THE GENETIC BASIS OF IMPULSIVE PERSONALITY TRAITS:

A PRIORITIZED SUBSET APPROACH

by

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(Under the Direction of James MacKillop, PhD)

ABSTRACT

This study explored the genetic basis of impulsive personality traits, defined as performance on the Barratt Impulsiveness Scale, Version 11 (BIS-11) and the UPPS-P Impulsive Behavior Scale (UPPS-P), using a prioritized subset approach in a sample of 983 healthy young adults of European ancestry. The study used multivariate analysis to assess the relationship between impulsive personality traits and: 1) 21 *a priori* single nucleotide polymorphisms previously associated with impulsive personality traits; 2) 13,337 high-value addiction (HVA) markers (from the SmokeScreen© array); and 3) ~5M genome-wide loci. This study identified a significant relationship between impulsive personality traits and two previously identified candidate loci (rs6313 and rs6311), both within the 5-HT2a receptor gene (*HTR2a*). Follow-up analyses suggested that the effects were specific to the BIS-11 Motor and Non-planning subscales. Analyses of the HVA loci and genome-wide loci yielded no statistically significant findings, but suggestive associations were present for loci in *BIK, STOX2, ITGB1,* and *LMNTD1*. This study further implicates loci within *HTR2a* with self-reported impulsive personality traits for future replication and identified suggestive loci from the HVA and genome-wide analyses.

INDEX WORDS: Impulsivity; Personality Traits; Genetics; Endophenotype; Addiction

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DEDICATION

To Jennifer, Steven, and Ryan.

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INTRODUCTION

Addictive disorders are associated with a wide array of negative outcomes including comorbid psychopathology, poor health, decreased work productivity, HIV infection, social dysfunction, violence, and increased suicide risk (Compton, Thomas, Stinson, & Grant, 2007; Dalton, Cate-Carter, Mundo, Parikh, & Kennedy, 2003; Kessler, 2004; Trull, 2000). One of the primary foci of addiction research is on the risk and protective factors that contribute to the development, maintenance, and resolution of these disorders. In particular, genetic influences stand out as a major influence on addictive disorders yet remain largely enigmatic in terms of the mechanism of their influence.

Research comparing rates of co-occurrence of addictive disorders among monozygotic and dizygotic twins has yielded substantive evidence of strong genetic components (Agrawal & Lynskey, 2008; Goldman, Oroszi, & Ducci, 2005). In a review conducted by Agrawal and Lynskey (2008), the concordance rates of different substance use disorders in monozygotic and dizygotic twins drawn from numerous registries yielded the finding that 50-70% of the variance in smoking and alcohol use disorder is attributable to genetic factors. Additionally, Goldman et al. (2005) pooled data from numerous twin registries, determining that addictive disorders also exhibited greater than or equal to 50% genetic variance, including gambling, opiates, and cocaine.

These twin studies rest upon an equal environments assumption. This assumption maintains that monozygotic and dizygotic twins perceive and experience their environments

equally similarly. Critics maintain that monozygotic twin pairs have more similar environments, leading to an inflated heritability estimate of certain traits (Horwitz, Videon, Schmitz, & Davis, 2003a, 2003b; Pam, Kemker, Ross, & Golden, 1996; Richardson & Norgate, 2005). Indeed, there is overwhelming evidence that monozygotic twins are treated more similarly than dizygotic twins. For example, monozygotic twins are more likely to have the same playmates, share the same room, dress alike, and as adults they are more likely to keep in contact than dizygotic twins (Kendler, 1986). In fact, the similarity in concordance of twins can be traced all the way back to the gestational period, where that dizygotic twins do not share a placenta (as monozygotic twins do) and are at increased risk for certain cancers likely due to differential hormone exposure (Braun, Ahlbom, Floderus, Brinton, & Hoover, 1995; Lambalk & Boomsma, 1998; Swerdlow, De Stavola, Maconochie, & Siskind, 1996). However, a recent study found minimal impact of sharing a chorion (i.e., outermost membrane of the embryo) on concordance rates of a measure of externalizing (van Beijsterveldt et al., 2015). Furthermore, environmental similarity during childhood has not been found to predict twin similarity in personality, attitudes, intelligence, nor a number of psychiatric disorders (including alcoholism) (for a review, see Kendler, Neale, Kessler, Heath, & Eaves, 1993). In addition, studies have largely found tenuous or non-existent relationships between twin physical similarity, similarity of parental behavior towards twins, and perceived zygosity (when dizygotic twins are identified incorrectly as monozygotic) with variation in twin personality (Morris-Yates, Andrews, Howie, & Henderson, 1990; Plomin, Willerman, & Loehlin, 1976), eating attitudes (Klump, Holly, Iacono, McGue, & Willson, 2000), behavioral problems (Cronk et al., 2002), and psychiatric disorders (Eaves, Foley, & Silberg, 2012; Kendler et al., 1993; Xian et al., 2000). Finally, there is evidence that more similar parental treatment of monozygotic versus dizygotic twins occurs in response to the greater

similarity of actions initiated by monozygotic pairs (Lytton, 1977), and this is most likely because they are genetically more similar than dizygotic twins, which is not in and of itself a violation of the assumption. Thus, although there are reasons to be cautious about twin estimates of heritability, the evidence of genetic influences on addictive disorders from twin studies is substantial.

Furthermore, novel methods of heritability analysis, such as Genome-wide Complex Trait Analysis (GCTA; Yang, Lee, Goddard, & Visscher, 2011), have been used to estimate the total genetic effects attributable to common single-nucleotide polymorphisms (SNPs) on the genome. GCTA has yielded approximately half of the twin heritability estimate of variance (16-36%) for addictive disorders (Palmer et al., 2015; Vrieze, McGue, Miller, Hicks, & Iacono, 2013). While the remaining variance is putatively attributable to rare SNP effects, additive and non-additive structural variation (e.g., copy-number variations, insertions/deletions), gene-environment interaction, and gene-gene interaction (Manolio et al., 2009a; Zuk, Hechter, Sunyaev, & Lander, 2012), GCTA nonetheless yields evidence of substantial genetic variance conferred by common SNPs.

Despite persuasive evidence of aggregate genetic influences, there has been difficulty in identifying specific candidate genes that consistently account for large variation in addictive disorders; this is known as the "missing heritability" problem (Manolio et al., 2009). Furthermore, little is understood about the mechanisms of these genetic associations. In addition to the difficulty in characterizing most of the genetic variation in addictive disorders, there has been an interesting absence of convergence between *a priori* driven candidate gene studies and agnostic genome-wide association studies (GWAS). Candidate gene studies have primarily focused on genes that are associated with the biological mechanisms upon which drugs of abuse

act (e.g., dopamine systems, opiod systems, and γ-aminobutyric acid [GABA] systems; Hall, Drgonova, Jain, & Uhl, 2013). While rodent knockout studies (i.e., studies which inactivate one or more genes) have confirmed the importance of these systems in addiction liability, they provide little evidence that normal human genetic variation (as opposed to total gene inactivation) in these genes is relevant (see Hall et al., 2013). Furthermore, researchers have found that aggregate risk scores of common candidate risk alleles were not able to discriminate between healthy controls and individuals with alcohol dependence (Yan et al., 2013). On the other hand, SNPs *empirically derived* from two GWAS studies (all SNPs significant at $p < .01$) considered in aggregate were found to predict alcohol dependence only marginally worse than family history (mean estimate of .549 versus .686) (Yan et al., 2013). Therefore, there is little evidence from human genetic studies to support the role of these candidate genes in consistently distinguishing addiction liability when considering the inconsistency in findings across studies, the bias towards publishing positive results, and largely divergent GWAS findings.

There has been some convergence across GWAS for different classes of genes that appear to play a role. Associations from GWAS of addiction liability seem to be overwhelmingly comprised of genes coding for cell adhesion molecules, enzyme production, and transcriptional regulation (for a review see Hall et al., 2013). In most instances, the *a priori* monoamine system genes are entirely absent, whereas counterparts that are biologically upstream are over represented. Only GWAS of nicotine dependence show evidence of involvement of monoaminergic-related genes (Tobacco Genetics Consortium, 2010) and strong evidence of an *a prio*ri finding of a SNP (rs16969968) within a nicotine receptor gene (*CHRNA5*) on chromosome 15 (Saccone et al., 2007), which was replicated and expanded to neighboring genes in subsequent large-scale GWAS (e.g., Tobacco Genetics Consortium, 2010; Thorgeirsson et al.,

2010). Difficulty in identifying and replicating significant SNPs in addictive disorders (particularly *a priori* SNPs) is likely due to two factors: 1) the conditions are complex, heterogeneous disorders (i.e., multiple possible arrays of symptoms can qualify for a diagnosis of the disorder); 2) they may develop from multiple developmental pathways (Ray, 2012).

An Endophenotype Approach to Addiction

Given this difficulty in characterizing the genetic basis of these polythetic disorders, an endophenotype approach may prove worthwhile in clarifying genetic contributions by elucidating underlying mechanisms of these influences. The endophenotype approach seeks to examine simpler, more narrow phenotypes that are both associated with the disorder of interest and putatively more closely tied to a specific genetic basis within a limited number of genes. Endophenotypes are intended to offer substantial benefits to the characterization of the genetic risk for addictive disorders via two purported benefits: 1) by being more narrow phenotypes they theoretically will have stronger relationships with a more limited number of genes; and 2) they may facilitate the interpretation of mechanism, namely, by identifying loci which are relevant to both the endophenotype and the disorder. Consistent with this perspective, a recent meta-analysis found that trait, neuropsychological, and neurobiological measures of impulsivity had stronger genetic effects than a diagnostic phenotype (i.e., ADHD symptoms; Jonas and Markon 2014). However, other studies have identified limited evidence of increased power with intermediate phenotypes (Greenwood et al., 2013; Malone et al., 2014; Need et al., 2009; Stein et al., 2012), and in the case of psychophysiological endophenotypes which are expensive to measure (e.g., P3 amplitude), it is likely not useful for aiding in discovery (for a review see Flint, Timpson, & Munafò, 2014).

With regard to the second benefit, by better understanding mechanisms of genetic influence, endophenotypes may contribute to identification of genetically influenced etiological pathways for addictive disorders. Furthermore, successful identification of valid endophenotypes may ultimately improve treatment or prevention efforts (for a full review, see MacKillop & Munafò, 2013), making investigations in this area an ongoing priority area in addiction genetics research. In sum, although larger effect sizes are not guaranteed for intermediate phenotypes, they may be reflective of underlying disease processes and as such, may facilitate the understanding of genetic influences.

Impulsivity as an Endophenotype for Addictive Disorders

One phenotype that has been consistently linked to psychiatric disorders, and addictive disorders in particular, is impulsivity (de Wit, 2009; Lejuez et al., 2010; MacKillop et al., 2011; Stanford et al., 2009). Impulsivity refers to a family of constructs that can be broadly categorized into three primary domains: impulsive personality traits (i.e., self-reported impulsive tendencies), response inhibition (i.e., ability to inhibit a prepotent response on experimental tasks), and decision making propensities (i.e., preferences for smaller immediate rewards versus larger delayed rewards). The focus of the present study is on impulsive personality traits, as measured by the Barratt Impulsiveness Scale, Version 11 (BIS-11) (Patton, Stanford, & Barratt, 1995) and the UPPS-P Impulsive Behavior Scale (UPPS-P; Cyders et al., 2007; Whiteside & Lynam, 2001). The BIS-11 and UPPS-P have been translated into numerous languages, and shown good validity and reliability (Billieux et al., 2012; Cándido, Orduña, Perales, Verdejo-García, & Billieux, 2012; Fossati, Di Ceglie, Acquarini, & Barratt, 2001; Li & Chen, 2007; Someya et al., 2001; Verdejo-García, Lozano, Moya, Alcázar, & Pérez-García, 2010).

This study did not be focus on behavioral measures of impulsivity, such as tasks which require participants to select between smaller immediate rewards and larger delayed rewards (i.e., delayed reward discounting) or inhibit a prepotent response (e.g., Go-No-Go), because they are qualitatively different in terms of measurement and are not correlated with the self-report measures (Amlung, Gray, & MacKillop, 2016; Bari & Robbins, 2013; MacKillop et al., in press; Reynolds, Ortengren, Richards, & de Wit, 2006). As such, the literature reviewed herein predominantly pertains to impulsive personality traits, with a particular focus on the BIS-11 and the UPPS-P. Specifically, the subscales that are reviewed and are the focus of this study are: the three BIS-11 second-order subscales: i) Attentional subscale, which reflects the ability to focus on a task at hand; ii) the Motor subscale, which reflects the tendency to act on the spur of the moment; iii) the Non-planning subscale, which reflects the ability to plan and think carefully about the future; and the UPPS-P subscales: i) (lack of) Premeditation, which is a propensity to act without considering potential consequences; ii) Negative Urgency, which is a propensity for acting on immediate cues when experiencing negative affect; iii) Positive Urgency, which is a propensity for acting on immediate cues when experiencing positive affect; iv) (lack of) Perseverance, which reflects an inability to follow through on tasks. Of note, Sensation Seeking (i.e., an orientation toward engaging in high energy and thrill behaviors) was not included within this study because it is generally found to be an indicator of reward sensitivity rather than impulse regulation (Duckworth & Kern, 2011; Kirby & Finch, 2010; Magid, Maclean, & Colder, 2007). Additionally, Sensation Seeking was not correlated with the other impulsive personality trait subscales in initial phenotyping of the dataset from which the proposed project is derived (MacKillop et al., in press).

A number of criteria have been proposed to clarify whether a characteristic can be considered an endophenotype, including: 1) the endophenotype is associated with the illness; 2) the endophenotype is heritable; 3) the endophenotype is primarily state-independent (manifests whether or not the illness is active); 4) within families, endophenotype and illness co-segregate; 5) the endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population (Flint & Munafò, 2007; Gottesman & Gould, 2003; Gottesman & Shields, 1973). The existing literature reveals that impulsive personality traits largely satisfy these criteria and are therefore a promising endophenotype for addictive disorders. For example, extensive research supports a relationship between impulsive personality traits and risky behaviors, addictive disorders, and other psychopathology (Coskunpinar, Dir, & Cyders, 2013; Stanford et al., 2009). Higher total BIS-11 scores have been identified in cocaine dependent adults (Lane, Moeller, Steinberg, Buzby, & Kosten, 2007; Moeller et al., 2001; Patkar et al., 2004). Additionally, regular ecstasy users have been shown to have higher total BIS-11 and Motor subscale scores than control participants (Bond, Verheyden, Wingrove, & Curran, 2004). Furthermore, higher total scale and all three subscale scores have been identified in methamphetamine-dependent participants (B. Lee et al., 2009) and methadone-maintained former heroin addicts (Cohen, Grebchenko, Steinfeld, Frenda, & Galynker, 2008; Nielsen et al., 2012), as compared to controls. A meta-analytic review of the UPPS-P subscales and alcohol use identified significant relationships between all subscales and multiple facets of drinking (i.e., quantity, frequency, dependence, problems, binge drinking) (Coskunpinar et al., 2013). Likewise, in a recent meta-analysis the UPPS-P subscales were all significantly related to alcohol and substance use (weighted mean effect sizes = .19-.30) (Berg, Latzman, Bliwise, & Lilienfeld, 2015). Similarly, many individual studies have extended impulsive personality traits

to other domains of addictive behavior such as pathological gambling (Torres et al., 2013), food addiction (Murphy, Stojek, & MacKillop, 2013), and uncontrolled eating (Leitch, Morgan, & Yeomans, 2013; Meule, 2013).

Several studies have examined the role of impulsive personality traits, specifically BIS-11 total and subscales, in predicting treatment outcomes for substance users. BIS-11 has been associated with subsequent outcomes in treatment seeking cigarette smokers (López-Torrecillas, Perales, Nieto-Ruiz, & Verdejo-García, 2014; Sheffer et al., 2012), individuals with alcohol dependence (Bowden-Jones, McPhillips, Rogers, Hutton, & Joyce, 2005; Charney, Zikos, & Gill, 2010; Evren, Durkaya, Evren, Dalbudak, & Cetin, 2012), and cocaine users (Moeller et al., 2001; Patkar et al., 2004; Schmitz et al., 2009; Winhusen et al., 2013). Notably, some studies have failed to find a difference in impulsive personality traits among lapsing and non-lapsing smokers (Krishnan-Sarin et al., 2007), polysubstance users (De Wilde, Verdejo-García, Sabbe, Hulstijn, & Dom, 2013), and pathological gamblers (De Wilde, Goudriaan, & Sabbe, 2013), or even found an opposite effect in individuals with alcohol use disorders (Papachristou, Nederkoorn, Giesen, & Jansen, 2014). However, these studies with null or contradictory findings had much smaller sample sizes (largest $N = 37$), with as few as nine participants in an abstinent group. Of note, there is a surprising dearth of studies exploring the predictive validity of the UPPS-P subscales of treatment outcome. In fact, only one study of individuals with substance dependence (most had polysubstance dependence) has been conducted, and there were no significant differences in any of the subscales among lapsers and abstainers (Stevens et al., 2015). In sum, the majority of studies have identified a relationship between BIS-11 scores and addiction treatment outcome, but some small studies have found null or contradictory findings, and limited research exists on UPPS-P and treatment outcome.

In addition to associations with addictive disorders, research supports the heritability of impulsive personality traits. One twin study compared the concordance of BIS (utilizing a principal components analysis derived aggregate of 17 items from several versions of the BIS) in pairs of male monozygotic and dizygotic twins, found that non-additive genetic influences accounted for approximately half of the variance in trait impulsiveness (Seroczynski, Bergeman, & Coccaro, 1999). Another study found strong evidence of heritability (47-63%) as well as strong genetic continuity (76%) of BIS-11 total scores (adapted for youth) from mid (11-13 years) to late (14-16 years) adolescents (Niv, Tuvblad, Raine, Wang, & Baker, 2012). A final twin study found strong evidence of 49% heritability in UPPS-P scores; (Gustavson, Miyake, Hewitt, & Friedman, 2014), using a single score derived from Negative Urgency, Positive Urgency, and (lack of) Premeditation. Furthermore, impulsive personality traits have been found higher in siblings of chronic stimulant users than controls, but highest in the chronic stimulant users, suggesting that impulsive personality traits are an endophenotype for stimulant dependence that may be exacerbated by chronic drug exposure (Ersche, Turton, Pradhan, Bullmore, & Robbins, 2010).

In sum, the associations between impulsive personality traits and addictive disorders, elevated presence in monozygotic twins (as compared to dizygotic), elevated presence in healthy siblings of stimulant users, and the strong psychometric properties of the BIS-11 and UPPS-P, all suggests that impulsive personality traits are promising endophenotypes (Gottesman & Gould, 2003).

Impulsivity and Addictive Disorders as a Recursive Process

The causal relationship between impulsive personality traits and addictive disorder initiation, severity, and remission appears to be bidirectional. In other words, impulsive

personality traits can be both a cause and consequence in addictive disorders. There is robust evidence that impulsive personality traits lead to initiation of addictive behaviors, are exacerbated by addictive behaviors, and may attenuate when these behaviors subside. In terms of trait-based impulsivity predating the onset of substance use and misuse, a study of 1,002 participants examined the association of negative emotionality and constraint at age 17 with the timing of onset and development of drug use disorders three years later. Higher negative emotionality and lower constraint were associated with the subsequent development of nicotine, alcohol, and illicit substance use disorders at three-year follow-up (Elkins, King, McGue, & Iacono, 2006). These traits are relevant to those under study here as negative emotionality has been associated with Negative Urgency at a medium effect size (Lynam, Miller, Miller, Bornovalova, & Lejuez, 2011), and constraint has been associated with the BIS-11 subscales at small to medium effect sizes (Reynolds et al., 2006), suggesting they are overlapping constructs. In a study of 5,632 young adults, Quinn and Harden (2013) used longitudinal data from ages 15-26 to examine whether changes in a latent factor of self-reported impulsivity predicted the escalation of alcohol, marijuana, and cigarette use in young adulthood. Indeed, individuals who declined more slowly in impulsivity increased in alcohol, marijuana, and cigarette use more rapidly. Furthermore, in two cross-sectional studies, early-onset alcoholics have been shown to score higher on the BIS-11 than late-onset alcoholics (Dom et al., 2006; Joos et al., 2013).

Similar to the BIS-11, the UPPS-P subscale of Positive Urgency has been found to predict increases in risky sexual behavior and illegal drug use (Zapolski, Cyders, & Smith, 2009), gambling behavior (Cyders & Smith, 2008), and alcohol consumption (Settles, Cyders, & Smith, 2010) and consequences (Cyders, Flory, Rainer, & Smith, 2009) over the course of the first year of college even after controlling for preliminary involvement in those behaviors.

Negative Urgency has also been found to predict smoking initiation (Doran & Trim, 2013) and in distress-related coping motives which led to subsequent increases in drinking over the course of the first year of college (Settles et al., 2010; but see Doran & Trim, 2013 and Settles, Cyders, & Smith, 2010). Cross-sectionally, Negative Urgency, Positive Urgency, and (lack of) Perseverance have been found to be associated (either directly or indirectly) with drinker status in a large sample of 5th grade students (Gunn & Smith, 2010). Finally, a meta-analysis of the UPPS-P subscales found (lack of) Premeditation to be associated with alcohol use initiation in adolescence (Stautz & Cooper, 2013).

While much evidence exists that impulsive personality traits influence substance use and abuse, other findings suggest a bidirectional relationship in which increases or decreases in substance use commensurately affect self-reported impulsivity. For example, one study followed a cohort of 1,434 high school graduates through college and found that impulsive personality traits, as measured by the Zuckerman-Kuhlman Personality Questionnaire, increased as a function of heavy drinking as well as increased heavy drinking over time (Quinn, Stappenbeck, & Fromme, 2011). In addition, there is a growing body of research suggesting that treating drug use reduces impulsive personality traits. For example, in a group of substance abusers tracked throughout their enrollment in a therapeutic community, which included treatment as usual, their baseline levels on the BIS-11 (M = 74.9) were found to decrease significantly by the time of release approximately nine months later (M = 61.4) (Bankston et al., 2009). It is notable that the post-treatment impulsivity average was comparable to the general population and substantively lower than the designated high impulsivity cut off of 74 which is one SD above the average (Patton et al., 1995). One recent study found that patient substance users (primarily with alcohol and opiate dependence) undergoing short term detoxification (~15 days) exhibited decreased

BIS-11 total scores from admission to discharge (Cicolini et al., 2014). These studies demonstrate that even temporary removal from substances of abuse may lead to a reduction in impulsive personality traits and in these two studies the total BIS-11 total score at discharge was comparable to the general population average (62-64, Patton et al., 1995; Stanford et al., 2009). Similarly, a recent study examined a community sample of cocaine users and found that BIS-11 total, Motor, and Attentional scores decreased in users who also reported decreasing use at a one-year follow-up (Hulka et al., 2015). In the only study to assess change in UPPS-P over the course of treatment, Negative Urgency and (lack of) Premeditation decreased across 4 weeks of treatment at a residential substance abuse treatment center (Littlefield et al., 2015). A final notable study of impulsive personality traits found that in a 16-year prospective study of individuals with alcohol use disorders, greater Alcoholic Anonymous attendance was associated with decreased drinking and a significant reduction in impulsive personality traits (Blonigen, Timko, Moos, & Moos, 2009; Blonigen, Timko, & Moos, 2013). It will be important for future studies to assess BIS-11 and UPPS-P scores longitudinally and to assess at follow-ups extending beyond the end of treatment, as it is quite likely that one may have impulsive personality trait scores that are below their baseline because the beginning and end of treatment is often where client stability is minimal and maximal, respectively. Alternatively, individuals who continue to abstain from substance abuse may exhibit a continual decline in impulsive personality traits.

Collectively, this body of research suggests the following: 1) impulsive personality traits predispose one to initiate substance use and progress to abuse; 2) substance abuse further increases levels of impulsive personality traits; and 3) treatment for and cessation from substances precipitate reductions in impulsive personality traits. Although more studies are needed, particularly for the second point (i.e., drug use increases impulsive personality traits),

current findings suggest that impulsive personality traits may not be exclusively a cause or consequence of addictive behavior; both processes may be operating in addicted individuals. This suggests that studying genetic influences on impulsive personality traits in individuals involved in addictive behavior may be challenging because drug abuse itself creates a 'moving target'. Furthermore, impulsive personality traits change throughout development (Littlefield et al., 2016; Steinberg et al., 2008) and therefore a wide age range can introduce further variability in the measurement of these constructs. Therefore, to maximize resolution of genetic effects, this study examined the genetic basis of impulsive personality traits in a sample of young adults with limited substance use involvement. This enabled capturing the innate trait within the context of a specific stage of development and less affected by environmental factors (e.g., chronic substance abuse).

The Neurobiology of Impulsive Personality Traits

Underlying neuroanatomical basis. Neurobiological research has suggested a link between problems of impulse control and frontostriatal regions which are largely directly modulated by dopaminergic neurotransmitters (Jentsch & Taylor, 1999). Indeed, a number of studies have examined the relationship between impulsive personality traits and blood flow to frontostriatal regions while performing reward anticipation tasks (i.e., tasks which isolate neural functioning during the time period immediately before reward receipt) in a functional magnetic resonance imaging (fMRI) scanner. In healthy participants, ventral striatal activity during a card guessing task (which compared activation to positive feedback versus negative feedback, and positive feedback indicated greater monetary reward after the task) has been shown to be correlated with higher BIS-11 total scores (Forbes et al., 2009). A study of healthy adults found that impulsive personality traits (measured by the Temperament and Character Inventory [TCI;

Cloninger, Przybeck, Svrakic, & Wetzel, 1994]) are associated with increased activity in the amygdala and anterior cingulate cortex (ACC) when anticipating delivery of a sucrose solution (Kerr et al., 2015). Similarly, it has been found that in weight-concerned females, Non-planning scores were associated with greater ventral striatal activity during presentation of highly caloric foods (as compared to less caloric foods) (van der Laan, Barendse, Viergever, & Smeets, 2015).

Two studies have been conducted exploring the relationship between impulsive personality traits with unique salient content (i.e., alcohol cues and emotional cues). In the first, Negative Urgency was associated with bilateral ventromedial prefrontal cortex (vmPFC) activation to alcohol odors in social drinkers, suggesting it plays a role in reward salience (Cyders et al., 2014b). In a second study (same sample), Negative Urgency was related to right lateral orbitofrontal cortex (OFC) activation and left amygdala activation to negative emotional cues (Cyders et al., 2014a). These studies suggest that Negative Urgency is related to reactivity to salient cues in the environment, namely drug and (negative) emotional cues.

In contrast to the other fMRI research, a study of detoxified males with alcohol dependence, found that their activation of the ventral striatum and ACC was negatively correlated with total BIS-10 (an older version of the BIS) scores when anticipating a monetary reward (Beck et al., 2009). However, this finding may be specific to alcohol dependence, as addiction neurobiology research suggests that participants exhibiting heavy stimulant use tend to exhibit reduced reactivity to non-drug rewards (for a review, see Leyton & Vezina, 2014). The current body of research suggests that healthy participants with elevated impulsive personality traits exhibit elevated reward reactivity, however, following prolonged heavy drug use their reactivity may become confined to drug-related rewards.

An additional body of research has arisen with a particular focus on how these traits relate to irregularity of neural networks during resting state (i.e., a paradigm which measures brain activity when not engaged in any particular task). In an fMRI study, the group of low BIS-11 participants exhibited a functionally connected network comprised of cortical structures implicated in regulation and control as well as subcortical appetitive drive structures, whereas in the high BIS-11 group, this network was broken into 2 distinct modules, where the cortical control structures became isolated from the subcortical drive structures (Davis et al., 2013). This suggests that high impulsivity is related to reduced connectivity between cognitive control regions and subcortical drive regions. Another recent study explored the relationship between functional connectivity of several neural networks and UPPS-P subscales and BIS-11 total in healthy controls and individuals with alcohol use disorders (Zhu, Cortes, Mathur, Tomasi, & Momenan, 2015). It was found that in alcohol dependent participants, Negative Urgency was inversely associated with connectivity of the amygdala-striatal network (the impulsive system). In healthy controls, Positive Urgency was negatively correlated with the anterior default mode network, which is potentially an indicator of a diminished ability to access possible representations of negative consequences. In tests of between network connectivity, OFC network connectivity with default mode and executive control networks was negatively correlated with Negative Urgency, suggesting that this may be a biomarker for impulsivity. Similarly, another study found impulsive personality traits were associated with reduced connectivity between the ACC and the right amygdala (Kerr et al., 2015). Finally, a study, which used resting state electroencephalogram (EEG), identified similar issues of irregular connectivity, finding that greater Positive Urgency was related to frontal asymmetry (i.e., greater

left-frontal activity and reduced right-frontal activity in the inferior frontal gyrus) (Gable, Mechin, Hicks, & Adams, 2015).

Although nascent, brain imaging research indirectly implicates impulsive personality traits in the variation of neural regions and dysregulation of fundamental neural networks of reward, inhibition, and self-reflection, largely via dopaminergic functioning. This notion is further supported by the only morphometric study to date which found impulsive personality traits (measured by the BIS-11 and subscales) were associated with reduced gray matter volumes in regions associated with inhibition and action selection (i.e., bilateral OFC and left ACC; Matsuo et al., 2009). Therefore research broadly implicates impulsive personality traits with unique variation in structural morphometry and neural reactivity in cortical control structures and subcortical appetitive structures during incentive-reward, cue reactivity, and emotional reactivity tasks.

Dopamine. Several studies explored the relationship between impulsive personality traits and neurotransmitter systems, namely, dopaminergic functioning. Using positron emission tomography (PET) to measure striatal dopamine receptor D_2 and D_3 (D2/D3) availability, a study of healthy participants found the Non-planning subscale of the BIS-11 was associated with greater ventral striatal D2/D3 receptor availability (Reeves et al., 2012). A similar study looking at several striatal subdivisions in healthy participants, found Non-planning and Attentional subscales of the BIS-11 were significantly associated with greater D2/3 receptor availability in the post-commissural caudate, a region implicated in attention, judgment of alternative outcome, and inhibitory control (Kim et al., 2014). Additional studies found contrary findings. For example, in one study, diminished midbrain D_2/D_3 autoreceptor binding and greater amphetamine-induced dopamine release in the striatum was associated with higher levels of BIS-

11 total scores (Buckholtz et al., 2010). Another group found no relationship between impulsive personality traits and D_2/D_3 binding, yet identified reduced ventral striatal dopamine release (following amphetamine administration) in participants who experienced low to moderate levels of stress; whereas the high stress group exhibited low dopamine release regardless of impulsivity levels (Oswald et al., 2007). Finally, in methamphetamine dependent participants, it was found that BIS-11 total score was associated with lower D_2/D_3 receptor availability in the caudate nucleus and nucleus accumbens (B. Lee et al., 2009). Finally, in a recent study of healthy female participants using a monetary incentive delay (MID) task, which probes incentive-reward neural responses (e.g., Knutson, Adams, Fong, & Hommer, 2001), there was a negative indirect effect of the Impulsiveness facet of the NEO Personality Inventory-Revised (NEO-PI-R; Costa & McCrae, 1992) on nucleus accumbens dopaminergic release (measured using PET) that was mediated by medial prefrontal cortex (mPFC) anticipatory BOLD response (measured via fMRI) (Weiland et al., 2014). On the whole, although there are inconsistencies, impulsive personality traits appear to be associated with variation in ventral and dorsal striatal D2/D3 receptor availability and release of dopamine, potentially mediated by mPFC, but a clear direction of effect (and in what populations) has yet to be established. More studies will need to be conducted with large healthy samples, parallel PET procedures, common impulsive personality trait measures, and standardized quantification of the striatum.

Serotonin. The functioning of serotonin (5-HT) is also implicated in impulsivity and is thought to exert this influence through several modulatory effects on dopaminergic neurotransmission in frontostriatal circuitry (Pattij & Vanderschuren, 2008; Winstanley, Theobald, Dalley, & Robbins, 2005). In particular, 5-HT2a and 5-HT2c receptors innervate the core regions implicated in valuation in impulsive behavior: the ventral tegmental area, nucleus

accumbens, and prefrontal cortex (Cunningham & Anastasio, 2014). 5-HT2a receptors are highly expressed in the prefrontal cortex where they modulate cortical activity and local network oscillations necessary for executive function (Aznar & Hervig, 2016). Altered 5-HT2a expression or receptor ligand binding levels have frequently been linked to addictive disorders (Anastasio et al., 2011; Cao et al., 2014; do Prado-Lima et al., 2004; Fletcher et al., 2011; Wilson et al., 2013). Despite a theoretical basis for the relevance of serotonin functioning, only one study explored the effects of serotonin manipulations on impulsive personality traits, finding that administering a selective serotonin reuptake inhibitor to violent offenders (at least one prior offense) with high scores on the BIS-11 (> 70), precipitated a 35% reduction in BIS-11 scores at three month follow-up (Butler et al., 2010). However, this study had no placebo group, only 20 participants completed the follow-up, and the reduction in scores may be a regression to the mean. Although preliminary evidence exists regarding the role of variation in genes related to 5-HT function in relation to impulsive personality traits (discussed in the following section), it will be important for future studies to explore the impact of long term serotonin manipulations (e.g., selective serotonin reuptake inhibitors) on impulsive personality trait levels.

Other biological systems. Monoamine oxidase (MAO; i.e., enzymes that catalyze the deamination of monoamines, including serotonin and dopamine) functioning has also been explored for its role in impulsive personality traits. In an early study, it was found that impulsive personality traits (i.e., the Impulsiveness scale from the Impulsiveness-Venturesome-Empathy [IVE; Eysenck & Eysenck, 1978]) were associated with lower platelet MAO activity (Schalling, Edman, Åsberg, & Oreland, 1988). In a study of participants with antisocial personality disorder, MAO-A total distribution volume (MAO-A V_T; an index of MAO-A density) in the ventral striatum was negatively correlated with the impulsivity subscale of the NEO PI-R (Kolla et al.,

2015). Another study found a significant negative relationship between MAO-A activity in the OFC and total scores on the Estonian version of the BIS-11 in children (Paaver et al., 2007). These findings suggest a neuromodulatory role of MAO-A on impulsivity, potentially through increased potentiation of dopamine in those with reduced MAO-A density (for a review see Finberg, 2014).

A recent study explored the link between BIS-11 and physiological arousal. Specifically this study administered a stop signal task (i.e., a measure of prepotent response inhibition) and found that higher total BIS-11 scores were associated with greater skin conductance response (an indicator of physiological arousal) to stop trials (i.e., trials requiring an inhibitory response; Zhang et al., 2015). Additionally, in women it was found that higher total BIS-11 scores were associated with reduced Granger causality (i.e., a measurement of the causal relationship among variables) of vmPFC activity on skin conductance. Although results should be interpreted with caution given this study is the first of its kind, these results suggest a connection between impulsive personality traits and physiological arousal and that this connection may be partially attributable to diminished vmPFC regulation of arousal.

Genetic Influences on Impulsive Personality Traits

Molecular genetic association studies have suggested a role of several biological systems in impulsive personality traits, most notably monoaminergic neurotransmission, and in particular dopaminergic and serotonergic activity. In addition to being reviewed below, all previous molecular genetic association study findings are summarized in Table 1.

Dopamine. Research on the role of dopaminergic genes on impulsive personality traits has been mixed, with many effects not replicating consistently across studies. In terms of the positive findings, one locus that has been studied relatively frequently in relation to impulsivity

and addiction is the Taq1A locus (rs1800497) of the ankyrin repeat and kinase domain containing I gene (*ANKK1*), which is proximal to the *DRD2* gene and is related to dopamine D2 receptor densities and binding affinity (Jönsson et al., 1999; Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991; Noble, 2003; Pohjalainen et al., 1998; Thompson et al., 1997). One study found a significant relationship in a group of 387 nonsmoking college students between the A1 allele of rs1800497 and Negative Urgency (Doran, Schweizer, Myers, & Greenwood, 2013). However, another study found that in participants with alcohol dependence, the Taq1A A2/A2 and A1/A2 genotypes were significantly associated with higher BIS-11 total scores than A1/A1 (Limosin et al., 2003). Notably, an interaction effect of high levels of childhood adversity and possession of the A1 allele of *ANKK1* (rs1800497) was related to higher scores on a latent factor of impulsive personality traits from multiple measures (including the UPPS-P), suggesting the relationship may be contingent upon environmental context (Carver, LeMoult, Johnson, & Joormann, 2014).

The G allele of the rs4680 locus within the *COMT* gene, which is responsible for degradation of catecholamines (primarily dopamine), has been identified as a risk allele for higher scores on the Non-planning subscale, as well as on a latent factor of impulsive personality traits (Carver, LeMoult, Johnson, & Joormann, 2014; Soeiro-De-Souza, Stanford, Bio, Machado-Vieira, & Moreno, 2013). Additionally two studies found a relationship between the 9 repeat variant of *DAT1* the 3'UTR VNTR, which putatively influences dopamine signaling in the striatum, and higher BIS-11 total scores (Forbes et al., 2009; Paloyelis, Asherson, Mehta, Faraone, & Kuntsi, 2010). Furthermore, the BIS-11 total scale score has been positively associated with the short allele of the *DRD4* exon 3 variable number tandem repeat (VNTR) polymorphism, which codes for D4 receptor expression (Schilling, Kuhn, Sander, & Gallinat,

2014; Varga et al., 2012). Higher impulsive personality traits have also been linked with an interaction of greater childhood adversity and the long allele of *DRD4* VNTR (rs1805186) possession (Carver et al., 2014). Notably, all aforementioned dopaminergic loci have also been exhibited failure to replicate or opposite direction of effects in other studies (Congdon, Lesch, & Canli, 2008; Eisenberg et al., 2007; Forbes et al., 2009; Paloyelis et al., 2010; Varga et al., 2012).

Serotonin. The short form of the serotonin transporter-linked polymorphic region (*5-HTTLPR*), which is related to a reduced availability of serotonin (Greenberg et al., 1999), has been associated directly with higher BIS-11 total scores (Racine, Culbert, Larson, & Klump, 2009; Sakado, Sakado, Muratake, Mundt, & Someya, 2003) or in interaction with low platelet monoamine oxidase activity (Paaver et al., 2007). Furthermore, another study found an interaction effect of the short form of *5-HTTLPR* with experience of childhood adversity and higher scores on a latent factor of impulsive personality traits (Carver, Johnson, Joormann, Kim, & Nam, 2011).

Other studies have reported significant relationships between BIS-11 and other components of the serotonin system including the G allele at the C(-1019)G locus (rs6295) of the 5-HT1a receptor gene (*HTR1a*), the T allele of the T102C locus (rs6313), the GG genotype of the A1438G locus (rs6311) of the 5-HT2a receptor gene (*HTR2a*), and AA genotype of the A1997G locus (rs13212041) of the 5-HT1b receptor gene (*HTR1b*) (Benko et al., 2010; Preuss, Koller, Bondy, Bahlmann, & Soyka, 2001; Varga et al., 2012; Racine *et al.*, 2009). Although numerous relationships have been identified within these studies, it is noteworthy that other studies have not replicated some of these relationships or have found opposing effects for *5-HTTLPR*, *HTR2a* (rs6313), and *HTR1a* (rs6295) (Jakubczyk *et al.*, 2012; Roiser, Müller, Clark, & Sahakian, 2007; Varga et al., 2012).

Glycogen synthase kinase-3 (GSK3) has also been studied in relation to impulsivity because of its role in mediating serotonergic functioning (W. Zhou et al., 2012). In particular, the T allele of rs1732170 and the G allele of the rs334558 loci of the GSK3 β gene (*GSK3β*) have been associated with higher scores on the Attentional subscale in participants with bipolar disorder (Jiménez et al., 2014).

Other biological systems. In addition to explorations of the dopaminergic and serotonergic systems, efforts have been made to examine other biological systems which may impact impulsive personality traits. For example, the broader monoaminergic system has been explored for is putative role in impulsivity and aggression. Specifically, Negative Urgency mediated the relationship between the A allele of the rs1465108 SNP of the monoamine oxidase A gene (*MAOA*), a gene that encodes for the MAO-A enzyme, which deaminates monamines, and aggression in Caucasian undergraduate students (Chester et al., 2015). This adds to the growing body of literature suggesting that low functioning of MAO-A may increase susceptibility for negative affect and subsequent impulsivity and aggression (Gallardo-Pujol, Andrés-Pueyo, & Maydeu-Olivares, 2013; Kuepper, Grant, Wielpuetz, & Hennig, 2013; McDermott, Tingley, Cowden, Frazzetto, & Johnson, 2009).

An additional neurotransmitter which has been explored is GABA, a primary inhibitory neurotransmitter which is implicated in psychological disorders such as depression, anxiety, and drug addiction (Kumar, Sharma, Kumar, & Deshmukh, 2013). 10 loci from the GABA receptor subunit alpha-2 gene (*GABRA2*) have been associated with NEO-PI-R Impulsiveness scores (Villafuerte et al., 2012; Villafuerte, Strumba, Stoltenberg, Zucker, & Burmeister, 2013). However, another group failed to find an association between any of the 6 *GABRA2* SNPs tested

and BIS-11 total scores (including rs279858 which was associated in the other studies) (Dick et al., 2013).

In the only study of the μ-opioid receptor 1 gene (*OPRM1*) to date it was found that in 214 healthy male social drinkers, those with a G allele of the A118G locus (rs1799971) had significantly higher scores on the UPPS (lack of) Premeditation subscale (Pfeifer et al., 2015). This relationship is potentially attributable to the role of μ-opioid receptor in reward processing (Le Merrer, Becker, Befort, & Kieffer, 2009).

At a broader level, a number of loci related to overall central nervous system functioning have been explored in relation to impulsive personality traits. The met allele of the Val66Met locus (rs6265) of *BDNF*, a gene which contributes to neuronal differentiation and survival (Poo, 2001), has been associated with a latent factor of impulsive personality traits (Carver et al., 2014), as well as the Attentional subscale in methamphetamine users (Su et al., 2014). Additionally, the C allele of the rs11624704 SNP within the neuroexin-3 (*NRXN3*) gene, which contributes to the development and function of synapses, has been associated with the Attentional subscale in men (Stoltenberg, Lehmann, Christ, Hersrud, & Davies, 2011). The T allele of the rs324981 SNP within the neuropeptide S receptor gene (*NPSR1*), which mediates central nervous system mechanisms related to arousal, activity, and anxiety, has been associated with increased disinhibition as measured by the Adaptive and Maladaptive Impulsivity Scale (AMIS; Laas et al., 2015). However, in a subsample of the original dataset it was not associated with BIS-11 total scores (Laas et al., 2015) and in a former study it was not associated with disinhibition (Laas et al., 2014). The CC genotype of the rs2228570 locus of the Vitamin D3 receptor gene (*VDR*) has been significantly associated with BIS-11 total and Attentional subscale scores in males with alcohol dependence (Wrzosek et al., 2014). Vitamin D is of interest for its

wide downstream effects on overall central nervous system functioning such as GABAergic neurotransmission (Féron et al., 2005; Garcion, Wion-Barbot, Montero-Menei, Berger, & Wion, 2002), nerve growth factor (Dursun, Gezen-Ak, & Yilmazer, 2011), and calcium homeostasis regulation (Fernandes de Abreu, Eyles, & Féron, 2009). Synaptosomal-associated protein, 25 kDa (SNAP-25) has been explored for its relationship with impulsive personality traits due to its role in exocytosis via targeting and fusion of vesicles to the cell membrane (Mohrmann et al., 2013). Specifically, the T-T haplotype of the *SNAP-25* gene (i.e., rs3746544 and rs1051312) and the TT genotype of rs1051312 has been associated with lower total BIS-11 scores (Németh, Kovács-Nagy, Székely, Sasvári-Székely, & Rónai, 2013).

Summary of Molecular Genetic Findings. Current understanding of the molecular genetic basis of BIS-11 is nascent and inconsistent, making it at best equivocal. In addition to studies which failed to replicate many of the aforementioned relationships, it is important to consider that underreporting of statistical tests and unpublished null findings (i.e., "the file drawer problem"; Rosenthal, 1979) are known to be particularly prevalent within gene association studies (Munafò, Clark, & Flint, 2004). Furthermore, as previously noted, GWAS have suggested that the primary genes that appear to be related to addictive disorders are often of a different functionality (e.g., cell adhesion, transcriptional regulation, enzymes) than most of the candidate loci studied (Hall et al., 2013). In sum, there are mixed findings regarding genetic contributions to impulsive personality traits, with the most support for genes affecting the function of the serotonergic and dopaminergic systems.

Proposed Project

There is a substantial body of research linking impulsive personality traits with addictive disorders. Impulsive personality traits have been shown to be heritable and increase risk for

addictive disorder initiation and severity. Additionally, candidate gene studies have identified associations between numerous genes (largely serotonergic and dopaminergic) and levels of impulsive personality traits. However, these molecular associations have been inconsistent, most studies have used small sample sizes, and no studies to date have conducted genome-wide examinations of impulsive personality traits. Furthermore, many of these studies utilized individuals with current substance use disorders, which as the above review demonstrated, can impact levels of impulsivity. Finally, the previous studies did not systematically assess associations across multiple primary measures of impulsivity simultaneously (i.e., BIS-11 and UPPS-P subscales).

The proposed project sought to address these issues. Specifically, this study investigated genetic influences on impulsive personality traits (defined as performance on the BIS-11 and UPPS-P subscales) using a larger sample size and wider genomic scope than previous studies and did so in healthy individuals without significant drug or alcohol abuse. Healthy young adults who do not have histories of addiction permit an examination of genetic associations in the absence of such confounding exposures. This study used a multivariate analysis of the relationship between loci and the subscales of the BIS-11 and UPPS-P. This enabled an estimation of both overall relationship with impulsive personality traits as well as a more fine-grained exploration of the specific associations with individual subscales. Furthermore, hierarchical analytical approach was employed, in which groups of SNPs with higher priority were analyzed in stratified subsets (Lin & Lee, 2012). Traditional GWAS studies tend to be underpowered because of the large number of statistical tests required and this approach increased the power of detecting associations by correcting for false discovery rate (FDR) in prioritized subsets, prior to full genome-wide correction.

The first aim of the proposed project was to examine the relationship between impulsive personality traits and *a priori* loci (Table 1). This aim provided a strong test of previously reported associations in the literature. The second aim was to assess the relationship between impulsive personality traits and ~13,000 high-value addiction (HVA) markers prioritized in the SmokeScreen© array by BioRealm (i.e., a small business funded by the National Institute on Drug Abuse to develop this array; Baurley et al., 2016). The high-value SNP list is a compilation of loci from peer-reviewed publications and research consortia, including the Pharmacogenetics of Nicotine Addiction Treatment (PNAT) Consortium and the NeuroSNP project (Bergen et al., 2013; Saccone et al. 2009). This aim enhanced power by enabling a formal assessment of loci which are much more theoretically relevant to addiction than atheoretical genome-wide loci. Finally, for the third aim, impulsive personality trait subscales were examined across the genome for exploratory purposes. This aim enabled an atheoretical characterization across the genome. In this way, the study provided a strong test of *a priori* relationships, a principled examination of high-value addiction markers, and a genome-wide scan.

CHAPTER 2

METHOD

Procedure

Participants were recruited at two sites (Athens, GA and Chicago, IL). To avoid confounding environmental and developmental factors in assessing the genetic basis of impulsive personality traits, this study recruited healthy young adults. Inclusion criteria were English fluency, between 18 and 30 years of age, and self-reported Caucasian race and non-Hispanic ethnicity (in order to control for population stratification; Hutchison, Stallings, McGeary, & Bryan, 2004). Exclusion criteria were >12 on the Alcohol Use Disorders Identification Test (AUDIT) or Drug Use Disorders Identification Test (DUDIT) and treatment in the last 12 months or current need for treatment for: depression, bipolar disorder, general anxiety, social anxiety, post-traumatic stress disorder, obsessive compulsive disorder, panic attacks/disorder, phobia, schizophrenia or related conditions, anorexia, bulimia, binge eating.

Upon arrival to the experimental session, participants were administered the informed consent. Following this, participants were asked to provide a urine sample for the drug screening and a breath sample to test for blood alcohol content (BAC) level. Participants with a BAC above .00 were informed that they cannot participate (though no participants tested above .00). All assessment measures were administered on the computer utilizing Inquisit software (Inquisit 3.0.6.0, 2012) and Survey Monkey (http://surveymonkey.com). Assessments were counterbalanced across participants to prevent ordering effects. Participants were given two five-minute breaks for refreshments (water, snacks) and/or use the restroom. To acquire DNA

samples participants were asked to provide a saliva sample in an Orangene DNA kit (DNA Genotek Inc., Kanata, ON, Canada). Following completion of the study, participants were debriefed and compensated for their time. The majority of participants were young adults from the community who received $40 compensation for their time ($10/hour); a subset were university undergraduates who received four research credits (*n* = 296). Additionally, all participants had a one in six chance to receive between $10-$100 based on their responses to one of the tasks.

Measures

Demographics. Comprehensive demographics were assessed including, sex, age, race, income, education and other descriptive variables.

Alcohol and drug abuse. Alcohol abuse was measured using the Alcohol Use Disorders Identification Test (AUDIT; Saunders, Babor, de la Fuente, & Grant, 1993). The AUDIT contains 10 questions each scored from 0 to 4. Questions pertain to quantity, frequency, and consequences associated with drinking. Drug abuse was measured using the Drug Use Disorders Identification Test (DUDIT; Berman, Bergman, Palmstierna, & Schlyter, 2005). The DUDIT is the same format as the AUDIT with one additional question regarding frequency of polysubstance use.

Impulsive personality traits. The Barratt Impulsiveness Scale, Version 11 (BIS-11) is a 30-item measure of impulsive personality traits (Patton et al., 1995). Items are on a scale from 1-4 (1 = rarely/never; 2 = occasionally; 3 = often; 4 = almost always/always). The responses were examined within the second order factors (i.e., Attentional, Motor, and Non-planning). The Attentional subscale reflects the ability to focus on the task at hand and the amount of thought insertions and racing thoughts one has (e.g., "*I often have extraneous thoughts when thinking*").

The Motor subscale reflects the tendency to act on the spur of the moment and consistency of lifestyle (e.g., "*I do things without thinking*"). The Non-planning subscale reflects the ability to plan and think carefully and one's enjoyment of challenging mental tasks (e.g., "*I am a careful thinker*").

The UPPS-P Impulsive Behavior Scale (UPPS-P) is 59-item measure of impulsive personality traits (Cyders et al., 2007; Whiteside & Lynam, 2001). Items are on a scale from 1-4 (1 = agree strongly; 2 = agree; 3 = disagree; 4 = disagree strongly). Four of the five subscales were used in this study (Sensation Seeking was excluded because it was not correlated with the other impulsive personality trait subscales in initial phenotyping of the dataset from which the proposed project is derived; MacKillop et al., in press): Negative Urgency, a propensity for acting on immediate cues when experiencing negative affect (e.g., "*When I feel bad, I will often do things I later regret in order to make myself feel better now.*"; reverse score); (lack of) Premeditation, a propensity to act without considering potential consequences (e.g., "*I like to stop and think things over before I do them.*"); (lack of) Perseverance, an inability to follow through on tasks (e.g., "*I generally like to see things through to the end.*"); and Positive Urgency, a propensity for acting on immediate cues when experiencing positive affect (e.g., "*When I am in a great mood, I tend to get into situations that could cause me problems.*"; reverse scored).

SNP Genotyping and Quality Control

Genotyping was performed using the Illumina PsychArray BeadChip platform, which calls ~600,000 markers and has optimized tag SNP content from the International HapMap Project to capture the maximum amount of common variation. All quality control filtering was implemented in PLINK v1.9 (Chang, Chow, Tellier, Purcell, & Lee, 2015). SNPs were filtered for call rates < 98%, Hardy-Weinberg Equilibrium (HWE) violations of $p < 1 \times 10^{-6}$, MAF < 5%,

and invariance. This left 437,652 SNPs prior to imputation. Imputation of missing genotypes and of new SNPs was performed with IMPUTE2 v.2.3.1 (Howie, Donnelly, & Marchini, 2009). Imputed SNPs were excluded for exhibiting an information score of < .3, MAF < 5%, HWE violations of $p < 1 \times 10^{-6}$, missingness > 5%, and multiallelic status. Imputed SNPs with confidence < .9 were set to missing for individuals. Of the 26 *a priori* loci examined, five were excluded for excessive missing values (>5%; rs334558, rs1442060, and rs1051312), poor imputation accuracy (rs3746544), and presence on the sex chromosome (rs1465108). The VNTR loci were not genotyped and therefore were not included in this study. Following quality control, 21 *a priori* loci, 13,337 of the 20,652 HVA SNPs, and 4,887,762 genome-wide SNPs were present for analysis.

Participant Quality Control

1,000 participants had valid genotyping data (call rates $\geq$ 98%, inbreeding coefficient absolute value $\leq$ .02, concordant self-reported sex and X-chromosome determined sex) and satisfied the inclusion/exclusion criteria. To verify and correct the misclassification of self-reported race, principal components analysis (PCA; Price et al., 2006) was conducted. Two population outliers were identified and removed by visual inspection of the principal components plot (see Figure 1). 13 participants were excluded for missing one or both measures of impulsive personality traits. Finally, participants were assessed for cryptic relatedness using GCTA software (Yang *et al.*, 2011), and two were removed for relatedness > .05, leaving a final sample of 983 unrelated European-ancestry participants. Sample characteristics are detailed in Table 2.

Power Analysis

GWAPower (Feng, Wang, Chen, & Lan, 2011) was used to generate power estimates for 983 individuals (for an overview of power analyses for each strata see Table 3). Specifically,

statistical power was examined for each strata of statistical tests. Genetic effect size estimates used in the power analyses were taken from a reasonable range expected for complex traits: .005-.050 (Burton et al., 2007; McCarthy et al., 2008). For aim 1 (21 *a priori* loci), a nominal significance of $p < .05$ was utilized in the power analysis. For aim 2 (prioritized HVA loci), a Bonferroni correction was applied in the calculation of the power analysis. However, these estimates were highly conservative as a Benjamini-Hochberg false discovery rate (FDR) correction was applied to the resultant *p*-values from the analyses (Benjamini & Hochberg, 1995). Although nominally significant *a priori* loci were accepted as meaningful findings, to further assess confidence in results a FDR correction was also applied to the resultant *p*-values from the *a priori* analyses. A FDR approach cannot be applied to power analyses because it requires the empirical *p*-values to generate the appropriate FDR correction rate. A FDR approach rank orders the empirical *p*-values and adjusts for the expected proportion of rejected null hypotheses using a linear step-up function. Specifically, it applies the formula: $P_{(i)} \leq (i/m)*q$, where P = empirical significance values; i = order of significance; m = number of tests; q = established FDR correction rate (.05). For example, in a series of five tests that yield the *p*-values .003, .004, .025, .05, and .89, the first three values would be significant because $.025 \leq (3/5)*.05$ (adjusted FDR = .03). In contrast, a Bonferroni correction would yield a significance threshold of .05/5 = .01 and only two of these *p*-values would survive the correction. For aim 3, SNPs were examined for genome-wide significance at a nominal *p*-value less than 5×10^{-8}, as this is a consensus within the field for valid genome-wide significance (Dudbridge & Gusnanto, 2008; Hoggart, Clark, De Iorio, Whittaker, & Balding, 2008; Pe'er, Yelensky, Altshuler, & Daly, 2008). For aim 3, power ranged from .001-.968, with the median effect size of .015 yielding power of .071, suggesting that there was poor power to detect multiple significant SNPs. In sum,

the power analyses suggest that there was good power to detect relatively small effects for the first aim, but the second and third aims were underpowered to detect genetic effects smaller than .5% of variance. This is to be expected, as the second and third aims of the study were exploratory and not testing specific hypotheses. Therefore, the top 50 HVA and genome-wide SNPs were also reported to avoid excessive type-II error rate and to prioritize them for future inquiry.

Data Analysis

Preliminary analyses. The internal reliability coefficients and the interrelationships among the UPPS-P and BIS-11 subscales were calculated. All phenotypic variables were standardized to Z-scores prior to the multivariate genetic analyses. Covariates for the study were ascertained via a multivariate linear mixed model of the impulsive personality trait subscales with four covariates: sex, age, income, and site (i.e., Athens or Chicago). Each covariate was tested as a fixed factor, while the other three covariates included as control variables. Only variables which were significantly associated in the combined models will be included as covariates in subsequent analyses. These analyses took place in SPSS 20.0 (IBM Corp., 2011).

Primary analyses. Genome-wide Efficient Mixed Model Association (GEMMA) software (X. Zhou & Stephens, 2012) was utilized to examine the MLMM associations between the loci from each strata (21 *a priori* loci, 13,377 HVA loci, and 4,887,762 genome-wide SNPs) and the impulsive personality trait subscales. The MLMM accounts for the cryptic relatedness among individuals, which is modeled out as a random effect (i.e., the genetic correlation between individuals). Any significant multivariate relationships were unpacked by examining linear relations among the significant loci and each individual subscale. To maximize resolution of effects, an additive genetic effect model was used whereby participants were given a score for each SNP from 0-2 indicating the number of minor alleles.

CHAPTER 3

RESULTS

Preliminary Analyses

The subscales exhibited adequate to high internal reliability: Attentional, $\alpha = .70$; Motor, $\alpha = .63$; Non-planning, $\alpha = .68$; Negative Urgency, $\alpha = .87$; (lack of) Premeditation, $\alpha = .85$; (lack of) Perseverance, $\alpha = .84$; Positive Urgency, $\alpha = .93$. A correlation matrix of the impulsive personality traits subscales can be found in Table 4. All subscales were significantly correlated ($ps < 5 \times 10^{-9}$). In the MLMM, gender, age, and site were found to be significant, respectively F (4, 978) = 11.06, $p = 1.7 \times 10^{-14}$, Wilk's $\Lambda = .93$, partial $\eta^2 = .07$; F (4, 978) = 1.81, $p = 4.4 \times 10^{-7}$, Wilk's $\Lambda = 0.84$, partial $\eta^2 = .02$; F (4, 978) = 4.35, $p = .00009$, Wilk's $\Lambda = .97$, partial $\eta^2 = .03$, and were thus included as covariates. Income was not significantly related to the impulsive personality traits subscales (F (4, 978) = 1.01, $p = .46$, Wilk's $\Lambda = 0.96$, partial $\eta^2 = .01$) and therefore was not covaried in all other analyses.

Primary Analyses

A priori loci. Of the 21 *a priori* loci assessed, two loci (rs6313, rs6311) were significantly associated with impulsive personality traits in the multivariate analyses ($p = .002, .003$, respectively; see Table 5). These two *p*-values survive FDR correction even when treating these 21 statistical tests as independent (adjusted FDR = .005). Notably, a pruning procedure in PLINK (i.e., "--indep-pairwise") suggests that 9 of the 21 loci offer largely redundant information ($r^2 > .8$; highly correlated loci are noted in Table 5). In particular, the relationship between rs6313 and rs6311 is $r^2 = .996$. In follow-up analyses with the individual subscales,

these two loci were significantly associated with the Motor (rs6313: B = -.101, SE = .046, p = .027; rs6311: B = -.098, SE = .046, p = .032) and Non-planning subscales (rs6313: B = -.122, SE = .046, p = .008; rs6311: B = -.119, SE = .046, p = .010). The T allele of rs6313 and the A allele of rs6311 were associated with reduced impulsivity.

High-value addiction markers. Of the 13,337 HVA loci, none survived FDR correction. The strongest association was in the B-cell lymphoma 2 interacting-killer (*BIK*) gene on chromosome 22, position 43518324, (p = .00005; rs4988406). The next two strongest associations were in the storkhead box 2 (*STOX2*) gene on chromosome 4, position 184919470 (p = .000097; rs17090674) and the integrin beta 3 (*ITGB3*) gene on chromosome 17, position 45335537 (p = .000098; rs1969269). The top 50 most significant associations are included in Table 6.

Genome-wide association. The genome-wide scan did not yield any significant associations. The strongest association was at chromosome 4, position 5132226 ($p = 8.8 \times 10^{-8}$; rs13122329), within the *STOX2* gene. Notably, this locus is in the same gene as the second most associated HVA loci. Follow-up analyses confirm that rs13122329 and rs17090674 (i.e., the HVA loci) are highly correlated (r^2 = .94). The next two strongest associations were in an uncharacterized region (LOC101927263) in a non-coding RNA gene on chromosome 15, position 96905460 ($p = 1.89 \times 10^{-7}$; rs35721523) and the lamin domain tail containing 1 (*LMNTD1*) gene on chromosome 12, position 25669019 ($p = 2.02 \times 10^{-7}$; rs67068739). The top 50 most significant hits are included in Table 7. Figure 2 depicts the results of the GWAS using both Quantile-Quantile (Q-Q) plots and Manhattan plots. As can be seen in the Q-Q plot, the majority of markers fit null expectations and no markers exhibit evidence suggesting association beyond chance.

CHAPTER 4

DISCUSSION

This study examined the genetic basis of impulsive personality traits, as measured by the BIS-11 and UPPS-P subscales, in the largest sample to date. A hierarchical analytic approach was utilized that included analysis of *a priori* loci that have been previously associated with impulsive personality traits, HVA markers, and a GWAS. This study identified robust evidence for two previously identified candidate loci (rs6313 and rs6311), but also called into question the remaining 19 loci for which no association was found. Analyses of the HVA and genome-wide loci yielded no significant associations, however, among the top HVA and GWAS hits were loci present within the *STOX2* gene. The absence of empirically significant loci in the latter two aims was expected given the sample size and the top 50 most significant HVA and genome-wide loci are included in Tables 6 and 7 to prioritize them for future inquiry.

For the first *a priori* strategy, associations between rs6313 and rs6311 (within the *HTR2a* gene) and impulsive personality traits were identified. Specifically, the T allele of rs6313 and the A allele of rs6311 were associated with reduced levels of impulsive personality traits, with effects specific to the BIS-11 Motor and Non-planning subscales. The rs6311 finding is consistent with a study that found the GG genotype of rs6311 was associated with increased BIS-11 total scores in 135 individuals with alcohol dependence (Preuss *et al.*, 2001). However, inconsistent with the current study's findings, one study found the T allele of rs6313 was been significantly associated with increased BIS-11 total scores in a sample of 344 young women (Racine *et al.*, 2009), while another study found no relationship between rs6313 and BIS-11 total

scores in 304 individuals with alcohol dependence (Jakubczyk *et al.*, 2012). Differences in findings may be attributable to smaller and different samples (e.g., women only, individuals with alcohol dependence) in these previous studies.

One recent meta-analysis explored the relationships of these two loci with alcohol and drug abuse (Cao et al., 2014). Specifically, the meta-analysis found the T allele rs6313 was protective in studies of opioid and alcohol dependence/abuse and this result extended to combined analyses with the Study of Addiction: Genetics and Environment (SAGE) dataset. On the contrary, rs6311 was not consistently associated with opioid and alcohol dependence/abuse. Although there was some evidence of the A allele being associated with alcohol dependence/abuse, specifically in Europeans, this did not replicate in the combined analyses with the SAGE dataset. These results are surprising because the T allele and A allele are in almost total linkage disequilibrium (LD), and therefore the minor alleles of rs6313 and rs6311 would be expected to have consistent effects (either promoting or protecting risk from drug abuse). These inconsistencies in the role of the minor alleles of rs6313 and rs6311 may be resolved with future, larger studies.

Recent work on the direct role of rs6313 and rs6311 SNPs on expression of the *HTR2a* gene has provided valuable clues into the biological mechanism of allelic variation. One recent study catalogued the mRNA transcripts expressed from the *HTR2a* gene in the dorsolateral prefrontal cortex from individuals with schizophrenia and unaffected controls, examined in aggregate (Ruble et al., 2016). The C allele of rs6313 and G allele of rs6311 were found to be associated with higher expression of 5’ UTR in *HTR2a* (consistent with previous studies, Smith et al., 2013; Smith et al., 2014) and the T allele of rs6313 and A allele of rs6311 were associated with higher expression of *HTR2a-AS1* (i.e., a long non-coding RNA gene on the antisense strand

that is hosted by *HTR2a*) exon 14. Greater expression of 5' UTR is associated with greater translational efficiency and protein production, presumably leading to widespread higher 5-HT2a concentration (Smith et al., 2013, 2014). It is unlikely that high expression of 5' UTR is all "good" or "bad" because 5-HT2a interacts with numerous neurotransmitter systems, and injections of agonists or blockades in rats can have opposing effects on impulsivity, depending on the region the injection occurs (Hadamitzky et al., 2009; Robinson et al., 2008; Wischhof et al., 2011). While the downstream effects of increased expression of *HTR2a-AS1* are not yet known, it has been speculated to have a regulatory role (Ruble et al., 2016). Alterations in 5-HT2a expression or receptor ligand binding levels have been linked to numerous psychological disorders (for a review see Aznar et al., 2016) and recently highlighted as a potential treatment for psychological disorders (Mestre et al., 2013). Additional studies will establish the relationship between these loci, gene function, and risk for impulsivity and addictive disorders. However, the functionality of the A allele of rs6311 and T allele of rs6313 is presumably protective given their association with lower impulsive personality in this study.

There were no significant HVA or genome-wide loci after correcting for false discovery rates. Although a sample size of almost 1,000 individuals is much larger than any previous study on impulsive personality traits, it is still comparatively small relative to genome-wide studies on many complex traits (Burton *et al.*, 2007, McCarthy *et al.*, 2008). The most significant HVA loci were rs4988406 in the *BIK* gene, rs1969269 in the *ITGB3* gene, and rs17090674 in the *STOX2* gene. The possible role of the *BIK* gene in impulsive personality traits is not clear because it is primarily expressed in the heart and muscle (Verma, Budarf, Emanuel, & Chinnadurai, 2000) and is implicated in cell apoptosis (Adams & Cory, 1998). *ITGB3* is perhaps more clearly relevant because it has been associated whole-blood serotonin levels (Weiss et al., 2004; Weiss

et al., 2006; Coutinho et al., 2007), antidepressant drug response (Probst-Schendzielorz, et al., 2015), and autism etiology (Schuch et al., 2014). Given these associations, it is likely that the relationship between *ITGB3* and impulsive personality traits is attributable to its effect on serotonin regulation. Understanding of the functionality of the *STOX2* gene (and of the specific locus rs17090674) is limited, with current research suggesting it is implicated in differentiation of trophoblast cells and embryonic development (van Dijk *et al.*, 2005, Fenstad *et al.*, 2010).

Notably, the most significant genome-wide loci was rs13122329, also in the *STOX2* gene. The SNPs rs17090674 and rs131223329 were highly correlated, suggesting they offer redundant information. The fact that the most significant genome-wide loci was in the same gene and highly correlated with a HVA marker of high significance, suggests a higher degree of confidence in a true positive because, of the ~5M genome-wide SNPs tested, the vast majority were overwhelming comprised of loci in separate genes than the HVA loci. While this is promising, understanding of the functionality of either loci and of *STOX2* on impulsivity-related processes is unclear. Very limited research exists on the role of the other two strongest associations in the genome-wide analysis (rs35721523 in an RNA gene and rs67068739 in the *LMNTD1* gene) at the individual locus or at the gene level.

The findings of this study should be considered in the context of its limitations. Although a strength of this study was a healthy sample because it minimized current substance use influences on impulsive personality traits, it was limited in its ability to explore the relationship between these loci and drug abuse. The findings in this study suggest that BIS-11 Motor and Non-planning subscales may be intermediate mechanisms that explain the putative influence of rs6313 and rs6311 on addictive processes, yet this remains to be tested. A notable strength of this study was the use of a multivariate approach because it enables a capturing of the overall effect

on impulsive personality traits with little to no reduction in likelihood of identifying individual subscale effects (Galesloot et al., 2014). However, some of the *a priori* variants examined were derived from studies which used alternative measures of impulsive personality traits not included in this study. Therefore given the unique sample and variable impulsive personality trait measures, it is possible that these differences contributed to the failure to replicate the previously identified relationships.

Nonetheless, this study makes novel contributions to the study of impulsive personality traits, particularly in the strong implication of two loci in *HTR2a*. As is often the trend in attempts to replicate candidate gene effects for complex traits (Duncan & Keller, 2011), this study casts doubt onto many previously identified candidate relationships. Only two of the 21 candidate loci tested in this study were replicated, which suggests many previously identified loci may be false-positives or at least exert smaller effects than previously identified. In addition to highlighting loci within *HTR2a* for future replication, this study provides suggestive loci from the HVA markers list and genome-wide analyses. Based on the aforementioned research on impulsive personality trait heritability, it is likely that larger sample sizes will yield more positive results. Impulsivity plays a role across a broad array of health conditions, therefore continued inquiry into the genetic determinants of impulsivity is likely to provide a wealth of valuable knowledge for improving health.

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Table 1

A priori loci previously associated with impulsive personality traits

Chr	Locus	Gene	Risk Allele	Measure	Sample Size	Reference
3	rs1732170	GSK3β	T	BIS-11 Attentional	188	Jiménez, 2014
			--	total, Motor, Non-planning		
3	rs334558	GSK3β	G	BIS-11 Attentional	185	Jiménez, 2014
			--	total, Motor, Non-planning		
4	rs693547	GABRA2	T	NEO-PI-R Impulsiveness	295	Villafuerte, 2013
4	rs519270	GABRA2	T	NEO-PI-R Impulsiveness	295	Villafuerte, 2013
4	rs279858	GABRA2	G	NEO-PI-R Impulsiveness	431	Villafuerte, 2012
			--	BIS-11 total	884	Dick, 2013
4	rs279847	GABRA2	A	NEO-PI-R Impulsiveness	295	Villafuerte, 2013
4	rs279843	GABRA2	T	NEO-PI-R Impulsiveness	295	Villafuerte, 2013
4	rs279826	GABRA2	G	NEO-PI-R Impulsiveness	436	Villafuerte, 2012
4	rs279827	GABRA2	G	NEO-PI-R Impulsiveness	295	Villafuerte, 2013
4	rs426463	GABRA2	C	NEO-PI-R Impulsiveness	295	Villafuerte, 2013
4	rs10805145	GABRA2	C	NEO-PI-R Impulsiveness	295	Villafuerte, 2013
4	rs1442060	GABRA2	A	NEO-PI-R Impulsiveness	295	Villafuerte, 2013
5	3’UTR VNTR	DAT1	9-repeat	BIS-11A total	68	Paloleyis, 2010
			9-repeat	BIS-11 total	86	Forbes, 2009
			--	BIS-11 total	86	Congdon, 2008
5	rs6295	HTR1a	GG	IVE-I; BIS-11 total, Motor, Attentional	724	Benko, 2010
			--	Non-planning		
			--	BIS-11 total	687	Varga, 2012
6	rs13212041	HTR1b	AA	BIS-11 total	686	Varga, 2012
6	rs1799971	OPRM1	G	UPPS-P Premeditation	214	Pfiefer, 2015
			--	Negative Urgency, Perseverance		
7	rs324981	NPSR1	T	AMIS Disinhibition	1247	Laas, 2015
			--	BIS-11 total	764[1]	Laas, 2015
			--	AMIS Disinhibition	416	Laas, 2014
11	exon 3 VNTR	DRD4	Short form	BIS-11 total	192	Schilling, 2014

			Short form	BIS-11 total	686	Varga. 2012
			Long form*	Latent IPT construct	298	Carver, 2014
			--	BIS-11A total	68	Paloyelis, 2010
			--	BIS-11 total	86	Congdon, 2008
			--	BIS-11 total	86	Forbes, 2009
			--	BIS-11 total, Attentional, Motor, Non-planning	168-185	Eisenberg, 2007
11	rs6265	BDNF	T	Latent IPT construct	298	Carver 2014
			T	BIS-11 Attentional	138	Su 2014
11	rs1800497	ANKK1	T	UPPS-P NU	121	Doran, 2013
			--	BIS-11 total	683	Varga, 2012
			--	BIS-11 total, Attentional, Motor, Non-planning; EIQ	168-185	Eisenberg, 2007
			C	BIS-10 total	92	Limosin, 2003
			T*	Latent IPT construct	298	Carver, 2014
12	rs2228570	VDR	CC	BIS-11 total, Attentional	148[2]	Wrzosek, 2014
			--	Motor, Non-planning		
13	rs6313	HTR2a	T	BIS-11 total	344	Racine, 2009
			--	BIS-11 total	284	Jakubczyk, 2012
13	rs6311	HTR2a	GG	BIS-11 total	135	Preus, 2001
14	rs11624704	NRXN3	C	BIS-11 total, Attentional	439	Stoltenberg, 2011
			--	Motor, Non-planning		
17	5-HTTLPR	SLC6A4	Short form	BIS-11 total	319	Racine, 2009
			Short form	BIS-11 total, Attentional	123	Sakado, 2003
			--	Motor, Non-planning		
			Short form**	BIS-11 total	374	Paaver, 2007
			Short form*	Latent IPT construct	303	Carver, 2011
			--	BIS-11 total	683	Varga, 2012
			--	BIS-11 total, Attentional, Motor, Non-planning; IVE-I	30	Roiser, 2007
20	rs3746544-	SNAP25	T-T	lower BIS-11 total scores	869	Németh, 2013

	rs1051312		haplotype			
22	rs4680	COMT	AA	BIS-11 Non-planning	82	Soeiro-De-Souza, 2013
			--	total, Attentional, Motor		
			AA	BIS-11 total	680	Varga, 2012
			--	BIS-11A total	68	Paloyelis, 2010
			--	BIS-11 total	86	Forbes, 2009
			GG	Latent IPT construct	298	Carver, 2014
X	rs1465108	MAOA	A	UPPS-P Negative Urgency	277	Chester, 2015

Note. VNTR = variable number tandem repeat; IPT = impulsive personality traits; IVE-I = Impulsiveness-Venturesome-Empathy Impulsiveness subscale; Eysenck Impulsivity Questionnaire (EIQ). Unless otherwise noted, risk alleles were associated with higher scores on the measures listed ("--" indicates that no relationship was found). *The effects were identified in an interaction with childhood adversity relating to higher latent IPT scores. **The effects were identified in an interaction with low platelet monoamine oxidase activity relating to higher BIS-11 total scores. [1]315 males and 449 females analyzed separately, [2] 106 males and 42 females analyzed separately, effects were only present for males.

Table 2
Participant characteristics (N = 983)

Variable	**% / Mean (SD) / Median**
Age	21.65 (3.30)
Sex	62.2% Female
Income	$60,000 – $89,999
Years of education	14.53 (2.21)[1]

Note. [1]*N = 982*.

Table 3
Power analyses

Prioritized Subset	**Effect Size (R^2)**	**Type I Error Correction**	**Power**
21 *a priori* loci	.005	nominal $p < .05$	.272
	.010		.626
	.015		.850
	.025		.986
	.050		1.000
13,337 HVA loci	.005	$p < \sim.000004$ (Bonferroni)	.012
	.010		.091
	.015		.268
	.025		.701
	.050		.996
4,887,762 genome-wide loci	.005	$p < 5 \times 10^{-8}$	.001
	.010		.014
	.015		.071
	.025		.375
	.050		.968

Table 4

Pearson correlations among impulsive personality traits

Variable	1	2	3	4	5	6
1. Attentional	----	----	----	----	----	----
2. Motor	.378**	----	----	----	----	----
3. Non-planning	.413**	.474**	----	----	----	----
4. Negative Urgency	.399**	.295**	.410**	----	----	----
5. Premeditation	.312**	.479**	.592**	.306**	----	----
6. Perseverance	.440**	.174**	.494**	.357**	.362**	----
7. Positive Urgency	.332**	.281**	.345**	.594**	.323**	.275**

Note: ** = $p < 5 \times 10^{-9}$.

Table 5

Associations between a priori loci and impulsive personality traits

Chr	Locus	Gene	Missing	Minor Allele	MAF	P
3	rs1732170	GSK3β	0	T	.402	.466
4	rs693547[1]	GABRA2	0	A	.413	.494
4	rs519270[2]	GABRA2	3	T	.407	.440
4	rs279858[1,2]	GABRA2	2	C	.411	.368
4	rs279847[1,2]	GABRA2	23	T	.408	.215
4	rs279843[1,2]	GABRA2	17	T	.411	.345
4	rs279826[2]	GABRA2	6	G	.431	.448
4	rs279827[2]	GABRA2	8	G	.433	.498
4	rs426463[2]	GABRA2	8	C	.433	.491
4	rs10805145[2]	GABRA2	44	C	.435	.575
5	rs6295	HTR1a	2	C	.497	.878
6	rs13212041	HTR1b	34	C	.216	.914
6	rs1799971	OPRM1	0	G	.127	.957
7	rs324981	NPSR1	0	T	.451	.591
11	rs6265	BDNF	0	T	.200	.487
11	rs1800497	ANKK1	0	A	.183	.875
12	rs2228570	VDR	0	A	.414	.475
13	**rs6313[3]**	**HTR2a**	**0**	**A**	**.419**	**.002**
13	**rs6311[3]**	**HTR2a**	**7**	**T**	**.418**	**.003**
14	rs11624704	NRXN3	0	C	.150	.754
22	rs4680	COMT	0	G	.482	.780

Note. Matching superscripts (i.e., [1-3]) indicate loci are in high LD (i.e., $r^2 > .8$). Bolding of loci indicates significant effects were identified. Follow-up univariate analyses were only conducted for loci with significant multivariate effects.

Table 6

Top 50 high-value addiction loci hits

Chr	SNP	Gene	Position	Missing	Minor	MAF	P
22	rs4988406	BIK	43518324	47	C	.165	5.01E-05
4	rs17090674	STOX2	184919470	16	T	.280	9.73E-05
17	rs1969269	ITGB3	45335537	16	A	.099	9.81E-05
22	rs11574528	Intergenic	43527681	31	T	.170	1.08E-04
1	rs4651467	Intergenic	188557023	1	A	.342	1.34E-04
6	rs4236127	HCRTR2	55056177	0	C	.180	1.39E-04
6	rs12526414	HCRTR2	55061694	0	T	.180	1.39E-04
6	rs10948894	HCRTR2	55065964	0	C	.180	1.39E-04
6	rs10498801	MLIP	55066964	0	A	.180	1.39E-04
6	rs3134689	HCRTR2	55054752	20	G	.204	1.61E-04
6	rs3122148	HCRTR2	55065989	0	G	.202	1.84E-04
6	rs9396060	HCRTR2	55079046	0	C	.151	1.85E-04
6	rs12662510	HCRTR2	55079891	0	G	.151	1.85E-04
6	rs3134696	HCRTR2	55062101	4	C	.197	2.21E-04
17	rs3892085	ITGB3	45340480	2	G	.102	2.23E-04
17	rs35265764	ITGB3	45363546	0	T	.102	2.57E-04
17	rs2292864	ITGB3	45367681	0	T	.102	2.57E-04
7	rs3735486	CCM2	45105117	5	G	.370	2.88E-04
17	rs2292867	ITGB3	45357489	7	T	.119	2.94E-04
7	rs16869529	CUX2	101736364	0	T	.051	3.09E-04
1	rs985616	Intergenic	86639629	0	T	.298	4.15E-04
6	rs6908401	ncRNA	169564716	31	T	.139	4.29E-04
8	rs3735999	JRK	143746069	0	C	.376	5.25E-04
2	rs11686212	TRAPPC12	3392295	0	G	.387	5.34E-04
6	rs9367622	HCRTR2	55069173	3	C	.151	5.61E-04
17	rs3785872	ITGB3	45372075	7	A	.099	5.67E-04

20	rs3761264	GNAS	57413371	43	T	.447	5.93E-04
8	rs2059547	ncRNA	54193095	0	C	.121	6.80E-04
13	rs4941701	ncRNA	33485476	4	G	.085	6.98E-04
17	rs1009312	ITGB3	45332140	23	A	.166	7.03E-04
17	rs2015049	ITGB3	45332231	23	A	.166	7.03E-04
17	rs11871447	ITGB3	45331618	19	G	.167	7.35E-04
17	rs11871251	ITGB3	45331427	20	A	.167	7.78E-04
6	rs12661910	ncRNA	169584388	4	C	.143	8.10E-04
2	rs3731900	FAM134A	220046975	0	C	.383	8.27E-04
17	rs11871407	ITGB3	45331358	17	G	.167	8.80E-04
6	rs7775839	TRAPPC3L	116821146	0	C	.456	8.90E-04
6	rs2800708	ncRNA	127437617	23	C	.474	9.83E-04
1	rs2784140	SLC6A17	110738296	0	A	.485	1.06E-03
10	rs11258843	FRMD4A	14100232	13	T	.125	1.18E-03
3	rs6771162	Intergenic	152239295	2	A	.298	1.26E-03
16	rs7187167	Intergenic	1349209	0	T	.274	1.28E-03
2	rs4954757	ncRNA	139992742	7	A	.457	1.30E-03
6	rs633399	TUBB4BP7	153220274	0	A	.28	1.32E-03
16	rs7196984	Intergenic	7797128	17	T	.104	1.34E-03
11	rs2514462	ncRNA	80949350	49	C	.219	1.37E-03
7	rs1568734	ACTR3B	152535908	34	T	.284	1.38E-03
6	rs9367621	HCRTR2	55040290	34	T	.444	1.39E-03
1	rs2020861	FMO2	171168585	0	G	.445	1.42E-03
7	rs6975902	Intergenic	7964238	0	A	.246	1.48E-03

Note. Chr = chromosome; MAF = minor allele frequency; ncRNA = non-coding RNA.

Table 7

Top 50 genome-wide association hits

Chr	SNP/DIV	Gene	Position	Missing	Minor	MAF	P
4	rs13122329	STOX2	184910905	34	A	.272	8.81E-07
15	rs35721523	ncRNA	96905460	0	C	.096	1.89E-06
12	rs67068739	LMNTD1	25669019	19	C	.055	2.02E-06
12	rs73298424	LMNTD1	25669626	19	C	.055	2.02E-06
4	rs35046209	STOX2	184909246	33	A	.271	2.17E-06
2	rs11413062[1]	ncRNA	156985519	15	GA	.104	2.95E-06
9	rs76880586	Intergenic	80906267	31	C	.136	3.33E-06
4	rs11731795	STOX2	184910269	31	A	.271	3.33E-06
2	rs6736241	ncRNA	156975459	0	T	.104	3.50E-06
9	rs12004671	Intergenic	80905154	29	A	.136	3.86E-06
2	rs16840025	ncRNA	156982591	4	A	.103	4.28E-06
2	rs76117428	ncRNA	156967584	13	G	.099	4.53E-06
11	rs4910143	AMPD3	10499103	46	A	.380	4.55E-06
7	rs2893480	NPSR1-AS1	34535028	41	T	.398	4.57E-06
2	rs16840040	ncRNA	156986318	21	C	.102	5.25E-06
2	rs72902130	ncRNA	156971379	6	A	.101	5.91E-06
2	rs1839190	STK39	168852690	27	G	.382	6.29E-06
6	rs6931897	KLHL32	97456655	2	A	.136	6.57E-06
4	rs35723722	STOX2	184900053	18	A	.272	6.83E-06
15	rs12440174	ncRNA	96905176	18	G	.091	6.85E-06
2	rs56301904	STK39	168851549	23	T	.383	6.95E-06
2	rs67275848	STK39	168851608	23	T	.383	6.95E-06
2	rs72902129	ncRNA	156969427	10	A	.100	7.05E-06
9	rs72745652	PSAT1	80940221	10	T	.088	7.24E-06
2	rs4667998	STK39	168853936	30	T	.381	7.29E-06
2	rs72883966	STK39	168819345	19	C	.39	7.34E-06

11	rs199710465[1]	Intergenic	87738869	28	GT	.127	7.67E-06
6	rs6920385	KLHL32	97445618	7	G	.134	8.00E-06
2	rs4667995	STK39	168852219	24	C	.384	8.16E-06
2	rs72885771	STK39	168853997	33	C	.381	8.82E-06
7	rs17169823	NPSR1-AS1	34538735	38	A	.398	8.94E-06
7	rs17169824	NPSR1-AS1	34538744	38	T	.398	8.94E-06
6	rs56127974	ADGRB3	69922386	17	A	.104	8.96E-06
5	rs1514578	Intergenic	62402611	5	G	.299	9.18E-06
11	rs143157064	Intergenic	87739765	26	T	.128	9.29E-06
9	rs62565651	PSAT1	80933744	10	A	.087	9.45E-06
6	rs9320375	KLHL32	97449042	0	A	.135	9.79E-06
6	rs13437270	KLHL32	97449362	0	T	.135	9.79E-06
6	rs6568697	KLHL32	97449713	0	A	.135	9.79E-06
6	rs6568698	KLHL32	97450004	0	C	.135	9.79E-06
6	rs6568699	KLHL32	97450121	0	A	.135	9.79E-06
6	rs4839891	KLHL32	97450714	0	A	.135	9.79E-06
6	rs34355781[1]	KLHL32	97451240	0	ATTTG	.135	9.79E-06
6	rs1119220	KLHL32	97451911	0	G	.135	9.79E-06
6	rs1119221	KLHL32	97451987	0	A	.135	9.79E-06
6	rs4839892	KLHL32	97453730	0	A	.135	9.79E-06
6	rs4839893	KLHL32	97453895	0	A	.135	9.79E-06
6	rs4839894	KLHL32	97454070	0	G	.135	9.79E-06
6	rs3032643	KLHL32	97455921	0	C	.135	9.79E-06
6	rs6912134	KLHL32	97456425	0	C	.135	9.79E-06

Note. Chr = chromosome; DIV = deletion insertion variation; MAF = minor allele frequency; ncRNA = non-coding RNA. [1] = DIV locus.

Figure Captions

Figure 1. Principal components analysis plot (PC1/PC2). The plot displays the top two axes of variation in 985 self-reported European American participants. The two participants (in red) that notably diverge from the PC1/PC2 distribution were excluded.

Figure 2. A) Q-Q and B) Manhattan plot of genome-wide association for impulsive personality traits multivariate regression models with adjustment for sex, age, and site. Significance values were $-\log_{10}$ transformed in order to display the smaller *p*-values as larger in the figures. The Q-Q plot depicts the observed and expected *p*-values. The dotted lines represent 95% confidence intervals. The majority of SNPs fit null expectations and no markers show evidence for a true association. The Manhattan plot displays level of significance for each SNP, organized by chromosomal position from chromosomes 1-22. The blue line indicates suggestive significance (10^{-5}). No SNPs achieve genome-wide significance ($p < 5 \times 10^{-8}$).

Figure S1

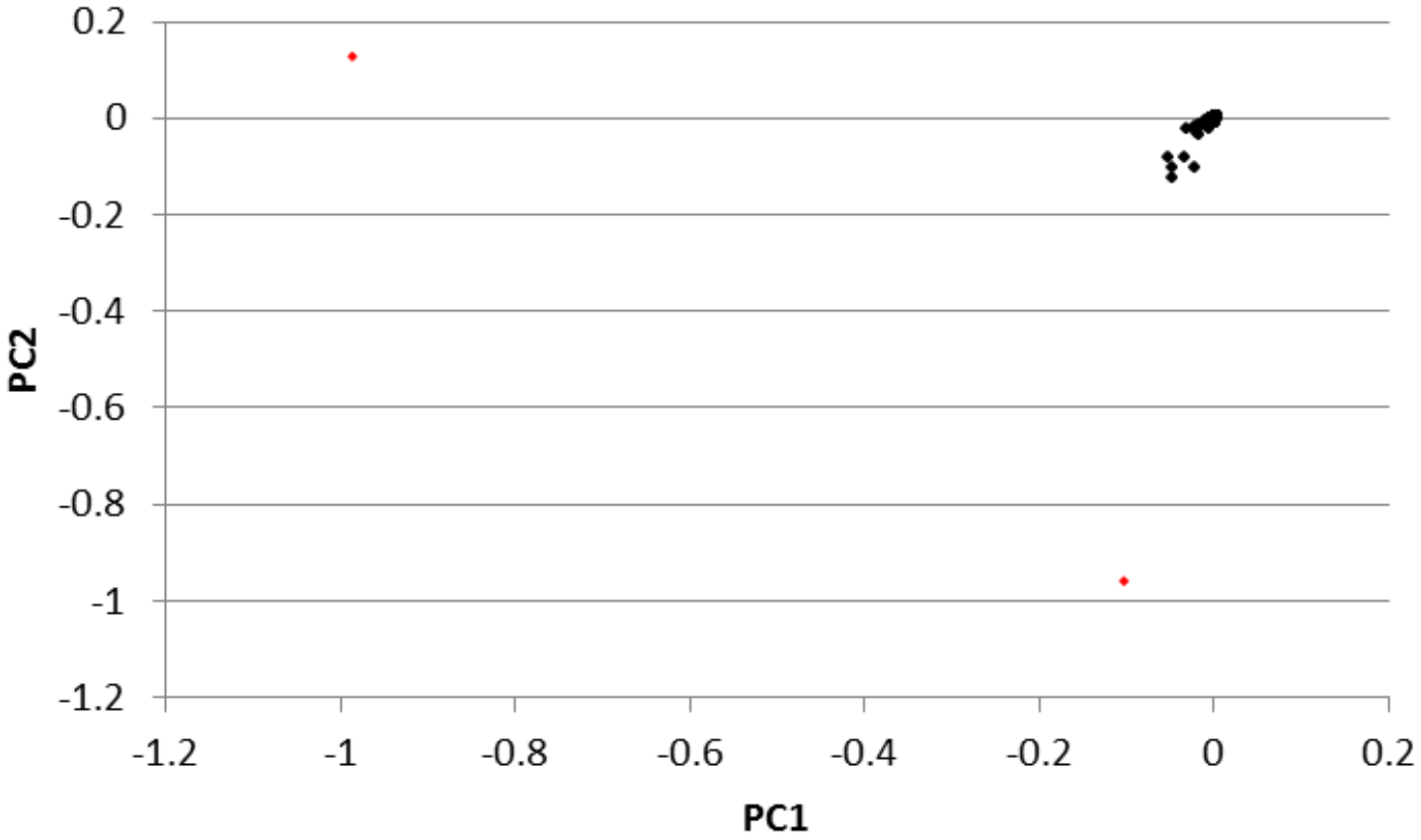
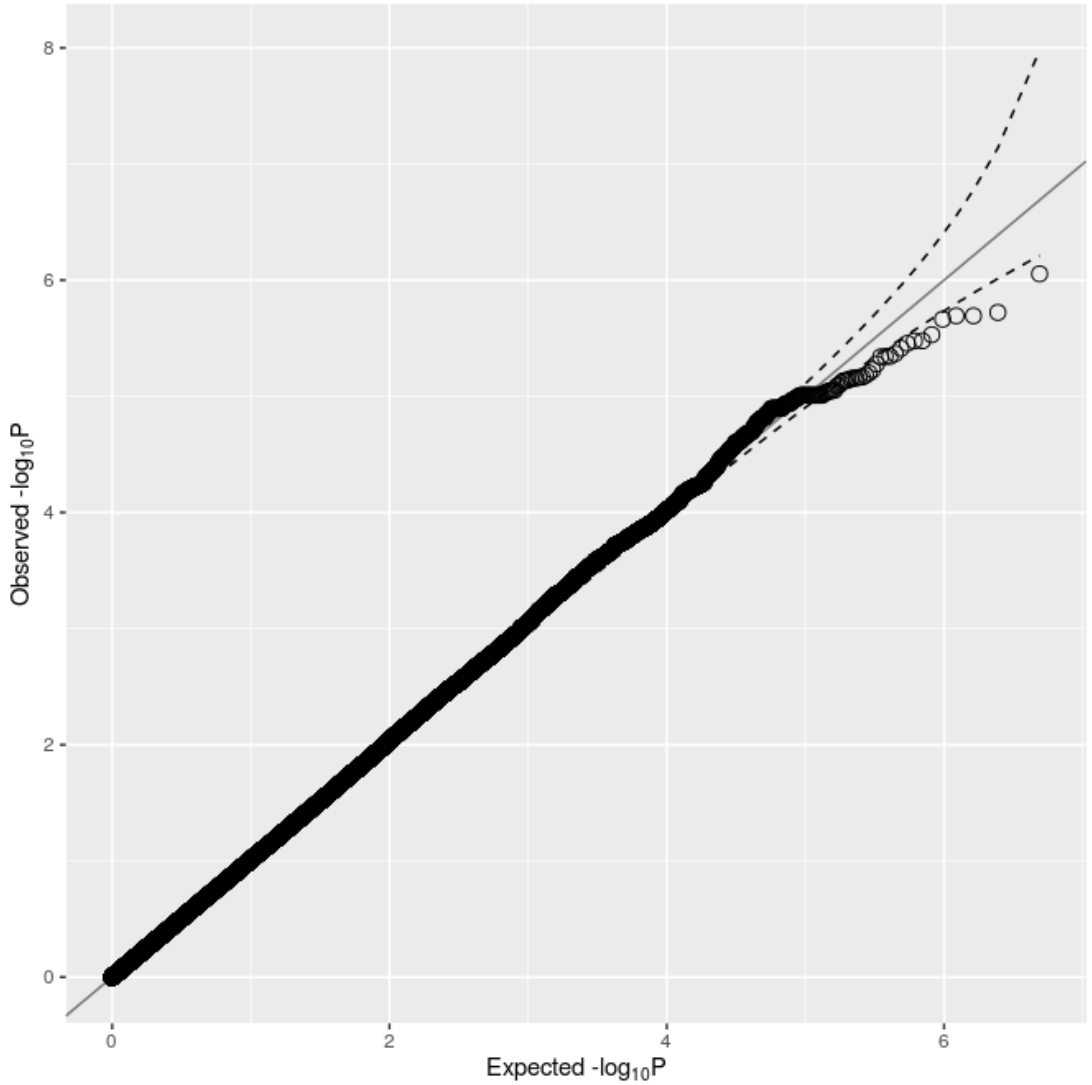


Figure 2

A



B