GENETIC INFLUENCES OF DOPAMINE AND GABA ON ADOLESCENT
COGNITION

A Dissertation
submitted to the Faculty of the
Graduate School of Arts and Sciences
of Georgetown University
in partial fulfillment of the requirements for the
degree of
Doctor of Philosophy
in Neuroscience

By

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Washington, DC
August 29, 2017

ProQuest Number: 10746640

ProQuest 10746640

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ABSTRACT

Adolescence is a time of exploration, but also risk taking, such as alcohol use.

What places individuals' at risk has not been fully elucidated. Twin studies of adult

alcohol use disorders (AUD's) found genetics account for around 60% of the variability.

Numerous genetic association studies have been done, though most investigated linkage

with genetic loci; not how loci confer risk. If genes associated with adult AUD's have

impact during adolescence and alcohol use initiation, it's likely they impact cognitive

functioning, predisposing adolescents to such risky decision-making. Three genetic

polymorphisms associated with adult AUD's are the C allele of C957T in the dopamine

receptor D2 gene (DRD2), the 10 repeat allele (10R) of the 40 bp VNTR in the dopamine

transporter gene (DAT1), and the G allele of rs279826 in the GABA-A receptor α2

subunit gene (GABRA2). The current investigation longitudinally investigated these

polymorphisms on adolescent cognitive functioning using fMRI. This included inhibitory

control (Go-NoGo task), attentional bias (ecStroop task), and risky decision-

making/reward response (WoF task). fMRI analyses included activation differences and

functional connectivity. Lastly, genetic influence on alcohol use initiation was

investigated. It was hypothesized risk alleles had lower inhibitory control, greater

attentional bias, risky decision-making, reward response, and risk to alcohol use

initiation. DRD2 suggested the C allele had less neural efficiency during the Go-NoGo

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and WoF. They were less accurate during the ecStroop, and became more neuronally reactive to stimuli as they aged. DAT1 only affected WoF, with 10R making more risky decisions, having less neural efficiency and greater response to reward. Results for GABA were opposing, suggesting the lower risk A allele had lower neuronal efficiency during the Go-NoGo and ecStroop, while the G allele made more risky decisions, had less neural efficiency and greater response to reward during the WoF. However, two results suggest developmental effects during the ecStroop, in that cognitive control for the G allele decreases over adolescence. Lastly, no polymorphism was associated with alcohol use initiation. Though this study found no association with alcohol use initiation, it supports the proposition of studying genetic effects associated with adult AUD's on adolescent cognitive function.

Many cheers go out to my fellow students in the IPN. We helped each other over the years of the program grow, push, and go further.

I would like to thank my family for their support and helping me develop the ability to think on my own. Without that, I probably could not have become a scientist.

Last, but not least, I want to thank the love of my life, Jaime Stevens, and her constant support through this journey. You are a shining star that has helped me keep going.

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CHAPTER I: Introduction

Adolescence is a time of exploration of the environment, with newfound autonomy, but also a time of greater risk taking, which can include dangerous behaviors such as use of alcohol and illicit drugs. This developmental period is also a time of significant brain maturation, particularly in the prefrontal cortex (PFC) that provides "top-down" cognitive control and the limbic system that is involved in emotional and reward related responses (Dahl, 2004; Duijvenvoorde, Achterberg, Braams, Peters, & Crone, 2016; Tomás Paus, 2005; Rubia, 2013). However, research suggests that limbic structures mature at a quicker rate than the PFC. In particular, the cognitive processes that are supported by the limbic system such as emotionally salient stimuli, novelty, and rewards more generally are heightened during adolescence, whereas the PFC is not yet fully developed and as such does not provide sufficient top-down executive control of those responses. This is known as the dual systems model (Casey, Jones, & Somerville, 2011; Ernst, Pine, & Hardin, 2006; Galvan, Hare, Voss, Glover, & Casey, 2007; Harden & Tucker-Drob, 2011; Shulman, Harden, Chein, & Steinberg, 2016). This relative immaturity of executive control processes can increase tendencies for impulsive and risky decision making during adolescence (Steinberg et al., 2008). However, there are large individual differences between adolescents regarding risky decision-making and impulsivity; therefore, understanding the underlying causes of these differences is important for mitigating the negative consequences of these behaviors including initiation of alcohol use.

Disorders that involve addiction, such as AUD's, are known to have a strong genetic component. For instance, twin studies have shown alcohol use disorders are

around 60% heritable (Heath et al., 1997; Tsuang, Bar, Harley, & Lyons, 2001). A multitude of genes have been investigated, either through candidate gene approaches, or through the use of genome-wide association studies. However, many of these studies only looked for an association between the gene and addictive behavior and did not investigate how these genes could lead to such behavior (Bierut et al., 2010; Dick & Foroud, 2003; Fauth-Bühler & Kiefer, 2016; Köhnke, 2008). It is likely some of these genes are having negative impact on executive functioning, such as reduced inhibitory control or less control over attentional biases to salient stimuli such as alcohol cues, which could lead individuals to pursue a greater amount of risky behaviors. In support of this prospective, twin studies have shown a high convergence of genetic risk factors in constructs such as AUD's, attention-deficit/hyperactivity disorder (ADHD), conduct disorder and antisocial personality (Krueger et al., 2002; Young, Stallings, Corley, Krauter, & Hewitt, 2000). Factors common to all of these are behavioral disinhibition and reduced executive function. As these are less well developed during adolescence, it is pertinent to study the extent to which genetic effects on these cognitive processes account for variations in these behaviors and ultimately lead to heightened adolescent risk taking.

The neurotransmitter dopamine is fundamental in reward processing, and therefore has been studied extensively in regards to addiction (Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015; Schultz, 2013). However, its action is not limited to reward and is important for other brain functions, including cognitive function mediated by the PFC (Cools & D'Esposito, 2011). Two dopaminergic pathways are crucial for reward processing. The mesolimbic pathway transmits dopamine from the ventral tegmental area (VTA) to the ventral striatum, which includes the nucleus accumbens, and is important in

registering the receipt of reward (Carlezon & Thomas, 2009; Ikemoto, 2010). Second is the nigrostriatal pathway originating in the substantia nigra and projecting to the dorsal striatum, containing the caudate and putamen (Haber, Fudge, & McFarland, 2000; Rice & Cragg, 2008). These regions are critical in control of motor movement, but also are important in associative learning involving reward (Asaad & Eskandar, 2011; Haruno & Kawato, 2005; Kätsyri, Hari, Ravaja, & Nummenmaa, 2013). In relation to cognitive function, a third dopaminergic pathway, mesocortical, originates in the VTA, but instead projects to the PFC (Ikemoto, 2010). It increases cognitive function, by potentially increasing stability of neural networks needed to complete a cognitive task currently being performed (Cools & D'Esposito, 2011).

Dopamine has several receptors, one of which is the dopamine receptor D2 (DR2), encoded by the DRD2 gene. DR2 is traditionally viewed as an autoreceptor having an inhibitory role on dopamine release, though research has shown in certain situations through alternative splicing, other versions can be formed having excitatory effects postsynaptically (Beaulieu & Gainetdinov, 2011). One of the polymorphisms affecting the DRD2 gene is a SNP, known as both C957T and rs6277, which has been implicated in alcohol misuse, with the C allele more often being associated with risk compared to the T allele (Hill et al., 2008; Kraschewski et al., 2009; Ponce et al., 2008; Swagell et al., 2012; Voisey et al., 2012). Further studies in adults have found the C allele associated with less inhibitory control, greater reward related memory formation in hippocampal and striatal regions, and worse control of attentional resources (Beste, Stock, Epplen, & Arning, 2016; Colzato, Slagter, de Rover, & Hommel, 2011; Richter et al., 2017; M. J. White, Lawford, Morris, & Young, 2009). These studies further support

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the prospective of investigating the impact genes associated with adults AUD's have on adolescent cognitive functioning. Lastly, studies of DRD2 have shown a developmental effect during adolescence, in which expression is decreasing until reaching adult levels, and further highlights the need to investigate C957T developmentally during this period (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000; Weickert et al., 2007).

Dopaminergic function in the brain is not only mediated by receptors, but also through controlling the amount of dopamine in the synapse by its clearance. A primary way clearance is facilitated is reuptake into the presynaptic neuron, through the protein called the dopamine transporter (DAT) encoded by the DAT1 gene (Zahniser, Larson, & Gerhardt, 1999). DAT has the highest expression in regions including the striatum, VTA and substantia nigra where it is the primary mechanism of dopamine clearance (Hall et al., 1999; Sasaki et al., 2012). It is also expressed in cortical areas such as the PFC, but in lower amounts, where other dopamine clearance mechanisms exist such as catechol-O-methyltransferase and the norepinephrine transporter (Käenmäki et al., 2010; Morón, Brockington, Wise, Rocha, & Hope, 2002). The DAT1 gene contains a 40-base pair variable number tandem repeat (VNTR) polymorphism that the most common number of repeats are 9 (9R) and 10 (10R) (Vandenbergh et al., 1992). The 10R allele has most often been linked with alcohol misuse (Barkley, Smith, Fischer, & Navia, 2006; Guo, Cai, Guo, Wang, & Harris, 2010; Guo, Roettger, & Shih, 2007; Guo, Tong, Xie, & Lange, 2007; Hopfer et al., 2005; Stogner, 2015). Its influence on inhibitory control has been extensively studied, in both adults and adolescents, though most often in the context of ADHD. The majority of studies have found more association of the 10R with both ADHD and lower inhibitory control (Bédard et al., 2010; Braet et al., 2011; Congdon,

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Constable, Lesch, & Canli, 2009; Dresler et al., 2010; Kasparbauer et al., 2015; Loo et al., 2003). However, more investigation is needed in typically developing adolescence. A limited amount of studies have directly investigated risky decision-making experimentally in typically developed adults, finding the 10R to make more risky decisions and one of the studies found greater activation in the ventral striatum while making decisions (Mata, Hau, Papassotiropoulos, & Hertwig, 2012; Zhong, Chark, Ebstein, & Chew, 2012). However, more research is needed in regard to DAT1s affect directly on risky decision making. Lastly, the 10R has been associated with less attentional control in an adult sample during an attentional blink paradigm (Colzato, Pratt, & Hommel, 2010). Expression of DAT1 increases through childhood, but stabilizes before adolescence (Meng, Ozawa, Itoh, & Takashima, 1999). However, given most the research of DAT1 during adolescence involved ADHD, more investigation is warranted in typically developing youth.

Another neurotransmitter system that has been implicated in multiple genetic studies of alcohol use is gamma-Aminobutyric acid (GABA). GABA is the main inhibitory neurotransmitter throughout the brain, and therefore affects almost every brain region and function. One of its mechanisms of action is through the $GABA_A$ receptor (Kilb, 2012). These receptors are pentameric containing five protein subunits. Two subunits in a given $GABA_A$ receptor are the α-subunit, though in humans, there are six different forms, being α1-6 (Chebib & Johnston, 1999). Investigations have found single nucleotide polymorphisms (SNP's) in the α2-subunit gene of the receptor to be associated with adult alcohol misuse. One of the SNP's, rs279826, has repeatedly been associated, with the G allele versus the A allele conferring risk in the majority of investigations

(Agrawal et al., 2006; H. J. Edenberg et al., 2004; Kramer et al., 2008; Trucco, Villafuerte, Heitzeg, Burmeister, & Zucker, 2014; Uhart et al., 2013; Villafuerte et al., 2012; Villafuerte, Strumba, Stoltenberg, Zucker, & Burmeister, 2013). In addition, two adult studies have found the G allele was linked with greater self reported impulsivity, with one of these also finding it associated with greater response to reward using fMRI (Villafuerte et al., 2012, 2013), and three studies in adolescence found it was linked with externalizing behaviors (Dick et al., 2009; Trucco, Villafuerte, Heitzeg, Burmeister, & Zucker, 2016; Villafuerte, Trucco, Heitzeg, Burmeister, & Zucker, 2014). These studies highlight rs279826 has effects on cognitive processing. Lastly, the α2-subunit has a developmental effect, in that expression of it decreases over adolescence until reaching adult levels, showing the importance of investigating rs279826 during this developmental period (Cruz, Eggan, & Lewis, 2003; Duncan et al., 2010; Hashimoto et al., 2009).

Risky decision-making can take many forms. For instance, it can be choosing to drink alcohol and drive or having unprotected sex. For purposes of this investigation, it refers to making a decision when there is uncertainty in the outcome between choices, which could lead to beneficial or adverse results. One way to investigate this experimentally is to have individuals make a choice between variable monetary reward and loss probabilities. The Wheel of Fortune task (WoF) is an example of this (Ernst et al., 2004). Participants choose between larger amounts of money with a low probability of winning but high probability of losing, versus a smaller amount of money with a higher probability of winning but lower chance of losing. Therefore, comparing when they choose low versus high probability trails gives a measure of how often they make risky decisions. In addition, investigating brain activity during winning trials give a proxy

for reward responsiveness. Brain regions found to underlie this task include the orbitofrontal cortex (OFC), medial PFC (mPFC), anterior cingulate (ACC) and subcortical structure such as the nucleus accumbens (Ernst et al., 2005; Shad et al., 2011). The WoF task has been shown to be sensitive to differentiating adolescents with and without a family history of alcohol use, and predicting future adolescent binge drinking, and is therefore an excellent task for investigating risky decision-making (Cservenka, Jones, & Nagel, 2015; Cservenka & Nagel, 2013; S. A. Jones, Cservenka, & Nagel, 2016).

Various cognitive processes can play a role in risky decision-making, one of which is inhibitory control. Inhibitory control is the ability to inhibit or regulate prepotent behavioral responses, overriding strong but inappropriate behavioral tendencies (Simmonds, Pekara, & Mostofsky, 2008). It is typically experimentally investigated by having an individual repeatedly press a button building up a prepotent response, and on specific cues, they are supposed to inhibit the button press. A common task for this is the Go-NoGo, which the participant sees a rapid sequence of single letters and they are supposed to press a button for all letters except one (Riccio, Reynolds, Lowe, & Moore, 2002). A metaanalysis of fMRI studies has shown multiple brain regions to be involved including the inferior and middle frontal gyri, insula, premotor area, inferior parietal lobe and subcortical regions such as the putamen (Simmonds et al., 2008). Lastly, there is extensive literature showing that lower inhibitory control during adolescence increases propensity for initiation of alcohol use (Barnes, Welte, Hoffman, & Dintcheff, 1999; Bates & Labouvie, 1995; Krank et al., 2011; W. A. Mason et al., 2011; Norman et al., 2011; Ohannessian & Hesselbrock, 2007; Quinn, Stappenbeck, & Fromme, 2011; H. R.

White et al., 2011). Therefore, understanding factors that lead to lower inhibitory control are pertinent.

A second cognitive function known to play a role in risky decision-making is attentional bias. Attentional bias is defined as the selective allocation of attention to a particular class of stimuli and can be mediated by emotional salience, such as cues that indicate reward, pleasure or threat (Field & Cox, 2008; J. M. G. Williams, Mathews, & MacLeod, 1996). It can have adaptive effects, such as when there is a threat and should be acted upon. However, it can have maladaptive effects, such as when an individual with an alcohol use disorder (AUD) sees alcohol cues, causing a craving for alcohol, and cognitive control is needed to divert the bias (Field, Munafò, & Franken, 2009). It has long been known AUD's are associated with attentional bias, but whether becoming addicted created the bias, or the bias existed before was not known (Field & Cox, 2008). However, studies have since shown that attentional bias can predict transition into future heavy usage of alcohol during adolescence (Janssen, Larsen, Vollebergh, & Wiers, 2015; Thush & Wiers, 2007). Attentional bias is often investigated having individuals perform a task that has neutral and emotionally valenced stimuli, and comparing performance between the two. One such task is the Emotional Counting Stroop (ecStroop), in which one to four words is displayed on a screen, and the participants is only instructed to count the number of words. However, the words can have neutral or emotionally valenced meaning, such as negative or alcohol related words, and compare performance between the trial types (Whalen, Bush, Shin, & Rauch, 2006). A recent metaanalysis of the ecStroop found brain regions including the superior frontal gyrus, mPFC, ACC, insula and fusiform gyrus were common to all the studies (Song et al., 2017). Given that

attentional bias has been shown to help predict future alcohol use adolescence, it is pertinent to investigate mechanisms that lead to greater bias.

The current investigation presents data from the Adolescent Development Study (ADS), a longitudinal study using behavioral and neuroimaging measures during adolescence to identify neurodevelopmental precursors and consequences of alcohol misuse (Fishbein, Rose, Darcey, Belcher, & VanMeter, 2016). We sought to investigate the impact the GABA α2 rs279826, DRD2 C957T and DAT1 VNTR polymorphisms have on adolescent cognitive functioning, hypothesizing the risk alleles would have negative impact. This included effects on inhibitory control, attentional bias, risky decision-making, reward response and initiation of alcohol and illicit substance use. Inhibitory control was measured by a Go-NoGo task, attentional bias by the ecStroop, and lastly risky decision-making and reward response by the WoF. All three tasks were performed while undergoing fMRI, and analyses included BOLD activation differences and functional connectivity using psychophysiological interactions (PPI). Following the participants longitudinally allowed us to investigate if there were developmental effects for the three genotypes, and also determine which adolescents had initiated alcohol and drug use. For more specific background and hypotheses for each genotype, each genetic chapter contains a more detailed introduction for each gene.

CHAPTER II: Methods

The methods used for each genetic data chapter utilized the same methods

outlined in this chapter. The only differences were in genotyping of the participants, as

each gene required different reagents and or protocol. These differences are highlighted

in the Genotyping section. The Georgetown University IRB approved all procedures for

this study. Parents provided signed written informed consent for their own and child's

participation. The child provided written assent. A Certificate of Confidentiality was

obtained from the National Institute on Alcohol Abuse and Alcoholism.

Participants

The Adolescent Development Study (ADS) focuses on a community sample of

135 early adolescents and a caregiver from the greater Washington, D.C. area. They were

recruited using a variety of strategies, primarily using a marketing database and a call

center that contacted households likely to have a child in the eligible age range and

factors related to socioeconomic status and ethnicity. Additional strategies included door-

knocking, in-person contacts in public areas, and social media all concentrated in "high

risk" communities (e.g., low income, high crime rate). Participants were followed

longitudinally, from a substance naïve baseline through two follow-up visits spaced

approximately 18-months apart. The data reported in this dissertation is from the baseline

and first follow-up visit. Adolescent inclusion criteria included age (11-13 years old) at

baseline and right-handedness. Adolescents were excluded for the following reasons:

self/parent-reported history of mental illness, serious brain injury (e.g., an injury that

included loss of consciousness, blackouts, headaches, dizziness, nausea, or loss of motor

control), or contraindications for MRI (such as metal implants). There were no inclusion

or exclusion criteria regarding the parent themselves. Since the ADS was interested in investigating precursors and subsequent effects of alcohol use, Asians were excluded from enrollment based on evidence that some protection may be afforded against alcohol misuse due to a polymorphism leading to hypoactivity of the aldehyde dehydrogenase 2 family enzyme that metabolizes alcohol, which can cause a toxic and unpleasant state (Chen et al., 1999; Li, Zhao, & Gelernter, 2012; Thomasson et al., 1991). For a more detailed description of the studies methods see (Fishbein et al., 2016)

Intelligence Quotient and Socioeconomic Status

Participants' estimated full-scale intelligence quotient (IQ) was calculated using the Kaufman Brief Intelligence Test, Second Edition (Kaufman & Kaufman, 2004). Socioeconomic Status (SES) was calculated based on both the household income and average of the parent's education. To ensure normality a z-score transformation was applied separately to the family's household income and the average of both parent's years of education. The final SES measure reported herein is based on the average of these two z-scores (Manuck, Phillips, Gianaros, Flory, & Muldoon, 2010).

Drug Surveys

Two separate drug surveys were administered to assess substance use in our population: the Tobacco, Alcohol, and Drug (TAD) questionnaire and the Drug Use Screening Inventory - Revised (DUSI-R). The TAD was a survey created specifically for the ADS study, and consists of the alcohol and drug portion of the Semi-Structured Interview for the Genetics of Alcoholism (Bucholz et al., 1994; Fishbein et al., 2016). The TAD records age of onset, amount, frequency and duration of use. The range of substances included in the TAD questionnaire included: tobacco, alcohol, marijuana,

cocaine, methamphetamine, ecstasy, opiates, salvia, inhalants, and illegally used

prescription drugs, along with an open-ended "any other substances" set of questions.

Assessment is with reference to both the period since the previous visit (i.e., the last 18

months) and past 30 days. This allows us to account for different drug-taking patterns

between individuals and distinguish those who consume the same total quantity in a

typical week but who may vary in use frequency (e.g., using a large amount of alcohol

once or twice per week [i.e., "binge" drinking] vs. smaller quantities five times per

week). While the TAD solely focuses on questions regarding substance use, the DUSI

also measures adolescent behavior, health, social competence, school and work

performance, family and peer relationships, and recreation, along with the different forms

of substance use (Tarter & Hegedus, 1991). The questions on the DUSI, given to both the

parent and the child, were directed towards either the child's lifetime or the last 18

months. For purposes of this dissertation, the child's responses were used to assess

substance use initiation. In the case of a discrepancy between answers on the two drug

surveys, a custom follow-up survey is created that specifically asks about the discrepant

answers and is administered to the child either the following visit or over email through a

secure online survey to clarify drug use.

Genotyping

Saliva was collected through passive drool from the adolescent participants into

2.5 mL cryovial tubes and kept frozen at -80° C until they were analyzed by the

Genomics Core Facility in the Huck Institutes for the Life Sciences at Penn State

University. Upon DNA extraction, 2.5 mls of lysis buffer containing salts, detergent and

proteinase K was added to the saliva samples and DNA was extracted using the method

and equipment specified by (Freeman et al., 2003). After extraction the DNA was re-suspended in 250 ul of Tris EDTA (10 mM Tris-HCl, 1 mM EDTA, pH 8.0) buffer. The DNA was quantified by measuring the absorbance at 260 nm using a Nanodrop spectrophotometer (Nanodrop, Wilmington, DE). After quantification, samples were aliquoted into storage vials and placed in an -80°C locked freezer. The sample was tracked in the freezer location with other purification details using a LIMs system purchased from the Institute of Psychiatry in London.

For DRD2 C957T and GABA rs279826, Taqman SNP Genotyping Assays were performed using an Allelic Discrimination Assay (Life Technologies, Carlsbad, CA) protocol. The context sequence of the DRD2 C957T Taqman assay was [VIC/FAM] TCTTCTCTGGTTTGGCGGGGCTGTC**[A/G]**GGAGTGCTGTGGAGACCATGGTGG G. The context sequence of the GABA rs279826 Taqman assay was [VIC/FAM] CAATCACTTTGCTCAATACCAATCA**[A/G]**AGGGTTTTTTGTTGTTGTTGTTGTT. 100 nanograms of DNA were combined in a volume of 5 microliters with 2X Universal PCR Mix (Life Technologies) and 1/40 the volume of the Taqman SNP assay in a 7900HT (Life Technologies) 384 well platform. The samples were amplified by PCR as follows: a 10 min hold at 95 C, followed by 45 to 50 cycles of 15 sec at 92 C and then 1:30 min at 60 C in a 7900HT PCR System. After amplification, a post-read was performed for analysis by automatic and manual clustering.

The DAT1 VNTR was amplified using the methods of (Anchordoquy, McGeary, Liu, Krauter, & Smolen, 2003). The primer sequences were: forward, 5'-TGTGGTGTAGGGAACGGCCTGAG-3' (fluorescently labeled), and reverse: 5'-CTTCCTGGAGGTCACGCTCAAGG-3'. After amplification all VNTR fluorescent-

labeled products were analyzed using the 3730XL DNA Analyzer (Applied Biosystems, Foster City, CA). One half ul of LIZ-500 standard and 10 ul of formamide were added to 1 ul of the PCR Reaction and products were separated on a 50 cm capillary array. Genotypes were identified using Genotyper software v4.0 (Applied Biosystems, Foster City, CA).

Go-NoGo fMRI Task

A traditional Go-NoGo task was utilized in which participants viewed single letters presented serially on a screen. This task uses a block design with alternating blocks of Go-NoGo (45 seconds) and Fixation (12-16 seconds) each repeated 5 times. During the Go-NoGo blocks a series of 30 letters is presented for 200 ms each, followed by a 1300 ms fixation. Subjects are instructed to press the button in their right hand as quickly as possible for every letter except the letter 'Q'. A total of 150 letters are presented in this design of which 27 are the target letter 'Q', thus providing a sufficient number of individual events to accurately model inhibitory control (Riccio et al., 2002). As there are many more Go trials, a prepotent response to press the button is built up, making it harder to inhibit on NoGo trials. Behavioral data that was analyzed included the percentage of correct Go and NoGo trials, and reactions times for incorrect NoGo and correct Go trials. The Go-NoGo task was presented using the E-prime 2 software package (http://www.pstnet.com/eprime.cfm), and made visible to the participants in the MRI scanner using a projector and mirror attached to the head coil.

Emotional Counting Stroop fMRI Task (ecStroop)

An Emotional Counting Stroop task was used to measure attentional bias for both alcohol-related and negatively valenced words compared to neutral words (Whalen et al.,

2006). The task was comprised of eight blocks with 20 trials per block, consisting of the

three word conditions: four blocks of neutral words, two blocks of negative emotion

words, and two blocks of alcohol-related words. During each trial, the same word was

presented in a vertical list one to four times for 1500 ms. Participants were instructed to

respond with the corresponding button box (four boxes were fastened together), using the

pointer and index finger of both hands, as quickly and as accurately as possible. Average

reaction time (RT) and accuracy were calculated for each condition to measure

attentional bias. Presentation of the stimuli was the same as Go-NoGo specs listed above.

Wheel of Fortune Task (WoF)

A modified version of the WoF was used as a measure of functional response to

variable reward and loss probabilities, reward/loss anticipation, and magnitude of

rewards/losses (Ernst et al., 2004; Smith et al., 2009). On each trial the participant was

presented with a pie chart (i.e., the wheel), which visually represented the odds of

winning or losing either a large or small amount of money. For example, a smaller pink

portion of the wheel represented the odds of winning or losing a large amount of money,

while the remaining larger blue portion represented the odds of winning or losing a

smaller amount. Across 90 trials, the odds were randomly varied between 10% vs. 90%

(32–42 trials) and 30% vs. 70% (48–58 trials) wheel configurations. For the 10/90

wheels, the amounts used were split evenly between $9/$1 and $18/$2. For the 30/70

trials, the amounts were split between $7/$3 and $21/$9. In each trial, the wheel and

dollar amounts were presented for 3000 ms or until the subject made a choice. The choice

was followed by a 3000 ms delay, and then a 3000 ms feedback phase. During the

feedback, the subject was shown whether they won or lost with their last selection, and

presented with their running total. To encourage participants to make a selection for each trial, if they did not respond quickly enough (within 3000 ms), they would automatically lose the higher dollar amount shown in the current wheel. The task was presented as a slow event-related design with temporal jitter provided by a variable between-trial fixation (2500–10,000 ms set based on a Poisson distribution). As it can take up to 21 min to complete all trials, the task was broken up into three separate runs of 30 trials each. While the amounts won or lost were theoretical since the participant was explicitly told they would not actually win the money, they were encouraged to try to maximize their gains and exceed their previous total winnings before each run. Behavioral data analyzed was the percentage of risky decisions made and reaction times for high risk and low risk decisions, as well as average of both.

MRI Image Acquisition, Processing and Analysis

For anatomical localization and spatial normalization a structural MRI acquisition was collected using a 3D T1-weighted MPRAGE image with the following parameters: TR/TE=1900/2.52 ms, TI=900 ms, 176 slices, slice resolution=1.0 mm^3. FMRI acquisition used T2*-weighted gradient-echo planar imaging (EPI) during the WoF task. The blood oxygenation level dependent (BOLD) functional MRI acquisition parameters were: TR/TE 2500/30 ms, 90° flip angle, in-plane resolution 3.0 mm^2, 47 slices, slice thickness=3.0 mm.

Image preprocessing and statistical analyses were carried out using the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). Preprocessing included correction for interleaved slice timing and realignment of all the images to mean fMRI image to correct for head motion artifacts between images. Realigned images were then coregistered to the

anatomical MPRAGE. The MPRAGE was then segmented and transformed into the Montreal Neurological Institute (MNI) standard stereotactic space using linear regularization. Lastly, the linear regularization parameters were applied to normalize the fMRI images into MNI space, and the data were spatially smoothed using a Gaussian kernel of 6 mm^3 full-width half maximum (FWHM). A scrubbing algorithm utilizing framewise displacement (FD) was used to assess participant movement during the fMRI scans (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Participants were excluded from analyses if they had more than 1mm framewise displacement in over 20% of their volumes.

First-level statistics were performed including regressors encoding for trials during which the subject chose either the 10% or 30% probability, high risk (HR) decisions; another for 70% or 90% probability, low risk (LR) decisions; and two more for winning (Win) and losing (Lose) feedback trials as well nuisance regressors for movement. The contrasts of interest were high-risk decisions greater than low risk decisions (HR>LR), and winning greater than losing feedback (Win>Lose). The regressors were convolved with the canonical hemodynamic response function and a 128-s temporal high-pass filter was applied to the data to exclude low-frequency artifacts such as MRI signal drift.

For each task one or more sets of regions of interest (ROIs) were created for the psychophysiological interaction (PPI) analyses using 3 mm spheres based on regions identified from the relevant literature. For the correct NoGo>correct Go contrast from the Go-NoGo task the ROIs consisted of the right inferior and middle

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frontal gyri and right insula based on the locations reported in a metaanalysis (Simmonds

et al., 2008). Additional ROIs included the right and left subthalamic nucleus

from a previous study (Aron & Poldrack, 2006). For the ecStroop task, ROI's for the left and right medial PFC (mPFC), right insula, left dorsolateral PFC (DLPFC), right fusiform gyrus and left anterior cingulate cortex (ACC) were based on the locations reported in a metaanalysis of this task (Song et al., 2017), and were used for both the negative>neutral and alcohol>neutral contrasts. To create ROIs for the WoF HR>LR contrast, regions were based on the results from a study

Table 2.1: Peak Coordinates to make PPI ROI's			
Anatomical Region	Peak MNI Coordinates		
	x	y	z
Go-NoGo Task			
Right Insula	39	5	1
Right Inferior Frontal Gyrus	41	30	26
Right Middle Frontal Gyrus	37	52	3
Right Subthalamic Nucleus	10	-15	-5
Left Subthalamic Nucleus	-10	-15	-5
ecStroop Task			
Left ACC	-6	14	26
Left DLPFC	-50	30	18
Left mPFC	-8	12	54
Right mPFC	6	14	48
Right Insula	34	-46	24
Right Fusiform Gyrus	44	-68	-10
WoF Task (HR>LR Contrast)			
Left ACC	-3	36	28
Right ACC	12	36	24
Left OFC	-42	15	-8
Right OFC	39	18	-4
Left mPFC	-24	45	28
Right mPFC	45	42	24
WoF Task (Win>Lose Contrast)			
Right Nucleus Accumbens	10	14	-6
Left Caudate	-14	14	12
Left Insula	-40	18	-8
Right Insula	40	14	-6
Left Putamen	-22	10	-4

investigating the WoF task in adolescents (Shad et al., 2011) including the left and right

anterior cingulate, right and left medial PFC, and right and left orbitofrontal cortex

(OFC). To create ROI's for the WoF Win>Lose contrast, a recent metaanalysis of

adolescent reward processing for positive valence was used (Silverman, Jedd, & Luciana,

2015). This resulted in the following ROIs: left caudate, right nucleus accumbens, the left

and right insula and left putamen. Peak coordinates for all ROI's are shown in Table 2.1.

Functional connectivity was analyzed using the Psychophysiological Interaction (PPI) toolbox in SPM8 (Friston et al., 1997). Using each participant's first-level statistics, the first eigenvariate time series of BOLD activity was extracted as the mean of all voxels within the seed ROI's separately for each contrast. These time courses were then deconvolved based on the model for the canonical hemodynamic response function, multiplied by the psychological task contrast to create the PPI term, which was reconvolved with the canonical hemodynamic response function. For each participant, a design matrix was created in which one regressor represented the convolved eigenvariate of the seed region as the physiological term, a second regressor represented the psychological task contrast of interest, and a third regressor contained the PPI term. In addition, motion parameters were included as nuisance variables. The interaction term, the PPI regressor, was then used to interrogate similar task-related activity patterns— functional connectivity—across the brain, creating the final contrast images for each participant.

Group level analyses of each gene were conducted using the first-level BOLD and PPI contrast images separately for the contrasts for each task. Participants that made no HR decisions on the WoF were excluded because the contrast of HR>LR could not be constructed. Since the data is longitudinal, containing repeated measures, statistics were performed using GLM Flex Fast2 (http://mrtools.mgh.harvard.edu/index.php?title=GLM_Flex_Fast2). GLM Flex Fast2 uses partitioned error terms, instead of a single error term as used in SPM8, giving a more accurate fit of data with repeated measures. For all analyses, a 2x2 repeated measures ANOVA was used, with genotype as the between subject factor, and time as the within

subject factor. Importantly, a subject factor was also included which models each participant separately and accounts for individual differences such as IQ or SES. Therefore, to include covariates to control for them in the model, such as IQ or SES, would be collinear with the subject factor, and statistically invalid. To correct for multiple comparisons, 3dClustsim was used for cluster correction (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html), utilizing a minimum uncorrected threshold of p-value < 0.005 to determine clusters and a whole brain family-wise error (FWE) to correct for multiple comparisons, with a FWE p-value < 0.05 being considered significant. Since genetic polymorphisms often have a small effect size, an underlying cluster defining threshold of p-value < 0.005 was used to retain power (Flint & Munafò, 2007; Walters & Owen, 2007).

Statistical Analyses (Behavioral)

Group level analyses of demographic and behavioral data were performed using the IBM SPSS Statistics program for Macintosh (Version 22.0; http://www-01.ibm.com/software/analytics/spss/). Behavioral data from each task were analyzed with a 2x2 repeated measure ANOVA, with genotype as the between subject factor, and time as the within subject factor. The number of subjects reporting initiation of substance use at the second follow-up visits was compared between genotypes using an odds ratio (OR).

CHAPTER III: Effects of DRD2 C957T on Adolescent Cognition

Introduction

The dopaminergic system, known for playing roles in reward-seeking behavior and cognitive abilities, matures over adolescence. Research suggests that dopamine levels are at their highest in the PFC and limbic system during adolescence, which is hypothesized to contribute to heightened risky decision making in this developmental period (Badanich, Adler, & Kirstein, 2006; Goldman-Rakic & Brown, 1982; Haycock et al., 2003; Luciana, Wahlstrom, Porter, & Collins, 2012; Philpot, Wecker, & Kirstein, 2009). In addition, dopamine receptors are changing during this period. One such receptor is the dopamine D2, or DRD2, which is expressed both presynaptically and postsynaptically and, through the presynaptic counterpart, has inhibitory effects on dopamine neurons (Usiello et al., 2000). The expression of DRD2 decreases over childhood and adolescence, potentially playing a role in the cognitive changes seen in adolescence (Andersen et al., 2000; Weickert et al., 2007). This asserts the need to investigate dopamine from a developmental perspective, as its function could vary between childhood, adolescence and adulthood.

The DRD2 gene has a few single nucleotide polymorphisms in it, one being C957T, also known as rs6277, which is in a coding exon. It has been shown to alter the expression of DRD2 in vivo with PET imaging. However, the C allele was associated with less DRD2 expression in the striatum, but more expression in the cortex, possibly due to differing dopamine regulation in these two regions (M. Hirvonen et al., 2005; M. M. Hirvonen et al., 2009). The C allele has also been associated with alcohol and tobacco misuse (Ponce et al., 2008; Swagell et al., 2012; Voisey et al., 2012), worse cognitive

functioning (Beste et al., 2016; Colzato et al., 2011; Klaus et al., 2017; Rodriguez-Jimenez et al., 2007; Villalba, Devieux, Rosenberg, & Cadet, 2015; Xu et al., 2007) and more bias to reward (Richter et al., 2017; M. J. White et al., 2009). While some studies have found the T allele being associated with alcohol use (Hill et al., 2008; Kraschewski et al., 2009), having worse working memory and inhibitory control (Colzato, van den Wildenberg, & Hommel, 2013; Hill, Lichenstein, Wang, Carter, & McDermott, 2013), there are more studies demonstrating the C allele is linked to risk.

Relatively few studies have investigated the impact of C957T on brain function or structure. One study investigated reward learning and found the C allele had greater activation in the hippocampus and striatum during the encoding phase (Richter et al., 2017). One study showed the C allele to be associated with greater white matter connectivity between the striatum and frontal cortex, though it did not relate these differences to behavior (Markett et al., 2017). Another study found the C allele was associated with lower caudate volume, but better working memory (Hill et al., 2013). A couple studies investigated the effects of nicotine withdrawal. For instance, one found the C allele had greater increases in cerebral blood flow using arterial spin labeling in the orbitofrontal and insular cortices when abstaining from cigarette use, suggesting a stronger withdrawal effect (Wang et al., 2008). The second study investigated the interaction between C957T and rs1044396 in the cholinergic nicotinic receptor during a visualspatial attention task in which nicotine-naïve individuals were administered nicotine. Individuals with the C allele had increased activation in frontal and temporal regions, and also improved performance, suggesting they were more sensitive to nicotine (Breckel et al., 2015). However, more studies are needed to investigate the effects of

C957T on cognitive brain function. In addition, none of the aforementioned MRI studies investigated adolescents, and given the changes in the dopamine system during adolescence, it is pertinent to directly assess the impact of C957T during this developmental period.

The current investigation presents data from the Adolescent Development Study (ADS), a prospective, longitudinal study using behavioral and neuroimaging measures during adolescence to identify neurodevelopmental precursors and consequences of alcohol misuse (Fishbein et al., 2016). In particular, we report longitudinal analyses using the first two time points spaced 18 months apart to determine if DRD2 C957T has differential effects on four separate facets of cognitive functioning: inhibitory control, attentional bias, high- versus low-risk decision making, and response to positive/rewarding feedback. In order to assess the neural influences, both BOLD activation and functional connectivity using psychophysiological interactions (PPI) were used. We hypothesized the C allele would be associated with worse inhibitory control and greater activation of regions involved with this process such as the inferior and middle frontal gyri and lower connectivity involving these regions. Second, we hypothesized the C allele would have more attentional bias as well as greater activation in and lower connectivity among brain regions involved with attentional bias such as the anterior cingulate (ACC), dorsal lateral PFC (DLPFC), insula and precuneus. Third, the C allele would make more high-risk choices with enhanced brain activity and lower connectivity between key regions including the orbitofrontal cortex (OFC), medial PFC (mPFC) and ACC. In addition, we predict that the individuals with the C allele would exhibit greater activity in and connectivity between the nucleus accumbens, caudate and OFC during

feedback for winning trials. Lastly, we investigated whether C957T was associated with initiation of alcohol and illicit substance use, hypothesizing the C allele would be associated with higher rates of initiation at the 18-month follow-up.

Results

Cohort Characteristics

A total of 92 participants were genotyped and had imaging data at both the first two waves of collection. For each of the three tasks individually, participants were excluded for too much movement, MRI artifacts and problems with the collection of behavioral responses. Therefore, the number of participants analyzed varied by the task. Genetic analysis for the Go-NoGo resulted in the following N per genotype: 13 T/T, 23 T/C, and 32 C/C. For the ecStroop the N per genotype group was: 14 T/T, 26 T/C, and 35 C/C. The N per genotype group for the WoF was: 11 T/T, 17 T/C, and 24 C/C. Results reported herein combined the T/T and T/C genotypes, named the T's group, and were compared with the CC group. Other combinations were tested, including combining the T/C and C/C genotypes and using ANOVA between

Table 3.1: Demographics by DRD2 Genotype			
Measure	T's (N= 46)	CC (N= 46)	*p*-value
Age	12.9 (SD= 0.72)	12.5 (SD= 0.72)	**0.016***
Sex	28 F/ 18 M	23 F/ 23 M	0.402
Ethnicity	37 White 3 African American 2 Latino 4 Multiracial	13 White 27 African American 2 Latino 4 Multiracial	**<0.001***
SES	0.22 (SD= 0.88)	-0.18 (SD= 1.03)	**0.047***
IQ	115.7 (SD= 12.3)	105.1 (SD= 14.7)	**<0.001***

all three genotypes, and yielded minimal results. In addition, many of the research articles on C957T have also combined the T/T and T/C genotypes. For the analysis of the initiation of substance use, there were not enough users to look at specific substances such as alcohol or marijuana. Therefore, initiation regardless of substance was compared.

There was no significant effect of DRD2 on substance use initiation using the full 92 participants (T's=6 users; CC=6 users; odds ratio=1.0; p=1.0). Demographics for the full sample of 92 participants for these two groups are shown in Table 3.1.

Go-NoGo

Only fMRI results that survive p< 0.05 cluster corrected are reported. Behaviorally, groups responded to the task similarly, with no statistical differences between the T's and CC groups for accuracy or

Figure 3.1: DRD2 Main Effect Results for Go-NoGo. A) BOLD activation in left superior temporal gyrus. B) BOLD activation in right postcentral gyrus. In both, the CC group had higher activation and connectivity. Images shown at p<0.05 cluster corrected.
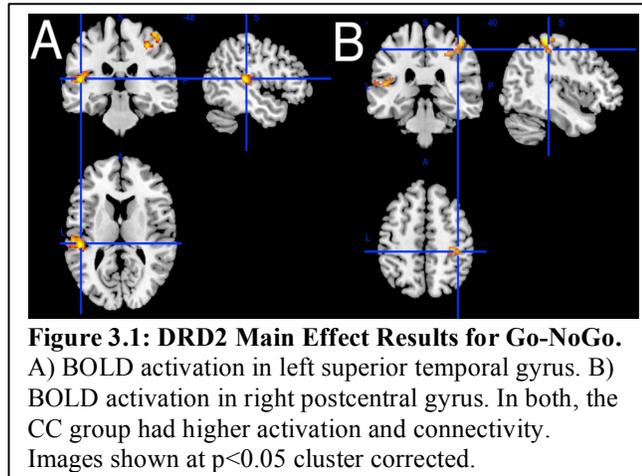
reaction times (Table 3.2). Analysis of activation differences for the fMRI BOLD contrast for inhibitory control (correct NoGo greater than correct Go) found a main effect of the CC group having higher activation in the left superior temporal gyrus and right postcentral gyrus (Figure 3.1). There were no significant differences found for any of the PPI ROI's. Given there were no behavioral differences, this suggests the CC group needed to recruit more neuronal resources to achieve the same performance. For detailed fMRI results, see Table 3.3.

ecStroop

When comparing the groups on behavior, the CC adolescents had lower accuracy on negatively-valenced emotion words (p=0.032) and showed a trend for less accuracy on alcohol words (p=0.053) but no significant differences in reaction times (Table 3.2). Analysis of BOLD activity comparing alcohol words greater than neutral words revealed a DRD2 allele x time interaction in the left medial prefrontal cortex

Table 3.2: Task Performance by DRD2 Genotype

Measure	T's		CC		DRD2 Main Effect *p*-value	DRD2 X Time Interaction *p*-value
	Wave 1	Wave 2	Wave 1	Wave 2		
Go-NoGo Task						
% Correct NoGo Trials	54.5 SE=4.0	67.0 SE= 2.8	54.0 SE=3.7	68.6 SE=3.0	0.906	0.616
% Correct Go Trials	97.0 SE= 1.0	98.0 SE= 1.2	95.6 SE= 0.8	97.5 SE= 0.7	0.453	0.378
Incorrect NoGo RT (ms)	272.76 SE= 6.5	272.8 SE= 9.2	270.4 SE= 8.8	275.9 SE= 8.1	0.969	0.614
Correct Go RT (ms)	316.6 SE=10.	325.0 SE=11.3	305.4 SE=8.3	322.2 SE=10.3	0.594	0.464
ecStroop Task						
Neutral Word RT (ms)	753.9 SE=10.3	699.4 SE=10.5	745.5 SE=11.8	703.6 SE=12.4	0.878	0.451
% Correct Neutral Word	87.2 SE=1.6	92.2 SE=1.3	84.1 SE=1.7	91.4 SE=0.9	0.204	0.393
Negative Word RT (ms)	781.7 SE=13.3	730.5 SE=11.	742.3 SE=16.0	722.5 SE=13.9	0.117	0.194
% Correct Negative Word	86.7 SE=1.5	80.0 SE=2.1	83.4 SE=1.7	90.1 SE=1.4	**0.032***	**0.051**
Alcohol Word RT (ms)	769.6 SE=10.5	719.6 SE=14.8	746.7 SE=12.3	726.6 SE=14.3	0.524	0.189
% Correct Alcohol Word	83.6 SE=1.9	78.0 SE=1.9	81.8 SE=1.7	88.0 SE=1.4	**0.053**	0.183
Negative Minus Neutral RT's (ms)	27.8 SE=11.7	31.1 SE=7.4	-3.2 SE=13.6	18.9 SE=9.2	0.089	0.422
Alcohol Minus Neutral RT's (ms)	15.7 SE=10.7	20.2 SE=7.3	1.2 SE=11.4	23.0 SE=9.6	0.494	0.433
WoF Task						
% High Risk Decisions	15.0 SE=2.3	12.8 SE=1.9	12.1 SE=1.9	10.4 SE=1.7	0.300	0.849
High Risk Decisions RT (ms)	1299.2 SE=77.0	1335.3 SE=88.1	1292.2 SE=75.0	1138.6 SE=74.0	0.292	0.121
Low Risk Decisions RT (ms)	1064.4 SE=55.5	967.7 SE=54.4	965.3 SE=50.7	885.3 SE=45.8	0.173	0.813

and left orbitofrontal cortex, such that activity decreased over the 18-month follow-up for the T's group but increased over time for the CC group (Figure 3.2). This could suggest as they are developing, the CC group has increasing attentional bias to alcohol words while the T's group is decreasing.

The PPI analysis of negative words greater than neutral words resulted in a significant DRD2

Figure 3.2: DRD2 X Time Interactions for ecStroop Alcohol>Neutral. A) BOLD activations in the left mPFC and OFC. B) Plot of the mPFC interaction shown in A. C) Left DLPFC ROI connectivity with left frontal lobe. D) Plot of interaction shown in C. Images shown at p<0.05 cluster corrected.

genotype x time interaction of connectivity between the left DLPFC ROI and a substantial area of the left PFC including the middle and superior frontal gyri, dorsal cingulate cortex, and supplemental motor area (Figure 3.3). A similar pattern for the left

DLPFC ROI was seen for alcohol greater than neutral words with greater connectivity with the same brain regions (Figure 3.2). In both cases, the T's group had increased connectivity at the 18-month follow-up, while the CC group had

Figure 3.3: DRD2 X Time Interactions for ecStroop Negative>Neutral. A) Left DLPFC ROI connectivity with left frontal lobe. B) Plot of interaction shown in A. Image shown at p<0.05 cluster corrected.

decreased connectivity. This could suggest that over time the T's group might be
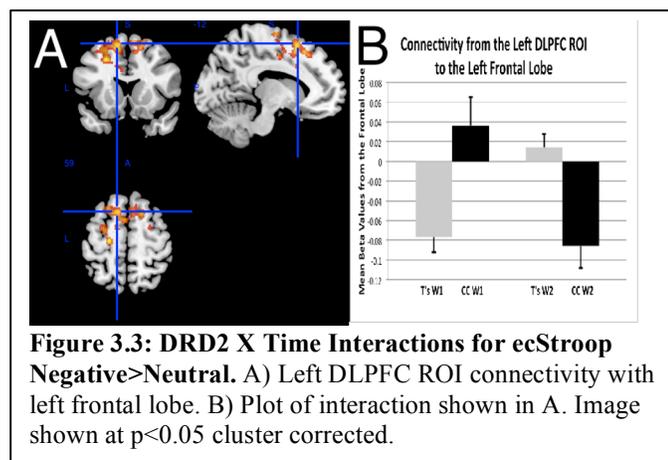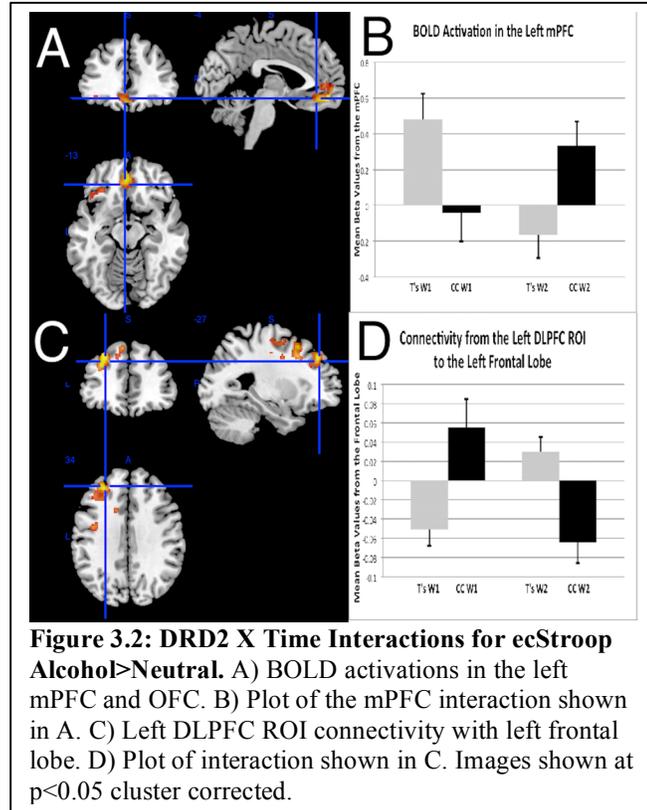
developing better control over attentional bias because of increased connectivity in PFC

regions involved in executive function, while the CC group might have less cognitive

control due to a reduction in connectivity. However, these effects do not appear to be

specific for negative or alcohol words, but rather a more general effect with regards to

attentional bias as the same pattern was seen for both contrasts. For details results of the

ecStroop fMRI results, see Table 3.4.

WoF

Behavioral results were not significantly different for percentage of risky decisions or reaction times (Table 3.2). The PPI analysis of high risk greater than low risk decisions indicated that the T's group had significantly higher connectivity between the left anterior cingulate ROI and a cluster in the left superior and middle temporal gyri (Figure 3.4). Similarly, T's had significantly more connectivity from the left medial PFC ROI to the right superior/middle

Figure 3.4: DRD2 Main Effect Results for WoF HR>LR. A) Left ACC ROI connectivity with superior and middle temporal gyri. B) Left mPFC ROI connectivity with bilateral middle temporal gyri. C) Right mPFC connectivity with bilateral precuneus and postcentral gyri. D) Right mPFC connectivity with bilateral cuneus. In images, the T's group had higher connectivity. Images shown at p<0.05 cluster corrected.

temporal gyri and the left superior/middle temporal gyri (Figure 3.4). Further, the T's

genotype adolescents had greater connectivity from the right medial PFC ROI to the

bilateral cuneus, the left middle temporal gyrus, the bilateral precuneus, the left

postcentral gyrus, and the right pre-postcentral gyri (Figure 3.4). Lastly, a significant DRD2 X time interaction was found between the right orbital frontal ROI to the bilateral ACC, with T's connectivity increasing over time while CC group decreased (Figure 3.5).

Figure 3.5: DRD2 X Time Interactions for WoF HR>LR. A) Right OFC ROI connectivity with bilateral ACC. B) Plot of interaction shown in A. Image shown at p<0.05 cluster corrected.
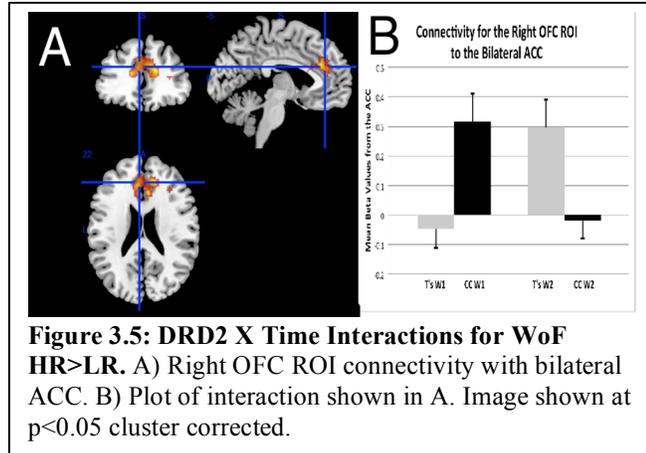
Comparison between BOLD activation of wining>losing feedback yielded a significant result in the left inferior frontal gyrus, left inferior parietal lobule, and right occipital lobe, with the CC group exhibiting lower activation (Figure 3.6). An examination of connectivity with the contrast wining greater than losing feedback yielded significantly greater connectivity for the CC group between the right nucleus accumbens ROI and the right cuneus and posterior cingulate gyrus, as well as between the left caudate ROI and the bilateral cuneus and calcarine sulcus (Figure 3.6). For detailed fMRI results for the WoF task, see Table 3.5.

Figure 3.6: DRD2 Main Effect Results for WoF Win>Lose. A) BOLD activation in left inferior frontal gyrus. B) BOLD activation in left parietal lobe. C) Right nucleus accumbens ROI connectivity with right cuneus and posterior cingulate. D) Left caudate ROI connectivity with bilateral cuneus. In A and B, the T's group had higher activation, and in C and D the CC group had higher connectivity. Image shown at p<0.05 cluster corrected.

Table 3.3: DRD2 fMRI Results for the Go-NoGo Task

Anatomical Region(s)	Cluster Size	Peak MNI Coordinates			Peak Stat.	DIR.	Caucasian Only
		x	y	z			
BOLD Activation Results							
Left Superior Temporal Gyrus	316	-48	-30	12	-4.13	CC	X
Right Postcentral Gyrus	342	40	-34	62	-4.87	CC	X
PPI Results							
No Results							
Abbreviations: DIR.= Direction of the group effect; Int.= DRD2 X Time interaction; Peak Stat.= Peak statistic, T-statistic for group comparisons, F-statistic for interactions. Caucasian Only: Y= cluster survived multiple corrections; X= cluster was present but didn't survive multiple corrections; - = cluster was not present.							

Table 3.4: DRD2 fMRI Results for the ecStroop Task

Anatomical Region(s)	Cluster Size	Peak MNI Coordinates			Peak Stat.	DIR.	Caucasian Only
		x	y	z			
Alcohol>Neutral Words							
BOLD Activation Results							
Left mPFC	398	-4	54	-12	22.64	Int.	-
Left OFC	304	-40	28	-12	17.88	Int.	-
PPI Results							
Left DLPFC ROI to left Middle/Superior Frontal Gyri/dACC/SMA	1944	-26	14	42	20.06	Int.	Y
Negative>Neutral Words							
BOLD Activation Results							
No Results							
PPI Results							
Left DLPFC ROI and Left Middle/Superior Frontal Gyri/dACC/SMA	2661	-18	-8	44	29.87	Int.	Y
Abbreviations: DIR.= Direction of the group effect; Int.= DRD2 X Time interaction; Peak Stat.= Peak statistic, T-statistic for group comparisons, F-statistic for interactions. Caucasian Only: Y= cluster survived multiple corrections; X= cluster was present but didn't survive multiple corrections; - = cluster was not present.							

Table 3.5: DRD2 fMRI Results for the WoF Task							
Anatomical Region(s)	Cluster Size	Peak MNI Coordinates x	y	z	Peak Stat.	DIR.	Caucasian Only
High Risk> Low Risk Decisions							
BOLD Activation Results							
No Results							
PPI Results							
Left ACC ROI to Left Superior/Middle Temporal Gyri	731	-54	-54	22	5.27	T's	X
Left mPFC ROI to Right Superior/Middle Temporal Gyri	1154	52	-46	4	5.21	T's	X
Left mPFC ROI to Left Superior/Middle Temporal Gyri	1395	-54	-54	20	4.68	T's	X
Right mPFC ROI to Bilateral Cuneus	768	-8	-72	10	3.85	T's	-
Right mPFC ROI to Left Middle Temporal Gyrus	449	-28	-72	16	4.15	T's	-
Right mPFC ROI to Bilateral Precuneus and Left Postcentral Gyrus	1254	-16	-28	72	4.31	T's	Y
Right mPFC ROI to Right Pre-Postcentral Gyri	413	16	-34	60	4.78	T's	X
Right OFC ROI to Bilateral ACC	1327	8	26	26	22.28	Int.	-
Winning>Losing Feedback							
BOLD Activation Results							
Left Inferior Frontal Gyrus	408	-50	22	22	4.02	T's	X
Left Inferior Parietal Lobule	309	-52	-48	42	4.27	T's	X
Right Occipital Lobe	312	34	-72	14	4.24	T's	X
PPI Results							
Right Nucleus Accumbens ROI to Right Cuneus/Posterior Cingulate	502	12	-76	28	-4.03	CC	X
Left Caudate ROI to Bilateral Cuneus	599	10	-84	12	-3.78	CC	-

Abbreviations: DIR.= Direction of the group effect; Int.= DRD2 X Time interaction; Peak Stat.= Peak statistic, T-statistic for group comparisons, F-statistic for interactions. Caucasian Only: Y= cluster survived multiple corrections; X= cluster was present but didn't survive multiple corrections; - = cluster was not present.

Genetic Population Stratification Effects on fMRI Data

There is concern in the genetic literature that population stratification can have impact on results causing false positives, and this concern has been raised in regards to genetic brain imaging studies (Hariri & Weinberger, 2003; Thomas & Witte, 2002; Zubicaray et al., 2008). Population stratification can happen when the distribution of genetic alleles differs between different racial/ethnic backgrounds. To address these possible effects, significant brain imaging results were reanalyzed using only Caucasian participants. There were not enough participants of African American or Latino backgrounds to analyze separately. If significant clusters were indeed false positives caused by stratification, then upon reanalysis the clusters should no longer exist. In contrast, evidence points against stratification if the clusters remain, even if uncorrected for multiple comparisons as this would likely happen from reduced power due to the lower number of participants in the analyses. This is because population stratification is not a serious threat to analyses in a more homogeneous population; Caucasians for instance (Wacholder, Rothman, & Caporaso, 2002). Results are shown in Table 3.3, 3.4 and 3.5. Analyses for the Go-NoGo data showed all the original significant clusters either survived correction for multiple comparisons or retained uncorrected group differences. Given no group differences fully went away, it suggests there are no population stratification effects. In contrast, for the ecStroop, 2 of the 4 original significant clusters did not show any group effects when analyzing Caucasians only. In addition, both of these two clusters were for the alcohol>neutral word contrast, suggesting fairly strong stratification effects to alcohol words. Therefore, interpretation for these two clusters should be taken with caution, and might not be reflective of people of Caucasian descent.

Lastly, analyses of the WoF revealed 4 of the original 13 did not show any uncorrected or corrected group differences, suggesting weak stratification effects. However, the majority of results for the WoF do not appear to be impacted by population stratification.

Discussion

In the current report, we investigated the effects DRD2 C957T longitudinally during adolescence on three cognitive domains: inhibitory control, attentional bias and risky decision-making involving reward. Its influence of substance use initiation was also investigated. It was hypothesized the C risk allele would have negative impact on some or all of these domains. In support of the hypotheses, evidence suggests the C allele confers less efficient inhibitory control seen by BOLD activity during the Go-NoGo task. It was also shown the C allele may cause greater attentional bias for negative and potentially alcohol related stimuli as demonstrated by the ecStroop task. Additionally, the PPI data from this task suggests C957T has a developmental effect, in that the T allele group is able to maintain behavioral accuracy while requiring less neural connectivity as they age. During the WoF task, PPI data suggest the C allele group have less connectivity between decision-making areas while making risky decisions, and greater connectivity between reward processing areas for positive results. Lastly, contrary to studies of C957T on adult substance misuse problems, there was no association of substance use initiation during the age range investigated in this report.

Go-NoGo

During the Go-NoGo task there were no behavioral differences, such as accuracy or reaction times. However, a main effect was found in that the higher risk CC group did show heightened BOLD activity in the superior temporal gyrus and postcentral gyrus.

Though the superior temporal gyrus shows up in many inhibitory control paradigms, there is no consensus regarding the role it plays. It has been shown to also be involved in awareness of motor movement, paying attention to relative features of stimuli, switching tasks and working memory (Leube et al., 2003; Park et al., 2011; Paulus, Feinstein, Leland, & Simmons, 2005; M. A. Williams, McGlone, Abbott, & Mattingley, 2005). Therefore, its function in cognition is diverse. Given that the Go-NoGo task involves motor inhibition and the CC group had greater activation, this could imply they may have to pay more attention to their motor movements to achieve the same performance. This is also supported by the enhanced activity seen in the postcentral gyrus, which is involved with somatosensory perception, such as touch (Kurth et al., 1998). There were no differences seen for the PPI data. Therefore, in support of the hypothesis, results suggest the CC group have less efficient inhibitory control and may have to recruit additional neural resources to implement it.

ecStroop

Analyses of the ecStroop task suggest the CC group has more attentional bias as indicated by lower accuracy for negative words and a trend for alcohol related words. Investigation of the fMRI data yielded interesting results. There were no significant main effects of C957T. Instead, all of the findings were from the results of the C957T genotype X time interactions, suggesting there is a strong developmental effect for C957T involving the ecStroop during the ages investigated. BOLD activation interactions were found during for alcohol>neutral words in the mPFC and OFC. In both cases, the CC group had increased activity as they aged, while the T's group had decreased activity between the two time points. Both these regions are known to respond to reward, emotion

and potentially saliency in general (Euston, Gruber, & McNaughton, 2012; Ogawa et al., 2013; Rothkirch, Schmack, Schlagenhauf, & Sterzer, 2012). Therefore, it is likely the CC group is becoming more sensitive to the saliency of the alcohol words as they age, and therefore a greater attentional bias to them, whereas the opposite pattern was seen for the T's group. However, caution should be taken as to the generalization of these results for the mPFC and OFC, as analyses of Caucasians only suggested population stratification effects, and therefore these results might not be relevant to individuals of Caucasian descent. Further research is warranted to verify this point. The PPI data for alcohol>neutral revealed an interaction for connectivity from the DLPFC ROI and a large cluster spanning much of the left PFC and supplementary motor area. The T's group developed greater connectivity and the CC group had less connectivity as they aged. The DLPFC is well known for its role in top-down cognitive and attentional control (Gläscher et al., 2012; Ochsner, Silvers, & Buhle, 2012). However, since connectivity differences were seen in such a large cluster spanning many brain regions, it is hard to specifically infer the meaning of this finding. The result does suggest, though, the T's group is developing better cognitive control over this time period, which could lead to less attentional bias to alcohol related words. For the contrast of negative>neutral, there were no BOLD activation differences. However, PPI results showed a very similar interaction seen for the DLPFC during the alcohol>neutral words, spanning the same regions. This suggests that the T's group is developing better cognitive control for attentional bias in more generally and not just for alcohol related stimuli (Gläscher et al., 2012; Ochsner et al., 2012). Together these results support the hypothesis the C allele confers risk, as it is suggested the CC group has more attentional bias to alcohol related words, which is also

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getting stronger as they age. In addition, the T's group appears to be developing better cognitive control as they age, regardless of word type.

WoF

Investigation of the WoF task showed the higher risk CC group may have less ability to efficiently use a network of regions involved in risk-reward evaluation during risky decision-making. For the contrast of high>low risk decisions, there were no BOLD activation differences. However, results for the PPI analyses showed the lower risk T's group had higher connectivity between regions involved in risky decision-making and the superior/middle temporal gyri. These regions included both the ACC and mPFC. The superior/middle temporal gyri are involved in many processes. However, in context to risky decision-making these regions have been found to be involved with decisions that involve uncertainty or probabilities, as well as representation of number processing (Gullick, Sprute, & Temple, 2011; Kovas et al., 2009; Pierce & McDowell, 2016; Yang et al., 2016). Therefore, the T's group might have better ability to calculate the gains and loses when faced with the conflict of making a decision when risk is involved. Since there were no behavioral differences on the task, this could also represent having to recruit additional neural resources for the same performance. However, as seen in the GABA and DAT1 chapters, greater connectivity during the high >low risk decision contrast was associated with making less risky decisions, we posit the T's group for DRD2 has better coordination between regions involved in evaluation of risky decisions, though this effect might not be strong enough to cause a behavioral difference on the task. Lastly, there was a C957T X time interaction seen for connectivity between the OFC and ACC, such that connectivity increased over time for the T's group, but

decreased for the CC group. The OFC is known for playing a role in the evaluation of potential rewards and the ACC is involved with cognitive control when conflict is present (Fellows, 2007; Kerns et al., 2004; Shenhav, Botvinick, & Cohen, 2013; Steiner & Redish, 2012). This could signify during the ages investigated, the T's group is developing better resolution of conflict when evaluating the possible gains and loses when making decisions when risk is involved.

For the win>lose contrast, there were contradictory findings. The higher risk CC group had lower BOLD activation to reward in a couple regions, including the inferior frontal gyrus. In contrast, they also had higher connectivity between the nucleus accumbens and posterior cingulate, as well as between the caudate and cuneus. The PPI results indicate that the CC group has greater communication between areas related to reward processing when presented with positive outcomes. The nucleus accumbens has long been known as a region that integrates rewarding stimuli and the posterior cingulate has been linked with self-reflective thought and internal attention, and greater connectivity could signify the CC group focuses upon rewards more (Carlezon & Thomas, 2009; Leech & Sharp, 2014). The caudate is known for reward processing and reinforcement learning and the cuneus has been shown to be important in the early discrimination between rewarding and non-rewarding stimuli, and this could lead to greater reinforcement of the behavior that brought the reward (Asaad & Eskandar, 2011; Doñamayor, Schoenfeld, & Münte, 2012; Haruno & Kawato, 2005). However, the finding that the CC group had lower activity in the inferior frontal gyrus is difficult to interpret. One of its most well known functions is inhibitory control, but it is not traditionally thought of as part of the reward networks (Simmonds et al., 2008). Though

not specific to reward, some studies have looked at the role of the inferior frontal gyrus in reappraisal, or the conscious inhibition of emotional responses, and found increased activity in this area was associated with decreased limbic activity (Ochsner et al., 2004; Phan et al., 2005). Another study using an emotional Go-NoGo also found increased inferior frontal gyrus activity was associated with decreased limbic activity (Berkman, Burklund, & Lieberman, 2010). Therefore, the reduced activity in the inferior frontal gyrus function in the CC group during response to reward could represent reduced inhibitory control of emotional processing related areas, but that is beyond the scope of this investigation and warrants further research. In summary, results support the hypothesis the C allele is associated with less efficient decision making when risk is involved, and greater integration for positive outcomes in reward networks.

Conclusions

As discussed in the introduction, the C allele of the C957T DRD2 polymorphism is associated with changes in the expression of DRD2 receptors, and could explain the differences seen in this investigation. Specifically, the C allele is associated with less DRD2 expression in the striatum, but more expression in the cortex, possibly due to different mechanisms of dopamine regulation in these two regions (M. Hirvonen et al., 2005; M. M. Hirvonen et al., 2009). The DRD2 receptor can have inhibitory effects on dopamine release by acting as an autoreceptor on dopamine neurons (Usiello et al., 2000). Therefore, in the striatum, for the C allele, there would be less inhibition of dopamine release, resulting in a larger dopamine response. This could explain why the C allele was associated with greater connectivity in the reward network for rewarding feedback during the WoF task (Schultz, 2013). In contrast, the C allele has more DRD2

receptors in the cortex, which would result in less dopamine release. Dopamine function in the cortex is important for cognitive functioning, and has been shown to follow an inverted U pattern. That is, too little or too much dopamine in the cortex can result in declines of cognitive function, known as the inverted-U hypothesis (Mattay et al., 2003). This in turn could explain the less efficient cognitive functioning seen during inhibitory control, attentional bias and risky decision-making, since the C allele is associated with decreased dopamine in the cortex. In summary, our results are consistent with what is known about the DRD2 receptor and the effects of the C957T polymorphism on its expression.

The current investigation helps support previous research showing the C allele can have negative impact in multiple domains. The C allele has been shown to impact cognitive functioning (Beste et al., 2016; Colzato et al., 2011; Klaus et al., 2017; Rodriguez-Jimenez et al., 2007; Villalba et al., 2015; Xu et al., 2007). Directly related to the tasks in the current study, it was previously shown to be associated with less inhibitory control worse attentional control during an attentional blink task (Beste et al., 2016; Colzato et al., 2011). In addition, results support previous studies finding C957T has impact on reward processing, in which the C allele was associated with heightened reward based learning and worse temporal discounting (Richter et al., 2017; M. J. White et al., 2009). However, one study found the T allele was associated with less inhibitory control (Colzato et al., 2013). This could be from differences in the task, but could have to do with development, as that study found the greatest effect in an elderly population, whereas our study was during adolescence. Investigations of the effects of C957T on substance use problems have been mixed to which allele confers risk (Hill et al., 2008;

Kraschewski et al., 2009; Ponce et al., 2008; Swagell et al., 2012; Voisey et al., 2012). We did not find any effect of C957T on substance use initiation during the age ranges investigated. It could reflect the young age of our participants, short time span between our waves of data collection, or perhaps C957T has more effect on problem use instead of initiation itself.

Even though the current investigation is longitudinal, one limitation is the limited time of observation, as the second time point is 18 months after the baseline. Future follow-ups will allow for more detailed analyses spanning a greater amount of adolescence. Perhaps even more important than the restricted time between successive measurements is the fact that the number of adolescents that initiated substance use in our study was somewhat limited. This undoubtedly had an impact on our ability to detect differences between the two allele groups in this regard though continued follow-up could mitigate this limitation.

In conclusion, this is the first investigation to look at the DRD2 C957T polymorphism impact on multiple cognitive domains, and their underlying neural mechanisms, during adolescence. The results support the hypotheses of the C allele of DRD2 C957T being associated with less efficient inhibitory control, more attentional bias, less efficient decision making when risk is involved and stronger reward processing. However, it was not associated with substance use initiation. In addition, for both attentional bias and risky decision-making, C957T appears to have a developmental effect during this age range, as all the results found were DRD2 X time interactions. This is probably reflective of DRD2 receptor expression changing over adolescence (Andersen et al., 2000; Weickert et al., 2007).

CHAPTER IV: Effects of DAT1 VNTR on Adolescent Cognition

Introduction

The dopaminergic system has long been known for playing a role in reward seeking behavior as well as cognitive functioning. In addition, this system also matures during adolescence such that dopamine levels are at their highest in the PFC and limbic system during adolescence, which is hypothesized to contribute to the heightened risky decision making in this developmental period (Badanich et al., 2006; Goldman-Rakic & Brown, 1982; Haycock et al., 2003; Luciana et al., 2012; Philpot et al., 2009). This also points to the need to investigate dopamine from a developmental perspective. One way to investigate the effects of dopamine on risky decision-making is through genetic polymorphisms that alter dopamine function, which could lead to individual differences for adolescent risky decision-making. One such gene, DAT1/SLC6A3 encodes the dopamine active transporter (DAT), which is responsible for clearing dopamine out of the synapse. It has a 40-base pair variable number tandem repeat (VNTR) polymorphism located in the 3' untranslated region (3'UTR) of the gene, with the common alleles being the 9 repeat and 10 repeat (9R and 10R) (Vandenbergh et al., 1992), which has been shown to effect transcription levels of DAT. While there is some evidence that 10R increases transcription compared to the 9R (Heinz et al., 2000; van de Giessen et al., 2009; van Dyck et al., 2005), a recent metaanalysis of human studies suggests that the 10R has decreased DAT transcription, which would lead to higher levels of dopamine in the synapse (Faraone, Spencer, Madras, Zhang-James, & Biederman, 2014). Given that dopamine levels are already elevated during adolescence, the 10R could amplify risky decision-making compared to the 9R by increasing dopamine levels even more (Badanich

et al., 2006; Goldman-Rakic & Brown, 1982; Haycock et al., 2003; Luciana et al., 2012; Philpot et al., 2009).

There is a lot of evidence that DAT1 VNTR is associated with increased risk-taking behaviors and reduced inhibitory control. For instance, the 10R has been linked with greater alcohol and tobacco use, sexual promiscuity and violence (Guo et al., 2010; Guo, Roettger, et al., 2007; Guo, Tong, et al., 2007; Hopfer et al., 2005; Stogner, 2015; Timberlake et al., 2006) though some studies have found risk associated with the 9R, for examples see (Barkley et al., 2006; Guo, Wilhelmsen, & Hamilton, 2007). One behavioral study experimentally investigated the effects of DAT1 on risky decision-making, finding individuals with the 10R made more risky decisions (Mata et al., 2012). Another study using fMRI did not find behavioral differences in risky decision-making, but individuals with the 10R had higher activation in the ventral striatum during risky decision making (Zhong et al., 2012). However, both these studies on risky decision-making investigated adults. Investigations of the effects of DAT1 on inhibitory control have primarily focused on individuals with attention deficit hyperactivity disorder (ADHD). Three studies in children with ADHD and one in typically developed adults found the 10R to be associated with lower inhibitory control as assessed behaviorally or elevated BOLD activity in the PFC (Bédard et al., 2010; Braet et al., 2011; Kasparbauer et al., 2015; Loo et al., 2003). While two studies in adults, one of which investigated ADHD, found the opposite with the 9R having lower inhibitory control (Congdon et al., 2009; Dresler et al., 2010). Taken together there is much evidence that the 10R allele is associated with greater risky decision-making and behaviors as well as problems with inhibitory control.

The current investigation presents data from the Adolescent Development Study (ADS), a prospective, longitudinal study using behavioral and neuroimaging measures during adolescence to identify neurodevelopmental precursors and consequences of alcohol misuse (Fishbein et al., 2016). In particular, we report longitudinal analyses using the first two time points spaced 18 months apart to determine if DAT1/SLC6A3 has differential effects on four separate facets of cognitive functioning: inhibitory control, attentional bias, high- versus low-risk decision making, and response to positive/rewarding feedback. In order to assess the neural influences, both BOLD activation and functional connectivity using psychophysiological interactions (PPI) were used. We hypothesized the 10R would be associated with worse inhibitory control and greater activation of regions involved with this process such as the inferior and middle frontal gyri and lower connectivity involving these regions. Second, we hypothesized the 10R would have more attentional bias as well as greater activation in and lower connectivity among brain regions involved with attentional bias such as the anterior cingulate (ACC), dorsal lateral PFC (DLPFC), insula and precuneus. Third, the 10R would make more high-risk choices with enhanced brain activity and lower connectivity between key regions including the orbitofrontal cortex (OFC), medial PFC (mPFC) and ACC. In addition, we predict that the individuals with the 10R would exhibit greater activity in and connectivity between the nucleus accumbens, caudate and OFC during feedback for winning trials. Lastly, we investigated whether DAT1/SLC6A3 was associated with initiation of alcohol and illicit substance use, hypothesizing the 10R would be associated with higher rates of initiation at the 18-month follow-up.

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Results

Cohort Characteristics

A total of 92 participants were genotyped and had imaging data at both the first two waves of collection. Only participants with the 9R and 10R DAT1 alleles were included in analyses, as the other alleles are too rare to include them as separate groups in the current sample, leaving 85 participants. For each of the three tasks individually, participants were excluded for too much movement, MRI artifacts and problems with the collection of behavioral responses. Therefore, the number of participants analyzed varied by the task. Genetic analysis for the Go-NoGo resulted in the following N per

Table 4.1: Demographics by DAT1 Genotype			
Measure	9R (N=31)	10R (N=54)	*p*-value
Age	12.7 (SE=0.15)	12.7 (SE=0.09)	0.969
Sex	21 F/ 10 M	28 F/ 26 M	0.177
Ethnicity	17 White 9 African American 1 Latino 4 Multiracial	32 White 15 African American 3 Latino 4 Multiracial	0.846
SES	-0.24 (SE=0.19)	0.28 (SE=0.12)	**0.022***
IQ	109.6 (SE=1.8)	112.5 (SE=2.2)	0.304

genotype: 2 9R/9R, 18 9R/10R, and 43 10R/10R. For the ecStroop the N per genotype group was: 4 9R/9R, 21 9R/10R, and 44 10R/10R. The N per genotype group for the WoF was: 3 9R/9R, 17 9R/10R, and 31 10R/10R. Given the small numbers of the 9R/9R genotype groups, they were combined with the 9R/10R genotype group and are referred to as the 9R group. Demographics for the full sample of 85 participants for these two groups are shown in Table 4.1.

Table 4.2: Task Performance by DAT1 Genotype

Measure	9R		10R		DAT1 Main Effect *p*-value	DAT1 X Time Interaction *p*-value
	Wave 1	Wave 2	Wave 1	Wave 2		
Go-NoGo Task						
% Correct NoGo Trials	54.7 SE= 4.3	70.2 SE= 3.1	55.1 SE=3.5	68.7 SE=2.6	0.913	0.686
% Correct Go Trials	97.5 SE= 0.8	98.0 SE= 1.0	96.5 SE= 0.5	98.6 SE= 0.3	0.812	0.118
Incorrect NoGo RT (ms)	274.69 SE= 9.8	272.8 SE= 6.6	273.4 SE= 6.5	281.6 SE= 7.2	0.719	0.410
Correct Go RT (ms)	312.2 SE=11.7	319.9 SE=8.5	315.6 SE=7.8	332.0 SE=9.9	0.583	0.510
ecStroop Task						
Neutral Word RT (ms)	742.3 SE=11.3	713.4 SE=12.6	753.4 SE=11.3	690.9 SE=10.9	0.700	0.064
% Correct Neutral Word	85.3 SE=1.8	89.9 SE=2.0	86.2 SE=1.7	93.1 SE=0.6	0.230	0.456
Negative Word RT (ms)	773.5 SE=16.3	734.3 SE=13.6	756.6 SE=24.1	719.0 SE=11.5	0.323	0.951
% Correct Negative Word	84.0 SE=2.3	89.2 SE=2.1	83.4 SE=1.7	91.2 SE=1.1	0.709	0.441
Alcohol Word RT (ms)	761.4 SE=12.5	730.0 SE=14.8	762.1 SE=11.5	713.3 SE=11.1	0.555	0.472
% Correct Alcohol Word	80.2 SE=2.6	87.7 SE=1.8	81.8 SE=1.7	89.7 SE=1.2	0.387	0.873
Negative Minus Neutral RT's (ms)	31.2 SE=15.3	20.9 SE=11.3	3.1 SE=12.2	23.1 SE=7.0	0.333	0.166
Alcohol Minus Neutral RT's (ms)	19.1 SE=11.9	16.7 SE=11.0	8.6 SE=10.8	22.4 SE=7.4	0.798	0.487
WoF Task						
% High Risk Decisions	7.7 SE=0.8	8.5 SE=1.1	17.8 SE=2.2	14.0 SE=1.9	**0.002***	0.104
High Risk Decisions RT (ms)	1333.3 SE=83.5	1126.8 SE=81.1	1302.8 SE=65.5	1333.6 SE=81.7	0.362	**0.057**
Low Risk Decisions RT (ms)	997.5 SE=55.5	869.0 SE=44.9	1049.4 SE=50.6	978.7 SE=51.6	0.229	0.427

Behavioral Results

There were no behavioral differences found for either the Go-NoGo or ecStroop tasks (Table 4.2). However, there was a significant main effect of DAT1 for percent high-risk decisions (p=0.002; see Table 4.2), with the 10R group making more high-risk decisions than the 9R group. Additionally, a trend towards an interaction of DAT1 and time for high-risk reaction times (p=0.057; see Table 4.2) was found, with the 9R being quicker at Wave2. For the analysis of the initiation of substance use, there were not enough users to look at specific substances such as alcohol or marijuana. Therefore, initiation regardless of substance was compared. There was no significant effect of DAT1 on substance use initiation using the full 85 participants (9R=5 users; 10R=7 users; odds ratio=0.775; p=0.687).

fMRI Results

Only fMRI results lower than p<0.05 cluster corrected are reported. There were no significant differences found for the Go-NoGo or the ecStroop tasks. For the WoF, detailed results are shown in Table 4.3. No BOLD activation differences were found for high- versus low-risk decision-making, but there were main effect differences found in connectivity from the PPI analysis,
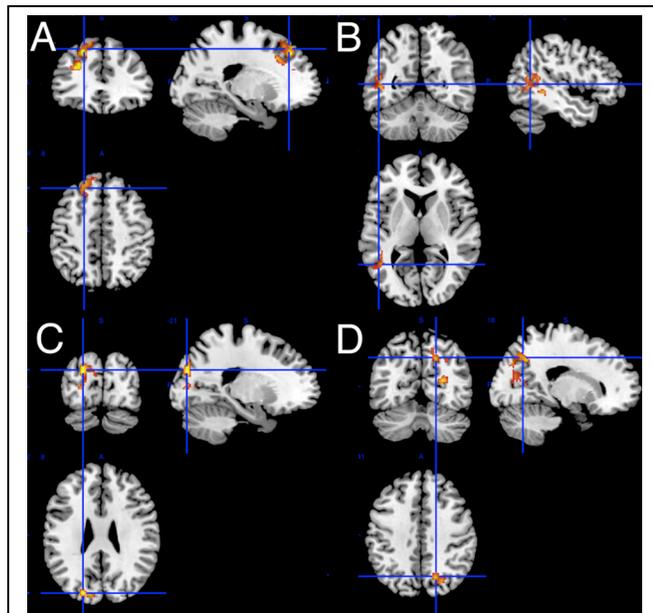
Figure 4.1: DAT1 Main Effect Results for WoF HR>LR. A) Left mPFC ROI connectivity with left superior frontal gyrus. B) Left mPFC ROI connectivity with left middle temporal gyrus. C) Right mPFC ROI connectivity with left cuneus. D) Right OFC ROI connectivity with right precuneus. In all four, the 9R group had higher connectivity. Images shown at p<0.05 cluster corrected.

shown in Figure 4.1. PPI data analysis showed higher connectivity between the right OFC and the right precuneus for the 9R group. The 9R group also showed higher connectivity between the left mPFC and the left superior frontal gyrus and the left middle temporal gyrus. Likewise, the 9R group had higher connectivity between the right mPFC and the left cuneus. Additionally, there was a significant interaction between DAT1 and time for the connectivity between the right OFC and the right anterior cingulate such that 10R had higher connectivity at Wave1 and 9R at Wave2 (Figure 4.2). A significant interaction was also found between DAT and time for the connectivity between the right mPFC and left anterior cingulate such that 10R had higher connectivity at Wave1 and 9R at Wave2 (Figure 4.2).

Figure 4.2: DAT1 X Time Interactions for WoF HR>LR. A) Right OFC ROI connectivity with right ACC. B) Plot of interaction shown in A. C) Right mPFC connectivity with left ACC. D) Plot of interaction shown in B. Images shown at p<0.05 cluster corrected.

Figure 4.3: DAT1 Main Effect Results for WoF Win>Lose. A) BOLD activation in the right premotor area. B) Left insula ROI connectivity to left OFC. C) Left caudate ROI connectivity to left OFC. D) Left caudate ROI connectivity to right ACC. In all four, the 10R group had higher activation or connectivity. Images shown at p<0.05 cluster corrected.

Analysis of the BOLD activity data for Win>Loss showed a significant main effect of DAT1, with the 10R group having greater activation in the premotor area than the 9R group (Figure 4.3A). The PPI results showed higher connectivity for the 10R group between the left caudate and a cluster containing the right mPFC/anterior cingulum (Figure 4.3B). The 10R group also showed higher connectivity between the left caudate and a cluster containing the left middle frontal gyrus and OFC (Figure 4.3C). Lastly, higher connectivity was also found between the left insula and a cluster containing the left mPFC/OFC, again, with the 10R group having higher connectivity than the 9R group (Figure 4.3D). No interactions between DAT and development were found for the BOLD or PPI data.

Table 4.3: DAT1 fMRI Results for the WoF Task							
Anatomical Region(s)	Cluster Size	Peak MNI Coordinates			Peak Stat.	DIR.	Caucasian Only
		x	y	z			
High Risk> Low Risk Decisions							
BOLD Activation Results							
No Results							
PPI Results							
Right OFC ROI and Right Precuneus	769	26	-66	16	-4.40	9R	Y
Left mPFC ROI and Left Superior Frontal Gyrus	339	-26	40	26	-4.58	9R	Y
Left mPFC ROI and Left Middle Temporal Gyrus	353	-52	-66	0	-4.24	9R	Y
Right mPFC ROI and Left Cuneus	247	-22	-84	26	-4.31	9R	X
Right OFC ROI and Right ACC	489	22	42	-4	19.27	Int.	X
Right mPFC ROI and Left ACC	248	-18	34	28	18.26	Int.	-
Winning>Losing Feedback							
BOLD Activation Results							
Right Premotor area	274	48	-16	50	3.91	10R	Y
PPI Results							
Left Caudate ROI and Right mPFC/ACC	807	14	40	22	5.39	10R	X
Left Caudate ROI and Left Middle Frontal Gyrus/OFC	564	-36	46	0	4.74	10R	X
Left Insula ROI and Left mPFC/OFC	657	-26	16	-18	5.34	10R	Y
Abbreviations: DIR.= Direction of the group effect; Int.= DAT1 X Time interaction; Peak Stat.= Peak statistic, T-statistic for group comparisons, F-statistic for interactions. Caucasian Only: Y= cluster survived multiple corrections; X= cluster was present but didn't survive multiple corrections; - = cluster was not present.							

Genetic Population Stratification Effects on fMRI Data

There is concern in the genetic literature that population stratification can have impact on results causing false positives, and this concern has been raised in regards to genetic brain imaging studies (Hariri & Weinberger, 2003; Thomas & Witte, 2002; Zubicaray et al., 2008). Population stratification can happen when the distribution of genetic alleles differs between different racial/ethnic backgrounds. To address these possible effects, significant brain imaging results were reanalyzed using only Caucasian participants. There were not enough participants of African American or Latino backgrounds to analyze separately. If significant clusters were indeed false positives caused by stratification, then upon reanalysis the clusters should no longer exist. In contrast, evidence points against stratification if the clusters remain, even if uncorrected for multiple comparisons as this would likely happen from reduced power due to the lower number of participants in the analyses. This is because population stratification is not a serious threat to analyses in a more homogeneous population; Caucasians for instance (Wacholder et al., 2002). Results are shown in Table 4.3. Five clusters remained significant while controlling for multiple comparisons. Another four clusters, though they did not survive controlling for multiple comparisons, still exhibited group differences of smaller cluster sizes. These findings most likely reflect decreased power due to the smaller number of participants included in the analyses and not stratification. Only one cluster no longer had any group differences, being the PPI gene X time interaction during the high risk > low risk decision contrast between the right mPFC ROI and Left ACC. These results suggest for DAT1, there are minimal population stratification effects present during the WoF task.

Discussion

In this study we sought to investigate the influence of DAT1/SLC6A3 on inhibitory control, attentional bias and risky decision making during adolescence and the neural mechanisms underlying them. There were no effects of DAT1 on the Go-NoGo or ecStroop tasks. However, effects were found for the WoF task. Behaviorally the 10R group made more risky decisions. Even though the two groups did not show any differences in BOLD activity while making risky decisions, the 9R group had higher functional connectivity between brain regions involved in decision-making. This higher connectivity could reflect greater executive control when making decisions, which could account for them making less risky decisions. In addition, the 10R group had greater BOLD activity during positive feedback, as well as greater connectivity between brain regions involved with reward processing. This suggests the 10R group could be more responsive to rewards. However, at the ages investigated here, DAT1 genotype did not predict initiation of substance use. This could be due to the DAT1 VNTR not having an impact on substance use at this age, or it could reflect the fact that relatively few adolescents had began using substances, and therefore insufficient power for such analysis.

When faced with making risky decisions, several studies have shown a common set of brain regions are recruited including the OFC, mPFC and ACC (Shad et al., 2011; Smith et al., 2009). In our study, there were notable functional connectivity differences involving these regions between the two DAT1 genotypes for the contrast of HR>LR. For example, the 9R group displayed more connectivity between the left mPFC and left superior frontal gyrus. The mPFC is thought to integrate signals when making a decision,

such as the anticipated reward value and how this fits with the individual's goals (Euston et al., 2012). In addition, the superior frontal gyrus has been shown to be recruited when uncertainty is involved (Volz, Schubotz, & Von Cramon, 2005). Therefore, the 9R group might be better at evaluating probabilistic uncertainty and integrating this when making a risky decision. The 9R group also had higher connectivity between the right OFC and precuneus. When making decisions, the OFC is thought to reflect the anticipated value of a reward as well as updating future behavior due to the outcome of the decision regarding that reward (Fellows, 2007; Steiner & Redish, 2012). While the precuneus has been shown to be involved in self reflective processes (Cavanna & Trimble, 2006). Therefore, the 9R group might be better at reflecting on, or have greater awareness of, the potential rewards and consequences as reflected by the greater connectivity between these two regions in comparison to the 10R group, which in turn could lead to changes in behavior when making a decision. Another important finding is the 9R group having more connectivity between the mPFC and cuneus, which has been shown to play a role in decision-making and reward evaluation. For instance, one study combining EEG and MEG found it is important in the early discrimination between rewarding and non-rewarding stimuli (Doñamayor et al., 2012). Greater connectivity between these regions could allow the mPFC to quickly identify the probabilities of reward when making decisions.

During the HR>LR contrast, three DAT1 X time interactions were also found. Two involved connectivity with the ACC: one with the OFC and the other with the mPFC. Both interactions were characterized by the 9R having greater connectivity at Wave 2 versus Wave 1, while the opposite was seen for the 10R group. This suggests the

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DAT1 VNTR has developmental effects during adolescence. The ACC plays a role in resolving cognitive conflict, such as those present in the WoF task does when the participant needs to make a choice between high-reward/low-probability versus low-reward/high-probability options (Kerns et al., 2004; Shenhav et al., 2013). Therefore, the increased connectivity of the ACC with the OFC and mPFC could over time enhance the 9R group's ability to deal with this conflict when making decisions though it is important to note that this not reflected in a change in the number of high-risk choices the 9R group made between the two time points perhaps because they made relatively few high-risk choices in the first place. In support of this, the third DAT1 X time interaction showed the 9R group had a trend for quicker reaction times when making high-risk decisions at Wave2 versus Wave1, suggesting they had less cognitive conflict when making the decision at Wave2. Overall, these results suggest the 9R group may be better equipped to make decisions when faced with choices involving different levels of risk and reward potentially due to greater awareness of rewards and consequences, quicker detection of the probabilities and a higher capacity to cope with uncertainty when making decisions. In addition, evidence suggests these abilities are improving in the 9R group as they develop. However, further research is warranted to directly test these assertions.

The current study, also, highlighted differences in response to reward (i.e., Win>Loss) between the two DAT1 groups. During positive rewarding feedback, the 10R group had higher BOLD activation in the premotor area. Studies have shown this area integrates reward information from both the mPFC and striatum, and it has been hypothesized to be instrumental in coordinating the implementation of behaviors related to reward (Elliott, Newman, Longe, & Deakin, 2003; Peterson & Seger, 2013;

Ramkumar, Dekleva, Cooler, Miller, & Kording, 2016). Since the premotor area was more responsive to rewarding feedback, this could be related to the 10R group making more high-risk choices. The PPI analyses also showed the 10R group had higher connectivity between the left caudate and two clusters containing the OFC and mPFC. The caudate is very sensitive to reward and is important in making associations involved with reward on a trial by error basis, or instrumental learning (Asaad & Eskandar, 2011; Haruno & Kawato, 2005). One of the roles of the OFC is to evaluate performance/behavior based upon reward signals (Fellows, 2007; Steiner & Redish, 2012) and connections between the OFC and caudate have been shown to play a role in compulsive behaviors (Fineberg et al., 2010). Higher connectivity between these regions during reward processing, such as when the subject is informed they won, might reinforce compulsive behaviors and could help explain why the 10R group made more risky decisions. The left caudate also had higher connectivity to the right mPFC in the 10R group. One of the roles of the mPFC is to integrate reward signals and evaluate how they align with goals (Euston et al., 2012). Higher connectivity between these regions during reward processing could reinforce goals and behaviors that have brought higher reward values in the past. The 10R group also had higher connectivity between the left insula and a region spanning the left mPFC and OFC. The insula is important for representing the subjective experience of internal emotional and physiological states, such as the subjective pleasant feeling when receiving a reward (Singer, Critchley, & Preuschoff, 2009). Higher connectivity between the insula and mPFC/PFC could lead to reinforcement for high-risk decisions when presented with wins versus losses, potentially biasing future decisions toward greater reward even if it is more risky. Together, these

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results suggest the 10R group may have a more reactive reward system, and prior positive rewards may have a greater impact during the decision making process when risk is involved.

Conclusions

Dopamine has wide-ranging effects in the brain, including impacting cognitive function mediated by the PFC and reward processing in the striatum. DAT expression is highest within the striatum, ventral tegmental area and substantia nigra (Hall et al., 1999; Sasaki et al., 2012). However, it has been found in other brain regions in smaller quantities such as the PFC (Schwendt et al., 2009; Sekine et al., 2003). As described in the introduction, the DAT1 VNTR has been shown to impact expression levels of DAT, with a recent metaanalysis showing the 10R allele resulting in decreased expression, which would lead to more dopamine in the synapse (Faraone et al., 2014). In the striatum, this could lead to greater reward sensitivity, which fits with our finding of the 10R group having higher connectivity involving the caudate. In the PFC, it has been shown that an optimal amount of dopamine is needed; too much or too little impairs cognitive functioning, known as the inverted-U hypothesis (Mattay et al., 2003). If the 10R group has too much dopamine signaling in the PFC, due to less expression of DAT, this could account for the reduced connectivity they exhibited during risky decision-making, and might account for them making more risky decisions though it should be noted that DAT1 did not have any effect on the Go-NoGo or ecStroop tasks. Even though DAT is expressed in the PFC, the main methods of dopamine clearance in this part of the brain are catechol-O-methyltransferase and the norepinephrine transporter (Käenmäki et al., 2010; Morón et al., 2002). In contrast, DAT is the primary form of dopamine clearance in

the striatum (Cragg, Hille, & Greenfield, 2000; Mateo, Budygin, John, Banks, & Jones, 2004; Morón et al., 2002). Therefore, it is possible the DAT1 VNTR has more impact on striatal function. Since performance during the WoF task requires evaluating potential rewards and loses, which relies strongly on striatal function, this could help account for the genetic differences observed during the WoF. Overall, the current study supports previous studies showing the 10R allele of DAT1 being associated with risky behaviors. While more research is needed, our results are in line with the view that the 10R allele is associated with greater sensitivity to rewards and the associated reward processing circuitry leading to increased risk taking.

Even though the current investigation is longitudinal, one limitation is the limited time of observation, as the second time point is 18 months after the baseline. Future follow-ups will allow for more detailed analyses spanning a greater period of adolescence. Perhaps even more important than the restricted time between successive measurements is the fact that the number of adolescents that initiated substance use in our study was somewhat limited. This undoubtedly had an impact on our ability to detect differences between the two allele groups with regard to rates of initiation though continued follow-up could mitigate this limitation.

In conclusion, the current investigation supports the hypothesis that the 10R allele of DAT1 is associated with greater risky decision-making during adolescence. This may arise from them having less functional connectivity within the neural networks involved with decision making, resulting in reduced ability to refrain from making risky decision. In addition, the 10R allele appears to have greater connectivity in reward processing networks, making them more responsive to rewards and possibly influencing their

decisions when higher rewards are present. Our study provides strong evidence for

significant differences in functional connectivity during risky decision-making and

reward processing between the two DAT1 alleles and a developmental change in these

effects as reflected in the DAT1 X time interactions.

CHAPTER V: Effects of GABA rs279826 on Adolescent Cognition

Introduction

The molecule gamma-Aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the brain, having impact on almost every brain system, though its actions are complex. Recent advances in MRI have allowed in vivo measurements of GABA in conjunction with cognition. Two studies have found prefrontal GABA levels to be associated with working memory such that higher GABA levels predict better memory performance, though one study reported reduced levels of GABA after multiple runs for the task (Michels et al., 2012; Yoon, Grandelis, & Maddock, 2016). Another study found higher levels in the striatum predicted better cognitive control (Haag et al., 2015). More direct evidence has come from studies using pharmaceuticals that directly impact the GABAergic system. For instance, administering benzodiazepines, GABA positive allosteric modulators, has been shown to reduce working memory, learning, attention, behavioral inhibition and object recognition (Acheson, Reynolds, Richards, & de Wit, 2006; Deakin, Aitken, Dowson, Robbins, & Sahakian, 2004; Makaron et al., 2013; Snyder et al., 2005). However, benzodiazepines have also been shown to reduce activity in limbic reward processing regions, which was predictive of fewer high-risk decisions (Arce, Miller, Feinstein, Stein, & Paulus, 2006). Additionally, bicuculline, a GABA antagonist, has been shown to reduce working and short-term memory (Auger & Floresco, 2015). One source of variation in these studies could be due to the fact that there are multiple GABA receptors. The GABA-A ionotropic receptor is constructed of 5 subunits, having two α's, two β's and one Υ. However, each of these receptors can have multiple types of these subunits. For instance, there are six types of α subunits, α_{1-6}, and

specific benzodiazepines can be more selective for particular receptors and a given

subunit and not others, eliciting different types of effects.

Early genetic research into the effect of genetics on differential responses

highlighted the possible role of the α2 subunit in adult alcohol use disorders (AUDs),

with a few single nucleotide polymorphisms having been identified as conferring risk,

including rs279826 (Agrawal et al., 2006; Howard J Edenberg et al., 2004). However,

many subsequent studies have found the G versus A allele was associated with risk of

AUDs (Kramer et al., 2008; Uhart et al., 2013; Villafuerte et al., 2012, 2013). However,

one study found the A allele conferred risk and another found the A allele only conferred

risk when individuals had experienced major stressful life events (Kiive, Laas, Vaht,

Veidebaum, & Harro, 2017; Philibert et al., 2009). In addition, a couple studies have

investigated the cognitive processes by which rs279826 might impart risk. Both these

studies found the G allele to be associated with higher impulsivity, and one of them found

the G allele to have higher activity in the insula during anticipation of reward using fMRI

(Villafuerte et al., 2012, 2013). These results suggest that G allele of rs279826 confers

risk possibly through its impact on inhibitory control and reward processing.

Interestingly, it has been shown that the expression of the α2 subunit in the brain

has a developmental trajectory such that it decreases from a peak in childhood through

adolescence until it achieves adult levels (Cruz et al., 2003; Duncan et al., 2010;

Hashimoto et al., 2009). Therefore, it is pertinent to investigate rs279826 during these

developmental periods, as its effects could be altered. Three studies found the G allele

was associated with overall externalizing behavior scores during adolescence (Dick et al.,

2009; Trucco et al., 2016; Villafuerte et al., 2014). Another study found at 13-14 years of

age, the G allele predicted rule breaking, but not alcohol use problems. However, during a follow-up visit, rule breaking at 13-14 years of age was predictive of alcohol use problems at 17-18 years of age (Trucco et al., 2014). However, none of these studies involving adolescents used experimental paradigms to measure the effects of rs279826 on specific cognitive processes therefore such investigations are needed to further understand the effects of this gene on cognition during adolescence. In addition, the single investigation that has utilized fMRI to understand the effects of rs279826 on brain function was in adults. Therefore, it is also pertinent to further investigate the effects of rs279826 on brain function, and in particular, during adolescence.

The current investigation presents data from the Adolescent Development Study (ADS), a prospective, longitudinal study using behavioral and neuroimaging measures during adolescence to identify neurodevelopmental precursors and consequences of alcohol misuse (Fishbein et al., 2016). In particular, we report longitudinal analyses using the first two time points spaced 18 months apart to determine if GABA α2 subunit SNP rs279826 has differential effects on four separate facets of cognitive functioning: inhibitory control, attentional bias, high- versus low-risk decision making, and response to positive/rewarding feedback. In order to assess the neural influences, both BOLD activation and functional connectivity using psychophysiological interactions (PPI) were used. Given that more studies have found the G allele to be associated with risk, we hypothesized it would have negative impact on the cognitive constructs being studied. In particular, we hypothesized the G allele would be associated with worse inhibitory control, greater activation of regions involved with it such as the inferior and middle frontal gyri and lower connectivity involving these regions. Second, it was hypothesized

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the G allele would increase attentional bias via greater activation in and lower

connectivity involving brain regions involved with attentional bias, particularly the

anterior cingulate (ACC), dorsal lateral PFC (DLPFC), insula and precuneus. Third, the

G allele would be associated with more high-risk choices with enhanced brain activity

and lower connectivity between key regions including the orbitofrontal cortex (OFC),

medial PFC (mPFC) and ACC. In addition, we predicted that the individuals with the G

allele would exhibit greater activity in and connectivity between the nucleus accumbens,

caudate and OFC during feedback for winning trials. Lastly, we investigated whether

rs279826 was associated with initiation of alcohol and illicit substance use, hypothesizing

the G allele would be associated with higher rates of initiation at the 18-month follow-up.

Results

Cohort Characteristics

A total of 92 participants were genotyped and had imaging

data at both the first two waves of collection. For each of the three tasks individually, participants were excluded for too much movement, MRI artifacts and

Table 5.1: Demographics by GABA Genotype			
Measure	A's (N= 72)	GG (N= 20)	*p*-value
Age	12.7 (SD= 0.73)	12.5 (SD= 0.77)	0.297
Sex	43 F/ 29 M	8 F/ 12 M	0.134
Ethnicity	41 White 20 African American 4 Latino 7 Multiracial	10 White 10 African American 0 Latino 0 Multiracial	0.184
SES	0.02 (SD= 0.96)	0.01 (SD= 1.05)	0.971
IQ	109.9 (SD= 13.6)	112.8 (SD= 17.3)	0.443

problems with the collection of behavioral responses. Therefore, the number of

participants analyzed varied by the task. Genetic analysis for the Go-NoGo resulted in the

following N per genotype: 18 A/A, 36

A/G, and 14 G/G. For the ecStroop the N per genotype group was: 21 A/A, 35 A/G, and 19 G/G. The N per genotype group for the WoF was: 13 A/A, 25 A/G, and 14 G/G.

Results reported herein combined the A/A and A/G genotypes, named the A's group, and were compared with the GG group. Other combinations were tested, including combining the A/G and G/G genotypes and using ANOVA between all three genotypes, and yielded minimal results. In addition, many of the research articles on rs279826 have also combined the A/A and A/G genotypes. For the analysis of the initiation of substance use, there were not enough users to look at specific substances such as alcohol or marijuana. Therefore, initiation regardless of substance was compared. There was no significant effect of GABA on substance use initiation using the full 92 participants (A's=11 users; GG=1 users; odds ratio=0.292; p=0.253). Demographics for the full sample of 85 participants for these two groups are shown in Table 5.1.

 Go-NoGo

There were no behavioral differences between genotype groups for this task, including accuracy and reaction times (Table 5.2). The low risk group, the combined A genotypes, displayed greater BOLD activation for the inhibitory control contrast of correct NoGo > correct Go trials in two clusters both containing the left supramarginal and postcentral gyri

Figure 5.1: GABA Main Effect Results for Go-NoGo. A) BOLD activation in left supramarginal gyrus. B) Right insula ROI connectivity with right parietal lobules and right cingulate. In both, the A's group had higher activation and connectivity. Images shown at p<0.05 cluster corrected.
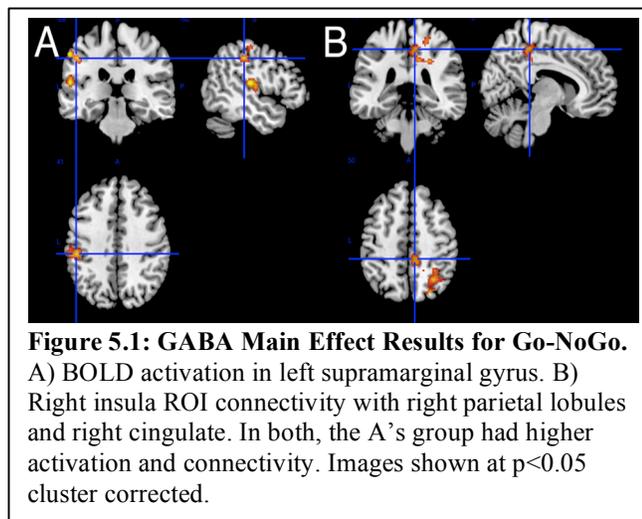
(Figure 5.1). See Table 5.3 for complete details of the fMRI results. Given there

Table 5.2: Task Performance by GABA Genotype						
Measure	A's		GG		GABA Main Effect *p*-value	GABA X Time Interaction *p*-value
	Wave 1	Wave 2	Wave 1	Wave 2		
Go-NoGo Task						
% Correct NoGo Trials	53.5 SE= 3.1	67.1 SE= 2.5	57.1 SE=5.8	70.1 SE=3.2	0.529	0.897
% Correct Go Trials	96.4 SE= 0.7	97.4 SE= 0.9	96.1 SE= 1.1	99.0 SE= 0.4	0.628	0.116
Incorrect NoGo RT (ms)	268.8 SE= 6.6	272.8 SE= 7.6	281.7 SE= 6.5	279.6 SE= 6.9	0.427	0.644
Correct Go RT (ms)	307.8 SE=7.8	322.0 SE=9.1	323.2 SE=10.6	329.4 SE=13.5	0.471	0.566
ecStroop Task						
Neutral Word RT (ms)	753.8 SE=9.9	700.6 SE=9.6	738.8 SE=9.4	703.7 SE=14.7	0.704	0.349
% Correct Neutral Word	86.3 SE=1.4	91.5 SE=1.0	84.2 SE=2.2	92.8 SE=1.3	0.835	0.274
Negative Word RT (ms)	762.0 SE=13.2	727.4 SE=10.3	767.0 SE=14.5	724.8 SE=16.7	0.946	0.785
% Correct Negative Word	82.7 SE=1.5	90.4 SE=1.1	86.1 SE=2.5	90.7 SE=2.0	0.384	0.372
Alcohol Word RT (ms)	769.6 SE=9.0	722.0 SE=9.9	727.5 SE=16.1	725.6 SE=18.3	0.177	0.080
% Correct Alcohol Word	81.1 SE=1.5	89.0 SE=1.1	80.7 SE=3.1	88.8 SE=1.9	0.889	0.948
Negative Minus Neutral RT's (ms)	8.2 SE=10.8	26.8 SE=6.8	28.2 SE=15.7	21.1 SE=11.4	0.529	0.340
Alcohol Minus Neutral RT's (ms)	15.8 SE=9.0	21.4 SE=7.1	-11.3 SE=14.9	21.8 SE=10.5	0.174	0.274
WoF Task						
% High Risk Decisions	11.4 SE=1.5	10.5 SE=1.4	19.6 SE=3.4	14.8 SE=2.8	**0.026***	0.213
High Risk Decisions RT (ms)	1272.5 SE=66.1	1226.8 SE=72.8	1359.6 SE=86.5	1292.6 SE=102.0	0.483	0.878
Low Risk Decisions RT (ms)	995.2 SE=43.2	909.2 SE=42.2	1082.5 SE=79.9	985.3 SE=71.2	0.276	0.888

were no behavioral differences, one interpretation is the A's genotypes might have less

efficient neural processing during inhibitory control and have to recruit additional neural

resources to achieve the same performance. There were no other BOLD differences

found. The PPI analyses showed that during inhibitory control, the A's group had higher

connectivity between the right insula ROI and the right mid-cingulum, right

superior/inferior parietal lobules and the left precuneus cortex (Figure 5.1). Higher

connectivity can mean better coordination between the brain regions, but given there were no behavioral differences, it could also mean the A's required more coordination between the regions to achieve to same performance as the GG group. No other PPI results survived correction. Together, contrary to our hypotheses, these results suggest the lower risk A's group might have less efficient neural circuitry related to inhibitory control.
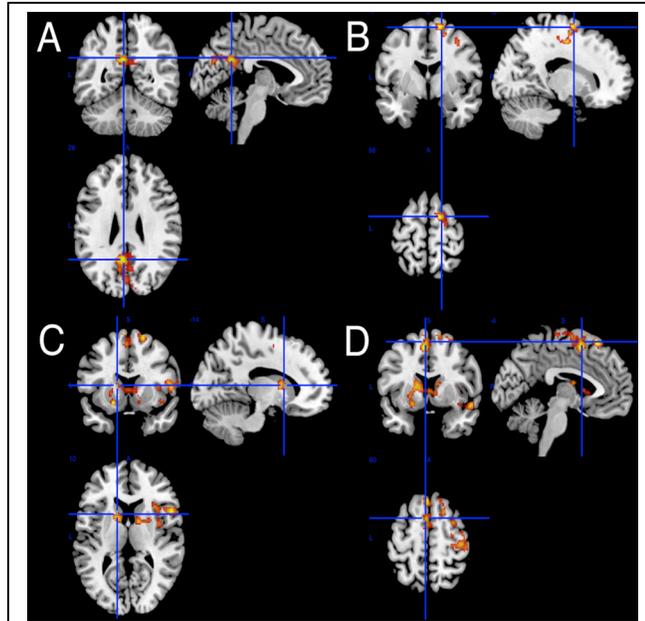
Figure 5.2: GABA Main Effect Results for ecStroop Alcohol>Neutral. A) Higher BOLD activation in the bilateral precuneus for the A's group. B) Right mPFC ROI connectivity with right supplementary motor area. C) Left ACC ROI connectivity with left caudate and right insula. D) Left ACC ROI connectivity with left supplementary motor area and precentral gyrus. The GG group had higher connectivity for all PPI results. Images shown at p<0.05 cluster corrected.

ecStroop

There were no behavioral differences for accuracy or reaction times (Table 5.2). Analyses of the BOLD data showed the A's group had higher activation for alcohol>neutral words in the bilateral precuneus/posterior cingulate. See Table 5.4 for complete details of the fMRI results. This suggests that despite having no significant differences in attentional bias to alcohol words the A's group nonetheless activated this area more. PPI results for alcohol>neutral showed the GG group had higher connectivity between the left dACC ROI and many regions of the brain. These included the right inferior frontal gyrus/insula, the left caudate/putamen, right pre-postcentral gyri and left supplementary motor area. The GG group also had higher connectivity for

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alcohol>neutral between the right

mPFC ROI and a cluster containing

the right supplementary motor area

(Figure 5.2). As these results

involve greater connectivity with

ROI's involved with executive

function, the GG group may be able

to exert more control over

attentional bias to alcohol words.

Lastly, there was a gene X time

interaction for alcohol>neutral from

the right insula ROI to the right

caudate, in that the GG decreased

connectivity between Wave1 and

Wave2 (Figure 5.3).

Similar to the

alcohol>neutral contrast, the GG

groups had higher connectivity

between the left dACC and many

brain regions for the

negative>neutral contrast. These

included the bilateral mPFC,

bilateral caudate and right pre-
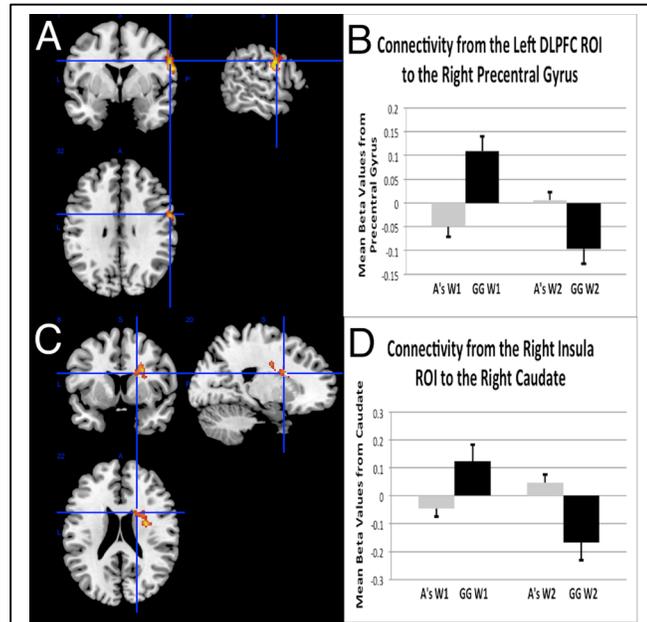
Figure 5.3: GABA X Time Interactions for ecStroop.
A) Connectivity for Negative>Neutral between the left
DLPFC ROI and right precentral gyrus. B) Plot of
interaction shown in A. C) Connectivity for
Alcohol>Neutral between the right insula and right
caudate. D) Plot of interaction shown in C. Images
shown at p<0.05 cluster corrected.
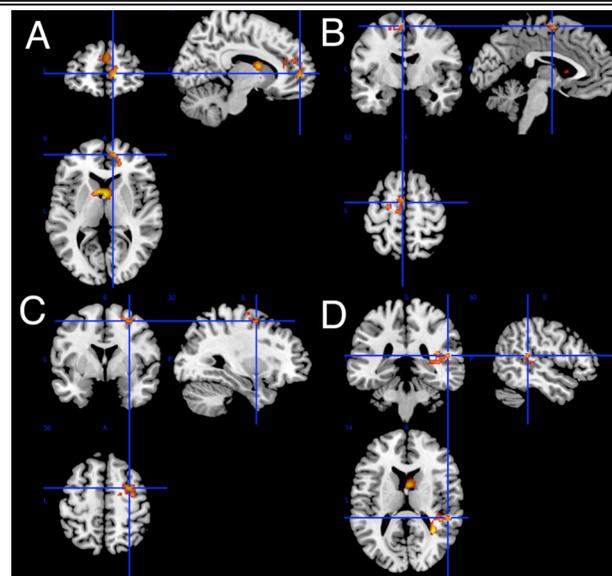
**Figure 5.4: GABA Main Effect Results for ecStroop
Negative>Neutral.** A) Left ACC ROI connectivity with
caudate and bilateral mPFC. B) Right mPFC ROI
connectivity with right supplementary motor area. C)
Left mPFC ROI connectivity with right superior frontal
gyrus. D) Right mPFC ROI connectivity with right
superior temporal gyrus. In all four, the GG group had
higher connectivity. Images shown at p<0.05 cluster
corrected.

postcentral gyri. The GG group had higher connectivity between the left mPFC ROI and right superior/middle frontal gyri near the supplementary motor area. The GG group also had higher connectivity between the right mPFC ROI and two clusters. These included the right superior temporal gyrus and left supplementary motor area (Figure 5.4). Many of the PPI results for negative>neutral are similar to alcohol>neutral and may suggest the GG group is able to exert more control over attentional bias in general, and not specifically to negative or alcohol related words. Lastly, there was a gene X time interaction for negative>neutral from the left DLPFC ROI and the right pre-postcentral gyri such that the GG group decreased connectivity between Wave1 and Wave2 (Figure 5.3).

WoF

With respect to behavioral performance on the WoF task, the GG higher risk group made a significantly greater number of high-risk decisions (p= 0.026; Table 3). See Table 5.5 for complete details of the fMRI results. There were no differences in BOLD activation for the high risk>low risk contrast. However, PPI analyses of high risk>low risk decisions showed that the A's group had greater connectivity from the left ACC ROI and three clusters. These included the left precuneus/posterior cingulate, left supramarginal gyrus and the bilateral supplementary motor area. The A's group also had greater connectivity from the right ACC ROI and a massive cluster containing much of the left parietal and temporal lobes, the right putamen, bilateral supplementary motor area/mid cingulate and the left pre-postcentral gyri. In addition, the A's group also had greater connectivity from the left mPFC ROI and left precuneus/ posterior cingulum and
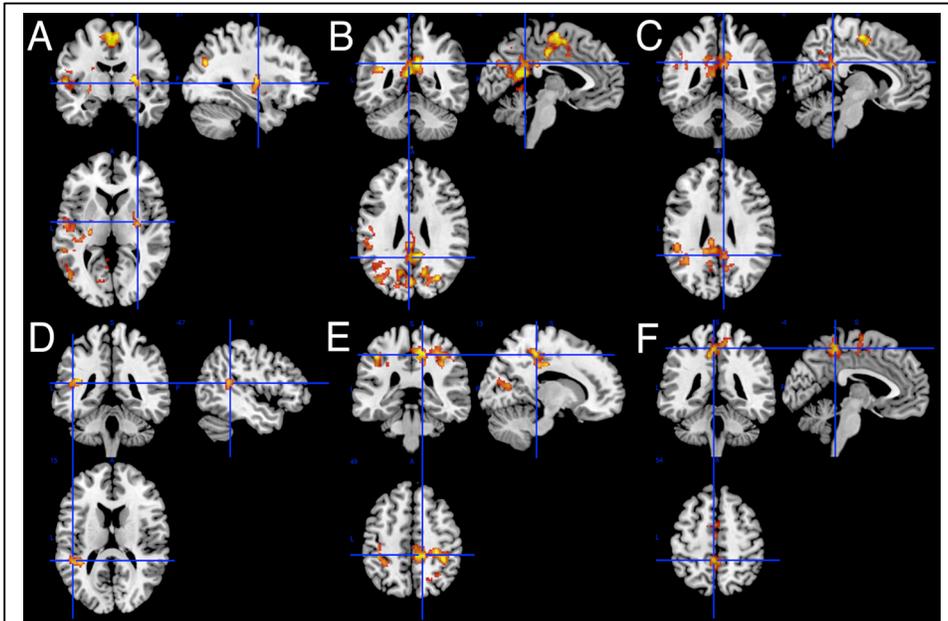
Figure 5.5: GABA Main Effect Results for WoF HR>LR. A) Right ACC ROI connectivity with right putamen and bilateral mid-cingulate. B) Right ACC ROI connectivity with left temporal and bilateral parietal lobes. C) Left ACC ROI connectivity with left supplementary motor area and bilateral posterior cingulate. D) Left OFC ROI connectivity with the left superior temporal gyrus. E) Right OFC ROI connectivity with multiple posterior brain regions. F) Left mPFC ROI connectivity with left precuneus and bilateral supplementary motor area. In all images, the A's group had higher connectivity. Images shown at p<0.05 cluster corrected.

bilateral supplementary motor area. Also, the A's had greater connectivity from the left OFC ROI and the left superior temporal gyrus. Lastly, they had greater connectivity from the right OFC ROI and precuneus/ posterior cingulate, left superior/middle temporal gyri, right precuneus, right pre-postcentral gyri and mid cingulate and left pre-postcentral gyri (Figure 5.5). Taken together the above PPI results suggest the A's group had greater connectivity in regions involved in decision making, and given they also made less risky decisions, this suggests they are more efficient in recruiting networks to evaluate the potential costs versus benefits of choosing the higher-risk option.

For the winning>losing feedback contrast, the GG group had higher activation in four clusters. These included the left putamen, the right cuneus/precuneus, right precentral gyrus and left postcentral gyrus. These BOLD results suggest the GG group is

more responsive to rewarding feedback. PPI results for the contrast of winning>losing feedback showed the GG group had higher connectivity between the left insula ROI and left hippocampus. Given the role of the hippocampus in memory and learning, this could suggest reward has stronger influence on these processes in the GG group (Figure 5.6). There were no other PPI results for the winning>losing feedback.
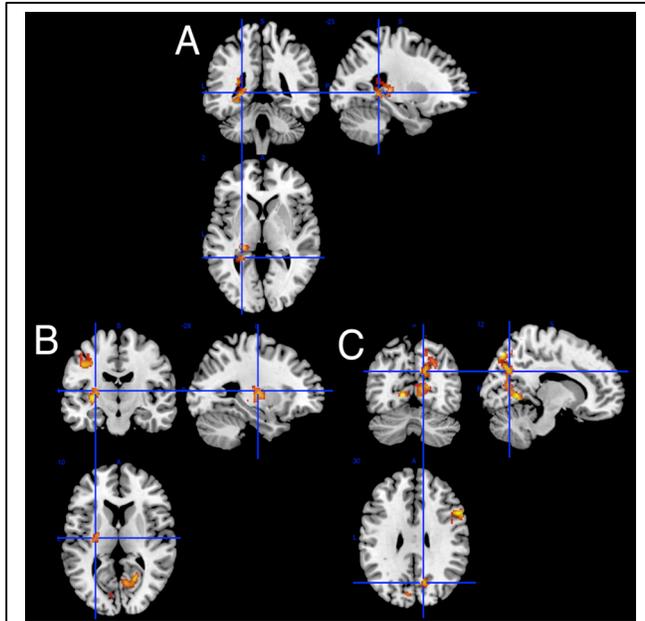
Figure 5.6: GABA Main Effect Results for WoF Win>Lose. A) Left insula ROI connectivity with left hippocampus. B) BOLD activation in left putamen. C) BOLD activation in multiple posterior regions and right precentral gyrus. In all three, the GG group had higher activation and connectivity. Images shown at p<0.05 cluster corrected.

Table 5.3: GABA fMRI Results for the Go-NoGo Task

Anatomical Region(s)	Cluster Size	Peak MNI Coordinates x	y	z	Peak Stat.	DIR.	Caucasian Only
BOLD Activation Results							
Left Supramarginal/Postcentral Gyri	409	-52	-18	14	4.80	A's	X
Left Supramarginal/Postcentral Gyri	278	-58	-28	46	4.06	A's	X
PPI Results							
Right Insula ROI to Right Mid-Cingulum	399	26	-36	36	3.61	A's	-
Right Insula ROI to Right Superior/Inferior Parietal Lobules	549	30	-72	48	3.73	A's	X
Right Insula ROI to Left Precuneus	309	-30	-84	32	3.98	A's	-
Abbreviations: DIR.= Direction of the group effect; Int.= GABA X Time interaction; Peak Stat.= Peak statistic, T-statistic for group comparisons, F-statistic for interactions. Caucasian Only: Y= cluster survived multiple corrections; X= cluster was present but didn't survive multiple corrections; - = cluster was not present.							

Table 5.4: GABA fMRI Results for the ecStroop Task

Anatomical Region(s)	Cluster Size	Peak MNI Coordinates x	y	z	Peak Stat.	DIR.	Caucasian Only
Negative>Neutral Words							
BOLD Activation Results							
No Results							
PPI Results							
Left dACC ROI to Bilateral mPFC	593	14	52	0	-4.05	GG	-
Left dACC ROI to Bilateral Caudate	499	2	6	6	-4.38	GG	Y
Left dACC ROI to Right Pre-Postcentral Gyri	433	34	-8	66	-3.70	GG	Y
Left mPFC ROI to Right Superior/Middle Frontal Gyri	261	16	-6	68	-3.72	GG	Y
Right mPFC ROI to Right Superior Temporal Gyrus	387	32	-52	14	-4.21	GG	X
Right mPFC ROI to Left Supplementary Motor Area	234	-18	-16	68	-3.76	GG	X
Left DLPFC ROI to Right Pre-Postcentral Gyri	264	62	-4	24	23.57	Int.	-
Alcohol>Neutral Words							
BOLD Activation Results							
Bilateral Precuneus/Posterior Cingulate	675	-8	-52	26	4.23	A's	X
PPI Results							
Left dACC ROI to Right Inferior Frontal Gyrus/Insula	750	54	16	10	-4.06	GG	X
Left dACC to Left Caudate/Putamen	862	14	0	16	-4.66	GG	X
Left dACC ROI to Right Pre-Postcentral Gyri	869	-2	28	58	-4.55	GG	X
Left dACC ROI to Left Supplementary Motor Area	456	-6	6	54	-4.47	GG	-
Right mPFC ROI to Right Supplementary Motor Area	593	14	-2	66	-4.05	GG	X
Right Insula ROI to Right Caudate	322	28	-4	24	18.65	Int.	-
Abbreviations: DIR.= Direction of the group effect; Int.= GABA X Time interaction; Peak Stat.= Peak statistic, T-statistic for group comparisons, F-statistic for interactions. Caucasian Only: Y= cluster survived multiple corrections; X= cluster was present but didn't survive multiple corrections; - = cluster was not present.							

Table 5.5: GABA fMRI Results for the WoF Task							
Anatomical Region(s)	Cluster Size	Peak MNI Coordinates			Peak Stat.	DIR.	Caucasian Only
		x	y	z			
High Risk> Low Risk Decisions							
BOLD Activation Results							
No Results							
PPI Results							
Left ACC ROI to Left Precuneus/Posterior Cingulate	1145	-16	-40	22	4.53	A's	Y
Left ACC ROI to Left Supramarginal Gyrus	460	-40	-54	32	4.19	A's	Y
Left ACC ROI to Bilateral Supplementary Motor Area	410	-8	-2	52	4.58	A's	Y
Right ACC ROI to Right Putamen	207	26	-8	10	4.64	A's	Y
Right ACC ROI to much of the Left Parietal/Temporal Lobes	5770	4	-62	44	4.98	A's	Y
Right ACC to Bilateral Supplementary Motor Area/Mid-Cingulate	1100	0	-18	44	6.01	A's	Y
Right ACC ROI to Left Pre-Postcentral Gyri	508	-30	-30	52	4.69	A's	Y
Left mPFC ROI to Left Precuneus/Posterior Cingulate	418	-6	-42	52	4.00	A's	Y
Left mPFC ROI to Bilateral Supplementary Motor Area	284	0	-14	48	3.94	A's	-
Left OFC ROI to Left Superior Temporal Gyrus	252	-42	-44	18	4.33	A's	X
Right OFC ROI to Right Precuneus/Posterior Cingulate	307	10	-70	14	4.21	A's	-
Right OFC ROI to Left Superior/Middle Temporal Gyri	315	-34	-50	20	3.85	A's	Y
Right OFC ROI to Right Precuneus	260	26	-66	40	3.89	A's	Y
Right OFC ROI to Right Pre-Postcentral Gyri & Mid-Cingulate	1073	38	-40	48	4.73	A's	Y
Right OFC ROI to Left Pre-Postcentral Gyri	514	-42	-36	46	4.25	A's	Y
Winning>Losing Feedback							
BOLD Activation Results							
Left Putamen	360	-32	-14	0	-4.08	GG	Y
Right Precuneus/Cuneus	1783	16	-56	2	-4.92	GG	Y
Right Precentral Gyrus	569	56	12	34	-4.97	GG	Y
Left Postcentral Gyrus	248	-32	-18	40	-4.10	GG	Y
PPI Results							
Left Insula ROI to Left Thalamus/Hippocampus	356	-26	-28	4	-3.94	GG	X
Abbreviations: DIR.= Direction of the group effect; Int.= GABA X Time interaction; Peak Stat.= Peak statistic, T-statistic for group comparisons, F-statistic for interactions. Caucasian Only: Y= cluster survived multiple corrections; X= cluster was present but didn't survive multiple corrections; - = cluster was not present.							

Genetic Population Stratification Effects on fMRI Data

There is concern in the genetic literature that population stratification can have impact on results causing false positives, and this concern has been raised in regards to genetic brain imaging studies (Hariri & Weinberger, 2003; Thomas & Witte, 2002; Zubicaray et al., 2008). Population stratification can happen when the distribution of genetic alleles differs between different racial/ethnic backgrounds. To address these possible effects, significant brain imaging results were reanalyzed using only Caucasian participants. There were not enough participants of African American or Latino backgrounds to analyze separately. If significant clusters were indeed false positives caused by stratification, then upon reanalysis the clusters should no longer exist. In contrast, evidence points against stratification if the clusters remain, even if uncorrected for multiple comparisons as this would likely happen from reduced power due to the lower number of participants in the analyses. This is because population stratification is not a serious threat to analyses in a more homogeneous population; Caucasians for instance (Wacholder et al., 2002). Results are shown in Table 5.3 for the Go-NoGo, Table 5.4 for the ecStroop and Table 5.5 for the WoF. For the Go-NoGo, no clusters survived correction for multiple comparisons. Three clusters did show group differences uncorrected, suggesting reduced power for these clusters from analyzing fewer participants and therefore not stratification effects. In contrast, two PPI clusters fully went away, between the right insula ROI, right mid-cingulum and left precuneus. This could indicate population stratification effects of GABA on the Go-NoGo, especially since these two clusters comprise 2/5ths of the original findings. However, there were no significant allelic distribution differences between races, which argues against the

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possibility of stratification effects happening. During analyses of the ecStroop using only Caucasians, out of the 14 original significant clusters, only 4 clusters did not show any corrected or uncorrected group differences. Therefore, minimal false positives possibly due to stratification effects of GABA are impacting the ecStroop. Interestingly, however, two of the original 14 were GABA X time interactions, both of which didn't show any effects during the Caucasian only analyses. Therefore, developmental effects for the ecStroop might be influenced by population stratification. Lastly, reanalyzes of the WoF data found out of the original 20 significant clusters, only 2 clusters did not show any corrected or uncorrected group differences. This highly suggests there are no stratification effects of GABA for the WoF.

Discussion

In this study, we investigated the effects GABA α2 subunit SNP rs279826 longitudinally during adolescence on three cognitive domains: inhibitory control, attentional bias and risky decision-making involving reward. Its influence of substance use initiation was also investigated. It was hypothesized the G risk allele would have negative impact on some or all of these domains. However, the effect of rs279826 varied depending on which domain was being investigated. In particular, the G risk allele seemed to confer more efficient inhibitory control and less attentional bias. However, the G allele was associated with more risky decision-making and greater activation of reward processing areas and networks. In addition to these findings, there were two results that suggest a developmental effect. Specifically, gene X time interactions were seen for the ecStroop task such that the GG group decreased connectivity between Wave1 and Wave2, whereas for all PPI main effects they had higher connectivity. Lastly, contrary to

studies demonstrating that the GG allele of rs279826 confers risk of AUD's in adults, there was no association with substance use initiation during the age range investigated in this study.

Go-NoGo

Investigation of the Go-NoGo task yielded a few results, which suggest the lower risk A's group may have less efficient inhibitory control. Even though the two groups did not differ in performance on the task, the A's group had greater BOLD activation in two separate clusters both containing the left supramarginal gyrus. Since there were no behavioral differences, one interpretation is that the A's group may need to recruit additional neuronal resources to achieve the same performance. The supramarginal gyrus has been associated with many functions, including action planning and visual search to discriminate between stimuli (Króliczak & Frey, 2009; Weidner, Krummenacher, Reimann, Muller, & Fink, 2009). This could mean using inhibitory control requires greater cognitive demand for the A's group, leading to the recruitment of greater attentional resources to decipher the correct course of action. The A's did have higher connectivity between the insula and a few clusters including the mid-cingulate. The insula consistently shows up during inhibitory control paradigms and recently it was shown to be important in the detection and processing of signals signifying the need to inhibit an action (Cai, Ryali, Chen, Li, & Menon, 2014). The mid-cingulate has been shown to be involved with intentional motor control and thus, higher connectivity between the insula and mid-cingulate could signify better integration of inhibitory signals with the control of movement (Hoffstaedter et al., 2014). However, since there were no behavioral differences, this could instead suggest the A's group needed to recruit this

circuit to a greater extent in order to achieve the same performance. However, even though racial backgrounds did not significantly differ on allelic distributions of GABA, analysis of Caucasians only suggested possible population stratification effects for the insula and mid-cingulate connectivity, and results should be taken with caution when generalizing these finding to individuals of Caucasian descent. Together, contrary to the hypothesis, these results suggest the lower risk A's group have less efficient inhibitory control and need to recruit additional neural resources to implement it.

ecStroop

During the ecStroop task, there were no behavioral differences between the groups. However, analyses of the BOLD activation data during the alcohol>neutral contrast resulted in a main effect such that the lower risk A's group had greater activation in a cluster containing the precuneus/posterior cingulate. No activation differences were found for negative>neutral. Both these regions have been associated with self-reflective processes and autobiographical memory (Cavanna & Trimble, 2006; Leech & Sharp, 2014). In addition, recent work has shown activity in the precuneus is positively correlated with cognitive bias (R. Jones & Bhattacharya, 2014). Therefore, greater neuronal activity in the precuneus for the A's group could indicate they have more attentional bias to alcohol words. However, this did not translate into behavioral differences on the task and additional research is needed to verify this postulation.

The PPI results for both contrasts, alcohol>neutral and negative>neutral, had many similar patterns. For instance, in both contrasts, the GG group had higher connectivity between the ACC and caudate as well as between the ACC and precentral gyrus. The ACC has long been known to play a role in resolving cognitive conflict,

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which is present in the ecStroop task for emotionally salient words into the task (Kerns et al., 2004; Shenhav et al., 2013). The caudate is known to play roles in involuntary attentional capture, instrumental learning and habit formation; all of which involve salience encoding (Anderson, Laurent, & Yantis, 2014; Asaad & Eskandar, 2011; Graybiel, 2008). Higher connectivity in the GG group between these structures could indicate better top-down control between the ACC and involuntary attentional responses encoded in the caudate to negative and alcohol related stimuli. As mentioned above, the GG groups also had higher connectivity for both contrasts between the ACC and the precentral gyri. The precentral gyrus is primarily involved with initiating motor movement, and the ACC has been shown to exert control over motor movements (Matsumoto, Suzuki, & Tanaka, 2003; T. Paus, 2001; Z. M. Williams, Bush, Rauch, Cosgrove, & Eskandar, 2004). Direct interpretation of this is difficult, but it could be that the ACC might be able to resolve conflicting motor commands reaching the precentral gyrus due to biases initiated by the task, as correct completion of the task requires implementing the proper motor command out of multiple choices. These PPI results suggest the GG group potentially has better top-down control of attentional bias during this age range, but in a more general manner, not specific to alcohol or negative words. However, in the absence of behavioral differences on the task, there is an alternative explanation for the PPI results. Higher connectivity with the ACC could result from greater demand on cognitive control to resolve attentional bias in the GG group. This would support the hypothesis the GG group has more attentional bias. However, analysis of the BOLD data showed the A's group had a greater neuronal response to alcohol words in the precuneus, an area positively correlated with attentional bias (R. Jones &

Bhattacharya, 2014). Since the A's group had a heightened response to alcohol words, this suggests less efficient top-down use of cognitive control. This supports the first supposition, that greater ACC connectivity seen for the GG group is associated with greater control over attentional bias.

Lastly, a couple of results suggest these ecStroop findings may change over time. There was a genotype X time interaction during the alcohol>neutral contrast, in that connectivity from the insula to the caudate decreased for the GG group between wave 1 and 2. Another interaction was found for the negative>neutral contrast, with the GG group also decreasing over time between the DLPFC and precentral gyri. Since connectivity is decreasing over time for the GG group, they may develop less control over attentional bias. Even though the ecStroop did not show a lot of evidence of population stratification, it should be noted that both these interactions did go away when reanalyzed with Caucasians only, and therefore might not affect individuals of Caucasian background even though there were no significant differences in the allelic distribution of GABA between races. Future follow-up is needed to investigate if these changes persist over adolescence and if they generalize to all races equally.

WoF

Unlike the other two tasks the results of the WoF task were in line with our predictions such that the GG group made more risky decisions, supporting the hypothesis the G allele confers risk. Interestingly, despite the greater number of risky decisions during the task there were no BOLD activation differences for the high risk>low risk decision contrast. However, the PPI analysis showed the A's group had higher connectivity in multiple regions involved in risky decision-making. For instance, they

had greater connectivity between the ACC and the precuneus/posterior cingulate. As noted above, the ACC is involved with the resolution of cognitive conflict and the precuneus/posterior cingulate are linked with internal reflection processes (Cavanna & Trimble, 2006; Kerns et al., 2004; Leech & Sharp, 2014; Shenhav et al., 2013). This could be interpreted as the A's having better ability to engage areas involved in reflection for high versus low risk options. Greater connectivity between the ACC and putamen was also found. Besides its role in motor function, the putamen has been shown to help encode actions that lead to success/reward and reward processing that involves active participation to achieve the reward (Haruno & Kawato, 2005; Kätsyri et al., 2013). The increased connectivity between these areas for high risk versus low risk decisions could imply that the A's had better encoding of the limited probability of rewards for the high-risk choices. Another finding was the A's group had higher connectivity with the ACC and supplementary motor area. The supplementary motor area is involved in coordinating internally generated motor movements and stores learned actions as well as the reward values associated with these actions (Nachev, Kennard, & Husain, 2008; Wunderlich, Rangel, & O'Doherty, 2009). Lastly, the A's group had greater connectivity between both the mPFC and OFC with the precuneus, both of which could be interpreted as better reward-guided decision-making (Rushworth, Noonan, Boorman, Walton, & Behrens, 2011). Overall, this shows the A's group had better connectivity and coordination between multiple regions known to play a role in risky decision-making, which may facilitate better decision-making when risks are involved.

Lastly, during the winning>losing feedback contrast, the GG group had heightened BOLD responses to reward processing regions, including the putamen and

precuneus. As the putamen helps encode actions that led to success/reward during situations that involve active participation to achieve the reward, a heightened response could lead to greater subsequent reinforcement of those actions, which might be one mechanism leading to heightened risk for this genotype (Haruno & Kawato, 2005; Kätsyri et al., 2013). The precuneus is reported in many reward related studies; however, there is lack of consensus regarding its exact role in reward processing. It is involved with internal thought, self-reflection and episodic memory (Cavanna & Trimble, 2006; Kerns et al., 2004; Leech & Sharp, 2014; Shenhav et al., 2013; Wagner, Shannon, Kahn, & Buckner, 2005). As such, this could imply the GG group is reflecting on the rewarding outcome more. This in turn could cause a strengthening of the episodic memory being made from their decision that led to the reward, as rewards have been shown to lead to greater potentiation of memories (A. Mason, Farrell, Howard-Jones, & Ludwig, 2017; Miendlarzewska, Bavelier, & Schwartz, 2016; Wittmann et al., 2005). Interestingly, the only PPI result for winning>losing feedback, was that the GG group had higher connectivity between the insula and hippocampus. The insula is important for representing the subjective experience of internal emotional and physiological states, such as the subjective pleasant feeling when receiving a reward (Singer et al., 2009). This further supports the possibility that the GG genotype has a greater influence on the encoding of events related to rewards. However, both these conjectures require further investigation. Together, the results of the WoF suggest the A's group engage areas of executive control during risky decision making, while the GG group is more responsive to rewards and potentially encode positive reinforcement more strongly both of which lead to higher risk taking.

Conclusions

The current investigation found the GABA α2 subunit SNP rs279826 had different effects on cognition, depending on the task analyzed. Results suggest the A allele had negative impact on inhibitory control and attentional bias, while the G allele had negative impact on risky decision-making and reward response with respect to neural efficiency. This highlights the importance of studying genetic effects on multiple cognitive processes, as they can have opposing effects depending on what is being studied. A reported example of this is the Val158Met polymorphism of the catechol-O-methyltransferase (COMT) gene. It has been shown the Met allele is associated with better cognitive performance, while the Val allele has better emotional processing (Mier, Kirsch, & Meyer-Lindenberg, 2010). One explanation for the effects seen for rs279826 could be developmental timing. The α2 subunit has been shown to decrease levels of expression over adolescence until it stabilizes in adulthood (Cruz et al., 2003; Duncan et al., 2010; Hashimoto et al., 2009). Therefore, rs279826 could have different effects depending on the exact age range investigated and task being used. Evidence for this was found for the ecStroop task. Two gene X time interactions were seen, in that connectivity decreased between Wave1 and Wave2 for the GG group. With future follow-up with this sample, it is likely, at least for the ecStroop, the GG group will instead have worse overall attentional bias and/or less neuronal efficiency. Another, less plausible explanation could lie with differences in GABAergic circuitry throughout the brain. The cortex has a vast network of glutamate neurons, which is the primary excitatory neurotransmitter in the brain, projecting both locally and other regions of the brain (Bannister, 2005; Fame, MacDonald, & Macklis, 2011). In the cortex, GABA functions

selectively by locally inhibiting various parts of the glutaminergic networks in a precise temporal manner, leading to synchronization of these networks (Cardin et al., 2009; Sohal, 2012). However, in the striatum GABA is the predominant neurotransmitter, with much less glutaminergic representation, which combined complicates the interpretation of the effect of GABAergic transmission (Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo, 2014; DeLong & Wichmann, 2009). Striatal circuits can contain a series of GABA neurons, with GABAergic transmission leading to either net excitatory or inhibitory effects depending on the specific circuit (Calabresi et al., 2014; DeLong & Wichmann, 2009). Therefore, factors influencing GABAergic transmission, such as rs279826, could have different effects on tasks that rely more heavily on striatal function, such as the WoF.

The current investigation both contradicts and supports prior research involving rs279826. Research in adults has shown rs279826 to be associated with alcohol use problems, with all but two studies showing the G allele was associated with risk (Kiive et al., 2017; Kramer et al., 2008; Philibert et al., 2009; Uhart et al., 2013; Villafuerte et al., 2012, 2013). We did not find any association with substance use initiation. However, one study investigated the effects of rs279826 on alcohol use during adolescence, which also did not find any association (Trucco et al., 2014). It could be the effects of rs279826 are not related to the initiation of alcohol but instead to its addictive effects, which would be seen later in life.

In regards to cognition, two adult studies found the G allele was associated with greater self-reported impulsivity whereas we found the A allele having less efficient inhibitory control (Villafuerte et al., 2012, 2013). This could be due to differences in the

measures used or the developmental stage of life. Importantly, one of these studies did find the G allele had a higher response to reward using fMRI, congruent with our current findings (Villafuerte et al., 2012). Lastly, three studies found the G allele was associated with greater externalizing behavior during adolescence (Dick et al., 2009; Trucco et al., 2016; Villafuerte et al., 2014). However, these investigations used surveys that create conglomerate scores drawn from many aspects of the adolescent's lives and do not look at specific cognitive processes. Our results suggest rs279826 probably has different effects depending on the specific cognitive domain studied and studies using conglomerate scores combining many aspects could miss these effects.

Even though the current investigation was longitudinal, one limitation is the limited time between observations, as the second time point was 18 months after the baseline. Future follow-ups will allow for more detailed analyses of the developmental trajectories. The restricted time between successive measurements could also have limited the number of adolescents that initiated substance use, which undoubtedly had an impact on our ability to detect differences between the two allele groups in this regard though continued follow-up could mitigate this limitation.

In conclusion, the current investigation highlights the importance of studying genetic effects on multiple cognitive domains. Contrary to our hypotheses, the A allele was associated with less efficient inhibitory control, illustrated by the increased neuronal resources required to achieve equivalent performance. Similarly, this was also seen for attentional bias, with the A's group having lower connectivity with regions involved with cognitive control and greater neural response to alcohol versus neutral words. In contrast, supporting the hypothesis the G allele confers risk, it was linked with less efficient risky

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decision-making and a greater reward response. This was shown by the GG group

making a greater number of high-risk decisions, having lower connectivity with regions

involved with decision-making, and an elevated neuronal response to rewarding

feedback.

CHAPTER VI: Discussion

The current investigation sought to identify the impact three genetic polymorphisms associated with adults AUD's have on adolescent cognition and brain function as well as substance use initiation. Specifically, it was hypothesized the alleles that been shown to confer risk would have a negative impact on cognitive domains known to be associated with risk for AUD's in a typically developing adolescent population. The domains we investigated included inhibitory control, attentional bias, risky decision-making and reward responsiveness. One polymorphism, rs279826, is in the α2 subunit gene of the GABA-A receptor, with the G allele conferring risk in most studies. The other two polymorphisms affect the dopamine system: the DAT1 VNTR and DRD2 C957T. DAT1 encodes the dopamine transporter, with the 10 repeat allele more often conferring risk, and DRD2 encodes the dopamine receptor D2, with the C allele most often being associated with risk. In addition to the effects these genes have, the adolescents were followed longitudinally to investigate if these effects change over development since both the GABA-A receptor and the dopamine system have a developmental trajectory that includes adolescence. Lastly, the genetic effects on the initiation of alcohol and substance use were investigated. Results on cognition were highly varied between the three genes, with most supporting our hypotheses, but a few were contrary to our hypotheses. However, in regard to alcohol and substance use initiation, there was no association found for any of the genes.

The most consistent results with our hypotheses were found for DRD2 C957T. Evidence from all three tasks implicated individuals with two C alleles to have less efficient neural processing and connectivity patterns. During the Go-NoGo task in the

absence of behavioral differences, the CC group exhibited greater activity in the left superior temporal gyrus, which has been associated with awareness of motor movement (Leube et al., 2003). The Go-NoGo is a motor inhibition task; therefore, this result suggest the CC group need to pay more attention to their motor movements to achieve the same performance. During the WoF, the CC group had lower connectivity between both the left and right mPFC and multiple areas when making risky decisions. The mPFC is thought to integrate signals when making a decision, such as the anticipated reward value and how this fits with the individual's goals, and therefore the CC group may have a harder time making decisions when risk is present (Euston et al., 2012). The CC group also had higher connectivity during rewarding feedback involving both the right nucleus accumbens and left caudate. These areas are integral to reward processing, and this could indicate they have stronger response in the reward processing network when receiving winning feedback during the task (Asaad & Eskandar, 2011; Carlezon & Thomas, 2009; Doñamayor et al., 2012; Haruno & Kawato, 2005). Lastly, results for the ecStroop indicate strong developmental effects for C957T, as all fMRI results consisted of gene X time interactions. During the Alcohol>Neutral contrast, the CC group had greater activation in the left OFC and left mPFC at Wave2 versus Wave1, suggesting a heightened attentional response to the words over development (Euston et al., 2012; Ogawa et al., 2013; Rothkirch et al., 2012). In addition, connectivity involving the left DLPFC with much of the left PFC decreased in the CC group between the two Waves, suggesting they had lower cognitive control over attentional bias during Wave2 (Gläscher et al., 2012; Ochsner et al., 2012). Lastly, though not a gene X time interaction, main

effects were seen for the CC group having less accuracy for both alcohol and negative words, also suggesting greater attentional bias.

The findings for DRD2 suggests it has wide ranging effects in the population studied, having impact on many different types of cognitive functioning. This can be explained by the fact that it is distributed in many brain regions including subcortical regions such as the striatum and limbic system, but also in the frontal cortex (M. Hirvonen et al., 2005; M. M. Hirvonen et al., 2009). These regions are known to play a role in a wide range of functions, ranging from executive functioning, emotions and reward processing, and have been shown to play roles in risk taking behaviors such as alcohol misuse (Bühler & Mann, 2011). However, the effect DRD2 has likely depends on whether cortical or subcortical structures are being investigated. The DRD2 receptor is inhibitory on dopamine function, causing less dopamine to be released. The C allele has been associated with less DRD2 expression in the striatum, but more in the frontal cortex (M. Hirvonen et al., 2005; M. M. Hirvonen et al., 2009). Therefore, there would be greater dopamine function in reward related areas in the striatum, but less dopamine function in the frontal cortex. It has been shown that an optimal amount of dopamine is needed in the frontal cortex; too much or too little impairs cognitive functioning, known as the inverted-U hypothesis (Mattay et al., 2003). Though there were no differences seen due to DRD2 on alcohol use initiation, all three of the cognitive constructs it impacted have been shown to play a role in predicting either current or future alcohol use during adolescence. For instance, lower inhibitory control has been associated with current adolescent alcohol use as well as predicting future use (Barnes et al., 1999; Bates & Labouvie, 1995; Krank et al., 2011; W. A. Mason et al., 2011; Norman et al., 2011;

Ohannessian & Hesselbrock, 2007; Quinn et al., 2011; H. R. White et al., 2011). In regards to attentional bias, studies have shown that attentional bias can predict transition into future heavy usage of alcohol during late adolescence (Janssen et al., 2015; Thush & Wiers, 2007). Lastly, The WoF task has been shown to be sensitive to differentiating adolescents with and without a family history of alcohol use, and predicting future binge drinking in late adolescence (Cservenka et al., 2015; Cservenka & Nagel, 2013; S. A. Jones et al., 2016). Therefore, even though we didn't find an association of DRD2 with alcohol initiation during early-mid adolescence, it is likely the effects DRD2 has on the neural networks underlying these cognitive functions could lead to alcohol misuse later in adolescence by imparting a confluence of greater impulsivity, attentional bias and propensity to take risks. This would be in alignment with many of the above studies, as they did not find relationships between these cognitive constructs and alcohol misuse until late adolescence. Future follow up is needed to verify this proposition, and to what degree each of the three cognitive constructs is playing a role.

Analyses of the DAT1 VNTR showed its effects were task dependent. There were no significant differences for both the Go-NoGo and ecStroop tasks. However, WoF results were similar to that seen for DRD2 C957T. The 10R group also had lower connectivity between the left and right mPFC and multiple areas including the left ACC and middle frontal gyrus when making risky decisions, suggesting the group may have a harder time making decisions when risk is present (Euston et al., 2012). In addition, the 10R group also had lower connectivity involving the left caudate with the left and right mPFC, left OFC, and right ACC while receiving winning feedback. However, unlike DRD2 C957T, it was shown the 10R group made a greater percentage of high-risk

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decisions during the task. Two gene X time interactions were also observed for the HR>LR contrast, in that the 10R group had decreased connectivity with bilateral ACC with right OFC and right mPFC at Wave2. Since the ACC is involved with resolving cognitive conflict and the OFC and mPFC with emotional response to reward, this suggests the 10R group had a harder time choosing between high and low risk decisions as they developed, which was reflected in a trend for the interaction of gene and time for reaction time during high-risk choices only with the 10R group taking longer at in Wave2 than the 9R group (Kerns et al., 2004; Shenhav et al., 2013).

It is of interest that DAT1 did not show any effects for the Go-NoGo or ecStroop tasks, and informs how it could be inferring influence on risky behaviors such as alcohol misuse. Even though DAT1 is expressed in the frontal cortex, its highest expression is in areas including the striatum and VTA, regions well known for their role in reward processing (Hall et al., 1999; Sasaki et al., 2012; Schwendt et al., 2009; Sekine et al., 2003). In addition, it is not the primary method of dopamine clearance in the frontal cortex, where catechol-O-methyltransferase (COMT) and the norepinephrine transporter (NET) play a larger role (Käenmäki et al., 2010; Morón et al., 2002). In contrast, DAT1 is the main method of clearance in the striatum (Cragg et al., 2000; Mateo et al., 2004; Morón et al., 2002). Therefore, DAT1 should have more impact on cognitive functions that rely on reward processing, such as evaluating potential wins and losses during the WoF task, which is reflected in the results of the current study. Therefore, in contrast to DRD2, which had effects on all three cognitive constructs investigated, DAT1 appears to be highly selective to risky-decision making and reward processing, at least at the age range investigated. This is likely due to greater

dopaminergic functioning, as the 10R allele has been shown to decrease DAT expression, thereby causing more dopamine to remain in the synapse (Faraone et al., 2014). There was no association between DAT1 and alcohol initiation, but as mentioned above for DRD2, the WoF has been found to predict future alcohol misuse in late adolescence (Cservenka et al., 2015; Cservenka & Nagel, 2013; S. A. Jones et al., 2016). It is likely results seen at the earlier stages of adolescence in this study would then play a role in behaviors that could lead to consequent alcohol misuse, through a propensity to make risky decisions and being more responsive to the rewarding effects of alcohol use. Future follow up is needed to verify if the WoF measurements predict future misuse of alcohol in our sample.

The most contradictory results were found for GABA α2 subunit rs279826. In support of our hypothesis of the G allele conferring risk, carriers of two G alleles were found to make a greater percentage of risky decisions. In addition, the GG group exhibited lower functional connectivity with many regions involved with decision-making when risk is involved such as the bilateral ACC and bilateral OFC with multiple areas including the left precuneus (left ACC) and the right putamen (right ACC and right OFC), suggesting less cognitive control and ability to evaluate potential outcomes of the decision, respectively (Fellows, 2007; Kerns et al., 2004; Shenhav et al., 2013; Steiner & Redish, 2012). During rewarding feedback, the GG group had stronger BOLD activation in reward related regions such as the left putamen, suggesting they are more responsive to reward (Haruno & Kawato, 2005; Kätsyri et al., 2013). Contrary to our hypotheses, results for both the Go-NoGo and ecStroop suggest the A allele group has less efficient inhibitory control and ability to control attentional bias. While there were no behavioral

differences for the Go-NoGo task, individuals with the A allele carriers had greater

BOLD activation in the left supramarginal gyrus, an area involved with action planning,

which could suggest they had to recruit additional neural resources to achieve the same

performance (Króliczak & Frey, 2009). There were also no behavioral differences during

the ecStroop task. However, A allele carriers had a heightened BOLD response to alcohol

related versus neutral words in the bilateral precuneus, an area shown to positively

correlate with cognitive bias, suggesting a greater neural response is needed to deal with

attentional bias these words have (R. Jones & Bhattacharya, 2014). The A allele carriers

also exhibited lower connectivity from the left dACC and many regions including the left

caudate and right insula for both alcohol and negative words, suggesting they need

greater coordination between areas involved in conflict management to exert control over

attentional bias (Kerns et al., 2004; Shenhav et al., 2013).

The reasons for the disparate results for GABA between the tasks is likely

numerous. Results from the PPI analyses might offer one explanation. In particular, two

gene X time interactions were seen for the ecStroop. In both cases, carriers of two G

alleles had decreased connectivity from Wave1 to Wave2 for both negative (left DLPFC

to right pre-central gyrus) and alcohol-related words (right insula to right caudate). In

addition, expression of the GABA α2 subunit has been shown to decrease over

adolescence (Cruz et al., 2003; Duncan et al., 2010; Hashimoto et al., 2009). This is in

contrast to the main effects of genotype, in which the GG group had greater connectivity.

This suggests over adolescent development, the effects of the two alleles of the rs279826

gene are changing over time, in a task dependent manner. Another explanation that could

explain the results has to do with recent concern over interpreting fMRI results in the

absence of behavioral differences. For instance, most often when differences are seen in brain activity, it is interpreted the group with greater activation had to recruit more neural resources to achieve the same behavioral performance (Poldrack, R, 2015). However, it has been argued that such BOLD activity differences could instead reflect individuals utilizing different cognitive strategies to perform a task, and do not reflect less efficient use of neural resources, and therefore having no relevance on behavior performance (Ihne, Gallagher, Sullivan, Callicott, & Green, 2016; Poldrack, R, 2015). In this view, neither allele group could be inferring risk during the Go-NoGo or ecStroop, but instead neural differences might only reflect different strategies used by the two groups. Addressing this possibility is beyond the scope of the current investigation and future research is warranted. Possible solutions could be to include harder tasks that can cause behavioral differences, as the version of the Go-NoGo used in the current study might have been too easy for participants to perform, and relate these differences back to brain based measures.

A novel finding of the current investigations of DAT1, DRD2 and GABA is that they converged upon and had impact on the WoF task, possibly having important implications during adolescence. As mentioned in the first paragraph of the general introduction, there is a neurodevelopmental phenomenon known as the dual systems model. It has been shown both the PFC and limbic/striatal regions of the brain are maturing during adolescence (Dahl, 2004; Duijvenvoorde, Achterberg, Braams, Peters, & Crone, 2016; Tomás Paus, 2005; Rubia, 2013). However, the limbic/striatal regions, which are involved with emotional and reward related responses, mature at a younger age than the PFC, known for its role in executive function and top-down control of such

responses (Casey, Jones, & Somerville, 2011; Ernst, Pine, & Hardin, 2006; Galvan, Hare, Voss, Glover, & Casey, 2007; Harden & Tucker-Drob, 2011; Shulman, Harden, Chein, & Steinberg, 2016). This causes greater reward related responses during adolescence, as they have not fully developed the ability to control those responses. The WoF task is known to rely on brain regions involved with reward processing and risk assessment, including limbic and striatal areas (Ernst et al., 2005; Shad et al., 2011). Since all three genes had impact on the WoF, including more risky-decision making and reward responsiveness, it is likely genes associated with adult alcohol use disorders might share common mechanisms during adolescence. Specifically, during a developmental period when there is already heightened reward responsiveness coupled with less executive function, these genes could confer risk by further increasing limbic responses beyond what could be considered normative. This could influence decision-making, biasing behavior toward outcomes associated with a greater reward value, with less concern of the risks associated with those possible outcomes. Therefore, preventive strategies that aim to either dampen or control their over-responsive limbic systems could be of importance for adolescents carrying alleles of genes associated with adult alcohol use disorders.

Even though the current investigation was longitudinal, one limitation is the limited time between observations, as the second time point was 18 months after the baseline. Future follow-ups will allow for more detailed analyses of the developmental trajectories. The restricted time between successive measurements could also have limited the number of adolescents that initiated substance use, which undoubtedly had an

impact on our ability to detect differences between allele groups in this regard, though continued follow-up could mitigate this limitation.

In conclusion, the current investigation supports our hypothesis that genes associated with adult AUD's can be conferring risk by having negative impact on specific cognitive domains during adolescence. Many genetic studies have only investigated if genes confer risk for AUD's, and do not investigate possible mechanisms of how those genes come to confer risk. Even though none of the three genes predicted alcohol initiation during the age range studied, it was found these genes have a differential impact on inhibitory control, attentional bias, risky decision-making and reward responsiveness. It could be these genes are not associated with initiation of alcohol use, but have a role in problematic use. For instance, when individuals with less inhibitory control begin using alcohol, it could lead to a greater escalation of use. Therefore, future follow-up is needed to elucidate the relationship of the influence these genes are having on adolescent cognitive function and future alcohol use problems.

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