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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

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Conflict of interest

The authors do not have any actual or potential conflict of interest to disclose.

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Contributors

HDW, AAP, and JM were responsible for the study concept; JM, HDW, and AAP were responsible for study design and protocol; JCG and JW provided additional refinement to the study design and protocol; JCG and JW contributed to data collection; JCG and JJ conducted data analysis; JCG, JM, HDW, AAP, and JW contributed to data interpretation; JG drafted the manuscript; JM, HDW, AAP, and JW provided critical revision for important intellectual content. KMH conducted imputation. AAP, KMH, and JJ consulted on quality control of genetic data. All authors contributed to and have approved the final manuscript.

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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-HT_{2A} 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.

Keywords

Impulsivity; genetics; endophenotype; personality traits; serotonin

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 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, Turton, Pradhan, Bullmore, & Robbins, 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 of missing genotypes and of additional SNPs was performed with IMPUTE2 v.2.3.1 (Howie et al., 2009) using the 1000 Genomes Phase 3 b37 reference panel (1000 Genomes Consortium, 2015). Imputed SNPs were excluded for exhibiting an information score of < .3 (Marchini and Howie, 2010), MAF < 5%, HWE violations of $p < 1 \times 10^{-6}$, missingness > 5%, and multiallelic status. Imputed SNPs with confidence < .9 were set to missing. Of the 3 *a priori* loci from the recent GWAS of personality (rs3814424, rs6981523, rs9611519; Lo et al., 2016) and the 15 *a priori* loci from prior impulsive personality trait research (see Table 1), two were excluded for excessive missing values (rs1051312, rs334558), one was excluded for poor imputation accuracy (rs3746544), and one was excluded because it was on the X chromosome (rs1465108). VNTR loci were not genotyped and therefore were not included in this study. Following quality control, 14 *a priori* loci and 4,887,762 genome-wide SNPs were available for association analysis.

2.4. Participant Quality Control

1,000 participants had valid genotyping data (call rates > 98%, inbreeding coefficient absolute value < .02, concordant self-reported sex and X-chromosome determined sex) and satisfied the inclusion/exclusion criteria. To correct any self-reported race that is misclassified as Caucasian, 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 S1). 13 participants were excluded for missing one or both measures of impulsive personality traits. Finally, participants were assessed for cryptic relatedness (Yang et al., 2011), and two were removed for relatedness > .05, leaving a final sample of 983 unrelated European-ancestry participants (Table 2).

2.5. Data Analysis

The internal reliability coefficients and the interrelationships among the UPPS-P and BIS-11 subscales were calculated. 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 (MLMM) of the impulsive personality subscales with four covariates: sex, age, income, and site (i.e., Chicago, IL or Athens, GA). Each candidate covariate was examined as a fixed factor, while the other three covariates were included as control variables and only variables which were significantly associated in the combined models were included as covariates in subsequent analyses. Genome-wide Efficient Mixed Model Association (GEMMA) software (Zhou and Stephens, 2012) was utilized to examine the MLMM associations between the loci from each strata and the impulsive personality

subscales. The MLM accounts for the cryptic relatedness among individuals, which is modeled out as a random effect (i.e., the genetic correlation between individuals). To manage type I error inflation, for the first prioritized subset (14 *a priori* loci), a Benjamini-Hochberg FDR correction was applied to the resultant *p*-values from the analyses (Benjamini and Hochberg, 1995). For the atheoretical genome-wide scan, 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 (e.g., Pe'er et al., 2008). Any significant multivariate relationships were unpacked by examining linear relations among the significant loci and each individual subscale. Because GWA analyses comprised a large panel of SNPs, the top 50 genome-wide loci were also reported to avoid excessive type II error rate and inform future inquiries.

3. Results

3.1. Preliminary Analyses

A correlation matrix of the impulsive personality subscales (including internal reliabilities) can be found in Table 3. All subscales were significantly correlated ($p_s < 5 \times 10^{-9}$) and exhibited acceptable internal reliability. In the MLM, gender, age, and site were each found to be significant, respectively $F(4, 976) = 11.18, p = 1.14 \times 10^{-13}$, Wilk's $\Lambda = .93$, partial $\eta^2 = .08$; $F(4, 976) = 1.80, p = 6.0 \times 10^{-6}$, Wilk's $\Lambda = 0.85$, partial $\eta^2 = .02$; $F(4, 976) = 4.37, p = .00009$, Wilk's $\Lambda = .97$, partial $\eta^2 = .03$, and were thus included as covariates. Examination of Pearson correlations among the covariates and impulsive personality subscales indicated that individuals from the Athens site were more impulsive and, generally consistent with the literature, males had significantly higher positive urgency and motor impulsivity (Coskunpinar and Cyders, 2013), and younger individuals were more impulsive across four of the subscales (Steinberg et al., 2008) (see supplementary Table S1). Income was not significantly related to the impulsive personality subscales ($F(4, 976) = 1.06, p = .38$, Wilk's $\Lambda = 0.97$, partial $\eta^2 = .01$) and therefore was not covaried in all other analyses.

3.2. *A priori* loci

Of the 14 *a priori* loci assessed, two loci (rs6313, rs6311) were significantly associated with impulsive personality in the multivariate analyses (nominal $p_s = .002, .003$, respectively; see Table 4). These two associations survive even a stringent Bonferroni correction among the *a priori* loci (adjusted $\alpha = .004$). Notably, rs6313 and rs6311 are essentially in total linkage disequilibrium (LD) and therefore offer largely redundant information ($r^2 = .996$). In examining the individual subscales, these two loci were selectively 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 lower impulsivity. The lower significance values ($p = .002, .003$) at the multivariate level as compared to the individual subscale level ($p_s .008-.03$) attest to the value of utilizing this statistical approach when exploring multiple correlated phenotypes (Galesloot et al., 2014).

Given the differences in impulsivity by site, we conducted exploratory analyses testing *a priori* SNPs by site interactions in GEMMA and using a Bonferroni correction to minimize Type I errors. No significant interactions were present.

3.3. Genome-wide associations

The genome-wide scan did not yield any significant associations at $p < 5 \times 10^{-8}$. The strongest association was rs13122329 in the *STOX2* gene on chromosome 4 ($p = 8.81\text{E-}7$). The next two strongest associations were rs35721523 in an uncharacterized region (LOC101927263) in a non-coding RNA gene on chromosome 15 ($p = 1.89\text{E-}6$) and rs67068739 in the lamin domain tail containing 1 (*LMNTD1*) gene on chromosome 12 ($p = 2.02\text{E-}6$). The top 50 most significant hits are included in supplementary materials (Table S2). The results of the GWAS are depicted using both Manhattan plots (Figure S2) and Quantile-Quantile (Q-Q) plots (Figure S3). As can be seen in the Q-Q plot, the majority of markers fit null expectations and no markers suggest associations beyond chance.

4. Discussion

This study sought to assess genetic influences on impulsive personality traits, one of three major domains comprise the superordinate construct of impulsivity, to better understand heritable risk for addiction and other psychiatric disorders involving disinhibition. We examined the genetic basis of impulsive personality traits using a hierarchical approach to examine *a priori* loci and genome-wide variation. In terms of the *a priori* loci, we identified robust evidence for two previously identified candidate loci (rs6313 and rs6311) within *HTR2a*, but failed to support the remaining 12 loci. Specifically, the T allele of rs6313 and the A allele of rs6311 were associated with lower levels of impulsivity, 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 was associated with higher BIS-11 total scores in 135 individuals with alcohol dependence (Preuss et al., 2001), but is not consistent with other studies (Racine et al., 2009; Jakubczyk et al., 2012). These differences in findings may be attributable to smaller and different samples in the previous studies (e.g., females only, individuals with alcohol dependence).

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. However, for rs6311, there was some evidence of the A allele being associated with alcohol dependence/abuse in Europeans, but this did not replicate in the combined analyses with the SAGE dataset. Cao et al.'s results are somewhat surprising because the T allele and A allele are in almost total LD, and therefore these minor alleles should have consistent effects, either promoting or protecting risk from drug abuse.

Although neither rs6313 nor rs6311 alter the encoded protein, recent work on the direct role of these SNPs on expression of the *HTR2A* gene has provided valuable clues into the biological mechanism of allelic variation. The C allele of rs6313 and G allele of rs6311 have been found to be associated with higher expression of 5' UTR in *HTR2A* (Ruble et al.,

2016; Smith et al., 2014, 2013). 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., 2014, 2013). 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). The functionality of the A allele of rs6311 and T allele of rs6313 is presumably protective given their association with lower impulsivity in this study, but additional studies will be needed to clarify the relationship between these loci, gene function, and risk for impulsivity and addictive disorders.

Beyond these alleles, it was notable that the other *a priori* candidate SNPs tested were not replicated, which may be related to features of our subject sample, unidentified SNP by environment effects (e.g., childhood adversity; Carver et al., 2014; Dick et al., 2015), or the previous findings may be false-positives. The analyses of genome-wide loci yielded no statistically significant associations, perhaps because the present sample of 983 was underpowered for high-dimensional and genome-wide analysis of these traits. Nonetheless, given the rigorous phenotypic assessment, the loci with the highest associations still inform future analyses. Indeed, the top 50 loci are provided in the supplementary materials so that future investigations can prioritize these suggestive loci.

This study has several limitations that bear mentioning. The sample size was sufficient for strong tests of small effect sizes in *a priori* loci, but only to detect large effect sizes in the genome-wide tests. We recruited a low substance exposure sample to minimize possible confounding effects of drug use on impulsive personality traits, but this also limited the ability to generalize to studies that tested some of the *a priori* loci in individuals exhibiting problematic substance use. In addition, by recruiting a generally healthy sample, we may have excluded other impulsive subpopulations. An additional limitation is that we did not account for history of moderate to severe traumatic brain injury which, similar to heavy drug use, is an environmental exposure that may increase impulsive personality traits (e.g., Rochat et al., 2010; Wood and McHugh, 2013). However, this is mitigated somewhat by the low base rate of traumatic brain injury in the general population (Roizenbeek et al., 2013) and presumably even lower rate in this selected sample. Furthermore, this study was not designed to test the overlapping heritability between addictive disorders and impulsive personality traits. It will be important for future investigations to test overlapping heritability of impulsive personality traits and addictive disorders (and other disorders of disinhibition) as well as verify the findings from this study in well-powered investigations of healthy samples and samples matched in psychopathology to previous investigations. Our finding that BIS-11 Motor and Non-planning subscales are associated with rs6313 and rs6311 suggest that these SNPs may contribute to intermediate mechanisms (i.e., via impulsive personality traits) that contribute to addictive disorders or other conditions associated with impulsivity, but these links could not be tested directly in this study. Finally, although it was beyond the scope of this study to explore the genetics of other domains of impulsivity (i.e., response inhibition and decision making), these domains are no less relevant to addiction and other disorders of disinhibition (Amlung et al., 2016; Jackson and MacKillop, 2016; Smith et al., 2014) and thus should be explored as well.

Nonetheless, this study makes novel contributions to our understanding of genetic influences on impulsive personality traits, particularly in the support for previously published studies implicating SNPs in *HTR2A*. Future studies with larger sample sizes will be necessary to reveal other associations reliably, but, considering the robust evidence that impulsive personality traits are both associated with a variety of psychiatric conditions and are heritable (Bevilacqua and Goldman, 2013), continued inquiry into its genetic determinants remains an important goal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- A multivariate genetic analysis is applied to impulsive personality traits (IPTs).
- Significant loci within the *HTR2A* gene are identified.
- Doubt is cast on many previously identified candidate loci for IPTs.
- The GWAS results highlight suggestive candidates for future investigation.

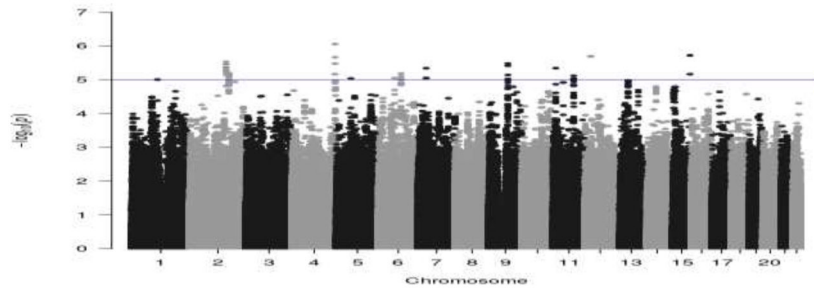


Figure 1. Manhattan plot of genome-wide association for impulsive personality traits multivariate regression models with adjustment for sex, age, and site. Significance values were $-\log_{10}$ transformed in order to display the smaller p -values as larger in the figure. The Manhattan plot displays 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 ($p < 5 \times 10^{-8}$).

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 total, Motor, Non-planning	188	Jiménez, 2014
3	rs334558	GSK3β	G	BIS-11 Attentional total, Motor, Non-planning	185	Jiménez, 2014
5	3' UTR VNTR	DAT1	9-repeat	BIS-11 total	884	Dick, 2013
			9-repeat	BIS-11A total	68	Palolevis, 2010
			--	BIS-11 total	86	Forbes, 2009
			--	BIS-11 total	86	Congdon, 2008
5	rs6295	HTR1A	GG	BIS-11 total, Motor, Attentional Non-planning	724	Benko, 2010
			--	BIS-11 total	687	Varga, 2012
6	rs13212041	HTR1B	AA	BIS-11 total	686	Varga, 2012
6	rs1799971	OPRM1	G	UPPS-P Premeditation	214	Pfeifer, 2015
			--	Negative Urgency, Perseverance		
			--	BIS-11 total	764/	Laas, 2015
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

Chr	Locus	Gene	Risk Allele	Measure	Sample Size	Reference
12	rs2228570	VDR	T*	Latent IPT construct	298	Carver, 2014
			CC	BIS-11 total, Attentional	148 ²	Wrzosek, 2014
13	rs6313	HTR2A	T	Motor, Non-planning	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,	30	Roiser, 2007
				Attentional, Motor, Non-planning; scores		
20	rs3746544-rs1051312	SNAP25	T-T haplotype	lower BIS-11 total IVE-1	869	Németh, 2013
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
X	rs1465108	MAOA	GG	Latent IPT construct	298	Carver, 2014
			A	UPPS-P Negative Urgency	277	Chester, 2015

Note. VNTR = variable number tandem repeat; IPT = impulsive personality traits. Bolding Urgency indicates loci were genotyped (or imputed) and assessed in the current study. 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.

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) ^I

Note.

^IN = 982.

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Table 3

Pearson correlations among impulsive personality traits

Variable	1	2	3	4	5	6
1. Attentional ($\alpha = .70$)	---	---	---	---	---	---
2. Motor ($\alpha = .63$)	.378*	---	---	---	---	---
3. Non-planning ($\alpha = .68$)	.413*	.474*	---	---	---	---
4. Negative Urgency ($\alpha = .87$)	.399*	.296*	.411*	---	---	---
5. Premeditation ($\alpha = .85$)	.313*	.479*	.592*	.307*	---	---
6. Perseverance ($\alpha = .84$)	.440*	.174*	.494*	.357*	.362*	---
7. Positive Urgency ($\alpha = .93$)	.332*	.280*	.344*	.594*	.323*	.275*

Note:

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

Table 4

Associations between *a priori* loci and impulsive personality traits.

Chr	Locus	Gene	Missing	Minor Allele	MAF	P
3	rs1732170	GSK3 β	0	T	.402	.466
5	rs6295	HTR1A	2	C	.497	.878
6	rs13212041	HTR1B	34	C	.216	.914
6	rs1799971	OPRM1	0	G	.127	.957
11	rs6265	BDNF	0	T	.200	.487
11	rs1800497	ANKK1	0	A	.183	.875
12	rs2228570	VDR	0	A	.414	.475
13	rs6313/	HTR2A	0	A	.419	.002
13	rs6311/	HTR2A	7	T	.418	.003
14	rs11624704	NRXN3	0	C	.150	.754
22	rs4680	COMT	0	G	.482	.780
5	rs3814424 ^c	LINC00461	15	T	.170	.229
8	rs6981523 ^d	XKR6	7	C	.460	.542
22	rs9611519 ^d	L3MBTL2/CHADL	1	T	.271	.995

Note.

^f loci are in high LD (i.e., $r^2 = .996$). Bolding of loci indicates significant effects were identified. Follow-up univariate analyses were only conducted for loci with significant multivariate effects.
^{c,d} previously associated with Conscientiousness and Neuroticism, respectively, in recent GWAS (Lo et al., 2016).