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BRIEF REPORT

Allelic variation in dopamine D2 receptor gene is associated with attentional impulsiveness on the Barratt Impulsiveness Scale (BIS-11)

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ABSTRACT

Objectives: Previous studies have postulated that noradrenergic and/or dopaminergic gene variations are likely to underlie individual differences in impulsiveness, however, few have shown this. The current study examined the relationship between catecholamine gene variants and self-reported impulsivity, as measured by the Barratt Impulsiveness Scale (Version 11; BIS-11)

Methods: Six hundred and seventy-seven non-clinical adults completed the Barratt Impulsiveness Scale (BIS-11). DNA was analysed for a set of 142 single-nucleotide polymorphisms (SNPs) across 20 autosomal catecholamine genes. Association was tested using an additive regression model with permutation testing used to control for the influence of multiple comparison.

Results: Analysis revealed an influence of rs4245146 of the dopamine D2 receptor (DRD2) gene on the BIS-11 attention first-order factor, such that self-reported attentional impulsiveness increased in an additive fashion with each copy of the T allele.

Conclusions: These findings provide preliminary evidence that allelic variation in DRD2 may influence impulsiveness by increasing the propensity for attentional lapses.

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DRD2; catecholamine; attention; impulsivity; BIS

Introduction

Impulsivity is a complex construct characterised by a predisposition to respond to internal or external stimuli without forethought or regard of potentially negative consequences (Moeller et al. 2001). Impulsivity is a core symptom of numerous psychiatric disorders, such as ADHD (Kuntsi et al. 2006), personality disorders (Swann et al. 2011) and disorders related to substance use and addiction (Sher et al. 2000; Ersche et al. 2010; Shenassa et al. 2012). It is also a personality trait that exists along a continuum in the general population (Tellegen 1982; Eysenck & Eysenck 1985; Costa & McCrae 1992) where it can be adaptive (Gerbing et al. 1987; Dickman & Meyer 1988; Miller et al. 2004; Vigil-Colet & Morales-Vives 2005) or maladaptive (Mitchell 1999; Slutske et al. 2005; Paaver et al. 2006; Bornovalova et al. 2008; Nilsson et al. 2010).

Impulsiveness has a strong heritable component (Seroczynski et al. 1999; Congdon & Canli 2008; Bezdijan et al. 2011; Fineberg et al. 2014). Studies indicate that genetic variation in the genes encoding biogenic neurotransmitter pathways (serotonergic, dopaminergic and noradrenergic) are an important contributing factor to individual differences in impulsiveness (Robbins 2005; Congdon & Canli 2008; Mitchell & Potenza 2014). It has been hypothesised that impulsiveness arises, in part, from impaired serotonergic and/or catecholaminergic transmission (Levy 1991; Hollander & Rosen 2000; Arnsten & Li 2005; Winstanley 2011). Genetic, pharmacological, animal and neuroimaging studies support this proposal, and emphasise the role of prefrontal and anterior cingulate cortices (Seo et al. 2008; Winstanley 2011; Baarendse & Vanderschuren 2012; Bari & Robbins 2013; Castellanos-Ryan & Séguin 2015). Recruitment of these brain regions is dependent on the localisation and metabolism of monoaminergic neurotransmitters (Congdon & Canli 2008; Mitchell & Potenza 2014). However, despite evidence for the heritability of impulsivity and the role of monoamine systems, the DNA variants that might give rise to individual differences in impulsivity remain largely unknown.

Of those genetic association studies that have been conducted, the majority have focussed on serotonergic

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polymorphisms (Evenden 1999; Carver & Miller 2006; Stanford et al. 2009). These studies have examined the relationship between allelic variations in DNA polymorphisms and self-reports of impulsive behaviour on measures such as the Barratt Impulsiveness Scale (BIS; Patton et al. 1995). The BIS was developed to specifically measure impulsiveness, in contrast to other 'action-oriented' traits such as sensation-seeking, extraversion and risk taking (Barratt, 1985). Its scales are both valid and highly reliable across different populations and settings (see, e.g., Patton et al. 1995). In many cases, significant associations have been identified with BIS total scores and various aspects of the serotonin system. These include polymorphisms of the serotonin transporter gene promoter region (*5-HTTLPR*; Baca-Garcia et al. 2005), the serotonin-2a receptor gene (Bjork et al. 2002), the tryptophan hydroxylase-2 gene (de Lara et al. 2007) and the *HTR1B* receptor gene (Zouk et al. 2007). In addition, significant associations have been identified with BIS scores and genes that catalyse the deamination of monoamines, such as monoamine oxidase A (*MAO-A*; Passamonti et al. 2006; Soeiro-De-Souza et al. 2013). However, not all studies have replicated these results (Paaver et al. 2007; Roiser et al. 2007).

The mixed results yielded in previous studies are likely attributable to a number of factors. For example, vast differences in sample size, age, gender and clinical characteristics, as well as the scope of genes analysed, make direct comparisons across candidate gene studies difficult. In addition, a considerable shortcoming of past studies is that they have evaluated impulsivity as a unitary construct, by analysing and reporting BIS total scores, and have ignored the multidimensional nature of impulsivity.

Eysenck and Eysenck (1977) seminally proposed that impulsivity is not a unitary concept, as once assumed, but rather comprises four factors: narrow impulsiveness, risk-taking, non-planning and liveliness. Barratt (1985) further proposed that impulsiveness comprises three major sub-traits: cognitive, motor and non-planning. Subsequently, Patton and colleagues (1995) suggested six correlated first-order components that subsume the original three second-order components, whereby two first-order components load on each second-order component. The subdomains are as follows: (1) attention: 'focussing on current tasks', subsumes attentional impulsiveness; (2) cognitive instability: 'intruding thoughts', subsumes attentional impulsiveness; (3) motor impulsiveness: 'acting quickly', composes motor impulsiveness; (4) perseverance: 'stable lifestyle', composes motor impulsiveness; (5) cognitive complexity: 'enjoys mental challenges', forms non-planning impulsiveness; and (6) self-control: 'plans and thinks deliberately', forms non-planning impulsiveness. Analysis of these subscales provides important information that would typically be missed by total scores, such as the subtle differences of varying clinical syndromes (Patton et al. 1995). Currently no studies have identified a significant association between BIS scores and noradrenergic gene polymorphisms (Sequeira et al. 2004; Eisenberg et al. 2007; Congdon et al. 2008), and only one has associated a dopaminergic gene polymorphism with this scale (Varga et al. 2012). Varga et al. (2012) reported a significant additive effect of dopaminergic and serotonergic gene variants on trait impulsivity, whereby presence of both the dopamine D4 receptor (DRD4) 7-repeat and *HTR1B* alleles lowered impulsiveness. This is of interest, as substantial pharmacological and metabolite evidence implicates disordered dopamine and noradrenaline neurotransmission in mediating impulsiveness (de Wit et al. 2002; Pattij & Vanderschuren 2008; Swann et al. 2013). Furthermore, lesion studies in animals and functional imaging in humans highlights the role of the nucleus accumbens, an area rich in dopaminergic and noradrenergic innervation and receptors, in impulsivity (Basar et al. 2010). Correspondingly, individuals with clinical disorders marked by altered striatal dopamine receptor levels, such as alcohol dependence (Setiawan et al. 2014), score higher on self-rated measures of impulsivity (Coffey et al. 2003; Mitchell et al. 2005; Lawrence et al. 2009). The limited survey of catecholamine genes in previous studies may account for the lack of genetic associations identified. This paper redresses this shortcoming in the literature.

The present study utilised a large sample of healthy, young adults to evaluate the association between catecholamine gene variation and individual differences in trait impulsivity. As impulsiveness is a multidimensional construct, it was hypothesised that noradrenergic and dopaminergic single-nucleotide polymorphisms (SNPs) would be significantly associated with impulsive behaviour as measured by BIS subscales.

Materials and methods

Participants

Six hundred and seventy-seven right-handed young adult participants of Caucasian descent were recruited from the University of Queensland (UQ), Monash University, and the wider communities of Brisbane and Melbourne, Australia. All reported no history of neurological or psychiatric illness, as well as no regular use of illicit recreational drugs, using a study-specific

questionnaire. All provided informed consent according to the ethical approvals of UQ and Monash University. Participants completed the 30-item Barratt Impulsiveness Scale (Version 11; BIS-11). One participant was excluded from analyses because they gave inconsistent responses. Saliva was collected from each participant with Oragene kits (DNAgenotek, Ottowa). The final sample included 676 individuals (314 males and 361 females; mean age =21.34 years, SD =4.16).

Genetic variant selection

SNPs were selected from autosomal catecholamine genes, namely those that are involved in the synthesis, degradation, transport and receptor signalling of dopamine and noradrenaline (as identified in the KEGG [http://www.genome.jp/kegg/pathway.html] and Gene Ontology [http://www.geneontology.org)] metabolic pathway databases; see Cummins et al. 2014). In total, 143 SNPs on 20 genes were selected.

Genotyping

Genotyping was performed by the Australian Genome Research Facility (AGRF) using iPLEX GOLD chemistry with a Sequenom MassArray on an Autoflex Spectrometer (Sequenom, San Diego, CA, USA).

Genetic association analysis

Permutation methods are considered the gold standard for multiple comparison correction because they provide unbiased control for type 1 error while maintaining statistical power (Berry et al. 2011). Furthermore, permutation methods make no assumption about the shape of the underlying population distribution, and thus are ideally suited for analysing BIS scores which commonly show skewed distributions. Accordingly, a permutation-based analysis was performed separately for each BIS-11 first- and second-order subscale using MATLAB (v. 2008a; http://www.mathworks.com/products/). Full details of this method are provided in the Supplemental Information (see also Cummins et al. 2014; Sham & Purcell, 2014 for further details on 'full-scale' permutation methods).

Results

Genotyping

A quality control process on the genotyping data led to the removal of 38 subjects who were missing more than 10% of their genotypic data. Similarly, SNPs were removed under a quality control process if they were missing more than 3% of their genotypic data. A further four SNPs were removed because they were not suitable for additive regression analysis (rs62388321; rs3730287; rs77943502; rs11568324). All of the remaining SNPs were in Hardy–Weinberg equilibrium (at $P = 0.001$). The remaining sample comprised 637 subjects (289 males and 348 females; mean age =21.42 years, SD =4.19).

Table 1. Descriptive statistics of BIS-11 scores ($N = 637$).

	Minimum	Maximum	M (SD)
First-order factors			
Attention	5	20	10.43 (2.71)
Cognitive instability	3	12	6.15 (1.67)
Motor impulsiveness	0	27	15.00 (3.28)
Perseverance	4	14	7.35 (1.73)
Cognitive complexity	5	19	10.57 (2.37)
Self-control	6	23	12.52 (3.18)
Second-order factors			
Attentional impulsiveness	8	28	16.58 (3.71)
Motor impulsiveness	13	35	22.37 (3.91)
Non-planning impulsiveness	12	37	23.09 (4.62)
Total score	37	94	62.04 (9.77)

M: mean; SD: standard deviation.

Descriptive statistics of BIS-11 scores

Table 1 provides a detailed summary of the descriptive statistics for each of the BIS-11 first- and second-order subscales. Data were highly consistent with those reported by Stanford et al. (2009). As the BIS-11 scores were not normally distributed, we tested for genetic associations using our distribution-free permutation analysis that corrects for multiple related comparisons at the level of genotype (full scale permutation).

Genetic association analyses

Analysis revealed a significant additive association between allelic variation in rs4245146 of the dopamine D2 receptor (DRD2) gene and the BIS-11 attention first-order subscale ($P = 0.034$, partial $\eta^2 = 0.01$); corrected for multiple comparisons at the level of SNP), such that scores on the attention subscale increased in an additive fashion with each copy of the T allele indicative of heightened attentional impulsiveness (See Figure 1). A map showing the LD relations across the DRD2 gene can be found in a supplementary figure available online. Post hoc power calculations indicated that given a true relationship of similar effect size between this SNP and the BIS-11 attention first-order subscale, a replication with sample size of 637 subjects and an alpha value of 0.05 would give 96% power to detect the relationship. No other SNP survived the

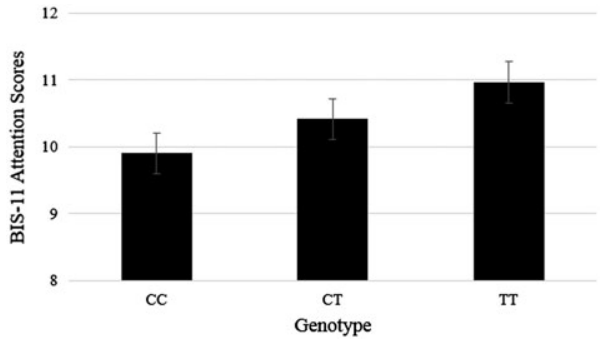

Figure 1. The relationship between BIS-11 attention first-order factor scores and genotype at the DRD2 SNP, rs4245146. Attention scores (mean and standard error) increased additively with increased possession of the T-allele of rs4245146, indicative of greater self-reported problems of attention.

permutation correction across the other first-order factors, any second-order subscales, or total scores. The corrected and uncorrected genetic association results across 137 SNPs for each of the six BIS-11 first-order subscales, and their corresponding minor allele frequencies, are presented in Table 2.

Discussion

Here we investigated the association between catecholamine gene polymorphisms and self-reported impulsiveness within a young adult population. The current study used a large sample size and found a significant, additive association between allelic variation in rs4245146 of DRD2 and the BIS-11 attention first-order subscale. Our results provide evidence that allelic variation in DRD2 may influence the propensity for attentional lapses (i.e., difficulty focussing on current tasks) which may in turn impact impulsiveness.

There is a priori evidence to suspect that allelic variation in DRD2 might predict self-reported measures of attention. Several disorders marked by deficits in attention, such as ADHD and substance-use disorders, have been associated with allelic variation in DRD2. For instance, researchers have suggested that the Taq1A polymorphism may increase an individual's susceptibility to ADHD (Comings et al. 1991; Faraone & Biederman 1998; Paclt et al. 2010). In addition, Rodríguez-Jiménez et al. (2006) found that the A1 allele of the Taq1 polymorphism was associated with poorer sustained attention in individuals with alcohol dependence. Although past studies of attention-related phenotypes have only identified a link with the DRD2 Taq1A SNP (and not other DRD2 SNPs), this is likely a result of the extensive focus on this SNP within psychiatric genetics (Wong et al. 2000; Mitaki et al. 2013). Notably, no prior study has identified an association between the DRD2 gene and variations in self-reported attention within the general population. Thus, the current study extends this literature by identifying that allelic variation in rs4245146 of DRD2 influences attentional impulsiveness in a young adult population, using a self-report measure.

Anxiety-related disorders have been associated with the DRD2 rs4245146 SNP, associated here with self-reported measures of inattention. Specifically, Sipilä et al. (2010) identified that the C-allele of rs4245146 was associated with generalised anxiety disorder, as well as a collective group of anxiety disorders. To our knowledge, the current study is the first to identify an association between rs4245146 and self-reported measures of inattention. Given the novelty of this finding, replication in larger sample sizes is required. Further research should also consider applying a multiple testing correction for the number of BIS subscales examined, as this was a limitation of the current study. In addition, as anxiety has been found to negatively impact attentional control (Forster et al. 2015), future research could investigate the relationship between anxiety, the BIS-11 attention subscale and DRD2 rs4245146.

As with the majority of genetic associations in complex disorders, rs4245146 is mapped to the non-coding region of DRD2 (intron 1). The importance of the non-coding genome in gene regulation has recently been realised (ENCODE Project Consortium 2012). The genome wide annotation of variants (GWAVA) tool (which uses machine learning algorithms to discriminate common control variants from those implicated in diseases) indicates that rs4245146 is potentially functional. Specifically, rs4245146 has a GWAVA-TSS (transcription start site) score of 0.51 (whereby scores of 0.5 are considered 'likely to be functional'). Further, to determine if rs4245146 is likely to affect the binding of *trans*-acting factors (e.g., enhancer and/or transcription bandaging factors), RegulomeDB (a database that identifies DNA features and regulatory elements in non-coding regions of the human genome) shows that rs4245146 maps to the binding sites of polymerase (RNA) II Subunit A (POLR2A), which encodes the largest subunit of RNA polymerase II and Tripartite Motif Containing 28 (TRIM28) that mediates transcriptional control. These findings emphasise the potential importance of rs4245146 in controlling DRD2 expression. However, it is important to note that these bioinformatic predictions require empirical evidence to establish the role of rs4245146 in the control of DRD2 expression.

Table 2. The relationship between catecholamine gene variants and BIS-11 first-order factor scores.

			P value											
Chromosome/ Gene	Marker ID	MAF	$Attn_{UnCorr}$	$Attn_{Corr}$	CI_{UnCorr}	CI_{Corr}	MI_{UnCorr}	MI_{Corr}	$Pers_{UnCorr}$	$Pers_{Corr}$	CC_{UnCorr}	CC_{Corr}	$S\text{-}C_{UnCorr}$	$S\text{-}C_{Corr}$
2/ADRA2B	rs2312955	0.24	0.32	1.00	0.29	1.00	0.16	1.00	0.98	1.00	0.22	1.00	0.34	1.00
3/DRD3	rs3732790	0.29	0.72	1.00	0.91	1.00	0.27	1.00	0.58	1.00	0.07	0.99	0.05	0.93
3/DRD3	rs2134655	0.19	0.89	1.00	0.44	1.00	0.61	1.00	0.50	1.00	0.25	1.00	0.65	1.00
3/DRD3	rs963468	0.29	0.54	1.00	0.96	1.00	0.47	1.00	0.58	1.00	0.05	0.95	0.05	0.94
3/DRD3	rs324036	0.12	0.85	1.00	0.86	1.00	0.62	1.00	0.38	1.00	0.39	1.00	0.46	1.00
3/DRD3	rs167771	0.15	0.78	1.00	0.74	1.00	0.42	1.00	0.12	1.00	0.41	1.00	0.20	1.00
3/DRD3	rs324029	0.24	0.53	1.00	0.13	1.00	0.46	1.00	0.92	1.00	0.41	1.00	0.31	1.00
3/DRD3	rs11706283	0.11	0.50	1.00	0.91	1.00	0.07	1.00	0.33	1.00	0.28	1.00	0.31	1.00
3/DRD3	rs7633291	0.18	0.76	1.00	0.52	1.00	0.36	1.00	0.17	1.00	0.27	1.00	0.67	1.00
3/DRD3	rs6280	0.26	0.34	1.00	0.28	1.00	0.96	1.00	0.70	1.00	0.32	1.00	0.22	1.00
3/DRD3	rs9825563	0.25	0.47	1.00	0.96	1.00	0.68	1.00	0.77	1.00	0.90	1.00	0.77	1.00
3/DRD3	rs17605608	0.18	0.10	1.00	0.28	1.00	0.10	1.00	0.52	1.00	0.35	1.00	0.33	1.00
3/DRD3	rs6762200	0.27	0.84	1.00	0.93	1.00	0.81	1.00	0.59	1.00	0.44	1.00	0.86	1.00
4/DRD5	rs10033951	0.24	0.38	1.00	0.79	1.00	0.45	1.00	0.52	1.00	0.39	1.00	0.63	1.00
4/DRD5	rs1967550	0.27	0.53	1.00	0.45	1.00	0.59	1.00	0.57	1.00	0.58	1.00	0.51	1.00
5/SLC6A3	rs40358	0.12	0.84	1.00	0.48	1.00	0.86	1.00	0.93	1.00	0.86	1.00	0.99	1.00
5/SLC6A3	rs37020	0.29	0.17	1.00	0.71	1.00	0.53	1.00	0.74	1.00	0.23	1.00	0.56	1.00
5/SLC6A3	rs10053602	0.18	0.97	1.00	0.63	1.00	0.10	1.00	0.30	1.00	0.66	1.00	0.52	1.00
5/SLC6A3	rs393795	0.18	0.10	1.00	0.86	1.00	0.47	1.00	0.21	1.00	0.07	1.00	0.95	1.00
5/SLC6A3	rs11737901	0.26	0.27	1.00	0.57	1.00	0.65	1.00	0.94	1.00	0.19	1.00	0.69	1.00
5/SLC6A3	rs460000	0.18	0.20	1.00	0.91	1.00	0.41	1.00	0.16	1.00	0.09	1.00	0.94	1.00
5/ADRB2	rs1042713	0.24	0.49	1.00	0.37	1.00	0.97	1.00	0.26	1.00	0.70	1.00	0.28	1.00
5/ADRB2	rs1042714	0.29	0.67	1.00	0.93	1.00	0.49	1.00	0.31	1.00	0.80	1.00	0.12	1.00
5/ADRA1B	rs2030373	0.19	0.35	1.00	0.24	1.00	0.50	1.00	0.59	1.00	0.94	1.00	0.55	1.00
5/ADRA1B	rs6884105	0.26	0.84	1.00	0.36	1.00	0.98	1.00	0.26	1.00	0.87	1.00	0.70	1.00
5/ADRA1B	rs756275	0.08	0.09	1.00	0.77	1.00	0.23	1.00	0.66	1.00	0.02	1.00	0.08	1.00
5/ADRA1B	rs6892282	0.31	0.80	1.00	0.11	1.00	0.86	1.00	0.53	1.00	0.25	1.00	0.49	1.00
5/ADRA1B	rs6888306	0.21	0.08	1.00	0.24	1.00	0.79	1.00	0.66	1.00	0.03	0.89	0.32	1.00
5/ADRA1B	rs13162302	0.16	0.91	1.00	0.38	1.00	0.78	1.00	0.67	1.00	0.51	1.00	0.93	1.00
5/ADRA1B	rs7737796	0.29	0.56	1.00	0.10	1.00	0.82	1.00	0.48	1.00	0.22	1.00	0.74	1.00
5/ADRA1B	rs17057305	0.13	0.03	1.00	0.27	1.00	0.82	1.00	0.68	1.00	0.05	1.00	0.41	1.00
5/ADRA1B	rs12653825	0.24	0.69	1.00	0.75	1.00	0.50	1.00	0.70	1.00	0.76	1.00	0.48	1.00
5/ADRA1B	rs952037	0.23	0.31	1.00	0.77	1.00	0.36	1.00	0.23	1.00	0.56	1.00	0.91	1.00
5/ADRA1B	rs11953285	0.12	0.20	1.00	0.38	1.00	0.25	1.00	0.24	1.00	0.60	1.00	0.58	1.00
5/DRD1	rs686	0.27	0.11	1.00	0.19	1.00	0.31	1.00	0.66	1.00	0.31	1.00	0.12	1.00
5/DRD1	rs5326	0.11	0.39	1.00	0.66	1.00	0.87	1.00	0.82	1.00	0.13	1.00	0.47	1.00
5/DRD1	rs265981	0.27	0.13	1.00	0.17	1.00	0.35	1.00	0.83	1.00	0.39	1.00	0.12	1.00
7/DDC	rs11575553	0.09	0.62	1.00	0.77	1.00	0.33	1.00	0.31	1.00	0.80	1.00	0.92	1.00
7/DDC	rs11238131	0.25	0.43	1.00	0.53	1.00	0.16	1.00	0.69	1.00	0.43	1.00	0.41	1.00
7/DDC	rs17634958	0.11	0.56	1.00	0.44	1.00	0.38	1.00	0.67	1.00	0.85	1.00	0.52	1.00
7/DDC	rs6592952	0.31	0.61	1.00	0.81	1.00	0.22	1.00	0.41	1.00	0.56	1.00	0.30	1.00
7/DDC	rs3807566	0.30	0.27	1.00	0.92	1.00	0.86	1.00	0.24	1.00	0.81	1.00	0.13	1.00
7/DDC	rs880028	0.18	0.90	1.00	0.62	1.00	0.07	1.00	0.82	1.00	0.88	1.00	0.25	1.00
7/DDC	rs1817074	0.26	0.67	1.00	0.74	1.00	0.00	0.09	0.11	1.00	0.39	1.00	0.18	1.00
7/DDC	rs12535064	0.20	0.69	1.00	0.95	1.00	0.05	0.99	0.26	1.00	0.49	1.00	0.28	1.00
7/DDC	rs3735273	0.20	0.54	1.00	0.76	1.00	0.00	0.61	0.76	1.00	0.91	1.00	0.83	1.00
7/DDC	rs11575334	0.31	0.25	1.00	0.61	1.00	0.33	1.00	0.45	1.00	0.54	1.00	0.57	1.00
7/DDC	rs2329340	0.27	0.77	1.00	0.77	1.00	0.29	1.00	0.55	1.00	0.84	1.00	0.32	1.00
7/DDC	rs10249420	0.20	0.88	1.00	0.81	1.00	0.16	1.00	0.71	1.00	0.81	1.00	0.55	1.00
7/DDC	rs7807335	0.21	0.83	1.00	0.90	1.00	0.28	1.00	0.60	1.00	0.83	1.00	0.54	1.00
7/DDC	rs12666409	0.20	0.96	1.00	0.82	1.00	0.10	1.00	0.55	1.00	0.71	1.00	0.85	1.00
8/ADRA1A	rs1157690	0.15	0.45	1.00	0.84	1.00	0.40	1.00	0.57	1.00	0.83	1.00	0.86	1.00
8/ADRA1A	rs17055923	0.18	0.05	1.00	0.16	1.00	0.92	1.00	0.96	1.00	0.88	1.00	0.49	1.00
8/ADRA1A	rs4732641	0.24	0.75	1.00	0.55	1.00	0.92	1.00	0.42	1.00	0.13	1.00	0.94	1.00
8/ADRA1A	rs1048101	0.28	0.32	1.00	0.51	1.00	0.51	1.00	0.42	1.00	0.28	1.00	0.20	1.00
8/ADRA1A	rs60593443	0.09	0.86	1.00	0.75	1.00	0.26	1.00	0.15	1.00	0.58	1.00	0.53	1.00
8/ADRA1A	rs472151	0.30	0.79	1.00	0.95	1.00	0.27	1.00	0.77	1.00	0.39	1.00	0.21	1.00
8/ADRA1A	rs2322333	0.27	0.26	1.00	0.58	1.00	0.07	0.97	0.29	1.00	0.31	1.00	0.03	0.80
8/ADRA1A	rs10503800	0.23	0.71	1.00	0.94	1.00	0.01	0.43	0.71	1.00	0.38	1.00	0.06	0.99
8/ADRA1A	rs574647	0.23	0.45	1.00	0.65	1.00	0.12	1.00	0.51	1.00	0.70	1.00	0.82	1.00
8/ADRA1A	rs577366	0.20	0.11	1.00	0.87	1.00	0.30	1.00	0.12	1.00	0.15	1.00	0.03	0.99
8/ADRA1A	rs472865	0.11	0.93	1.00	0.31	1.00	0.14	1.00	0.78	1.00	0.92	1.00	0.55	1.00
8/ADRA1A	rs2046186	0.16	0.99	1.00	0.37	1.00	0.00	0.58	0.84	1.00	0.49	1.00	0.10	1.00
8/ADRA1A	rs580739	0.22	0.44	1.00	0.48	1.00	0.31	1.00	0.88	1.00	0.40	1.00	0.68	1.00
8/ADRA1A	rs13274396	0.20	0.99	1.00	0.99	1.00	0.78	1.00	0.42	1.00	0.67	1.00	0.99	1.00
8/ADRA1A	rs563097	0.13	0.43	1.00	0.85	1.00	0.69	1.00	0.80	1.00	0.68	1.00	0.81	1.00
8/ADRA1A	rs528257	0.28	0.70	1.00	0.81	1.00	0.53	1.00	0.84	1.00	0.57	1.00	0.59	1.00
8/ADRA1A	rs3808585	0.22	0.90	1.00	0.71	1.00	0.11	1.00	0.81	1.00	0.79	1.00	0.32	1.00

(*continued*)

Table 2. Continued

			P value											
Chromosome/ Gene	Marker ID	MAF	Attn $_{UnCorr}$	Attn$_{Corr}$	CI$_{UnCorr}$	CI$_{Corr}$	MI$_{UnCorr}$	MI$_{Corr}$	Pers$_{UnCorr}$	Pers$_{Corr}$	CC$_{UnCorr}$	CC$_{Corr}$	S-C$_{UnCorr}$	S-C$_{Corr}$
8/ADRB3	rs9694197	0.09	0.63	1.00	0.14	1.00	0.55	1.00	0.77	1.00	0.89	1.00	0.32	1.00
8/ADRB3	rs4998	0.08	0.84	1.00	0.27	1.00	0.55	1.00	0.80	1.00	0.97	1.00	0.52	1.00
9/DBH	rs1611115	0.17	0.25	1.00	0.40	1.00	0.14	1.00	0.47	1.00	0.89	1.00	0.99	1.00
9/DBH	rs2797849	0.26	0.32	1.00	0.82	1.00	0.67	1.00	0.93	1.00	0.53	1.00	0.77	1.00
9/DBH	rs1548364	0.29	0.73	1.00	0.40	1.00	0.34	1.00	0.22	1.00	0.37	1.00	0.27	1.00
9/DBH	rs2519152	0.30	0.76	1.00	0.66	1.00	0.22	1.00	0.69	1.00	0.44	1.00	0.85	1.00
9/DBH	rs2797853	0.26	0.47	1.00	0.47	1.00	0.42	1.00	0.30	1.00	0.89	1.00	0.77	1.00
9/DBH	rs6479643	0.27	0.78	1.00	0.66	1.00	0.85	1.00	0.76	1.00	0.35	1.00	0.80	1.00
9/DBH	rs77905	0.31	0.75	1.00	0.58	1.00	0.49	1.00	0.75	1.00	0.83	1.00	0.99	1.00
9/DBH	rs10761412	0.26	0.16	1.00	0.92	1.00	0.34	1.00	0.75	1.00	0.71	1.00	0.87	1.00
9/DBH	rs6271	0.08	0.12	1.00	0.70	1.00	0.76	1.00	0.69	1.00	0.69	1.00	0.48	1.00
9/DBH	rs129882	0.17	0.02	0.98	0.19	1.00	0.05	1.00	0.51	1.00	0.78	1.00	0.08	1.00
10/ADRA2A	rs521674	0.22	0.99	1.00	0.21	1.00	0.84	1.00	0.97	1.00	0.43	1.00	0.60	1.00
10/ADRA2A	rs1800544	0.22	0.90	1.00	0.24	1.00	0.96	1.00	0.84	1.00	0.49	1.00	0.65	1.00
10/ADRA2A	rs11195419	0.12	0.30	1.00	0.25	1.00	0.99	1.00	0.79	1.00	0.36	1.00	0.66	1.00
10/ADRA2A	rs602618	0.23	0.73	1.00	0.33	1.00	0.82	1.00	0.94	1.00	0.40	1.00	0.64	1.00
10/ADRB1	rs3813720	0.27	0.67	1.00	0.81	1.00	0.88	1.00	0.60	1.00	0.04	0.88	0.70	1.00
11/DRD4	rs3758653	0.14	0.68	1.00	0.97	1.00	0.56	1.00	0.14	1.00	0.28	1.00	0.76	1.00
11/DRD4	rs11246226	0.30	0.01	0.23	0.20	1.00	0.02	0.57	0.20	1.00	0.32	1.00	0.63	1.00
11/DRD4	rs7395429	0.30	0.01	0.31	0.20	1.00	0.04	0.82	0.28	1.00	0.27	1.00	0.47	1.00
11/TH	rs3842727	0.25	0.89	1.00	0.24	1.00	0.28	1.00	0.20	1.00	0.85	1.00	0.56	1.00
11/TH	rs2070762	0.30	0.64	1.00	0.17	1.00	0.47	1.00	0.91	1.00	0.27	1.00	0.36	1.00
11/TH	rs7483056	0.28	0.53	1.00	0.20	1.00	0.19	1.00	0.53	1.00	0.18	1.00	0.70	1.00
11/TH	rs6356	0.26	0.24	1.00	0.03	0.88	0.20	1.00	0.13	1.00	0.69	1.00	0.38	1.00
11/TH	rs10840489	0.13	0.26	1.00	0.44	1.00	0.46	1.00	0.65	1.00	0.62	1.00	0.78	1.00
11/ANKK1	rs10891545	0.13	0.43	1.00	0.05	1.00	0.50	1.00	0.94	1.00	0.40	1.00	0.90	1.00
11/ANKK1	rs17115439	0.24	0.76	1.00	0.85	1.00	0.91	1.00	0.72	1.00	0.93	1.00	0.66	1.00
11/ANKK1	rs7118900	0.16	0.66	1.00	0.55	1.00	0.50	1.00	0.13	1.00	0.05	1.00	0.57	1.00
11/ANKK1	rs2734849	0.30	0.66	1.00	0.93	1.00	0.85	1.00	0.98	1.00	0.92	1.00	0.90	1.00
11/ANKK1	rs1800497	0.17	0.57	1.00	0.50	1.00	0.53	1.00	0.15	1.00	0.15	1.00	0.55	1.00
11/DRD2	rs6279	0.23	0.96	1.00	0.40	1.00	0.42	1.00	0.25	1.00	0.22	1.00	0.55	1.00
11/DRD2	rs1076560	0.14	0.63	1.00	0.97	1.00	0.18	1.00	0.29	1.00	0.73	1.00	0.76	1.00
11/DRD2	rs2283265	0.14	0.51	1.00	0.90	1.00	0.20	1.00	0.53	1.00	0.72	1.00	0.76	1.00
11/DRD2	rs2440390	0.11	0.56	1.00	0.32	1.00	0.29	1.00	0.97	1.00	0.95	1.00	0.26	1.00
11/DRD2	rs2471851	0.14	0.56	1.00	0.97	1.00	0.30	1.00	0.48	1.00	0.84	1.00	0.68	1.00
11/DRD2	rs12364051	0.27	0.55	1.00	0.16	1.00	0.82	1.00	0.81	1.00	0.50	1.00	0.45	1.00
11/DRD2	rs17115583	0.10	0.63	1.00	0.37	1.00	0.40	1.00	0.64	1.00	0.20	1.00	0.50	1.00
11/DRD2	rs4245146	0.31	0.001*	0.03*	0.28	1.00	0.61	1.00	0.94	1.00	0.20	1.00	0.77	1.00
11/DRD2	rs4460839	0.11	0.39	1.00	0.01	1.00	0.40	1.00	0.39	1.00	0.88	1.00	0.02	1.00
11/DRD2	rs7131056	0.29	0.41	1.00	0.29	1.00	0.27	1.00	0.61	1.00	0.46	1.00	0.06	0.97
11/DRD2	rs4350392	0.11	0.59	1.00	0.58	1.00	0.74	1.00	0.12	1.00	0.81	1.00	0.16	1.00
16/SLC6A2	rs2397771	0.28	0.05	0.94	0.42	1.00	0.21	1.00	0.33	1.00	0.07	0.99	0.97	1.00
16/SLC6A2	rs3785143	0.08	0.01	1.00	0.14	1.00	0.48	1.00	0.48	1.00	0.92	1.00	0.51	1.00
16/SLC6A2	rs36024	0.27	0.45	1.00	0.47	1.00	0.31	1.00	0.04	0.82	0.13	1.00	0.88	1.00
16/SLC6A2	rs36021	0.29	0.49	1.00	0.45	1.00	0.58	1.00	0.50	1.00	0.82	1.00	0.76	1.00
16/SLC6A2	rs36017	0.31	0.35	1.00	0.28	1.00	0.63	1.00	0.99	1.00	0.26	1.00	0.94	1.00
16/SLC6A2	rs1345429	0.32	0.27	1.00	0.30	1.00	0.81	1.00	0.95	1.00	0.16	1.00	0.81	1.00
16/SLC6A2	rs3785157	0.25	0.34	1.00	0.74	1.00	0.50	1.00	0.68	1.00	0.01	0.48	0.24	1.00
16/SLC6A2	rs5568	0.25	0.15	1.00	0.02	0.74	0.94	1.00	0.33	1.00	0.03	0.91	0.25	1.00
16/SLC6A2	rs8047672	0.16	0.90	1.00	0.66	1.00	0.48	1.00	0.66	1.00	0.08	1.00	0.05	1.00
16/SLC6A2	rs36009	0.09	0.09	1.00	0.10	1.00	0.90	1.00	0.07	1.00	0.52	1.00	0.05	1.00
16/SLC6A2	rs1800887	0.19	0.61	1.00	0.62	1.00	0.40	1.00	0.84	1.00	0.08	1.00	0.27	1.00
16/SLC6A2	rs8049681	0.14	1.00	1.00	0.74	1.00	0.99	1.00	0.20	1.00	0.11	1.00	0.24	1.00
16/SLC6A2	rs2242447	0.25	0.14	1.00	0.41	1.00	0.61	1.00	0.11	1.00	0.23	1.00	0.83	1.00
16/SLC6A2	rs7194256	0.14	0.92	1.00	0.70	1.00	1.00	1.00	0.19	1.00	0.11	1.00	0.25	1.00
16/SLC6A2	rs9930182	0.19	0.57	1.00	0.68	1.00	0.65	1.00	0.77	1.00	0.12	1.00	0.36	1.00
20/ADRA1D	rs8183794	0.16	0.85	1.00	0.38	1.00	0.55	1.00	0.08	1.00	0.04	1.00	0.94	1.00
20/ADRA1D	rs6116268	0.31	0.94	1.00	0.38	1.00	0.24	1.00	0.24	1.00	0.57	1.00	0.62	1.00
20/ADRA1D	rs1556832	0.30	1.00	1.00	0.54	1.00	0.29	1.00	0.21	1.00	0.63	1.00	0.31	1.00
20/ADRA1D	rs8118409	0.20	0.98	1.00	0.98	1.00	0.55	1.00	0.79	1.00	0.26	1.00	0.74	1.00
20/ADRA1D	rs4815670	0.30	0.42	1.00	0.96	1.00	0.40	1.00	0.59	1.00	0.89	1.00	0.07	0.98
20/ADRA1D	rs6133098	0.22	0.28	1.00	0.92	1.00	0.71	1.00	0.02	0.89	0.20	1.00	0.16	1.00
20/ADRA1D	rs6084670	0.20	0.59	1.00	0.69	1.00	0.36	1.00	0.39	1.00	0.91	1.00	0.85	1.00
20/ADRA1D	rs3787442	0.30	0.16	1.00	0.74	1.00	0.51	1.00	0.02	0.71	0.03	0.83	0.21	1.00
20/ADRA1D	rs6052456	0.18	0.14	1.00	0.64	1.00	0.96	1.00	0.83	1.00	0.63	1.00	0.85	1.00
22/COMT	rs737866	0.23	0.01	0.71	0.63	1.00	0.98	1.00	0.72	1.00	0.12	1.00	0.20	1.00
22/COMT	rs740603	0.31	0.23	1.00	0.35	1.00	0.09	0.99	0.71	1.00	0.27	1.00	0.83	1.00
22/COMT	rs4680	0.31	0.23	1.00	0.40	1.00	1.00	1.00	0.88	1.00	0.89	1.00	0.56	1.00
22/COMT	rs9332377	0.13	0.05	1.00	0.63	1.00	0.71	1.00	0.42	1.00	0.96	1.00	0.39	1.00

BIS-11: Barratt's Impulsiveness Scale, 11th version; MAF: minor allele frequency; Attn: attention; CI: cognitive instability; MI: motor impulsiveness; pers: perseverance; CC: cognitive complexity; S-C: self-control; UnCorr: uncorrected; Corr: corrected;.

*Significant *P* value, $\alpha = 0.05$.

This study had a number of limitations. First, the cohort had a mean age of 21.4 years (SD = 4.16) and is therefore best described as a young-adult population. Arguably, since maturation of brain regions underlying impulsivity, such as the prefrontal cortex, is ongoing across this age range, then this may have actually enhanced the sensitivity of our study to detect genetic influences on impulsivity. Future studies should assess whether the relationships identified here hold in adolescence or later adulthood. Second, since data were collected at two different sites, one could question the comparability of data across sites. A statistically significant difference between sites was observed for only one of the ten variables studied (motor impulsivity, first order) and was of small effect size (Cohens $d = 0.26$) (see Supplemental Table available online). We therefore suggest that site-related differences minimally impacted our results. Third, given recruitment from University student populations as well as the general community, our study results may not generalise to broader population bases or to clinical cohorts marked by high levels of impulsivity. Nevertheless, if anything, such influences should have truncated the distributions of impulsivity scores in our study and negatively impacted our ability to detect genetic associations. We acknowledge however, that replication in population-based samples of young adults would be desirable.

In summary, this study provided evidence that allelic variation in rs4245146 of DRD2 predicts self-reported attentiveness, a key aspect of impulsiveness. Future studies should examine the functional impact of DRD2 gene variants on attentional impulsiveness across development and in the context of clinical disorders of attention, such as ADHD.

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