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The Dopamine D_3 Receptor Gene and Posttraumatic Stress Disorder

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Abstract

The dopamine D_3 receptor (*DRD3*) gene has been implicated in schizophrenia, autism, and substance use-disorders and is related to emotion reactivity, executive functioning, and stress-responding, processes impaired in posttraumatic stress disorder (PTSD). This aim of this candidate gene study was to evaluate *DRD3* polymorphisms for association with PTSD. The discovery sample was trauma-exposed white, non-Hispanic veterans and their trauma-exposed intimate partners (N = 491); 60% met criteria for lifetime PTSD. The replication sample was 601 trauma-exposed African American participants; 24% met criteria for lifetime PTSD. Genotyping was based on high-density bead chips. In the discovery sample, four single nucleotide polymorphisms (SNPs), rs2134655, rs201252087, rs4646996, and rs9868039, showed evidence of association with PTSD and withstood correction for multiple testing. The minor alleles were associated with reduced risk for PTSD (odds ratio range: 0.59 – 0.69). In the replication sample, rs2251177, located 149 base pairs away from the most significant SNP in the discovery sample, was nominally associated with PTSD in men (odds ratio: 0.32). Although the precise role of the D_3 receptor in PTSD is not yet known, its role in executive functioning and emotional reactivity, and the sensitivity of the dopamine system to environmental stressors, could potentially explain this association.

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Keywords

Dopamine receptor; DRD3; posttraumatic stress disorder; molecular genetics

The dopamine system is involved in incentive/reward motivation (Beninger, 1983; Berridge & Robinson, 1998), motor control, and impulsivity (Dalley et al., 2007) and has been linked to the pathophysiology of substance-related disorders (Heidbreder et al., 2005; Pierce & Kumaresan, 2006), depression (Weiss et al., 1981), schizophrenia, and response to anti-psychotic drugs (Schwartz et al., 2000). The functioning of the dopamine system is thought to be affected by environmental stressors, and this sensitivity may help explain the link between life stress and onset of psychotic symptoms (Furuyashiki, 2012). There are two main types of dopamine receptors: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4); the former has stimulatory effects and the latter is inhibitory. The D_3 receptor has particular relevance to psychiatric phenotypes because it is expressed in brain regions thought to govern emotion and emotional responses to stress, reward motivation, and executive function (Sokoloff et al., 1990), such as the nucleus accumbens, and, to a lesser extent, the anterior cingulate gyrus, amygdala, and hippocampus (Gurevich & Joyce, 1999; Pennartz et al., 1994). The D_3 receptor has been associated with startle reactivity (Halberstadt & Geyer, 2009), sensorimotor gating (Bristow et al., 1996; Giakoumaki et al., 2007; Swerdlow et al., 2009), memory, social recognition and responding (Loiseau & Millan, 2009; Watson et al., 2012), and cognitive impairment (Millan et al., 2010).

Prior research suggests that the dopamine D_3 receptor gene (*DRD3*) may play a role in the etiology of a wide range of psychopathology including schizophrenia (Crocq et al., 1992; Dominguez et al., 2007; Ishiguro et al., 2000; Kennedy et al., 1995; Talkowski et al., 2006; Williams et al., 1998; Zhang et al., 2011), autism spectrum disorders (de Krom et al., 2009; Staal & de Krom, 2012), alcohol craving (Agrawal et al., 2013), nicotine dependence (Wei et al., 2012), depression (Dikeos et al., 1999), impulsivity among violent offenders (Retz et al., 2003), and obsessive-compulsive personality disorder (Light et al., 2006). The association between *DRD3* and multiple psychiatric disorders is consistent with the finding that genes exert shared effects across mental disorders (Smoller et al., 2013); this suggests the importance of evaluating genes shown to have association with one psychiatric phenotype in other psychiatric populations.

The D_3 receptor's relationship to psychiatric impairment may be mediated by the receptor's role in stimulus and stressor-related social learning, memory, executive functioning, and emotional reactivity. These processes are particularly relevant to posttraumatic stress disorder (PTSD) as the disorder is typified by heightened fear responsivity to stressors (e.g., hyperarousal symptoms, emotional reactivity to trauma cues) and executive function deficits (e.g., concentration problems, difficulty regulating anger and other emotions). Given this, we sought to conduct the first candidate gene study of the association between *DRD3* and PTSD using data from a sample of 491 white, non-Hispanic, trauma-exposed military veterans and their cohabitating trauma-exposed intimate partners and an independent replication sample of 601 trauma-exposed African American men and women who participated in the Detroit Neighborhood Health Study (Goldmann et al., 2011). Given prior

evidence for sex differences in the prevalence of PTSD (Kessler et al., 1995), and genetic work suggesting that *DRD3* may be related to alcohol dependence in men but not women (Wodarz et al., 2003), we also evaluated if sex moderated the association between *DRD3* and PTSD.

Methods

Discovery Sample Participants

The complete discovery sample included 852 veterans and their intimate partners who participated in one of two research studies. Ancestry was determined with the program STRUCTURE, which performs a Bayesian clustering analysis to assign subjects to ancestry groups, using 10,000 randomly chosen markers with minor allele frequency (MAF) > .05 (Falush et al., 2003; Pritchard et al., 2000). This process identified three groups, the largest of which was 540 participants who self-identified as white non-Hispanic. This study was based on 491 of them (364 veterans and 127 non-veteran partners) who reported lifetime exposure to a traumatic event and had valid lifetime PTSD interview data. Trauma exposure histories as a function of sex are detailed in Wolf et al., (2013): men and women did not differ in total trauma exposure but men were more likely to report combat exposure and women more likely to report sexual trauma. There was no evidence of PTSD-associated population substructure in this sample (Logue et al., 2012). The majority of participants were male (65%), and the mean age was 51.95 years (range: 21 – 75). In this sample, 60.29% (n = 296, comprised of 251 veterans and 45 non-veteran partners) met *DSM-IV* diagnostic criteria for lifetime PTSD. In Logue et al. (2012), we also presented results of an African American subset of the VA sample (n = 84). We do not present results of this subsample here, as there was no evidence for association between *DRD3* and PTSD, and this null effect could not be interpreted given the low power associated with such a small sample.

Measures

Clinician Administered PTSD Scale (CAPS; Blake et al., 1995)—The CAPS assesses the 17 *DSM-IV* PTSD symptoms on frequency and intensity scales (each ranging from 0-4). PTSD diagnosis was calculated using a commonly-used and validated scoring rule (Weathers et al., 1999) which required endorsement of at least 1 reexperiencing, 3 avoidance and numbing, and 2 hyperarousal symptoms, each at a frequency of 1 or greater and an intensity of 2 or greater. Inter-rater reliability for lifetime diagnosis, as determined by a second rater making independent ratings from videotaped recordings of approximately 25% of the total participant interviews was excellent (κ = .87).

Traumatic Life Events Questionnaire (TLEQ; Kubany et al., 2000)—The TLEQ is a self-report instrument that assesses history of exposure to 22 different types of traumatic experiences that meet the *DSM-IV* PTSD Criterion A1. The measure also assesses whether the experience met Criterion A2 and asks the respondent to indicate the number of times each event occurred on a 7-point scale ranging from “never” to “more than five times.” The TLEQ has shown good test-retest reliability and predictive validity with respect to PTSD diagnoses (Kubany et al., 2000).

Procedure

Participants completed one of two research protocols with identical interview assessment procedures and the data from the two studies were combined for these analyses. One study recruited trauma-exposed military veterans and their cohabitating intimate partners; the other recruited trauma-exposed military veterans who screened positive for PTSD over the telephone. Both studies included comprehensive structured diagnostic interviews of all participants that were digitally videotaped for purposes of quality control and evaluating inter-rater reliability. The studies were approved and reviewed annually by the appropriate institutional review boards. Additional procedural details are provided in Logue et al. (2012).

Genotyping

DNA was isolated from peripheral blood samples on a Qiagen AutoPure instrument with Qiagen reagents and samples normalized using PicoGreen assays (Invitrogen). Samples were run on an Illumina OMNI 2.5-8 array and scanned using an Illumina HiScan System according to the manufacturer's protocol. Details of the quality control procedure are described in detail elsewhere (Logue et al., 2012). We restricted our attention to the 26 *DRD3* single nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) greater than 5%. None of these SNPs failed a test of Hardy-Weinberg Equilibrium (i.e., all $p > .01$). *DRD3* is located on chromosome 3 and spans 70,756 bases between 113,847,499 and 113,918,254 base pair (bp); SNP locations were derived from the hg19 human-genome assembly (February 2009).

Data Analyses

SNPs in *DRD3* were examined for association with lifetime PTSD diagnosis using the standard χ^2 case/control test of association in PLINK; this is an allelic test which compares the frequency of the minor allele in cases and controls under the assumption of an additive model (Purcell et al., 2007). We corrected for multiple-testing across the gene using the MAX(T) permutation procedure with 5000 replications. We also stratified the sample by sex and ran the same analysis to evaluate potential sex differences and used the PLINK logistic regression test to evaluate if any of the SNPs interacted with sex. Linkage disequilibrium (LD) was evaluated using the program Haploview (Barrett et al., 2005).

Replication Sample

The replication sample comprised 601 trauma-exposed African American (per self-report and confirmed by multidimensional scaling analysis of genome-wide SNP data in PLINK) men and women living in Detroit, MI who participated in one of three waves of data collection in the Detroit Neighborhood Health Study (additional details provided in Goldmann et al., 2011; Logue et al., 2012; Uddin et al., 2010). The sample we evaluated was predominately female (57%), and the mean age was 52.59 years (range: 18 – 95 years). Participants had been exposed to one or more traumas (see Breslau et al., 1998). Twenty-four percent ($n = 142$) met criteria for lifetime PTSD as determined by structured interview administered over the telephone. The interview, using the PTSD Checklist, assessed the extent to which participants had been bothered by each of the 17 *DSM-IV* PTSD symptoms

on a 1 to 5 scale (Weathers et al., 1993) in relation to a specific, stressful event. To meet criteria for the diagnosis, participants had to endorse *DSM-IV* PTSD Criteria A1 and A2, at least one reexperiencing, three avoidance and numbing, and two hyperarousal symptoms, each at a symptom rating of three ("moderately") or higher, and endorse clinically significant impairment in functioning. In addition, the diagnosis required that the symptoms were present for at least a month. DNA was extracted from whole blood or saliva and evaluated on an Illumina HumanOmniExpress BeadChip. We evaluated all *DRD3* SNPs available on this chip; 11 of these overlapped the SNPs evaluated in the discovery sample. The analytic approach paralleled those in the discovery sample.

Results

Discovery Sample

Main effects—Six of the 26 SNPs in *DRD3* showed nominal evidence of association ($p < .05$) with lifetime PTSD (see Table 1 and Figure 1). Four of these withstood correction for multiple testing: rs2134655, rs201252087, rs4646996, and rs9868039, with corrected *p*-values ranging from .005 to .049 (see Table 1). For each of these SNPs, the minor allele was less common among individuals with PTSD, suggesting a protective effect against risk for PTSD (odds ratios [ORs] ranged from 0.59 - 0.69; see Table 1). These four SNPs were in high LD with each other (see Table 2). Secondary data analyses revealed that results for these four SNPs were unchanged when we controlled for total trauma exposure and when we controlled for the non-independence of the 116 couples included in the analyses using a sandwich estimator to adjust the standard errors in Mplus 7.11 (Muthén & Muthén, 2012). The prevalence of lifetime PTSD among participants with one copy of the protective allele on rs2134655 (the most significant SNP) was 33%; it was 62% for those with no copies of the minor allele (there were no participants with two copies of the minor allele).

SNP by sex effects—We next evaluated these associations in men and women separately. In men ($n = 339$), the same six SNPs that were nominally significant in the full sample again showed nominally significant associations with PTSD. One of these (rs201252087) withstood correction for multiple testing (OR = .60, uncorrected $p = .003$, corrected $p = .04$). In women ($n = 215$), that same SNP (rs201252087) was not significantly associated with PTSD (OR = .69, uncorrected $p = .10$, corrected $p = .57$). Only one SNP (rs2134655) showed a nominally significant association with PTSD in women, but it did not withstand multiple testing correction (OR = .59, uncorrected $p = .03$, corrected $p = .23$); that SNP also evidenced a nominally significant association in the male subsample that did not withstand permutation testing (OR = .61, uncorrected $p = .010$, corrected $p = .10$). There was no evidence for a SNP × Sex interaction for rs201252087, as evaluated by a formal interaction test performed in PLINK (interaction term $p = .67$, smallest p for any of the other SNP × Sex interaction terms = .21). Given that men were more often exposed to combat and women more often exposed to sexual assault (see Wolf et al., in press), we conducted secondary analyses to determine if the *potential* differential strength of association between the SNPs and PTSD as a function of sex was actually attributable to these exposure variables instead. We found no evidence of SNP interactions with sexual assault history or combat exposure.

Replication Sample

The four SNPs showing evidence of association with PTSD in the discovery sample (rs2134655, rs201252087, rs4646996, and rs9868039) were not on the SNP array used in the replication sample. Of the 23 SNPs available for analysis, only rs9828046 and rs2251177 were located in close physical proximity (< 150 bp) to rs2134655, the most strongly associated SNP from the discovery sample. None of the SNPs in the replication sample evidenced a significant association with PTSD in the full sample; however, one SNP, rs2251177 located at 113,858,350 bp, just failed to meet the threshold for a nominal association (OR = 0.67, uncorrected p = .06, corrected p = .60; see Table 1). The prevalence of PTSD among those with two copies of the minor allele at this location was 21.4%; it was 17.3% for those with one copy and 25.7% for those with no copies. This SNP is 149 bp away from the most significant SNP identified in the discovery sample (rs2134655) and 3,239 bp away from the second most significant SNP identified in the discovery sample (rs201252087). Secondary data analyses controlling for trauma exposure revealed that this association became non-significant in the full sample (OR= .69, p = .11). We also stratified this sample by sex and evaluated the SNPs separately for men (n = 257) and women (n = 344). In the men, the G allele of rs2251177 showed evidence of a nominally significant association with PTSD (OR = 0.32, uncorrected p = .01) although the corrected p-value after permutation testing was.17. This SNP remained nominally significant when controlling for trauma (OR = .35, uncorrected p = .03). None of the SNPs were significant in the female subsample (association result for rs2251177: OR = 0.86, uncorrected p = .54, corrected p = . 1.0). The test of the SNP × Sex interaction for rs2251177 failed to reach statistical significance (p = .09); none of the other SNPs evidenced a significant SNP × Sex interaction. We were unable to test for SNP interactions with trauma type in this sample as we did not have data on specific trauma types.

Discussion

DRD3 has previously been associated with a broad range of psychiatric disorders and the receptor encoded by the gene is important for executive functioning, emotional reactivity, and responding to environmental stressors. Given this, we examined the gene in relationship to PTSD. In our discovery sample of white, non-Hispanic trauma-exposed veterans and their spouses, four SNPs (rs2134655, rs201252087, rs4646996, and rs9868039) were associated with lifetime PTSD after adjustment for multiple testing. In an independent sample of trauma-exposed African Americans, one SNP (rs2251177), in close physical proximity to the most significant SNP identified in the discovery sample (rs2134655), evidenced a nominally significant association with PTSD in the male subsample; this same SNP just failed to meet the threshold for a nominal association with PTSD in the full replication sample. The minor alleles of these SNPs were protective against risk for PTSD, given trauma exposure. We would not expect rs2134655 (the most significant SNP identified in the discovery sample) to be significant in the replication sample because of differences in the MAF across Caucasian and African American populations (27% versus 6%, respectively, per the International HapMap Project). Similarly, we would not expect rs2251177 (the most significant SNP identified in the replication sample) to be significant in the discovery sample because that SNP is monomorphic (i.e., invariant) among the

Caucasian population. Nevertheless, the physical proximity of these two SNPs across the two samples *may* suggest that a single risk locus in this region of *DRD3* is implicated in risk for PTSD (i.e., these SNPs may be markers for the same functional variant).

The SNP that showed the strongest association with PTSD in the discovery sample (rs2134655) has also been implicated in prior work with other psychiatric disorders. In a study of white individuals living in the United States, it was nominally associated with schizophrenia (Talkowski et al., 2006) and, in samples of European ancestry, this SNP was part of a haplotype block associated with risk for schizophrenia with the T allele protective (Costas et al., 2009). That effect was consistent with the direction of effect in this study.

Other SNPs associated with PTSD in this study have been shown to be related to other psychiatric phenotypes. For example, rs9817063, which was nominally associated with PTSD in the discovery sample, was nominally associated with activity in the ventral striatum (as assessed via functional magnetic resonance imaging) and with treatment response to electroconvulsive therapy for depression (Dannlowski et al., 2011). In addition, rs963468, which just failed to meet the corrected *p*-value threshold for statistical significance in the discovery sample, was implicated as part of a haplotype block in risk for schizophrenia (Nunokawa et al., 2010) and also showed a nominal association with nicotine dependence (Huang et al., 2008).

The precise role of the D_3 receptors in PTSD and associated disorders has not yet been elucidated, but the available evidence suggests it plays a role in at least two processes of relevance to PTSD: amygdala-mediated fear and anxiety processes and executive functioning. The receptor has been shown to be upregulated in basal, central, and lateral amygdaloid nuclei in individuals with depression (Klimek et al., 2002) and also appears to mediate anxiety following a social stressor (Hood et al., 2010). Imaging studies suggested that increased D_2 and D_3 receptor availability in prefrontal regions was associated with greater amgydala response to unpleasant images (Kobiella et al., 2009). Similarly, in animal models, the D_3 receptor plays a role in behavioral responding to stressors (Xi et al., 2004). These studies have relevance to PTSD as imaging research implicates enhanced amygdala activation and fear responding in PTSD (Patel et al., 2012). Moreover, heightened negative emotional reactivity to trauma cues, anger, and hypervigilance are symptoms of PTSD that may be related to the functioning of the D_3 receptors in the limbic brain regions governing emotional arousal and reactivity.

The prefrontal cortex and D_3 receptor also play a role in working memory and executive function (Black et al., 2002). Evidence for this comes from research suggesting that D_3 antagonists are potential therapeutic agents for the treatment of the cognitive dysfunction and confusion common to psychosis (Joyce & Millan, 2005) and from work showing the role of D_3 receptors in working memory (Ersche et al., 2011). Moreover, the Ser9Gly *DRD3* polymorphism has been shown to be associated with perseverative errors (Lane et al., 2008) as well as with other indices of executive functioning (Bombin et al., 2008). PTSD also is associated with executive function deficits (Polak et al., 2012), decreased activation of pre-frontal brain regions (Patel et al., 2012), and impaired concentration. Together, this raises

the possibility that dysfunction at the site of D_3 receptors at least partially accounts for the cognitive deficits seen in PTSD. More research is needed to directly test this possibility.

Finally, prior research suggests that the D_3 receptors function differently in men compared to women. In one study, men expressed greater amounts of dopamine in striatal brain regions following exposure to amphetamine (Munro et al., 2006). D_2/D_3 receptor availability was also shown to confer risk for nicotine dependence in men but not women (Brown et al., 2012) and may be more strongly associated with the positive symptoms of schizophrenia in men compared to women (Glenthoj et al., 2006). Sex-specific effects of the gene have also been reported previously: the BA1I *DRD3* polymorphism was associated with alcohol dependence among men, but not women, with a history of delirium tremens (Wodarz et al., 2003). In this study, we did not find evidence of statistically significant genotype by sex interactions; this issue would benefit from further investigation in larger samples that are adequately powered to detect potential interactive and sex-specific effects.

Limitations and Conclusions

Limitations of the study include the relatively small sample size for genetic association analysis and the inability to compare the exact same polymorphisms across the discovery and replication samples. It is difficult to conduct comparisons across different racial and ethnic groups due to differences in genetic variation (i.e., MAF) across these groups, thus our replication sample was not ideal for confirming results observed in the discovery sample. We were also unable to disentangle the potential effects of sex from those of trauma exposure history; moreover, we were under-powered to detect sex-specific effects thus our findings with respect to potential sex differences should be interpreted with caution and considered preliminary. In addition, we have previously reported results of a genome-wide genetic association study (i.e., an atheoretical, empirical test) with PTSD (Logue et al., 2012) in this sample and that study did not find an effect for *DRD3* when genome-wide association standards (i.e., $p < 5 \times 10^{-8}$) were applied; however we think it is important to conduct a hypothesis-driven candidate gene study as this may identify weaker effects attributable only to a subset of the population that would otherwise be missed in genome-wide scans. This is the first study to report an association between *DRD3* and PTSD and, as such, additional replication is needed.

In conclusion, the results of this study provide initial evidence that polymorphisms in *DRD3*, perhaps reflecting a single risk locus, may be associated with lifetime PTSD diagnosis. The findings are consistent with the results of prior genetic research on other psychiatric phenotypes and with studies of the role of the D_3 receptor in emotional reactivity and executive functioning. The relationship between *DRD3* and PTSD may also be a reflection of the sensitivity of the dopamine system to stress.

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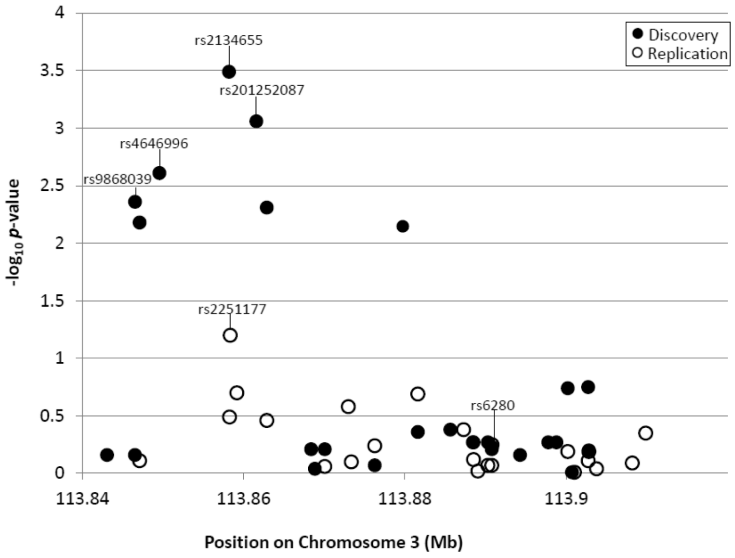

Figure 1.

The figure shows the nominal (uncorrected) *p*-values (in $-\log_{10}$) at each base pair location for all SNPs evaluated for association with PTSD in the discovery (filled circles) and replication (open circles) samples. The four SNPs that were significant after permutation testing in the discovery sample and the most significant SNP in the replication sample are identified, as is rs6280, a commonly studied *DRD3* polymorphism.

Table 1

SNPs in DRD3 (Chromosome 3) with at Least Nominal Evidence of Association with Lifetime PTSD in the Discovery and/or Replication Samples

Sample	SNP	bp	Minor Allele	Freq Aff	Freq Unaff	OR	*p* (uncorrected)	*p* (corrected)
D	**rs9868039**	**113846542**	**A**	**0.41**	**0.50**	**0.6883**	**0.004**	**0.049**
D	rs9817063	113847108	G	0.53	0.44	1.427	0.007	0.07
D	**rs4646996**	**113849565**	**A**	**0.44**	**0.54**	**0.6724**	**0.002**	**0.03**
D	**rs2134655**	**113858201**	**A**	**0.28**	**0.32**	**0.5907**	**0.0003**	**0.005**
R	rs2251177	113858350	G	0.11	0.15	0.6733	0.06	0.60
D	**rs201252087**	**113861589**	**G**	**0.38**	**0.48**	**0.6447**	**0.0009**	**0.013**
D	rs963468	113862887	A	0.45	0.36	1.457	0.005	0.051

Note. *DRD3* = dopamine receptor D3; PTSD = posttraumatic stress disorder; SNP = single nucleotide polymorphism; D = discovery sample; R = replication sample; bp = base pair; freq = frequency; aff = affected; unaff = unaffected; OR = odds ratio. SNPs that were significant after permutation testing are highlighted in bold font.

Table 2

Linkage Disequilibrium among the Four DRD3 SNPs showing the Strongest Association with PTSD in the Discovery Sample

SNP	rs9868039	rs4646996	rs2134655	rs201252087
rs9868039	--			
rs4646996	*D*' = .89	--		
	R^2 = .68			
rs2134655	*D*' = .99	*D*' = .99	--	
	R^2 = .42	R^2 = .36		
rs201252087	*D*' = .99	*D*' = .99	*D*' = .99	--
	R^2 = .86	R^2 = .75	R^2 = .75	

Note. *DRD3* = dopamine receptor D3; PTSD = posttraumatic stress disorder; SNP = single nucleotide polymorphism.