DRD2 VARIATION AND FRONTOSTRIATAL MORPHOLOGY: GENETIC AND VOLUMETRIC PREDICTORS OF RESILIENCE TO SUBSTANCE USE DISORDERS

by

Sarah Lichenstein

B. A. in Psychology, Bard College, 2008

Submitted to the Graduate Faculty of

The Dietrich School of Arts & Sciences in partial fulfillment

of the requirements for the degree of

M. S. in Psychology

University of Pittsburgh

2013

UNIVERSITY OF PITTSBURGH

THE DIETRICH SCHOOL OF ARTS & SCIENCES

This thesis was presented

by

Sarah Lichenstein

It was defended on

September 4, 2013

and approved by

Shirley Hill, PhD, Professor

Stephen Manuck, PhD, Distinguished University Professor

Erika Forbes, PhD, Associate Professor

Thesis Advisor: Shirley Hill, PhD, Professor

DRD2 VARIATION AND FRONTOSTRIATAL MORPHOLOGY: GENETIC AND VOLUMETRIC PREDICTORS OF RESILIENCE TO SUBSTANCE USE DISORDERS

Sarah Lichenstein, M.S.

University of Pittsburgh, 2013

Individuals with a family history of alcohol dependence are at increased risk for all substance use disorders (SUDs). Common genetic, morphological, and personality characteristics are thought to contribute to the greater addiction susceptibility among this population. The identification of predictors of resilience to any SUD could improve our understanding of the etiology of addiction and guide future prevention and interventions efforts. Aberrant dopaminergic transmission and frontostriatal circuitry have been identified in substance dependent individuals and their unaffected relatives in association with greater impulsivity. Therefore, the current study sought to evaluate variation in the C957T polymorphism of the dopamine D2 receptor gene (SNP rs6277) and volume of the orbitofrontal cortex (OFC) and caudate nucleus as predictors of resilience to SUD among individuals at high familial risk and normal controls. Families with multiple cases of alcohol dependence, known as multiplex families, are ideal for studying disease-related genotypes and endophenotypes. The present study included offspring from multiplex alcohol dependence families and control families who received annual clinical diagnostic assessments, MRI scans, and provided blood samples for genotyping. Binary logistic mixed model regression analyses were conducted to quantify the relationships between genetic and morphological variation and SUD onset by age 20. The results revealed a significant association between C957T variation and resilience in young adulthood (p = .046). A risk by

gene interaction was also observed for OFC volume, such that among HR offspring only, DRD2 genotype was a significant predictor of total OFC volume (p = .034). The identification of mechanisms mediating the association between DRD2 variation and resilience to SUD could contribute to the development of future preventative interventions for high-risk individuals.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Alcohol and drug use disorders are prevalent neuropsychiatric conditions associated with a myriad of negative outcomes for affected individuals, their families, and communities (Hasin, Stinson, Ogburn, & Grant, 2007; Sullivan, 2007). Based on epidemiological data from 2002, Hasin et al. (2007) estimated the lifetime prevalence of alcohol abuse and dependence at 17.8% and 12.5%, and the lifetime prevalence of drug abuse and dependence at 7.7% and 2.6%, respectively. Alcohol and drug use disorders represent an enormous burden to society, leading to premature mortality (Mokdad, Marks, Stroup, & Gerberding, 2004; Neumark, Van Etten, & Anthony, 2000) increased rates of crime and incarceration (Volkow & Li, 2005), and massive annual costs to the healthcare system (Hasin et al., 2007). A better understanding of the etiological mechanisms supporting the development and maintenance of these conditions is essential for designing effective prevention and intervention strategies.

Alcohol and drug abuse and dependence, collectively referred to as substance use disorders (SUD), frequently co-occur (Hasin et al., 2007), and comorbidity significantly worsens the course of these disorders as well as their treatment prognosis (Ciraulo, Piechniczek-Buczek, & Iscan, 2003; Hasin et al., 2007; Rubio et al., 2008; Sullivan, 2007). Additionally, alcohol and drug abuse share a number of biological correlates, including morphological, functional, and neuroreceptor abnormalities, particularly within the dopamine (DA) system (Volkow & Li, 2005). Based on their similar clinical presentation, high comorbidity, and common

neurobiological characteristics, alcohol and drug use disorders have been proposed to share some mutual etiological pathways.

1.1 INTERGENERATIONAL TRANSMISSION OF RISK

Offspring of male (Hill, Shen, et al., 2008; Marmorstein, Iacono, & McGue, 2009) and female (Hill, Tessner, & McDermott, 2011) alcoholics are significantly more likely to develop both alcohol and drug use disorders than the general population. Therefore, research with children from affected families offers a unique opportunity to investigate premorbid risk factors for the development of psychopathology. The increased morbidity observed in this population is thought to result from a combination of genetic and environmental risk factors (Eiden, Edwards, & Leonard, 2007; Enoch, 2012; Hill, 2010; Hill, Steinhauer, Locke-Wellman, & Ulrich, 2009; Iacono, Malone, & McGue, 2003; Melchior, Choquet, Le Strat, Hassler, & Gorwood, 2011; Tessner & Hill, 2010). However, the manner in which these factors interact to increase the likelihood of developing SUD remains to be fully elucidated.

1.2 ENDOPHENOTYPES – INTERMEDIATE MARKERS OF RISK

A variety of genes have been implicated in alcoholism risk, relating to a broad array of functions (Conner, Hellemann, Ritchie, & Noble, 2010; Hill, Hoffman, et al., 2008; Hill, Wang, et al., 2011; Hill, Wang, et al., 2009; Hill, Weeks, Jones, Zezza, & Stiffler, 2012; Morozova, Goldman, Mackay, & Anholt, 2012; Tessner & Hill, 2010). However, given the complex nature of

psychiatric disorders, it is unlikely that single genes will be identified that can substantially explain individual susceptibility to mental illness. Therefore, much of the current research on the intergenerational transmission of risk has focused on intermediate phenotypes, or endophenotypes, that may be more directly related to variation in specific genes than the broader disease phenotype. Identifying measurable components that mediate the link between genetic variation and psychiatric outcomes may be a more fruitful approach to improving our understanding of the processes underlying the etiology of mental illness than pursuing specific genetic antecedents to individual disorders (Gottesman & Gould, 2003).

Component processes of decision-making have been frequently targeted as potential endophenotypes for SUD, as maladaptive decision-making is thought to be a primary contributor to both the initiation and maintenance of problematic substance use (Lucantonio, Stalnaker, Shaham, Niv, & Schoenbaum, 2012; Tessner & Hill, 2010). Impulsivity is one construct that is often implicated in poor-decision making and resultant risky behavior. Prior research has shown that impulsivity is heritable (Anokhin, Golosheykin, Grant, & Heath, 2011), predictive of substance use onset (Lukasiewicz et al., 2008) and significantly more common among substance abusers (Noel et al., 2011; Verdejo-Garcia, Perales, & Perez-Garcia, 2007) and their families (Hill, Zubin, & Steinhauer, 1990). Specifically, twin studies have estimated that 44% of variation in impulsivity is attributable to genetic influences, as measured by the control subscale of multidimensional personality questionnaire (MPQ; Tellegen et al., 1988). Therefore, a better understanding of the mechanisms underlying impulsive behavior could yield powerful insights into heritable etiological pathways to SUD.

Extensive data suggests structural and functional deficits are present in alcohol and drug dependent individuals (Volkow & Li, 2005). As first suggested by Hill et al. (2001), volumetric

aberrations may provide the structural underpinnings of behavioral characteristics that are typical of individuals with a family history of alcohol dependence. Therefore, neural abnormalities have also been examined as possible mechanisms through which genetic variation influences the likelihood of developing these disorders. Among high-risk (HR) offspring, morphological abnormalities have been reported in the amygdala (Benegal, Antony, Venkatasubramanian, & Jayakumar, 2007; Hill et al., 2001), cerebellum (Benegal et al., 2007; Hill, Wang, et al., 2011), orbitofrontal cortex (Hill, Wang, et al., 2009), superior frontal cortex, cingulate, parahippocampal gyri, and thalamus (Benegal et al., 2007). Moreover, there is evidence that structural variation also has a substantial influence on patterns of functional brain activation (Hermundstad et al., 2013; Honey, Thivierge, & Sporns, 2010; Johansen-Berg, 2009; Lu et al., 2009).

Beyond improving our understanding of the etiology of these conditions, the successful identification of endophenotypes for SUD also has implications for the development of prevention and intervention efforts. The discovery of measurable premorbid markers of vulnerability affords the opportunity to direct preventative efforts towards those at highest risk. Furthermore, uncovering modifiable characteristics that facilitate the disease process could unveil novel intervention targets to promote resilience among otherwise high-risk individuals. Thus, the discovery of endophenotypes for addiction has the potential to provide powerful insights into mechanisms supporting both risk and resilience.

1.3 INHIBITORY CONTROL

Executive functioning refers to a constellation of capacities that enable a person to successfully engage in independent, purposive, self-directed, and self-serving behavior (Lezak, Howieson, Bigler, & Tranel, 2012). Response inhibition is one facet of executive functioning that has a particularly significant impact on an individuals' ability to adapt their behavior to changing circumstances (Barnes, Dean, Nandam, O'Connell, & Bellgrove, 2011). Indeed, poor response inhibition, known alternatively as inhibitory control or effortful control, is considered a primary dimension of impulsivity (White, Lawford, Morris, & Young, 2009); it is robustly associated with risky, maladaptive behaviors, and has been reliably associated with substance use and abuse in both animal models and human populations (Izquierdo & Jentsch, 2012; Schulte, Muller-Oehring, Sullivan, & Pfefferbaum, 2012; Verdejo-Garcia et al., 2007). Thus, a better understanding of this trait may offer important insights into the pathophysiology of a common deficit across addictive disorders. Similarly, proficiency in inhibitory control may constitute a powerful resilience factor (Nederhof et al., 2010) that could help protect against the development of SUD among HR individuals.

1.3.1 Neurobiological basis of inhibitory control – orbitofrontal cortex

The orbitofrontal cortex (OFC) has been implicated in affect, inhibition, and decision-making (Menzies et al., 2008). In particular, evidence from both animal and human studies robustly supports the importance of this region for inhibitory control (Elliott & Deakin, 2005; Hill, Tessner, Wang, Carter, & McDermott, 2010; Izquierdo & Jentsch, 2012; Lawrence, Jollant, O'Daly, Zelaya, & Phillips, 2009; Price, 2007). Congruently, both structural and functional

abnormalities in this region have been reliably reported in individuals with SUD (Alia-Klein et al., 2011; Cardenas et al., 2011; Dom, Sabbe, Hulstijn, & van den Brink, 2005; Ersche et al., 2011; Moreno-Lopez et al., 2012), in association with inhibitory control deficits (Ersche et al., 2011; Hill, Wang, et al., 2009). Furthermore, volumetric variation in the OFC has also been shown to be a strong predictor of treatment response, highlighting the potential importance of obitofrontally-supported inhibition in resilience (Cardenas et al., 2011).

1.3.2 Poor inhibitory control – cause or consequence?

Despite findings that both neuropsychological and neurobiological markers of impaired inhibitory control are established correlates of addiction, the question remains of whether this characteristic represents a premorbid risk factor or a consequence of these disorders (Dawes et al., 2000). In animal models, rats who exhibit poor inhibitory control have been found to be more vulnerable to addiction (Izquierdo & Jentsch, 2012), and prospective human research has found that disinhibitory pathologies (Dawes et al., 2000; Hill, Steinhauer, et al., 2009; Hill, Tessner, et al., 2011) and their biological correlates (Iacono et al., 2003) often precede and predict subsequent SUD.

Additionally, Ersche and colleagues (2012) reported that non-abusing siblings of stimulant dependent individuals demonstrated inhibitory control deficits of a comparable magnitude to those of their affected siblings. Congruently, Hill et al. (2009) reported volumetric abnormalities in the OFC of non-substance abusing HR offspring, in addition to those who had developed SUD, which correlated with diminished self-reported effortful control capacity. Taken together, these finding strongly suggest that deficient inhibitory control represents a

heritable premorbid risk factor for addiction, underlain by morphological abnormalities in the OFC, which may represent a potential target for intervention.

1.4 NOVELTY SEEKING

Novelty seeking (NS) is a heritable temperamental trait originally defined in the context of Cloninger's psychobiological model of personality (Cloninger, Svrakic, & Przybeck, 1993). An individual characterized by high NS displays a bias towards "frequent exploratory activity in response to novelty, impulsive decision making, [and] extravagance in approach to cues of reward" (Cloninger et al., 1993, p. 977). High NS has been linked with greater impulsivity, deficient response inhibition as well as poor decision-making (Evren, Durkaya, Evren, Dalbudak, & Cetin, 2012; Lukasiewicz et al., 2008). Individuals with both alcohol and drug abuse/dependence display high levels of novelty seeking compared to control subjects (Chen, Chen, Du, Fan, & Zhao, 2008; Lukasiewicz et al., 2008; Noel et al., 2011) and high NS predicts a higher quantity of drinking, greater severity of dependence, and significantly poorer treatment prognosis (Evren et al., 2012).

1.4.1 Neurobiological basis of novelty seeking – the role of the caudate nucleus

Despite the relevance of novelty seeking to addiction, there is a relative paucity of research on its neurobiological basis. Since Cloninger's (1993) original conceptualization, NS has been supposed to depend on dopaminergic functioning. Indeed, dopaminergic gene variation has been found to predict individual differences in NS in some studies (Benjamin et al., 2000;

Demetrovics et al., 2010; J. Li et al., 2011; Nyman et al., 2009), though some have not been able to replicate this relationship (Hill, Zezza, Wipprecht, Locke, & Neiswanger, 1999). Specifically, there is evidence to suggest that D2 receptor availability in the striatum may influence variation in this characteristic (Bjork, Knutson, & Hommer, 2008; Cohen, Schoene-Bake, Elger, & Weber, 2009; Gjedde, Kumakura, Cumming, Linnet, & Moller, 2010; Huang et al., 2010; Leyton et al., 2002; Zald et al., 2008).

The dopamine (DA) system has long been thought to play a crucial role in the pathophysiology of addiction (Volkow & Li, 2005). In particular, DA D2 receptor abnormalities have been reported among current and past alcohol and drug users (Volkow & Li, 2005), as well as individuals at elevated risk for these conditions (Volkow et al., 2006). Although the precise nature of dopamine's contribution to the course of SUD remains unclear, variation within this system remains a primary candidate endophenotype for alcohol and substance abuse and dependence.

The caudate nucleus is a structure within the striatum that plays an important role in a range of different functions, including the control of approach, attachment, and goal-directed behaviors, as well as the assessment of incentive salience (Grahn et al., 2008; Villablanca, 2010). Therefore, hypofunctionality of this structure could presumably result in lesser sensitivity to the potentially negative consequences of approach behaviors, as well as overvaluation of the positive salience of possible outcomes. The caudate is also a rich source of dopaminergic projections to the cortex and is thought to be among the structures with the highest D2 receptor density, making it a vital contributor to the regulation of overall dopaminergic transmission in the brain (Kessler et al., 1993).

There is a growing body of literature demonstrating the importance of the caudate nucleus in alcohol and drug use disorders. Evidence from both translational and human studies have demonstrated associations between structural and neurochemical abnormalities in the caudate and substance use (Johansson & Hansen, 2002), dependence (Moreno-Lopez et al., 2012), and treatment prognosis (Wang et al., 2012).

1.4.2 Novelty seeking – cause of consequence?

There is a substantial body of literature supporting the notion that high novelty seeking represents a pre-existing risk factor for the development of psychopathology, not merely a correlate of substance use and abuse. Both animal and human studies have demonstrated that individuals characterized by high NS display significantly greater susceptibility to substance use and abuse based on a variety of indices (Belin, Berson, Balado, Piazza, & Deroche-Gamonet, 2011; Cummings et al., 2011; Pawlak, Ho, & Schwarting, 2008; Vidal-Infer et al., 2012). Furthermore, low NS was found to be protective among adolescents who were exposed to childhood family adversity (Fergusson & Lynskey, 1996). Therefore, NS appears to be a premorbid trait that significantly impacts risk for subsequent psychopathology.

Congruently, there is preliminary evidence to suggest that abnormalities in the caudate nucleus may also be present prior to the onset of psychopathology. A recent study found childhood maltreatment to be associated with reduced caudate volume, in the absence of any psychiatric disorders (Dannlowski et al., 2012). Because childhood abuse is one of the most robust predictors of later psychopathology, these finding suggest that caudal atrophy may represent an intermediate mediator of risk (Dannlowski et al., 2012). Further, Hill et al. (in press) found smaller caudate volume among HR offspring with externalizing disorders. Based

on the strong association between externalizing psychopathology and risk for SUD, these data further corroborate the contention that the caudate may play an important role in the etiology of addiction.

1.5 RATIONALE FOR THE INTEGRATION OF NS AND INHIBITORY CONTROL IN A RISK MODEL FOR SUD

Despite strong research support for the relationship between NS and alcohol dependence, some negative findings remain (Miettunen & Raevuori, 2012). Thus, it may be the case that this trait is not sufficient to independently predict problematic drinking behavior. Indeed, one study reported that NS was a significantly stronger predictor of outcome in subjects with at least one alcohol dependent parent than in controls with no family history (Grucza et al., 2006). Furthermore, studies of alcoholic individuals have found that high NS tends to co-occur with poor response inhibition and decision-making (Noel et al., 2011). Thus, it may be the combination of novelty seeking with other familial risk factors that renders individuals most vulnerable to addiction (Evren et al., 2012).

Poor decision-making and risky behaviors are especially common during adolescence, and this spike in impulsive behavior is thought to result in part from developmental variation in the brain (Blakemore & Robbins, 2012). During this time, the systems supporting novelty seeking and inhibitory control are naturally unbalanced (Steinberg, 2010). Whereas the capacity for impulse control increases with age in a linear fashion, sensation seeking appears to follow a quadratic developmental trajectory (Steinberg, 2010). Therefore, middle adolescence is characterized by a convergence of high sensation seeking and low impulse control, which,

combined with environmental factors such as low parental supervision and the availability of drugs of abuse, substantially increases the likelihood that these individuals will engage in risky behaviors (Steinberg, 2010). The co-occurrence of this surge in risky behaviors with this innate mismatch between these appetitive and inhibitory functions implies that variation in these characteristics may help to explain individual differences in addiction susceptibility across the lifespan. Congruently, an optimal balance between novelty seeking and inhibitory control may represent a resilient phenotype that is protective against the development of SUD.

1.6 RATIONALE FOR INTEGRATING THE OFC AND CAUDATE NUCLEUS INTO A MODEL OF DISEASE RISK

Just as the combination of high NS and low inhibitory control is likely to be a stronger predictor of SUD outcome than either construct independently, an examination of the functional relationships between frontostriatal structures is likely to yield a more comprehensive understanding of related behaviors than a consideration of either structure in isolation. Indeed, many researchers have shifted away from examining individual structures toward the study of neural circuits and their concomitant behavioral analogues (Galvan et al., 2006; R. C. Gur, Gunning-Dixon, Bilker, & Gur, 2002; R. E. Gur et al., 2004).

For example, Gur and colleagues (2002) found that women displayed a greater ratio of OFC to amygdala volume, compared to their male participants. These findings suggest that female subjects possess a greater amount of frontal tissue to regulate input from the amygdala, which may partially explain sex-differences in emotional regulation, and aggression in particular. Similarly, Galvan et al. (2006) found that whereas adolescents displayed a pattern of striatal

activation that closely resembled adults, their OFC activity paralleled childhood functioning. These data support the notion that poor decision-making in adolescence is reflective of a suboptimal developmental state in which appetitive systems are more developed than the control systems necessary to regulate them. These findings strongly support the utility of examining the balance between systems to better understand behavior, as well as substantiating the importance of frontostriatal development in reward-based decision-making.

1.6.1 Relationship between OFC and caudate nucleus

There is evidence to suggest that interactions between the caudate nucleus and the OFC play an important role in regulating decision-making processes (Finger et al., 2011; Grahn et al., 2008; Semrud-Clikeman et al., 2000; Soriano-Mas et al., 2013). Disruptions of connectivity between these regions have been shown to impact inhibitory control, reversal learning, as well as the assessment of response contingencies (Grahn et al., 2008). There is evidence to suggest that the caudate regulates OFC activity via two dopaminergic signaling pathways with opposing effects (Colzato, van den Wildenberg, Van der Does, & Hommel, 2010). According to this view, D1 receptor-mediated neurotransmission supports reward-seeking actions, whereas D2 receptor activity facilitates the avoidance of non-rewarding actions (Colzato et al., 2010). Thus, D2 receptor activity in the caudate may contribute directly to the suppression of disadvantageous responses in favor of new adaptive strategies (Colzato et al., 2010; Grahn et al., 2008).

Striatal D2 receptor density has been found to be positively associated with brain activity in the OFC (Ghahremani et al., 2012; Volkow et al., 2006) and response inhibition, providing further support for the notion that the caudate modulates “frontal” functioning through dopaminergic transmission (Ghahremani et al., 2012). Therefore, there is likely to be an

interaction between OFC and caudate functioning in predicting SUD outcomes, both based on each structure's involvement in complimentary appetitive and inhibitory processes, as well as their mutual regulatory influence via frontostriatal dopaminergic transmission.

Extant literature has implicated abnormalities within this frontostriatal DA system in SUD. Specifically, low D2 receptor availability has been reported in alcohol-preferring rodents (Swagell et al., 2012), and systemic D2 agonism has been shown to reduce alcohol consumption in this population (Dyr, McBride, Lumeng, Li, & Murphy, 1993; Swagell et al., 2012). In human subjects, low D2 binding has been associated with greater drug reinforcing effects (Volkow et al., 1999), increased craving for alcohol (Heinz et al., 2005) and greater likelihood of relapse among recovering addicts (Swagell et al., 2012).

1.7 FRONTOSTRIATAL ABNORMALITIES IN HR OFFSPRING

Preliminary research in HR populations supports the suggestion that altered frontostriatal dopaminergic signaling may represent an important etiological pathway to SUD. For example, one study found that whereas individuals without a family history of alcohol use disorders displayed deactivation in the ventral caudate during successful inhibition, HR subjects did not, reflecting a possible premorbid bias towards motivational responding among HR individuals (Heitzeg, Nigg, Yau, Zucker, & Zubieta, 2010). Although a second study failed to detect group differences in striatal activity during a similar experimental paradigm (Bjork et al., 2008), Ivanov et al. (2012) found that HR children with ADHD displayed significantly greater activity in the caudate head, left OFC, as well as the left insula cortex during reward anticipation as well as greater left OFC activation upon reward receipt compared to children with ADHD who lacked a

family history of SUD. Together, these findings suggest that greater sensitivity of frontostriatal reward circuitry may be a predisposing factor for the development of SUD.

1.8 FRONTOSTRIATAL DOPAMINE TRANSMISSION AND RESILIENCE

In an effort to identify factors that may protect individuals from developing SUD, a small number of studies have looked at whether there are certain neurobiological characteristics that distinguish HR individuals who are resilient to the development substance use problems from those who succumb. Volkow and colleagues (2006) reported significantly greater striatal D2 receptor availability among nonalcoholic HR offspring, which was positively correlated with metabolism in the OFC, compared to individuals without a family history of AUD. Similarly, Heitzeg et al. (2008; 2010) reported distinct patterns of orbitofrontal activation among resilient children of alcoholics during successful inhibition and emotion processing, compared to affected offspring. Together, these data suggest that hyperfunctionality of the frontostriatal dopamine system may represent a protective factor among individuals who are otherwise at high risk for SUD.

1.9 GENETIC INFLUENCES

By definition, endophenotypes are heritable characteristics (Gottesman & Gould, 2003). The merit of the endophenotype concept lies in its ability to help bridge the gap between genotype and phenotype by uncovering specific etiological pathways to diseases with complex genetics.

Thus, in order to uncover viable endophenotypes for SUD, the aim is to identify mechanisms that are at least partially genetically determined.

Although the current discussion has covered multiple phenotypes with various biological underpinnings, i.e. novelty seeking, poor response inhibition, frontostriatal structure, function, and neurochemistry, there is evidence to suggest that these characteristics tend to be inherited together. Thus, there is reason to assume that this constellation of risk factors shares some genetic antecedents. For example, in a strain of rats bred for high novelty seeking behavior, Flagel et al. (2010) reported a significantly higher degree of behavioral disinhibition, less overall striatal D2 mRNA, and greater sensitivity to D2 receptor agonism, compared to their low novelty seeking counterparts. These findings robustly substantiate the idea that high novelty seeking and poor inhibitory control are genetically linked characteristics, which are partially mediated by dopaminergic functioning in the striatum. Therefore, genetic determinants of D2 receptor function represent likely candidate precursors to this cluster of risky traits.

Indeed, variation in the D2 receptor gene (DRD2) has been associated with risk for SUD in human subjects (Noble, 2003). The C957T polymorphism (SNP rs6277) of the DRD2 gene is one source of D2 variation that has received substantial empirical attention (Hill, Hoffman, et al., 2008). Genotypic variation at this site, evidenced by a C/T substitution, has been found to explain 18% of the variance in striatal D2 receptor density (Hirvonen et al., 2004, 2005). In vivo, the C/C genotype is associated with the lowest striatal D2 binding, T/T carriers exhibit the highest level of binding, whereas heterozygotes are characterized by intermediate D2 receptor expression (Hirvonen et al., 2004, 2005).

Functionally, some authors have reported a positive relationship between the T/T variant and neurocognitive functioning in healthy individuals (Frank, Moustafa, Haughey, Curran, &

Hutchison, 2007; Rodriguez-Jimenez et al., 2006; Swagell et al., 2012; White et al., 2009). However, other findings indicate that T/T homozygotes display significantly worse behavioral inhibitory efficiency, as well as higher dysfunctional impulsivity (Colzato et al., 2010). One hypothesized explanation for these discrepant findings posits that there may be a quadratic relationship between dopaminergic activity and performance, such that both excessive and deficient dopaminergic transmission may have disadvantageous effects (Colzato et al., 2010).

C957T variation has also been linked with SUD outcome (Hill, Hoffman, et al., 2008; Swagell et al., 2012). A case/control study detected an association between the C-allele and alcohol dependence, whereas a within-family linkage study found the T-allele to confer greater risk. This discrepancy may be a further reflection of a non-linear relationship between D2 receptor density and function. Furthermore, Hirvonen et al. (2009) have reported opposing effects of C957T genotype on striatal and extrastriatal D2 receptor density, making it difficult to predict the behavioral consequences of allelic variation. Additionally, interplay with the environment may be partially responsible for these inconsistencies. Gene-by-environment interactions have been reported for reward sensitivity, delay discounting (White et al., 2009), as well as cigarette smoking (Perkins et al., 2008). Thus, the result of C957T variation may be partially dependent on contextual factors.

DA is critical for early brain development (Andersen, 2003), and there is reason to question whether functional variation in the C957T polymorphism may be associated with gray matter changes in the brain. Studies have found that various other genes thought to influence the quantity of D2 receptors are related to volumetric variation (Chakravarty et al., 2012; Montag, Weber, Jentgens, Elger, & Reuter, 2010). Although the relationship between C957T and morphology has not been studied, this polymorphism has been linked with neuropsychological

functions known to be closely related to brain volume, such as working memory (Ding, Qin, Jiang, Zhang, & Yu, 2012; Pangelinan et al., 2011; Xu et al., 2007). Because morphology represents a phenotype that is more proximal to genetic variation than behavior, and comparatively less susceptible to environmental influences, elucidating the intermediate effects of C957T variation on brain volume may help disentangle some of the discrepancies in the current literature regarding the downstream effects of the DRD2 gene on psychopathology.

The current study aimed to contribute to the growing literature on the underlying mechanisms of intergenerational transmission of risk for SUD. Based on extant data demonstrating the importance of the frontostriatal dopamine system for adaptive decision-making and substance use outcomes, it was hypothesized that morphological variation within this system might provide the ability to discriminate HR offspring who ultimately develop SUD from those who are resilient. It was further hypothesized that variation within the rs6277 SNP of the DRD2 gene might influence both frontostriatal brain volumes and the likelihood of resilience to SUD in young adulthood. By elucidating genetic, neurobiological, and behavioral markers of risk, it may be possible to unveil novel intervention targets to foster resilience among individuals at high risk for SUD.

2.0 METHODS

2.1 SAMPLE

2.1.1 Recruitment

The sample included in the current analyses represents a subset of participants in an ongoing longitudinal study in which offspring from families with a high density of alcoholic members are compared with offspring from control families. HR families were selected based on an adult proband pair of alcohol dependent brothers. Targeted families were excluded if either member of the proband pair, or any first-degree relative, had a primary diagnosis of recurrent Major Depressive Disorder (MDD), Bipolar Disorder (BD), Primary Drug Dependence (PDD) or Schizophrenia by DSM-III criteria based on the Diagnostic Interview Schedule (DIS) (Robins, Helzer, Croughan, & Ratcliff, 1981). Offspring of the proband pair and their siblings were eligible for the longitudinal follow-up. Accordingly, not all HR offspring were the children of alcoholics though they had a significantly higher density of familial alcohol dependence through aunts, uncles and grandparents (an average of four first- and second-degree relatives). Control families were selected for a proband pair of same-sex adult siblings. Probands and their first-degree relatives were free of any Axis I psychopathology according to the DIS.

All offspring were eligible for participation in the MRI portion of the study. Subjects were sent letters describing the adjunctive study procedures, and respondents were screened for the presence of ferromagnetic metal in or on their body. Female subjects were also screened for pregnancy using Icon 25 hCG (Beckman Coulter, Fullerton, California) pregnancy kits.

2.1.2 Offspring assessments

Each child/adolescent offspring received an annual clinical assessment for DSM-III diagnoses using the Schedule for Affective Disorders and Schizophrenia (K-SADS) until age 19 (Chambers et al., 1985). Thereafter, annual clinical follow-ups included the Composite International Diagnostic Interview (CIDI; Janca, Robins, Cottler, & Early, 1992) to determine the presence or absence of DSM-IV diagnoses and the CIDI-Substance Abuse Module (CIDI-SAM; Cottler, Robins, & Helzer, 1989) to measure the quantity, frequency and pattern of substance use. Interrater reliability for diagnostic instruments exceeded 90%.

2.2 MEASURES

Trail Making Test (TMT; Reitan, 1971; Tombaugh, 2004). The Trail Making Test is a widely used neuropsychological test that consists of 2 parts, A and B, which has been shown to have adequate test-test reliability (Matarazzo, Wiens, Matarazzo, & Goldstein, 1974). Part A measures the speed of cognitive processing whereas performance on Part B reflects executive functioning capacity (Sanchez-Cubillo et al., 2009). The difference score (Trails B-A) is thought to be a relatively pure measure of cognitive control, and correlates with a variety of other tests of

executive control capacity (Chaytor, Schmitter-Edgecombe, & Burr, 2006; Sanchez-Cubillo et al., 2009).

The Stroop Color and Word Test (Golden, 1978). The Stroop Color and Word Test has been used in numerous studies to measure the effectiveness of focused attention and inhibitory control (Lezak et al., 2012). This measure yields three scores based on the number of items completed on each of three stimulus sheets, and displays adequate test-retest reliability (Franzen, Tishelman, Sharp, & Friedman, 1987). An Interference score, included in the current analyses, is thought to reflect the ability to inhibit overlearned or prepotent responses in the face of conflicting information (Savitz & Jansen, 2003).

Multidimensional Personality Questionnaire (MPQ; Tellegen et al., 1988). The MPQ is a self-report instrument that measures 11 primary personality dimensions and 3 higher-order factors along with 3 validity scales. The current analyses included the primary trait dimension of Control. Individuals with high scores on this scale describe themselves as reflective, cautious, careful, plodding, rational, sensible, level-headed, and liking to plan activities in detail. Scales from the MPQ show high heritability based on studies of twins reared apart. MPQ personality traits have been found to be reliable over time, with 30-day test-retest correlations ranging from .82-.92. Previous studies have shown low Control Scale scores among alcohol dependent individuals (Hill, Zubin, & Steinhauer, 1990) and individuals with drug use disorders (McGue, Slutske, & Iacono, 1999).

Tridimensional Personality Questionnaire (TPQ; Cloninger, 1987). The TPQ is a self-report instrument, which measures 3 dimensions: Harm Avoidance, Novelty Seeking and Reward Dependence. The current analyses incorporated scores on the Novelty Seeking (NS) subscale. An individual who has high scores on this dimension is thought to have a tendency

toward frequent exploratory activity and intense exhilaration in response to novel or appetitive stimuli (Cloninger, 1987). The NS subscale has been shown to have high internal consistency (Miettunen et al., 2004) and good test-retest reliability (Kuo, Chih, Soong, Yang, & Chen, 2004).

Diagnostic Interview Schedule (DIS; Robins et al., 1981). The DIS is a highly structured interview that assesses alcohol dependence and other Axis I psychiatric diagnoses according to DSM-III criteria, which has demonstrated very good test-retest reliability.

Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS; Chambers et al., 1985). The K-SADS is a semi-structured diagnostic interview that assesses current and prior episodes of psychopathology in children and adolescents according to DSM-III criteria, which has been demonstrated to have acceptable test-retest reliability.

Composite International Diagnostic Interview (CIDI; Janca et al., 1992). The CIDI is a fully structured interview that assesses the presence, severity, and treatment of psychiatric disorders according to both DSM-IV and International Classification of Disease (ICD) criteria, which has been shown to have good diagnostic concordance with clinical assessments.

Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM; Cottler et al., 1989). The CIDI-SAM is an expanded version of the substance abuse section of the CIDI that includes a more detailed assessment of the onset, symptomatology, consequences, and pattern of substance usage, including the quantity and frequency of use in the past 12 months. This measure has been shown to have very good test-retest reliability.

Four Factor Index of Social Status (Hollingshead, 1975). The Hollingshead Four Factor Index of Social Status is a measure of socioeconomic status based on education, occupation, sex, and marital status. SES scores were computed for each offspring at the time of study entry.

Drinking During Pregnancy (DDP) Questionnaire. The DDP is a structured interview designed to assess the quantity and frequency drug and alcohol use during pregnancy, which was administered to mothers of high- and low-risk offspring at their first clinical assessment (Hill, unpublished). Prior research has demonstrated retrospective reports of drinking during pregnancy to be reliable when compared to information obtained contemporaneously (Jacobson et al., 1991).

Magnetic resonance imaging. Subjects were scanned on a GE 1.5 Tesla scanner in the Department of Radiology MR Research Center. T1-weighted, T2-weighted, and axial proton density images were obtained. Regions of interest were drawn using BRAINS2 (Magnotta et al., 2002), a program that uses a semiautomated segmentation approach to provide reliable and valid structural volumetric measurements. Two raters who were blind to subject identity and risk group status traced the volumes of the OFC, caudate, and intracranial volume (ICV) according to the guidelines established by Lacerda et al. (2003) and Looi et al. (2008) (Hill, Wang, et al., 2009).

Genotyping. DRD2 genotyping was completed in house by project technicians using SNP rs6277 analyzed on the Biotage PSQ 96MA Pyrosequencer (Biotage AB, Uppsala, Sweden). An amplimer containing the polymorphism was generated by PCR in 96-well plates in a 50 uL total reaction volume, containing 10 ng of human genomic DNA; 1X GeneAmp® PCR Gold Buffer; 2.5 mM magnesium chloride; 200 uM dNTPs; 1 unit of AmpliTaq Gold™ taq polymerase; and 1 pmol of each of the unmodified forward primer 5'-CACCACGGTCTCCACAGCA-3' and the biotinylated reverse primer 5'-GGGCATGGTCTGGATCTCAAA-3'. Thermal cycling included 45 cycles at an annealing temperature of 60 degrees. The Biotage workstation was used to isolate the biotinylated single

strand from the double strand PCR products. The isolated product was then sequenced using the complimentary sequencing primer 5'-GGTCTCCACAGCACTC-3'. At the polymorphic site, the minor allele was detected by the presence of a C nucleotide whereas the major allele was detected by the presence of a T nucleotide.

2.3 DATA ANALYSIS

In order to assess whether variation in the DRD2 gene and frontostriatal brain structure predict resilience to SUD, a series of mixed model regression analyses were performed to test each of the pathways depicted in Figure 1, labeled a-f. Due to the nested nature of the current dataset, a family identifier was incorporated into each model as a random effects variable to account for the presence of multiple siblings from the same family. Prior to testing the primary hypotheses, data were explored to assess the normality of the dependent variables, and an exploratory survival analysis was conducted to determine the age at which subjects would be classified as either resilient to, or affected by SUD.

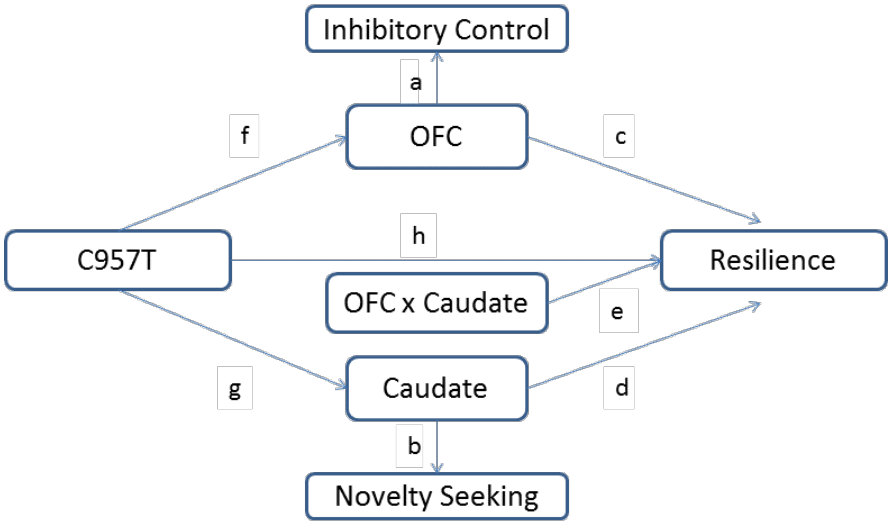

Figure 1. Heuristic model of pathways of interest. Labels a-f correspond to the statistical hypotheses tested.

2.3.1 Statistical hypotheses

2.3.1.1 Behavioral hypotheses

- Greater total OFC volume will predict better performance on the Trail Making Test, the Stroop Color/Word Interference Task, and greater MPQ Control scores (a).
- Greater total caudate volume will predict lower TPQ novelty seeking (b).

2.3.1.2 Morphological hypotheses

- Larger total volumes of the OFC (c) and caudate nucleus (d) will be associated with a greater likelihood of resilience in young adulthood.

- The relationship between OFC volume and resilience will vary as a function of caudate volume (e).

2.3.1.3 Genetic hypotheses

- Variation within the rs6277 SNP will be associated with OFC (f) and caudate (g) volume.
- rs6277 variation will predict adolescent-onset SUD (h).

2.3.2 Behavioral analyses

In order to substantiate the presumed relationship between OFC morphology and inhibitory control (a) as well as that between caudate volume and NS (b), a series of generalized linear mixed model (GLMM) analyses were conducted, allowing for the inclusion of continuous predictor variables. Outcome variables were tested in separate models and scores were included as continuous measures.

Additionally, risk, intracranial volume (ICV), gender, age, and prenatal substance exposure were entered as covariates in each regression model. Prior research has identified a variety of neurocognitive deficits among HR offspring that are thought to result from an array of biological and environmental factors that cluster within families with a high density of alcoholic members (Hill, 2010; Tessner & Hill, 2010). Therefore, risk was included as a factor in an effort to isolate the variance attributable to OFC and caudate volume from the known effects of familial risk. ICV was included to partial out the effects of the regions of interest from overall brain size.

Because adolescence is known to be a time during when the brain is undergoing widespread regional developmental changes (Giedd et al., 2009), and specific regions appear to

progress at differing rates in males and females (Hedman, van Haren, Schnack, Kahn, & Hulshoff Pol, 2012), age and gender were also tested as covariates. Finally, the possible influence of prenatal exposure was included in the statistical analysis plan, as it has been shown to impact morphology of both the OFC (Walhovd et al., 2007) and the caudate (Eckstrand et al., 2012). Covariates that failed to have a significant effect on the target variable were dropped from the final models to maximize power, with the exception of ICV.

2.3.3 Defining resilience

The decision of who to categorize as "resilient" is a complex one. Because the sample was, on average, relatively young at the time that MRI and neuropsychological assessments were done, incomplete knowledge of their ultimate SUD status cannot be known (HR M=18.1 SD=4.2; LR M=17.6 SD=5.8). Accordingly, it is not possible to determine whether those subjects who have not yet developed SUD will do so over the course of their lifetime. However, though the sample is fairly young, the base-rate of SUD is relatively high due to the ascertainment schema used to select the original set of families. Consequently, an early onset of substance use disorder has already been seen (Hill, Steinhauer, et al., 2009; Hill, Tessner, et al., 2011). Presently, 39% of the sample met criteria for SUD by the time of their last follow-up assessment, resulting in sufficient power to test the proposed hypotheses. Furthermore, a robust literature has demonstrated that early onset of substance abuse drastically increases the risk for lifetime SUD (Grant & Dawson, 1997; Hill, Steinhauer, et al., 2009), and profoundly worsens the prognosis for treatment (Evren et al., 2012; MacPherson, Magidson, Reynolds, Kahler, & Lejuez, 2010; Nees et al., 2012). Therefore, the identification of predictors of resilience among this population is of great clinical value.

Subjects in the larger cohort were enrolled between the ages of 8-13 years and have been followed to an average age of 24 years. The sub-sample for which MRI data was available also included a predominantly younger group most of whom were enrolled under the age of 14 and have been followed at least until age 20. Nonetheless, there is some variation in the amount of time that participants have been followed as well as their age at their last clinical assessment. Therefore, in order to select a distinct time point to use as the threshold for resilience, an exploratory Kaplan-Meier (1958) survival analysis was conducted to determine the 25th, 50th, and 75th percentile for age of SUD onset. This information allowed for the creation of a data-driven bivariate definition of resilience that maximized the number of cases that could be included. Because half of the sample was recruited based on risk status, there were sufficient participants in both the resilient and affected categories to conduct the subsequent analyses.

2.3.4 Morphological analyses

Binary logistic mixed model regression analyses were conducted to explore the independent and interactive effects of OFC and caudate structure on SUD outcome. Because HR offspring are significantly more likely to develop SUD than the general population (Hill, Steinhauer, et al., 2009; Hill, Tessner, et al., 2011), all models predicting resilience included risk status as a factor to assess whether the study variables account for variance in outcome beyond the influence of family history. Separate models were constructed to quantify the effects of OFC (c) and caudate (d) volume, as well as their interaction (e). ICV, gender, age, and prenatal exposure were included as covariates.

2.3.5 Genetic analyses

A final series of mixed models were constructed to measure the effect of DRD2 variation on the intermediate phenotype of frontostriatal brain structure, as well as the downstream clinical phenotype of resilience. Additive and dominant models of genetic influence were tested. For the dominant model, each subject was classified based on whether or not they possess *any* minor (C) alleles in the rs6277 SNP. To address the effect of genetic variation on brain structure, linear mixed models were constructed with DRD2 as the predictor variable, covarying risk, ICV, age, gender, and prenatal exposure, with OFC (f) and caudate (g) volumes as separate continuous outcome variables.

Finally, to examine the influence of DRD2 variation on the likelihood of resilience in young adulthood (h), binary logistic mixed models were constructed with gene variation and risk status as predictors, covarying for gender. The direction of the associations between rs6277 variation and both morphology and outcome remains exploratory based on the conflicting literature in this domain. Nonetheless, there is ample data to support the notion that an effect of this polymorphism is present. All statistical analyses were conducted with IBM SPSS Statistics for Windows, Version 20. Armonk, NY: IBM Corp.

3.0 RESULTS

3.1 SAMPLE CHARACTERISTICS

A total of 130 participants were included in the current analyses, including 71 HR subjects and 59 low-risk (LR) individuals. The HR and LR groups did not differ significantly in gender, scan age, age at study entry, age at last follow-up or length of clinical follow-up. Based on mean levels of socioeconomic status (SES), subjects in the HR group had a significantly lower SES at the time of study entry. However, this may not represent a meaningful difference because the mean SES of both risk groups corresponds to the same Hollingshead social stratum, representing medium business, minor professional and technical workers. Nonetheless, SES was tested as a covariate and found to be non-significant in all of the subsequent analyses. See Table 1 for sample characteristics.

Table 1. Sample Characteristics

	Whole Sample (N=130)		High-Risk (N=71)		Low-Risk (N=59)		HR vs. LR	
	N	%	N	%	N	%	χ^2	*p*
Males	65	50	38	53.5	27	45.8	0.776	NS
Right-Handed	123	94.6	68	95.8	55	93.2	0.413	NS
	M	*SD*	*M*	*SD*	*M*	*SD*	*t*	*p*
SES[a]	43.18	10.553	41	11.25	45.76	9.09	-2.611	**0.01***
Scan Age	17.93	4.981	18.21	4.2	17.59	5.8	0.683	NS
Age at Study Entry	11.59	3.454	11.21	3.29	12.05	3.62	-1.385	NS
Age at Last Follow-up	22.7	4.943	22.97	4.53	22.37	5.42	0.686	NS
Length of Follow-up	11.1	5.92	11.76	5.96	10.32	5.82	1.385	NS

Note. SES = socioeconomic status (Hollingshead Four Factor Index)
[a]N=129; HR N=70, LR N=59.
*p < .05, **p < .01.

Thirty-nine percent (N=51) of study participants met criteria for alcohol or drug abuse or dependence by their last follow-up assessment. Table 2 presents outcome data on each substance use diagnosis for the entire sample as well as for each risk group. As expected, HR offspring exhibited a higher incidence of substance-related pathology, with statistically significant disparities observed for every disorder except drug dependence.

Table 2. Lifetime Substance Use Diagnoses among High- and Low-Risk Participants

	Whole Sample (N=130)			High-Risk (N=71)			Low-Risk (N=59)			High-Risk vs. Low-Risk					
	Alcohol	Drug	SUD	Alcohol	Drug	SUD	Alcohol	Drug	SUD	Alcohol		Drug		SUD	
	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	χ^2	p	χ^2	p	χ^2	p
Any	33.8 (44)	23.1 (30)	39.2 (51)	45.1 (32)	31 (22)	52.1 (37)	20.3 (12)	13.6 (8)	23.7 (14)	8.802	**.003****	5.513	**.019***	10.89	**.001****
Abuse	23.1 (30)	17.7 (23)	30.8 (40)	35.2 (25)	26.8 (19)	45.1 (32)	8.5 (5)	6.8 (4)	13.6 (8)	12.98	**.000****	8.834	**.003****	15.02	**.000****
Dependence	23.8 (31)	16.2 (21)	28.5 (37)	31 (22)	21.1 (15)	36.6 (26)	15.3 (9)	10.2 (6)	18.6 (11)	4.391	**.036***	2.856	0.091	5.114	**.024***

Note. SUD = substance use disorder.

*p < .05, **p < .01.

3.2 BEHAVIORAL ANALYSES

3.2.1 Task performance

Summary statistics on participants' performance on the MPQ Control subscale, TMT, Stroop Task, and TPQ novelty seeking subscale are presented in Table 3. Significant differences between HR and LR participants were seen in temperament measures of inhibitory control and novelty seeking, with HR subjects characterized by lower self-reported inhibitory control capacity ($t(90) = -3.333$, $p = .001$) and higher novelty seeking ($t(68) = 2.115$, $p = .038$). No significant risk-group differences in behavioral task performance were observed.

Table 3. Mean Inhibitory Control and Novelty Seeking Scores among High- and Low-Risk Participants

	Whole Sample			High-Risk (HR)			Low-Risk (LR)			HR vs. LR	
	N	*M*	*SD*	N	*M*	*SD*	N	*M*	*SD*	*t*	*p*
MPQ Control	92	14.34	4.92	49	12.82	4.61	43	16.07	4.74	-3.333	**0.001****
TMT B-A	114	21.98	15.52	62	24.06	16.83	52	19.5	13.56	1.574	NS
Stroop Interference	62	53.23	10.33	38	52.05	9.88	24	55.08	10.97	-1.127	NS
TPQ Novelty Seeking	70	17.43	4.85	38	18.53	4.96	32	16.13	4.441	2.115	**0.038***

Note. MPQ = Multidimensional Personality Questionnaire; TMT = Trail Making Test; TPQ = Tridimensional Personality Questionnaire.
*p < .05, **p < .01.

3.2.2 Volumetric data

Structural MRI data for the OFC, caudate nucleus and total ICV are summarized in Table 4. As previously reported (Hill, Wang, et al., 2011), HR offspring had significantly larger total ICV than low-risk subjects ($t(128) = 3.348$, $p = .001$). No other significant volumetric differences were observed between risk groups.

Table 4. Volumetric Data for the Orbitofrontal Cortex, Caudate Nucleus and Total Intracranial Volume

	Whole Sample (N=130)		High-Risk (N=71)		Low-Risk (N=59)		HR vs. LR	
	M	*SD*	*M*	*SD*	*M*	*SD*	*t*	*p*
Total OFC Volume[a]	27.02	6.37	27.58	5.82	26.34	6.98	1.101	0.273
Total Caudate Volume	9.54	1.27	9.7	1.42	9.35	1.04	1.631	0.105
Total ICV	1392.24	129.6	1425.63	124.37	1352.05	125.22	3.348	**.001****

Note. OFC = orbitofrontal cortex; ICV = intracranial volume.
[a]N = 129; LR N = 58.
*p < .05, **p < .01.

3.2.3 Brain-behavior correlations

Bivariate Pearson correlations were calculated to explore interrelationships within the behavioral measures as well as their associations with the brain volumes of interest. As expected, significant intercorrelations were observed between the inhibitory control measures (MPQ Control, TMT, and Stroop), and a significant negative association between temperamental inhibitory control and novelty seeking was observed ($r = -0.722$, $p = .000$). Additionally, a

significant correlation was found between total caudate volume and novelty seeking (r = 0.356, p = .002), such that larger volume of the caudate nucleus was associated with greater self-reported novelty seeking. Correlation results are summarized in Table 5.

Table 5. Inter-correlations between Impulsivity Measures and Frontostriatal Brain Volumes

	TMT B-A	Stroop	NS	OFC	Caudate
MPQ Control	-0.156	**.299***	**-0.722****	-0.145	-0.177
TMT B-A		**-.349****	0.095	0.004	-0.148
Stroop Interference			0.1	-0.231	0.121
TPQ Novelty Seeking				0.144	**.356****
Total OFC Volume					0.118

Note. Pearson bivariate correlations. MPQ = Multidimensional Personality Questionnaire; TMT = Trail Making Test; TPQ = Tridimensional Personality Questionnaire; OFC = orbitofrontal cortex.
*p < .05, **p < .01.

3.2.4 Regression analyses

3.2.4.1 OFC volume and inhibitory control

No main effect of total OFC volume on any of the inhibitory control measures was observed. Removal of individuals who met criteria for SUD prior to their MRI scan (N=17) did not change the pattern of results (data not shown). The final models are summarized in Table 6.

Table 6. Regression Analyses of the Relationship between OFC Volume and Inhibitory Control

	Model 1 - MPQ Control			Model 2 - Stroop			Model 3 - TMT B-A		
	Est.	*SE*	*p*	Est.	*SE*	*p*	Est.	*SE*	*p*
Total OFC	-0.117	0.099	0.241	-0.353	0.294	0.235	0.378	0.323	0.245
ICV	0.002	0.006	0.689	-0.004	0.013	0.744	-0.028	0.017	0.094
Risk	-2.958	1.224	**0.018***		NS			NS	
Prenatal Alcohol Exposure	-0.04	0.017	**0.024***		NS		0.186	0.069	**0.009****
Scan Age		NS			NS		1.085	0.325	**0.001****

Note. Generalized linear mixed model analyses. MPQ = Multidimensional Personality Questionnaire; TMT = Trail Making Test; OFC = orbitofrontal cortex; ICV = intracranial volume.
*p < .05, **p < .01.

3.2.4.2 Caudate volume and novelty seeking

A highly significant association was observed between volume of the caudate nucleus and self-reported novelty seeking (B = 1.541, p = .002). Risk status was also a significant predictor of novelty seeking (B = 2.762, p = .031), but no significant risk by caudate interaction was found. These results remained significant when individuals meeting criteria for SUD prior to scanning were removed. Model statistics are summarized in Table 7.

Table 7. Regression Analysis of the Relationship between Caudate Volume and Novelty Seeking

	TPQ Novelty Seeking		
	Est.	*SE*	*p*
Total Caudate Volume	1.541	0.473	**0.002****
ICV	-0.005	0.005	0.309
Risk	2.762	1.256	**.031***

Note. Generalized linear mixed model analyses. TPQ = Tridimensional Personality Questionnaire; ICV = intracranial volume.
*p < .05, **p < .01.

3.3 MORPHOLOGICAL ANALYSES

3.3.1 Defining resilience

A Kaplan-Meier (1958) survival curve for age at SUD onset is presented in Figure 2. The results showed that of the 51 individuals who had a SUD diagnosis by the time of their last follow-up assessment, 25.5% met criteria by age 17, 51.0% met criteria by age 18, and 78.4% met criteria at age 20. Based on these data, absence of any SUD diagnosis by age 20 was selected as the criterion to categorize subjects as resilient to SUD. The use of this timepoint allowed for the inclusion of the maximum number of SUD cases and minimal elimination of subjects with insufficient follow-up.

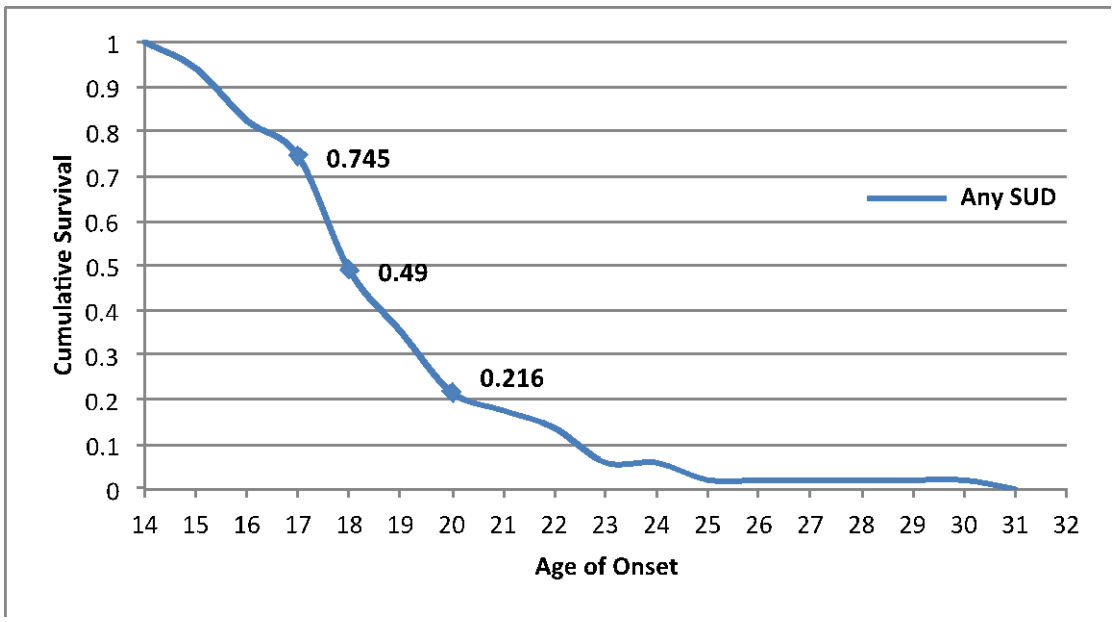

Figure 2. Kaplan-Meier survival analysis of SUD onset. Highlighted data points correspond to the ages at which 25.5%, 51%, and 78.4% of those who would eventually meet criteria developed SUD.

A subset of 94 subjects who had completed at least one young adult follow-up and made it to age 20 was included in subsequent analyses. The subsample was characterized by an older mean scan age, older mean age at last follow-up, and longer length of follow-up compared to the full sample. However, the subsample did not differ in any other demographic or morphological characteristics (See Table 8 for subsample characteristics).

Table 8. Summary Characteristics of Subsamples with Genetic and Clinical Follow-up Data and Comparisons to Full Dataset

	Whole Sample (N=130)		Subsample with Age 20 Clinical Data (N=94)		Comparison to Whole Sample		Subsample with Genetic Data (N=103)		Comparison to Whole Sample		Subsample with Genetic and Clinical Data (N=86)		Comparison to Whole Sample	
	N	%	N	%	χ^2	*p*	N	%	χ^2	*p*	N	%	χ^2	*p*
Males	65	50	51	54.3	0.396	0.529	53	51.5	0.049	0.825	47	54.7	0.449	0.503
High-Risk	71	54.6	55	58.5	0.336	0.562	62	60.2	0.73	0.393	54	62.8	1.419	0.234
Right-Handed	123	94.6	88	93.6	0.099	0.752	98	95.1	0.033	0.856	82	95.3	0.058	0.81
	M	*SD*	*M*	*SD*	*t*	*p*	*M*	*SD*	*t*	*p*	*M*	*SD*	*t*	*p*
SES[a]	43.18	10.553	42.04	10.46	0.797	0.426	41.65	10.72	1.088	0.278	41.34	10.41	1.256	0.21
Scan Age	17.93	4.981	19.78	4.2	-3.001	**.003****	19.26	4.45	-2.122	**0.035***	20.12	4.12	-3.5	**.001****
Age at Study Entry	11.59	3.454	11.85	3.59	-0.544	0.587	11.66	3.57	-0.147	0.883	11.6	3.6	-0.025	0.98
Age at Last Follow-up	22.7	4.943	24.79	4.07	-3.353	**.001****	23.94	4.63	-1.959	**0.05***	25.13	4.08	-3.783	**.000****
Length of Follow-up	11.1	5.92	12.94	5.82	-2.297	**.023***	12.28	6.06	-1.488	0.138	13.52	5.72	-2.975	**.003****
Total OFC[a]	27.02	6.37	27.06	6.76	-0.05	0.96	26.59	6.25	0.511	0.61	26.64	6.52	0.419	0.675
Total Caudate	9.53	1.27	9.51	129.6	0.156	0.876	9.54	1.32	-0.034	0.973	9.55	1.31	-0.065	0.948
Total ICV	1392.24	129.6	1405.64	129.4	-0.764	0.446	1399.93	132.12	-0.446	0.656	1407.84	128.77	-0.868	0.386

Note. SES = socioeconomic status (Hollingshead Four Factor Index); OFC = orbitofrontal cortex; ICV = intracranial volume.

[a]Whole Sample N = 129.

*$p < .05$, **$p < .01$.

3.3.2 Associations between morphology and outcome

Binary logistic regression models were constructed to quantify the associations between risk status, frontostriatal morphology, and resilience at age 20. Risk status robustly predicted SUD outcome in young adulthood (B = 1.19, p = .009). No association was observed between OFC or caudate volume and resilience, nor was there a significant moderation effect (Table 9). Again, removal of individuals with SUD diagnoses prior to the MRI did not alter the patter of results.

Table 9. Regression Analyses of Relationships between Frontostriatal Volumes and Resilience at Age 20

	Model 1 Risk Status			Model 2 OFC Volume			Model 3 Caudate Volume			Model 4 Moderation		
	Est.	*SE*	*p*	Est.	*SE*	*p*	Est.	*SE*	*p*	Est.	*SE*	*p*
Risk	1.19	0.499	**.009***	1.302	0.55	**.020***	1.351	0.566	**.019***	1.344	0.556	**.018***
Total OFC Volume				0.002	0.046	0.973						
Total ICV				-0.001	0.003	0.682	-0.003	0.002	0.296	-0.003	0.003	0.357
Total Caudate Volume							0.267	0.21	0.207			
OFCxCaudate[a]										0.004	0.005	0.427

Note. Binary logistic mixed model analyses. OFC = orbitofrontal cortex; ICV = intracranial volume.
[a]Variables for total OFC volume and total caudate volume were multiplied to create interaction term.
*p < .05, **p < .01.

3.4 GENETIC ANALYSES

3.4.1 Descriptive statistics

Genetic data were obtained for a subset of 103 subjects (See Table 8). Genotype frequencies are summarized in Table 10 for the entire subsample, as well as for each risk group. No significant risk group differences in genotype frequency were observed ($\chi^2(2) = 4.059$, $p = .131$).

In the absence of selection pressures, nonrandom mating, or other disturbing influences, the distribution of genotypes at a given locus should remain constant over generations, as defined by the Hardy-Weinberg equilibrium. Because this sample is comprised of multiple members from 39 families, the observed genotype frequencies are known to be influenced by assortative mating. Therefore, one member of each contributing family was selected at random to assess whether genotype frequencies were consistent with the Hardy-Weinberg equilibrium in the absence of familial influences. The distribution of C957T genotypes in this randomly selected subsample did not depart from equilibrium (TT=15, CT=19, CC=5; $\chi^2(1) = 0.07$, $p = .79$).

Table 10. Genotype Frequencies

	Overall Sample (N=103)		High-Risk (N=62)		Low-Risk (N=41)	
	N	%	N	%	N	%
TT	38	36.9	20	32.3	18	43.9
CT	50	48.5	35	56.5	15	36.6
CC	15	14.6	7	11.3	8	19.5

3.4.2 DRD2 and morphology

Effects of genotype on morphology were tested on both additive and dominant models of genetic influence, using linear mixed models. Under the additive model, a significant effect of genotype ($F(2, 91.13) = 4.313$, $p = .016$), as well as a significant genotype by risk interaction ($F(3, 67.6) = 2.732$, $p = .05$), was observed for total OFC volume. No significant main effect of genotype on caudate volume was found (Table 11). Consistent with previous analyses, the removal of individuals affected by SUD prior to their MRI scan did not alter the pattern of results.

Table 11. Regression Analyses of Additive Effect of DRD2 Gene Variation on Frontostriatal Morphology

	OFC						Caudate	
	Combined Sample (N = 103)		High-Risk (N = 62)		Low-Risk (N = 41)		Combined Sample (N = 103)	
	F	*p*	*F*	*p*	*F*	*p*	*F*	*p*
C957T	4.313	**0.016***	3.625	**0.034***	1.742	0.19	0.735	0.483
Total ICV	62.871	**0.000****	**24.058**	**0.000****	40.494	**0.000****	34.293	.000**
Prenatal Alcohol	NS		NS		NS		4.834	**.031***
C957T*Risk	2.732	**.05***					NS	

Note. Linear mixed model analyses. OFC = orbitofrontal cortex; ICV = intracranial volume.
*p < .05, **p < .01.

Follow-up analyses were conducted to examine the relationship between genotype and morphology within each risk group. The results revealed a significant association between genotype and brain volume among HR participants only ($F(2, 52.37) = 3.625$, $p = .034$). Among HR offspring, each additional C-allele was associated with greater total volume of the OFC (Figure 3).

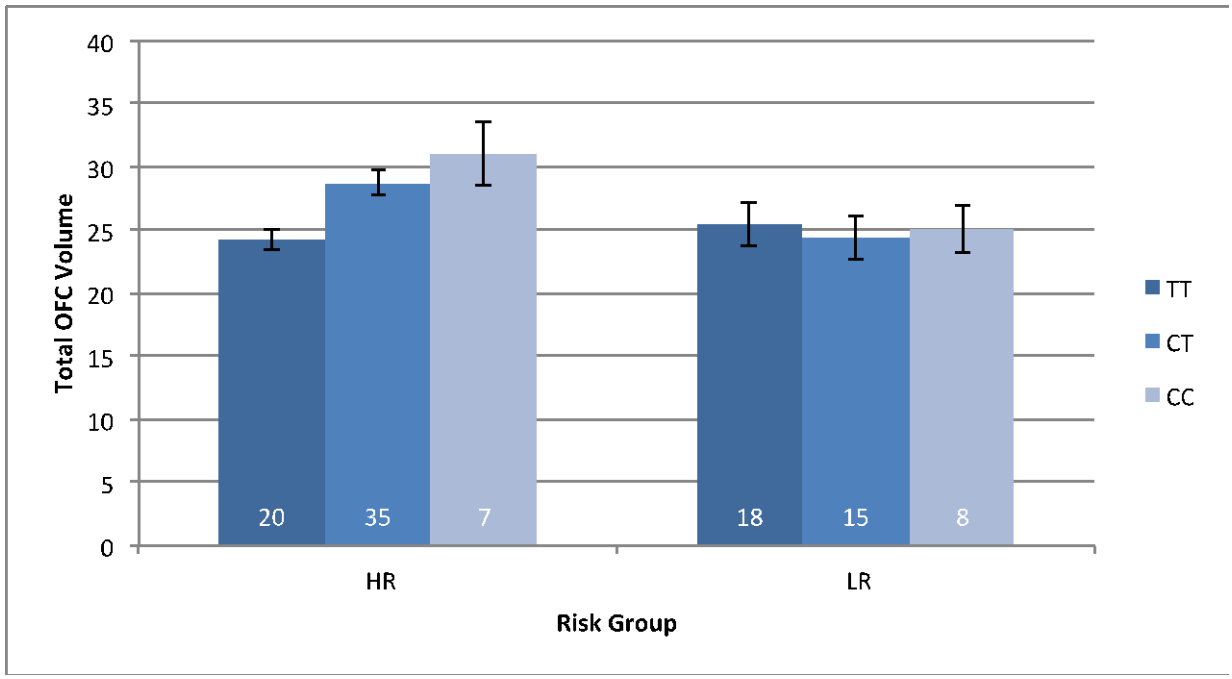

Figure 3. Mean OFC volume by genotype and risk group. Among HR offspring only, each additional C-allele was associated with greater OFC volume. The error bars represent SEMs, and sample sizes for each group appear at the base of each column.

Due to the relatively low frequency of the CC genotype in our sample (14.6%), the relationship between genetic variation and frontostriatal brain volume was also tested on a dominant model of genetic influence, combining the CC and CT groups, to maximize statistical power. The results were consistent with the previous analyses, with the C-allele associated with significantly greater volume of the OFC among HR offspring ($F(1, 55.55) = 6.475$, $p = .014$) (Table 12).

Table 12. Regression Analyses of Dominant Effect of DRD2 Gene Variation on Frontostriatal Morphology

	OFC						Caudate	
	Combined Sample (N = 103)		High-Risk (N = 62)		Low-Risk (N = 41)		Combined Sample (N = 103)	
	F	*p*	*F*	*p*	*F*	*p*	*F*	*p*
C957T_anyC	8.107	**.005****	6.475	**.014***	3.214	0.082	1.22	0.273
TotalICV	64.22	**.000****	25.202	**.000****	40.937	**.000****	34.723	**.000****
Prenatal Exp	NS		NS		NS		4.655	**.034***
C957T_anyC*Risk	3.795	**.028***					NS	

Note. Linear mixed model analyses. OFC = orbitofrontal cortex; ICV = intracranial volume.
*p < .05, **p < .01.

3.4.3 DRD2 and resilience in young adulthood

Binary logistic mixed models were constructed to quantify the influence of DRD2 variation on the likelihood of developing an SUD diagnosis by age 20. A subset of 86 individuals for whom both genetic and clinical follow-up data were available was included in these analyses (See Table 8 for subsample characteristics). The results of the additive model showed a significant influence of genotype (B = 2.202, p = .046), above and beyond the effect of risk group status (B = 1.411, p = .022) (Table 13). In fact, the likelihood of resilience in young adulthood was found to increase in a linear fashion with each additional C-allele (Figure 4).

Table 13. Additive and Dominant Models of Effect of DRD2 Variation on Resilience to SUD at Age 20

	Additive Model (TT vs. CT vs. CC)			Dominant Model (TT vs. CT/CC)		
	Est.	*SE*	*p*	Est.	*SE*	*p*
C957T	2.202	1.087	**0.046***	1.363	0.528	**0.012***
Risk	1.411	0.604	**0.022***	1.516	0.596	**0.013***

*p < .05, **p < .01.

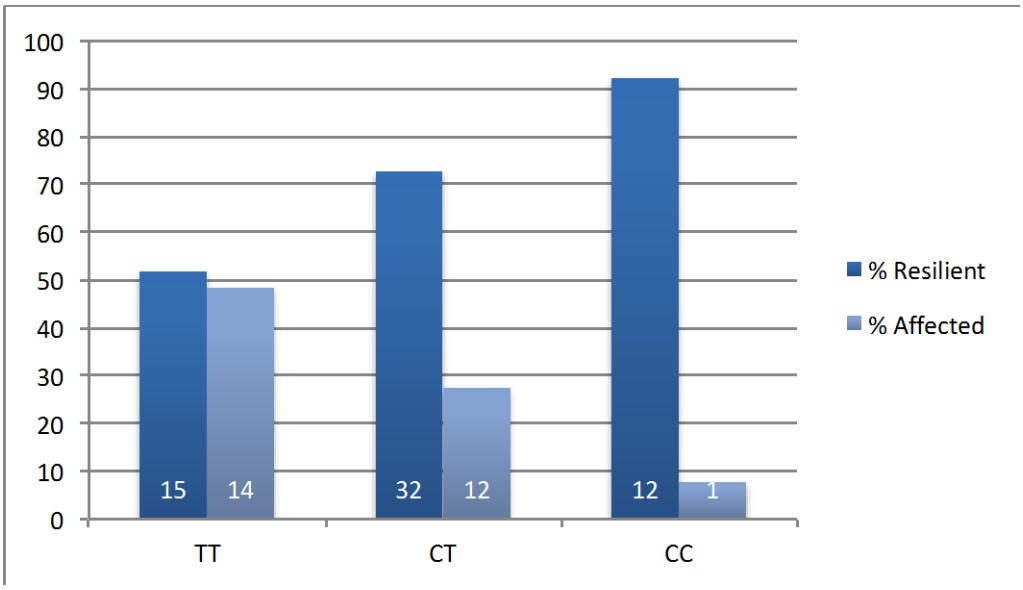

Figure 4. Percentage of resilient offspring by genotype. The C-allele conferred an additive protective effect across risk groups. Sample sizes for each group are presented at the base of each column.

4.0 DISCUSSION

The aim of the current study was to identify neurobiological variants that promote resilience to SUD, in order to better understand the neural basis of risk for these conditions and to inform prevention and intervention efforts for individuals at high risk. Based on the literature implicating impulsivity as a powerful premorbid predictor of both alcohol and drug abuse, genetic and structural characteristics associated with certain facets of impulsivity were evaluated.

The results of these analyses revealed that the minor allele of the C957T polymorphism of the DRD2 gene had an additive protective effect, significantly increasing the likelihood of resilience to SUD in young adulthood across risk groups. A gene by risk interaction was also observed for OFC volume, such that each additional C-allele was associated with greater OFC volume. However, this effect was only observed among the HR offspring. Additionally, larger volume of the caudate predicted greater self-reported novelty seeking behavior. Future research is needed to uncover the mechanisms underlying the observed genetic effects, and to explore the clinical applications of these findings for HR populations.

4.1 BEHAVIORAL ANALYSES

4.1.1 Caudate volume predicts novelty seeking

An initial set of analyses was conducted to test whether volumetric variation in the frontostriatal structures under investigation had a significant influence on inhibitory control and novelty seeking in the current sample. Consistent with the study hypotheses, bilateral caudate volume was found to be a significant predictor of self-reported novelty seeking behavior. However, contrary to the original hypothesis, larger volumes were found to be associated with greater novelty seeking behavior.

Although the direction of this association differs from the original study hypothesis, these findings do align with extant research reporting an association between larger caudate volume and increased impulsivity in both healthy (Ducharme et al., 2011) and pathological populations (Glenn, Raine, Yaralian, & Yang, 2010), including substance-abusing individuals. For example, Churchwell et al. (2012) found that adolescents with co-occurring methamphetamine and cannabis abuse displayed increased striatal volume as well as greater novelty seeking compared to controls. Additionally, larger caudate volumes have also been reported in cocaine-dependent individuals (Ersche et al., 2011; Jacobsen, Giedd, Gottschalk, Kosten, & Krystal, 2001), in association with impaired attentional control (Ersche et al., 2011). The current findings add to the literature in suggesting that this characteristic pre-dates the onset of substance use pathology, and thus may contribute to risk for SUD.

Conversely, smaller volume of the caudate has also been reported in HR offspring with externalizing disorders (Hill et al., in press) and those exposed to childhood abuse (Dannlowski

et al., 2012). Further, greater striatal D2 receptor density has been associated with lesser impulsivity in substance abusers (B. Lee et al., 2009) as well as healthy volunteers (Ghahremani et al., 2012). Clearly, future studies are necessary to clarify the role of striatal volume and D2 receptor density in human impulsivity and risk for SUD.

4.1.2 No association between total OFC volume and inhibitory control

Contrary to our predictions, we failed to detect a significant relationship between OFC volume and inhibitory control in the current dataset. This may be partially attributable to the relatively smaller sample of individuals with behavioral data (See Table 3). Alternatively, a previous analysis including a subsample of the offspring included in the current analysis identified a significant association between performance on the MPQ Control subscale and white matter volume in the right OFC (Hill, Wang, et al., 2009), whereas the current analyses focused on total OFC volume. Similarly, prior studies showing a relationship between impulsivity and OFC volume reported specific associations with orbitofrontal gray matter (Gansler et al., 2011; A. K. Lee, Jerram, Fulwiler, & Gansler, 2011; Matsuo et al., 2009; Schilling et al., 2013). Therefore, segmented volumes may be more influential in the determination of inhibitory control than variation in total OFC volume, and future analyses should separately explore the relationship between these inhibitory control measures and gray and white matter in the OFC.

Further, differences in measurements of impulsivity may also have influenced these null findings. Prior studies (Gansler et al., 2011; A. K. Lee, Jerram, Fulwiler, & Gansler, 2011; Matsuo et al., 2009; Schilling et al., 2013) have relied on different scales than those included in the current analyses (i.e. Barratt Impulsiveness Scale, Cloningers' Revised Temperament and

Character Inventory Impulsiveness), and several of these studies reported specific associations between OFC volume and discrete facets of impulsivity, whereas the MPQ Control scale provides an estimate of overall impulsive behavior. Therefore, the current measures may have been less sensitive to the effects of volumetric variation in the OFC.

Additionally, a number of prior reports used voxel-based morphometry to measure the OFC, whereas the current study employed a manually-traced region of interest approach. Prior research has demonstrated that these methods can yield inconsistent findings regarding gray matter associations (Giuliani, Calhoun, Pearlson, Francis, & Buchanan, 2005). Therefore, variation in imaging methodologies may have also contributed to our null findings regarding the importance of OFC volume to impulsivity. Finally, a substantial proportion of the human literature demonstrating OFC involvement in impulsivity comes from studies of brain activity (Elliott & Deakin, 2005), rather than structural imaging. Therefore, it may be the case that these aspects of inhibitory control are more closely related to functional or neurochemical alterations in this brain region.

4.2 MORPHOLOGICAL ANALYSES

Contrary to our predictions, we did not find a significant relationship between frontostriatal brain volumes and resilience in young adulthood. It is possible that the time point selected for defining resilience could have contributed to this null finding. Indeed, at age 20, these offspring have not yet reached the legal drinking age, so their use of both alcohol and drugs partially depends on the availability of these substances. Therefore, environmental factors may have a

greater impact on these individuals' behavior in this age range, which may have obscured the hypothesized relationships between morphology and SUD in our sample.

4.3 GENETIC ANALYSES

4.3.1 C957T genotype predicts OFC volume in HR offspring

Linear mixed model analyses revealed that among HR offspring, the C-allele was associated with greater total volume of the OFC in an additive manner, such that each additional copy of the minor allele predicted greater regional volume. Although to our knowledge this is the first study to examine the influence of C957T variation on morphology, these finding are consistent with prior work reporting that each additional C-allele is associated with greater cortical D2 receptor density (Hirvonen et al., 2009), and prior research has demonstrated positive correlations between measures of D2 receptor density and grey matter volume across multiple frontal cortical regions (Woodward et al., 2009). Therefore, the current findings are consistent with the existing literature on the functional role of the C957T polymorphism.

Given the importance of the OFC for affect, inhibition, and decision-making (Menzies et al., 2008), this effect may represent one mechanism by which C957T variation influences behavior. Variation at this locus has been linked to an array of different outcomes, including SUD (Hill, Hoffman, et al., 2008; Swagell et al., 2012; Yang et al., 2008), other psychopathology (Davis et al., 2012; Lawford et al., 2005; Voisey et al., 2009; Whitmer & Gotlib, 2012), impulsivity and inhibitory control (Colzato, van den Wildenberg, & Hommel, 2013; Colzato et

al., 2010), cognition (Rodriguez-Jimenez et al., 2006), learning (Frank et al., 2007), as well as personality (Montag, Bleek, Faber, & Reuter, 2012). This observed effect on OFC volume may help to explain the diverse downstream functions associated with C957T variation.

Surprisingly, the effect of genetic variation on morphology was only seen among HR individuals. Hirvonen et al. (2009) previously reported an association between C957T variation and extrastriatal D2 receptor density in a sample of healthy volunteers, so we had anticipated that this effect would also be present among LR individuals. However, the prior study included only male participants with a substantially older mean age than our participants (28.7 ± 7.4 years) (Hirvonen et al., 2009), which may have contributed to the inconsistency. Additionally, multiplex families are enriched for genes contributing to disease susceptibility. It may also be the case that our failure to detect this effect is attributable to the relatively smaller sample of low-risk participants with genetic data (HR N=61; LR N=42). Future studies with larger samples are needed to clarify the nature of the relationship between C957T variation and OFC volume across risk groups.

4.3.2 C957T variation predicts resilience in young adulthood

We observed a significant association between genotype and risk for substance-related pathology by young adulthood, such that each additional C-allele conferred a greater likelihood of resilience at age 20, across both risk groups. This finding extends prior work from our lab, which reported an association between the T-allele and risk for alcohol dependence (Hill, Hoffman, et al., 2008), showing that the protective effect of the C-allele extends across substance use disorders.

4.3.2.1 Supporting literature

The current findings align with a number of prior studies reporting a protective effect of the minor allele. Research examining the influence of C957T genotype on addictive behavior in the context of broader dopaminergic genetic variation has also implicated the T-allele in increased risk for substance abuse. Conner et al. (2010) reported greater substance use among males carrying larger numbers of hypodopaminergic risk gene variants, including the T-allele of the C957T SNP. Additionally, Wernicke et al. (2009) reported that homozygosity of a haplotype including the C-allele was overrepresented in never smokers compared to ever smokers. Further, the major allele has also been implicated in risk for a number of other classes of psychopathology (Davis et al., 2012; Fan et al., 2010; Huuhka et al., 2008).

4.3.2.2 Potential mechanisms of genetic effect

Prior studies have demonstrated a relationship between C957T variation and impulsivity, reporting greater dysfunctional impulsivity and poorer inhibitory control among T/T carriers (Colzato et al., 2013; Colzato et al., 2010). Greater impulsivity has also been linked to reduced volume of the OFC (Gansler et al., 2011; Hill, Wang, et al., 2009; A. K. Lee et al., 2011; Matsuo et al., 2009; Schilling et al., 2013) as well as higher risk for substance-related pathology (Forbes et al., 2009). Therefore, the larger OFC volume observed among HR C-carriers in the current sample may represent one mechanism by which genotype influences outcome.

Additionally, C957T variation has also been shown to impact neurocognitive functioning. Prior research has demonstrated an association between the major allele and poorer working memory performance (Markett, Montag, Walter, & Reuter, 2011), as well as greater susceptibility to nicotine-induced working memory deficits (Jacobsen, Pugh, Mencl, &

Gelernter, 2006). T-carriers have also been found to exhibit poorer attention (Felten et al., 2012) and worse episodic memory performance (S. C. Li et al., 2013). Therefore, C957T variation may impact risk for poor psychiatric outcomes via effects on various domains of cognitive functioning. Collectively, these studies support the contention that the C-allele is protective against alcohol, nicotine, and drug use as well as other psychopathology, and this effect may be partially attributable to OFC-mediated reductions in various domains of impulsivity, and improved neurocognitive functioning.

4.3.2.3 Opposing literature

Conversely, a number of studies have implicated the C-allele in risk for alcoholism (Kraschewski et al., 2009; Ponce et al., 2008; Swagell et al., 2012), nicotine dependence (Voisey et al., 2012), schizophrenia (Betcheva et al., 2009; Hanninen et al., 2006; Hoenicka et al., 2006; Lawford et al., 2005; Monakhov, Golimbet, Abramova, Kaleda, & Karpov, 2008), PTSD (Voisey et al., 2009), and poorer cognitive performance in a number of domains (Bolton et al., 2010; Colzato, Slagter, de Rover, & Hommel, 2011; Rodriguez-Jimenez et al., 2006; Xu et al., 2007). Substantial methodological variation exists within the literature, including populations sampled, study designs, inclusion criteria, and age of study participants. Nonetheless, it is important to consider other factors that may be driving the divergent findings.

Importantly, a number of studies have identified interactions between C957T variation and genetic variation at other loci (Markett et al., 2011; White et al., 2009) as well as environmental factors (White et al., 2009), indicating that analyses limited to this single SNP will likely be insufficient to resolve the discrepant findings on this topic. HR individuals are thought to carry a variety of gene variants that contribute to their increased susceptibility to

substance use. Thus, the current findings likely reflect interactions among a number of genes and environmental features, which have yet to be identified. Future research should explore how C957T variation interacts with other risk factors to contribute to risk for psychopathology.

4.4 STUDY LIMITATIONS AND FUTURE DIRECTIONS

Although the current study had many strengths, including the use of a prospective, longitudinal study design, the inclusion of ultra-high-risk offspring with an unusually dense family history, and the examination of multimodal biological predictor variables, there were also several limitations. The use of age 20 as our threshold for resilience may have contributed to our negative morphological findings, as individuals' behavior during this stage of development may be more subject to confounding environmental influences. Further, individuals who develop SUD beyond the age of 20 would be classified as resilient by the current definition, yet they may exhibit biological and personality characteristics that are more typical of the affected group. As these offspring continue to be followed, future studies should examine whether frontostriatal brain structure would be a significant predictor of SUD outcome later in development.

Additionally, although the current study included a large sample with volumetric data, scan age varied across the participants included. Although scan age was not a significant covariate in any of the analyses, this may have introduced some confounding heterogeneity. Further, some affected individuals had their SUD onset prior to the time of their MRI scan, and drug and alcohol exposure are known to have widespread neurotoxic effects on gray matter in the brain. Nonetheless, removal of individuals with pre-scan exposure did not alter the pattern of

results reported. Additionally, behavioral and genetic data were only available for a subset of these participants, which limited our power to detect effects of these variables. Future studies should include larger samples with less variability in scan age and prior substance exposure.

The inclusion of a single candidate gene also limits our ability to interpret the observed association between DRD2 variation and resilience. Recent studies have emphasized the importance of considering the additive effects of multiple gene variants (Derringer et al., 2010; Forbes et al., 2009; Nikolova, Ferrell, Manuck, & Hariri, 2011). Further, due to the opposing effects of C957T variation on subcortical and cortical D2 receptor binding, it is not possible to discern whether lesser striatal receptor density or greater D2 availability in the frontal cortex is driving these effects. Therefore, future studies using multilocus genetic analyses may help to clarify how variation in dopaminergic neurotransmission influences SUD outcomes.

Additionally, our findings may have been limited by the sole focus on structural variables. A substantial literature has implicated variation in frontostriatal brain activity and white matter integrity in reward processing (Finger et al., 2011; Galvan et al., 2006; Ivanov, Liu, Shulz, et al., 2012; Yau et al., 2012), response inhibition (Heitzeg et al., 2010), emotional monitoring (Heitzeg et al., 2008), and delay-discounting (Peper et al., 2013). Patterns of frontostriatal brain activation have also been shown to predict relapse among alcoholics (Heinz, Beck, Grusser, Grace, & Wrase, 2009), as well as treatment response in other psychiatric populations (Forbes et al., 2010). Further, a number of studies have identified differences in task-related brain activation between controls and resilient individuals at high risk for SUD (Devito et al., 2013; Heitzeg et al., 2008; Heitzeg et al., 2010) as well as other psychiatric disorders (Frangou, 2011; Lisiecka et al., 2013), indicating that protective patterns of neural responding may mitigate other genetic risk factors. Therefore, future studies should explore

whether measures of frontostriatal brain activation or connectivity may prospectively predict SUD outcomes.

Finally, HR offspring are at greater risk for a variety of internalizing and externalizing disorders, and other psychiatric diagnoses further increase the likelihood of their developing SUD (Hill, Shen, et al., 2008; Hill, Tessner, et al., 2011). Therefore, by limiting our definition of resilience to the absence of alcohol or drug use disorders, we may be including individuals affected by other conditions in our resilient group. In the future, it will be important to test whether the protective effect of the C-allele of the C957T polymorphism extends across other psychiatric disorders.

4.5 CONCLUSIONS

This is the first study to report an association between DRD2 variation and resilience to any SUD by young adulthood. A variety of mechanisms may account for this effect, including genetic effects on OFC volume, impulsivity, cognitive functioning, or reward processing as well as interactions with other genes and environmental factors. Future studies should identify the factors mediating this association in order to elucidate pathways through which DRD2 gene variation impacts clinical outcomes. The successful discovery of endophenotypes of risk for SUD has the potential to guide future prevention and intervention efforts and promote resilience among individuals at high risk.

5.0 BIBLIOGRAPHY

Alia-Klein, N., Parvaz, M.A., Woicik, P.A., Konova, A.B., Maloney, T., Shumay, E., . . . Goldstein, R.Z. (2011). Gene x disease interaction on orbitofrontal gray matter in cocaine addiction. *Archives of general psychiatry, 68*(3), 283-294. doi: 10.1001/archgenpsychiatry.2011.10

Andersen, S.L. (2003). Trajectories of brain development: point of vulnerability or window of opportunity? *Neuroscience and biobehavioral reviews, 27*(1-2), 3-18.

Anokhin, A.P., Golosheykin, S., Grant, J.D., & Heath, A.C. (2011). Heritability of delay discounting in adolescence: a longitudinal twin study. *Behavior genetics, 41*(2), 175-183. doi: 10.1007/s10519-010-9384-7

Barnes, J.J., Dean, A.J., Nandam, L.S., O'Connell, R.G., & Bellgrove, M.A. (2011). The molecular genetics of executive function: role of monoamine system genes. *Biological psychiatry, 69*(12), e127-143. doi: 10.1016/j.biopsych.2010.12.040

Belin, D., Berson, N., Balado, E., Piazza, P.V., & Deroche-Gamonet, V. (2011). High-novelty-preference rats are predisposed to compulsive cocaine self-administration. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 36*(3), 569-579. doi: 10.1038/npp.2010.188

Benegal, V., Antony, G., Venkatasubramanian, G., & Jayakumar, P.N. (2007). Gray matter volume abnormalities and externalizing symptoms in subjects at high risk for alcohol dependence. *Addiction biology, 12*(1), 122-132. doi: 10.1111/j.1369-1600.2006.00043.x

Benjamin, J., Osher, Y., Kotler, M., Gritsenko, I., Nemanov, L., Belmaker, R.H., & Ebstein, R.P. (2000). Association between tridimensional personality questionnaire (TPQ) traits and three functional polymorphisms: dopamine receptor D4 (DRD4), serotonin transporter promoter region (5-HTTLPR) and catechol O-methyltransferase (COMT). *Molecular psychiatry, 5*(1), 96-100.

Betcheva, E.T., Mushiroda, T., Takahashi, A., Kubo, M., Karachanak, S.K., Zaharieva, I.T., . . . Toncheva, D.I. (2009). Case-control association study of 59 candidate genes reveals the DRD2 SNP rs6277 (C957T) as the only susceptibility factor for schizophrenia in the

Bulgarian population. *Journal of human genetics, 54*(2), 98-107. doi: 10.1038/jhg.2008.14

Bjork, J.M., Knutson, B., & Hommer, D.W. (2008). Incentive-elicited striatal activation in adolescent children of alcoholics. *Addiction, 103*(8), 1308-1319. doi: 10.1111/j.1360-0443.2008.02250.x

Blakemore, S.J., & Robbins, T.W. (2012). Decision-making in the adolescent brain. *Nature neuroscience, 15*(9), 1184-1191. doi: 10.1038/nn.3177

Bolton, J.L., Marioni, R.E., Deary, I.J., Harris, S.E., Stewart, M.C., Murray, G.D., . . . Price, J.F. (2010). Association between polymorphisms of the dopamine receptor D2 and catechol-o-methyl transferase genes and cognitive function. *Behavior genetics, 40*(5), 630-638. doi: 10.1007/s10519-010-9372-y

Cardenas, V.A., Durazzo, T.C., Gazdzinski, S., Mon, A., Studholme, C., & Meyerhoff, D.J. (2011). Brain morphology at entry into treatment for alcohol dependence is related to relapse propensity. *Biological psychiatry, 70*(6), 561-567. doi: 10.1016/j.biopsych.2011.04.003

Chakravarty, M.M., Felsky, D., Tampakeras, M., Lerch, J.P., Mulsant, B.H., Kennedy, J.L., & Voineskos, A.N. (2012). DISC1 and Striatal Volume: A Potential Risk Phenotype For mental Illness. *Frontiers in psychiatry / Frontiers Research Foundation, 3*, 57. doi: 10.3389/fpsyt.2012.00057

Chambers, W.J., Puig-Antich, J., Hirsch, M., Paez, P., Ambrosini, P.J., Tabrizi, M.A., & Davies, M. (1985). The assessment of affective disorders in children and adolescents by semistructured interview. Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. *Archives of general psychiatry, 42*(7), 696-702.

Chaytor, N., Schmitter-Edgecombe, M., & Burr, R. (2006). Improving the ecological validity of executive functioning assessment. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, 21*(3), 217-227. doi: 10.1016/j.acn.2005.12.002

Chen, X.X., Chen, H.H., Du, J., Fan, C.L., & Zhao, M. (2008). Analysis on personality characteristics of heroin addicts and relation to initial drug use age. *Chinese Journal of Clinical Psychology, 16*(6), 662-664.

Churchwell, J.C., Carey, P.D., Ferrett, H.L., Stein, D.J., & Yurgelun-Todd, D.A. (2012). Abnormal striatal circuitry and intensified novelty seeking among adolescents who abuse methamphetamine and cannabis. *Developmental neuroscience, 34*(4), 310-317. doi: 10.1159/000337724

Ciraulo, D.A., Piechniczek-Buczek, J., & Iscan, E.N. (2003). Outcome predictors in substance use disorders. *The Psychiatric clinics of North America, 26*(2), 381-409.

Cloninger, C.R. (1987). Neurogenetic adaptive mechanisms in alcoholism. *Science, 236*(4800), 410-416.

Cloninger, C.R., Svrakic, D.M., & Przybeck, T.R. (1993). A psychobiological model of temperament and character. *Archives of general psychiatry, 50*(12), 975-990.

Cohen, M.X., Schoene-Bake, J.C., Elger, C.E., & Weber, B. (2009). Connectivity-based segregation of the human striatum predicts personality characteristics. *Nature neuroscience, 12*(1), 32-34. doi: 10.1038/nn.2228

Colzato, L.S., Slagter, H.A., de Rover, M., & Hommel, B. (2011). Dopamine and the management of attentional resources: genetic markers of striatal D2 dopamine predict individual differences in the attentional blink. *Journal of cognitive neuroscience, 23*(11), 3576-3585. doi: 10.1162/jocn_a_00049

Colzato, L.S., van den Wildenberg, W.P., & Hommel, B. (2013). The genetic impact (C957T-DRD2) on inhibitory control is magnified by aging. *Neuropsychologia, 51*(7), 1377-1381. doi: 10.1016/j.neuropsychologia.2013.01.014

Colzato, L.S., van den Wildenberg, W.P., Van der Does, A.J., & Hommel, B. (2010). Genetic markers of striatal dopamine predict individual differences in dysfunctional, but not functional impulsivity. *Neuroscience, 170*(3), 782-788. doi: 10.1016/j.neuroscience.2010.07.050

Conner, B.T., Hellemann, G.S., Ritchie, T.L., & Noble, E.P. (2010). Genetic, personality, and environmental predictors of drug use in adolescents. *Journal of substance abuse treatment, 38*(2), 178-190. doi: 10.1016/j.jsat.2009.07.004

Cottler, L.B., Robins, L.N., & Helzer, J.E. (1989). The reliability of the CIDI-SAM: a comprehensive substance abuse interview. *British journal of addiction, 84*(7), 801-814.

Cummings, J.A., Gowl, B.A., Westenbroek, C., Clinton, S.M., Akil, H., & Becker, J.B. (2011). Effects of a selectively bred novelty-seeking phenotype on the motivation to take cocaine in male and female rats. *Biology of sex differences, 2*, 3. doi: 10.1186/2042-6410-2-3

Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., . . . Kugel, H. (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological psychiatry, 71*(4), 286-293. doi: 10.1016/j.biopsych.2011.10.021

Davis, C., Levitan, R.D., Yilmaz, Z., Kaplan, A.S., Carter, J.C., & Kennedy, J.L. (2012). Binge eating disorder and the dopamine D2 receptor: genotypes and sub-phenotypes. *Progress*

in neuro-psychopharmacology & biological psychiatry, 38(2), 328-335. doi: 10.1016/j.pnpbp.2012.05.002

Dawes, M.A., Antelman, S.M., Vanyukov, M.M., Giancola, P., Tarter, R.E., Susman, E.J., . . . Clark, D.B. (2000). Developmental sources of variation in liability to adolescent substance use disorders. *Drug and alcohol dependence, 61*(1), 3-14.

Demetrovics, Z., Varga, G., Szekely, A., Vereczkei, A., Csorba, J., Balazs, H., . . . Barta, C. (2010). Association between Novelty Seeking of opiate-dependent patients and the catechol-O-methyltransferase Val(158)Met polymorphism. *Comprehensive psychiatry, 51*(5), 510-515. doi: 10.1016/j.comppsych.2009.11.008

Derringer, J., Krueger, R.F., Dick, D.M., Saccone, S., Grucza, R.A., Agrawal, A., . . . Bierut, L.J. (2010). Predicting sensation seeking from dopamine genes. A candidate-system approach. *Psychological science, 21*(9), 1282-1290. doi: 10.1177/0956797610380699

Devito, E.E., Meda, S.A., Jiantonio, R., Potenza, M.N., Krystal, J.H., & Pearlson, G.D. (2013). Neural Correlates of Impulsivity in Healthy Males and Females with Family Histories of Alcoholism. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. doi: 10.1038/npp.2013.92

Ding, H., Qin, W., Jiang, T., Zhang, Y., & Yu, C. (2012). Volumetric variation in subregions of the cerebellum correlates with working memory performance. *Neuroscience letters, 508*(1), 47-51. doi: 10.1016/j.neulet.2011.12.016

Dom, G., Sabbe, B., Hulstijn, W., & van den Brink, W. (2005). Substance use disorders and the orbitofrontal cortex: systematic review of behavioural decision-making and neuroimaging studies. *The British journal of psychiatry : the journal of mental science, 187*, 209-220. doi: 10.1192/bjp.187.3.209

Ducharme, S., Hudziak, J.J., Botteron, K.N., Ganjavi, H., Lepage, C., Collins, D.L., . . . Karama, S. (2011). Right anterior cingulate cortical thickness and bilateral striatal volume correlate with child behavior checklist aggressive behavior scores in healthy children. *Biological psychiatry, 70*(3), 283-290. doi: 10.1016/j.biopsych.2011.03.015

Dyr, W., McBride, W.J., Lumeng, L., Li, T.K., & Murphy, J.M. (1993). Effects of D1 and D2 dopamine receptor agents on ethanol consumption in the high-alcohol-drinking (HAD) line of rats. *Alcohol, 10*(3), 207-212.

Eckstrand, K.L., Ding, Z., Dodge, N.C., Cowan, R.L., Jacobson, J.L., Jacobson, S.W., & Avison, M.J. (2012). Persistent dose-dependent changes in brain structure in young adults with low-to-moderate alcohol exposure in utero. *Alcoholism, clinical and experimental research, 36*(11), 1892-1902. doi: 10.1111/j.1530-0277.2012.01819.x

Eiden, R.D., Edwards, E.P., & Leonard, K.E. (2007). A conceptual model for the development of externalizing behavior problems among kindergarten children of alcoholic families: role of parenting and children's self-regulation. *Developmental psychology, 43*(5), 1187-1201. doi: 10.1037/0012-1649.43.5.1187

Elliott, R., & Deakin, B. (2005). Role of the orbitofrontal cortex in reinforcement processing and inhibitory control: evidence from functional magnetic resonance imaging studies in healthy human subjects. *International review of neurobiology, 65*, 89-116. doi: 10.1016/S0074-7742(04)65004-5

Enoch, M.A. (2012). The influence of gene-environment interactions on the development of alcoholism and drug dependence. *Current psychiatry reports, 14*(2), 150-158. doi: 10.1007/s11920-011-0252-9

Ersche, K.D., Barnes, A., Jones, P.S., Morein-Zamir, S., Robbins, T.W., & Bullmore, E.T. (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain : a journal of neurology, 134*(Pt 7), 2013-2024. doi: 10.1093/brain/awr138

Ersche, K.D., Jones, P.S., Williams, G.B., Turton, A.J., Robbins, T.W., & Bullmore, E.T. (2012). Abnormal brain structure implicated in stimulant drug addiction. *Science, 335*(6068), 601-604. doi: 10.1126/science.1214463

Evren, C., Durkaya, M., Evren, B., Dalbudak, E., & Cetin, R. (2012). Relationship of relapse with impulsivity, novelty seeking and craving in male alcohol-dependent inpatients. *Drug and alcohol review, 31*(1), 81-90. doi: 10.1111/j.1465-3362.2011.00303.x

Fan, H., Zhang, F., Xu, Y., Huang, X., Sun, G., Song, Y., . . . Liu, P. (2010). An association study of DRD2 gene polymorphisms with schizophrenia in a Chinese Han population. *Neuroscience letters, 477*(2), 53-56. doi: 10.1016/j.neulet.2009.11.017

Felten, A., Montag, C., Kranczioch, C., Markett, S., Walter, N.T., & Reuter, M. (2012). The DRD2 C957T polymorphism and the Attentional Blink-A genetic association study. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. doi: 10.1016/j.euroneuro.2012.09.010

Fergusson, D.M., & Lynskey, M.T. (1996). Adolescent resiliency to family adversity. *Journal of child psychology and psychiatry, and allied disciplines, 37*(3), 281-292.

Finger, E.C., Marsh, A.A., Blair, K.S., Reid, M.E., Sims, C., Ng, P., . . . Blair, R.J. (2011). Disrupted reinforcement signaling in the orbitofrontal cortex and caudate in youths with conduct disorder or oppositional defiant disorder and a high level of psychopathic traits. *The American journal of psychiatry, 168*(2), 152-162. doi: 10.1176/appi.ajp.2010.10010129

Flagel, S.B., Robinson, T.E., Clark, J.J., Clinton, S.M., Watson, S.J., Seeman, P., . . . Akil, H. (2010). An animal model of genetic vulnerability to behavioral disinhibition and responsiveness to reward-related cues: implications for addiction. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 35*(2), 388-400. doi: 10.1038/npp.2009.142

Forbes, E.E., Brown, S.M., Kimak, M., Ferrell, R.E., Manuck, S.B., & Hariri, A.R. (2009). Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. *Molecular psychiatry, 14*(1), 60-70. doi: 10.1038/sj.mp.4002086

Forbes, E.E., Olino, T.M., Ryan, N.D., Birmaher, B., Axelson, D., Moyles, D.L., & Dahl, R.E. (2010). Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. *Cognitive, affective & behavioral neuroscience, 10*(1), 107-118. doi: 10.3758/CABN.10.1.107

Frangou, S. (2011). Brain structural and functional correlates of resilience to Bipolar Disorder. *Frontiers in human neuroscience, 5*, 184. doi: 10.3389/fnhum.2011.00184

Frank, M.J., Moustafa, A.A., Haughey, H.M., Curran, T., & Hutchison, K.E. (2007). Genetic triple dissociation reveals multiple roles for dopamine in reinforcement learning. *Proceedings of the National Academy of Sciences of the United States of America, 104*(41), 16311-16316. doi: 10.1073/pnas.0706111104

Franzen, M.D., Tishelman, A.C., Sharp, B.H., & Friedman, A.G. (1987). An investigation of the test-retest reliability of the Stroop Color-Word Test across two intervals. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, 2*(3), 265-272.

Galvan, A., Hare, T.A., Parra, C.E., Penn, J., Voss, H., Glover, G., & Casey, B.J. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 26*(25), 6885-6892. doi: 10.1523/JNEUROSCI.1062-06.2006

Gansler, D.A., Lee, A.K., Emerton, B.C., D'Amato, C., Bhadelia, R., Jerram, M., & Fulwiler, C. (2011). Prefrontal regional correlates of self-control in male psychiatric patients: Impulsivity facets and aggression. *Psychiatry research, 191*(1), 16-23. doi: 10.1016/j.pscychresns.2010.09.003

Ghahremani, D.G., Lee, B., Robertson, C.L., Tabibnia, G., Morgan, A.T., De Shetler, N., . . . London, E.D. (2012). Striatal dopamine D(2)/D(3) receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 32*(21), 7316-7324. doi: 10.1523/JNEUROSCI.4284-11.2012

Giedd, J.N., Lalonde, F.M., Celano, M.J., White, S.L., Wallace, G.L., Lee, N.R., & Lenroot, R.K. (2009). Anatomical brain magnetic resonance imaging of typically developing children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(5), 465-470. doi: 10.1097/CHI.0b013e31819f2715

Gjedde, A., Kumakura, Y., Cumming, P., Linnet, J., & Moller, A. (2010). Inverted-U-shaped correlation between dopamine receptor availability in striatum and sensation seeking. *Proceedings of the National Academy of Sciences of the United States of America, 107*(8), 3870-3875. doi: 10.1073/pnas.0912319107

Glenn, A.L., Raine, A., Yaralian, P.S., & Yang, Y. (2010). Increased volume of the striatum in psychopathic individuals. *Biological psychiatry, 67*(1), 52-58. doi: 10.1016/j.biopsych.2009.06.018

Golden, C.J. (1978). *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Chicago, Illinois: Skoelting.

Gottesman, II, & Gould, T.D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *The American journal of psychiatry, 160*(4), 636-645.

Grahn, J.A., Parkinson, J.A., & Owen, A.M. (2008). The cognitive functions of the caudate nucleus. *Progress in neurobiology, 86*(3), 141-155. doi: 10.1016/j.pneurobio.2008.09.004

Grant, B.F., & Dawson, D.A. (1997). Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *Journal of substance abuse, 9*, 103-110.

Grucza, R.A., Robert Cloninger, C., Bucholz, K.K., Constantino, J.N., Schuckit, M.I., Dick, D.M., & Bierut, L.J. (2006). Novelty seeking as a moderator of familial risk for alcohol dependence. *Alcoholism, clinical and experimental research, 30*(7), 1176-1183. doi: 10.1111/j.1530-0277.2006.00133.x

Gur, R.C., Gunning-Dixon, F., Bilker, W.B., & Gur, R.E. (2002). Sex differences in temporo-limbic and frontal brain volumes of healthy adults. *Cerebral cortex, 12*(9), 998-1003.

Gur, R.E., Kohler, C., Turetsky, B.I., Siegel, S.J., Kanes, S.J., Bilker, W.B., . . . Gur, R.C. (2004). A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. *Biological psychiatry, 55*(5), 512-517. doi: 10.1016/j.biopsych.2003.10.009

Hanninen, K., Katila, H., Kampman, O., Anttila, S., Illi, A., Rontu, R., . . . Lehtimaki, T. (2006). Association between the C957T polymorphism of the dopamine D2 receptor gene and schizophrenia. *Neuroscience letters, 407*(3), 195-198. doi: 10.1016/j.neulet.2006.08.041

Hasin, D.S., Stinson, F.S., Ogburn, E., & Grant, B.F. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of general psychiatry, 64*(7), 830-842. doi: 10.1001/archpsyc.64.7.830

Hedman, A.M., van Haren, N.E., Schnack, H.G., Kahn, R.S., & Hulshoff Pol, H.E. (2012). Human brain changes across the life span: a review of 56 longitudinal magnetic resonance imaging studies. *Human brain mapping, 33*(8), 1987-2002. doi: 10.1002/hbm.21334

Heinz, A., Beck, A., Grusser, S.M., Grace, A.A., & Wrase, J. (2009). Identifying the neural circuitry of alcohol craving and relapse vulnerability. *Addiction biology, 14*(1), 108-118. doi: 10.1111/j.1369-1600.2008.00136.x

Heinz, A., Siessmeier, T., Wrase, J., Buchholz, H.G., Grunder, G., Kumakura, Y., . . . Bartenstein, P. (2005). Correlation of alcohol craving with striatal dopamine synthesis capacity and D2/3 receptor availability: a combined [18F]DOPA and [18F]DMFP PET study in detoxified alcoholic patients. *The American journal of psychiatry, 162*(8), 1515-1520. doi: 10.1176/appi.ajp.162.8.1515

Heitzeg, M.M., Nigg, J.T., Yau, W.Y., Zubieta, J.K., & Zucker, R.A. (2008). Affective circuitry and risk for alcoholism in late adolescence: differences in frontostriatal responses between vulnerable and resilient children of alcoholic parents. *Alcoholism, clinical and experimental research, 32*(3), 414-426. doi: 10.1111/j.1530-0277.2007.00605.x

Heitzeg, M.M., Nigg, J.T., Yau, W.Y., Zucker, R.A., & Zubieta, J.K. (2010). Striatal dysfunction marks preexisting risk and medial prefrontal dysfunction is related to problem drinking in children of alcoholics. *Biological psychiatry, 68*(3), 287-295. doi: 10.1016/j.biopsych.2010.02.020

Hermundstad, A.M., Bassett, D.S., Brown, K.S., Aminoff, E.M., Clewett, D., Freeman, S., . . . Carlson, J.M. (2013). Structural foundations of resting-state and task-based functional connectivity in the human brain. *Proceedings of the National Academy of Sciences of the United States of America, 110*(15), 6169-6174. doi: 10.1073/pnas.1219562110

Hill, S.Y. (2010). Neural plasticity, human genetics, and risk for alcohol dependence. *International review of neurobiology, 91*, 53-94. doi: 10.1016/S0074-7742(10)91003-9

Hill, S.Y., De Bellis, M.D., Keshavan, M.S., Lowers, L., Shen, S., Hall, J., & Pitts, T. (2001). Right amygdala volume in adolescent and young adult offspring from families at high risk for developing alcoholism. *Biological psychiatry, 49*(11), 894-905.

Hill, S.Y., Hoffman, E.K., Zezza, N., Thalamuthu, A., Weeks, D.E., Matthews, A.G., & Mukhopadhyay, I. (2008). Dopaminergic mutations: within-family association and linkage in multiplex alcohol dependence families. *American journal of medical genetics.*

Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics, 147B(4), 517-526. doi: 10.1002/ajmg.b.30630

Hill, S.Y., Lichenstein, S.D., Wang, S., Carter, H., Tessner, K., & McDermott, M. (in press). Caudate volume in offspring from multiplex alcohol dependence families: Genetic variation predicts reduced volume and neuropsychological performance in association with externalizing psychopathology.

Hill, S.Y., Shen, S., Lowers, L., Locke-Wellman, J., Matthews, A.G., & McDermott, M. (2008). Psychopathology in offspring from multiplex alcohol dependence families with and without parental alcohol dependence: a prospective study during childhood and adolescence. *Psychiatry research, 160*(2), 155-166. doi: 10.1016/j.psychres.2008.04.017

Hill, S.Y., Steinhauer, S.R., Locke-Wellman, J., & Ulrich, R. (2009). Childhood risk factors for young adult substance dependence outcome in offspring from multiplex alcohol dependence families: a prospective study. *Biological psychiatry, 66*(8), 750-757. doi: 10.1016/j.biopsych.2009.05.030

Hill, S.Y., Tessner, K., Wang, S., Carter, H., & McDermott, M. (2010). Temperament at 5 years of age predicts amygdala and orbitofrontal volume in the right hemisphere in adolescence. *Psychiatry research, 182*(1), 14-21. doi: 10.1016/j.pscychresns.2009.11.006

Hill, S.Y., Tessner, K.D., & McDermott, M.D. (2011). Psychopathology in offspring from families of alcohol dependent female probands: a prospective study. *Journal of psychiatric research, 45*(3), 285-294. doi: 10.1016/j.jpsychires.2010.08.005

Hill, S.Y., Wang, S., Carter, H., Tessner, K., Holmes, B., McDermott, M., . . . Stiffler, S. (2011). Cerebellum volume in high-risk offspring from multiplex alcohol dependence families: association with allelic variation in GABRA2 and BDNF. *Psychiatry research, 194*(3), 304-313. doi: 10.1016/j.pscychresns.2011.05.006

Hill, S.Y., Wang, S., Kostelnik, B., Carter, H., Holmes, B., McDermott, M., . . . Keshavan, M.S. (2009). Disruption of orbitofrontal cortex laterality in offspring from multiplex alcohol dependence families. *Biological psychiatry, 65*(2), 129-136. doi: 10.1016/j.biopsych.2008.09.001

Hill, S.Y., Weeks, D.E., Jones, B.L., Zezza, N., & Stiffler, S. (2012). ASTN1 and alcohol dependence: family-based association analysis in multiplex alcohol dependence families. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics, 159B*(4), 445-455. doi: 10.1002/ajmg.b.32048

Hill, S.Y., Zezza, N., Wipprecht, G., Locke, J., & Neiswanger (1999). Personality traits and dopamine receptors (D2 and D4): linkage studies in families of alcoholics. *American journal of medical genetics (Neuropsychiatric genetics), 88*, 634-641.

Hill, S.Y., Zubin, J., & Steinhauer, S.R. (1990). Personality resemblance in relatives of male alcoholics: a comparison with families of male control cases. *Biological psychiatry, 27*(12), 1305-1322.

Hirvonen, M., Laakso, A., Nagren, K., Rinne, J.O., Pohjalainen, T., & Hietala, J. (2004). C957T polymorphism of the dopamine D2 receptor (DRD2) gene affects striatal DRD2 availability in vivo. *Molecular psychiatry, 9*(12), 1060-1061. doi: 10.1038/sj.mp.4001561

Hirvonen, M., Laakso, A., Nagren, K., Rinne, J.O., Pohjalainen, T., & Hietala, J. (2005). C957T polymorphism of the dopamine D2 receptor (DRD2) gene affects striatal DRD2 availability in vivo. *Molecular psychiatry, 10*, 889.

Hirvonen, M.M., Lumme, V., Hirvonen, J., Pesonen, U., Nagren, K., Vahlberg, T., . . . Hietala, J. (2009). C957T polymorphism of the human dopamine D2 receptor gene predicts extrastriatal dopamine receptor availability in vivo. *Progress in neuro-psychopharmacology & biological psychiatry, 33*(4), 630-636. doi: 10.1016/j.pnpbp.2009.02.021

Hoenicka, J., Aragues, M., Rodriguez-Jimenez, R., Ponce, G., Martinez, I., Rubio, G., . . . Palomo, T. (2006). C957T DRD2 polymorphism is associated with schizophrenia in Spanish patients. *Acta psychiatrica Scandinavica, 114*(6), 435-438. doi: 10.1111/j.1600-0447.2006.00874.x

Hollingshead, A.B. (1975). *Four Factor Index of Social Status*. Connecticut: Department of Sociology, Yale University.

Honey, C.J., Thivierge, J.P., & Sporns, O. (2010). Can structure predict function in the human brain? *NeuroImage, 52*(3), 766-776. doi: 10.1016/j.neuroimage.2010.01.071

Huang, H.Y., Lee, I.H., Chen, K.C., Yeh, T.L., Chen, P.S., Yang, Y.K., . . . Chen, C.C. (2010). Association of novelty seeking scores and striatal dopamine D(2)/D(3) receptor availability of healthy volunteers: single photon emission computed tomography with (1)(2)(3)i-iodobenzamide. *Journal of the Formosan Medical Association = Taiwan yi zhi, 109*(10), 736-739. doi: 10.1016/S0929-6646(10)60119-2

Huuhka, K., Anttila, S., Huuhka, M., Hietala, J., Huhtala, H., Mononen, N., . . . Leinonen, E. (2008). Dopamine 2 receptor C957T and catechol-o-methyltransferase Val158Met polymorphisms are associated with treatment response in electroconvulsive therapy. *Neuroscience letters, 448*(1), 79-83. doi: 10.1016/j.neulet.2008.10.015

Iacono, W.G., Malone, S.M., & McGue, M. (2003). Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology, 48*(2), 147-178.

Ivanov, I., Liu, X., Clerkin, S., Schulz, K., Friston, K., Newcorn, J.H., & Fan, J. (2012). Effects of motivation on reward and attentional networks: an fMRI study. *Brain and behavior, 2*(6), 741-753. doi: 10.1002/brb3.80

Ivanov, I., Liu, X., Shulz, K., Fan, J., London, E., Friston, K., . . . Newcorn, J.H. (2012). Parental substance abuse and function of the motivation and behavioral inhibition systems in drug-naive youth. *Psychiatry research, 201*(2), 128-135. doi: 10.1016/j.pscychresns.2011.08.004

Izquierdo, A., & Jentsch, J.D. (2012). Reversal learning as a measure of impulsive and compulsive behavior in addictions. *Psychopharmacology, 219*(2), 607-620. doi: 10.1007/s00213-011-2579-7

Jacobsen, L.K., Giedd, J.N., Gottschalk, C., Kosten, T.R., & Krystal, J.H. (2001). Quantitative morphology of the caudate and putamen in patients with cocaine dependence. *The American journal of psychiatry, 158*(3), 486-489.

Jacobsen, L.K., Pugh, K.R., Mencl, W.E., & Gelernter, J. (2006). C957T polymorphism of the dopamine D2 receptor gene modulates the effect of nicotine on working memory performance and cortical processing efficiency. *Psychopharmacology, 188*(4), 530-540. doi: 10.1007/s00213-006-0469-1

Jacobson, S.W., Jacobson, J.L., Sokol, R.J., Martier, S.S., Ager, J.W., & Kaplan, M.G. (1991). Maternal recall of alcohol, cocaine, and marijuana use during pregnancy. *Neurotoxicology and teratology, 13*(5), 535-540.

Janca, A., Robins, L.N., Cottler, L.B., & Early, T.S. (1992). Clinical observation of assessment using the Composite International Diagnostic Interview (CIDI). An analysis of the CIDI Field Trials--Wave II at the St Louis site. *The British journal of psychiatry : the journal of mental science, 160*, 815-818.

Johansen-Berg, H. (2009). Imaging the relationship between structure, function and behaviour in the human brain. *Brain structure & function, 213*(6), 499-500. doi: 10.1007/s00429-009-0220-x

Johansson, A.K., & Hansen, S. (2002). Novelty seeking and harm avoidance in relation to alcohol drinking in intact rats and following axon-sparing lesions to the amygdala and ventral striatum. *Alcohol and alcoholism, 37*(2), 147-156.

Kaplan, E.L., & Meier, P. (1958). Nonparametric estimation from incomplete observations. *Journal of American Statistical Association, 53*, 457-481.

Kessler, R.M., Whetsell, W.O., Ansari, M.S., Votaw, J.R., de Paulis, T., Clanton, J.A., . . . Manning, R.G. (1993). Identification of extrastriatal dopamine D2 receptors in post mortem human brain with [125I]epidepride. *Brain research, 609*(1-2), 237-243.

Kraschewski, A., Reese, J., Anghelescu, I., Winterer, G., Schmidt, L.G., Gallinat, J., . . . Wernicke, C. (2009). Association of the dopamine D2 receptor gene with alcohol dependence: haplotypes and subgroups of alcoholics as key factors for understanding receptor function. *Pharmacogenetics and genomics, 19*(7), 513-527.

Kuo, P.H., Chih, Y.C., Soong, W.T., Yang, H.J., & Chen, W.J. (2004). Assessing personality features and their relations with behavioral problems in adolescents: Tridimensional Personality Questionnaire and Junior Eysenck Personality Questionnaire. *Comprehensive psychiatry, 45*(1), 20-28. doi: 10.1016/j.comppsych.2003.09.011

Lacerda, A.L., Hardan, A.Y., Yorbik, O., & Keshavan, M.S. (2003). Measurement of the orbitofrontal cortex: a validation study of a new method. *NeuroImage, 19*(3), 665-673.

Lawford, B.R., Young, R.M., Swagell, C.D., Barnes, M., Burton, S.C., Ward, W.K., . . . Morris, C.P. (2005). The C/C genotype of the C957T polymorphism of the dopamine D2 receptor is associated with schizophrenia. *Schizophrenia research, 73*(1), 31-37. doi: 10.1016/j.schres.2004.08.020

Lawrence, N.S., Jollant, F., O'Daly, O., Zelaya, F., & Phillips, M.L. (2009). Distinct roles of prefrontal cortical subregions in the Iowa Gambling Task. *Cerebral cortex, 19*(5), 1134-1143. doi: 10.1093/cercor/bhn154

Lee, A.K., Jerram, M., Fulwiler, C., & Gansler, D.A. (2011). Neural correlates of impulsivity factors in psychiatric patients and healthy volunteers: a voxel-based morphometry study. *Brain imaging and behavior, 5*(1), 52-64. doi: 10.1007/s11682-010-9112-1

Lee, B., London, E.D., Poldrack, R.A., Farahi, J., Nacca, A., Monterosso, J.R., . . . Mandelkern, M.A. (2009). Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 29*(47), 14734-14740. doi: 10.1523/JNEUROSCI.3765-09.2009

Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., & Dagher, A. (2002). Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 27*(6), 1027-1035. doi: 10.1016/S0893-133X(02)00366-4

Lezak, M.D., Howieson, D.B., Bigler, E.D., & Tranel, D. (2012). *Neuropsychological Assessment* (5th ed.). USA: Oxford University Press.

Li, J., Ma, H., Zhou, H., Huang, Y., Wu, L., & Zhu, G. (2011). Association between DARPP-32 gene polymorphism and personality traits in healthy Chinese-Han subjects. *Journal of molecular neuroscience : MN, 44*(1), 48-52. doi: 10.1007/s12031-011-9505-7

Li, S.C., Papenberg, G., Nagel, I.E., Preuschhof, C., Schroder, J., Nietfeld, W., . . . Backman, L. (2013). Aging magnifies the effects of dopamine transporter and D2 receptor genes on backward serial memory. *Neurobiology of aging, 34*(1), 358 e351-310. doi: 10.1016/j.neurobiolaging.2012.08.001

Lisiecka, D.M., Carballedo, A., Fagan, A.J., Ferguson, Y., Meaney, J., & Frodl, T. (2013). Recruitment of the left hemispheric emotional attention neural network in risk for and protection from depression. *Journal of psychiatry & neuroscience : JPN, 38*(2), 117-128. doi: 10.1503/jpn.110188

Looi, J.C., Lindberg, O., Liberg, B., Tatham, V., Kumar, R., Maller, J., . . . Wahlund, L.O. (2008). Volumetrics of the caudate nucleus: reliability and validity of a new manual tracing protocol. *Psychiatry research, 163*(3), 279-288. doi: 10.1016/j.pscychresns.2007.07.005

Lu, L.H., Dapretto, M., O'Hare, E.D., Kan, E., McCourt, S.T., Thompson, P.M., . . . Sowell, E.R. (2009). Relationships between brain activation and brain structure in normally developing children. *Cerebral cortex, 19*(11), 2595-2604. doi: 10.1093/cercor/bhp011

Lucantonio, F., Stalnaker, T.A., Shaham, Y., Niv, Y., & Schoenbaum, G. (2012). The impact of orbitofrontal dysfunction on cocaine addiction. *Nature neuroscience, 15*(3), 358-366. doi: 10.1038/nn.3014

Lukasiewicz, M., Neveu, X., Blecha, L., Falissard, B., Reynaud, M., & Gasquet, I. (2008). Pathways to substance-related disorder: a structural model approach exploring the influence of temperament, character, and childhood adversity in a national cohort of prisoners. *Alcohol and alcoholism, 43*(3), 287-295. doi: 10.1093/alcalc/agm183

MacPherson, L., Magidson, J.F., Reynolds, E.K., Kahler, C.W., & Lejuez, C.W. (2010). Changes in sensation seeking and risk-taking propensity predict increases in alcohol use among early adolescents. *Alcoholism, clinical and experimental research, 34*(8), 1400-1408. doi: 10.1111/j.1530-0277.2010.01223.x

Magnotta, V.A., Harris, G., Andreasen, N.C., O'Leary, D.S., Yuh, W.T., & Heckel, D. (2002). Structural MR image processing using the BRAINS2 toolbox. *Computerized medical imaging and graphics : the official journal of the Computerized Medical Imaging Society, 26*(4), 251-264.

Markett, S., Montag, C., Walter, N.T., & Reuter, M. (2011). Evidence for the modality independence of the genetic epistasis between the dopaminergic and cholinergic system on working memory capacity. *European neuropsychopharmacology : the journal of the*

European College of Neuropsychopharmacology, 21(2), 216-220. doi: 10.1016/j.euroneuro.2010.10.011

Marmorstein, N.R., Iacono, W.G., & McGue, M. (2009). Alcohol and illicit drug dependence among parents: associations with offspring externalizing disorders. *Psychological medicine, 39*(1), 149-155. doi: 10.1017/S0033291708003085

Matarazzo, J.D., Wiens, A.N., Matarazzo, R.G., & Goldstein, S.G. (1974). Psychometric and clinical test-retest reliability of the Halstead impairment index in a sample of healthy, young, normal men. *The Journal of nervous and mental disease, 158*(1), 37-49.

Matsuo, K., Nicoletti, M., Nemoto, K., Hatch, J.P., Peluso, M.A., Nery, F.G., & Soares, J.C. (2009). A voxel-based morphometry study of frontal gray matter correlates of impulsivity. *Human brain mapping, 30*(4), 1188-1195. doi: 10.1002/hbm.20588

McGue, M., Slutske, W., & Iacono, W.G. (1999). Personality and substance use disorders: II. Alcoholism versus drug use disorders. *Journal of consulting and clinical psychology, 67*(3), 394-404.

Melchior, M., Choquet, M., Le Strat, Y., Hassler, C., & Gorwood, P. (2011). Parental alcohol dependence, socioeconomic disadvantage and alcohol and cannabis dependence among young adults in the community. *European psychiatry : the journal of the Association of European Psychiatrists, 26*(1), 13-17. doi: 10.1016/j.eurpsy.2009.12.011

Menzies, L., Chamberlain, S.R., Laird, A.R., Thelen, S.M., Sahakian, B.J., & Bullmore, E.T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neuroscience and biobehavioral reviews, 32*(3), 525-549. doi: 10.1016/j.neubiorev.2007.09.005

Miettunen, J., Kantojarvi, L., Ekelund, J., Veijola, J., Karvonen, J.T., Peltonen, L., . . . Joukamaa, M. (2004). A large population cohort provides normative data for investigation of temperament. *Acta psychiatrica Scandinavica, 110*(2), 150-157. doi: 10.1111/j.1600-0047.2004.00344.x

Miettunen, J., & Raevuori, A. (2012). A meta-analysis of temperament in axis I psychiatric disorders. *Comprehensive psychiatry, 53*(2), 152-166. doi: 10.1016/j.comppsych.2011.03.008

Mokdad, A.H., Marks, J.S., Stroup, D.F., & Gerberding, J.L. (2004). Actual causes of death in the United States, 2000. *JAMA : the journal of the American Medical Association, 291*(10), 1238-1245. doi: 10.1001/jama.291.10.1238

Monakhov, M., Golimbet, V., Abramova, L., Kaleda, V., & Karpov, V. (2008). Association study of three polymorphisms in the dopamine D2 receptor gene and schizophrenia in the

Russian population. *Schizophrenia research, 100*(1-3), 302-307. doi: 10.1016/j.schres.2008.01.007

Montag, C., Bleek, B., Faber, J., & Reuter, M. (2012). The role of the DRD2 C957T polymorphism in neuroticism in persons who stutter and healthy controls. *Neuroreport, 23*(4), 246-250. doi: 10.1097/WNR.0b013e3283505b8a

Montag, C., Weber, B., Jentgens, E., Elger, C., & Reuter, M. (2010). An epistasis effect of functional variants on the BDNF and DRD2 genes modulates gray matter volume of the anterior cingulate cortex in healthy humans. *Neuropsychologia, 48*(4), 1016-1021. doi: 10.1016/j.neuropsychologia.2009.11.027

Moreno-Lopez, L., Catena, A., Fernandez-Serrano, M.J., Delgado-Rico, E., Stamatakis, E.A., Perez-Garcia, M., & Verdejo-Garcia, A. (2012). Trait impulsivity and prefrontal gray matter reductions in cocaine dependent individuals. *Drug and alcohol dependence, 125*(3), 208-214. doi: 10.1016/j.drugalcdep.2012.02.012

Morozova, T.V., Goldman, D., Mackay, T.F., & Anholt, R.R. (2012). The genetic basis of alcoholism: multiple phenotypes, many genes, complex networks. *Genome biology, 13*(2), 239. doi: 10.1186/gb-2012-13-2-239

Nederhof, E., Bouma, E.M., Riese, H., Laceulle, O.M., Ormel, J., & Oldehinkel, A.J. (2010). Evidence for plasticity genotypes in a gene-gene-environment interaction: the TRAILS study. *Genes, brain, and behavior, 9*(8), 968-973. doi: 10.1111/j.1601-183X.2010.00637.x

Nees, F., Tzschoppe, J., Patrick, C.J., Vollstadt-Klein, S., Steiner, S., Poustka, L., . . . Flor, H. (2012). Determinants of early alcohol use in healthy adolescents: the differential contribution of neuroimaging and psychological factors. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 37*(4), 986-995. doi: 10.1038/npp.2011.282

Neumark, Y.D., Van Etten, M.L., & Anthony, J.C. (2000). "Drug dependence" and death: survival analysis of the Baltimore ECA sample from 1981 to 1995. *Substance use & misuse, 35*(3), 313-327.

Nikolova, Y.S., Ferrell, R.E., Manuck, S.B., & Hariri, A.R. (2011). Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 36*(9), 1940-1947. doi: 10.1038/npp.2011.82

Noble, E.P. (2003). D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics, 116B*, 103-125. doi: 10.1002/ajmg.b.10005

Noel, X., Brevers, D., Bechara, A., Hanak, C., Kornreich, C., Verbanck, P., & Le Bon, O. (2011). Neurocognitive determinants of novelty and sensation-seeking in individuals with alcoholism. *Alcohol and alcoholism, 46*(4), 407-415. doi: 10.1093/alcalc/agr048

Nyman, E.S., Loukola, A., Varilo, T., Ekelund, J., Veijola, J., Joukamaa, M., . . . Peltonen, L. (2009). Impact of the dopamine receptor gene family on temperament traits in a population-based birth cohort. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics, 150B*(6), 854-865. doi: 10.1002/ajmg.b.30908

Pangelinan, M.M., Zhang, G., VanMeter, J.W., Clark, J.E., Hatfield, B.D., & Haufler, A.J. (2011). Beyond age and gender: relationships between cortical and subcortical brain volume and cognitive-motor abilities in school-age children. *NeuroImage, 54*(4), 3093-3100. doi: 10.1016/j.neuroimage.2010.11.021

Pawlak, C.R., Ho, Y.J., & Schwarting, R.K. (2008). Animal models of human psychopathology based on individual differences in novelty-seeking and anxiety. *Neuroscience and biobehavioral reviews, 32*(8), 1544-1568. doi: 10.1016/j.neubiorev.2008.06.007

Peper, J.S., Mandl, R.C., Braams, B.R., de Water, E., Heijboer, A.C., Koolschijn, P.C., & Crone, E.A. (2013). Delay Discounting and Frontostriatal Fiber Tracts: A Combined DTI and MTR Study on Impulsive Choices in Healthy Young Adults. *Cerebral cortex, 23*(7), 1695-1702. doi: 10.1093/cercor/bhs163

Perkins, K.A., Lerman, C., Grottenthaler, A., Ciccocioppo, M.M., Milanak, M., Conklin, C.A., . . . Benowitz, N.L. (2008). Dopamine and opioid gene variants are associated with increased smoking reward and reinforcement owing to negative mood. *Behavioural pharmacology, 19*(5-6), 641-649. doi: 10.1097/FBP.0b013e32830c367c

Ponce, G., Hoenicka, J., Jimenez-Arriero, M.A., Rodriguez-Jimenez, R., Aragues, M., Martin-Sune, N., . . . Palomo, T. (2008). DRD2 and ANKK1 genotype in alcohol-dependent patients with psychopathic traits: association and interaction study. *The British journal of psychiatry : the journal of mental science, 193*(2), 121-125. doi: 10.1192/bjp.bp.107.041582

Price, J.L. (2007). Definition of the orbital cortex in relation to specific connections with limbic and visceral structures and other cortical regions. *Annals of the New York Academy of Sciences, 1121*, 54-71. doi: 10.1196/annals.1401.008

Reitan, R.M. (1971). Trail making test results for normal and brain-damaged children. *Perceptual and motor skills, 33*(2), 575-581.

Robins, L.N., Helzer, J.E., Croughan, J., & Ratcliff, K.S. (1981). National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. *Archives of general psychiatry, 38*(4), 381-389.

Rodriguez-Jimenez, R., Hoenicka, J., Jimenez-Arriero, M.A., Ponce, G., Bagney, A., Aragues, M., & Palomo, T. (2006). Performance in the Wisconsin Card Sorting Test and the C957T polymorphism of the DRD2 gene in healthy volunteers. *Neuropsychobiology, 54*(3), 166-170. doi: 10.1159/000098652

Rubio, G., Manzanares, J., Jimenez, M., Rodriguez-Jimenez, R., Martinez, I., Iribarren, M.M., . . . Palomo, T. (2008). Use of cocaine by heavy drinkers increases vulnerability to developing alcohol dependence: a 4-year follow-up study. *The Journal of clinical psychiatry, 69*(4), 563-570.

Sanchez-Cubillo, I., Perianez, J.A., Adrover-Roig, D., Rodriguez-Sanchez, J.M., Rios-Lago, M., Tirapu, J., & Barcelo, F. (2009). Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society : JINS, 15*(3), 438-450. doi: 10.1017/S1355617709090626

Savitz, J.B., & Jansen, P. (2003). The stroop color-word interference test as an indicator of ADHD in poor readers. *The Journal of genetic psychology, 164*(3), 319-333. doi: 10.1080/00221320309597986

Schilling, C., Kuhn, S., Romanowski, A., Banaschewski, T., Barbot, A., Barker, G.J., . . . Gallinat, J. (2013). Common structural correlates of trait impulsiveness and perceptual reasoning in adolescence. *Human brain mapping, 34*(2), 374-383. doi: 10.1002/hbm.21446

Schneider, S., Peters, J., Bromberg, U., Brassen, S., Miedl, S.F., Banaschewski, T., . . . Buchel, C. (2012). Risk taking and the adolescent reward system: a potential common link to substance abuse. *The American journal of psychiatry, 169*(1), 39-46. doi: 10.1176/appi.ajp.2011.11030489

Schulte, T., Muller-Oehring, E.M., Sullivan, E.V., & Pfefferbaum, A. (2012). Synchrony of corticostriatal-midbrain activation enables normal inhibitory control and conflict processing in recovering alcoholic men. *Biological psychiatry, 71*(3), 269-278. doi: 10.1016/j.biopsych.2011.10.022

Semrud-Clikeman, M., Steingard, R.J., Filipek, P., Biederman, J., Bekken, K., & Renshaw, P.F. (2000). Using MRI to examine brain-behavior relationships in males with attention deficit disorder with hyperactivity. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(4), 477-484. doi: 10.1097/00004583-200004000-00017

Soriano-Mas, C., Harrison, B.J., Pujol, J., Lopez-Sola, M., Hernandez-Ribas, R., Alonso, P., . . . Cardoner, N. (2013). Structural covariance of the neostriatum with regional gray matter volumes. *Brain structure & function, 218*(3), 697-709. doi: 10.1007/s00429-012-0422-5

Steinberg, L. (2010). A dual systems model of adolescent risk-taking. *Developmental psychobiology, 52*(3), 216-224. doi: 10.1002/dev.20445

Sullivan, E.V. (2007). Alcohol and drug dependence: brain mechanisms and behavioral impact. *Neuropsychology review, 17*(3), 235-238. doi: 10.1007/s11065-007-9039-5

Swagell, C.D., Lawford, B.R., Hughes, I.P., Voisey, J., Feeney, G.F., van Daal, A., . . . Young, R.M. (2012). DRD2 C957T and TaqIA genotyping reveals gender effects and unique low-risk and high-risk genotypes in alcohol dependence. *Alcohol and alcoholism, 47*(4), 397-403. doi: 10.1093/alcalc/ags047

Tellegen, A., Lykken, D.T., Bouchard, T.J., Jr., Wilcox, K.J., Segal, N.L., & Rich, S. (1988). Personality similarity in twins reared apart and together. *Journal of personality and social psychology, 54*(6), 1031-1039.

Tessner, K.D., & Hill, S.Y. (2010). Neural circuitry associated with risk for alcohol use disorders. *Neuropsychology review, 20*(1), 1-20. doi: 10.1007/s11065-009-9111-4

Tombaugh, T.N. (2004). Trail Making Test A and B: normative data stratified by age and education. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, 19*(2), 203-214. doi: 10.1016/S0887-6177(03)00039-8

Verdejo-Garcia, A.J., Perales, J.C., & Perez-Garcia, M. (2007). Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addictive behaviors, 32*(5), 950-966. doi: 10.1016/j.addbeh.2006.06.032

Vidal-Infer, A., Arenas, M.C., Daza-Losada, M., Aguilar, M.A., Minarro, J., & Rodriguez-Arias, M. (2012). High novelty-seeking predicts greater sensitivity to the conditioned rewarding effects of cocaine. *Pharmacology, biochemistry, and behavior, 102*(1), 124-132. doi: 10.1016/j.pbb.2012.03.031

Villablanca, J.R. (2010). Why do we have a caudate nucleus? *Acta neurobiologiae experimentalis, 70*(1), 95-105.

Voisey, J., Swagell, C.D., Hughes, I.P., Morris, C.P., van Daal, A., Noble, E.P., . . . Lawford, B.R. (2009). The DRD2 gene 957C>T polymorphism is associated with posttraumatic stress disorder in war veterans. *Depression and anxiety, 26*(1), 28-33. doi: 10.1002/da.20517

Voisey, J., Swagell, C.D., Hughes, I.P., van Daal, A., Noble, E.P., Lawford, B.R., . . . Morris, C.P. (2012). A DRD2 and ANKK1 haplotype is associated with nicotine dependence. *Psychiatry research, 196*(2-3), 285-289. doi: 10.1016/j.psychres.2011.09.024

Volkow, N.D., & Li, T.K. (2005). Drugs and alcohol: treating and preventing abuse, addiction and their medical consequences. *Pharmacology & therapeutics, 108*(1), 3-17. doi: 10.1016/j.pharmthera.2005.06.021

Volkow, N.D., Wang, G.J., Begleiter, H., Porjesz, B., Fowler, J.S., Telang, F., . . . Thanos, P.K. (2006). High levels of dopamine D2 receptors in unaffected members of alcoholic families: possible protective factors. *Archives of general psychiatry, 63*(9), 999-1008. doi: 10.1001/archpsyc.63.9.999

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., Gifford, A., . . . Pappas, N. (1999). Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. *The American journal of psychiatry, 156*(9), 1440-1443.

Walhovd, K.B., Moe, V., Slinning, K., Due-Tonnessen, P., Bjornerud, A., Dale, A.M., . . . Fischl, B. (2007). Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. *NeuroImage, 36*(4), 1331-1344. doi: 10.1016/j.neuroimage.2007.03.070

Wang, G.J., Smith, L., Volkow, N.D., Telang, F., Logan, J., Tomasi, D., . . . Fowler, J.S. (2012). Decreased dopamine activity predicts relapse in methamphetamine abusers. *Molecular psychiatry, 17*(9), 918-925. doi: 10.1038/mp.2011.86

Wernicke, C., Reese, J., Kraschewski, A., Winterer, G., Rommelspacher, H., & Gallinat, J. (2009). Distinct haplogenotypes of the dopamine D2 receptor gene are associated with non-smoking behaviour and daily cigarette consumption. *Pharmacopsychiatry, 42*(2), 41-50. doi: 10.1055/s-0028-1085444

White, M.J., Lawford, B.R., Morris, C.P., & Young, R.M. (2009). Interaction between DRD2 C957T polymorphism and an acute psychosocial stressor on reward-related behavioral impulsivity. *Behavior genetics, 39*(3), 285-295. doi: 10.1007/s10519-008-9255-7

Whitmer, A.J., & Gotlib, I.H. (2012). Depressive rumination and the C957T polymorphism of the DRD2 gene. *Cognitive, affective & behavioral neuroscience, 12*(4), 741-747. doi: 10.3758/s13415-012-0112-z

Woodward, N.D., Zald, D.H., Ding, Z., Riccardi, P., Ansari, M.S., Baldwin, R.M., . . . Kessler, R.M. (2009). Cerebral morphology and dopamine D2/D3 receptor distribution in humans: a combined [18F]fallypride and voxel-based morphometry study. *NeuroImage, 46*(1), 31-38. doi: 10.1016/j.neuroimage.2009.01.049

Xu, H., Kellendonk, C.B., Simpson, E.H., Keilp, J.G., Bruder, G.E., Polan, H.J., . . . Gilliam, T.C. (2007). DRD2 C957T polymorphism interacts with the COMT Val158Met polymorphism in human working memory ability. *Schizophrenia research, 90*(1-3), 104-107. doi: 10.1016/j.schres.2006.10.001

Yang, B.Z., Kranzler, H.R., Zhao, H., Gruen, J.R., Luo, X., & Gelernter, J. (2008). Haplotypic variants in DRD2, ANKK1, TTC12, and NCAM1 are associated with comorbid alcohol and drug dependence. *Alcoholism, clinical and experimental research, 32*(12), 2117-2127. doi: 10.1111/j.1530-0277.2008.00800.x

Yau, W.Y., Zubieta, J.K., Weiland, B.J., Samudra, P.G., Zucker, R.A., & Heitzeg, M.M. (2012). Nucleus accumbens response to incentive stimuli anticipation in children of alcoholics: relationships with precursive behavioral risk and lifetime alcohol use. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 32*(7), 2544-2551. doi: 10.1523/JNEUROSCI.1390-11.2012

Zald, D.H., Cowan, R.L., Riccardi, P., Baldwin, R.M., Ansari, M.S., Li, R., . . . Kessler, R.M. (2008). Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 28*(53), 14372-14378. doi: 10.1523/JNEUROSCI.2423-08.2008