3027160 x sex, etc.; (Keller, 2014)). Thus, two *a priori* analyses were conducted, yielding a bonferroni correction significance threshold of $p<0.025$. Given the ethnic diversity of the sample, p*ost-hoc* analyses in each of the six ancestral subsamples were conducted with recalculated covariate interaction terms. All covariates were the same as in the full-sample analyses, with the exception of the ancestral principal components, which were not included. Additionally, as only 23.6% of the sample had an AUDIT score of 8 or more, which qualifies as hazardous use of alcohol, an additional *post-hoc* logistic regression analysis was conducted in the full-sample to examine whether the interaction of *PER1* rs3027172 and CTQ also predicts the likelihood of an AUDIT score of 8 or more, indicative of more severe problematic drinking.

2.4 Results

2.4.1 Associations with sample demographics

Consistent with prior observations, men reported more problematic alcohol use (Hasin et al., 2007) and had higher bilateral reward-related VS reactivity to monetary gains (Nikolova et al., 2012; Spreckelmeyer et al., 2009); **Supplemental Table 2.3**). Ethnicity predicted self-report measures of stress, sleep, and alcohol use (**Supplemental Table 2.4**). Notably, African American and Asian 2 participants were characterized by relatively greater CTQ scores and reduced AUDIT scores, while Caucasian participants reported reduced CTQ scores and elevated AUDIT scores. African American participants also reported higher PSQI scores. *PER1* rs3027160 genotype

groups differed by ethnicity, wherein the minor allele carrier group had a higher percentage of Caucasian and a lower percentage of Asian1 and Asian2 participants (**Supplemental Table 2.5; Supplemental Figure 2.1**). Consistent with a prior report (Dong et al., 2011), *PER1* rs3027160 genotype groups differed according to AUDIT scores such that C allele carriers reported higher levels of problematic drinking (**Supplemental Table 2.5**); notably, however, this effect did not remain after controlling for covariates (see below). *PER1* rs3027160 genotype groups did not differ by CTQ scores, suggesting the lack of rGE.

2.4.2 PER1 rs3027160 and Early Life Stress Interact to Predict Problematic Drinking

There was no main effect of *PER1* genotype or CTQ scores on AUDIT scores after accounting for covariates (*PER1:* β=0.025, t=0.662, p=0.508; CTQ: β=-0.039, t=-0.983, p=0.325; **Supplemental Table 2.5**). Initial moderation analyses found that the interaction of *PER1* with early life stress (CTQ scores) significantly predicted problematic drinking (ΔR^2=0.0067, β=0.086, t=2.275, p=0.023) after accounting for main effects and covariates. This interaction remained significant after accounting for 2-way interactions between covariates with *PER1* rs3027160 and CTQ scores (an additional 18 covariates; ΔR^2=0.0106, β=0.124, t=2.86, p=0.004; **Supplemental Table 2.6**). Post-hoc analyses revealed that minor (C) allele carriers who retrospectively reported elevated early life stress (Johnson-Neyman significance for log-transformed CTQ values greater than 3.57, equivalent to 35.5) endorsed increased problematic drinking (**Figure 2.1**). Participants were partitioned into three groups based on the distribution of CTQ-scores (low = 3.22 – 3.37; medium = 3.37 – 3.59; high = 3.59 – 4.08) for post-hoc examination of simple slopes. These analyses revealed that *PER1* rs3027160 was associated with increased problematic drinking only in the high CTQ group (β=1.908, t= 2.474, p=0.014). These results are consistent with prior

reports of increased heavy drinking among adolescent *PER1* rs3027172 minor-allele carriers who have experienced high levels of psychosocial adversity (Dong & Bilbao, 2011). We further examined whether the *PER1*xCTQ interaction predicted the likelihood of an AUDIT score over 8 (defined as the threshold for hazardous use). Logistic regression revealed that the *PER1*xCTQ interaction was significantly associated with this AUDIT threshold of hazardous use (ΔR^2=0.0087, β=0.5908, z=2.128, p=0.033; **Supplemental Table 2.7**).

Given the ethnic diversity of the sample, p*ost-hoc* analyses were conducted in each ancestral sub-sample **(Supplemental Table 2.8, Supplemental Figure 2.3).** In these analyses the interaction of *PER1* and CTQ scores predicting AUDIT scores was only significant in one of the six subsamples (Asian 1; ΔR^2=0.1527, β=0.6178, t=3.4560, p=0.002), which was notably small (n=38 major allele homozygotes, 6 minor allele carriers). However, in five other subsamples the interaction coefficient was also positive (i.e. Caucasian N=305, β=0.0146, p = 0.812; African-American N=73, β=0.2195 p = 0.096; Asian 2 N=143, β=0.152, p = 0.063; Other N=61, β=0.1000, p = 0.480) and the shape of the interaction resembled the results from the Asian 1 subsample and the entire sample. The only subsample that did not show a similar pattern with regard to directionality was the Hispanic subsample, which was also the smallest (n=39, β= -0.0222, p = 0.4797). Finally, the original association of *PER1*xCTQ with AUDIT scores was repeated including participants originally excluded due to lack of imaging data (n=719); results did not meaningfully change (ΔR^2=0.0119 β=0.129, t=3.18, p=0.002; **Supplemental Table 2.9).**

2.4.3 *PER1 rs3027160* and Early Life Stress Do Not Interact to Predict Ventral Striatal Reactivity

Initial moderation analyses found that *PER1* rs3027160 genotype interacted significantly with early life stress (CTQ scores) to predict bilateral ventral striatal reactivity (ΔR^2=0.0068, β=0.0838,

t=2.145, p=0.032). In the context of high early life stress, minor-allele carriers had elevated ventral striatal reactivity. However, this interaction became non-significant after accounting for gene (*PER1* rs3027160) x covariate and environment (CTQ) x covariate interactions (ΔR^2=.0021, β=0.056, t=1.231, p=0.219; **Supplemental Figure 2.4, Supplemental Table 2.10**). *Post-hoc* analyses indicated that the CTQ x genotype interaction was no longer significant after the inclusion of the CTQ x ancestral principal component 1 (PC1) interaction term (β=-12.3664, t=-2.51, p=0.012; **Supplemental Figure 2.5**), and the CTQ x PSQI interaction term (β=-0.07234, t=-3.114, p=0.002; **Supplemental Figure 2.6**). PC1 correlates with PER1 genotype (Pearson's r = -0.237, p<0.001 and membership to the White, African American, Asian 2, and Hispanic subgroups (White: Pearson's r = -0.625, p<0.001, African American: Pearson's r = -0.177, p<0.001; Asian 2: Pearson's r = 0.951, p<0.001, Hispanic: r=-0.099, p<0.05), and the CTQxPC1 interaction term correlates with membership to the African American and Asian2 subgroups (African American: Pearson's r = -0.150, p<0.001; Asian2: r=0.228, p<0.001). This suggests that analyses that did not account for gene x covariate and environment x covariate interactions, were confounded by an interaction between ancestral origin and early life stress. Lastly, given the ethnic diversity of the sample, p*ost-hoc* analyses were conducted in each ancestral sub-sample **(Supplemental Table 2.11).** In these analyses the interaction of *PER1* and CTQ scores predicting ventral striatal reactivity was only significant in one of the six subsamples (African American; ΔR^2=0.0556, β=-0.31384, t=-2.082, p=0.042). Notably the direction of this interaction is negative, while the coefficient in the full sample is positive. However, in the five other subsamples the coefficient (i.e., positive) and shape of the interaction was in the same direction as in the full-sample analysis. Because the *PER1* x CTQ interaction was not associated with individual differences in reward-related ventral striatum activity when accounting for gene x covariate and environment x covariate interactions we did not test a mediational model.

2.5 Discussion

This study examined whether the *PER1* SNP, rs3027172, interacts with early life stress to predict problematic alcohol use and ventral striatum reactivity to reward. Two primary findings emerged. First, consistent with past research (Dong & Bilbao, 2011), minor C allele carriers who were exposed to elevated levels of childhood stress, had higher problematic alcohol use (**Fig. 1**). Second, in contrast to initial analyses suggesting that this interaction also predicts reward-related ventral striatum reactivity, when we appropriately accounted for gene x covariate and environment x covariate interactions (Keller, 2014), this interaction was no longer significant. Collectively, these findings provide additional evidence that psychosocial adversity during childhood confers risk for problematic drinking in rs3027172 C allele carriers, but suggest that this association is not driven, at least primarily, by effects on reward-related ventral striatum reactivity. More broadly, these findings highlight the need to account for gene x covariate and environment x covariate interactions in gene x environment and other forms of moderation-based research (Keller, 2014).

2.5.1 *PER1* rs3027172 Genotype and Early Life Stress Interact to Predict Problematic Alcohol Use

Consistent with a prior report showing that *mPer1*^{Brdm1} knockout mice and human minor C allele carriers at rs3027172 have increased alcohol consumption in the context of prenatal adversity (Dong et al., 2011), we found that young-adult C allele carriers had increased problematic alcohol use in the context of elevated early life stress. Notably, while Dong et al. (2011) evaluated psychosocial adversity within the family during the year prior to birth, early life stress was evaluated in the present study as stress experienced during childhood. However, contrary to Dong et al. (2011), who observed a main effect of *PER1* genotype on risk for alcohol abuse in their second sample, consisting of 2,184 Caucasian adults, we did not find any significant main-effects

of *PER1* rs3027172 after accounting for covariates (notably, this main effect was significant and in the direction reported by Dong et al., 2011 when covariates were not included; **Supplemental Table 2.5**). It is possible that we did not observe such a main effect due to our younger aged sample, the smaller sample size, and ethnic heterogeneity.

Given that *PER1* expression is sensitive to stress, it is not entirely surprising that the minor C allele was only associated with increased problematic alcohol use in the context of early life stress. *mPer1* expression in rodents is upregulated in peripheral tissues by acute stress (Yamamoto et al., 2005), and downregulated in the nucleus accumbens by chronic stress (Spencer et al., 2013). Accumulating evidence suggests these stress effects may be mediated through the HPA axis. In human and rodent cell cultures, *PER1* is upregulated by dexamethasone, a glucocorticoid receptor agonist (Polman et al., 2012; Reddy et al., 2009) with evidence that *PER1* is the most sensitive, of all genes, to low doses of dexamethasone (Reddy et al., 2012). Moreover, rs3027172 is located in the *PER1* promoter in a region that is similar to an E2-box binding site for members of the Snail transcription factor family. Snail transcription factors are well-known for their central role in mesoderm formation (Nieto, 2002), are expressed throughout the adult brain (Dong & Bilbao, 2011), and have been repeatedly shown to be regulated by stress hormones (for recent examples see (Cheng et al., 2013; Nesan & Vijayan, 2013; Shan et al., 2014). The minor C allele, which eliminates the similarity of this site to an E2-box, appears to reduce affinity of Snail1 for this binding site, and results in a 4-fold reduction of *PER1* mRNA expression in B-lymphoblastoid cell lines following incubation with cortisol (Dong & Bilbao, 2011). Together, these results suggest that the C allele at rs3027172 may increase risk for stress-associated problematic alcohol use by disrupting affinity of the Snail1 transcription factor with the *PER1* promoter and thereby reducing stress-related *PER1* expression. However, as *PER1* expression and cortisol were not assessed in participants of this study, this interpretation remains speculative.

2.5.2 *PER1* rs3027172 Genotype, Early Life Stress, and Reward-related Ventral Striatum Reactivity: The Need to Account for Covariate Interactions

A recent review (Keller, 2014) highlights that gene x environment interaction studies have not appropriately controlled for interactions between confounding variables and variables of interest, likely contributing to the low replication rate (27%) of gene x environment findings (Duncan & Keller, 2011). Thus, following these recommendations, terms accounting for potentially confounding early life stress and *PER1* genotype interactions with covariates were added to the *PER1* x ELS models predicting problematic alcohol use and ventral striatum reactivity (Keller, 2014). The *PER1* x ELS interaction continued to predict problematic alcohol use even after these additional covariates were added. However, the *PER1* x ELS interaction no longer significantly predicted ventral striatum reactivity after including gene x covariate and environment x covariate interaction terms. Post-hoc examination of these analyses revealed that the addition of CTQ x the first ancestral principal component (PC1) and CTQ x PSQI were significantly associated with ventral-striatal reactivity. As PC1 correlates with *PER1* genotype and the CTQxPC1 interaction term correlates with membership to the African American and Asian2 ethnic subgroups, this result may reflect relatively low numbers of minor-allele carriers in these populations (**Supplemental Table 2.4**), as well as ethnic subgroup differences in early life stress exposure and drinking behavior.

2.5.3 Incidental Findings

It is intriguing that those with high ELS and poor sleep quality were characterized by relatively blunted VS reactivity to reward (**Supplemental Figure 2.6**), as sleep disruption, similar to stress, is also predictive of drug and alcohol problems (Wong et al., 2010). Sleep disruption

has been previously associated with blunted striatal activation during a reward task (Holm et al., 2009), and familial risk for alcoholism has been linked to blunted striatal reactivity to reward in young adults (Yau et al., 2012). Thus, this incidental finding would suggest that the blunted ventral striatum reactivity observed may reflect that these participants, who experienced elevated levels of childhood stress and report greater levels of current sleep disruption, are at greater risk for drug and alcohol abuse, and warrants further study.

2.5.4 Limitations

The present study is not without its limitations. It is first important to consider that participants were university students, and thus results may not be entirely generalizable to the broader population. Epidemiological data suggest that alcohol use is heaviest in young adult years (Fillmore et al., 1991; Naimi et al., 2003) with problematic usage tapering off in the majority of individuals when they reach their mid-20s (Jackson et al., 2001). Given that more problematic usage in college is predictive of later alcohol use disorder (Schulenberg et al., 2001), these data identify important factors (i.e., early life stress and *PER1* variation) contributing to risk for problematic drinking in college, which in turn, confers risk for post-college alcohol use disorder. With regard to early life stress, CTQ total scores in this sample (i.e., M=33.24) were comparable to other community (e.g., metropolitan Memphis, Tennessee area, n=1,007, M = 31.7; (Scher et al., 2001) and college samples (e.g., UCSD; n=949, M = 35.2; (Wright et al., 2001), but are considerably lower than those typically observed in clinical samples (e.g., alcohol dependent inpatients n=100, M = 42.8; (Schäfer et al., 2007), and major depressive disorder and bipolar outpatients n=40, M = 47.8; (S. Watson et al., 2007). These results suggest that the moderating effect of *PER1* variation on problematic drinking arises at early life stress levels that are slightly above average (i.e. 35.5, See Johnson-Neyman area of significance in **Figure 2.1**). However, it

is important to consider that this relatively high functioning college student population may have had other protective factors that may have counteracted the effects of early life adversity.

Second, we must consider the limitations of our phenotypic assessments. With the exception of reward-related ventral striatum reactivity measures and *PER1* variation, all other variables relied upon self-report. It is particularly important to note that the retrospective recall of stress, occurring either recently or early in life, may encompass errors or be influenced by current mood or perception (Monroe, 2008). However, reports have demonstrated that the early life stress questionnaire used here and clinician-rated childhood abuse interviews demonstrate convergent validity (Scher et al., 2001). Another consideration is that while our blocked fMRI paradigm increases power to measure VS reactivity, it does so at the cost of some specificity (e.g., separating anticipation of reward from outcome, evaluating reward learning). This is particularly important in light of observations that reward processing is not a monolithic phenomenon and can be dissected into anticipatory, consummatory, and learning components (Berridge et al., 2009). Thus the finding of no association between the *PER1* x ELS interaction and VS reactivity in the present study does not rule out the possibility that this interaction may be associated with the neurobiological correlates of specific phases of reward processing.

Third, while the *PER1* x ELS interaction predicting problematic alcohol usage was significant in the full sample when accounting for ancestrally informative principal components, it did not reach significance in our largest ancestral subsamples (**Supplemental Table 2.8**). However, consistent with results from the entire sample, each ancestral subsample (with the exception of Hispanics), showed an interactive effect similar to that observed in the full sample. The lack of significance in our larger subsamples and power analysis suggests that subsample analyses were underpowered to detect the association. Notably, this effect did reach statistical significance in the Asian 1 subsample. Future research in various ancestral populations would be informative to clarify whether this association differs according to ancestral origin. Lastly, it is also possible that the findings in the full sample reflect a false positive, despite our best efforts to

control for potentially confounding variables (Keller, 2014), a prior report that is consistent with these data (Dong & Bilbao, 2011), and rodent work which is consistent with these results (Dong & Bilbao, 2011). Given the lack of consistency in many gene x environment interaction studies (Duncan & Keller, 2011) as well as the lack of significance in the European/European American subsample of the present study (the largest subsample), further replication of the reported results is clearly needed.

Fourth, our study did not collect measures of HPA axis function such as cortisol. Given evidence that rs3027172 genotype influences *PER1* expression in the context of cortisol (Dong et al., 2012), it will be important for future research to assess whether early life stress-related differences in cortisol mediate relationships between genotype and brain function and behavior. Ideally such investigation would be within the context of longitudinal studies.

Fifth, because this study is cross-sectional, we are unable to firmly establish predictive relationships between *PER1* genotype*,* ELS, and drinking behavior. That is, although our models imply a direction of effect, we cannot definitively determine if variability in one variable precedes variability in another. In particular, as already noted, the CTQ is retrospective and may be biased by current state. However, given the nature of our measures, a causal relationship is plausible. *PER1* rs3027172 genotype was established prior to the onset of behavior, and our self-report measures assess the occurrence of events that are non-temporally overlapping. The CTQ assess early life stress before the age of 17, and the AUDIT assess drinking behavior in the past year – all participants are over 18.

These limitations notwithstanding, the results of the present study extend evidence that early life stress increases problematic alcohol use in *PER1* rs3027172 minor C allele carriers (Dong & Bilbao, 2011). Moreover, the lack of significant ventral striatum results after appropriately controlling for potential interactive confounds, highlights the need for interaction research to properly control for covariates in an effort to reduce false-positive reports (Keller, 2014).

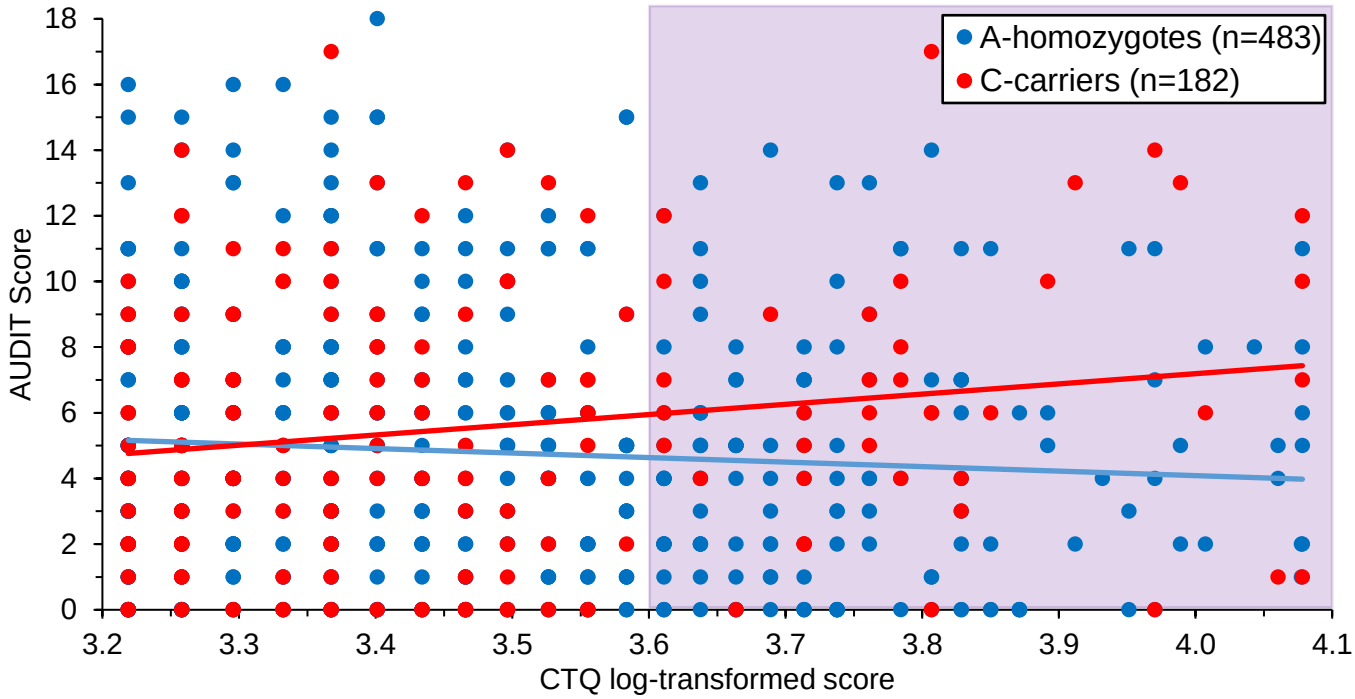
2.5.5 Acknowledgements

We are thankful to the Duke Neurogenetics Study (DNS) participants. We would like to thank F. Ahs, B. Brigidi, J. Carré, C. Davis, K. Faig, E. Goetz, A. Gorka, S. Jacobson, A. Knodt, K. McNealy, J. Minkel, and V. Sochat for assistance with data collection and processing.

2.5.6 Conflict of Interest Statement

Emily Drabant Conley works for the commercial entity 23andMe, the company that genotyped the DNS samples. No other potential conflicts of interest are present.

Figure 2.6.1: *PER1* rs3027160 and Early Life Adversity Interact to Predict Problematic Drinking. (ΔR^2=0.0106, β=0.124, t=2.86, p=0.00438).



C minor-allele carriers report increased problematic drinking behavior (AUDIT scores) in the context of early life stress (CTQ scores). The purple-shaded region denotes the regions of significance (i.e., CTQ log-transformed >3.57, equivalent to a score of 35.5).

2.6 Supplemental Information

Supplemental Table 2.6.1. Effect of exclusion due to non-availability of imaging data on self-report variables, self-report ethnicity, PER1 rs3027172 genotype, and presence of psychiatric diagnosis. *PER1* rs3027172 was unavailable for two participants excluded due to lack of imaging data.

	Included (SD) n=665	**Not included (SD) n=62**	**t/x^2**	***p***
CTQ	33.06 (7.65)	33.36 (8.41)	-0.266	0.791
AUDIT	4.84 (3.72)	5.01 (4.22)	-0.301	0.763
PSQI	4.76 (2.54)	4.93 (2.60)	-0.492	0.623
PER1 rs3027172 (carriers) *	n=182	n=17	0.006	0.939
Gender (Male)*	n=293	n=26	0.104	0.747
Psychiatric Diagnosis*	n=52	n=4	0.120	0.729
Caucasian*	n=305	n=27	0.123	0.726
African American*	n=73	n=10	1.477	0.222
Asian*	n=187	n=14	0.870	0.351
Hispanic*	n=39	n=5	0.483	0.487
Other*	n=62	n=5	0.107	0.743
Age	19.47 (1.20)	19.64 (1.24)	-1.070	0.385

CTQ = childhood trauma questionnaire, AUDIT = alcohol use disorders identification test. PSQI = Pittsburgh Sleep Quality Inventory.
***** = analyses were run as a chi-squared test. All others were run as t-tests.

Supplemental Table 2.6.2. Distribution and skewness of self-report variables.

	N	Minimum	Maximum	Mean	Std. Deviation	Skewness	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error
CTQTot	665	25	59.0405	33.24115	7.953584	1.282	0.095
PSQI	665	0	12.8329	4.907513	2.530686	0.739	0.095
AUDITTOT	665	0	18.0477	4.985393	4.149198	0.862	0.095

Supplemental Table 2.6.3. Effect of gender on self-report variables, VS reactivity, presence of psychiatric diagnosis, and ancestral subsamples.

	Men (SD) n=293	**Women (SD) n=372**	**t/x^2**	***p***
CTQ	33.59 (8.05)	32.96 (7.88)	1.016	0.310
AUDIT	6.15 (4.53)	4.07 (3.57)	6.633	<0.001
AUDIT>8*	n=102	n=55	36.451	<0.001
PSQI	4.77 (2.35)	5.02 (2.66)	-1.248	0.213
Bilateral VS Reactivity	0.0882 (0.168)	0.0588 (0.142)	2.431	0.015
Psychiatric Diagnosis*	n=25	n=27	0.369	0.543
Caucasian*	n=146	n=159	3.316	0.069
African American*	n=17	n=56	14.356	<0.001
Asian 1*	n=24	n=20	2.102	0.147
Asian 2*	n=60	n=83	3.27	0.568
Hispanic*	n=20	n=19	0.877	0.349
Other*	n=26	n=35	0.56	0.812
Age	19.69 (1.28)	19.6 (1.21)	0.971	0.35

CTQ = childhood trauma questionnaire, AUDIT = alcohol use disorders identification test. PSQI = Pittsburgh Sleep Quality Inventory. VS = ventral striatum.
***** = analyses were run as a chi-squared test. All others were run as t-tests.

Supplemental Table 2.6.4. Effect of Eigenstrat-determined ancestral background on age, self-report variables, VS reactivity, and *PER1* rs3027172 frequency.

	Caucaisan (C) n=305	**African American (AA) n=73n=73**	**Asian1 (A1) n=44**	**Asian2 (A2) n=143**	**Hispanic (H) n=39**	**Other (O) n=61**	**F/X^2**	***p***
CTQ	31.09 (6.71)	37.13 (9.64)	33.27 (7.64)	35.99(8.55)	32.89 (7.52)	33.07 (7.05)	12.340	**<0.001**
AUDIT	5.5 (4.21)	4.27 (4.14)	4.93 (4.91)	4.20 (3.56)	6.26 (4.61)	4.35 (3.84)	3.457	**0.004**
AUDIT>8*	n=85	n=13	n=10	n=26	n=14	n=9	12.703	**0.026**
PSQI	4.81 (2.38)	5.75 (2.59)	4.36 (2.67)	4.81 (2.57)	5.12 (2.97)	4.88 (2.58)	2.241	**0.049**
Bilateral VS Reactivity	0.0824 (0.1436)	0.0650 (0.1516)	0.0965 (0.1663)	0.0625 (0.1719)	0.0147 (0.1545)	0.0673 (0.1572)	1.722	0.127
Age	19.74 (1.23)	19.6 (1.13)	19.14 (1.15)	19.62 (1.25)	19.59 (1.33)	19.69 (1.09)	1.895	0.093
Psychiatric Diagnosis*	n=23	n=9	n=1	n=12	n=3	n=4	4.171	0.525
PER1 minor C carriers*	n=117 (MAF=0.44)	n=15 (MAF=0.21)	n=6 (MAF=0.14)	n=14 (MAF=0.10)	n=12 (MAF=0.36)	n=18 (MAF=0.30)	47.018	**<0.001**

Means are presented with SD indicated in ().
CTQ**:** Childhood Trauma Questionnaire
AUDIT: Alcohol Use Disorders Identification Test
PSQI: Pittsburgh Sleep Quality Index
Post-hoc t-tests of CTQ scores showed significant differences (ps < .05) for C<AA, C<A2, AA>A1, AA>H, AA>O, A2>A1, A2>H, and A2>O. For AUDIT scores there were significant differences (ps < .05) for C>AA, C>A2, C>O, H>AA, and H>A2. For PSQI scores there were significant differences (ps < .05) for AA>C, AA>A1, AA>A2, AA>O, and O>A1.
Post-hoc comparison of *PER1* minor-allele frequencies showed that the C subsample had more minor-allele carriers than expected, while the A1 and A2 subsamples had fewer minor-allele carriers than expected.
***** = analyses were run as a chi-squared test. All others were run as ANOVAs.

Supplemental Table 2.6.5. Effect of *PER1* rs3027172 on self-report variables, VS reactivity, presence of psychiatric diagnosis, and ancestral subsamples.

	Major Homozygotes (T/T) n=483	**Minor-Carriers (C/T & C/C) n=182**	**t/x^2**	***p***
CTQ	33.49 (7.83)	32.58 (8.26)	1.321	0.187
AUDIT	4.79 (4.13)	5.50 (4.16)	-1.970	**0.049**
AUDIT>8*	n=106	n=51	2.706	0.100
PSQI	4.79 (2.57)	5.21 (2.40)	-1.871	0.062
Bilateral VS Reactivity	0.0659 (0.1579)	0.0873 (0.1452)	-1.585	0.113
Psychiatric Diagnosis*	n=33	n=19	2.386	0.122
Caucasian*	n=188	n=117	34.246	**<0.001**
African American*	n=58	n=15	1.919	0.166
Asian 1*	n=38	n=6	4.470	**0.035**
Asian 2*	n=129	n=14	28.318	**<0.001**
Hispanic*	n=27	n=12	0.241	0.623
Other*	n=43	n=18	0.155	0.694
Gender*	Male n=208	Male n=85	0.710	0.399
Age	19.64 (1.27)	19.65 (1.16)	-1.30	0.896

Mean values presented with SD indicated in ()
CTQ**:** Childhood Trauma Questionnaire
AUDIT: Alcohol Use Disorders Identification Test
PSQI: Pittsburgh Sleep Quality Index
***** = analyses were run as a chi-squared test. All others were run as t-tests.

Supplemental Table 2.6.6. *Per1* rs30272172 and Early-life adversity significantly interact to predict problematic drinking behavior (AUDIT) even after controlling for gene x covariate and environment x covariate interactions.

Model		Standardized Coefficients Beta	t	Sig.
1	(Constant)	0.00000	0.14	0.888
	PER1xCTQ	0.08311	2.275	0.023
	PER1	0.02511	0.662	0.508
	CTQ	-0.03906	-0.983	0.326
	Sex	-0.45919	-6.44	<0.001
	Age	0.00819	2.812	0.005
	PC1	-0.94253	-2.054	0.040
	PC2	0.48167	2.093	0.037
	PC3	0.38632	0.407	0.684
	PC4	-0.05730	-0.596	0.552
	PC5	-0.08322	-0.196	0.845
	Diagnosis	0.01705	0.569	0.569
	PSQI	0.08971	6.244	<0.001
2	(Constant)		-0.401	0.689
	PER1xCTQ	0.12440	2.86	0.004
	PER1	0.03167	0.763	0.446
	CTQ	-0.05656	-1.378	0.169
	Sex	-0.44912	-6.192	<0.001
	Age	0.02641	2.606	0.009
	PC1	-0.27623	-2.45	0.015
	PC2	0.95930	1.878	0.061
	PC3	0.17948	0.763	0.446
	PC4	-0.52154	-0.541	0.588
	PC5	-0.08764	-0.267	0.789
	Diagnosis	0.00535	0.36	0.719
	PSQI	0.04061	5.973	<0.001
	PER1xSex	0.04154	1.12	0.263
	PER1xAge	0.02270	0.332	0.740
	PER1xPC1	-0.67215	-0.661	0.509
	PER1xPC2	-0.02694	-0.105	0.917
	PER1xPC3	1.15016	0.889	0.374
	PER1xPC4	-0.04809	-0.093	0.925
	PER1xPC5	-3.13558	-1.52	0.129
	PER1xDiagnosis	-0.07169	-0.695	0.488
	PER1xPSQI	0.00197	0.555	0.579
	CTQxSex	0.23220	1.465	0.143
	CTQxAge	0.03737	1.274	0.203
	CTQxPC1	10.71769	2.293	0.022
	CTQxPC2	-1.28053	-0.825	0.410

CTQxPC3	-0.28992	-0.625	0.532
CTQxPC4	0.60554	0.269	0.788
CTQxPC5	0.15017	0.144	0.885
CTQxDiagnosis	0.27597	0.532	0.595
CTQxPSQI	0.00408	0.185	0.853

Supplemental Table 2.6.7. *Per1* rs30272172 and Early-life adversity significantly interact to predict the likelihood of an AUDIT score over 8, which qualifies as problematic drinking behavior, controlling for gene x covariate and environment x covariate interactions.

		Standardized Coefficients		
Model		Beta	z	Sig.
1	(Constant)		-11.601	<0.001
	PER1xCTQ	0.59076	2.128	0.033
	PER1	0.20794	0.75	0.453
	CTQ	-0.46378	-1.569	0.117
	Sex	-2.59750	-5.505	<0.001
	Age	0.05302	0.819	0.413
	PC1	-0.74866	-0.956	0.339
	PC2	6.28589	1.555	0.120
	PC3	1.03993	0.735	0.462
	PC4	-3.86224	-0.634	0.526
	PC5	-2.27352	-1.112	0.266
	Diagnosis	0.06259	0.702	0.483
	PSQI	0.19009	4.389	<0.001
	PER1xSex	0.00788	0.033	0.973
	PER1xAge	-0.18799	-0.448	0.654
	PER1xPC1	0.03211	0.005	0.996
	PER1xPC2	0.84776	0.446	0.656
	PER1xPC3	3.28782	0.436	0.663
	PER1xPC4	1.02101	0.333	0.739
	PER1xPC5	-23.06285	-1.83	0.067
	PER1xDiagnosis	-0.45885	-0.728	0.467
	PER1xPSQI	0.01236	0.552	0.581
	CTQxSex	0.95418	0.939	0.348
	CTQxAge	0.20031	1.068	0.285
	CTQxPC1	52.17043	1.658	0.097
	CTQxPC2	-16.40813	-1.443	0.149
	CTQxPC3	-0.97334	-0.341	0.733
	CTQxPC4	13.86418	0.934	0.350
	CTQxPC5	3.83533	0.539	0.590
	CTQxDiagnosis	3.11261	1.019	0.308
	CTQxPSQI	0.02583	0.185	0.853

Supplemental Table 2.6.8. The interaction of *Per1* rs30272172 and Early-life adversity predicting problematic drinking behavior (AUDIT) in each of the six ethnic subsamples.

	Caucasian			African American			Asian 1		
	Standardized Coefficients			Standardized Coefficients			Standardized Coefficients		
	Beta	t	Sig.	Beta	t	Sig.	Beta	t	Sig.
(Constant)		0.219	0.827		0.103	0.918		1.011	0.3201
PER1xCTQ	0.0146	0.238	0.812	0.2195	1.691	0.096	0.6178	3.456	0.0017
PER1	-0.0047	-0.086	0.932	0.0770	0.686	0.496	0.0165	0.134	0.8943
CTQ	-0.0409	-0.714	0.476	-0.0917	-0.819	0.416	-0.3424	-2.151	0.0397
Sex	-0.6471	-4.296	<0.001	-1.6955	-4.581	<0.001	-0.4672	-1.068	0.2939
Age	0.0381	1.716	0.087	0.1216	2.235	0.029	-0.0283	-0.625	0.5364
Diagnosis	-0.0006	-0.031	0.976	-0.0408	-0.871	0.387	0.1510	1.048	0.3032
PSQI	0.0473	3.997	<0.001	0.0400	2.146	0.036	0.0564	3.029	0.005
PER1xSex	0.0109	0.250	0.803	0.1255	0.877	0.384	0.7021	2.761	0.0097
PER1xAge	0.0336	0.258	0.797	0.2633	0.629	0.532	1.2691	2.281	0.0298
PER1xDiagnosis	-0.0487	-0.236	0.813	-0.2486	-0.277	0.783	NA	NA	NA
PER1xPSQI	-0.0034	-0.664	0.507	0.0162	1.056	0.295	-0.1093	-1.650	0.1094
CTQxSex	0.2892	0.976	0.330	1.3655	2.632	0.011	0.0925	0.657	0.5161
CTQxAge	0.0525	1.058	0.291	-0.0059	-0.063	0.950	-0.0589	-0.255	0.8004
CTQxDiagnosis	2.5393	1.673	0.096	1.4537	0.675	0.503	NA	NA	NA
CTQxPSQI	-0.0047	-0.076	0.940	0.0344	0.362	0.719	-0.1976	-3.302	0.0025
	Asian 2			Hispanic			Other		
	Standardized Coefficients			Standardized Coefficients			Standardized Coefficients		
	Beta	t	Sig.	Beta	t	Sig.	Beta	t	Sig.
(Constant)		0.095	0.925		0.175	0.862		0.347	0.7302
PER1xCTQ	0.1523	1.873	0.063	-0.0222	-0.108	0.915	0.1000	0.713	0.4797
PER1	-0.0127	-0.139	0.890	0.6533	0.980	0.337	0.0832	0.545	0.5881
CTQ	0.1450	1.664	0.099	-0.2743	-0.499	0.623	-0.1926	-1.141	0.26
Sex	-0.3372	-1.394	0.166	-0.0112	-0.022	0.983	-0.8170	-1.954	0.0569
Age	0.0505	2.104	0.037	0.1068	1.338	0.194	-0.0460	-0.651	0.5185
Diagnosis	0.0428	2.085	0.039	-0.1103	-0.160	0.874	-0.1178	-1.683	0.0993
PSQI	0.0252	2.494	0.014	0.0843	3.012	0.006	-0.0175	-0.641	0.5248
PER1xSex	0.1679	1.105	0.271	0.0009	0.006	0.995	-0.1219	-0.821	0.4161
PER1xAge	0.1753	0.383	0.702	-0.4935	-1.149	0.262	-0.1824	-0.304	0.7622
PER1xDiagnosis	-0.3491	-0.719	0.474	-0.8346	-0.064	0.950	-0.0298	-0.051	0.9599
PER1xPSQI	0.0062	0.773	0.441	0.0525	3.164	0.004	-0.0083	-0.653	0.517
CTQxSex	0.0151	0.071	0.943	-0.5481	-0.751	0.460	1.3979	2.135	0.0383
CTQxAge	-0.0661	-1.120	0.265	-0.3051	-2.187	0.039	0.2007	1.879	0.0667
CTQxDiagnosis	-4.3074	-2.478	0.015	6.3800	0.129	0.898	-3.4493	-0.427	0.6717
CTQxPSQI	0.1233	2.443	0.016	-0.5383	-2.394	0.025	-0.0586	-0.448	0.6567

Supplemental Table 2.6.9. *Per1* rs30272172 and Early-life adversity significantly interact to predict problematic drinking behavior (AUDIT) when including participants originally excluded due to lack of neuroimaging data (n=719)

		Standardized Coefficients		
Model		Beta	t	Sig.
1		Estimate	t	p
	(Constant)	0.00000	-0.481	0.631
	PER1xCTQ	0.12899	3.18	0.002
	PER1	0.02569	0.64	0.522
	CTQ	-0.06265	-1.588	0.113
	Sex	-0.24119	-6.742	<0.001
	Age	0.07908	2.224	0.027
	PC1	-0.11301	-2.763	0.006
	PC2	0.08501	2.181	0.030
	PC3	0.03582	0.929	0.353
	PC4	-0.01396	-0.394	0.694
	PC5	-0.00892	-0.253	0.801
	PSQI	0.24666	6.687	<0.001
	Diagnosis	0.01260	0.322	0.748
	PER1xSex	0.03121	0.872	0.383
	PER1xAge	0.00386	0.103	0.918
	PER1xPC1	-0.02551	-0.518	0.605
	PER1xPC2	0.01055	0.277	0.782
	PER1xPC3	0.04689	1.001	0.317
	PER1xPC4	-0.00723	-0.191	0.848
	PER1xPC5	-0.05228	-1.491	0.136
	PER1xPSQI	0.03204	0.822	0.412
	PER1xDiagnosis	-0.03303	-0.958	0.338
	CTQxSex	0.05196	1.411	0.159
	CTQxAge	0.04450	1.272	0.204
	CTQxPC1	0.09390	2.41	0.016
	CTQxPC2	-0.03406	-1.005	0.315
	CTQxPC3	-0.02481	-0.671	0.503
	CTQxPC4	0.00100	0.028	0.978
	CTQxPC5	0.01056	0.284	0.777
	CTQxPSQI	0.00569	0.169	0.866

Supplemental Table 2.6.10. *Per1* rs3027172 and Early-life adversity do not significantly interact to predict ventral striatal reactivity when controlling for gene x covariate and environment x covariate interactions.

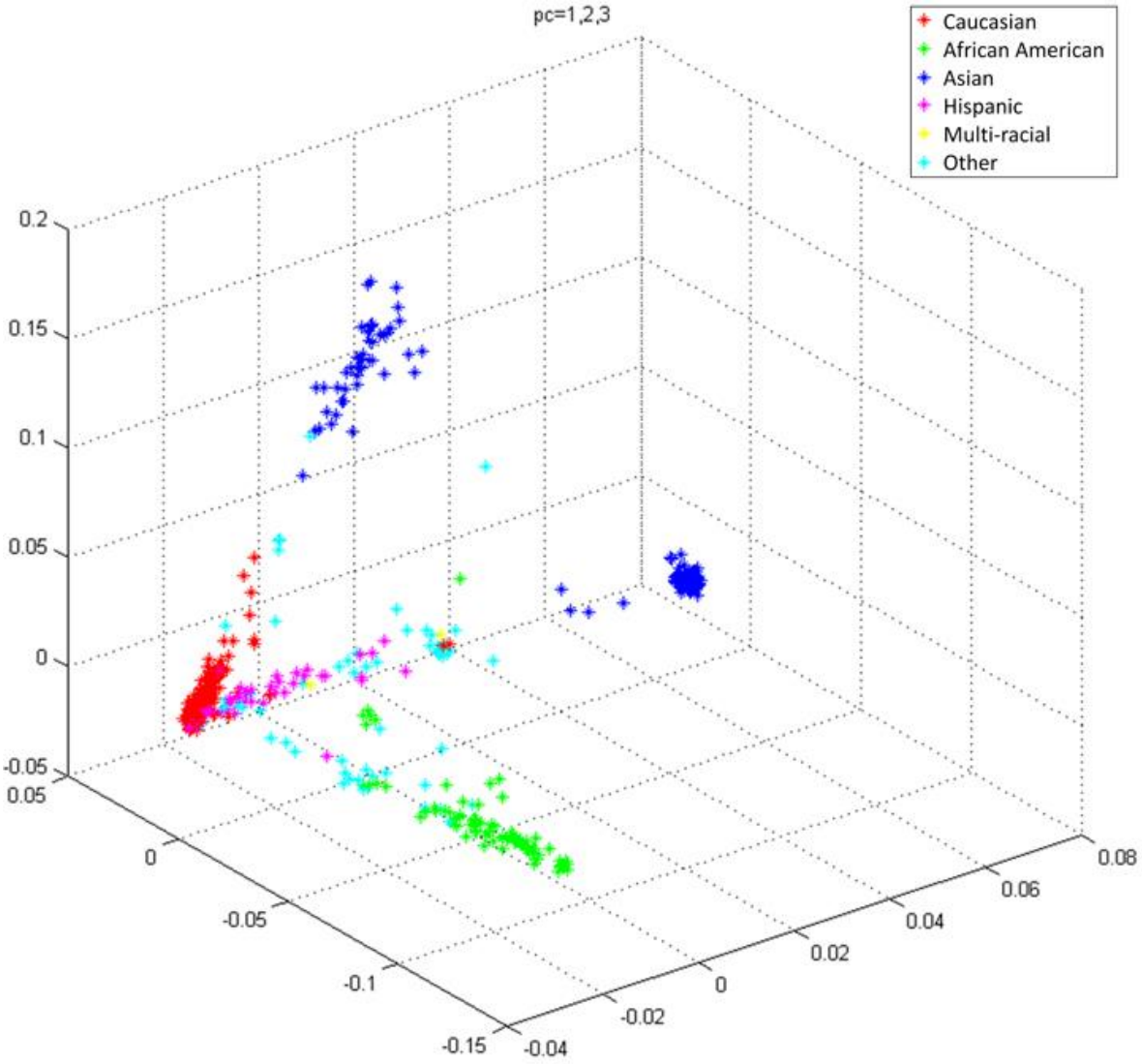
Model		Standardized Coefficients Beta	t	Sig.
1	(Constant)		0.132	0.895
	PER1xCTQ	0.08380	2.145	0.032
	PER1	0.06695	1.651	0.099
	CTQ	-0.04072	-0.958	0.338
	Sex	-0.17220	-2.258	0.024
	Age	-0.00505	-1.62	0.106
	PC1	-0.00742	-0.015	0.988
	PC2	0.01349	0.055	0.956
	PC3	0.63155	0.622	0.534
	PC4	0.07347	0.714	0.475
	PC5	0.30387	0.669	0.504
	Diagnosis	0.01000	0.312	0.755
	PSQI	-0.01828	-1.19	0.235
2	(Constant)		1.315	0.189
	PER1xCTQ	0.05643	1.231	0.219
	PER1	0.06268	1.434	0.152
	CTQ	-0.01241	-0.287	0.774
	Sex	-0.18633	-2.437	0.015
	Age	-0.01375	-1.287	0.199
	PC1	0.05786	0.487	0.627
	PC2	-0.03814	-0.071	0.944
	PC3	0.10406	0.42	0.675
	PC4	1.13770	1.12	0.263
	PC5	0.38340	1.107	0.269
	Diagnosis	0.01820	1.16	0.246
	PSQI	-0.00526	-0.734	0.463
	PER1xSex	0.06082	1.556	0.120
	PER1xAge	-0.02018	-0.28	0.780
	PER1xPC1	-0.46548	-0.434	0.664
	PER1xPC2	-0.29333	-1.082	0.280
	PER1xPC3	-0.73396	-0.538	0.590
	PER1xPC4	-0.32851	-0.605	0.545
	PER1xPC5	-1.67776	-0.772	0.441
	PER1xDiagnosis	-0.16886	-1.553	0.121
	PER1xPSQI	0.00510	1.364	0.173
	CTQxSex	0.27827	1.666	0.096
	CTQxAge	-0.00593	-0.192	0.848
	CTQxPC1	-12.36640	-2.51	0.012
	CTQxPC2	0.20059	0.123	0.902

CTQxPC3	0.59427	1.215	0.225
CTQxPC4	-0.99835	-0.421	0.674
CTQxPC5	-1.87894	-1.714	0.087
CTQxDiagnosis	-0.45213	-0.826	0.409
CTQxPSQI	-0.07234	-3.114	0.002

Supplemental Table 2.6.11. The interaction of *Per1* rs30272172 and Early-life adversity predicting ventral striatal reactivity in each of the six ethnic subsamples.

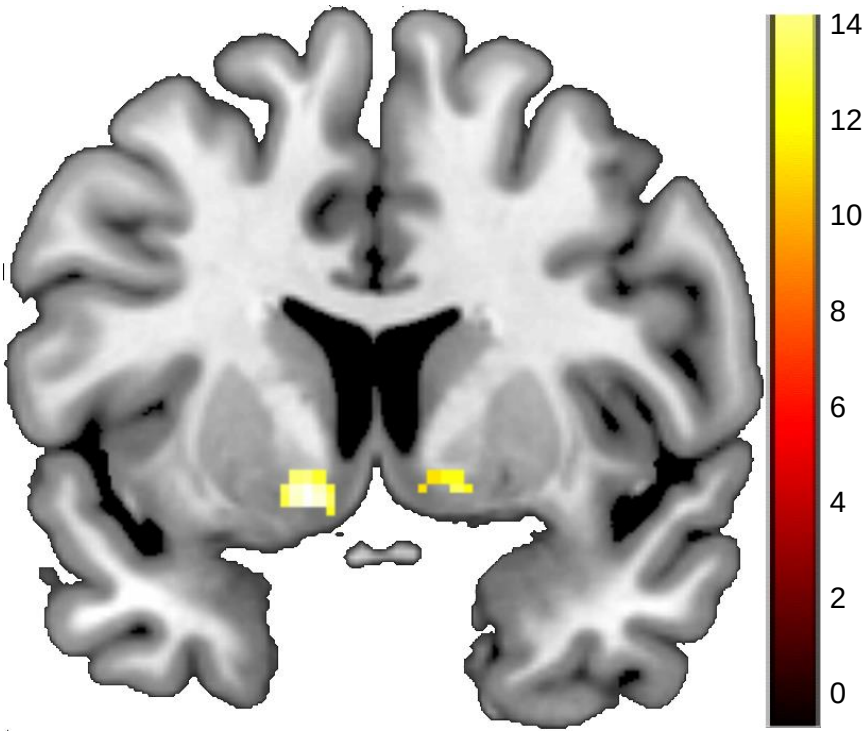
	Caucasian			African American			Asian 1		
	Standardized Coefficients			Standardized Coefficients			Standardized Coefficients		
	Beta	t	Sig.	Beta	t	Sig.	Beta	t	Sig.
(Constant)		0.501	0.617		0.184	0.855		0.294	0.771
PER1xCTQ	0.08772	1.351	0.178	-0.31384	-2.082	0.042	0.21491	0.808	0.426
PER1	0.00996	0.17	0.865	0.12838	0.985	0.329	0.02570	0.14	0.889
CTQ	0.06633	1.093	0.275	-0.00964	-0.074	0.941	0.08035	0.339	0.737
Sex	-0.26175	-1.642	0.102	-0.94633	-2.202	0.032	-0.14133	-0.217	0.830
Age	-0.01687	-0.718	0.473	-0.08550	-1.353	0.181	0.02846	0.423	0.676
Diagnosis	0.02733	1.238	0.217	0.07216	1.327	0.190	-0.07073	-0.329	0.744
PSQI	-0.00625	-0.499	0.618	-0.02841	-1.314	0.194	-0.00181	-0.065	0.948
PER1xSex	0.02901	0.627	0.531	-0.02871	-0.173	0.864	-0.19436	-0.513	0.612
PER1xAge	0.07696	0.559	0.576	0.16653	0.343	0.733	-0.58885	-0.711	0.483
PER1xDiagnosis	-0.24471	-1.122	0.263	0.68997	0.661	0.511	NA	NA	NA
PER1xPSQI	-0.00108	-0.202	0.840	0.00491	0.275	0.784	0.09226	0.935	0.357
CTQxSex	0.61757	1.97	0.050	-0.64824	-1.076	0.286	0.08910	0.425	0.674
CTQxAge	0.04816	0.917	0.360	-0.08222	-0.753	0.454	0.15804	0.46	0.649
CTQxDiagnosis	-1.16741	-0.727	0.468	-0.82865	-0.331	0.742	NA	NA	NA
CTQxPSQI	-0.09890	-1.506	0.133	-0.13670	-1.24	0.220	-0.07186	-0.807	0.426
	Asian 2			Hispanic			Other		
	Standardized Coefficients			Standardized Coefficients			Standardized Coefficients		
	Beta	t	Sig.	Beta	t	Sig.	Beta	t	Sig.
(Constant)		0.538	0.592		1.244	0.226		0.019	0.985
PER1xCTQ	0.01329	0.156	0.876	0.25508	0.908	0.373	0.16067	1.105	0.275
PER1	0.00206	0.021	0.983	-0.99849	-1.091	0.287	0.03870	0.245	0.808
CTQ	-0.18459	-2.027	0.045	-0.86761	-1.149	0.263	0.13523	0.773	0.444
Sex	-0.50103	-1.981	0.050	0.08126	0.114	0.910	0.47581	1.098	0.278
Age	-0.00034	-0.013	0.989	-0.15828	-1.445	0.162	-0.06020	-0.822	0.415
Diagnosis	-0.01393	-0.649	0.517	1.11597	1.183	0.249	0.07887	1.087	0.283
PSQI	-0.00495	-0.469	0.640	0.01784	0.464	0.647	-0.01529	-0.541	0.591
PER1xSex	-0.10256	-0.646	0.520	0.20057	1.055	0.302	0.30156	1.959	0.056
PER1xAge	-0.39560	-0.828	0.409	0.37238	0.632	0.534	-1.03469	-1.666	0.103
PER1xDiagnosis	-0.52694	-1.038	0.301	-23.38020	-1.306	0.204	-0.21398	-0.351	0.728
PER1xPSQI	0.01587	1.884	0.062	0.01315	0.577	0.570	-0.00374	-0.285	0.777
CTQxSex	0.37678	1.702	0.091	-0.37181	-0.371	0.714	0.15417	0.227	0.821
CTQxAge	-0.11857	-1.921	0.057	-0.04776	-0.249	0.805	0.07997	0.722	0.474
CTQxDiagnosis	0.12147	0.067	0.947	-89.10560	-1.316	0.201	4.74235	0.566	0.574
CTQxPSQI	-0.04378	-0.83	0.408	-0.42551	-1.378	0.181	-0.15048	-1.109	0.273

Supplemental Figure 2.6.1. Ancestral principal components.



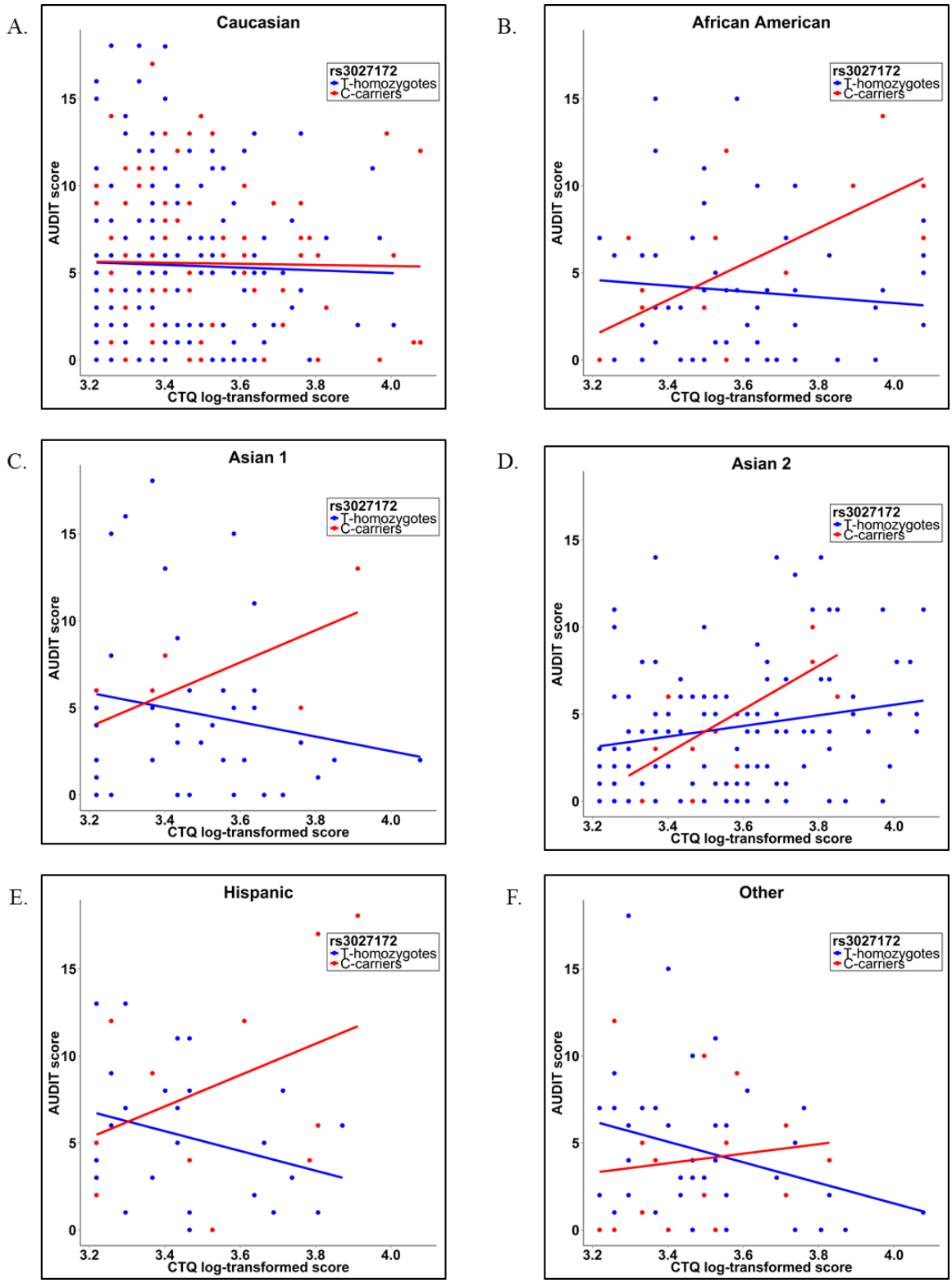
Ancestral principal components 1 – 3 generated using Eigenstrat. Color coding is of self-report of ethnicity. Based on these results participants who self-report as 'Asian' were split into two subgroups (Asian1 and Asian2) as their ancestral principle components separated into two distinct clusters according to k means clustering.

Supplemental Figure 2.6.2. Ventral striatal activation from the Positive>Negative feedback contrast of the Corticostriatal Reactivity task.

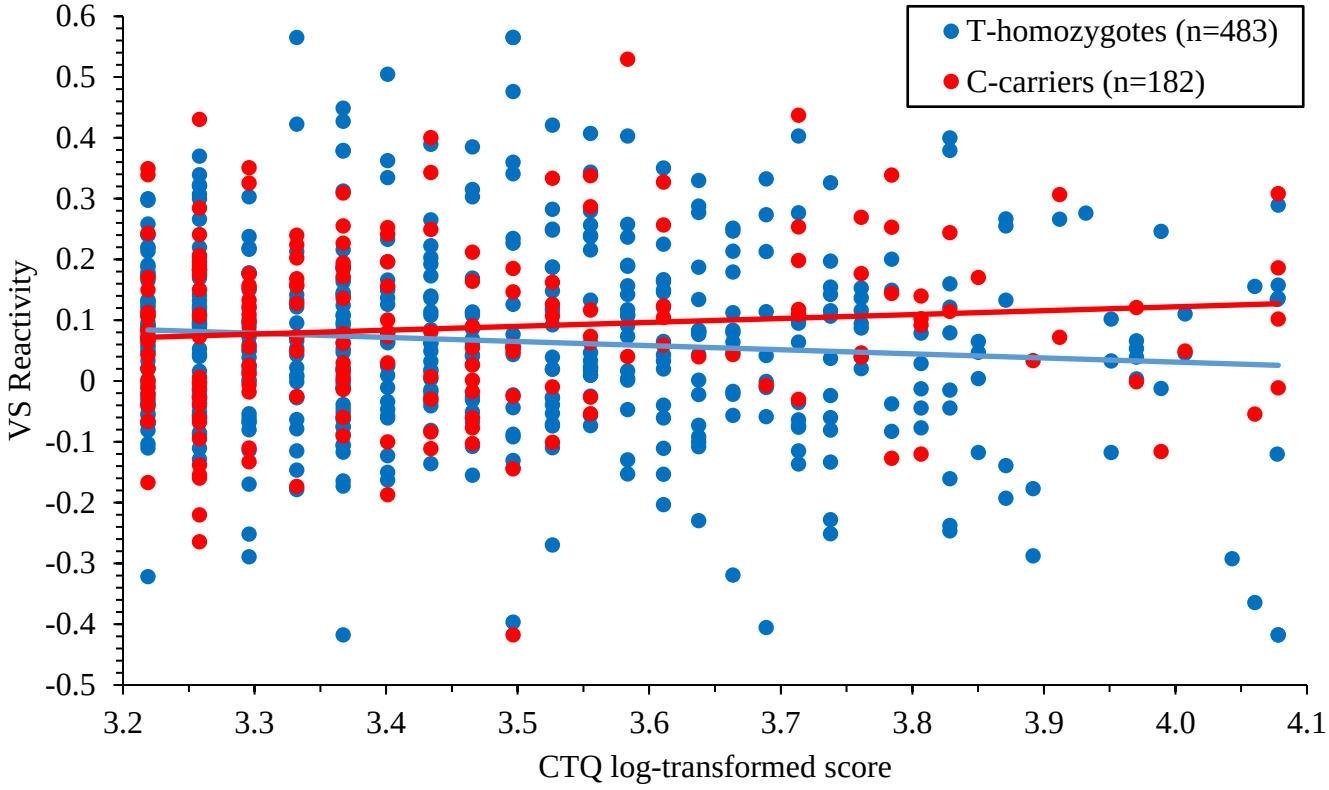


Statistical parametric map illustrating bilateral VS activation clusters for the contrast “positive reward> negative loss” with bilateral spherical 5mm ROIs centered on the points of peak activation from Hariri et al. (2006), overlaid onto a canonical structural brain image Montreal Neurological Institute coordinates and statistics *(p*<.05, family-wise error whole-brain corrected and ≥10 contiguous voxels): left hemisphere: x= -12, y= 8, z= -10, *t* = 13.59, *P*<.001, right hemisphere: x = 12, y = 10, z= -8, t=12.63, *p<.001*.

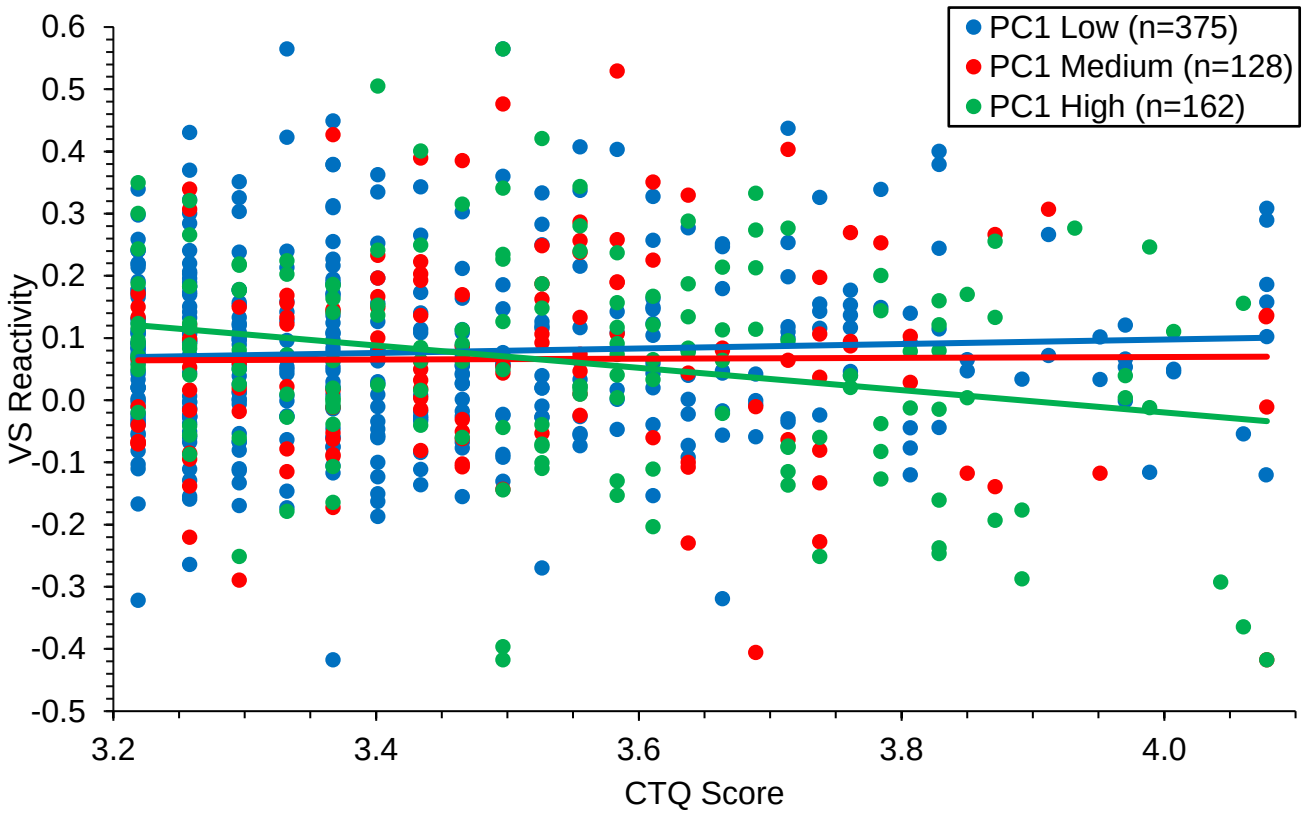
Supplemental Figure 2.6.3. The interaction of *Per1* rs30272172 and Early-life adversity predicting problematic drinking behavior (AUDIT) in each of the six ethnic subsamples**.**



Supplemental Figure 2.6.4. *PER1* rs3027172 and Early-Life Adversity Do Not Significantly Interact to Predict VS reactivity**.** (ΔR^2=.0021, b=0.056, t=1.231, p=0.219).

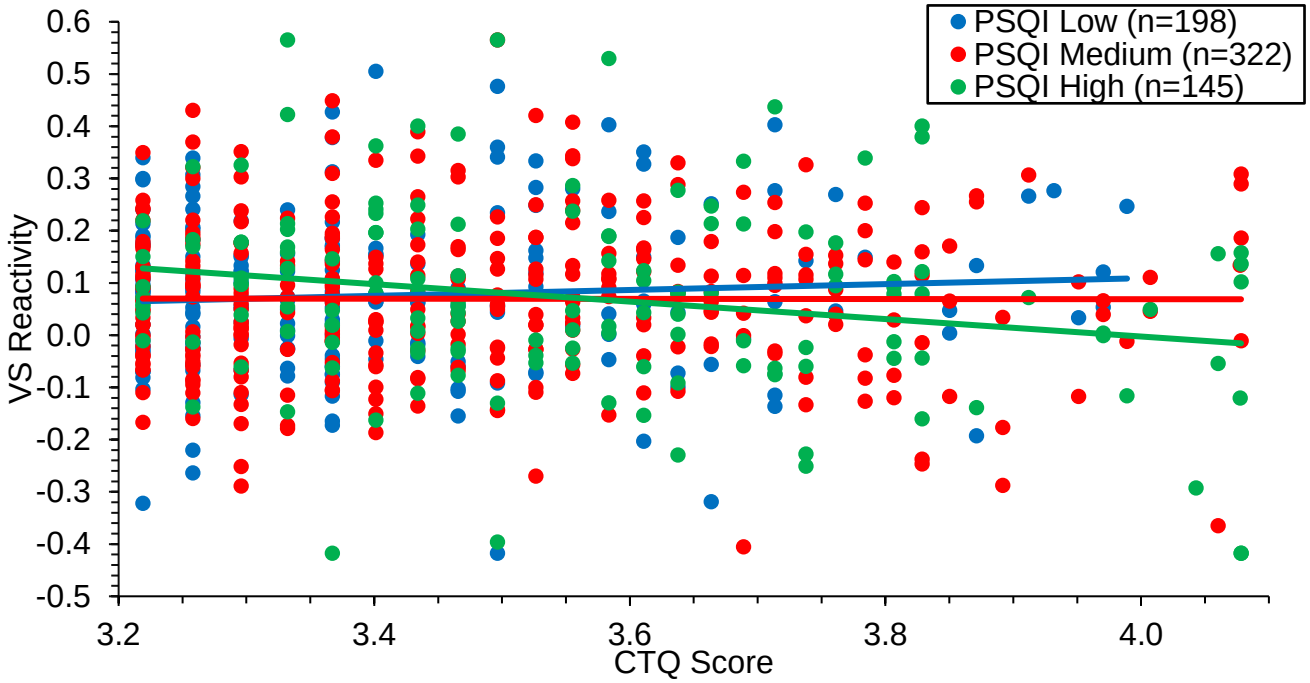


Supplemental Figure 2.6.5. Ancestral Principal Component 1 and Early-Life Adversity Interact to Predict VS reactivity. (ΔR^2=.0133, b=-0.132, t=-3.014, p=0.003).



The interaction of the ancestral principal component 1 (PC1) and CTQ scores was found to significantly predict ventral striatal (VS) reactivity when included as a covariate in the analysis examining the interaction of *PER1* rs3027172 and CTQ scores predicting VS reactivity (see Results; b=-12.3664, t=-2.51, p=0.01231). Follow-up analyses examining the interaction of PC1 and CTQ scores on VS reactivity, with age, sex, the other four ancestral principal components, PSQI, and presence of a psychiatric diagnosis, and interactions between these variables and variables of interest (PC1 and CTQ scores) as covariates, found that the PC1xCTQ interaction remained significant (ΔR^2=.0133, b=-0.132, t=-3.014, p=0.003). It was found that there was a significant negative relationship between CTQ scores and VS reactivity among participants with higher PC1 values (Johnson-Neyman significance for PC1 values greater than 0.0275). Participants were split into three PC1 groups based on the group standard deviation (low= -0.028 - -0.037, medium = -0.038 - 0.037, high = 0.038 - 0.0704). Examination of simple-slopes revealed a significant negative relationship between CTQ-scores and VS reactivity in the high PC1 group of participants (b=-0.173, t=-2.594, p=0.010). This group of high PC1 participants consists predominantly of members of the Asian2 subgroup (see Fig. S1).

Supplemental Figure 2.6.6. Sleep Quality and Early-Life Adversity Interact to Predict VS reactivity. (ΔR2=.0107, b=-0.1211, t=-2.682, p=0.007).



The interaction of PSQI scores (sleep quality) and CTQ scores was found to significantly predict ventral striatal (VS) reactivity when included as a covariate in the analysis examining the interaction of PER1 rs3027172 and CTQ scores predicting VS reactivity (see Supplemental Table 2.6.6; b=-0.0723, t=-3.114, p=0.0019). Follow-up analyses examining the interaction of PSQI and CTQ scores on VS reactivity, with age, sex, the five ancestral principal components, and presence of a psychiatric diagnosis, and interactions between these variables and variables of interest (PSQI and CTQ scores) as covariates, found that the PSQIxCTQ interaction remained significant (ΔR2=.0107, b=-0.1211, t=-2.682, p=0.007). It was found that there was a significant negative relationship between CTQ scores and VS reactivity among participants with higher PSQI values (Johnson-Neyman significance for PSQI scores greater than 7.3). Participants were split into three PSQI groups based on the group standard deviation (low= 0 – 4, medium = 5 - 6, high = 7 - 12). Examination of simple-slopes revealed a significant negative relationship between CTQ-scores and VS reactivity in the high PSQI group of participants (b=-0.176, t=-2.592, p=0.012).

Chapter 3: No effect of acute and early-life stress in a reward learning and processing paradigm

Baranger DAA, Desmarais A, Sputo K, Chang K, Pan W, Jones M, Kennedy M, Winstone J, Corral- Frías NS, Bogdan R. Minimal effects of acute and early-life stress in a reward learning and processing paradigm. (In preparation).

3.1 Abstract

It is clear that both early-life and acute stress contribute to the etiology of a host of psychiatric disorders, particularly depression and addiction. A large body of work points to altered functioning of corticostriatal circuits, leading to changes in reward behavior, as a possible mechanism underlying this association. While both acute and early-life stress have been studied independently, less is known about how these forms of stress interact, with regard to their impact on reward behaviors and circuits. The present study sought to examine whether early-life stress was associated with differences in within-subject effects of an acute-stress manipulation, on reward-learning behavior and concurrent event-related potentials (ERPs).

Female participants with elevated early-life stress (ELS; N=35) were recruited, as were female controls who were matched by group on age, ethnicity, income, and parental education (N=36). Participants completed a within-subject acute stress manipulation, consisting of both a trier social-stress test and a cold-pressor test – a counterbalanced control session occurred on a separate visit. Following the acute-stress or control manipulation, participants performed a signal detection reward-learning task while EEG data was collected. Self-report and physiological stress-responses were collected throughout both stress and control visits. Outcomes were analyzed with mixed-effect models.

All the stress-responses showed an effect of the acute-stress manipulation (i.e. anxiety, negative affect, salivary cortisol, and heart rate). While participants quickly learned the reward-associations, hypothesized effects of acute stress on reward learning (i.e. response bias), which have been previously reported, were not observed. ELS was not associated with reward learning or accuracy, nor did ELS interact with acute stress. Analyses of ERPs were largely negative as well, though a nominally significant effect of ELS on the feedback related negativity (FRN) in the predicted direction (i.e. reduced) was observed. An unexpected interaction between acute stress and ELS was observed in analyses of reaction-time (RT), wherein control participants were slower

than ELS participants during the control visit, and acute stress had opposite effects on their behavior – control participants sped-up, while ELS participants slowed-down.

We propose that increased motivation, as the rewards used here were larger than in prior work, may account for the null-effect of acute stress on reward learning. The unexpected interaction between ELS and acute stress on RT may reflect the inverted-U effect of stress hormones on hippocampal-dependent memory processes. Broadly, this work demonstrates that the effect of acute stress on reward behaviors may be smaller than previously reported, and may be moderated by motivation and demographic variables.

3.2 INTRODUCTION

Nearly half of all Americans will meet the criteria for a psychiatric disorder during their life (Kessler et al., 2005). The societal burden of such illness is large, both in terms of lives lost and in terms of economic cost, estimated at $2.5T worldwide (Bloom et al., 2011). While it remains unknown why some people become ill and others do not, stress during periods of development is one of the best predictors. Almost 40% of cases, particularly mood, anxiety, and substance abuse disorders, are associated with childhood adversity experienced before the age of 18 (Green et al., 2013). The pathogenic effects of stress are not restricted to events occurring during childhood; indeed, the risk for alcohol use and mood disorders increases following particularly stressful life events (Goodyer et al., 2000; Kendler, 1999; Keyes et al., 2013). As such, to completely understand how stress confers psychopathology risk, it is critical to examine how early life stress influences susceptibility to acute stress. Such knowledge will contribute to our understanding of psychiatric etiology, which ultimately may help improve psychiatric nosology and treatment.

One mechanism by which stress may increase risk for psychopathology is via disrupted reward processing. Various forms of stress-related psychopathology (e.g., depression, substance use disorders, PTSD) are associated impaired performance on tasks that are dependent on reward processing and associative learning (Diekhof et al., 2008; Nielen et al., 2009; Pizzagalli et al., 2008). Moreover, differential activation of reward regions during reward processing has been associated with future psychopathology (Bress et al., 2013; Gotlib et al., 2010). Research indicates that acute and early-life stress also produce similar behavioral reward learning deficits in controls (Berghorst et al., 2013; Bogdan & Pizzagalli, 2006; Pechtel & Pizzagalli, 2011, 2013). Notably, in healthy controls, performance on reward learning tasks both at baseline and under acute stress is associated with depression symptoms, particularly anhedonia (Bogdan & Pizzagalli, 2006; Pizzagalli et al., 2005). These effects extend to rodent research as well, where early-life and acute stress manipulations induce depression-like symptoms, such as reduced

interest in rewards (Hays et al., 2012; Leventopoulos et al., 2009; Matthews & Robbins, 2003; Rüedi-Bettschen et al., 2005), increased addiction susceptibility (Cruz et al., 2008; Der-Avakian & Markou, 2010; Kippin et al., 2008; Will et al., 1998), and impaired reward learning and decision making (Graham et al., 2010; Shafiei et al., 2012).

The mesolimbic dopaminergic pathway regulates many of the core processes underlying reward learning. Neurons in this pathway, which originates in the ventral tegmental area (VTA) and connects the nucleus accumbens (NAc) within the ventral striatum (VS), amygdala, hippocampus, and medial prefrontal cortex, carry signals indicating whether a reward is expected (reward prediction; RP) and whether the expected reward was received (reward prediction error; RPE) (Fiorillo et al., 2003; Nomoto et al., 2010; Schultz, 2000, 2007, 2013). In humans, these signals can be indexed via non-invasive functional magnetic resonance imaging (fMRI) of structures within the mesolimbic dopaminergic pathway, or by event-related potentials (ERPs) at the scalp. The feedback-related negativity (FRN) ERP is generally considered the best index of the neural RPE (Sambrook & Goslin, 2015), while the P300 (P3) ERP is correlated with RP signals at stimulus presentation (Goldstein et al., 2006; Pfabigan et al., 2014). Studies of the effects of stress on reward processing have found that both acute and early life stress blunt RPE signals, though this is largely in the context of tasks that do not have a learning component (Bogdan et al., 2011; Glienke et al., 2015; Kumar et al., 2014; Lewis et al., 2014; Novick et al., 2018; Porcelli et al., 2012). The impact of stress on RP signals remains less clear, as studies have found mixed results (Dillon et al., 2009; Kumar et al., 2014; Porcelli & Delgado, 2017). Even so, the effects of stress on the brain's reward circuitry has been proposed to mediate its effects on reward learning, and may also partially mediate the effects of stress on risk for psychopathology (Corral-Fr??as et al., 2015; Mclaughlin & Lambert, 2016).

No human studies, to our knowledge, have examined the combined effects of acute and early-life stress on reward learning behavior or neural activity during reward processing. However, a recent meta-analysis has found that early-life adversity is consistently associated with blunted

cortisol release to an acute stressor (Bunea et al., 2017). This finding echoes rodent research on the combined effects of acute stress and maternal separation - while acute stress increases the dopamine content of the nucleus accumbens, animals who experienced maternal separation exhibited no change in response to acute stress (Jahng et al., 2010). At present, the effects of acute stress in an ELS population on reward learning behavior, or on the neural activation of reward regions, remains unknown. The current study had three aims. First, to replicate prior associations of acute and early life stress with cortisol reactivity, reward learning, and reward processing. Second, to extend this literature by examining whether reward processing ERPs mediate associations between stress and reward learning behavior. Third, to test whether early life stress moderates the effects of acute stress on reward learning and reward processing.

3.3 METHODS

3.3.1 Participants

Eighty-five female participants aged 18-35 were recruited from the community according to reported high (n=43; moderate/severe abuse) or low (n=42; no/minimal abuse) early life stress (ELS) exposure. Groups were recruited to be matched on age, education, college student status, ethnicity, income, and parental education. Only women were recruited due to gender differences in stress-related biology that are theorized to increase stress-related psychopathology risk in women (Desantis et al., 2011). Exclusion criteria included history of psychosis, current use of psychotropic medications, and history of a head trauma resulting in a loss of consciousness. The study was advertised using the Washington University School of Medicine Research Participant Registry, the Washington University Undergraduate Research Participant Pool, flyers posted throughout the St. Louis metropolitan area, and social media posts. The study protocol was approved by the Washington University in St. Louis IRB and participants received a median of $124 in remuneration for completing the study (additional payment details are provided in the protocol section).

A survey including demographic questions and the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) was distributed to assess eligibility of interested potential participants. The CTQ asks participants to retrospectively report on the occurrence and frequency of emotional, physical, and sexual abuse as well as emotional and physical neglect before the age of 17. The instrument's five subscales, each representing one type of abuse or neglect, have robust internal consistency and convergent validity with a clinician-rated interviews of childhood abuse (Scher et al., 2001). Participants reporting moderate-severe physical (i.e., ≥10), sexual (i.e., ≥8), and/or emotional abuse (i.e., ≥13) during childhood (n=43) on the CTQ were recruited for the high ELS group. The CTQ neglect subscales were not used, due to concerns that cultural differences in standards of childcare (Grassi-Oliveira et al., 2014), as well as evidence that the

abuse subscales are most robustly predictive of mental health outcomes (Schilling et al., 2016), and poor psychometric validity of the physical neglect subscale in some samples (Karos et al., 2014).

Following study completion by each individual in the high ELS group, an individual was recruited for the low ELS group who was individually matched on age, education, college student status, ethnicity, income, and parental education to ensure that these potentially confounding variables did not differ across groups. Participants in the low ELS group were required to report no or minimal physical, sexual, or emotional abuse (i.e., CTQ scores ≤ 7, 5, 8 on these scales respectively) and a total CTQ score <36. With the exception of the endorsement of psychotic hallucinations and/or delusions, no psychiatric diagnosis or symptoms were exclusionary. Groups were not matched based on psychiatric conditions due to concerns that doing so would result in groups that are resilient to stress (i.e., participants in the high ELS group with no psychopathology) and/or vulnerable to psychopathology (i.e., participants in the low ELS group with psychopathology) that would complicate the interpretability of data. The recruitment survey was completed 1,233 times with 909 respondents (74%) meeting inclusion criteria (the majority of excluded respondents were male or had an intermediate CTQ score). Of these respondents, 226 (25%) met criteria for the moderate/high ELS group (hereafter referred to as “high ELS”); all were contacted and 43 (19%) were successfully recruited to the study. Once a high ELS participant completed the full study protocol (see below), we identified potential individually-matched low ELS participants (N=182), of whom 42 (23%) were successfully recruited.

Of 85 participants recruited, two withdrew. One did not tolerate the stress induction and chose to end the study (high ELS group); the other was unable to schedule a time to complete the second session (low ELS group). An additional three participants were excluded, one due to non-completion of the take home portion of the study protocol (low ELS group), and two endorsed hallucinations or delusions during the clinical interview (both high ELS group). The sample size, prior to data analysis and data exclusion due to poor performance (see below) was 80, with 40

participants in each group, which was our planned enrollment target due to observed effects of a laboratory acute stress on our primary variables of interest (i.e., response bias and ERP components) in samples of 40 (Bogdan & Pizzagalli, 2006; Bogdan et al., 2011). Following data exclusions and quality control procedures (described below), there were 35 high and 36 low ELS participants with complete behavioral data (**Table 3.1**) and 34 high and 35 low ELS participants with complete EEG data.

3.3.2 Study Protocol Overview

Study sessions occurred between 1-5 pm within 14 days of one another (6.4±1.6 days). Participants first completed informed consent with a senior laboratory member, who subsequently was not among those administering the acute stress manipulation (see below). Participants were informed that they would be asked to give a public speech on one of the two visits, and that a cold arm wrap would be placed on their arm during one of the two visits. Participants were randomized to receive a social and physical stress-induction on either the first or second visit counterbalanced with a control procedure. Participants matched across ELS groups received the stress manipulation in the same order. Salivary cortisol, heart rate and self-reported anxiety and negative and positive affect were collected throughout both visits. **Figure 3.1A** provides a schematic of a study session. Participants then completed a probabilistic reward learning task while electroencephalography (EEG) data were acquired on two separate laboratory visits. Participants completed additional self-report questionnaires on stress and mood and collected diurnal cortisol samples at home between the two visits. At the end of the second visit participants completed a structured clinical interview (MINI (Sheehan et al., 1998)), conducted by a trained clinician, which was used to identify lifetime and current psychiatric diagnosis, which with the exception of psychotic hallucinations and delusions, were not exclusionary or matched across groups. Participants who met criteria for a diagnosis and were not already receiving treatment were

provided with a list of local mental health resources. They were then debriefed as to the nature and goals of the study, the stress manipulation, and the task design. Participants were compensated $10/hour (~2 hours per visit), $20 for the take-home portion, and could win up to an additional $32 each time they completed the reward learning task (median total payment was $124).

3.3.3 Stress Manipulation

The stress induction, which combined the Trier Social Stress Test (TSST) (Buske-Kirschbaum et al., 1997) and a cold-pressor (CP) (Porcelli et al., 2012), was modeled after prior reports, which have found that combining social-cognitive (TSST) and physical stressors (CP) leads to an elevated and more prolonged stress-response(du Plooy et al., 2014).

TSST: Immediately prior to the probabilistic reward learning task and EEG data acquisition, an experimenter brought participants into a room with a desk and a curtain blocking half the room from view. Participants were first told that they have five minutes to prepare a five-minute speech on why they are qualified for a job that they are actually qualified for (e.g., they cannot claim to have super powers), and that they should try to be as compelling as possible, as if it were an actual job interview. After the five minutes, the curtain was drawn back to reveal video equipment (video camera, standing microphone, video screen, and bright lights). Two evaluators unknown to the participant wearing lab coats (one male and one female) entered the room, and sat facing the participant. The evaluators had no other interaction with the participant during either visit. The participant was told that they were being evaluated by the two experimenters in front of them and the study PI, who was viewing the session via video broadcast in another room. They were further informed that recorded video and audio would be used to assess verbal and non-verbal communication abilities. They were then given five minutes to deliver their speech, during which time the two experimenters did not provide any feedback, either facial or verbal, before, during, or after the performance. Following completion of the speaking task participants were

immediately administered a five minute math task by the two experimenters, in which they were asked to serially count down from a large prime (i.e. 1873) by another (i.e. 13) as fast and accurately as possible. On every error they were asked to stop and start again, and they were asked to go faster, regardless of their actual speed. When participants did not make an error for 30 seconds in a row, they were asked to start again with another large prime number and a different incremental decrease

CP: Following the TSST, participants were escorted to the EEG recording room. After the EEG net was fitted to a participants head, a cold pressor arm wrap (2-4^{o}C) was applied for two-minutes to further enhance the stress manipulation (Porcelli et al., 2012). The cold pressor was not socially evaluated, and was administered by the same study experimenters who collected the rest of the study data. The cold-pressor was subsequently re-administered half-way through the EEG protocol (15 minutes later) during the second task break (a 3-minute rest between the second and third blocks of the EEG task – see below), in order to further prolong the stress response.

Control Condition: In the control condition, which occurred on a separate day, participants were asked to copy a magazine article for five minutes in an empty room (a different room than the one used for the stress manipulation) by an experimenter who was not involved in the stress session. They then read a magazine article aloud for five minutes in the same room, and finally counted backwards from 5,000 by 1 at their own pace for five minutes, without any experimenter feedback. Instead of a cold pressor, a room temperature arm wrap was applied for two minutes, which was also applied during the break midway through the reward learning task. This control procedure takes the same amount of time and involves all the same physical activities (e.g. standing for five minutes). The order of sessions (stress/control) was counterbalanced across participants but kept consistent in pairs matched by group status (moderate-severe early life stress, none/minimal early life stress).

3.3.4 Stress Manipulation Assessment

Participant response to the acute-stress manipulation was assessed with self-reported mood, salivary cortisol, and heart rate. ***Self-reported Mood.*** Self-reported anxiety and negative and positive affect were assessed with the 20-item State Trait Anxiety Inventory - State (STAI-S) and 20-item Positive and Negative Affect Scale (PANAS) (Spielberger, 1983; Watson et al., 1988). These measures were administered four times – both at the beginning and end of the study visit, and participants completed them twice immediately after the stress-induction, once with reference to how they felt during the stressor, and once on how they were currently feeling. Both have been previously shown to be sensitive to acute stress manipulations (Bogdan & Pizzagalli, 2006).

Salivary Cortisol. Salivary samples were collected using Salivettes to assess cortisol at 4 time points: 1) 15 minutes after arriving the lab, after the first round of self-report questionnaires, 2) immediately following the stress/control procedure, 3) halfway through the probabilistic reward learning task (concurrent with the second cold pressor), and 4) at the end of the study visit. Cortisol was measured using enzyme-linked immunoabsorbent assay produced by DRG International (SLV-4635) according to manufacturer instructions.

More specifically, prior to use kits, reagents, and samples were brought to room temperature on the lab benchtop. Samples were centrifuged (3,000 g) for 10 minutes. Next, 120 µL of each sample, standards (0.0, 2.0, 5.0, 10.0, 20.0, 40.0, 80.0 ng/mL), and high and low cortisol control samples (to allow for inter-plate comparison) were aliquoted to a 96 well plate. Then, 100 µL from each well was then transferred to a 96 well ELISA plate pre-coated with mouse anti-cortisol antiserum, which was used for the remainder of the assay. Horseradish peroxidase-conjugated cortisol (200 µL) was added to each well on the ELISA plate and incubated on a mixer for 60 minutes. After emptying well contents, plates were washed 3 times with wash solution (400 µL/well) using an ELx50 plate washer (BioTek; Winooski, Vermont, USA). Residual wash solution was removed before 200 µL oftetramethylbenzidine (TMB) substrate solution was added to each well. The plate was then incubated on a mixer for 30 minutes. The reaction was stopped by adding

400 µL of 0.5M H 2SO4 stop solution and then read at 450 nm using an Epoch microplate spectrophotometer (BioTek; Winooski, Vermont, USA) and calculated using Gen5 software (BioTek; Winooski, Vermont, USA). Cortisol concentrations (ng/mL) were calculated from the optical densities by the Gen5 software using 4-parameter logistic regression.

Heart Rate. The Mio Alpha (mioglobal.com) wrist-worn heart rate watch was used to measure heart rate during the study. This wrist-watch was chosen to measure heart rate due to its comfort, minimal invasiveness, and accuracy of measurement (Parak & Korhonen, 2014; Spierer et al., 2015; Wallen et al., 2016). The wrist watch was placed on participants at the beginning of each visit, and was removed prior to the EEG session, so as to reduce avoidable noise in the EEG signal. Baseline heart rate was computed as average beats-per-minute (bpm) while participants completed initial STAI-S and PANAS assessments, and were measured for an EEG net. Stress response heart rate was computed as the average bpm during the 10-minute period of the stress induction or control procedure during which participants were standing (i.e. the speaking and math portions). Due to technical difficulties, heart rate data was not available for at least one session for 9 participants.

3.3.5 Behavioral Task

Participants completed a probabilistic reward learning task on both study visits (**Figure 3.1B**). The task is a visual discrimination task with disproportionate rewards, which has previously been shown to be sensitive to the effects of acute stress(Bogdan et al., 2010; Bogdan & Pizzagalli, 2006; Bogdan et al., 2011; Tripp & Alsop, 1999). In addition to overall accuracy and reaction time, the task allows the calculation of discriminability, a measure of a participant's ability to perceptually distinguish two similar stimuli (which can serve as an index of overall task difficulty), and response bias (the main performance variable of interest), which reflects a participant's tendency to select one stimulus.

In each trial, participants are presented with a face that is missing a mouth (**Figure 3.1B**). A mouth is briefly shown (100ms) and participants will indicate whether the mouth was long or short. Importantly, the size difference between the long and short stimuli is small (1mm), combined with the short stimulus presentation, makes discrimination difficult. Rewards (25 cents) are delivered for some, but not all, correct trials. While long and short stimuli are presented in equal number, correct responses to one (the "rich" stimulus) are rewarded three times more frequently than correct responses to the other (the "lean" stimulus). This manipulation typically induces a response bias, our primary behavioral measure, which provides an index of how well a participant modifies behavior according to reward reinforcement history (i.e., how likely they are to respond that a given stimulus is the "rich" one) (Pizzagalli et al., 2005). Which stimulus was "rich" was counterbalanced across sessions and participants. Reward feedback for correct responses was given according to a pseudo-randomized schedule, so that if a participant failed to make a correct response for a trial in which feedback was scheduled, reward feedback was delayed until the next correct identification of the same stimulus type (rich or lean). Reward feedback was presented for 1500ms and was followed by a blank screen for 250ms. If feedback was not given (i.e. the subject was inaccurate or was accurate but no feedback was scheduled), a blank screen was displayed for 1750ms. Participants completed four 80-trial blocks of the task (i.e. 40 rewards per block, 30 to the rich stimulus, and 10 to the lean), with a 30-second rest between the first and second, and third and fourth blocks, and a longer 3-minute rest between the second and third blocks. Relative to prior reports using this task (Bogdan & Pizzagalli, 2006; Pizzagalli et al., 2005), the task was in two ways: first, we increased the duration (i.e., 4 blocks of 80 trials) to increase the number of trials available for lean feedback presentations for ERP components; second, the amount of reward provided (i.e.,$0.25) was increased to facilitate recruitment and task engagement.

As in prior reports, a two-step procedure was used to identify outlier responses (Bogdan et al., 2010; Bogdan & Pizzagalli, 2006; Bogdan et al., 2011). First, trials with RTs <100 or >1500

ms were excluded. Second, for each subject, trials with RTs (following natural log transformation) falling outside the mean > 3 SDs were removed. Participants were excluded from all further analyses if >10% (i.e. 32) of trials for either of the two visits were removed for poor RT (N=8), or if they failed to achieve > 50% accuracy across either of the two sessions (50% is chance performance; N = 1). The final sample of N=71 participants consisted of N=35 ELS and N=36 controls. Following outlier removal, response bias (the main variable of interest) and discriminability were computed as follows:

Response bias:

$$\log b = \frac{1}{2}\log\left(\frac{(Rich_{correct} + 0.5) * (Lean_{incorrect} + 0.5)}{(Rich_{incorrect} + 0.5) * (Lean_{correct} + 0.5)}\right)$$

Discriminability:

$$\log d = \frac{1}{2}\log\left(\frac{(Rich_{correct} + 0.5) * (Lean_{correct} + 0.5)}{(Rich_{incorrect} + 0.5) * (Lean_{incorrect} + 0.5)}\right)$$

3.3.6 EEG collection and processing

EEG data were collected using a 128-channel sensor net (Electrical Geodesics) and Netstation software at the Behavioral Research and Imaging Neurogenetics (BRAIN) Lab at Washington University. EEG data was sampled at 500 Hz (16-bit precision; bandwidth, 0.01–100 Hz; impedances <45 kΩ) and referenced to the vertex. Data were resampled to 250 Hz and gross artifacts were manually removed. BrainVision software was used for ERP analyses (Brain Products). Spatially weighted linear interpolations were used to replace noisy channels and an independent component analysis was applied to remove common artifacts (e.g., eye blinks). For

each trial, EEG epochs were extracted 200 ms before and 800 ms after stimulus presentation and reward feedback for correct identification of the rich and lean stimuli. A manually evaluated semi-automatic artifact removal (±75μV criterion) was then applied to identify any remaining artifacts. Next, data were filtered (1–30 Hz; 12 dB roll-off), baseline-corrected (-200 to 0 ms before stimulus), and re-referenced to the average reference. The FRN was quantified 200–400 ms following reward feedback, and its peak scored for electrode sites Cz and FCz, where the FRN is maximal. The FRN was calculated for both lean and rich stimulus feedback, as well as each separately. As lean stimuli are rewarded three times less frequently than rich stimuli, increased FRN amplitude to lean rewards relative to rich rewards represents the RPE signal (greater activity to a less-likely reward). The P300 was quantified 250-350 ms stimulus presentation, and its peak latency scored at electrode sites Pz and CPz, where the P300 is maximal. The P300 was calculated for both lean and rich stimulus presentation, as well as each separately. Similar to the FRN, as rich stimuli are rewarded three times more frequently than lean, increased P300 amplitude to rich stimuli relative to lean represents the reward prediction (RP) signal (greater activity to a more likely reward). Two participants were excluded from EEG data analysis due to poor quality data (N=69 for EEG analyses – one from each group)

3.3.7 Statistical Analyses

Sample demographics and comparisons were computed in R (3.3.2) (R Core Team, 2014). Post quality control data were winsorized (to ± 3 SDs) to maintain variability while limiting the influence of extreme outliers that had no evidence to support exclusion. Variables with high skew (>1 or <-1) were transformed prior to analyses. Left-skewed variables were log-transformed, while right-skewed variables were squared.

The R ‘nlme’ package (Pinheiro et al., 2017) was used to fit a series of multilevel linear models with within subject effects of *Condition* (i.e., acute stress or control) and *Time/Block* (e.g., Block 1, 2, 3,4 of the reward learning task or cortisol measurement point) as well as the between

subject effect of *Early Life Stress Group* (i.e., moderate-sever, no/minimal) on stress manipulation (e.g., cortisol), behavioral performance (e.g., response bias), and EEG variables (e.g., FRN) of interest. Analyses of stimulus-specific task behavior (i.e., reaction time, accuracy, ERP components) included an additional within subject random slope for *Stimulus* (i.e., rich, lean). Models included both random intercept (i.e. participant) and random slope (i.e. manipulation condition, task block, cortisol time-point) components, with a continuous autoregressive correlation structure. Time/Block was first coded as both a linear and quadratic effect due to expectations that our collection protocol would result in quadratic effects for stress manipulation outcomes (i.e., an increase following the manipulation followed by a return to baseline), while behavioral reward and ERP components outcomes were expected to have linear components based on prior work. In instances where both linear and quadratic effects did not improve model fit, only the significant effect was retained in analyses.

All models controlled for age, socioeconomic status (SES), ethnicity (as several dummy-coded variables), and visit order (i.e. stress-first vs control-first). Covariates were Z-scored, and second-order interactions between covariates and primary variables were added (i.e. analyses testing whether the change in performance differed between stress conditions – a stress x block interaction – additionally controlled for interactions between all other covariates in the model and stress and block) (Baranger et al., 2016; Keller, 2014). SES was computed using self-reported parental education and family income – mother and father's education was each z-scored and then averaged, which was then averaged with the z-score of family income.

3.4 RESULTS

3.4.1 Demographics

As per the design of our matched recruitment strategy, the high ELS group reported greater ELS on the CTQ relative to the low ELS group, but did not differ on demographic variables, including age, college student status, ethnicity, parental education, or income (**Table 3.1**). The two groups did not differ in the number of days that occurred between the two visits, though the difference in the start times was larger in the low relative to high ELS participants. Consistent with an extensive body of evidence that early life stress increases risk for mental illness (Green et al., 2013), the ELS group had almost three-times the rate of psychiatric diagnoses as the low ELS group (74% vs 25%; **Table 3.1**). This was driven primarily by increased rates of depression, though anxiety disorders, which are well-documented to be highly comorbid with depression, also differed between groups.

3.4.2 Stress-response Manipulation Check

Self-reported mood, cortisol, and heart rate data show that the stress-induction was successful (**Figure 3.2 A-E**). Across measures (i.e. STAI, PANAS, and salivary cortisol), the addition of a linear-change parameter (in addition to quadratic change) worsened model-fit (i.e. increased BIC) – thus models with four observations (i.e. everything but heart-rate) only include a quadratic parameter for measurement time-point. There were significant main-effects of *stress-induction* and *time-point*, as well as a significant *stress x time interaction* for all stress outcomes (**Figure 3.2; Table 3.2**). Post-hoc comparisons revealed that cortisol, heart rate, anxiety, and negative affect were maximized while positive affect was minimized during/following the stress manipulation relative to baseline and the conclusion of the experiment. A significant main-effect of *ELS Group* was observed for the STAI and PANAS-Negative Affect scales due to reports of elevated anxiety and negative affect throughout both visits within the moderate/severe relative to

the no/minimal ELS group (**Table 3.2**). Correlations of the effect of stress (i.e. the within-subject change) found a strong correlation between STAI-S and PANAS-N ($r(69)=0.78$, $p=7.7x10^{-17}$), and a moderate correlation between salivary cortisol and heart rate ($r(61)=-0.382$,$p=0.002$) (**Figure 3.2E**).

Contrary to our expectations based on prior literature (e.g. (Bunea et al., 2017)), ELS group did not moderate the impact of acute stress on cortisol, heart rate, or self-reported mood (**Table 3.2**). As these hypothesized moderations were not observed, exploratory analyses tested whether scores on the CTQ abuse-subscales were correlated with the response to stress (i.e. within-subject change between sessions in multilevel models that did not include ELS group as a covariate). Nominally significant associations between PANAS-N scores and emotional and sexual abuse (CTQ-Emotional Abuse: $r(69)=0.37$, $p=0.002$; CTQ-Sexual Abuse: $r(69)=0.28$, $p=0.016$) were observed. As PANAS-N scores were fit with a quadratic model, a more negative effect-size indicates a larger change in response to the stress manipulation. Thus these correlations show that participants with higher emotional and sexual abuse reported less of an increase in negative affect in response to the stress manipulation. No associations with the other outcomes (including cortisol and heart-rate) were observed.

3.4.3 Primary Analyses of Behavioral Task Performance

A main effect of block revealed that as expected response bias increased across the four blocks of the task (**Table 3.3, Figure 3.3A**), indicating that participants successfully modified their behavior according to reward history over time. Addition of a quadratic term worsened model-fit across analyses of performance; as a result only the linear effect of block was included. Contrary to hypotheses, there were no simple effects of the *Condition* or *ELS Group* were on response bias (**Table 3.3**). There were no simple effects of Condition, ELS Group, or Block on discriminability

(**Figure 3.3B**). However, the interaction of stress-condition and counterbalancing was significant (**Table 3.3**), which was driven by a larger increase in discriminability on the second visit if the first visit was the control-manipulation.

Analyses of stimulus-specific effects (i.e., rich/lean) revealed expected strong effects of *Stimulus Type* on both accuracy and reaction time due to increased rich accuracy and reduced reaction time to the lean stimulus (**Table3, Figure 3.3C&D**). There was also an expected, but small, *Stimulus Type* x *Block* interaction wherein accuracy to lean stimuli decreased across blocks. Further, a *Condition* x *ELS Group* interaction also emerged for reaction time (**Table3**); low ELS participant's RT was faster in the stress condition, while high ELS participant's RT was slower. **Figure 3.3E**).

Post-hoc Exploratory Analyses: The robust response bias observed in block 1 of our task suggests that reward contingencies were learned quickly; however, restricting analyses to only the first 2 blocks, each split into sub-blocks of 40 trials (i.e., 4 sub-blocks), recapitulated our observed null effects. Further, because data were completed on separate days and prior exposure on this task can influence performance, we restricted analyses to only data acquired during the first study session, making our stress manipulation *Condition* factor a between subject variable; again null effects were observed.

3.4.4 ERP analysis

ERPs were collapsed across blocks for analyses to maximize trial numbers due to evidence of response bias within the first block. ERP waveforms provide observable evidence of FRN and P300 components (**Figure 3.4**). Similar to behavioral results and contrary to our hypotheses, there was no consistent simple effects of *Condition*, *ELS Group*, or an *ELS Group* x *Condition* interaction for the FRN (stats) or P300; further, there was no evidence of a differential P300 or FRN amplitude to stimulus type (i.e., rich or lean: stats) (**Figure 3.4**; **Table 3.4**). A weak effect of ELS was observed in one of the FRN channels, Cz, where ELS participants had a lower overall

response to reward feedback. However, this effect was not observed in the other channel, though the direction of effect was the same. The FRN channel FCz showed an interaction between the stress manipulation and counterbalancing, where the stress manipulation was associated with a reduced FRN only in participants who experienced the stress manipulation in their second visit (**Figure 3.4**; **Table 3.4**). There were no significant associations between the FRN or P300 and task performance.

3.5 DISCUSSION

The present study examined the effects of acute and early-life stress on reward learning and processing. Two primary findings emerged. First, in contrast to prior studies, we found no evidence that acute or early life stress were associated with variability in behavioral reward learning (i.e., response bias) or related neural indices (i.e., FRN, P300). Second, we found no evidence that ELS moderated the effects of acute stress on stress-related reactivity, or behavioral or neural indices of reward learning. Collectively these findings challenge prior studies suggesting that acute stress may disrupt novel reward learning and challenge the concept of stress-induced anhedonia as a mechanism through which stress promotes psychopathology.

3.5.1 Acute and Early Life Stress: Response Bias.

In contrast to hypotheses and prior observations (Bogdan et al., 2010; Bogdan & Pizzagalli, 2006; Bogdan et al., 2011), the acute-stress manipulation was not associated with a change in response bias. Further analyses found that stress responses (e.g. salivary cortisol) did not moderate the effect of acute stress on response bias. It was also hypothesized that ELS would be associated with reduced response bias, as ELS is a strong predictor of depression (Green et al., 2013), and depression is associated with reduced response bias (Huys et al., 2013; Pechtel et al., 2013; Pizzagalli et al., 2005; Vrieze et al., 2013). This effect was not observed, nor was ELS observed to moderate the effect of acute stress, which was also hypothesized. While the observed null effects were unexpected, we did find that our acute stress manipulation reliably induced physiological and emotional changes consistent with a stress manipulation, and that our task reliably induced behavioral change according to reinforcement contingencies (i.e., response bias). This same effect was also apparent as a stimulus x block interaction in the analysis of accuracy. As in prior reports, participants were more accurate, and responded faster, to rich

stimuli (Bogdan et al., 2011). As such, these null effects cannot be attributed to an inefficient stress manipulation or task

Unexpectedly, the effect of the acute stress manipulation on overall reaction time (RT) was moderated by ELS. Control participants responded more slowly than ELS participants during the control condition, yet ELS participants attained the same behavioral accuracy. Further, responses to the stress manipulation differed. While control participants responded more slowly under stress, ELS participants were faster to respond. This effect did not differ between rich and lean stimuli, suggesting that it is not accounted for by models such as altered reward sensitivity (Pizzagalli et al., 2005) or increased habitual responding (Schwabe & Wolf, 2009), which predict that the effect would vary as a function of the expected value of the stimulus. Instead, this interaction between acute stress and ELS echoes work on the inverted-U relationship between stress and memory performance, wherein an intermediate-level of stress promotes performance, but too-little or too-much stress hinders performance (Finsterwald & Alberini, 2014). This inverted-U relationship has largely been described with relation to hippocampal dependent processes (Baldi & Bucherelli, 2005; Salehi et al., 2010; T. M. Schilling et al., 2013) - the interaction of acute stress and ELS on RT may reflect the role of the hippocampus in the encoding of salient rewards and guiding attention (Delgado & Dickerson, 2012; Goldfarb et al., 2016; Jafarpour et al., 2017; Murty & Adcock, 2014).

We suggest four possible explanations for our non-replication of prior work. First, it is possible that prior findings (Bogdan et al., 2010; Bogdan & Pizzagalli, 2006; Bogdan et al., 2011) may represent false positives. Second, as the major psychosocial portion of the stress manipulation concluded prior to the reward learning task, it is possible that participants were not still experiencing stress during the reward learning task and may have even experienced relief. While we attempted to combat this by including a physical cold pressor that was reapplied, evidence does suggest that self-reported mood and cortisol levels had returned to baseline at the end of the behavioral task. Prior reports of acute stress inducing behavioral reward learning

deficits all used concurrent stressors (e.g., thereat of shock). Third, recent work corroborates our report of no effect of an acute-stress manipulation in reward paradigms, and has suggested that acute-stress effects may only be present the subset of participants with large cortisol or inflammatory responses to the stressor (Berghorst et al., 2013; Lewis et al., 2014; Treadway et al., 2016). However, we observed no correlation between stress-response and the effect of stress on reward-learning or that participants who were physiologically or emotionally response to the manipulation; as such it is improbable that this consideration accounts for our null findings. Fourth, the rewards used in the current study were larger than those used in prior work using the same task ($0.25 vs. $0.05 (Bogdan et al., 2010; Bogdan & Pizzagalli, 2006; Bogdan et al., 2011)). This may have increased motivation, leading to increased dopamine release (Berke, 2018) and faster learning of reward associations (Mosberger et al., 2016; Wang et al., 2017), ultimately rendering behavior less sensitive to the effects of our mild acute stress manipulation.

3.5.2 Acute and Early Life Stress: FRN and P300.

Analyses of ERP data found no evidence that amplitude (FRN and P300) differed between rich and lean stimuli in either the stimulus presentation or reward feedback phases, contrary to hypotheses. The behavioral data suggests that learning took place quite quickly, as performance and reaction time did not change across blocks. As such, the prediction-error hypothesis (Schultz, 2007) would predict that no prediction error signal would be present after learning (Glimcher, 2011), which may explain why FRN amplitudes at feedback did not differ. However, if this is the case, then it is surprising that the P300 showed no difference at stimulus presentation. We note that the P300 has largely been characterized as a potential reward prediction signal in the context of varying reward magnitude and valence (Bellebaum et al., 2010; Pfabigan et al., 2014), not varying probability of the same magnitude reward, as is the case in the present study. Indeed, prior work has found that at reward feedback the P300 correlates with reward magnitude (Yeung, 2004), so it may also code for reward magnitude at stimulus presentation. As potential reward

magnitude does not differ between lean and rich stimuli in the present study ($0.25 for both), a signal which codes for reward magnitude would not be expected to differ between them.

Finally, we note that few of the hypothesized associations with early life stress (ELS) were present. Apart from a small effect of ELS on the FRN in one of the two channels (Cz: β=-0.192, p=0.037), which was in the predicted direction but does not survive correction for multiple comparisons, hypothesized effects on the stress response, task behavior, and ERPs were not present. We employed a matched-group design, where control participants were recruited only if they matched an ELS subject on four demographic variables: age, ethnicity, family income, and parental education. This recruitment strategy was more stringent than most prior work, in which control groups are matched only by frequency (i.e. group means do not differ), or not matched at all. As a result, observed group differences (i.e. RT differences) are likely not attributable to these variables, and conversely, it is possible that prior reports may be biased by some confounding. We did not observe correlations between demographic variables and outcomes, though one effect of matching by group is that we are at reduced power to detect such associations, as we have constrained the variance of demographic variables.

The present study is not without its limitations. First, while we selected our sample size based on effects reported in prior work (Bogdan et al., 2010; Bogdan & Pizzagalli, 2006; Bogdan et al., 2011), it has since become increasingly clear that much of the literature, not only the work cited here, is underpowered (Nord et al., 2017). Indeed, a recent meta-analysis reports that the effect of ELS on salivary cortisol in response to acute stress is smaller than we had initially anticipated (Bunea et al., 2017). A benefit of our within-subject design is that we are well-powered to detect within-subject effects (i.e. the effects of acute stress on the change in response-bias). However, we are also likely underpowered to detect some of our original research questions, particularly between-subject comparisons of effects for which there was only one measurement (i.e. whether ELS moderates the effect of acute-stress on the change in response-bias). Second, a growing body of work suggests that the developmental timing of early life stressors is important,

and that stressors occurring before late adolescence may have a larger impact on reward function (Novick et al., 2018). However, our early-life stress measure, the Childhood Trauma Questionnaire (CTQ) did not assess when stressors occurred. Further work is needed to examine the effects of when stressors occur on future outcomes. Third, we have proposed increased motivation to be the primary factor underlying our null-effect of acute stress. However, we did not collect a measure of participant motivation - our interpretation is purely speculative.

While there is abundant evidence that acute and early-life stress effect reward processing (Holly & Miczek, 2016; Novick et al., 2018; Vaessen et al., 2015), the present study shows that these effects may be more subtle than the literature might suggest. Indeed, we demonstrate that it is possible to induce a robust stress-response that only minimally impacts reward behavior and processing. We propose that enhanced reward motivation may underlie these unexpected results.

Table 3.1. Comparison of control and Early-life Stress (ELS) groups

	Control (N=36)	ELS (N=35)	t/χ^2	p-value
Age	22.14 (4.37) [18-33]	22.63 (4.69) [18-35]	-0.4548	0.6507
College Student*	N=19 (52.78%)	N=20 (57.14%)	0.0172	0.8958
Caucasian*	N=11 (30.56%)	N=9 (25.71%)	0.0359	0.8497
African American*	N=8 (22.22%)	N=9 (25.71%)	0.0044	0.9469
Asian/American*	N=11 (30.56%)	N=13 (37.14%)	0.1127	0.7371
Hispanic*	N=5 (13.89%)	N=2 (5.71%)	0.5731	0.4490
Multi-racial/Other Ethnicity*	N=1 (2.78%)	N=2 (5.71%)	$6.00\text{x}10^{-4}$	0.9801
Mother's Education	3.75 (1.08) [1-5]	3.6 (1.12) [1-5]	0.5753	0.5669
Father's Education	3.94 (1.16) [1-5]	3.57 (1.44) [1-5]	1.1873	0.2394
Family Income	4.03 (1.50) [2-6]	3.80 (1.64) [1-6]	0.6095	0.5442
SES	0.12 (1.16) [-2.29-1.71]	-0.01 (1.24) [-2.29-1.71]	0.76	0.4499
Days Between Visits	6.22 (1.73) [2-9]	6.43 (1.38) [3-9]	-0.5575	0.5790
Difference in time of visits (min.)	47.08 (64.66) [0-180]	10.71 (25.61) [0-120]	3.1316	**0.0030**
CTQ Total	29.72 (2.86) [25-35]	52.77 (14.18) [37-108]	-9.4287	**$2.42\text{x}10^{-11}$**
CTQ Emotional Abuse	6.44 (1.48) [5-11]	13.77 (4.15) [6-24]	-9.8475	**$1.63\text{x}10^{-12}$**
CTQ Physical Abuse	6.14 (1.29) [5-9]	9.17 (3.45) [5-19]	-4.8773	**$1.50\text{x}10^{-5}$**
CTQ Sexual Abuse	5.06 (0.33) [5-7]	8.84 (5.22) [5-22]	-4.2665	**0.0001**
Any Diagnosis*	N=9 (25%)	N=26 (74.29%)	15.331	**$1.00\text{x}10^{-4}$**
Number of Diagnoses	0.39 (0.72) [0-2]	1.46 (1.27) [0-5]	-4.3366	**$6.38\text{x}10^{-5}$**
Depression/Episode*	N=9 (25%)	N=25 (71.43%)	13.5252	**$2.00\text{x}10^{-4}$**
Bipolar/Mania/Hypomania*	N=1 (2.78%)	N=3 (8.57%)	0.2957	0.5866
Anxiety/Panic/Agoraphobia*	N=1 (2.78%)	N=11 (31.43%)	8.4325	**0.0037**
Alcohol/Substance Use*	N=2 (5.56%)	N=1 (2.86%)	0	1
Anorexia/Binge Eating*	N=1 (2.78%)	N=3 (8.57%)	0.2957	0.5866
Antisocial Personality*	N=0 (0%)	N=1 (2.86%)	$2.00\text{x}10^{-4}$	0.9887
Obsessive Compulsive*	N=0 (0%)	N=2 (5.71%)	0.544	0.4608
Post-Traumatic Stress*	N=0 (0%)	N=5 (14.29%)	3.5654	0.059

* = test run as chi-squared test. All others run as t-tests.

Data is presented as Mean (SD) [Range].

CTQ = Childhood Trauma Questionnaire; SES = Socioeconomic Status

Table 3.2. Effect of stress manipulation on stress-response

Outcome	Variable	Beta	SE	df	t-value	p-value
STAI-S	Condition	-0.394	0.034	478	-11.422	**6.99×10^{-27}**
	Time-Point - quadratic	-8.965	0.510	478	-17.565	**1.18×10^{-53}**
	ELS	0.263	0.058	63	4.541	**2.58×10^{-5}**
	Condition x Time-Point	7.703	0.632	478	12.194	**5.75×10^{-30}**
	Condition x Time-Point x ELS	-0.490	0.632	478	-0.776	0.438
PANAS-Negative	Condition	-0.382	0.040	478	-9.660	**2.77×10^{-20}**
	Time-Point - quadratic	-7.918	0.520	478	-15.219	**6.19×10^{-43}**
	ELS	0.191	0.056	63	3.441	**0.001**
	Condition x Time-Point	8.395	0.773	478	10.860	**1.05×10^{-24}**
	Condition x Time-Point x ELS	0.944	0.774	478	1.220	0.223
PANAS-Positive	Condition	0.103	0.036	478	2.859	**0.004**
	Time-Point - quadratic	1.534	0.585	478	2.621	**0.009**
	ELS	-0.119	0.096	63	-1.238	0.220
	Condition x Time-Point	-1.443	0.679	478	-2.124	**0.034**
	Condition x Time-Point x ELS	-0.057	0.680	478	-0.083	0.934
Salivary Cortisol	Condition	-0.206	0.039	473	-5.237	**2.46×10^{-7}**
	Time-Point - quadratic	-1.478	0.526	473	-2.813	**0.005**
	ELS	0.011	0.088	63	0.130	0.897
	Condition x Time-Point	2.197	0.545	473	4.031	**6.46×10^{-5}**
	Condition x Time-Point x ELS	0.353	0.545	473	0.647	0.518
Heart Rate	Condition	-0.102	0.047	171	-2.153	**0.033**
	Time-Point - linear	8.304	0.473	171	17.573	**3.71×10^{-40}**
	ELS	0.051	0.081	55	0.630	0.532
	Condition x Time-Point	-1.679	0.620	171	-2.710	**0.007**
	Condition x Time-Point x ELS	0.945	0.621	171	1.522	0.130

Results of multi-level models examining the effects of the stress manipulation on stress outcome measures. Condition = stress manipulation or control visit. Time-Point = quadratic change across four measurements or linear change from baseline to manipulation (heart rate only). ELS = early life stress participant. STAI-S = State-Trait Anxiety Inventory – State; PANAS = Positive and Negative Affect Scale. Heart rate data was available for N=63 of the full N=73 sample. Effect sizes are standardized (i.e. all variables were z-scored prior to analyses).

Table 3.3. Effect of stress manipulation on task performance

Outcome	Variable	Beta	SE	df	t-value	p-value
Response-bias	Condition	0.024	0.048	461	0.504	0.615
	Block	1.858	0.782	461	2.377	**0.018**
	Counterbalancing	0.094	0.073	57	1.289	0.203
	ELS	-0.075	0.065	57	-1.145	0.257
	Condition x Block	0.046	0.911	461	0.051	0.959
	Condition x Counterbalancing	0.077	0.053	461	1.460	0.145
	Condition x Block x ELS	-0.582	0.924	461	-0.630	0.529
Discriminability	Condition	-0.018	0.033	461	-0.548	0.584
	Block	1.064	0.658	461	1.617	0.107
	Counterbalancing	0.067	0.099	57	0.681	0.499
	ELS	-0.039	0.089	57	-0.439	0.662
	Condition x Block	1.021	0.725	461	1.408	0.160
	Condition x Counterbalancing	-0.113	0.037	461	-3.052	**0.002**
	Condition x Block x ELS	0.350	0.736	461	0.476	0.634
Accuracy	Condition	-0.025	0.026	1016	-0.975	0.330
	Stimulus	-0.363	0.027	1016	-13.319	**2.01×10^{-37}**
	Block	0.813	0.737	1016	1.103	0.270
	Counterbalancing	0.050	0.065	63	0.775	0.441
	ELS	-0.024	0.059	63	-0.401	0.689
	Condition x Block	1.089	0.862	1016	1.264	0.207
	Stimulus x Block	-1.652	0.777	1016	-2.126	**0.034**
	Condition x Counterbalancing	-0.071	0.029	1016	-2.463	**0.014**
	Condition x ELS	-0.008	0.026	1016	-0.299	0.765
Reaction time	Condition	-0.006	0.025	1016	-0.232	0.816
	Stimulus	0.066	0.015	1016	4.441	**9.91×10^{-06}**
	Block	-0.659	0.500	1016	-1.318	0.188
	Counterbalancing	-0.101	0.114	63	-0.889	0.378
	ELS	-0.077	0.104	63	-0.741	0.461
	Condition x Block	0.898	0.652	1016	1.376	0.169
	Stimulus x Block	0.396	0.500	1016	0.791	0.429
	Condition x Counterbalancing	0.034	0.028	1016	1.232	0.218
	Condition x ELS	-0.080	0.025	1016	-3.163	**0.002**

Results of multi-level models examining the effects of the stress manipulation on task behavior. Condition = stress manipulation or control visit. Block = linear change across the four task blocks. ELS = early life stress participant. Effect sizes are standardized (i.e. all variables were z-scored prior to analyses).

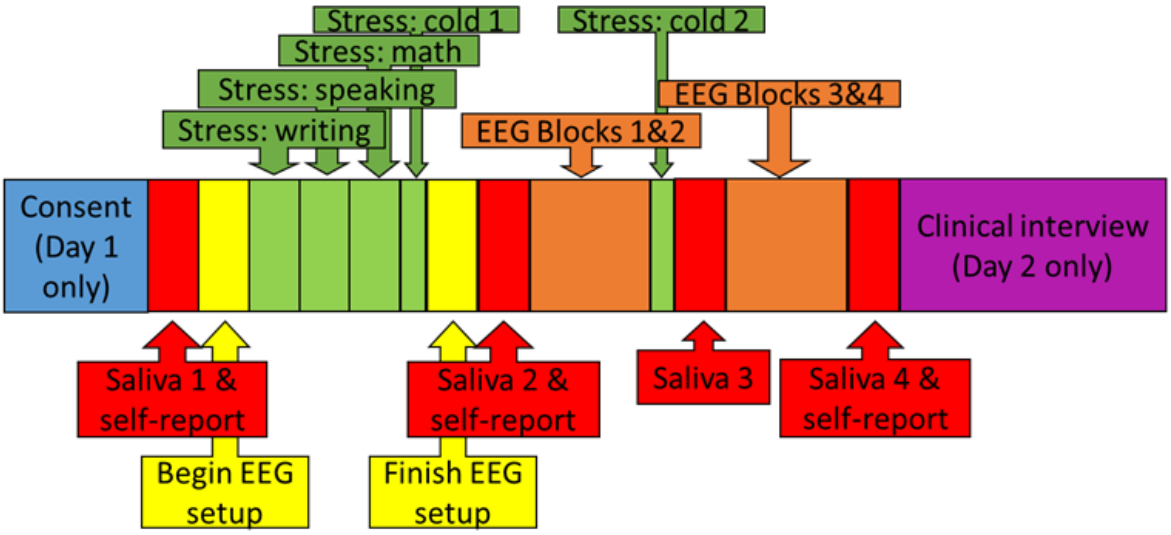
Table 3.4. Effect of stress manipulation on ERPs during task

Outcome	Variable	Beta	SE	df	t-value	p-value
FRN - FCz	Condition	-0.011	0.059	190	-0.180	0.857
	Stimulus	0.007	0.028	190	0.270	0.787
	ELS	-0.053	0.099	61	-0.529	0.599
	Condition x Stimulus	0.011	0.031	190	0.344	0.731
	Condition x Counterbalancing	-0.165	0.063	190	-2.602	**0.010**
FRN - Cz	Condition	-0.088	0.072	190	-1.222	0.223
	Stimulus	-0.020	0.023	190	-0.863	0.389
	ELS	-0.192	0.090	61	-2.134	**0.037**
	Condition x Stimulus	0.025	0.027	190	0.940	0.348
	Condition x Counterbalancing	-0.083	0.077	190	-1.087	0.278
P300 - CPz	Condition	0.068	0.057	190	1.198	0.232
	Stimulus	0.011	0.028	190	0.395	0.693
	ELS	0.087	0.093	61	0.942	0.350
	Condition x Stimulus	0.036	0.034	190	1.075	0.284
	Condition x Counterbalancing	-0.020	0.062	190	-0.328	0.743
P300 - Pz	Condition	0.067	0.058	190	1.154	0.250
	Stimulus	0.033	0.031	190	1.077	0.283
	ELS	0.007	0.093	61	0.075	0.941
	Condition x Stimulus	0.042	0.034	190	1.222	0.223
	Condition x Counterbalancing	0.011	0.065	190	0.172	0.863

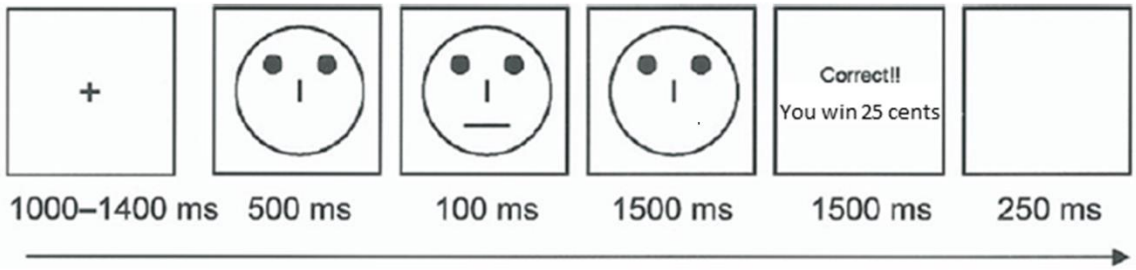
Results of multi-level models examining the effects of the stress manipulation on ERPs collected during task. FRN = 200-400ms after reward feedback. P300 = 250-350ms after stimulus presentation. Condition = stress manipulation or control visit. ELS = early life stress participant. Effect sizes are standardized (i.e. all variables were z-scored prior to analyses).

Figure 3.1. Study Design and task

A

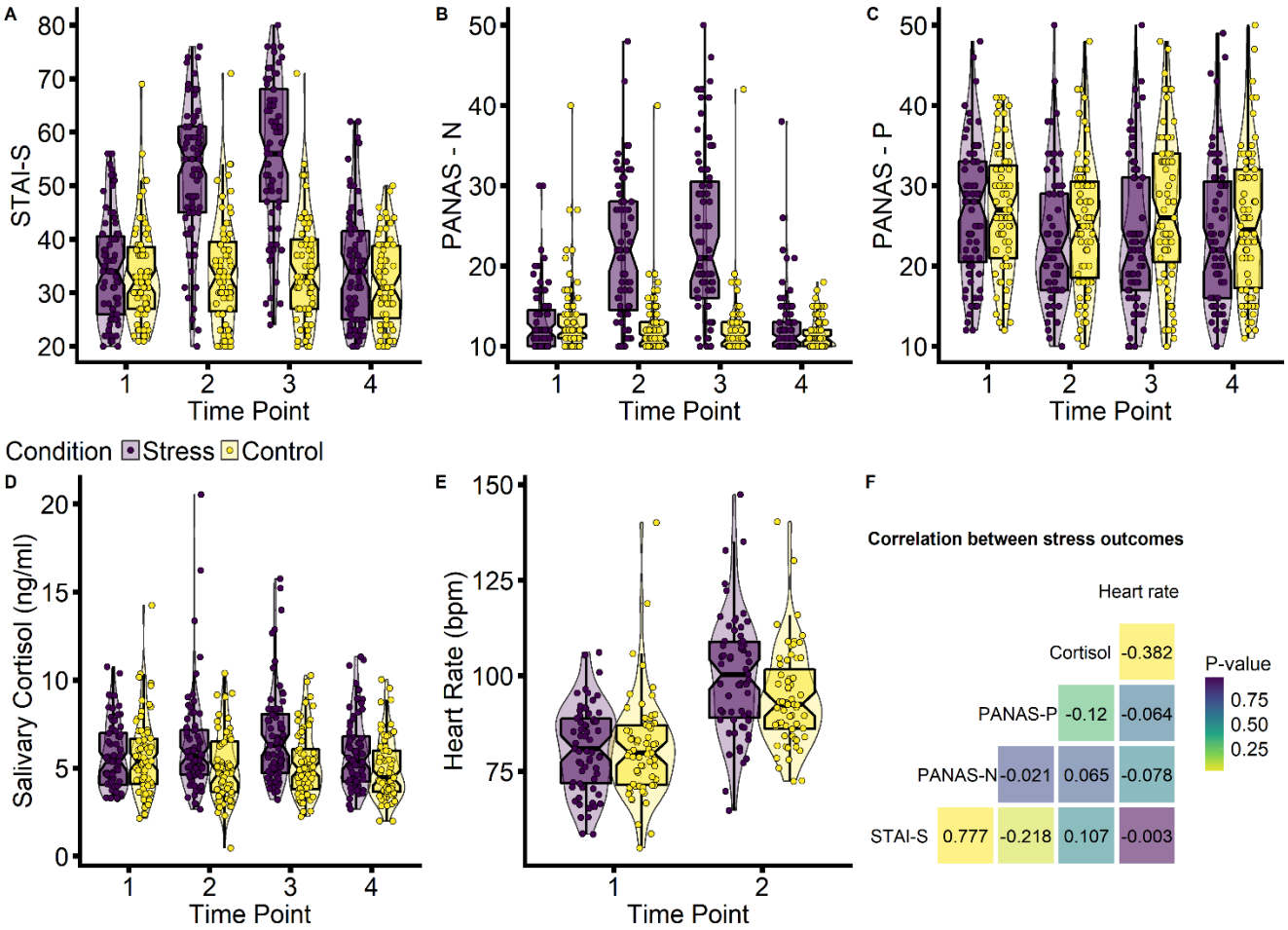


B



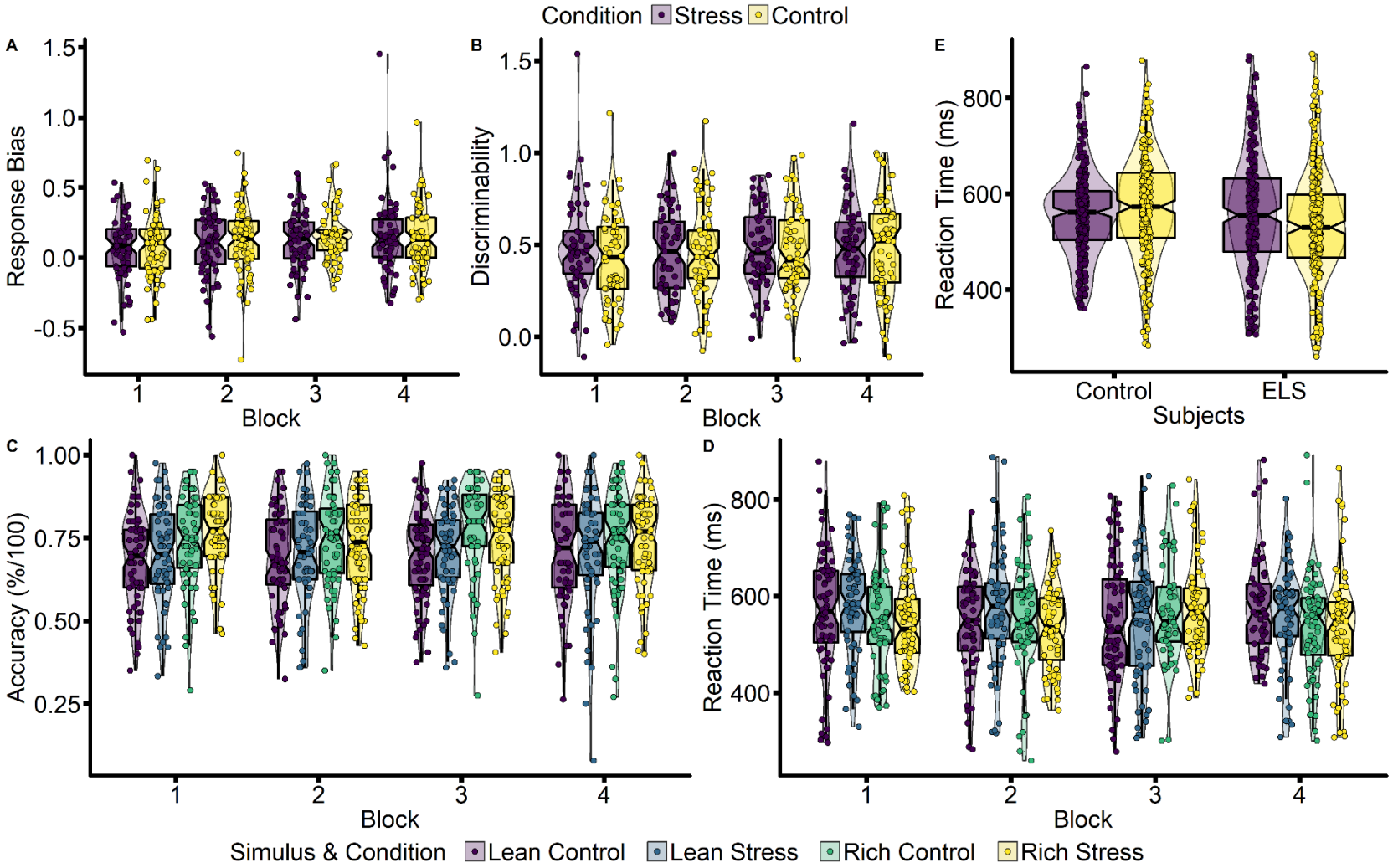
A: Schematic of study visit and the timing of stress induction. **B:** Reward Learning task – mouths differed by 10mm. If a reward was not scheduled, or if the participant was incorrect, and blank screen was shown for the same period of time.

Figure 3.2. Self-report and physiological responses to stress manipulation



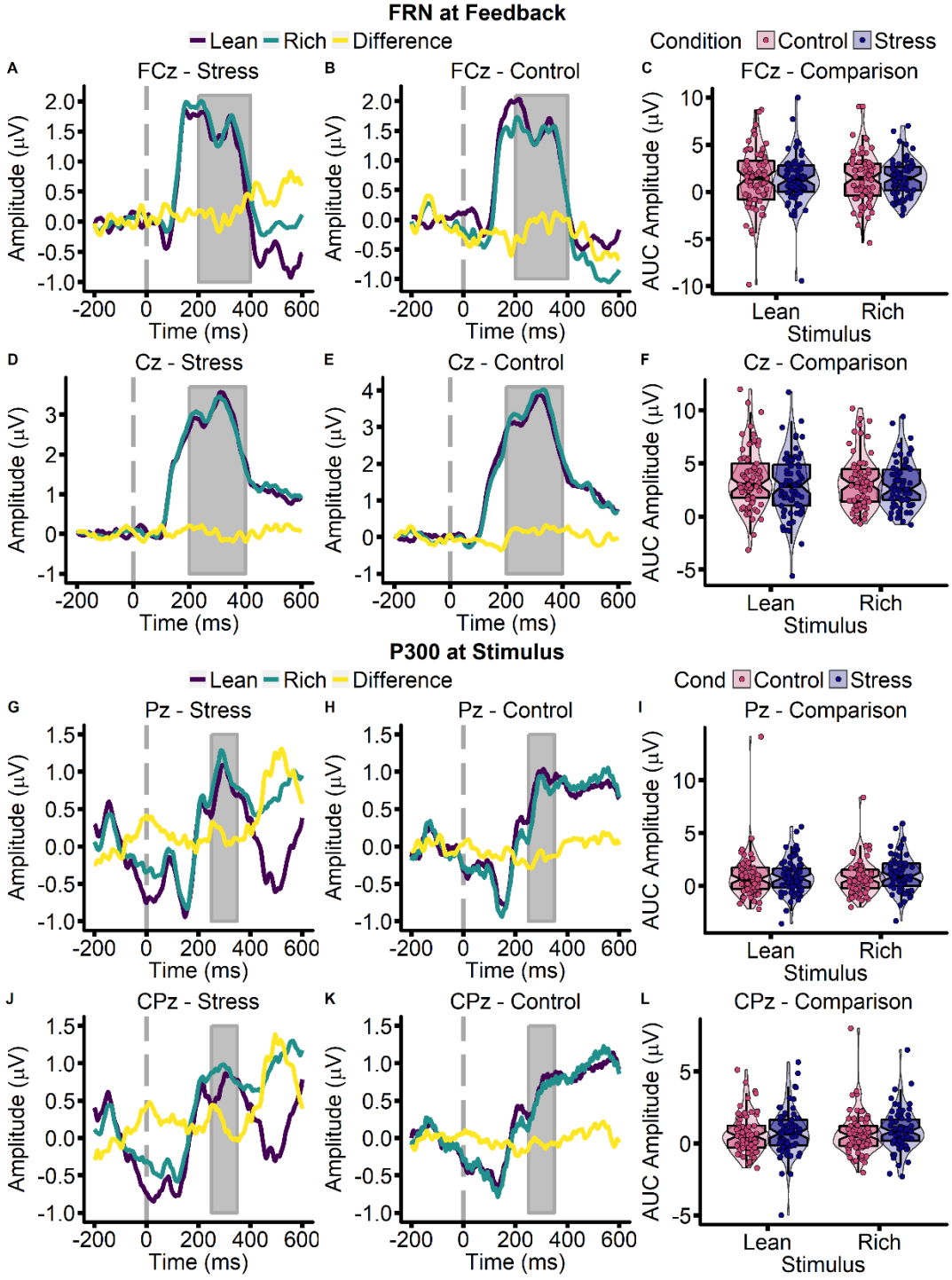
A-E: Boxplots display median and quartiles of distribution; notches represent 95% CI of median. **F:** Values are Pearson's correlation (r), colored by their significance. STAI-S = State-Trait Anxiety Inventory – State; PANAS = Positive and Negative Affect Scale. Associated statistics are reported in **Table 3.2**.

Figure 3.3. Effects of stress manipulation on task performance



A-E: Boxplots display median and quartiles of distribution; notches represent 95% CI of median. Condition = Stress manipulation or control visit. ELS = early life stress subject. Associated statistics are reported in **Table 3.3**.

Figure 3.4. Effects of stress manipulation on scalp ERPs



ERP responses to reward feedback and stimulus onset at *a priori* electrodes, averaged across all trials and all participants. **A,B,D,E,G,H,J,K:** Dashed gray-line indicates when the feedback or stimulus was displayed. Gray box highlights the selected are that was averaged for analyses. Difference (yellow lines) was computed as the difference of rich and lean.
C,F,I,L: Boxplots display median and quartiles of distribution; notches represent 95% CI of median. Condition = Stress manipulation or control visit. ELS = early life stress subject. AUC = Area Under the Curve. Associated statistics are reported in **Table 3.4**.

Chapter 4: Convergent evidence for predispositonal effects of brain volume on alcohol consumption

Author's Note: The material in this chapter was formatted for a Brief Report journal submission.

Baranger DAA, Demers CH, Elsayed NM, Knodt AR, Radtke SR, Desmarais A, Few LR, Agrawal A, Heath AC, Barch DM, Squeglia LM, Williamson DE, Hariri AR, Bogdan R. Convergent evidence for predispositional effects of brain volume on alcohol consumption. (Submitted) https://www.biorxiv.org/content/early/2018/04/13/299149.

4.1 Abstract

Alcohol consumption accounts for 5% of global disease burden. Using family and longitudinal data from three samples spanning childhood/adolescence to middle age, we demonstrate that replicable and genetically-conferred reductions in gray matter volumes of frontal gyri prospectively predict alcohol use. Further, gene expression in the frontal cortex is associated with genetic risk for alcohol consumption. Frontal volume is a promising prognostic biomarker for alcohol consumption liability.

4.2 Results and Discussion

Alcohol use and its associated negative consequences are ubiquitous international public health concerns. Worldwide, the average person aged 15 or older consumes 6.2 liters of alcohol annually, and alcohol use accounts for 6% of deaths and 5% of disease burden (World Health Organization, 2014). Consequently, it is critically important to advance efforts for prevention and identify individual differences that can serve as prognostic biomarkers of liability.

Neuroimaging studies have shown that alcohol consumption and use disorder are associated with smaller subcortical and cortical brain volumes, particularly among regions that feature prominently in emotion, memory, reward, cognitive control, and decision making (Lange et al., 2017; Yang et al., 2016). While there is evidence that these associations may arise as a consequence of drinking (e.g., reduced neurogenesis in non-human primate models, greater gray matter decline among adolescents following initiation of heavy drinking, gray matter normalization following abstinence among dependent individuals) (Kühn & Gallinat, 2013; Pfefferbaum et al., 2017; Taffe et al., 2010), emerging data suggest that these neural signatures may reflect

preexisting vulnerabilities that precede and predict drinking initiation and escalating use (Dager et al., 2015; Squeglia & Gray, 2016).

Here, we first identify replicable gray matter volume correlates of alcohol use. We then test whether reduced volume is: (1) attributable to shared predisposing factors (e.g., shared genetic influence) and/or results from alcohol use, (2) prospectively predictive of future drinking in young adulthood, and (3) predictive of drinking initiation in adolescence. To this end, we used data from 3 independent neuroimaging samples with family or longitudinal data: the Duke Neurogenetics Study (DNS; N=1,303) (Nikolova et al., 2015); Human Connectome Project (HCP; N=897) (David C. Van Essen et al., 2013); and Teen Alcohol Outcomes Study (TAOS; N=223) (Swartz et al., 2015) (**Supplemental Information**). Finally, we examined whether genetic risk for alcohol consumption is associated with genes and genetically-conferred differences in gene expression that are preferentially expressed in the regions identified by neuroimaging analyses and/or the brain more generally. Here, we applied gene-set enrichment, partitioned heritability, and transcriptome-wide (TWAS) (Gusev et al., 2016) analyses to genome-wide association study (GWAS) summary statistics from the UK Biobank (N=112,117) (Clarke et al., 2017) and AlcGen/CHARGE+ (N = 70,460) (Schumann et al., 2016) studies of alcohol consumption, and RNA-seq data from GTEX (N=81-103) (The GTEx Consortium et al., 2015) and the Common Mind Consortium (N=452) (Fromer et al., 2016).

Consistent with prior observations in unselected samples (Lange et al., 2017), as well as those with alcohol use disorder (Yang et al., 2016), whole brain discovery analyses in the DNS revealed that greater alcohol consumption is associated with lower gray matter volume across 8 clusters (**Figure 4.1**; **Supplemental Table 4.4.1**), encompassing regions identified in prior studies (Lange et al., 2017; Squeglia & Gray, 2016; Yang et al., 2016). The associations with two of these clusters (right insula, right superior/middle frontal gyrus) replicated within an ROI analysis in the HCP (**Figure 4.1**; **Supplemental Table 4.4.1**).

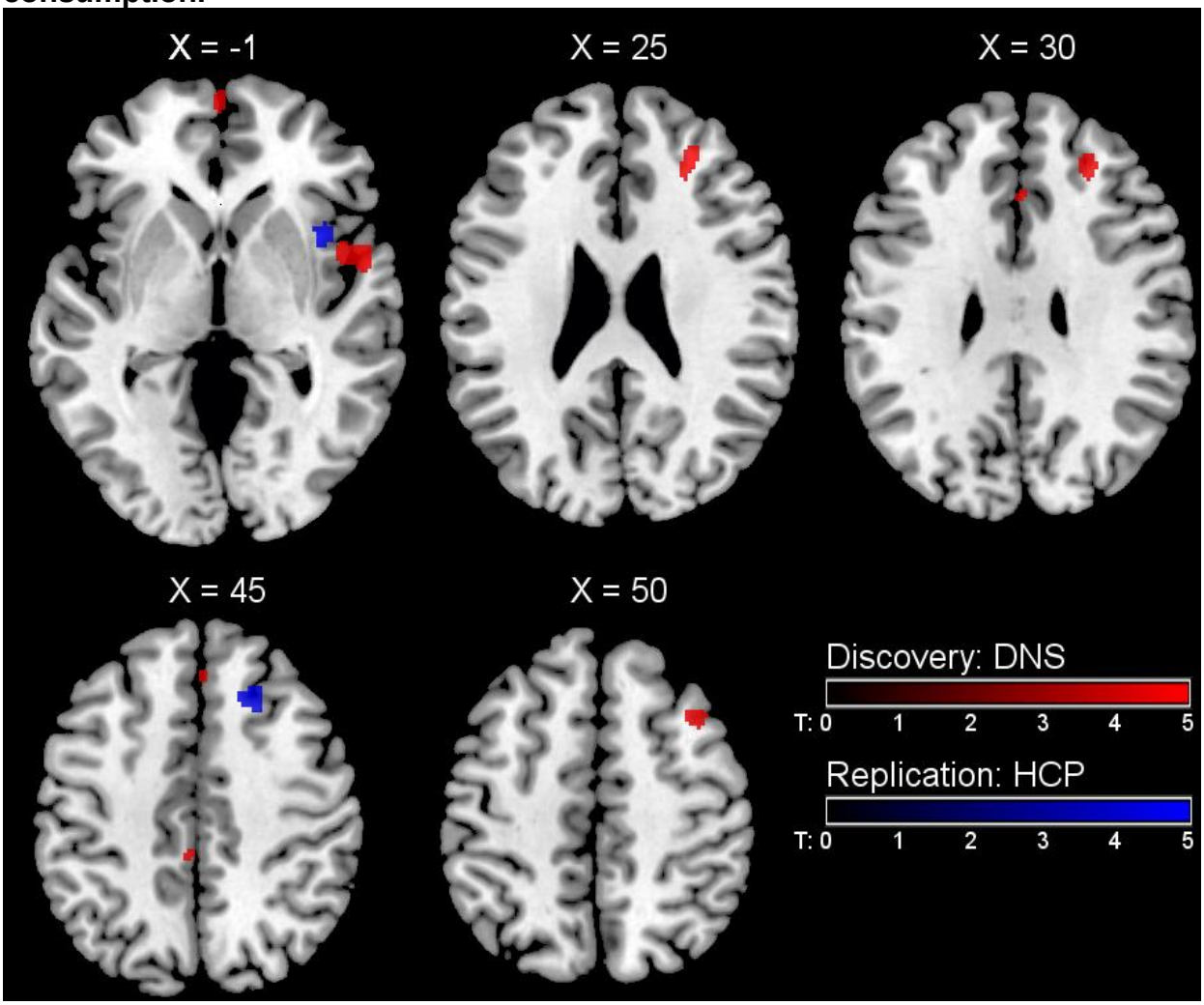
Family-based analyses in the HCP (N=804) revealed that alcohol consumption and gray matter volume of the right insula and right middle/superior frontal gyrus are moderately to largely heritable (**Figure 4.2A; Supplemental Table 4.4.2**). Moreover, decomposition analyses showed that phenotypic correlations between frontal and insular gray matter volume and alcohol consumption are attributable to shared genetic, but not environmental, influences (**Figure 4.2B; Supplemental Table 4.4.2**). Analyses within twin and sibling pairs in the HCP concordant or discordant for the extent of alcohol use revealed that, relative to siblings concordant for low alcohol use, siblings concordant for high use or discordant for use (i.e., one high use, one low use) had lower insular and frontal gray matter volumes (**Figure 4.2 C&D; Supplemental Table 4.4.3**). Further, brain volumes did not differ between low and high alcohol-using members of discordant pairs. As shared genetic and familial factors are matched within pairs, this pattern of results suggests that smaller gray matter volume of frontal gyri and insula are preexisting vulnerability factors associated with alcohol use, as opposed to a consequence of alcohol use.
Using available longitudinal data from the DNS (N=674), we found that lower gray matter volume of the right frontal gyri, but not insula, predicted increased future alcohol consumption, over and above baseline consumption, but only in individuals who are under the legal age of drinking (i.e., younger than 21) in the United States (**Figure 4.3A; Supplemental Table 4.4.4**). Similarly, in the TAOS longitudinal sample of children and adolescents, lower right middle and superior frontal gyrus volume predicted the initiation of alcohol use at an earlier age in those who were nondrinkers at baseline (**Figure 4.3B&C; Supplemental Table 4.4.5)**.

Gene-based association and partitioned heritability enrichment analyses of the UK Biobank GWAS of alcohol consumption revealed enrichment only among brain gene-sets. Moreover, Brodmann Area 9, which is in the frontal region in which we observed a negative association between volume and alcohol consumption that is attributable to shared genetic influence and predictive of drinking initiation, was among the regions with strongest enrichment (**Supplemental Figure 4.4.1, Supplemental Data**). A transcriptome-wide association analysis

(TWAS) similarly found that genetic risk for alcohol consumption was significantly associated with differences in gene expression across the brain, including Brodmann Area 9 (**Supplemental Figure 4.4.2**), which replicated in an independent dataset (**Supplemental Figure 4.4.2, Supplemental Table 4.4.6**). Notably, genetic risk for alcohol consumption was not significantly associated with the expression of any gene in the liver (**Supplemental Figure 4.4.2**).

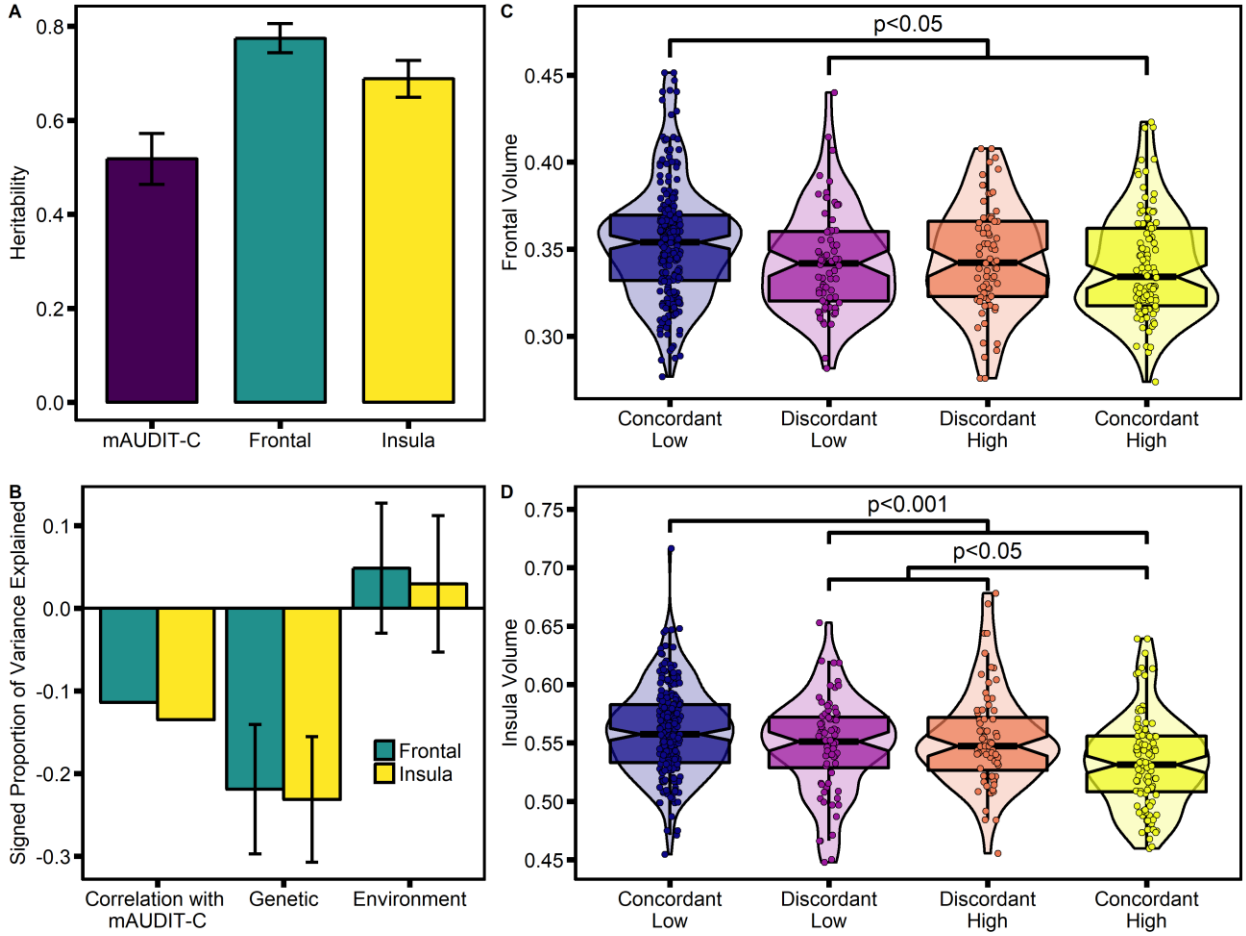
The above analyses in three independent samples provide unique convergent evidence that associations between middle/superior frontal gray matter volume and alcohol use are genetically-conferred, and predict future use and initiation. Taken alongside evidence that heavy alcohol consumption induces gray matter volume reductions (Kühn & Gallinat, 2013; Pfefferbaum et al., 2017; Taffe et al., 2010), our data raise the intriguing possibility that genetically-conferred reductions in regional gray matter volumes may promote alcohol use from adolescence to young adulthood, which may, in turn, lead to accelerated atrophy within these and other regions. Given evidence that genetic liability is shared across substance use involvement (Carey et al., 2016), our findings may generalize to other substances; this could be tested within genetically-informed and longitudinal studies enriched for other substance use, or large prospective studies, such as the recently launched Adolescent Brain Cognitive Development (ABCD) study (Volkow et al., 2017). While enrichment analyses implicate only brain pathways and TWAS identify replicable associations between genetic risk for alcohol consumption and gene expression in the frontal cortex, we cannot rule out the possibility that our observed effects are partially mediated by altered functioning of other pathways, such as alcohol metabolism in the liver (Dick & Agrawal, 2008). Regardless, our convergent evidence from three independent samples with familial or longitudinal data, as well as evidence of expression enrichment, extends the literature primarily focused on alcohol-induced brain atrophy by demonstrating that lower gray matter volume in middle/superior frontal gyri and insula may represent a preexisting genetic liability for drinking that could serve as a prognostic biomarker.

Figure 4.1: Identification of replicable volumetric associations with alcohol consumption.



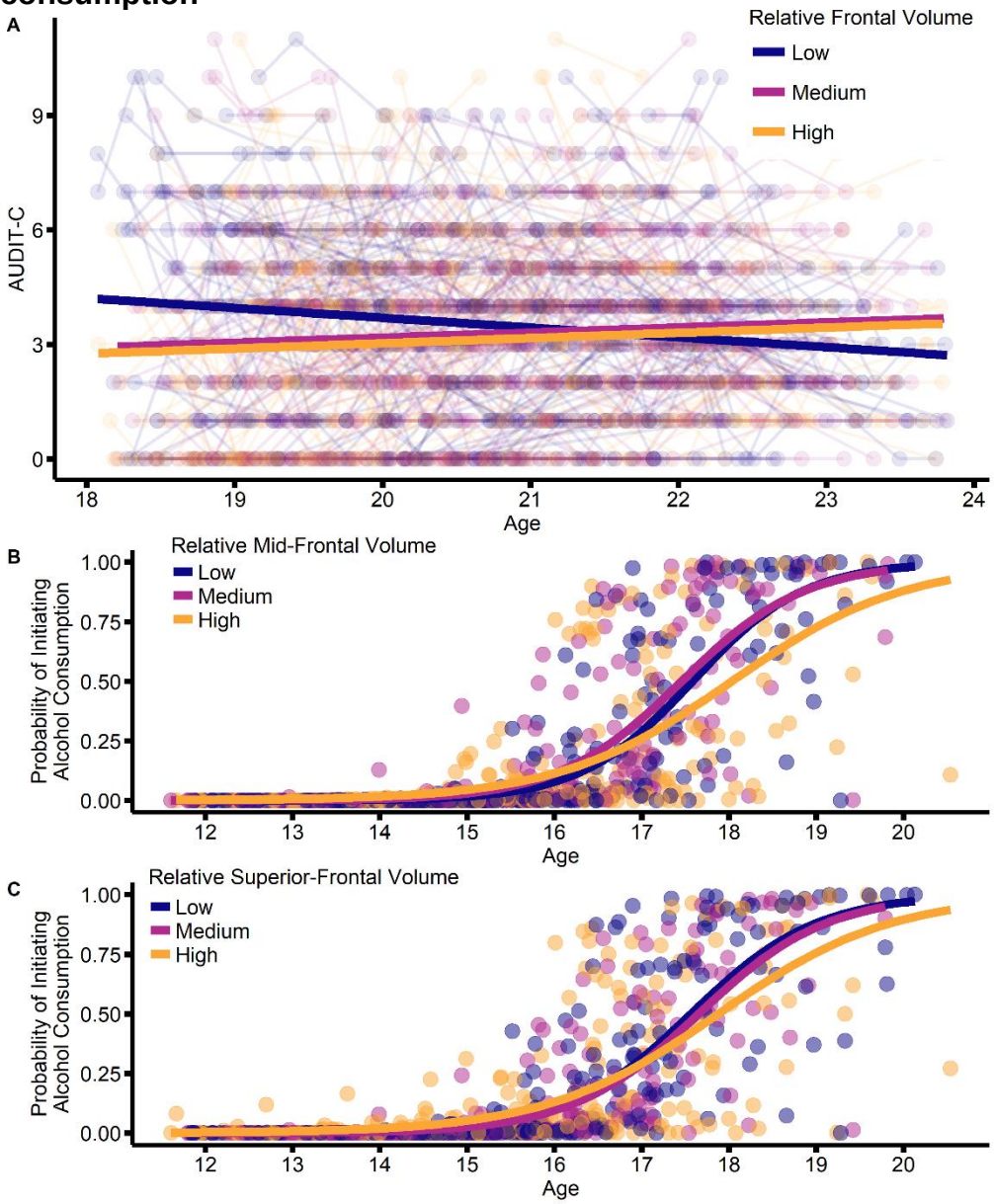
Statistical parametric map illustrating regions of reduced brain volume associated with increased alcohol consumption (**Supplemental Table 4.4.1**), overlaid onto a canonical structural brain image Montreal Neurological Institute coordinates and statistics (DNS: $p<0.05$, family-wise error whole-brain corrected, ≥10 contiguous voxels; HCP: $p<0.05$, family-wise error region-of-interest corrected, ≥10 contiguous voxels). Alcohol consumption was not associated with increased volume in any region. Notably, in the HCP dataset, the superior frontal gyrus cluster extended into the right middle frontal gyrus, and was located relatively far (34 mm dorsal) from the original right superior frontal cluster identified in DNS. In contrast, this peak in the HCP was located 11.6 mm away from the right middle frontal peak identified in the DNS. Thus, for the purposes of *post-hoc* analyses, the combined volume of both the right middle and superior frontal gyrus cortices was extracted from both samples. Cluster overlap at an uncorrected threshold is shown in **Supplemental Figure 4.4.3**. DNS = Duke Neurogenetics Study. HCP = Human Connectome Project.

Figure 4.2: Shared genetic predisposition between alcohol consumption and brain volume.



HCP: A) Alcohol consumption scores (mAUDIT-C) and gray-matter volume of the right insula and right middle/superior frontal cortex were all observed to be heritable (mAUDIT-C: 51.79%, $p<2.2x10^{-16}$; insula: 68.83%, $p<2.2x10^{-16}$; frontal: 74.46%, $p<2.2x10^{-16}$; **Supplemental Table 4.4.2**). **B)** Significant phenotypic correlations between mAUDIT-C scores and volumes of the right insula and middle/superior frontal gyri are attributable to shared genetic (Insula: -0.2314, p=0.0022; Frontal: -0.2192, p=0.0054), but not environmental factors (**Supplemental Table 4.4.2**). **C&D)** Distribution of (**C**) right insula and (**D**) right middle/superior frontal volumes by alcohol exposure group. High = mAUDIT-C score > sample mean + 0.5 SD (i.e. > 4.67); Low = mAUDIT-C score < sample mean - 0.5 SD (i.e. < 1.54); Concordant = both siblings are in same group; Discordant = one sibling is High, while other is Low. Contrast comparisons found evidence for predispositonal effects of brain volume on alcohol consumption in both cases (Insula: Graded Liability: β=-0.0037 [-0.0060,-0.0011], t=-1.974, p=0.0491, Predispositonal: β=0.0037 [0.0016, 0.0043], t=3.479, p=0.0006; Frontal: Predispositonal: β=0.0019 [0.0004, 0.0026], t=2.193, p=0.0290; **Supplemental Table 4.4.3)**. Box and whiskers represent median (notch = 95% CI of median) and standard deviations.

Figure 4.3: Frontal volume prospectively predicts alcohol use and initiation of consumption



A) DNS: Participants with reduced volume of the right middle/superior frontal cortex reported elevated alcohol consumption before the age of 20.85 years following the neuroimaging scan, and after accounting for baseline drinking (Frontal x Age interaction: β=0.150 [0.057, 0.246], t=3.976, p-fdr=0.008; **Supplemental Table 4.4.4**). **B&C)** TAOS: Participants with increased volume of the right middle and superior frontal cortex report initiation of alcohol consumption at an older age (Mid-Frontal x Age interaction: β=-57.042 [-118.96, -31.58], z=-2.37, p-fdr=0.036; Superior-Frontal x Age interaction: β=-60.74 [-113.26, -40.91], z=-2.43, p-fdr=0.036 **Supplemental Table 4.4.5).** Analyses were conducted with continuous data; partitioned into three equally-sized groups according to volume was done for display-purposes only.

4.3 Methods

4.3.1 Participants

Neuroimaging data were drawn from three independent samples: the Duke Neurogenetics Study (DNS; n=1,303), the Human Connectome Project (HCP; n=897), and the Teen Alcohol Outcome Study (TAOS; n=223).

Duke Neurogenetics Study (DNS): The DNS (cross-sectional; n=1334) assessed a wide range of behavioral, experiential, and biological phenotypes among young-adult (18-22 year-old) college students. Each participant provided informed written consent prior to participation in accord with the guidelines of the Duke University Medical Center Institutional Review Board and received $120 remuneration. All participants were in good general health and free of DNS exclusion criteria: (1) medical diagnosis of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease or lifetime psychotic symptoms; (2) use of psychotropic, glucocorticoid or hypolipidemic medication, and (3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension). DSM-IV Axis I and select Axis II disorders (Antisocial Personality Disorder and Borderline Personality Disorder) were assessed with the electronic Mini International Neuropsychiatric Interview (e-MINI) (Sheehan et al., 1998) and Structured Clinical Interview for the DSM-IV Axis II Personality Disorders (First et al., 1997). These disorders are not exclusionary as the DNS seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology. Participants were excluded from analyses due to: 1) non-completion of T1 structural scans (n=10), 2) scanner-related artifacts in MRI data (n=12), 3) incidental structural abnormalities (n=4), 4) missing or incomplete data (n=4), and genetic anomalies (e.g., Kleinfelter's syndrome; n=1). The final DNS sample consisted of 1,303 participants after quality assurance (**Supplemental Table 4.4.7**; age=19.70±1.25; 747 female; 258 with a DSM-IV Axis I disorder; **Supplemental Table 4.4.8**).

DNS participants were contacted every 3 months after initial study completion, and asked to complete a brief online assessment. Participants were entered into a lottery for a $50 gift-card following completion of each online assessment. Of the 734 participants who completed at least one online assessment (2,075 total responses), 705 completed the AUDIT questionnaire at least once, and 679 of these participants were among those included in initial DNS analyses (1,903 responses; **Supplemental Table 4.4.9**). Participants completed between 2 and 17 follow-ups (M=4.05, SD=2.62), between 28 and 1707 days after study completion (M=413.96, SD=331.22; age range: 18.33 - 23.82; **Supplemental Figure 4.4.4**).

Human Connectome Project (HCP): Data from participants contained in the HCP December 2015 public data release (N = 970), were considered for analyses. The HCP aims to recruit 1200 individuals (3-4 siblings per family, most including a twin pair) with the broad goal of examining individual differences in brain circuits and their relation to behavior and genetic background (Smith et al., 2015). Each participant provided informed written consent prior to participation in accord with the guidelines of the Washington University in St Louis Institutional Review Board and received $400 remuneration, as well as additional winnings ($5) and travel expenses. All participants were aged 22 to 35 years and free of the following exclusionary criteria: preterm birth, neurodevelopmental, neuropsychiatric, or neurologic disorders; a full list of exclusions is available in prior publication (Van Essen et al., 2012). Participants were excluded from analyses in the present study for poor quality structural MRI data (n=73), and non-completion of study questionnaires (n=3), resulting in a final sample of 894 (**Supplemental Table 4.4.7**; age=28.82±3.68; age range: 22-37; 393 males; 149 meeting criteria in a phone interview for a possible DSM-IV Axis I disorder (Bucholz et al., 1994) **Supplemental Table 4.4.8**).

Teen Alcohol Outcomes Study (TAOS): TAOS is a longitudinal study designed to examine the association between the development of depression and alcohol use disorders by recruiting

adolescents aged 11 – 15 (N = 330) at high and low familial risk for depression (high: at least one first-degree and one second-degree relative with a lifetime history of major depression; low: no first-degree and minimal second-degree relatives (< 20%) with a lifetime history of depression). Participant diagnoses were assessed through structured clinical interviews with the adolescent and parent separately, using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (Kaufman et al., 1997). Participants were excluded if they met criteria for a substance use disorder or reported binge drinking at baseline (based on National Institute on Alcohol Abuse and Alcoholism guidelines). Participants were permitted to present with anxiety disorders in the high familial depression risk group (specific phobia, N=9; social phobia, N=6; panic disorder, N=1; generalized anxiety disorder, N=12). No other forms of psychopathology were present within the sample at baseline.

Participants were contacted every year to complete diagnostic interviews and questionnaires, and also underwent a follow-up MRI scanning session during the 2nd-4th year of participation (these scans were not used in the present analysis). Participants provided assent, and parents provided written informed consent following procedures approved by the Institutional Review Board at the University of Texas Health Sciences Center at San Antonio, and received $165 remuneration, as well as additional winnings ($10), travel expenses, and $40 for each annual follow-up. Participants were excluded from analyses in the present study for non-completion of the MRI study session (n=17), poor quality structural MRI data (n=13), non-completion of follow-up visits (n=24), missing baseline self-report measures (n=40), and initiation of alcohol use prior to MRI scan (n=14), resulting in a final sample of n=223 (baseline age: 11-15; follow-up ages: 12-20; **Supplemental Table 4.4.7**).

4.3.2 Alcohol Use Assessment

DNS: Participants completed the 10-item Alcohol Use Disorders Identification Test (AUDIT), which was developed by the World Health Organization to screen for hazardous or dependent alcohol use patterns by assessing the frequency and nature of consumption over the past 12 months (Babor et al., 2001; Saunders et al., 1993). The AUDIT had reasonable internal consistency (α=0.81; M=5.22; SD=4.31; range 0-23). We computed the subscale score of the 3 items that correspond to the hazardous use or consumption domain of the AUDIT (AUDIT-C; Bush et al., 1998) (α=0.85; M=3.76; SD=2.64; range 0-12). Participants completed the AUDIT at baseline and during follow-up online assessments. In these follow-up assessments, the AUDIT questions were modified and instead asked about alcohol consumption following the participant's last assessment.

HCP: Participants completed the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994). From the SSAGA we created a metric, the modified AUDIT-C (mAUDIT-C), to approximate the 12-month AUDIT-C (α=0.786; M=3.42; SD=2.65; range 0-12). This used questions almost identical to those contained in the AUDIT-C, but with the difference that the SSAGA asks about frequency of drinking 5+ drinks in a 24-hour period, while the AUDIT asks about 6+ drinks.

TAOS: Adolescents were assessed at baseline and each annual follow-up session with the Substance Use Questionnaire (SUQ) (Molina et al., 2007). The SUQ assesses lifetime exposure to alcohol (e.g., have you ever had a drink, have you ever been drunk, age of first drink) and onset of regular use of a substance (i.e., at least once per month for at least six months). The SUQ also includes items assessing the average quantity and frequency of use for alcohol, marijuana, tobacco, and six other drug classes (sedatives, stimulants, opioids, cocaine, hallucinogens, other (e.g., ecstasy)), periods of abstinence, and accessibility of each substance. The SUQ contains questions identical to those on the AUDIT-C. Thus, as in HCP analyses, a modified AUDIT-C score was created (mAUDIT-C: α=0.893; M=0.45; SD=1.26; range 0-9). Initiation of alcohol

consumption was defined as attaining a score of 1 or greater on the mAUDIT-C (i.e. participant reports having consumed at least one full alcoholic beverage in the past year; N=82 initiated during the study; Age: M = 16.68, SD = 1.39, 14.12 – 19.64 yrs).

4.3.3 Self-report Questionnaires and Behavioral Phenotypes Covariates

Demographic and environmental variables known to be correlated with alcohol consumption were included in all analyses. In addition to age (Collins, 2016; Kendler et al., 2014; Meng et al., 2014), sex (Collins, 2016; Delker et al., 2016; Grittner et al., 2013; Meng et al., 2014), and ethnicity (Cacciola & Nevid, 2014; Delker et al., 2016), socioeconomic status (SES; income and education, or parental education) was included, as higher SES participants have been found to consume more alcohol, while lower SES is associated with higher rates of alcohol-related problems (Collins, 2016; Delker et al., 2016; Grittner et al., 2013; Kendler et al., 2014; Meng et al., 2014). Self-report of early-life and recent life-stress was also included, given the well-replicated association of stress with alcohol use and alcohol-related disorders (Enoch, 2011; Green et al., 2013; Keyes et al., 2012).

Socioeconomic Status – Income and Education

DNS: Participants completed three Likert-scale questions, (scores range from 1-11) where higher scores reflect having a higher socioeconomic status (more money, education, and respected jobs). Participants were asked to place themselves, their biological father during their childhood and adolescence, and their biological mother during their childhood and adolescence, on this scale. These three responses were averaged to compute a proxy for the participant's socioeconomic status (P-SES: α=0.816; M=7.44; SD=1.70; range 1.33-11). Since all participants in the DNS were enrolled in college at the time of the study, parental education (the average of the education of the participant's female and male guardian) was used as a proxy, which ranged

from 1 (some high school), to 9 (doctoral degree; MD, PhD, JD, or PharmD) (P-ED: α=0.70; M=7.09; SD=1.62).

HCP: Participants reported their total annual household income on a scale ranging from 1 (<$10,000), to 8 (>=$100,000) (SES: M=4.97; SD=2.18) as well as the number of years of education that they had completed (ED: M=14.89; SD=1.82; range=11-17).

TAOS: The parents of participants reported their annual income and their spouses annual income on a scale ranging from 0 (Less than $10,000) to 7 ($150,000 or more) (Self: M=4.27; SD=1.39; range=0-6. Spouse: M=4.12; SD=1.71; range=0-6.). Parents also reported their highest level of education and their spouses highest level of education on a 0 (Less than 9th grade) to 6 (Graduate or Professional Degree) scale (Self: M=2.67; SD=12.36; range=0-9. Spouse: M=4.03; SD=2.06; range=0-9.). An overall estimate of SES was calculated by averaging the standardized values of these variables.

Early-life stress

DNS: Participants completed the 28-item Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), which asks participants to retrospectively report on the occurrence and frequency of emotional, physical, and sexual abuse as well as emotional and physical neglect before the age of 17 (α=0.88; M=33.55; SD=8.76; range 25-76). The instrument's five subscales, each representing one type of abuse or neglect, have robust internal consistency and convergent validity with a clinician-rated interviews of childhood abuse (Scher et al., 2001). Total CTQ scores across the 5 subscales were used as a covariate.

HCP: The HCP did not include a measure of early-life stress.

TAOS: Participants completed the 28-item CTQ; total scores across the 5 subscales were used as a covariate in analyses (α=0.795; M=32.98; SD=8.76; range 25-64).

Perceived Stress

DNS: Participants completed the 10-item version of the Perceived Stress Scale (PSS) (Cohen et al., 1983), which instructs participants to appraise how unpredictable, uncontrollable, and stressful their daily life was in the preceding week. The PSS had good internal consistency (α=0.86; M=14.66; SD=6.08; range 0-37).

HCP: HCP participants completed the same 10-item version of the PSS, which had good internal consistency (α=0.90; M=13.07; SD=5.76; range 0-35).

TAOS: TAOS participants completed the Stressful Life Events Schedule (SLES) (Williamson et al., 2003), which assesses the presence of more than 80 possible stressors in the past 12 months, each rated on a 4-point scale (1-4). Each stressor is given a subjective stress score as rated by the adolescent and an objective stress rating by a consensus panel. For both subjective and objective stress, a summary score derived by summing the squares of each individual stressor. Herein we use the total subjective stress (M=31.52; SD=28.79; range 0-156).

Additional Measures in TAOS

Depressive Symptoms: As the TAOS sample was enriched for participants with a family history of depression, self-report of depressive symptoms was included as a covariate in all analyses. Participants completed the Mood and Feelings Questionnaire (MFQ) (Angold et al., 1995), a 33-item measure designed to detect clinically meaningful signs and symptoms of depressive disorders in children and adolescents (α=0.68; M=9.03; SD=8.01; range 0-52).

Tanner Stage: The tanner scale was used to assess pubertal status (Female: M=3.6, SD = 0.9; Male: M=2.97, SD=0.8) (Marshall & Tanner, 1969, 1970).

4.3.4 Magnetic Resonance Imaging: Acquisition and Processing of Gray Matter Volume Data

DNS: Two identical research-dedicated GE MR750 3 T scanners equipped with high-power high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high band-width up to 1 MHz were used to acquire data at the Duke-UNC Brain Imaging and Analysis Center (N=224, 17% of the sample, was scanned on the second scanner. Scanner is included as a covariate in all analyses). High-resolution T1-weighted images were obtained using a 3D Ax FSPGR BRAVO with the following parameters: TR = 8.148 s; TE = 3.22 ms; 162 sagittal slices; flip angle, 12°; FOV, 240 mm; matrix =256×256; slice thickness = 1 mm with no gap; and total scan time = 4 min and 13 s. Regional gray matter volumes were determined using the unified segmentation(Ashburner & Friston, 2005) and DARTEL normalization(Ashburner, 2007) modules in SPM12 (http://www.fil.ion.ucl.ac.uk/spm) (Kurth et al., 2015). Using this approach, individual T1-weighted images were segmented into gray, white, and CSF images then non-linearly registered to the existing IXI template of 550 healthy subjects averaged in standard Montreal Neurological Institute space, available with VBM8 (http://dbm.neuro.uni-jena.de/vbm/). Subsequently, gray matter images were modulated for nonlinear effects of the high-dimensional normalization to preserve the total amount of signal from each region, and smoothed with an 8mm FWHM Gaussian kernel. The voxel size of processed images was 1.5×1.5×1.5 mm. A gray matter mask for subsequent analyses was created by thresholding the final stage (6th) IXI template at 0.1.

HCP: High-resolution (0.7-mm isotropic voxels) anatomical images were acquired using a customized Siemens Skyra 3-T scanner with a 32-channel head coil (Glasser et al., 2013). Briefly, relevant steps for this study from the HCP processing pipeline within FSL v5.0.6 (Jenkinson et al., 2012) included: (1) Gradient distortion correction, (2) Coregistration and averaging of T1 and

T2 runs, (3) Linear registration of T1 and T2 runs, (4) FSL FNIRT brain extraction, (5) Field mad distortion correction, and (6) Bias field correction. Additional processing for VBM analyses were then applied. Brain-extracted images were grey matter-segmented before being registered to the MNI 152 standard space using non-linear registration (Andersson et al., 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Native grey matter images were then non-linearly registered to this study-specific template and multiplied by the Jacobian of the warp field to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. These images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm.

TAOS: Imaging data was collected using a Siemens 3T Trio scanner located at the Research Imaging Institute at the University of Texas Health Science Center, San Antonio (UTHSCSA). The study used an MRI protocol specifically optimized for GM thickness measurement (Kochunov & Davis, 2010). The protocol was designed to collect data to resolve the cortical ribbon across to cortex using isotropic spatial resolution of 0.8mm, voxel size =0.5mm· T1-weighted contrast was achieved using a magnetization prepared sequence with an adiabatic inversion contrast-forming pulse (scan parameters: TE/TR/TI=3.04/2100/785 ms, flip angle=11 degrees).

The processing of T1-weighted images consisted of removing non-brain tissues, global spatial normalization and radio frequency (RF) inhomogeneity correction. Non-brain tissues such as skin, muscle and fat was removed using an automated skull stripping procedure and images were corrected for radio-frequency (RF) inhomogeneity (Smith et al., 2006). A retrospective motion-correction technique was used to reduce subject motion-related artifacts (Kochunov et al., 2006). Next, images were imported into the structural analysis package, BrainVisa, and processed using its cortical extraction and parcellation pipelines (Kochunov et al., 2006). This pipeline extracts the pial and grey matter and white matter (WM) interface surfaces, performs

extraction, labeling and verification of sulcal surfaces (Mangin et al., 2004) and segments the cortical landscape into 15 cortical regions using the primary sulcal structures.

4.3.5 Statistical analysis

Sample demographics and comparisons, as well as associations of self-report measures with alcohol consumption, were computed in R (3.3.2) (R Core Team, 2014). Self-report questionnaire data were winsorized (to ± 3 SDs; DNS: AUDIT-C N=1, P-SES N=5, PSS N=6, CTQ N=25; HCP: mAUDIT-C N=3, PSS N=3; TAOS: SLES N=12, CTQ N=8; MFQC = 2) to maintain variability while limiting the influence of extreme outliers. Self-report variables with high skew (>1 or <-1) were transformed prior to analyses. Left-skewed variables (DNS: CTQ skew=1.34; TAOS: CTQ skew = 1.16, SLES skew = 1.23) were log-transformed, while right-skewed variables (DNS: P-ED skew=-1.43) were squared.

Discovery: A whole-brain voxel-based morphometry GLM regression analysis was conducted using SPM8 in the DNS sample to test whether alcohol consumption (AUDIT-C) is associated with differences in gray-matter volume. Covariates included sex, age, self-reported race/ethnicity (i.e., not-white/white, not-black/black, not Hispanic/Hispanic), scanner id, intracranial volume (ICV), presence of a diagnosis other than alcohol or substance abuse or dependence, perceived stress (PSS), parental education (P-ED), early-life stress (CTQ), and perceived economic status (P-SES). Analyses were thresholded at $p<0.05$ FWE with a cluster extent threshold of 10 contiguous voxels ($k_e=10$) across the entire search volume.

Replication: Replication analyses in the HCP sample examined whether alcohol consumption (mAUDIT-C) predicted differences in gray-matter volume only within regions of interest (ROIs) where associations were observed in the discovery DNS sample (**Figure 4.1, Supplemental**

Table 4.4.1). ROIs were defined by the AAL atlas (Tzourio-Mazoyer et al., 2002). A voxelwise GLM regression limited to these ROIs was conducted using multi-level block permutation-based non-parametric testing (FSL PALM v.alpha103; tail approximation $p<0.10$ with 5,000 permutations), which accounts for the family-structure of the HCP data while correcting for multiple comparisons across space(Winkler et al., 2016, 2014, 2015). Covariates included sex, age, self-reported race/ethnicity (i.e., not-white/white, not-black/black, not Hispanic/Hispanic), intracranial volume (ICV), twin/sibling status (dizygotic/not, monozygotic/not, half-sibling/not), presence of a diagnosis other than alcohol or substance abuse or dependence, perceived stress (PSS), education (ED), and economic status (SES). Analyses were thresholded at $p<0.05$ FWE with a cluster extent threshold of 10 contiguous voxels ($k_e=10$) across the entire search volume (i.e., across all ROIs collectively).

Post-hoc analyses

The total anatomical ROI volume of regions which replicated in the HCP (right Insula and right Middle/Superior Frontal Gyrus; see **Results**) were extracted from both datasets for use in *post-hoc* analyses. The total volume was used to reduce overestimation of effect sizes that can arise from selecting only those voxels that are specifically associated with the variable of interest(Vul et al., 2009).

Heritability: Heritability analyses were conducted using a subset of participants from the HCP, which excluded singletons and half-siblings (n=804). This resulted in a sample of 293 families, including 115 MZ twin-pairs, 64 DZ twin-pairs, and 422 non-twin siblings. The SOLAR-Eclipse software package (http://solar-eclipse-genetics.org)(Kochunov et al., 2015), in conjunction with the R package 'Solarius' (Ziyatdinov et al., 2016), was used for all heritability analyses. SOLAR (Sequential oligogenic linkage analysis routines) implements maximum likelihood variance decomposition methods to estimate phenotypic heritability (h^2; the fraction of phenotypic variance

attributable to additive genetic factors), as well as genetic (ρ_g) and environmental (ρ_e) correlations (the fraction of the correlation between two phenotypes that is attributable to either additive genetic or individual-specific environmental factors, respectively). SOLAR was used to estimate the heritability of gray-matter volume and alcohol consumption, as well as the co-heritability of volume and alcohol consumption. Covariates were identical to neuroimaging analyses. To ensure normality of measurements and accuracy of estimated parameters, an inverse normal transformation was applied to all continuous traits and covariates prior to analyses.

Discordant twin analysis: Following evidence that alcohol consumption is co-heritable.with volume of the right insula and middle/superior frontal gyrus (see **Main Text**), we examined whether same-sex twin and non-twin sibling pairs discordant for alcohol consumption differed from each other on brain volume. These analyses examined whether mAUDIT-C was associated with insular or middle/superior frontal volume after accounting for sibling-shared genetic background and experience. Same-sex siblings were considered “high alcohol consumers” or “low alcohol consumers” if their mAUDIT-C score was greater than 0.5 SD above the sample mean (mAUDIT-C > 4.67, or less than 0.5 SD below the sample mean (mAUDIT-C < 1.54), respectively. Of the original 476 sibling pairs, 214 pairs were removed because they did not meet this criteria. Concordant sibling-pairs were defined as a pair who were both in the same category of consumption (i.e. high or low), and additionally scored within 1 SD of each other (19 pairs failed to meet this last criteria). Discordant sibling-pairs were defined as a pair where siblings were in different categories (i.e. one is high and the other is low). This resulted in 117 concordant low alcohol consumer pairs (“low concordant”; mAUDIT-C M=0.84, SD=0.77), 54 concordant high alcohol consumer pairs (“high concordant”; mAUDIT-C M=7.13, SD=1.41), and 72 discordant sibling pairs (“low discordant”; mAUDIT-C M=1.25, SD=0.73; “high discordant”; mAUDIT-C M=6.47, SD=1.67). Participants could be included in more than one pair (N=368 individuals) when considering relationships with multiple siblings. Discordancy analyses were conducted using

linear mixed models, as sibling pairs are non-independent, using the 'Psych' (Revelle, 2015) and 'lme4' (Bates et al., 2015) packages in R to account for the multiple-sibling structure within families. Covariates were identical to those used in neuroimaging analyses.

Three contrasts were entered into mixed-effect models, which modeled 3 different possible associations between brain volume, alcohol consumption, and familial/predispositonal risk(Pagliaccio, Barch, et al., 2015). The first tested whether alcohol consumption may cause reduced brain volume, which would be evidenced by a difference in brain volume between the exposed and unexposed members of discordant pairs. Both the second and third contrasts tested the hypothesis that the association between reduced brain volume and alcohol consumption is driven by a shared predisposition towards both. This would be primarily evidenced by the discordant pairs – biological siblings who differ in their alcohol consumption – having the same volume, which would be reduced relative to concordant unexposed pairs. The second contrast tested that brain volume decreases as a function of increasing familial/predispositonal liability (i.e. graded liability), which would be additionally evidenced by reduced volume in concordant exposed pairs relative to discordant pairs. The third contrast tested whether any amount of shared familial/predispositonal risk would be reflected by the same reduction in volume, which would be additionally evidenced by no difference in volume between discordant pairs and concordant exposed siblings.

DNS longitudinal changes in alcohol consumption: Hierarchical density-based clustering (R 'dbscan' package) (Hahsler et al., 2017), was used to detect and remove outlier responses to the follow-up questionnaire. A scree-plot comparison of the minimum-points parameter (minPts; minimum number of points in a cluster) and the number of outliers found an elbow at minPts=35 when time-of-response was represented as time-since-baseline, and subsequently an elbow at minPts=14 when time-of-response was represented as participant age. This resulted in the removal of 112 responses that occurred more than 1,035 days after the baseline study visit, and

the removal of 17 responses that were given by participants older than 23.82 years old. The final dataset consisted of 1,756 responses from 674 participants, who gave 1-12 (M: 3.59, SD: 2.10) responses, 28-1,034 (M: 350.20, SD: 245.39) days after the baseline visit, between the ages of 18.33 and 23.82 (M: 20.93, SD: 1.24) years (**Supplemental Figure 4.4.4**).

The R 'nlme' package (Pinheiro et al., 2017) was used to fit a longitudinal multilevel linear model, examining whether brain-volume in the DNS sample predicted follow-up AUDIT-C questionnaire responses over time. The 'nlme' package was used as it can model different classes of correlation structures between observations, though it does not include logistic models. The model included both random intercept and random slope components, with a continuous autoregressive correlation structure. Time was coded as both the linear and quadratic age at the date of response (baseline or follow-up). Models tested the interaction between brain volume and age (i.e. does baseline ROI volume predict a different slope of change in drinking behavior as participant's age?). Covariates were Z-scored, and were identical to neuroimaging analyses, with the addition of second-order interactions between covariates and primary variables (Baranger et al., 2016; Keller, 2014). Each of the two ROIs were tested in separate models, and p-values were FDR corrected (4 tests – middle/superior x linear-age, middle/superior x quadratic-age, etc.).

TAOS longitudinal initiation of alcohol use: The R 'lme4 package (Bates et al., 2015) was used to fit a longitudinal logistic multilevel model, which tested whether baseline brain volume in non-drinking adolescents predicted future initiation of alcohol use. The model included both random intercept and random slope components, and time was coded as both the linear and quadratic age at the date of response. The model tested the interaction between brain volume and age (i.e. does baseline ROI volume predict a different likelihood of initiation as participant's age?). Covariates were Z-scored, and included demographic variables (age, sex, ethnicity, and SES), stress (CTQ and SLES), tanner-stage, MFQ-scores, family history of depression, age at MRI scan, and intracranial volume. Second-order interactions between covariates and primary

variables (e.g., Middle Frontal volume x Sex, Middle Superior volume x SES, Age x Sex, Age x SES, etc.) were also included(Baranger et al., 2016). Each of two ROIs were tested in separate models - right superior frontal cortex and right middle frontal cortex. Insula volume was excluded as it was not significant in the DNS analyses, but given the new sample we considered both right middle and right superior frontal ROIs separately. P-values were subsequently FDR corrected (4 tests).

SNP-Based Enrichment: We tested whether the SNP-based heritability of alcohol consumption is enriched in brain-expressed gene-sets and whether this enrichment is specific to any region. Stratified LD-score regression (Finucane et al., 2018, 2015) was applied to summary statistics from the genome-wide association study of alcohol consumption in the UK Biobank (N=112,117) (Clarke et al., 2017). Tissue-enriched gene-sets, provided by the Alkes Group (Bulik-Sullivan & Finucane, 2017), were generated using data from the GTEx Consortium (The GTEx Consortium et al., 2015). In this analysis, a gene is assigned to a gene-set if it shows greater enrichment in that tissue than 90% of genes. Gene-sets for brain regions were generated both by comparing each region to all non-brain tissues, and by comparing each brain region to all other regions. It was further tested whether the genetic associations with alcohol consumption are enriched in brain-expressed gene-sets. Gene-set analyses were conducted with MAGMA (de Leeuw et al., 2015), implemented through FUMA (Watanabe et al., 2017).

Transcriptome-Wide Analysis (TWAS): Following evidence that genetic associations with alcohol consumption are enriched in brain-expressed gene-sets, and that the SNP-based heritability of alcohol consumption is enriched in these gene-sets, we tested whether genetic risk for alcohol consumption is predictive of changes in post-mortem gene expression in the human brain. Pre-computed gene-expression RNA-seq weights for nine brain regions and the liver from GTEX (The GTEx Consortium et al., 2015) were downloaded and analyzed using the FUSION

suite (Gusev et al., 2016). We tested whether genetic risk for alcohol consumption, as determined by the results from the UK Biobank GWAS (Clarke et al., 2017), is associated with differential RNA expression. Results were bonferroni-corrected for n=9,839 tests across the ten regions. Replication of TWAS results was sought using independent GWAS data from an earlier study of alcohol consumption (N = 70,460) (Schumann et al., 2016) and computed gene-expression weights for the dorsolateral prefrontal cortex from the CommonMind Consortium (Fromer et al., 2016). As the gene that showed the strongest association in the discovery dataset was not present in the replication data, it was examined whether any of the gene-expression associations at p-fdr<0.05 were significant in the replication data.

4.4 Supplemental Information

4.4.1 Results

Comparison of discovery and replication samples

Sample comparisons are presented in **Supplemental Table 4.4.7**. The samples differed by sex, which was driven by fewer female participants in the TAOS sample (the DNS and HCP do not differ). Consistent with the recruitment of non-overlapping aged samples, HCP participants were all older than DNS participants, who were all older than TAOS participants. A significantly larger proportion of the participants from the HCP were Caucasian or African/African-American, while the DNS had a larger portion of Asian/Asian-American and Multi-racial/Native-American/Other participants. TAOS had the largest proportion of Hispanic participants. DNS participants had significantly higher AUDIT-C scores, which is unsurprising given observations of elevated hazardous alcohol consumption among younger college-aged populations (H. Wechsler et al., 2002). Similarly, the higher levels of self-reported perceived stress among DNS participants is consistent with prior observations of increased stress in college-student samples (Astin, 1998).

Association of covariates with alcohol consumption

Association of covariates with alcohol consumption are presented in **Supplemental Table 4.4.10**. In the DNS and HCP men reported higher levels of alcohol consumption than women, consistent with prior reports of sex-differences in alcohol use (Wilsnack et al., 2009). Notably, in TAOS, sex did not differ between initiators and non-initiators. Presence of a non-substance-related diagnosis was not associated with alcohol use in either the DNS or HCP. Consistent with prior reports, participants of European descent reported increased levels, while participants of African descent reported decreased levels (Galvan & Caetano, 2003; Lotfipour et al., 2015). In the DNS participants of Asian descent and of Multi-racial or Native-American descent reported the lowest amount of alcohol consumption (Lotfipour et al., 2015). These associations did not reach significance in the HCP, likely due to the smaller number of participants in these groups in this sample. Age was associated with alcohol consumption in all samples, though in differing directions, which is consistent with observations in North American samples that alcohol consumption increases once young adults turn 21 (legal drinking age), and subsequently

decreases as participants age(Fromme et al., 2010; Wilsnack et al., 2009). Of note, in TAOS alcohol-consumption initiators were younger at baseline. In the DNS, perceived SES (P-SES) and parental education (P-ED) were both positively correlated with alcohol consumption, while no association was observed with these phenotypes in the HCP or in TAOS. Perceived stress was not associated with alcohol consumption in any sample, which is consistent with some prior reports (Esper & Furtado, 2013; Tavolacci et al., 2013). Childhood trauma was associated with alcohol consumption in the DNS, and was trending in TAOS, consistent with an extensive literature indicating that early trauma increases risk for substance use (Baranger et al., 2016).

Lower gray matter volume associated with alcohol consumption: Clusters in the discovery DNS analysis

The analysis in the DNS discovery sample identified eight clusters of lower gray-matter volume, extending across eight different regions, associated with increased AUDIT-C scores ($p<0.05$ FWE-corrected, **Figure 1, Supplemental Table 4.4.1**). Significant clusters included two clusters in the right middle frontal cortex, a large cluster extending across the right superior temporal cortex and right insula, and clusters in the left medial orbital frontal cortex, bilateral middle cingulum, right superior frontal cortex, and right medial superior frontal cortex.

Longitudinal Data Results

DNS: Differences between longitudinal responders and non-responders are presented in **Supplemental Table 4.4.9**. Participants who completed at least one follow-up questionnaire were younger, had lower AUDIT-C and total AUDIT scores. Further, responders were more likely to be female and white and less likely to be black. Of the four brain volume x age interactions modeled (Frontal x Linear-Age, Frontal x Quadratic-Age, etc.), only the interaction between right middle/superior frontal volume and the linear change in age was significant after fdr-correction for multiple comparisons ($\beta=0.151$, $t=3.976$, $p=0.0007$, p-fdr=0.008; **Figure 3, Supplemental Table**

4.4.4). Examination of regions of significance found that lower frontal volume predicted greater drinking before the age of 20.85 years.

TAOS: Of the n=223 adolescents who were non-drinkers at baseline that were included in analyses, n=82 (36%) reported having consumed at least one full alcoholic beverage during one of their follow-up interviews (i.e. they initiated consumption). Of the four brain volume x age interactions modeled (Mid-Frontal x Linear-Age, Mid-Frontal x Quadratic-Age, etc.), the interactions between both right middle and superior frontal volume and the linear change in age were significant after fdr-correction for multiple comparisons (Middle frontal: β=-57.04, t= -2.37, p-fdr = 0.036; Superior frontal: β=-60.74, t = -2.43, p-fdr=0.036; **Figure 3, Supplemental Table 4.4.5**).

Tissue-specific Enrichment of Alcohol Consumption

Enrichment analyses found evidence of significant (bonferroni-corrected) enrichment of brain-enriched gene-sets in the genetic associations of alcohol consumption and the heritability of alcohol consumption (**Supplemental Figure 4.4.1A&B; Supplemental Data)**, relative to non-brain tissues. However, when gene-sets were generated by comparing brain-tissues only to each other, no gene-set survived correction for multiple comparisons (**Supplemental Figure 4.4.1C; Supplemental Data**). Notably, Brodmann Area 9 (BA9), which is included in the frontal ROI observed in our discovery and replication analyses, was among the significant regions in both analyses.

TWAS of Alcohol Consumption and Gene expression in the brain

TWAS identified several genes whose expression in the human brain was correlated with genetic risk for alcohol consumption (**Supplemental Figure 4.4.2; Supplemental Data**). Six genes survived bonferroni-correction for multiple comparison, one of which in the Frontal Cortex –

C16orf93. This gene was not present in the replication data set, but two of the three other genes which passed fdr-correction in the discovery data were - *CWF19L1* and *C18orf8*. Expression of both genes showed significant effects of genetic risk for alcohol consumption – fdr-correction for n=2 comparisons – in the same direction as the discovery dataset (**Supplemental Table 4.4.6**).

4.4.2 Post-hoc Associations of volume with behavior

Methods

Following the observation that frontal and insula volume are predictive of future alcohol use and initiation, are predispositional to alcohol consumption, and that genetic risk for alcohol consumption is associated with changes in gene expression in the frontal cortex (**Supplemental Results**), *post-hoc* exploratory analyses sought to test whether the effects of volume on alcohol consumption are mediated by cognitive or behavioral measures. Associations between total volume of the ROI, as well as volume of each significant cluster, and three classes of outcomes were tested: impulsivity, negative urgency, and intelligence. As measures of negative urgency were not collected in the HCP, associations with neuroticism were additionally examined. The association between impulsivity and alcohol consumption is well established (Amlung et al., 2017; Dick et al., 2010), and measures of impulsivity have been shown to be associated with the structure of both the insula and frontal cortex in large samples (Churchwell & Yurgelun-Todd, 2013; Holmes et al., 2016; Mackey et al., 2017; Pehlivanova et al., 2018). Negative urgency, a facet of impulsivity characterized by risky decision making when one is experiencing negative emotions, is associated with problematic drinking (Coskunpinar et al., 2013; Labrie et al., 2013; Stamates & Lau-Barraco, 2017), and shows correlations with neural responses to reward (Corral-Fríasa et al., 2015), as well as with structure of the frontal cortex (Muhlert & Lawrence, 2015). Childhood intelligence has been observed to be predictive of adult alcohol consumption (Kubička et al., 2001), with evidence of genetic correlations between proxy-measures of IQ (i.e. educational

attainment) and alcohol consumption (Clarke et al., 2017), and brain structure has been repeatedly linked to intelligence, with evidence that the two share genetic underpinnings (Brouwer et al., 2014; Noble et al., 2015; Toga & Thompson, 2005).

Delay Discounting

In delay discounting tasks participants choose between hypothetical amounts of money available immediately or after a delay. By varying the amount of money available immediately and the number of days that one would have to wait for the delayed money, participant 'indifference points' can be identified wherein the participant is equally likely to choose a smaller reward sooner versus a larger reward later. A preference for a smaller reward sooner (i.e., delay discounting) is considered a behavioral index of impulsivity (Green et al., 2014). The DNS and HCP used different protocols which are described below.

DNS: All combinations of immediate reward (varying from $0.10 to $105) and delay intervals [0, 7, 30, 90, 180, 365, or 1825 (i.e., 5 years) days] for the delayed reward of $100 were presented on a computer screen in randomized order(Hariri et al., 2006; Nikolova et al., 2015). 146 participants did not complete the delay discounting task, resulting in a final DNS sample of 1,157 for delay discounting analyses.

HCP: The delayed-reward amount was set to $200, with delays of 1, 6, 12 (1 year), 36 (3 years), 60 (5 years), or 120 months (10 years) presented in the order: 6, 36, 1, 60, 120, 12 months (Estle et al., 2006). Immediate reward amounts were adjusted on a trial-by-trial basis based upon participant response. Six participants did not complete the delayed-discounting task.

Impulsivity

DNS participants completed the 30-item self-report Barratt Impulsiveness Scale (BIS) (Patton et al., 1995). HCP participants completed the Achenbach Adult Self-Report (ASR) for Ages 18-59(Achenbach, 2009). As in prior reports (Pagliaccio et al., 2015), a coarse measure of impulsivity (ASR-Imp) was computed from three questions in the ADHD subscale of the ASR. **DNS**: Barratt Impulsiveness Scale assesses the personality/behavioral construct of impulsiveness and had good internal consistency (α=0.84; M=61.69; SD=9.55; range 37-113). **HCP**: Our Achenbach Adult Self-Report (ASR) impulsivity composite had acceptable internal consistency (ASR-Imp; α=0.79; M=1.29; SD=1.24; range 0-6).

Neuroticism

Participants in the DNS completed the 240-item NEO Personality Inventory-Revised (Costa & McCrae, 1992) (Neuroticism: α=0.85; M=86.04; SD=22.65; range: 37-113). Six participants did not complete the NEO. Participants in the HCP completed the 60-item NEO Five-Factor Inventory(Costa & McCrae, 1992) (Neuroticism: α=0.83; M=16.43; SD=7.17; range: 0 - 43).

Negative Urgency

Participants completed two measures of negative urgency – the Impulsivity sub-scale of the NEO-PI-R (Costa & McCrae, 1992) (α=0.71; M=17.07; SD=4.60; range: 3-32), and the substance-sue subscale of the brief COPE (BCOPE-sub) inventory. The BCOPE-sub consists of two items that assess how frequently respondents use drugs and alcohol as a coping mechanism(Ullman et al., 2005) (α = 0.92; M=2.53; SD=1.11; range: 0-8).

Intelligence

DNS: Intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II) 2-subtest version (D. Wechsler, 2011), consisting of the Vocabulary and Matrix Reasoning subtests. The total score was computed as the sum of age-adjusted performance on

the two sub-tests. 28 participants did not complete the WASI-II. **HCP:** Intelligence was assessed using the NIH toolbox (Gershon et al., 2013). Fluid intelligence was assessed using the Flanker Inhibitory Control and Attention Test, Picture Sequence Memory Test, List Sorting Test, Pattern Comparison Test, and Dimensional Change Card Sort Test. Crystallized intelligence was assessed using the Oral Reading and Picture Vocabulary tests. Age-adjusted scores were averaged for fluid and crystallized intelligence, respectively, which were then averaged to form a measure of intelligence (Casaletto et al., 2016).

Statistical Analysis

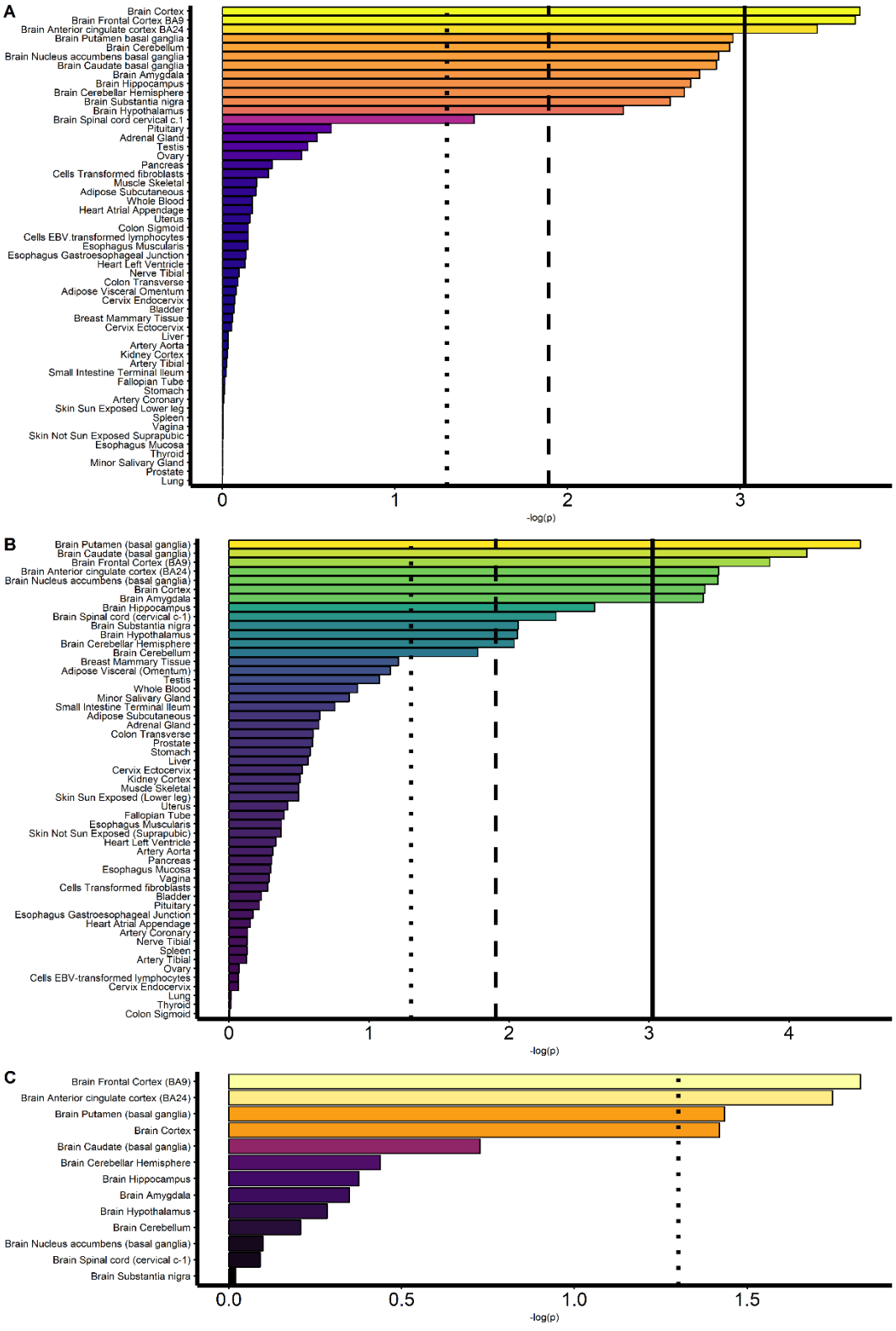
Analyses were conducted in R (3.4.2) (R Core Team, 2014). Covariates were identical to those used in neuroimaging analyses. As in other analyses, variables were transformed to correct for skew, and were winsorized as needed. All variables were z-scored. Linear regression models were used to test whether extracted brain volume predicted behavioral and self-report outcomes. Analyses in the HCP used linear mixed-effects models (Bates et al., 2015), which controlled for family as a random effect, and sibling-status (i.e. DZ twin, MZ twin, half-sibling) was entered as fixed-effect covariates. FDR-correction for multiple comparisons was applied the entire set of analyses for each study.

Results

Extracted volume of the frontal and insula ROI, and volume of each significant cluster, were not significantly associated with any of the behavioral measures, in either sample, after correcting for multiple testing (**Supplemental Tables 4.4.11&4.4.12**). This suggests that negative urgency, impulsivity, or IQ do not fully mediate the association between brain volume and alcohol consumption. Given nominally significant results for some of these analyses within our DNS

sample, it is possible that different behavioral mechanisms might represent risk at different ages and that these null results may represent type II error that larger samples might detect.

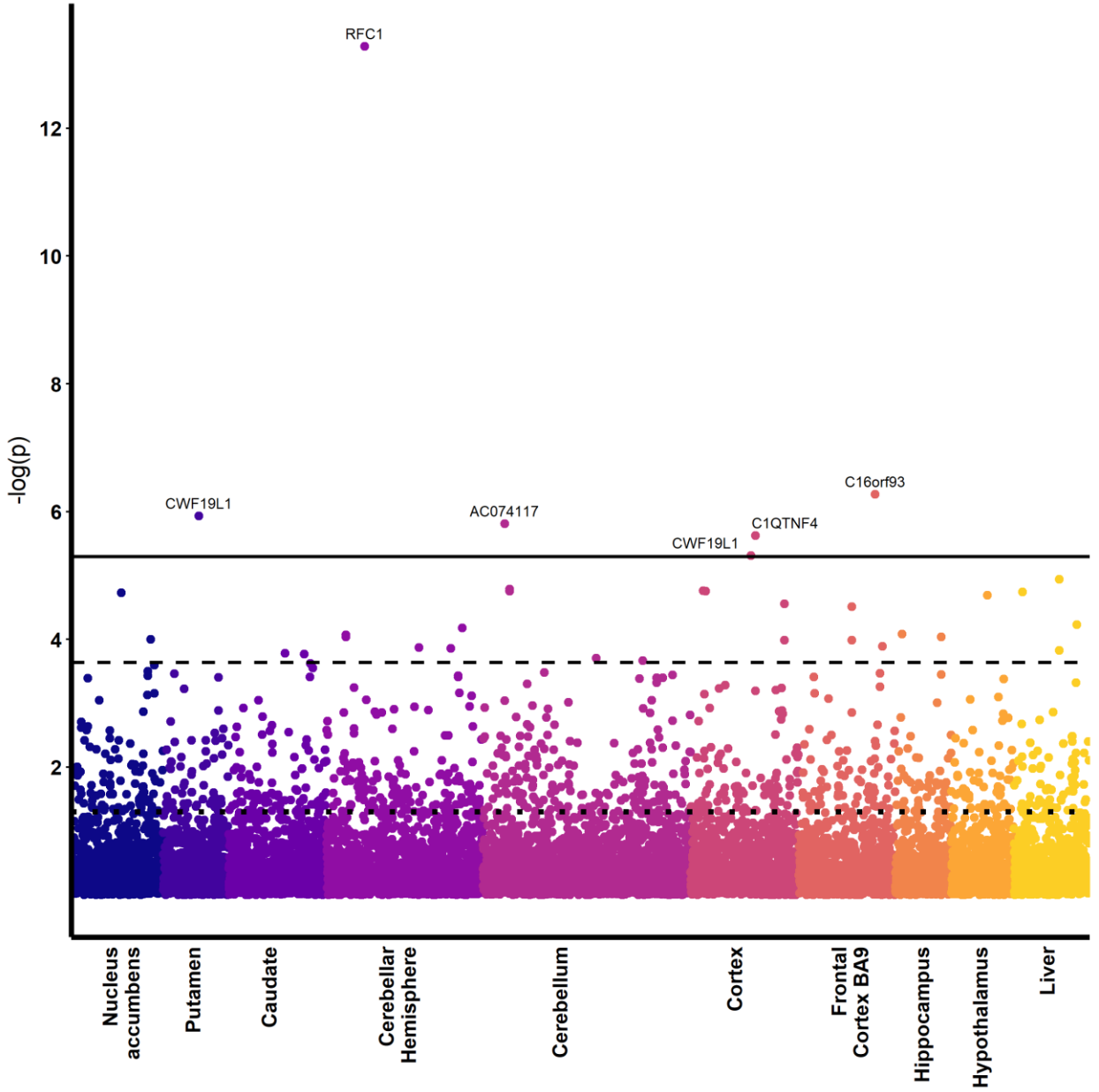
Supplemental Figure 4.4.1: Tissue-specific Enrichment of Alcohol Consumption Genomic Risk



Enrichment of alcohol consumption GWAS (UK Biobank, N=112,117) **A)** associations and **B&C)** heritability, in gene-sets defined by the relative expression of genes across **A&B)** all tissues, and

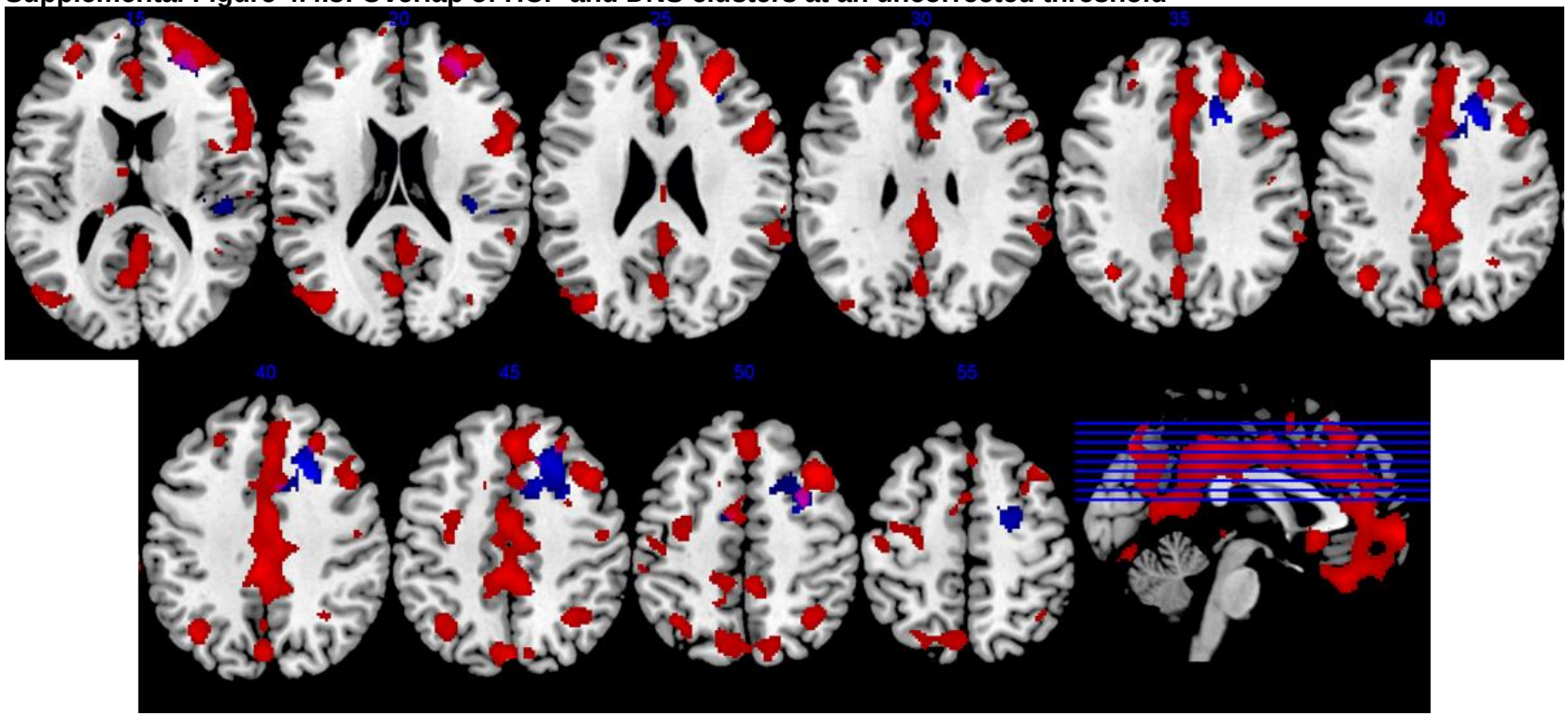
C) within the brain, in the GTEX data set (**Supplemental Data**). X-axis and color-scale represent the significance of the enrichment. Solid, dashed, and dotted lines represent Bonferroni-corrected, FDR-corrected, and nominally significant p-values, respectively.

Supplemental Figure 4.4.2: TWAS of alcohol consumption predicting gene expression



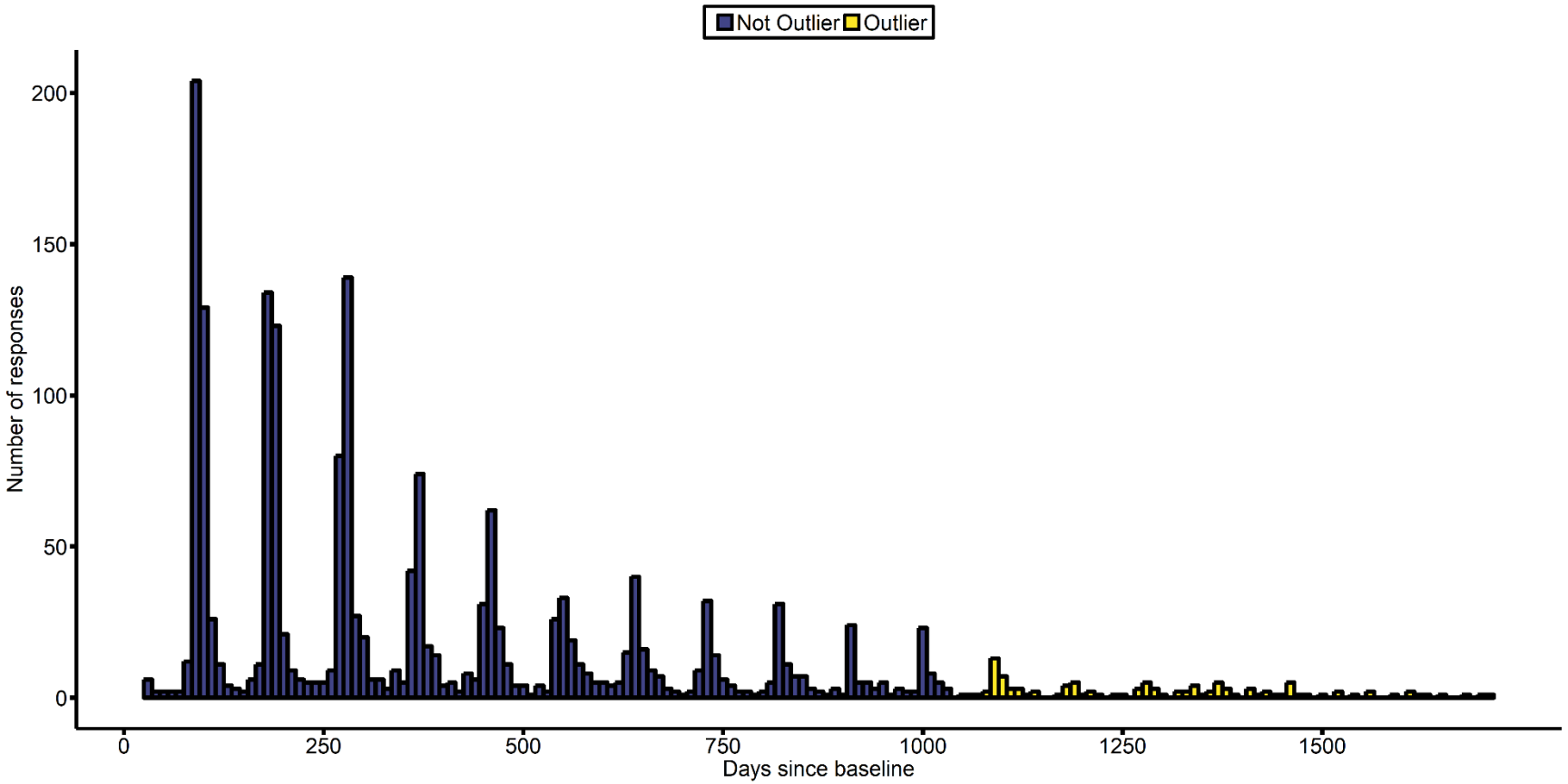
Genetic risk for alcohol consumption according to the UK Biobank GWAS (N=112,117) is associated with differences in human post-mortem gene expression (GTEx; Ns = 81 - 103), including frontal cortex BA9 (**Supplemental Data**). Notably, associations in the liver (far right) do not survive bonferroni-correction for multiple comparisons, though four are significant at a less-stringent FDR-based correction. Y-axis represents the significance of the association. Solid, dashed, and dotted lines represent Bonferroni-corrected, FDR-corrected, and nominally significant p-values, respectively.

Supplemental Figure 4.4.3: Overlap of HCP and DNS clusters at an uncorrected threshold



Overlap of volumetric associations in the frontal cortex with alcohol consumption in the DNS (red) and HCP (blue) samples (purple=overlap). Associations are displayed at an uncorrected threshold (DNS: $p<0.001$; HCP: $p<0.05$). For display purposes, different statistical thresholds were used due to the differential power of the two studies.

Supplemental Figure 4.4.4: Distribution of responses to DNS follow-up questionnaire



Histogram of responses to the DNS online follow-up questionnaire, which was emailed to participants every 3 months. Color indicates whether the clustering algorithm indicated the response to be an outlier or not – outliers occurred > 1053 days after the baseline visit and were excluded from analyses. Bins have a width of 10 days.

Supplemental Table 4.4.1. Location of volumetric reductions associated with alcohol consumption

DNS							
Index	**# voxels**	**p-FWE**	**T**	**x (mm)**	**y (mm)**	**z (mm)**	**AAL-Atlas Location**
1	279	0.003	5.24	27	39	25	R Middle Frontal
1.b		0.01	4.95	32	50	23	R Middle Frontal
2	344	0.004	5.14	56	3	0	R Superior Temporal
2.b		0.006	5.05	48	6	-5	R Insula
3	44	0.005	5.08	0	63	-3	L Medial Orbital Frontal
4	76	0.007	5.03	38	18	51	R Middle Frontal
5	64	0.007	5.03	-3	-33	42	L Middle Cingulum
6	23	0.019	4.8	2	27	30	R Middle Cingulum
7	17	0.023	4.75	29	62	8	R Superior Frontal
8	12	0.029	4.59	2	33	45	R Medial Superior Frontal
HCP							
Index	**# voxels**	**p-FWE**	**T**	**x (mm)**	**y (mm)**	**z (mm)**	**AAL-Atlas Location**
1	42	0.003	4.92	38	12	0	R Insula
2	88	0.008	4.7	20	24	42	R Superior/Middle Frontal

DNS = Duke Neurogenetics Study; HCP = Human Connectome Project. Coordinates are provided in MNI space.

Supplemental Table 4.4.2. Heritability and genetic correlation between gray-matter volume and alcohol consumption in the HCP

	mAUDIT-C	Right Insula	Right Middle/Superior Frontal Cortex
h^2 (SE)	0.5179 (0.0541)	0.6883 (0.0392)	0.7746 (0.0307)
p	**5.25×10^{-18}**	**1.97×10^{-32}**	**3.62×10^{-40}**
ρ_p	-	-0.1349	-0.114
p	-	**0.0006**	**0.0033**
ρ_g (SE)	-	-0.2314 (0.076)	-0.2192 (0.0784)
p	-	**0.0022**	**0.0054**
ρ_e (SE)	-	0.0294 (0.0825)	0.0483 (0.0787)
p	-	0.7214	0.541

h^2 = heritability; ρ_p = phenotypic correlation; ρ_g = genetic correlation; ρ_e = environmental correlation

Supplemental Table 4.4.3. Discordant sibling analysis in the HCP

Region	Variable	Estimate	t	p
Right Insula	**ICV**	-5.78×10^{-8}	-4.629	**4.78×10^{-6}**
	Sex	0.0052	0.892	0.3733
	Age	-0.0030	-5.571	**4.27×10^{-8}**
	MZ	-0.0057	-1.596	0.1111
	DZ	-0.0124	-2.659	**0.0081**
	W	0.0179	2.041	**0.0419**
	B	-0.0026	-0.253	0.8007
	A	0.0066	0.525	0.5998
	SES	0.0002	0.289	0.7726
	ED	1.20×10^{-5}	0.362	0.7176
	DX – Non Substance	-0.0054	-1.29	0.1978
	PSS	0.0002	0.967	0.3343
	Causal	0.0009	0.412	0.6806
	Graded	-0.0037	-1.974	**0.0491**
	Predispositonal	0.0037	3.479	**0.0006**
Region	**Variable**	**Estimate**	**t**	**p**
Right Middle/Superior Frontal Cortex	**ICV**	1.38×10^{-8}	1.315	0.1891
	Sex	0.0124	2.584	**0.0103**
	Age	-0.0029	-6.438	**3.01×10^{-10}**
	MZ	-4.89×10^{-5}	-0.016	0.9871
	DZ	-0.0059	-1.505	0.1329
	W	0.0139	1.899	0.0583
	B	0.0208	2.387	**0.0175**
	A	0.0217	2.058	**0.0402**
	SES	0.0008	1.06	0.2896
	ED	-1.87×10^{-5}	-0.665	0.5067
	DX – Non Substance	0.0092	2.557	**0.0109**
	PSS	0.0002	1.042	0.2980
	Causal	-0.0020	-1.037	0.3006
	Graded	0.0006	0.411	0.6810
	Predispositonal	0.0020	2.193	**0.0290**

SES = Socioeconomic status, PSS = Perceived Stress Scale, ED = education

Supplemental Table 4.4.4. Regression analyses of the association between brain volume and longitudinal alcohol consumption in DNS

Variable	β	Std.Error	DF	t-value	p-value
(Intercept)	**0.114**	**0.056**	**1726**	**2.022**	**0.043**
Age-linear	**0.085**	**0.037**	**1726**	**2.266**	**0.024**
Age-quadratic	-0.019	0.031	1726	-0.618	0.537
Baseline Age	-0.026	0.048	646	-0.546	0.585
Sex	**-0.164**	**0.044**	**646**	**-3.698**	**$2.35x10^{-4}$**
W	**0.161**	**0.062**	**646**	**2.615**	**0.009**
B	0.032	0.045	646	0.714	0.476
A	-0.047	0.058	646	-0.809	0.419
H	**0.093**	**0.039**	**646**	**2.360**	**0.019**
DX - Non Substance	0.016	0.035	646	0.440	0.660
PSS	-0.039	0.038	646	-1.025	0.306
P-SES	0.066	0.041	646	1.594	0.111
CTQ	0.014	0.038	646	0.375	0.708
P-ED	0.074	0.040	646	1.845	0.065
Scanner	0.029	0.032	646	0.932	0.351
ICV	0.107	0.059	646	1.795	0.073
Frontal	**-0.115**	**0.053**	**646**	**-2.185**	**0.029**
Age-linear x Frontal	**0.151**	**0.038**	**1726**	**3.976**	**$7.29x10^{-5}$**
Age-quadratic x Frontal	0.007	0.025	1726	0.275	0.783
Age-quadratic x Baseline Age	**-0.046**	**0.018**	**1726**	**-2.490**	**0.013**
Age-quadratic x Sex	**-0.057**	**0.022**	**1726**	**-2.602**	**0.009**
Age-quadratic x W	-0.001	0.031	1726	-0.022	0.982
Age-quadratic x B	-0.009	0.022	1726	-0.411	0.681
Age-quadratic x A	0.009	0.028	1726	0.322	0.747
Age-quadratic x H	-0.009	0.021	1726	-0.413	0.679
Age-quadratic x DX - Non Substance	0.017	0.018	1726	0.953	0.341
Age-quadratic x PSS	0.023	0.018	1726	1.269	0.205
Age-quadratic x P-SES	0.019	0.021	1726	0.883	0.377
Age-quadratic x CTQ	0.015	0.018	1726	0.799	0.424
Age-quadratic x P-ED	-0.006	0.020	1726	-0.284	0.777
Age-quadratic x Scanner	0.009	0.018	1726	0.479	0.632
Age-quadratic x ICV	-0.026	0.028	1726	-0.936	0.349
Age-linear x Baseline Age	-0.019	0.048	1726	-0.390	0.696
Age-linear x Sex	0.057	0.031	1726	1.876	0.061
Age-linear x W	-0.014	0.042	1726	-0.325	0.745
Age-linear x B	-0.021	0.030	1726	-0.702	0.483
Age-linear x A	-0.010	0.039	1726	-0.256	0.798
Age-linear x H	0.042	0.028	1726	1.519	0.129
Age-linear x DX - Non Substance	**-0.053**	**0.025**	**1726**	**-2.153**	**0.031**
Age-linear x PSS	-0.015	0.025	1726	-0.595	0.552
Age-linear x P-SES	-0.047	0.028	1726	-1.654	0.098

Age-linear x CTQ	0.004	0.026	1726	0.160	0.873
Age-linear x P-ED	0.024	0.027	1726	0.889	0.374
Age-linear x Scanner	0.018	0.024	1726	0.764	0.445
Age-linear x ICV	**-0.090**	**0.040**	**1726**	**-2.243**	**0.025**
Baseline Age x Frontal	-0.016	0.041	646	-0.386	0.700
Sex x Frontal	0.073	0.051	646	1.442	0.150
W x Frontal	-0.043	0.065	646	-0.669	0.503
B x Frontal	0.035	0.046	646	0.758	0.449
A x Frontal	-0.056	0.060	646	-0.924	0.356
H x Frontal	-0.018	0.043	646	-0.429	0.668
DX - Non Substance x Frontal	0.011	0.034	646	0.322	0.748
PSS x Frontal	0.023	0.038	646	0.605	0.546
P-SES x Frontal	0.009	0.043	646	0.213	0.832
CTQ x Frontal	-0.052	0.037	646	-1.407	0.160
P-ED x Frontal	0.034	0.042	646	0.819	0.413
Scanner x Frontal	0.001	0.035	646	0.038	0.970
ICV x Frontal	0.008	0.044	646	0.195	0.846

Volume of the right middle/superior frontal cortex is associated with future change in alcohol consumption (p-fdr=$4x10^{-4}$). Standardized effects and uncorrected p-values are presented.

Supplemental Table 4.4.5. Regression analyses of the association between brain volume and future alcohol use initiation in TAOS.

	Middle Frontal				Superior Frontal			
	β	SE	z	p	β	SE	z	p
(Intercept)	-6.64	156.30	-0.04	0.97	-6.35	132.19	-0.05	0.96
Age-linear	170.77	5767.82	0.03	0.98	157.94	2198.72	0.07	0.94
Age-quadratic	-27.21	4154.01	-0.01	0.99	-25.34	1750.80	-0.01	0.99
Sex	-0.04	0.94	-0.04	0.97	0.15	0.80	0.19	0.85
W	0.99	1.68	0.59	0.56	0.69	1.38	0.50	0.62
H	-0.18	1.63	-0.11	0.91	-0.23	1.32	-0.17	0.86
High-risk	0.30	0.82	0.37	0.71	0.05	0.73	0.07	0.95
GenPop	-2.70	1217.35	0.00	1.00	-3.35	1029.61	0.00	1.00
SLES	0.83	0.93	0.89	0.37	0.94	0.78	1.20	0.23
SES	-0.10	0.83	-0.13	0.90	-0.34	0.70	-0.48	0.63
CTQ	1.15	0.77	1.50	0.13	1.02	0.68	1.51	0.13
Tanner	-0.51	0.83	-0.61	0.54	-0.28	0.73	-0.39	0.70
MFQ	-0.03	0.85	-0.03	0.97	-0.11	0.71	-0.16	0.88
Baseline Age	-0.01	0.82	-0.01	0.99	0.10	0.71	0.15	0.88
Intracranial Volume (ICV)	-0.81	1.18	-0.68	0.50	-1.07	1.05	-1.02	0.31
Brain	1.58	114.78	0.01	0.99	2.18	118.72	0.02	0.99
Age-linear x Brain	**-57.04**	**24.04**	**-2.37**	**0.02**	**-60.74**	**24.99**	**-2.43**	**0.02**
Age-quadratic x Brain	-11.91	22.47	-0.53	0.60	11.99	21.43	0.56	0.58
Age-linear x Sex	-16.07	23.59	-0.68	0.50	-19.74	20.14	-0.98	0.33
Age-linear x W	-6.29	44.08	-0.14	0.89	-5.61	35.53	-0.16	0.87
Age-linear x H	2.52	42.77	0.06	0.95	3.35	34.36	0.10	0.92
Age-linear x High Risk	-12.31	20.19	-0.61	0.54	-6.61	18.37	-0.36	0.72
Age-linear x Gen-Pop	-24.67	44924.09	0.00	1.00	-3.90	17124.75	0.00	1.00
Age-linear x SLES	-9.99	24.93	-0.40	0.69	-15.30	21.04	-0.73	0.47
Age-linear x SES	25.87	21.32	1.21	0.23	26.53	17.57	1.51	0.13
Age-linear x CTQ	1.92	19.66	0.10	0.92	4.47	17.83	0.25	0.80
Age-linear x Tanner	16.91	19.24	0.88	0.38	15.46	18.07	0.86	0.39
Age-linear x MFQ	-11.20	19.34	-0.58	0.56	-12.20	16.73	-0.73	0.47
Age-linear x Baseline Age	10.07	21.73	0.46	0.64	3.79	18.30	0.21	0.84
Age-linear x ICV	20.43	28.01	0.73	0.47	21.73	25.25	0.86	0.39
Age-quadratic x Sex	12.71	18.66	0.68	0.50	20.88	15.54	1.34	0.18
Age-quadratic x W	15.10	30.63	0.49	0.62	4.74	24.89	0.19	0.85
Age-quadratic x H	6.69	27.90	0.24	0.81	1.36	22.93	0.06	0.95
Age-quadratic x High Risk	18.42	15.16	1.21	0.22	12.60	13.16	0.96	0.34
Age-quadratic x Gen-Pop	51.69	32354.53	0.00	1.00	41.45	13636.19	0.00	1.00
Age-quadratic x SLES	-2.61	20.93	-0.12	0.90	0.63	17.27	0.04	0.97
Age-quadratic x SES	-7.67	16.53	-0.46	0.64	-10.84	13.83	-0.78	0.43
Age-quadratic x CTQ	1.29	17.12	0.08	0.94	-2.24	15.00	-0.15	0.88
Age-quadratic x Tanner	-2.06	15.21	-0.14	0.89	0.47	13.83	0.03	0.97
Age-quadratic x MFQ	-20.32	16.51	-1.23	0.22	-18.46	14.09	-1.31	0.19

Age-quadratic x Baseline Age	-11.03	15.32	-0.72	0.47	-5.90	13.37	-0.44	0.66
Age-quadratic x ICV	18.31	21.99	0.83	0.41	7.89	20.98	0.38	0.71
Sex x Brain	-0.42	0.76	-0.55	0.58	-0.76	0.67	-1.14	0.25
W x Brain	-0.07	1.10	-0.06	0.95	0.39	0.89	0.43	0.67
H x Brain	0.25	1.06	0.23	0.81	0.52	0.87	0.59	0.56
High Risk x Brain	-0.01	0.59	-0.01	0.99	0.31	0.52	0.60	0.55
Gen-Pop x Brain	1.95	893.93	0.00	1.00	2.23	924.63	0.00	1.00
SLES x Brain	0.34	0.60	0.57	0.57	-0.08	0.53	-0.16	0.88
SES x Brain	0.64	0.64	1.00	0.32	0.67	0.54	1.25	0.21
CTQ x Brain	-0.12	0.66	-0.18	0.86	-0.11	0.57	-0.20	0.84
Tanner x Brain	0.52	0.65	0.80	0.43	0.25	0.58	0.44	0.66
MFQ x Brain	-0.20	0.70	-0.28	0.78	-0.15	0.58	-0.26	0.79
Baseline Age x Brain	0.73	0.68	1.07	0.29	0.21	0.51	0.41	0.68
ICV x Brain	-0.83	0.77	-1.09	0.28	-1.00	0.68	-1.48	0.14

Volume of the right middle and superior frontal cortices are both associated with future initiation of alcohol consumption (p-fdr=0.035, 0,035). Standardized effects and uncorrected p-values are presented.

Supplemental Table 4.4.6. TWAS Discovery and Replication

		Discovery – GTEX Frontal BA 9				Replication – CMC DLPFC			
Gene	**CHR**	**Locus Start**	**Locus End**	**TWAS Z**	**TWAS P**	**Locus Start**	**Locus End**	**TWAS Z**	**TWAS P**
C16orf93	16	30772519	30772656	5.0152	5.30E-07	-	-	-	-
CWF19L1	10	102000000	102000000	-4.1674	3.08E-05	102000000	102000000	-2.11116	0.0348
PHBP9	10	102000000	102000000	-3.8862	1.02E-04	-	-	-	-
C18orf8	18	21083473	21110576	3.831	1.28E-04	21083433	21111771	2.1613	0.0307

* Empty rows in replication data indicate that gene was not present in replication dataset. P-values are all uncorrected – all associations listed survive FDR correction.

Supplemental Table 4.4.7. Comparison of samples

	DNS (N=1303)	HCP (N=897)	TAOS^{+} (N=223)	t, F, χ^2	*p*
Age	19.7 (1.25) 18-22	28.82 (3.68) 22-37	13.42 (0.96) 11.61-15.33	F = 5420.39	$<1x10^{-300}$
Sex (% Female)	747 (57.33%)	504 (56.19%)	96 (43.05%)	$\chi 2$ = 15.93	**0.000347**
m/AUDIT-C	3.76 (2.64) 0-11.69	3.42 (2.65) 0-11.38	1.26 (1.95) 0-9	F = 89.43	**$3.38x10^{-38}$**
European/ European American	579 (44.44%)	597 (66.56%)	126 (56.5%)	$\chi 2$ = 105.31	**$1.35x10^{-23}$**
African/African American	148 (11.36%)	155 (17.28%)	3 (1.35%)	$\chi 2$ = 45.22	**$1.51x10^{-10}$**
Asian/Asian American	353 (27.09%)	45 (5.02%)	4 (1.79%)	$\chi 2$ = 225.94	**$8.68x10^{-50}$**
Hispanic	83 (6.37%)	73 (8.14%)	73 (32.74%)	$\chi 2$ = 157.54	**$6.18x10^{-35}$**
Multi-racial/Native American/Other	140 (10.74%)	27 (3.01%)	17 (7.62%)	$\chi 2$ = 45.29	**$1.46x10^{-10}$**
CTQ	33.39 (8.12) 25-59.81	-	32.98 (7.09) 25-64	t = 0.5	0.478993
PSS	14.65 (6.05) 0-32.89	13.07 (5.76) 0-35	-	t = 37.59	**$1.03x10^{-09}$**

Comparisons of measures that overlap across samples (DNS, HCP, TAOS). Continuous variables are presented in the format of: Mean (Standard deviation) Range. Dichotomous variables show the number of participants in that category, and the total percent of the sample that they comprise. Variables were winsorized prior to comparisons.

$^{+}$= TAOS comparisons of mAUDIT-C scores were done with the maximum score attained by each participant.

-=Variable not present in sample.

DNS = Duke Neurogenetics Study; HCP = Human Connectome Project; TAOS = Teen Alcohol Outcomes Study; AUDIT = Alcohol Use Disorder Identification Test; PSS = Perceived Stress Scale; CTQ = Childhood Trauma Questionnaire.

Supplemental Table 4.4.8. Frequency of Psychiatric Diagnosis in the DNS and HCP samples.

Dataset	Disorder	N
DNS	Any	258
	Depression	66
	Bipolar	35
	Anxiety	50
	OCD	16
	PTSD	2
	Alcohol Abuse	143
	Substance Abuse	47
	Eating Disorder	11
	Autism Spectrum	1
	Psychosis	3
HCP	Any	311
	Agoraphobia	55
	Panic Disorder	53
	Depression	75
	Alcohol Abuse/Dependence	176
	Marijuana Abuse/Dependence	103

80 participants in the DNS have more than one diagnosis.
103 participants in the HCP have more than one diagnosis.

Supplemental Table 4.4.9. Comparison of DNS subjects who did or did-not complete follow-up questionnaires

	No Follow-Up (N=624)	Follow-Up (N=679)	t/χ^2	*p*
AUDIT-C	4.0492 (2.6632)	3.4993 (2.595)	3.7694	**0.0002**
AUDIT Total	5.5913 (4.4163)	4.8778 (4.1872)	2.9869	**0.0029**
Age	19.8125 (1.2739)	19.592 (1.2265)	3.1765	**0.0015**
P-SES	7.5065 (1.6722)	7.3884 (1.7094)	1.2603	0.2078
P-ED	7.0232 (1.6025)	7.0751 (1.7291)	-0.562	0.5742
PSS	14.4852 (5.9435)	14.7976 (6.1404)	-0.9328	0.3511
CTQ	33.7902 (8.3233)	33.016 (7.9077)	1.7179	0.0861
Frontal Volume	0.4834 (0.0559)	0.4815 (0.0564)	0.6047	0.5455
Insula Volume	0.5498 (0.0539)	0.5505 (0.0547)	-0.2484	0.8038
ICV	1.4877 (0.1451)	1.4754 (0.1384)	1.5573	0.1196
Sex (number of female respondents)*	N=320 (51.28%)	N=427 (62.89%)	17.429	**2.98×10^{-05}**
Diagnosis (non substance-related) *	N=77 (12.34%)	N=72 (10.6%)	0.8037	0.3700
Caucasian*	N=253 (40.54%)	N=326 (48.01%)	7.0435	**0.0080**
African/African American*	N=86 (13.78%)	N=62 (9.13%)	6.5319	**0.0106**
Asian/Asian American*	N=171 (27.4%)	N=182 (26.8%)	0.0327	0.8564
Hispanic*	N=42 (6.73%)	N=41 (6.04%)	0.1582	0.6908
Multi-racial/Native American/Other*	N=72 (11.54%)	N=68 (10.01%)	0.6364	0.4250

*=Analysis was run as a chi-squared test, all others were run as t-tests.

AUDIT = Alcohol Use Disorder Identification Test; CTQ = Childhood Trauma Questionnaire; P-ED = Parental Education; P-SES = Perceived Socioeconomic Status; PSS = Perceived Stress Scale. ; ICV = Intracranial Volume

Supplemental Table 4.4.10. Association of Alcohol Consumption/Initiation with Covariates

Study	**DNS**		**HCP**		**TAOS***	
Variable	**statistic (t, F, r)**	***p***	**statistic (t, F, r)**	***p***	**statistic (t, χ^2)**	***p***
Sex (Female vs Male)	t = 9.1624	**2.70×10^{-19}**	t = 8.7447	**1.72×10^{-17}**	$\chi 2$ **=** 6.24×10^{-31}	1.0000
Diagnosis (non Substance-related) (vs none)	t = -0.3185	0.7505	t = -0.6746	0.5007	**-**	**-**
Ethnicity	F = 29.7684	**5.82×10^{-8}**	F = 2.6516	0.1038	$\chi 2$ **=** 6.5217	0.5890
European/ European American (vs not)	t = -7.6998	**2.84×10^{-14}**	t = -3.2474	**0.0012**	$\chi 2$ **=** 0.0424	0.8368
African/African American (vs not)	t = 3.1538	**0.0019**	t = 4.1931	**3.89×10^{-5}**	**-**	**-**
Asian/Asian American (vs not)	t = 5.0911	**4.54×10^{-7}**	t = 1.4615	0.1502	**-**	**-**
Hispanic (vs not)	t = -0.0295	0.9765	t = -0.9598	0.3398	$\chi 2$ **=** 0.0908	0.7631
Multi-racial/Native American/Other (vs not)	t = 2.2086	**0.0285**	t = -0.3249	0.7477	**-**	**-**
Age	r = 0.126	**5.10×10^{-6}**	r = -0.1222	**0.0002**	t = -2.8750	**0.0045**
P-SES/SES	r = 0.1747	**2.15×10^{-10}**	r = 0.0102	0.7604	t = -1.7684	0.0789
PSS/SLES	r = -0.0383	0.1669	r = 0.023	0.4908	t = -0.8601	0.3908
P-ED/ED	r = 0.0883	**0.0014**	r = -0.0153	0.6465	**-**	**-**
CTQ	r = -0.0966	**0.0005**	**-**	**-**	t = -1.6842	0.0945
Scanner (1 vs 2)	t = -0.5507	0.5822	**-**	**-**	**-**	**-**
High-risk for depression (TAOS-only)	**-**	**-**	**-**	**-**	t = 0.5780	0.4471
Tanner stage	**-**	**-**	**-**	**-**	t = -2.0118	**0.0459**
MFQ	**-**	**-**	**-**	**-**	t = 0.2417	0.8094

Association of model covariates with alcohol consumption (AUCIT-C/mAUDIT-C).
* = For analyses in TAOS, comparisons are between baseline measurements of participants who initiate, and those who do not.
Comparisons were run as t-tests, anovas, pearson correlations, or chi-squared tests. SES = Socioeconomic status, PSS = Perceived Stress Scale, ED = education, CTQ = Childhood Trauma Questionnaire, MFQ = Mood and Feelings Questionnaire; SLES = Stressful Life Events Schedule. DNS = Duke Neurogenetics Study; HCP = Human Connectome Project; TAOS = Teen Alcohol Outcomes Study
- = Not present in sample, not applicable, or insufficient numbers to run test.

Supplemental Table 4.4.11: Brain volume does not predict impulsivity, negative urgency, or intelligence.

		DNS					HCP				
Y	**X**	**Beta**	**Δ r^2**	**P**	**P-fdr**	**N**	**Beta**	**Δ r^2**	**P**	**P-fdr**	**N**
Coping	Frontal	-0.0876	0.0033	0.0293	0.1529	1303	-	-	-	-	-
	Insula	-0.0915	0.0036	0.0237	0.1529	1303	-	-	-	-	-
Self-report Impulsivity	Frontal	0.0487	0.0010	0.1909	0.2864	1303	-0.0844	0.0053	0.0103	0.0824	897
	Insula	0.0680	0.0020	0.0692	0.1529	1303	-0.0549	0.0046	0.1045	0.3739	897
IQ	Frontal	0.0760	0.0025	0.0514	0.1529	1275	0.0060	-5.24E-05	0.8295	0.9271	897
	Insula	0.0699	0.0021	0.0764	0.1529	1275	-0.0026	-2.71E-05	0.9271	0.9271	897
DDT - K	Frontal	-0.0891	0.0034	0.0436	0.1529	1157	-0.0142	3.62E-05	0.6877	0.9169	891
	Insula	-0.0320	0.0004	0.4720	0.5664	1157	0.0534	-0.0089	0.1402	0.3739	891
NEO - N5	Frontal	-0.0636	0.0018	0.1024	0.1756	1302	-	-	-	-	-
	Insula	-0.0478	0.0010	0.2232	0.2976	1302	-	-	-	-	-
NEO - N	Frontal	-0.0008	2.64E-07	0.9789	0.9789	1302	-0.0212	-0.0001	0.3848	0.6157	891
	Insula	-0.0080	2.73E-05	0.7879	0.8595	1302	-0.0308	0.0014	0.2337	0.4674	891

Parameters from linear regression models of brain volume predicting behavior. Covariates were the same as in whole-brain analyses. Coping = substance-use subscale of the brief COPE. Self-report impulsivity: DNS - Barratt Impulsiveness Scale; HCP - Achenbach Adult Self-Report Impulsivity. IQ: DNS: WASI-II; HCP: NIH Toolbox. DDT – K: Delayed discounting task. NEO-N: Neuroticism. NEO-N5: Neuroticism Impulsivity subscale. Standardized effect-sizes (ie beta values) are presented. Δ r^2: Change in model-fit when the x-variable is added (negative values indicate the model-fit decreased).

Supplemental Table 4.4.12: Brain volume clusters do not predict impulsivity, negative urgency, or intelligence.

Study	Y	X	Beta	Δ r^2	P	P-fdr	N
DNS	BCOPE - Sub	Insula_48_6_5	-0.0767	0.0044	0.0127	0.1110	1303
		MidFrontal_27_39_26	-0.0888	0.0048	0.0089	0.1110	1303
		MidFrontal_38_18_51	-0.0291	0.0006	0.3762	0.5424	1303
		SupFrontal_29_62_8	-0.0706	0.0030	0.0392	0.1880	1303
	BIS	Insula_48_6_5	0.0313	0.0007	0.2726	0.5424	1303
		MidFrontal_27_39_26	0.0402	0.0010	0.2010	0.4825	1303
		MidFrontal_38_18_51	-0.0006	$2.44x10^{-07}$	0.9840	0.9924	1303
		SupFrontal_29_62_8	0.0325	0.0006	0.3053	0.5424	1303
	IQ	Insula_48_6_5	0.0232	0.0004	0.4388	0.5850	1275
		MidFrontal_27_39_26	0.0793	0.0038	0.0163	0.1110	1275
		MidFrontal_38_18_51	0.0137	0.0001	0.6669	0.8003	1275
		SupFrontal_29_62_8	0.0329	0.0007	0.3219	0.5424	1275
	DDT - k	Insula_48_6_5	-0.0315	0.0007	0.3509	0.5424	1157
		MidFrontal_27_39_26	-0.0223	0.0003	0.5521	0.6974	1157
		MidFrontal_38_18_51	-0.0321	0.0007	0.3709	0.5424	1157
		SupFrontal_29_62_8	-0.0644	0.0025	0.0864	0.2593	1157
	NEO - N5	Insula_48_6_5	-0.0441	0.0014	0.1396	0.3721	1302
		MidFrontal_27_39_26	-0.0287	0.0005	0.3842	0.5424	1302
		MidFrontal_38_18_51	-0.0749	0.0037	0.0185	0.1110	1302
		SupFrontal_29_62_8	-0.0646	0.0025	0.0515	0.2059	1302
	NEO - N	Insula_48_6_5	0.0063	$2.98x10^{-05}$	0.7788	0.8608	1302
		MidFrontal_27_39_26	0.0002	$3.45x10^{-08}$	0.9924	0.9924	1302
		MidFrontal_38_18_51	-0.0431	0.0012	0.0730	0.2501	1302
		SupFrontal_29_62_8	0.0067	$2.71x10^{-05}$	0.7890	0.8000	1302
HCP	DDT - k	Frontal_20_24_42	0.0545	-0.0058	0.1084	0.4279	891
		Insula_38_12_0	0.0258	-0.0012	0.4520	0.5668	891
	ASR_IMP	Frontal_20_24_42	-0.0453	0.0008	0.1605	0.4279	897
		Insula_38_12_0	-0.0328	0.0034	0.3124	0.5668	897
	NEO - N	Frontal_20_24_42	0.0166	-0.0003	0.4960	0.5668	891
		Insula_38_12_0	-0.0198	0.0010	0.4195	0.5668	891
	IQ	Frontal_20_24_42	-0.0446	-0.0005	0.0747	0.4279	897
		Insula_38_12_0	-0.0115	$1.84x10^{-05}$	0.6506	0.6506	897

Parameters from linear regression models of brain volume predicting behavior. Covariates were the same as in whole-brain analyses. BCOPE - Sub = substance-use subscale of the brief COPE. BIS = Barratt Impulsiveness Scale; ASR IMP = Achenbach Adult Self-Report Impulsivity. IQ: DNS: WASI-II; HCP: NIH Toolbox. DDT – K: Delayed discounting task. NEO-N: Neuroticism. NEO-N5: Neuroticism Impulsivity subscale. Standardized effect-sizes (ie beta values) are presented. Δ r^2: Change in model-fit when the x-variable is added (negative values indicate the model-fit decreased).

Chapter 5: Discussion

5.1 Summary of primary findings

The present set of studies adopted a wide range of approaches (i.e., family-based design, neuroimaging, EEG, molecular genetics, bioinformatics, and laboratory-based stress induction) to identify sources of variance in alcohol-related neural phenotypes, and to test whether reward processing may link environmental and genetic risk to alcohol use. Broadly, two primary findings emerged. First, as described in **Chapter 4**, I find convergent evidence that alcohol-related reductions in brain volumes represent a genetically-conferred liability that promotes early alcohol use. While this may in turn lead to accelerated volume loss within these and other regions, these findings challenge predominant interpretations that smaller brain volumes tied to alcohol use emerge from the atrophy-inducing effects of alcohol (Pfefferbaum et al., 2017). Second, as described in **Chapters 2 and 3**, in contrast to a wealth of prior literature (Pizzagalli, 2014), I find no evidence that stress impacts behavioral or neural reward processing, challenging the notion that stress promotes alcohol use via its effects on reward processing. In **Chapter 2**, I report a replication of a previously reported gene-by-environment (GxE) interaction associated with alcohol use. While this report suggests that it is possible that genetic background may moderate the impact of stress on alcohol consumption, it should also be interpreted with great caution, given the caveats discussed below. Collectively, this work emphasizes the utility of neuroimaging phenotypes in dissecting the genetic underpinnings of alcohol consumption.

5.2 Brain structure, genetic risk, and alcohol use

The study presented in Chapter 4 leveraged several neuroimaging, genetic, and gene expression datasets to arrive at the conclusion that correlations between alcohol consumption and lower brain volume are the result of shared genetic factors influencing both traits. First, we identified replicable correlations between alcohol consumption and brain volume across two large independent adult data sets. The two regions which replicated – the right superior/middle frontal gyrus and the right insula – have both been observed to be reduced in patients with alcohol use disorders (Yang et al., 2016), as well as in heavy drinking adolescents (Pfefferbaum et al., 2016; Whelan et al., 2014). Prior studies have also observed correlations between alcohol consumption and structure of the insula and frontal cortex (Lange et al., 2017; Thayer et al., 2017). What is unique about this first contribution is that we have demonstrated that correlations between alcohol consumption and brain volume are replicable when (1) the measures of alcohol consumption are the same, and (2) when samples are free of psychosis.

Our second contribution was to assess whether there was evidence of a causal or predispositional relationship between alcohol consumption and brain volume. Prior longitudinal studies have found evidence that heavy alcohol consumption accelerates age-related shrinkage of several brain regions in both adults and adolescents (Luciana et al., 2013; Pfefferbaum et al., 2017; Squeglia et al., 2015; Sullivan et al., 2018), including both the frontal and insular cortex. Alternatively, there is also limited evidence from family-based studies of adolescents that genetic risk for alcohol dependence and consumption is association with reduced volume of the frontal cortex (Henderson et al., 2018; Wilson et al., 2015). We observed that brain volume and alcohol consumption were genetically correlated, and that alcohol consumption was predispositional for volume of the frontal cortex and insula. Notably, while the predispositional effect was more significant in the insula than the frontal cortex, examination of confidence-intervals (CIs) suggests that the effects in the two regions are not significantly different, as the CIs overlap. We believe

this to be the largest adult family-based study to examine this question. These results suggest that the modest correlation between alcohol consumption and lower brain volume in adults is likely not attributable to the same mechanisms that drive brain shrinkage in heavy alcohol use. Rather, lower brain volume was present before the initiation of alcohol use, and is driven by some of the same genetic factors that drive alcohol consumption.

Thus, for the third part of Chapter 4, we sought to test our hypothesis that lower brain volume is predispositional for future alcohol use. We tested whether brain volume was predictive of future alcohol consumption in a sample of young adults, and then whether it was predictive of initiation of alcohol use in an independent sample of children and adolescents. The prior literature is again inconsistent. While some studies have found that brain structure contributes to the prediction of heavy alcohol use in adolescents (Bertocci et al., 2017; Squeglia et al., 2016; Squeglia et al., 2014; Urošević et al., 2015; Whelan et al., 2014), others have not (Pfefferbaum et al., 2017; Seo et al., 2018). It is difficult to say where these discrepancies come from. Whelan et al. use the same sample that is later used in Seo et al., - the difference between the two is that Whelan et al. predict behavior 2 years later, while Seo et al. predict behavior 5 years later. While there are some additional differences between studies - Pfefferbaum et al. are unique in not including a measure of socioeconomic status in their models, and Seo et al. only examined a subset of all brain regions – it is unclear if this is sufficient to account for discrepancies.

We observed in the Duke Neurogenetics Study (DNS), a sample of young adults, that volume of the middle/superior frontal cortex, but not the insula, was predictive of future alcohol consumption, over and above current alcohol consumption. This analysis is unique in several regards: (1) As far as we can tell, it is the first to examine whether brain structure is predictive of future alcohol use in young adults (not adolescents). (2) It is also the first to examine whether brain structure is predictive of a continuous measure of alcohol consumption, rather than dichotomizing behavior. (3) The majority of participants responded only within 6 months of their MRI session – thus this analysis is also unique in testing whether brain structure is predictive of

relatively short-term changes in alcohol consumption behavior – the majority of prior studies cited tested whether structure was predictive of behavior 2 years later. As such, it is important to emphasize that our results are complimentary to the prior literature. Interpretations of the interaction between brain volume and age in the DNS are discussed below (see 'Brain structure and impulsivity').

The primary limitation of our analysis of longitudinal drinking behavior in the DNS is that participants had largely already initiated alcohol consumption prior to the baseline study visit, for an unknown amount of time. To address this limitation, we sought to test our original hypothesis, that brain volume is already lower prior to initiation of alcohol use, in a sample of non-drinking children and adolescents from the Teen Alcohol Outcomes Study (TAOS). We found that lower volume of both the superior and middle frontal cortex was predictive of an earlier age of alcohol use initiation, defined as the age at which the participant first reports consuming a full alcoholic beverage. As a reminder, an earlier age of initiation has been associated with increased risk for an alcohol use disorder in prior work (Aiken et al., 2018; Hingson et al., 2010). We did not examine continuous alcohol consumption as an outcome in this analysis, as only a small handful of participants progressed beyond this level of consumption. Again, this result is a unique and complimentary contribution to the field, as neither of the two prior studies to examine initiation of alcohol use included the superior or middle frontal cortex in their models (Bertocci et al., 2017; Urošević et al., 2015).

We propose that our neuroimaging results are consistent with a model wherein a portion of the genetic risk for alcohol consumption is mediated by changes to brain development. We then leveraged several open-access genetic datasets to test whether this model is plausible. Using the results of a recent GWAS for alcohol consumption (Clarke et al., 2017), we tested whether genetic associations with alcohol consumption, and the heritability of alcohol consumption, was enriched in genes that are highly expressed in the brain. We observed that, relative to all the other tissues assessed, including the liver, alcohol consumption associations

and heritability were enriched *only* in brain tissues, including the frontal cortex (the insula was not present in this dataset). One major limitation of this analysis is that genes are assigned to a tissue only if they are more upregulated in that tissue than in others. Indeed, it is clear this approach will miss genes that are important for brain function, as each gene set was comprised of the top 10% of genes that were highly expressed in each tissue, yet at least 80-95% (Bae et al., 2015) of all genes are expressed in the brain during at least one portion of development.

To address this limitation, we then sought to test whether genetic risk for alcohol consumption was associated with replicable changes in gene expression in the human brain. In our discovery sample (The GTEx Consortium et al., 2015) we found significant associations across the cortex, striatum, and cerebellum, including in the middle frontal cortex (BA9). Notably, associations with gene expression in the liver did not survive bonferroni correction. We then sought to replicate our associations with gene expression in the frontal cortex in an independent sample, using both a fully independent GWAS of alcohol consumption (Schumann et al., 2016) and a fully independent gene expression dataset (Fromer et al., 2016). While the top gene in our discovery analysis (*C16orf93*) was not present in the replication data, two of the genes which surpassed FDR-correction were - *CWF19L1* and *C18orf8/RMC1*. Associations with both these genes in replication analyses survived FDR correction, and were in the same direction as the discovery sample. One limitation of this replication is that the sample consisted of ~50% patients with schizophrenia, which may bias the results. To confirm that results are not biased, I have since tested whether the identified individual variants, that are both associated with genetic risk for alcohol consumption and predictive of gene expression, are replicably associated with gene expression in additional independent datasets of participants free of psychosis (these datasets were not used in the original analyses as they do not provide open-access subject-level genomic data; the Brain Cloud and BRAINEC datasets) (Ryten et al., 2009; Schubert et al., 2015). Both identified variants were predictive of the expression of their associated gene in the frontal cortex

in both samples, in the same direction as in our original analyses (rs12784396: *CWF19L1*; rs6507716: *C18orf8/RMC1*).

It is worth discussing some additional limitations of this set of analyses. First, similar to the concern that our replication data set included patients with schizophrenia, all of the gene-expression datasets included brain donors with alcohol consumption; indeed, 10 of the donors in our original discovery dataset died from substance overdose or alcohol-related liver damage. The high correspondence of results across multiple datasets suggests that alcohol consumption is not confounding these results, but given the wide prevalence of alcohol use across the world (Substance Use and Mental Health Administration, 2015), it will likely be impossible to ever definitively confirm in human adults that alcohol use is not a confound. Notably, neither of the identified genes have been found to be differentially expressed in the frontal cortex of donors with alcoholism (Liu et al., 2006). A second limitation is that these analyses are only sensitive to whether absolute levels of expression differ, and may be less sensitive to genes whose expression changes rapidly throughout the day (i.e. circadian genes) (Ferreira et al., 2018; Li et al., 2013). Finally, we should note that expression results are not cell-type specific, though we hope that in the future such an analysis will be possible (Ecker et al., 2017).

Our gene enrichment and expression analyses align with our interpretation of the neuroimaging data – it is plausible that differences in brain structure are reflective of genetic risk for alcohol consumption, as alcohol consumption associations are enriched in brain-expressed genes, and because genetic risk for alcohol consumption predicts replicable differences in gene expression in the frontal cortex. While neither of the two genes identified were well-known to us (e.g. they are not candidate genes), both are part of pathways that have been implicated in brain development. CWF19L1 is a human homolog of Cwf19, a component of the spliceosome (Galej et al., 2016). Two reports have identified rare mutations in *CWF19L1* as causes of autosomal recessive cerebellar ataxia (Burns et al., 2014; Nguyen et al., 2016) – symptoms include loss of control of bodily movements, as well as developmental delay and mental retardation, highlighting

the importance of CWF19L1 in brain development. C18orf8/RMC1 is part of the endocytic pathway, and has been identified as an upstream regulator, directing Rab7 to the late endosome (Vaites et al., 2017). Endosomes are sites of essential signal transduction (Murphy et al., 2009), and have long been recognized as playing important roles in brain development (Barford et al., 2017). Indeed, another Rab7 effector, WDR91, which also directs Rab7 to the late endosome, was recently identified as being essential for early postnatal brain development in mice (Liu et al., 2017). While there is scant evidence linking either gene to alcohol consumption, it is plausible that differential expression of these genes would result in changes to brain development, which could manifest as structural differences.

5.3 Brain structure and impulsivity

We have proposed that differences in brain structure, which are linked to genetic risk, predispose individuals to alcohol consumption. In the Introduction it was suggested that this effect would mediated by impulsivity. Indeed, most impulsivity constructs are associated with alcohol phenotypes (Dick et al., 2010), including delayed discounting and response inhibition (Fernie et al., 2013; Nigg et al., 2006; Squeglia et al., 2014), and meta-analyses indicate that almost all self-report measures of impulsivity traits are associated with alcohol outcomes (Stautz & Cooper, 2013). Moreover, it has been repeatedly observed that brain structure is correlated with impulsivity measures, including correlations between the frontal cortex, insula, and striatum with delayed discounting (Bjork et al., 2009; Pehlivanova et al., 2018; Tschernegg et al., 2015), and correlations between the frontal cortex and cingulate with motor impulsivity and sensation seeking (Holmes et al., 2016). However, in the Supplement to Chapter 4 we report that we found no evidence of correlations between volume of either the frontal cortex or the insula (both whole ROIs and individual significant clusters) with behavioral impulsivity, delayed discounting, or negative urgency measures of impulsivity, in either of our two large adult samples.

In retrospect, it is clear that perhaps we omitted an obvious comparison. In addition to being correlated with thickness of the middle frontal cortex (Holmes et al., 2016), sensation seeking has also been identified as being more strongly correlated with alcohol consumption in adolescents than other impulsivity measures (Dick et al., 2010; Stautz & Cooper, 2013). Examining the 'Excitement-seeking' subscale of the NEO personality questionnaire (see Methods in Chapter 4) (Costa & McCrae, 1992), which is a self-report measure of sensation seeking, we find that the clusters in the middle frontal cortex and insula, which were significantly associated with alcohol consumption, also show a significant negative correlation with sensation seeking. This would suggest that the associations between lower brain volume and increased alcohol consumption may be partially mediated by increased sensation seeking. However, a measure of sensation seeking is not available in our replication dataset (the HCP), and so we are not able to independently replicate this observation.

The hypothesis that the association between brain volume and alcohol consumption may be partially mediated by sensation seeking could also help to explain the interaction between age and volume we observed in the analysis predicting future alcohol consumption of young adults. In this analysis we observed that participants with lower volume were predicted to consume more alcohol than subjects with higher volume, but only until around the age of 21, at which point the groups were predicted to drink similar amounts. Coincidentally, a recent large international study has found that this age range is when sensation-seeking begins to decline (it peaks at 18-20 years old), and is when self-regulation begins to peak (it peaks at 23 years old) (Steinberg et al., 2018). If the predispositional effects of brain volume are mediated by sensation seeking, then brain volume may have less predictive utility as sensation seeking starts to decline. Additionally, it cannot be ignored that the legal drinking age in the United States is 21. Our observation of increased consumption prior to this age, only among participants with lower volume, is also consistent with findings that environmental context can moderate the expression of predispositonal risk (Young-Wolff et al., 2011).

There are some notable differences between the conclusions of our longitudinal analysis in the DNS and the results of our co-heritability analyses in the HCP replication sample. Most prominently, in the DNS insula volume was not predictive of future drinking behavior, while in the HCP both frontal cortex and insula volume are co-heritable with alcohol consumption. We must note some more limitations of the DNS longitudinal analysis. As participation in the longitudinal follow-up questionnaire was only compensated by the chance to win a gift card (this is not an atypical design for questionnaire-based studies), the participants in the subsample are younger, drink less, have lower sensation seeking, are more likely to be female, and are more likely to be Caucasian, than those participants in the DNS sample who did not respond to the questionnaire. Moreover, we must note that total insula volume is less strongly associated with alcohol consumption in the DNS than in the HCP, though the effects dos not significantly differ.
Thus, it seems most likely that the insula may not be longitudinally predictive in the DNS sample simply because it is a weaker variable being tested in a healthier subsample analysis.

Thus, this work suggests a model in which genetically-conferred reductions in brain volume promote early alcohol use, possibly via increased sensation seeking. Moreover, bioinformatic analyses are consistent in showing that a model in which genetic risk for alcohol consumption directly changes gene expression in the brain is plausible. We note that prior research has primarily interpreted correlations between brain structure and volume as indicative of alcohol-driven atrophy (e.g. Lange et al., 2017; Thayer et al., 2017), and longitudinal studies have found evidence that heavy alcohol use accelerates age-related reductions (Luciana et al., 2013; Pfefferbaum et al., 2017; Squeglia et al., 2015; Sullivan et al., 2018). However, prior studies have also found evidence that reduced volume is predictive of future heavy alcohol use (Bertocci et al., 2017; Squeglia et al., 2016; Whelan et al., 2014). Thus we must emphasize that, while our results challenge the interpretation that the association between alcohol use and brain structure is purely unidirectional, they do not contradict the empirical evidence. We propose that genetic risk contributes to lower volume of the frontal cortex and insula, which is predispositional for

initiation of alcohol use and alcohol consumption, and that chronic heavy alcohol use then accelerates the shrinkage of these regions and others.

An interesting future direction will be to examine when during development the volumetric reduction associated with genetic risk for alcohol first emerges. If they are apparent prior to puberty, it might imply that genetic mechanisms important for early brain development are the driving force. However, if they appear only after the onset of puberty, changes to the machinery governing synaptic pruning would be a likely candidate. It should be noted here that synaptic pruning is frequently cited as a possible mechanism for alcohol-induced atrophy (e.g. (Koob et al., 2014; Kyzar & Pandey, 2014; Nixon & Mcclain, 2010)). Indeed, if this later possibility is the case, one might hypothesize that the differences associated with genetic risk would increase over time. This might explain why the genetic correlations observed in the adult HCP sample are so strong, yet the prior adolescent literature is mixed. This hypothesis is also convergent with observations that the impact of heavy alcohol is moderated by familial risk for alcohol dependence (Pfefferbaum et al., 2017), suggesting that environmental and genetic risk may both modulate the same molecular processes. One of the strengths of the adolescent TAOS sample is that assessments of alcohol use were denser than most of the prior work, occurring annually for up to five years after the initial study visit. This rich phenotypic assessment enabled us to detect an effect that we likely would not have been able to see had assessments been sparser. Indeed, one hypothesis that is compatible both with our work and the prior literature, is that the effects of genetic risk for alcohol consumption on brain volume are rather subtle during adolescence, and gradually magnify as individuals age.

5.4 Early life stress and reward

Early life stress (ELS) is arguably the single strongest environmental predictor of risk for psychopathology, including alcohol dependence (Enoch, 2011). There is a large body of evidence indicating that ELS alters reward-related activity of the striatum (Boecker et al., 2014; Goff & Tottenham, 2014; Hanson et al., 2015; Novick et al., 2018; Teicher et al., 2016), which is in turn associated with alcohol dependence (Balodis & Potenza, 2015). This agrees well with studies from model organisms, such as rodents, where early-life chronic mild stress is associated with reduced dopamine release in the striatum (Willner, 2017) and elevated alcohol intake in adulthood (Becker et al., 2011). What then to make of the observations in Chapters 2 and 3 that ELS was not associated with striatal reward activity (Chapter 2) or altered reward learning or processing (Chapter 3)?

Two possible explanations are the timing of ELS and the specific nature of the ELS. Both chapters used the same measure of ELS, the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). This scale is widely used and has convergent validity with a clinician-rated interviews of childhood abuse (Scher et al., 2001). However, it does not assess when traumatic incidents took place, other than that they occurred before the respondent was 18 years old. A growing body of literature indicates that the impact of trauma varies depending on the age at which it occurs (Tottenham & Sheridan, 2010). While this literature has yet to converge on specific sensitive windows, some studies have identified infancy and puberty as the two most vulnerable periods (Dunn et al., 2013, 2017). Indeed, given that the brain is constantly changing and developing throughout childhood, one might hypothesize that the effect of trauma on adult outcomes (e.g. which behaviors are effected) will be dependent on which brain regions are changing the most at that time (Teicher et al., 2016). Evidence for similar effects has already been identified in the realm of fetal development, where for instance methamphetamine exposure in infant rodents

selectively impairs adult long-term memory only when the exposure coincides with hippocampal development (the equivalent of the third trimester in humans) (Jablonski et al., 2016).

Second, there is evidence that outcomes may vary depending on the specific nature of childhood trauma. Theoretical models propose that abuse and neglect will have differential effects on risk for psychopathology and underlying neurobiological correlates (Sheridan & McLaughlin, 2014). Indeed, the CTQ includes subscales for both abuse and neglect. The study in Chapter 3 recruited only participants who scored high on at least one of the abuse scales, but in Chapter 2 we combined abuse and neglect. Moreover, it is likely the case that the nature of the trauma interacts with the aforementioned developmental effects. The Bucharest Early Intervention Project is a famous study in which institutionalized, and largely neglected, infants in Romania were randomly selected for foster care, the results of which convinced the Romanian government to adopt a nationwide foster care system. The primary result of the project was that intervention was most effective before the age of 2, suggesting the presence a developmental period during which neglect had its worst effects (Zeanah et al., 2012). More recently, a longitudinal study has found that, while both abuse and neglect are broadly associated with both externalizing and internalizing disorders (Norman et al., 2012), neglect before the age of 6 is only associated with externalizing problems in adolescents (Miller et al., 2018). However, it should be noted that another recent study observed no effect of age of exposure for childhood abuse (Dunn et al., 2017), and that it can be difficult to disentangle the effects of abuse and neglect, given their high co-occurrence (Green et al., 2010).

In retrospect, there is already some evidence for an interaction between stress-type and developmental timing on future striatal reward function. Hanson et al. (Hanson et al., 2015) observed a negative association between ELS and striatal activation to rewards (N=72). In their post-hoc analyses they found that that this effect was driven by participants who experienced interpersonal stress (i.e. abuse directed at themselves, or between their parents) during early

childhood. While this finding remains to be replicated, it does suggest that consideration of stress-type and the age at which stress occurred bears further consideration.

5.5 Genetics and neuroimaging – limitations

Chapter 2 presents findings that a variant in the circadian gene *PER1* moderates the impact of ELS on alcohol consumption, an effect which was not mediated by altered reward reactivity. The *PER1* variant was chosen because a similar gene x environment (GxE) interaction with that same variant had been previously reported, and shown to have physiological consequences (Dong & Bilbao, 2011). There are two limitations to this analysis. First, a multi-ethnic sample was used. While the distribution of alleles of the *PER1* variant did not differ between ethnicities, we did not verify that the underlying correlations between this variant and the surrounding genome did not differ between ethnic groups. Such differences (which are an aspect of what is termed 'population stratification') have been shown to bias results and may generate false-negative and false-positive findings (Li et al., 2013). In our analysis of associations in each ethnic subsample, we found results that are directionally consistent in 5/6 of ethnicities, but the association was only significant in one of these (Asian; N=44), and the weakest association was in the largest subsample (Caucasian; N=305). It should be noted that the recent GxE GWAS examining the interaction between trauma and genetic risk on alcohol misuse did not identify associations at either the variant or gene level with any core circadian clock gene, including the *PER1* variant used in Chapter 2 (Polimanti et al., 2018).

The second limitation of the study in Chapter 2 is the use of a candidate-gene approach. Candidate-genes are extremely appealing, as they promise insight into the underlying biological mechanism, and provide an ethical extension of findings from gene knock-outs in model organisms. The proximal limitation of candidate genes is that they have a very poor track record. High profile associations, such as the interaction between the S allele of the 5-HTTLPR serotonin

transporter promoter region which was observed to increase risk for depression in the context of early life stress, have since not replicated in extremely well-powered studies (Culverhouse et al., 2018). Associations between candidate genes and neuroimaging phenotypes have similarly failed to yield replicable associations (Avinun et al., 2017; Harrisberger et al., 2015). Indeed, analyses of GWAS results for schizophrenia have found that, while a handful of candidate genes were significantly associated, as a whole, the associations with candidate genes were not higher than for any similarly-size random set of genes (Johnson et al., 2017).

The field of psychology has perhaps borne the greatest amount of attention surrounding the issue of replication and reproducibility, but this is in part a product of the willingness of psychologists to engage in large-scale critical self-evaluation (Aarts et al., 2015). Many of the issues contributing to the 'replication crisis' in psychology likely contribute to the poor replication of candidate-genes, particularly the problem of low power, which is a well-recognized contributor in imaging genetics (Bogdan et al., 2017). A meta-analysis of 234 neuroscience-related candidate gene studies found a median power of 10% (Nord et al., 2017). Candidate-gene associations are underpowered partly because, until relatively recently, it was not widely appreciated how small genetic effect sizes truly are. Indeed, the largest single replicable association with schizophrenia (OR=1.1) (Ripke et al., 2014) would require at least 8,000 schizophrenia cases to be replicated. Most candidate gene studies have many fewer participants, for instance the median sample size is 262 in Nord et al., 2017. It has been suggested that larger effect sizes would be expected with neuroimaging phenotypes, as they are closer to the underlying biology (Rose & Donohoe, 2013). However, large-scale GWAS of neuroimaging phenotypes have yet to find evidence that this is the case (Adams et al., 2016; Hibar et al., 2017), and direct comparisons of replicable effects have found that imaging-associated effects are just as small as schizophrenia-associated ones (Franke et al., 2016). It should be noted that the effect size estimates from some case-control GWAS may be underestimates (Stringer et al., 2011), as case-status is a somewhat arbitrary dichotomization of an underlying continuous phenotype (Plomin et al., 2009), though this is

unlikely to change the observation that the majority of candidate gene studies were underpowered.

What then, can be concluded from Chapter 2? Given the limitations listed above, as well as the lack of external replication (Carter et al., 2017), or robust internal replication (Bogdan et al., 2017), Chapter 2 may be best regarded as an additional piece of *suggestive* evidence that genetic variation of *PER1* contributes to variable long-term outcomes in response to ELS, which may be predispositional towards risk for alcohol abuse. In support of this interpretation, convergent evidence is found in animal models (Dong & Bilbao, 2011; Sarkar, 2012). However, it is quite difficult to translate animal findings to humans, for a variety of reasons, which should caution against the over-interpretation of seemingly convergent observations (Bracken, 2009; Garner, 2014; Mak et al., 2014). Thus, as is often the case with individual studies, we await further evidence.

5.6 Genetics and neuroimaging – future directions

Beyond candidate genes, there are several methods that can be brought to bear on questions of the influence of genetics on brain function and structure. One approach, adopted in Chapter 4, is to use a sample of twins. Twin studies have been used to study the influence of genes, and genetic risk, on brain function and structure since the late 1990's (Jansen et al., 2015). There are a handful of open-access twin datasets that include neuroimaging data, including the Human Connectome Project (Van Essen et al., 2012) and the Adolescent Brain Cognitive Development study (Barch et al., 2017; Casey et al., 2018). An alternative to twin studies, which is applicable to datasets that have already been collected, is to use Polygenic Risk Scores (PRS). PRS were already described in the Introduction, but briefly, they are a score reflecting an individual's genetic burden for a trait, based on results from independent studies. PRS results, as opposed to candidate genes, are replicable, though they only capture a small portion of the total

genetic burden (Bogdan et al., 2018). However, what is missed by twin studies and by a standard PRS, is that mechanistic hypotheses about particular molecular subsystems cannot be tested, as they can with candidate genes.

There are several possibilities for how to construct an imaging genetics analysis, if one has a mechanistic hypothesis. First, there are GWAS of some relevant quantitative traits. For instance, Luykx et al. (Luykx et al., 2014) conducted a GWAS of monoamine levels in cerebrospinal fluid, identifying an association with 5-HT1AA levels. The PRS for serotonin functioning, derived from these results, has since twice been linked to alcohol use (Wang & Chassin, 2018; Wang et al., 2018). Another approach is to manually construct a mechanistic score, weighted by the literature of effects of variants on relevant traits (e.g. variants associated with protein function or relevant proximal traits) (Iorio et al., 2017; Nikolova et al., 2011; Pagliaccio et al., 2015). One hurdle to applying this approach is that for some processes there may not be many non-candidate gene studies to draw on. Finally, an emerging approach, applying a logic similar to the construction of a mechanistic score, is to rely on large databases to generate scores in a data-driven fashion. Several studies have leveraged measures of gene expression to generate scores that are predictive of traits such as chronic pain (Parisien et al., 2017), Crohn's disease (Marigorta et al., 2017), and height (Gusev et al., 2016). Recent work suggests that a similar approach may be useful in the realm of mental illness – Pergola et al. (unpublished) (Pergola et al., 2018) report that a risk score generated from genes that are differentially expressed in the prefrontal cortex of patients with schizophrenia is more predictive of treatment response than a traditional polygenic risk score. One can imagine that data-driven gene expression scores in specific brain regions, that are limited to genes implicated in specific processes (e.g. expression of dopamine pathway genes in the striatum), may be a way to combine the robust replicability of polygenic risk scores with the mechanistic insights of candidate gene studies.

Finally, we note that another emerging approach is the use of bioinformatic analyses to drive the generation of, and to identify convergent evidence for, new neuroscience hypotheses. Results of GWAS (i.e. summaries of statistical results for all variants tested) for hundreds of traits are now public (e.g. 700+ on LD Hub (Zheng et al., 2017)), available for a wide variety of data-mining approaches. Enrichment analyses can be performed to identify biological pathways that may be implicated in the trait (de Leeuw et al., 2015; Watanabe et al., 2017), or as we did in Chapter 4, to identify brain regions expressing trait-associated genes (Finucane et al., 2015; The GTEx Consortium et al., 2015). New gene sets are still being developed, and there are several new ones that offer increased insight into the potential neural underpinnings of traits, including cell-type specific gene sets (Mckenzie et al., 2018), and sets of genes whose expression in the human brain is spatially and temporally correlated across development (i.e. from fetal to adult (Kang et al., 2011; Yousaf et al., 2018)). Gene, cell type, and brain region information can also be integrated with results of neuroimaging meta-analyses (i.e. Neurosynth (Fox et al., 2014; Yarkoni et al., 2011)) to test for convergent evidence implicating specific cognitive processes. Combining these approaches, one could move from a genome-wide association of a trait (or multiple traits) to hypotheses about which genes, pathways, cell types, brain regions, and cognitive processes are most likely to drive that trait.

5.7 Conclusions

An overarching feature of this work is that it combines replications of previous research with novel extensions. Indeed, the impact and utility this research is a direct result of how it replicates, or fails to replicate, prior findings. Results highlight that associations between early-life stress (**Chapters 2&3**) reward processing require further interrogation, suggesting that it will be important for future work to examine the potential impacts of the timing and nature of stress. In **Chapter 3** we use a within-subject design to show that the associations between acute stress

and reward processing and behavior are not as robust as suggested by the prior literature, suggesting that study-design choices such as reward amount moderate whether or not acute stress will impact reward processes. **Chapter 4** leverages internal replication and convergence to demonstrate that lower brain volume associated with alcohol consumption is likely reflective of genetic risk. Integrating this finding with the prior literature, we propose that genetically conferred reductions in volume promote early alcohol use, and that genetic risk then interacts with heavy alcohol use, further reducing volume. Future work, such as results from the ongoing longitudinal developmental ABCD study (Barch et al., 2017; Casey et al., 2018), will be able to directly test this hypothesis. **Chapter 4** additionally highlights the emerging utility of combining neuroimaging research with bioinformatic analyses. Future research will be able to leverage these resources to develop new hypotheses with convergent evidence.

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Curriculum Vitae

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Behavioral Research and Imaging Neurogenetics (BRAIN) Lab; Dr. Ryan Bogdan
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Education and Work

Washington University in St Louis, St Louis, MO (08/2012 – 08/2018)
Ph.D., Neuroscience
Advisors: Ryan Bogdan, Ph.D.; Deanna Barch, Ph.D.

National Institute of Mental Health, Bethesda, MD (06/2010 – 06/2012)
Research Assistant - Clinical Brain Disorders Branch; Joseph Callicott, M.D.

Duke University, Durham, NC (06/2009 – 05/2010)
Research Intern – Brain Imaging and Analysis Center; Joseph McClernon, Ph.D.

Wesleyan University, Middletown, CT (08/2006 – 05/2010)
B.A., Neuroscience and Behavior, Science in Society Program
Research: Schizophrenia Cognition Lab; Matthew Kurtz, Ph.D.

Publications

Baranger DAA, Desmarais A, Sputo K, Chang K, Pan W, Jones M, Kennedy M, Winstone J, Corral-Frías NS, Bogdan R. Minimal effects of acute and early-life stress in a reward learning and processing paradigm. (In preparation).

Baranger DAA, Demers CH, Elsayed NM, Knodt AR, Radtke SR, Desmarais A, Few LR, Agrawal A, Heath AC, Barch DM, Squeglia LM, Williamson DE, Hariri AR, Bogdan R. Convergent evidence for predispositonal effects of brain volume on alcohol consumption. (Submitted).

Baranger DAA, Few LR, Sheinbein D, Agrawal A, Oltmanns TF, Harms MP, Burgess GC, Knodt AR, Radtke SR, Heath AC, Barch DM, Hariri AR, Bogdan R.. Borderline personality disorder traits are not associated with gray matter volume in two large independent samples. (In preparation).

Karcher NR, Barch DM, Demers CH, **Baranger DAA**, Heath AC, Lynskey MT, Agrawal A. Understanding the Relationship between Cannabis Use and Psychotic-Like Experiences: Predisposition or Individual Specific Processes? (Submitted).

Bogdan R, **Baranger DAA**, Agrawal A. Polygenic risk scores in clinical psychology: Bridging genomic risk to individual differences. (2018) *Annual Review of Clinical Psychology*, (2018) 14.

Sheahan T, Valtcheva M, McIlvried L, Pullen M**, Baranger DAA**, Gereau IV R. Metabotropic glutamate receptor 2/3 (mGluR2/3) activation suppresses TRPV1 sensitization in mouse, but not human sensory neurons. *eNeuro* (2018) 0412-17.2018; doi: 10.1523/ENEURO.0412-17.2018

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Bogdan R, Pagliaccio D, **Baranger DAA**, Hariri AR. Genetic moderation of stress effects on the corticolimbic circuit. *Neuropsychopharmacology* (2015) 41(7), 275–296. doi:10.1038/npp.2015.216
Arnedo J, Mamah D, **Baranger DAA**, Harms MP, Barch DM, Svrakic D, de Erausquin GA, Cloninger CR. Decomposition of brain diffusion imaging data uncovers latent schizophrenias with distinct patterns of white matter anisotropy. *Neuroimage* (2015) 120, 43-54. doi:10.1016/j.neuroimage.2015.06.083

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Invited Talks

Baranger DAA. Evaluating Neural and Behavioral Markers of Psychiatric Risk. Developmental Affective Science Collective, University of Pittsburgh, May 2017.

Baranger DAA, Desmarais A, Carey C, Hariri AR, Bogdan R. Orexin/hypocretin system polygenic risk scores predict amygdala reactivity in two samples. Presented at the 2016 Society of Biological Psychiatry conference, Atlanta, GA, May 2016.

Baranger DAA, Few L, Sheinbein D, Agrawal A, Latzman RD, Barch D, Hariri AR, Bogdan R. Borderline personality disorder traits are not associated with gray matter volume in two large independent samples. Presented at the 2016 Society of Biological Psychiatry conference, Atlanta, GA, May 2016.

Research Funding

· 2018 T32 Postdoctoral Fellowship – IMPACT (Innovative Methods in Pathogenesis and Child Treatment)
· 2014 National Science Foundation Graduate Research Fellowship (GRF)
· 2013 T32-GM008151 Systems and Molecular Neurobiology
· 2010 National Institutes of Health Intramural Research Training Award (IRTA) Fellowship

· 2008 Summer Undergraduate Research Fellowship (SURF) – Cincinnati Children's Hospital

Awards

· 2018 Society of Biological Psychiatry Predoctoral Travel Fellowship Award
· 2017 crowdAI Machine Learning OpenSNP Height Prediction Competition 1st Place Award
· 2017 Spring WUSTL Graduate Student Senate Travel Award
· 2015 Fine Science & Merlie Traveling Fellowship
· 2015 Mortimer D. Sackler, M.D., Summer Institute Attendee
· 2015 WUSTL Graduate Research Symposium 2nd Place Poster in Science & Award
· 2015 International Imaging Genetics Conference 2nd Place Poster & Travel Award
· 2014 International Imaging Genetics Conference 2nd Place Poster & Travel Award
· 2013 Fine Science & Merlie Traveling Fellowship

Conference Posters

Baranger DAA, Demers CH, Elsayed NM, Knodt AR, Radtke SR, Desmarais A, Few LR, Agrawal A, Heath AC, Barch DM, Squeglia LM, Williamson DE, Hariri AR, Bogdan R. Convergent evidence for predispositonal effects of brain volume on alcohol consumption. Presented at the 2018 Society of Biological Psychiatry conference, New York, NY, May 2018.

Baranger DAA, Margolis S, Hariri AR, Bogdan R. Evidence for Diurnal Variation of Threat-related Amygdala Reactivity. Presented at the 2016 International Imaging Genetics Conference, January 2016, Irvine, CA.

Baranger DAA, Desmarais A, Carey C, Drabant EMD , Hariri AR, Bogdan R. Orexin/hypocretin system polygenic risk scores predict amygdala reactivity. Presented at the 2015 World Congress of Psychiatric Genetics, October 2015, Toronto, CA.

Baranger DAA, Carey CE, Margolis S, Conley EMD, Hariri AR, Bogdan R. A random forest circadian gene-set analysis component interacts with childhood stress to predict bilateral amygdala reactivity to faces. Presented at the 2015 International Imaging Genetics Conference, January 2015, Irvine, CA.

Baranger DAA, Drabant EMD, Bogdan R, and Hariri AR. PER2 circadian gene functional polymorphism rs11894491 moderates amygdala reactivity in the context of early life stress. Presented at the 2014 Society for Research in Psychopathology meeting, September 2014, Evanston, Illinois.

Baranger DAA, Ifrah C, Prather AA, Carey CE, Corral- Frías NS, Conley EMD, Hariri AR, Bogdan R, PERIOD1 rs3027172 is associated with increased risk for problematic drinking in the context of early life stress. Presented at the 2014 International Imaging Genetics Conference, January 2015, Irvine, CA.

Baranger DAA, Yates WD, White M, Chgen Q, Rasetti R, Mattay VS, Weinberger DR, Callicott JH; DISC1 Leu607Phe and Ser704Cys interact to reduce prefrontal-hippocampal coupling during a working memory task. Presented at the 2012 Society of Biological Psychiatry conference, Philadelphia, PA, May 2012.
Baranger DAA, Feighery EL, Dickinson DD, Rasetti R, Sust S, Zoltick B, Chen Q, Rypma B, Mattay VS , Weinberger DR, Callicott JH; COMT Val158Met polymorphism modulates prefrontal cortical efficiency in a processing speed task. Presented at the 2011 Society for Neuroscience conference, Washington, DC, November 2011.

Manuscript Reviews

2018 – Neuropsychologia
2016 – Biological Psychiatry (x3); Neuroimage (contributed); Proceedings of the National Academy of Sciences (contributed)
2014 – Cognitive, Affective, and Behavioral Neuroscience; Cortex (contributed, x2)
2013 **–** American Journal of Psychiatry (contributed)

Teaching, Leadership, and Outreach

Workshop Instructor, Interface of Psychology, Neuroscience, and Genetics — Summer 2017
3-day workshop on applying modern genetics techniques in mental-health research

Co-organizer, 1st Washington University BrainHack Hackathon — Spring 2017

Lecturer, Molecular Biology at the Cutting Edge — Spring 2016, 2017
"Neuroimaging and Genetics"

Student representative, Cognitive, Computational, and Systems Neuroscience Mini-Retreat Committee — Spring 2014 – 2017

Community Member, Washington University Center for the Integration of Research, Teaching, and Learning (WU-CIRTL) — Spring 2014 – 2017

Student representative, Neuroscience Program Retreat Committee — Spring 2013 – 2017

Neuroscience Team Leader, Young Scientist Program — Summer 2012 – 2017
Organized volunteers and equipment for demonstrations at Washington University, St. Louis area schools, and public events, for students (K-12) and community members, reaching over 3,000 people.

Peer Mentor, BP-ENDURE St. Louis Neuroscience Pipeline — Summer 2016

Bench Mentor, BP-ENDURE St. Louis Neuroscience Pipeline — Summer 2015

Teaching Assistant, Systems Neuroscience — Spring 2014

Science Tutor, Young Scientist Program Summer Focus — Summer 2013

Volunteer, Youth Exploring Science — Summer 2012 – 2013
Weekend neuroscience experience for disadvantaged and minority high school students

Mentored undergraduate students

Chloé Ifrah*, Orma Ravindranath, Seth Margolis*, Daniel Sheinbein*, Patrick England, Samantha Kahn, Aline Desmarais*, Sid Dalal*, Kendall Sputo, William Pan, Corey Meehan, Sid Dalal.
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