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Genetic analysis of impulsive personality traits: Examination of *a priori* candidates and genome-wide variation

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ABSTRACT

Impulsive personality traits are heritable risk factors and putative endophenotypes for addiction and other psychiatric disorders involving disinhibition. This study examined the genetic basis of impulsive personality traits, defined as scores on the Barratt Impulsiveness Scale (BIS-11) and the UPPS-P Impulsive Behavior Scale (UPPS-P). In 983 healthy young adults of European ancestry, the study examined genetic variation in relation to a combined phenotype of seven subscales based on high phenotypic intercorrelations. The study first tested 14 *a priori* loci that have previously been associated impulsive personality traits or closely related constructs. Second, the study included an exploratory genome-wide scan (i.e., GWAS), acknowledging that only relatively large effects would be detectable in a sample size of ~ 1000. *A priori* SNP analyses revealed a significant association between the combined impulsivity phenotype and two SNPs within the 5-HT2a receptor gene (*HTR2A*; rs6313 and rs6311). Follow-up analyses suggested that the effects were specific to the Motor and Non-planning subscales on the BIS-11, and also that the two loci were in linkage disequilibrium. The GWAS yielded no statistically significant findings. This study further implicates loci within *HTR2A* with certain forms of self-reported impulsivity and identifies candidates for future investigation from the genome-wide analyses.

1. Introduction

Despite extensive evidence from twin studies that genetic factors strongly influence addictive disorders (Agrawal and Lynskey, 2008; Goldman et al., 2005) and other disorders of disinhibition (e.g., attention-deficit/hyperactivity disorder [ADHD], borderline personality disorder; Faraone et al., 2005; Distel et al., 2008), the specific genes and polymorphisms responsible have been elusive (Schuckit, 2014). A promising approach to identify the genetic bases of polythetic disorders like addiction is the investigation of endophenotypes, or heritable phenotypes that are putatively simpler in genetic architecture and lie between genetic variation and a psychiatric disorder (Gottesman and Gould, 2003). Endophenotypes may shed light on the etiology of psychiatric disorders by identifying loci that are relevant to both the endophenotype and the disorder. Furthermore, these endophenotypes may ultimately be helpful to improve treatment or prevention efforts (for a full review, see MacKillop and Munafò, 2013).

One broad phenotype that has been consistently linked to psychiatric disorders involving self-regulatory deficits is impulsivity (Amlung et al., 2016; de Wit, 2009; MacKillop et al., 2011). 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), poor response inhibition (i.e., inability to inhibit a prepotent response on experimental tasks), and maladaptive decision making (e.g., preferences for smaller immediate rewards over larger delayed rewards). Although conceptually related, these forms of impulsivity are largely quantitatively distinct from one another (MacKillop et al., 2016; Reynolds et al., 2006).

Here, we focus on measures of impulsive personality traits from an investigation into the latent phenotypic structure of diverse measures of

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impulsivity. In that study, several measures of impulsivity aggregated into the three aforementioned domains and there was limited overlap between the domains (MacKillop et al., 2016). With regard to impulsive personality traits, MacKillop et al. (2016) included three subscales of the Barratt Impulsiveness Scale, Version 11 (BIS-11) (Patton et al., 1995) and five subscales of UPPS-P Impulsive Behavior Scale (UPPS-P) (Cyders et al., 2007; Whiteside and Lynam, 2001), and found that all three subscales of the BIS-11 and four of the five subscales of the UPPS-P contributed unique variance to an impulsive personality trait factor. The Sensation Seeking subscale on the UPPS-P did not load on the factor. The current study focuses explicitly on impulsive personality traits, not the other two domains, because they constitute quantitatively distinct phenotypes.

Both the BIS-11 and UPPS-P are reasonable choices for use as endophenotypes because they meet most of the criteria proposed for identifying endophenotypes (Flint and Munafò, 2007; Gottesman and Gould, 2003). For example, elevations on these measures are associated with risk-taking behaviors, addictive disorders, and other psychopathology (Berg et al., 2015; Coskunpinar et al., 2013; Stanford et al., 2009) and they show robust evidence of heritability (47–63%; Gustavson et al., 2014; Niv et al., 2012; Seroczynski et al., 1999). 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 et al., 2010). Association studies have implicated several genetic loci with scores on the BIS-11 and UPPS-P (see Table 1), most notably identifying genes involved in dopaminergic and serotonergic neurotransmission. These include *DAT1* (Forbes et al., 2009; Paloyelis et al., 2010), *DRD4* (Schilling et al., 2014; Varga et al., 2012), *ANKK1* (Doran and Trim, 2013; Limosin et al., 2003), *COMT* (Soeiro-De-Souza et al., 2013; Varga et al., 2012), *HTR1A* (Benko et al., 2010), *HTR1B* (Varga et al., 2012), *HTR2A* (Preuss et al., 2001; Racine et al., 2009), *SLC6A4* (Racine et al., 2009; Sakado et al., 2003), and *MAOA* (Chester et al., 2015). In addition, associations have been reported with variants in *BDNF* (Su et al., 2014), *OPRM1* (Pfeifer et al., 2015), *GSK3β* (Jiménez et al., 2014), *VDR* (Wrzosek et al., 2014), *NRXN3* (Stoltenberg et al., 2011), and *SNAP-25* (Németh et al., 2013). Yet, as we have discussed before (Hart et al., 2013), the loci identified in the aforementioned studies have also exhibited failure to replicate, and some have yielded opposing effects (e.g. Congdon et al., 2008; Eisenberg et al., 2007; Forbes et al., 2009; Jakubczyk et al., 2012; Paloyelis et al., 2010; Roiser et al., 2007; Varga et al., 2012). Many of these studies have used small sample sizes (Table 1, median $n = 192$) and have had relatively modest genomic scope. Furthermore, many of these studies included individuals with current substance use disorders, which complicates the interpretation because extended drug use can increase measures of impulsive personality (e.g., Quinn et al., 2011). Studying an endophenotype in healthy adults without histories of addiction allows investigators to study normal variation in a trait, without the confounding influence of drug use or psychiatric symptomatology. Finally, the previous studies did not systematically assess associations using multiple measures of impulsivity simultaneously to capture overlapping phenotypes.

The present project sought to address some of these limitations by investigating impulsive personality traits in a comparatively large sample of healthy, non-drug-abusing individuals (MacKillop et al., 2016), using a wide array of loci. Furthermore, we used a multivariate approach based on evidence that these phenotypes are correlated (MacKillop et al., 2016) and because multivariate methods can detect effects when only one of the variables is associated with a genetic locus (Galesloot et al., 2014). This allowed us to estimate both overall relationship with impulsive personality traits as well as a more fine-grained assessment of associations with individual subscales. The study used a hierarchical approach, first testing *a priori* loci, explicitly prioritizing loci that had previously been reported as significantly associated in the peer-reviewed literature of impulsive personality traits. Within this first set of analyses we also tested three loci that a recent GWAS found were associated with Neuroticism and Conscientiousness (Lo et al., 2016), two facets of personality closely related to impulsive personality traits (Whiteside and Lynam, 2001). Second, for completeness, we report an atheoretical genome-wide scan (i.e., GWAS), acknowledging that only relatively large effects would be detectable in a sample size of ~ 1000. Given the paucity of genome-wide studies in this area, this aim was intended to expand the genomic scope to detect previously unreported large magnitude associations, to inform hypotheses in future studies, and to avoid contributing to publication bias in the literature (e.g., Munafò et al., 2004).

2. Methods

2.1. Participants

Full phenotyping methods are provided in MacKillop et al. (2016). In brief, participants were recruited at two sites (Athens, GA and Chicago, IL). Inclusion criteria were English fluency, age 18–30 years, and self-reported Caucasian race and non-Hispanic ethnicity to minimize population stratification (Hutchison et al., 2004). Exclusion criteria were scores > 12 on the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) or the Drug Use Disorders Identification Test (DUDIT; Berman et al., 2005). In addition, all participants were screened for recent alcohol or drug use via breathalyzer or urine drug test before testing. A further exclusion criterion was treatment over the last 12 months or self-reported current need for treatment for: depression, bipolar disorder, general anxiety, social anxiety, post-traumatic stress disorder, obsessive compulsive disorder, panic attacks/disorder, phobia, schizophrenia spectrum disorders, anorexia, bulimia, or binge eating. We did not exclude ADHD because while heavy drug use introduces environmental exposure that can increase impulsivity (de Wit, 2009; Quinn et al., 2011; Quinn and Harden, 2013), impulsive personality traits and ADHD are related and likely have overlapping heritability without confounding environmental exposure (Berg et al., 2015; Jepsen et al., 2017). Participants completed assessments individually in a behavioral laboratory. DNA was collected via a saliva sample for DNA collection in an Oragene DNA kit (DNA Genotek Inc., Kanata, ON, Canada).

2.2. Phenotypes

We used the Barratt Impulsiveness Scale, Version 11 (BIS-11), a 30-item measure (Patton et al., 1995) with three second order factors: Attentional, Motor, and Non-planning, and four subscales from the 59-item measure, the UPPS-P Impulsive Behavior Scale (UPPS-P) (Cyders et al., 2007; Whiteside and Lynam, 2001): Negative Urgency, (lack of) Premeditation, (lack of) Perseverance and Positive Urgency. The 5th scale of the UPPS-P, Sensation Seeking, was not included because it was not strongly correlated with the other impulsive personality subscales (MacKillop et al., 2016). Likewise, we did *not* test loci associated with Extraversion from the recent GWAS (Lo et al., 2016), because Extraversion is most related to Sensation Seeking (Whiteside and Lynam, 2001). Demographic characteristics including sex, age, race, and income were recorded.

2.3. SNP genotyping and quality control

Genotyping was performed using the Illumina PsychArray BeadChip platform, which characterizes ~ 600,000 SNPs and has been optimized to capture the maximum amount of information about common variation. Quality control filtering was implemented in PLINK v1.9 (Chang et al., 2015). Autosomal SNPs were filtered for call rates < 98%, Hardy-Weinberg Equilibrium (HWE) violations of $p < 1 \times 10^{-6}$ and MAF < 5%. After filtering 437,652 SNPs remained for imputation. Imputation