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The Dopamine D_3 Receptor Gene and Posttraumatic Stress Disorder

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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). The aim of this candidate gene study was to evaluate *DRD3* polymorphisms for association with PTSD. The discovery sample was trauma-exposed White, non-Hispanic U.S. veterans and their trauma-exposed intimate partners ($N = 491$); 60.3% met criteria for lifetime PTSD. The replication sample was 601 trauma-exposed African American participants living in Detroit, Michigan; 23.6% met criteria for lifetime PTSD. Genotyping was based on high-density bead chips. In the discovery sample, 4 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 (*OR* range = 0.59 to 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 ($OR = 0.32$). 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.

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 antipsychotic drugs (Schwartz, Diaz, Pilon, & Sokoloff, 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 have stimulatory effects and the latter are inhibitory. The D_3 receptor has particular relevance to psychiatric phenotypes (e.g., psychiatric disorders and related endophenotypes) because it is expressed in brain regions thought to govern emotion and emotional responses to stress, reward motivation, and executive function (Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990), such as the nucleus accumbens, and to a lesser extent, the anterior cingulate gyrus, amygdala, and hippocampus (Gurevich & Joyce, 1999; Pennartz, Groenewegen, & Da Silva, 1994). The D_3 receptor has been associated with startle reactivity (Halberstadt & Geyer, 2009), sensorimotor gating (Bristow et al., 1996; Giakoumaki, Roussos, Frangou, & Bitsios, 2007; Swerdlow et al., 2009), stress-related behaviors (Xi et al., 2004), memory, social recognition and responding (Loiseau & Millan, 2009; Watson et al., 2012), and cognitive impairment (Millan et al., 2010).

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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, Okuyama, Toru, & Arinami, 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 behavior, social learning, memory, executive functioning, and emotional reactivity. These processes are particularly relevant to posttraumatic stress disorder (PTSD) as the *Diagnostic and Statistical Manual* (*DRM-IV*; 4th ed., American Psychiatric Association [APA], 1994) lists 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) as symptoms of the disorder. Given this, we sought to conduct the first candidate gene study of which we are aware of the association between *DRD3* and PTSD using data from two distinct samples. We expected variants in the *DRD3* gene to be associated with lifetime PTSD diagnosis in both samples. Given prior evidence for sex differences in the prevalence of PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 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 polymorphisms in *DRD3* and PTSD. We hypothesized that the association between SNPs in *DRD3* and PTSD would be larger in men compared to women.

Method

Participants

The discovery sample included 852 participants (590 veterans and 262 intimate partners) who participated in one of two research studies. Genetic variation differs across ancestral groups such that a given variant may be more common in one racial group than another (referred to as population stratification) and this can yield spurious genetic association results if the phenotype of interest also varies by racial group. Given this, we focused our analyses on the largest homogenous subpopulation in our sample and identified this group on the basis of their genetic variation. Specifically, 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, Stephens, & Pritchard, 2003; Pritchard, Stephens, & Donnelly, 2000). This process identified three groups, the largest of which was 540 participants who self-identified as White non-Hispanic. From this group, we eliminated 49 participants who did not report exposure to a *DSM-IV*-defined traumatic event, yielding a final sample of 491 (364 veterans and 127 nonveteran partners). 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. We also evaluated the possibility of population substructure, wherein genetic variation differs by subpopulations within a given racial group (e.g., White participants with northern vs. southern European ancestry), as allele frequency differences across these subpopulations may also lead to spurious genetic association results. There was no evidence of PTSD-associated population substructure in this sample (Logue et al., 2013). The majority of participants were male (65.0%), and the mean age was 51.95 years ($SD = 11.06$, range: 21–75). In this sample, 60.3% ($n = 296$, comprising 251 veterans and 45 nonveteran partners) met *DSM-IV* diagnostic criteria for lifetime PTSD.

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; Purcell et al., 2007) men and women living in Detroit, Michigan, who participated in one of three waves of data collection in the Detroit Neighborhood Health Study (DNHS; additional details provided in Goldmann et al., 2011; Logue et al., 2013; Uddin et al., 2010). The sample we evaluated in the current study was predominately female (57.2%), and the mean age was 52.59 years ($SD = 16.16$, range: 18–95 years). Participants had been exposed to one or more traumas (see Breslau et al., 1998); 23.6% ($n = 142$) met criteria for presumed lifetime PTSD as determined by structured interview administered over the telephone (see below).

Measures

The Clinician Administered PTSD Scale (CAPS; Blake et al., 1995) was administered in the discovery sample. It 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, Ruscio, & Keane, 1999), which required endorsement of at least one reexperiencing, three avoidance and numbing, and two hyperarousal symptoms, each at a frequency of 1 or greater and an intensity of 2 or greater. Interrater 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 ($\kappa = .87$).

The Traumatic Life Events Questionnaire (TLEQ; Kubany et al., 2000) was administered in the discovery sample. It 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 0 = *never* to 6 = *more than five times*. The TLEQ has shown good test-retest reliability and predictive validity with respect to PTSD diagnoses (Kubany et al., 2000).

In the replication sample, the PTSD Checklist (Weathers, Litz, Herman, Huska, & Keane, 1993) was administered as an interview over the telephone. It assessed the extent to which participants had been bothered by each of the 17 *DSM-IV* PTSD symptoms on a 1 = *not at all* to 5 = *extremely* scale in relation to a specific stressful event. To meet presumptive 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 3 (*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 (Goldmann et al., 2011).

Procedure

In the discovery sample, 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 interrater reliability. The studies were approved and reviewed annually by the VA Boston Healthcare System institutional review board.

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. DNA was available from 810 participants and from this group, we eliminated seven samples that had overall call rates less than 95%; the call rate in the remaining sample was 99.3%. Additional details of the quality control procedures are described in detail elsewhere (Logue et al., 2013). 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 $p > .01$).

In the replication sample, participants were recruited from a probability sample of Detroit-area households. Each wave of data collection included a 40-minute phone interview, for which participants received $25. They also completed an in-person sample collection, including blood for genotyping, for which they also received $25. 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.

Data Analysis

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). SNPs in *DRD3* were examined for association with lifetime PTSD diagnosis using the standard $\chi 2$ case/control test of association in PLINK in both samples (separately); 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 5,000 replications. In follow-up analyses in both samples, we entered total trauma exposure and the SNPs into a logistic regression in PLINK to evaluate if doing so changed the results of the SNP main effects. Because the discovery sample included 116 couples, we also modeled the nonindependence of these couples using a sandwich estimator to adjust the standard errors in Mplus 7.11 (Muthén & Muthén, 2012) and determined if doing so changed our main SNP effects in the discovery sample only. In both samples, we also stratified the sample by sex and evaluated the SNP main effects in each group separately to determine potential sex-specific effects and used the PLINK logistic regression test to evaluate if any of the SNPs interacted with (i.e., were moderated by) sex. Given that in the discovery sample, men were more often exposed to combat and women more often exposed to sexual assault (see Wolf et al., 2013), we also evaluated if combat exposure or sexual assault history interacted with the SNPs using PLINK logistic regression tests. Linkage disequilibrium (LD) was evaluated using the program Haploview (Barrett, Fry, Maller, & Daly, 2005). Among the 491 participants evaluated in the discovery sample, there was no missing phenotype data; the genotyping rate for the *DRD3* SNPs under investigation was greater than 99.9%. There was no missing data in the replication sample.

Results

We first evaluated the SNP main effects in the discovery sample. 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 [*OR*s] ranged from 0.59 to 0.69; see Table 1). These four SNPs were in high LD with each other (see Table 2). The prevalence of lifetime PTSD among

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	.41	.50	0.6883	.004	.049
D	rs9817063	113847108	G	.53	.44	1.427	.007	.069
D	**rs4646996**	113849565	A	.44	.54	0.6724	.002	.029
D	**rs2134655**	113858201	A	.28	.32	0.5907	.0003	.005
R	rs2251177	113858350	G	.11	.15	0.6733	.063	.597
D	**rs201252087**	113861589	G	.38	.48	0.6447	.0009	.013
D	rs963468	113862887	A	.45	.36	1.457	.005	.051

Note. $N = 491$ for discovery sample; $N = 601$ for replication sample. SNPs that were significant after permutation testing are in bold font. *DRD3* = dopamine receptor D_3; 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.

participants with one copy of the protective allele on rs2134655 (the most significant SNP) was 33.3%; it was 62.0% for those with no copies of the minor allele (there were no participants with two copies of the minor allele). The pattern of results for these four SNPs was unchanged when total trauma exposure was included in the analysis; results were also unchanged when we modeled the nonindependence of the 116 couples included in the analyses.

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 ($OR = 0.60$, uncorrected $p = .003$, corrected $p = .039$). In women ($n = 215$), that same SNP (rs201252087) was not significantly associated with PTSD ($OR = 0.69$, uncorrected $p = .100$, corrected $p = .568$). Only one SNP (rs2134655) showed a nominally significant association with PTSD in women, but it did not withstand multiple testing correction ($OR = 0.59$, uncorrected $p = .031$, corrected $p = .234$); that SNP also evidenced a nominally significant association in the male subsample that did not withstand permutation testing ($OR = 0.61$, uncorrected $p = .010$, corrected $p = .104$). There was no evidence that sex moderated the SNP main effect for rs201252087 (interaction term $p = .675$, smallest p for any of the other SNP × Sex interaction terms = .207). We found no evidence of SNP interactions with sexual assault history or combat exposure.

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

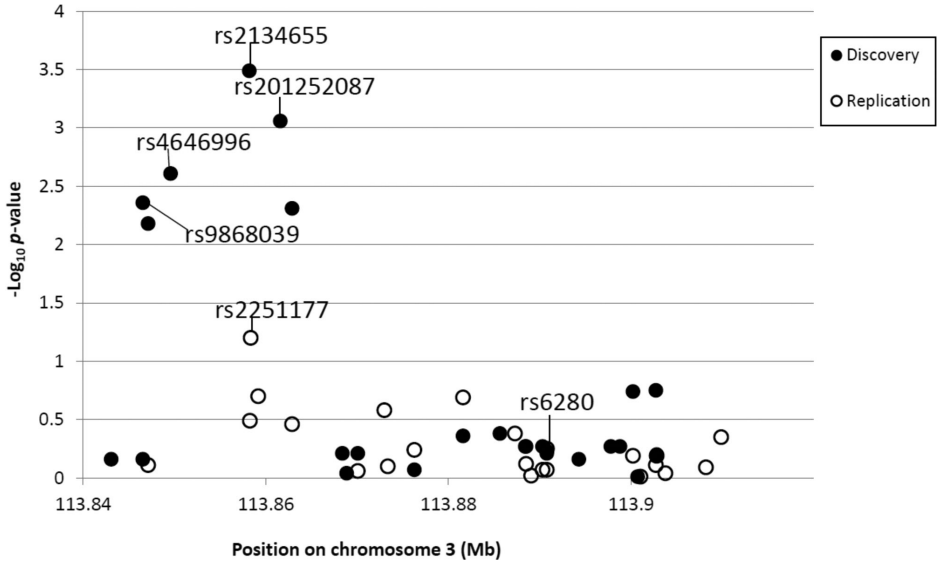

Figure 1. The figure shows the nominal (uncorrected) *p* values (in $-\log_{10}$) at each base pair location for all single nucleotide polymorphisms (SNPs) evaluated for association with posttraumatic stress disorder in the discovery (filled circles) and replication (open circles) samples. The four SNPs that were significant after permutation testing in the discovery sample ($N = 491$) and the most significant SNP in the replication sample ($N = 601$) are identified, as is rs6280, a commonly studied *DRD3* polymorphism.

Table 2
Linkage Disequilibrium Among the Four DRD3 SNPs Showing the Strongest Association With PTSD in the Discovery Sample

	1.		2.		3.	
SNP	D'	R^2	D'	R^2	D'	R^2
1. rs9868039						
2. rs4646996	.89	.68				
3. rs2134655	.99	.42	.99	.36		
4. rs201252087	.99	.86	.99	.75	.99	.75

Note. $N = 491$. D' is an index of linkage disequilibrium. *DRD3* = dopamine receptor D_3; PTSD = posttraumatic stress disorder; SNP = single nucleotide polymorphism.

replication sample. Of the 23 SNPs available for analysis in the replication sample, only rs9828046 and rs2251177 were located in close physical proximity (< 150 bp) to rs2134655, the most strongly associated SNP in 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 $p = .063$, corrected $p = .597$; 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). When trauma exposure was included in the model the association became nonsignificant in the full sample ($OR = 0.69$, $p = .106$). 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 $p = .011$) although the corrected p value after permutation testing was .172. This SNP remained nominally significant with trauma included in the model ($OR = 0.35$, uncorrected $p = .031$). None of the SNPs were significant in the female subsample (association result for rs2251177: $OR = 0.86$, uncorrected $p = .544$, corrected $p = 1.0$). The test of the SNP × Sex interaction for rs2251177 failed to reach statistical significance ($p = .093$); 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 (27.4% vs. 6.1%, 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 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, Payne, Ma, & Li, 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, Schenck, Han, Stockmeier, & Ordway, 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, Spreng, Shin, & Girard, 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, Witteveen, Reitsma, & Olff, 2012), decreased activation of prefrontal 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 if sex moderates the main effects of these SNPs.

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 underpowered to detect sex-specific effects. Thus, our findings with respect to potential sex differences should be interpreted with caution and considered preliminary. In the replication sample, PTSD was assessed using an interview version of a self-report measure, which is not the gold standard for diagnostic assessments. 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., 2013) 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 of which we are aware 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.

References

Agrawal, A., Wetherill, L., Bucholz, K. K., Kramer, J., Kuperman, S., Lynskey, M. T., ... Bierut, L. J. (2013). Genetic influences of craving for alcohol. *Addictive Behaviors*, *38*, 1501–1508. doi:10.1016/j.addbeh.2012.03.021

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Barrett, J. C., Fry, B., Maller, J., & Daly, M. J. (2005). Haploview: Analysis and visualization of LD and haplotype maps. *Bioinformatics*, *21*, 263–265. doi:10.1093/bioinformatics/bth457

Beninger, R. J. (1983). The role of dopamine in locomotor activity and learning. *Brain Research*, *287*, 173–196. doi:10.1016/0165-0173(83)90038-3

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Research Reviews*, *28*, 309–369. doi:10.1016/S0165-0173(98)00019-8

Black, K. J., Hershey, T., Koller, J. M., Videen, T. O., Mintun, M. A., Price, J. L., & Perlmutter, J. S. (2002). A possible substrate for dopamine-related changes in mood and behavior: Prefrontal and limbic effects of a D3-preferring dopamine agonist. *Proceedings from the National Academy of Sciences of the United States of America*, *99*, 17113–17118. doi:10.1073/pnas.012260599

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., & Charney, D. S. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress*, *8*, 75–90. doi:10.1007/BF02105408

Breslau, N., Kessler, R., Chilcoat, H. D., Schultz, L. R., Davis, G. C., & Andreski, P. (1998). Trauma and posttraumatic stress disorder in the community: The 1996 Detroit area survey of trauma. *Archives of General Psychiatry*, *55*, 626–632. doi:10.1001/archpsyc.55.7.626

Bristow, L. J., Cook, G. P., Gay, J. C., Kulagowski, J. J., Landon, L., Murray, F., ... Hutson, P. H. (1996). The behavioural and neurochemical profile of the putative dopamine D3 receptor agonist, (+)-PD 128907, in the rat. *Neuropharmacology*, *35*, 285–294. doi:10.1016/0028-3908(96)00179-7

Brown, A. K., Mandelkern, M. A., Farahi, J., Robertson, C., Ghahremani, D. G., Sumerel, B., ... London, E. D. (2012). Sex differences in striatal dopamine D2/D3 receptor availability in smokers and nonsmokers. *International Journal of Neuropsychopharmacology*, *15*, 989–994. doi:10.1017/S1461145711001957

Bombin, I., Arango, C., Mayoral, M., Castro-Fornieles, J. C., Gonzalez-Pinto, A., Gonzalez-Gomez, C., ... Patiño-Garcia, A. (2008). DRD3, but not COMT or DRD2, genotype affects executive functions in healthy and first-episode psychosis adolescents. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics*, *147B*, 873–879. doi:10.1002/ajmg.b.30710

Costas, J., Carrera, N., Dominguez, E., Vilella, E., Martorell, L., Valero, J., ... Carracedo, A. (2009). A common haplotype of DRD3 affected by recent positive selection is associated with protection from schizophrenia. *Human Genetics*, *124*, 607–613. doi:10.1007/s00439-008-0584-7

Crocq, M. A., Mant, R., Asherson, P., Williams, J., Hode, Y., Mayerova, A., ... Schwartz, J. C. (1992). Association between schizophrenia and homozygosity at the dopamine D3 receptor gene. *Journal of Medical Genetics*, *60*, 558–562. doi:10.1136/jmg.29.12.858

Dalley, J. W., Fryer, T. D., Britchard, L., Robinson, E. S. J., Theobald, D. E. H., Lääne, K., ... Robbins, T. W. (2007). Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science*, *315*, 1267–1270. doi:10.1126/science.1137073

Dannlowski, U., Domschke, K., Birosova, E., Lawford, B., Young, R., Voisey, J., ... Zwanzger, P. (2011). Dopamine D3 receptor gene variation: Impact on electroconvulsive therapy response and ventral striatum responsiveness in depression. *International Journal of Neuropsychopharmacology*, *18*, 1–17. doi:10.1017/S1461145711001659

de Krom, M., Staal, W. G., Ophoff, R. A., Hendriks, J., Buitelaar, J., Franke, B., ... van Ree, J. M. (2009). A common variant in DRD3 receptor is associated with autism spectrum disorder. *Biological Psychiatry*, *65*, 625–630. doi:10.1016/j.biopsych.2008.09.035

Dikeos, D. G., Papadimitriou, G. N., Avramopoulos, D., Karadima, G., Daskalopoulou, E. G., Souery, D., ... Stefanis, C. M. (1999). Association between the dopamine D3 receptor gene locus (DRD3) and unipolar affective disorder. *Psychiatric Genetics*, *9*, 189–195. doi:10.1097/00041444-199912000-00005

Dominguez, E., Loza, M. I., Padin, F., Gesteira, A., Paz, E., Paramo, M., ... Costas, J. (2007). Extensive linkage disequilibrium mapping at HTR2A and DRD3 for schizophrenia susceptibility genes in the Galician population. *Schizophrenia Research*, *90*, 123–129. doi:10.1016/j.schres.2006.09.022

Ersche, K. D., Roiser, J. P., Lucas, M., Domenici, E., Robbins, T. W., & Bullmore, E. T. (2011). Peripheral biomarkers of cognitive response to dopamine receptor agonist treatment. *Psychopharmacology*, *214*, 779–789. doi:10.1007/s00213-010-2087-1

Falush, D., Stephens, M., & Pritchard, J. K. (2003). Inference of population structure using multilocus genotype data: Linked loci and correlated allele frequencies. *Genetics*, *164*, 1567–1587.

Furuyashiki, T. (2012). Roles of dopamine and inflammation-related molecules in behavioral alterations caused by repeated stress. *Journal of Pharmacological Sciences*, *120*, 63–69. doi:10.1254/jphs.12R09CP

Giakoumaki, S. G., Roussos, P., Frangou, S., & Bitsios, P. (2007). Disruption of prepulse inhibition of the startle reflex by the preferential D(3) agonist ropinirole in healthy males. *Psychopharmacology*, *194*, 289–295. doi:10.1007/s00213-007-0843-7

Glenthoj, B. Y., Mackeprang, T., Svarer, C., Rasmussen, H., Pinborg, L. H., Friberg, L., ... Videbaek, C. (2006). Frontal dopamine D(2/3) receptor binding in drug-naive first-episode schizophrenic patients correlates with positive psychotic symptoms and gender. *Biological Psychiatry*, *60*, 621–629. doi:10.1016/j.biopsych.2006.01.010

Goldmann, E., Aiello, A., Uddin, M., Delva, J., Koenen, K., Gant, L. M., & Galea, S. (2011). Pervasive exposure to violence and posttraumatic stress disorder in a predominantly African American Urban Community: The Detroit Neighborhood Health Study. *Journal of Traumatic Stress*, *24*, 747–751. doi:10.1002/jts.20705

Gurevich, E. V., & Joyce, D. N. (1999). Distribution of dopamine D_3 receptor expressing neurons in the human forebrain: Comparison with D_2 receptor expressing neurons. *Neuropsychopharmacology*, *20*, 60–80. doi:10.1016/S0893-133X(98)00066-9

Halberstadt, A. L., & Geyer, M. A. (2009). Habituation and sensitization of acoustic startle: Opposite influences of dopamine D1 and D2-family receptors. *Neurobiology of Learning and Memory*, *92*, 243–248. doi:10.1016/j.nlm.2008.05.015

Heidbreder, C. A., Gardner, E. L., Xi, Z.-H., Thanos, P. K., Mugnaini, M., Hagan, J. J., & Ashby, C. R. Jr. (2005). The role of central dopamine D3 receptors in drug addiction: A review of pharmacological evidence. *Brain Research. Brain Research Reviews*, *49*, 77–105. doi:10.1016/j.brainresrev.2004.12.033

Hood, S. D., Potokar, J. P., Davies, S. J. C., Hince, D. A., Morris, K., Seddon, K. M., ... Argyropoulos, S. V. (2010). Dopaminergic challenges in social anxiety disorder: Evidence for dopamine D_3 desensitisation following successful treatment with serotonergic antidepressants. *Journal of Psychopharmacology*, *24*, 709–716. doi:10.1177/0269881108098144

Huang, W., Payne, T. J., Ma, J. Z., & Li, M. D. (2008). A functional polymorphism, rs6280, in DRD3 is significantly associated with nicotine dependence in European-American smokers. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics*, *147B*, 1109–1115. doi:10.1002/ajmg.b.30731

Ishiguro, H., Okuyama, Y., Toru, M., & Arinami, T. (2000). Mutation and association analysis of the 5′ region of the dopamine D3 receptor gene in schizophrenia patients: Identification of the Ala38Thr polymorphism and suggested association between DRD3 haplotypes and schizophrenia. *Molecular Psychiatry*, *5*, 433–438.

Joyce, J. N., & Millan, M. J. (2005). Dopamine D3 receptor antagonists as therapeutic agents. *Drug Discovery Today*, *10*, 917–925. doi:10.1016/S1359-6446(05)03491-4

Kennedy, J. L., Billett, E. A., Macciardi, F. M., Verga, M., Parsons, T. J., Meltzer, H. Y., ... Buchanan, J. A. (1995). Association study of dopamine D3 receptor gene and schizophrenia. *American Journal of Medical Genetics*, *60*, 558–562. doi:10.1002/ajmg.1320600615

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry*, *52*, 1048–1060. doi:10.1001/archpsyc.1995.03950240066012

Klimek, V., Schenck, J. E., Han, H., Stockmeier, C. A., & Ordway, G. A. (2002). Dopaminergic abnormalities in amygdaloid nuclei in major depression: A postmortem study. *Biological Psychiatry*, *52*, 740–748. doi:10.1016/S0006-3223(02)01383-5

Kobiella, A., Vollstadt-Klein, S., Buhler, M., Graf, C., Buchholz, H.-G., Bernow, N., ... Smolka, M. N. (2009). Human dopamine receptor D2/D3 availability predicts amygdala reactivity to unpleasant stimuli. *Human Brain Mapping*, *31*, 716–726. doi:10.1002/hbm.20900

Kubany, E. S., Haynes, S. N., Leisen, M. B., Owens, J. A., Kaplan A. S., Watson, S. B., & Burns, K. (2000). Development and preliminary validation of a brief broad-spectrum measure of trauma exposure: The Traumatic Life Events Questionnaire. *Psychological Assessment*, *12*, 210–224. doi:10.1037/1040-3590.12.2.210

Lane, H. Y., Liu, Y. C., Huang, C. L., Chang, Y. C., Wu, P. L., Huang, H. C., & Tsai, G. E. (2008). RGS4 polymorphisms predict clinical manifestations and responses to risperidone treatment in patients with schizophrenia. *Journal of Clinical Psychopharmacology*, *1*, 64–68. doi:10.1097/jcp.0b013e3181603f5a

Light, K. J., Joyce, P. R., Luty, S. E., Mulder, R. T., Frampton, C. M. A., Joyce, L. R. M., … Kennedy, M. A. (2006). Preliminary evidence for an association between a dopamine D3 receptor gene variant and obsessive-compulsive personality disorder in patients with major depression. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics*, *141B*, 409–413. doi:10.1002/ajmg.b.30308

Logue, M. W., Baldwin, C., Guffanti, G., Melista, E., Wolf, E. J., Reardon, A. F., … Miller, M. W. (2013). A genome-wide association study of posttraumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. *Molecular Psychiatry*, *18*, 937–942. doi: 10.1038/mp.2012.113

Loiseau, F., & Millan, M. J. (2009). Blockade of dopamine D(3) receptors in frontal cortex, but not in sub-cortical structures, enhances social recognition in rats: Similar actions of D(1) receptor agonists, but not of D(2) antagonists. *European Neuropsychopharmacology*, *19*, 23–33. doi:10.1016/j.euroneuro.2008.07.012

Millan, M. J., Buccafusco, J. J., Loiseau, F., Watson, D. J., Decamp, E., Fone, K. C., … Schneider, J. S. (2010). The dopamine D3 receptor antagonist, S33138, counters cognitive impairment in a range of rodent and primate procedures. *International Journal of Neuropsychopharmacology*, *13*, 035–1051. doi:10.1017/S1461145710000775

Munro, C. A., McCaul, M. E., Wong, D. F., Oswald, L. M., Zhou, Y., Brasic, J., … Wand, G. S. (2006). Sex differences in striatal dopamine release in healthy adults. *Biological Psychiatry*, *59*, 966–974. doi:10.1016/j.biopsych.2006.01.008

Muthén, L. K., & Muthén, B. O. (1998–2012). *Mplus user's guide* (7th ed.). Los Angeles, CA: Author.

Nunokawa, A., Watanabe, Y., Kaneko, N., Sugai, T., Yazaki, S., Arinami, T., … Someya, T. (2010). The dopamine D3 receptor (DRD3) gene and risk of schizophrenia: Case-control studies and an updated meta-analysis. *Schizophrenia Research*, *116*, 61–67. doi:10.1016/j.schres.2009.10.016

Patel, R., Spreng, R. N., Shin, L. M., & Girard, T. A. (2012). Neurocircuitry models of posttraumatic stress disorder and beyond: A meta-analysis of functional neuroimaging studies. *Neuroscience Biobehavioral Research*, *36*, 2130–2142. doi:10.1016/j.neubiorev.2012.06.003

Pennartz, C. M. A., Groenewegen, H. J., & Da Silva, F. H. (1994). The nucleus accumbens as a complex of functionally distinct neuronal ensembles: An integration of behavioural, electrophysiological, and anatomical data. *Progressive Neurobiology*, *42*, 719–761. doi:10.1016/0301-0082(94)90025-6

Pierce, R. C., & Kumaresan, V. (2006). The mesolimbic dopamine system: The final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience Biobehavioral Research*, *30*, 215–238. doi:10.1016/j.neubiorev.2005.04.016

Polak, A. R., Witteveen, A. B., Reitsma, J. B., & Olff, M. (2012). The role of executive function in posttraumatic stress disorder: A systematic review. *Journal of Affective Disorders*, *141*, 11–21. doi:10.1016/j.jad.2012.01.001

Pritchard, J. K., Stephens, M., & Donnelly, P. (2000). Inference of population structure using multilocus genotype data. *Genetics*, *155*, 945–959.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., … Sham, P. C. (2007). PLINK: A tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics*, *81*, 559–575. doi:10.3410/f.1162373.622875

Retz, W., Rösler, M., Supprian, T., Retz-Junginger, P., & Thome, J. (2003). Dopamine D3 receptor gene polymorphism and violent behavior: Relation to impulsiveness and ADHD-related psychopathology. *Journal of Neural Transmissions*, *110*, 561–572. doi:10.1007/s00702-002-0805-5

Schwartz, J.-C., Diaz, J., Pilon, C., & Sokoloff, P. (2000). Possible implications of the dopamine D3 receptor in schizophrenia and in antipsychotic drug actions. *Brain Research Reviews*, *31*, 277–287. doi:10.1016/S0165-0173(99)00043-0

Smoller, J. W., Craddock, N., Kendler, K., Lee, P. H., Neale, B. M., Nurnberger, J. I., … Sullivan, P. F. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *The Lancet*, *20*, 1371–1379. doi:10.1016/S0140-6736(12)62129-1

Sokoloff, P., Giros, B., Martres, M.-P., Bouthenet, M.-L., & Schwartz, J.-C. (1990). Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. *Nature*, *347*, 146–151. doi:10.1038/347146a0

Staal, W. G., & de Krom, M. (2012). Brief report: The dopamine-3-receptor gene (DRD3) is associated with specific repetitive behavior in autism spectrum disorder (ASD). *Journal of Autism and Developmental Disorders*, *42*, 885–888. doi:10.1007/s10803-011-1312-z

Swerdlow, N. R., Lelham, S. A., Owens, A. N. S., Chang, W.-L., Sassen, S. D. T., & Talledo, J. A. (2009). Pramipexole effects on startle gating in rats and normal men. *Psychopharmacology*, *205*, 689–698. doi:10.1007/s00213-009-1577-5

Talkowski, M. E., Mansour, H., Chowdari, K. V., Wood, J., Butler, A., Varma, P. G., … Nimgaonkar, V. L. (2006). Novel, replicated associations between dopamine D3 receptor gene polymorphisms and schizophrenia in two independent samples. *Society of Biological Psychiatry*, *60*, 570–577. doi:10.1016/j.biopsych.2006.04.012

Uddin, M., Aiello, A. E., Wildman, D. E., Koenen, K. C., Pawelec, G., de Los Santos, R., … Galea, S. (2010). Epigenetic and immune function profiles associated with posttraumatic stress disorder. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 9470–9475. doi:10.1073/pnas.0910794107

Watson, D. J., Loiseau, F., Ingallinesi, M., Millan, M. J., Marsden, C. A., & Fone, K. C. (2012). Selective blockade of dopamine D3 receptors enhances while D2 receptor antagonism impairs social novelty discrimination and novel object recognition in rats: A key role for the prefrontal cortex. *Neuropsychopharmacology*, *37*, 770–786. doi:10.1038/npp.2011.254

Weathers, F. W., Litz, B. T., Herman, D. S., Huska, J. A., & Keane, T. M. (1993, October). The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility. Paper presented at the 9th Annual Conference of the ISTSS, San Antonio, TX.

Weathers, F. W., Ruscio, A. M., & Keane, T. M. (1999). Psychometric properties of nine scoring rules for the Clinician-Administered Posttraumatic Stress Disorder Scale. *Psychological Assessment*, *11*, 124–133. doi:10.1037/1040-3590.11.2.124

Wei, J., Chu, C., Wang, Y., Yang, Y., Wang, Q., Li, T., … Ma, X. (2012). Association study of 45 candidate genes in nicotine dependence in Han Chinese. *Addictive Behaviors*, *37*, 622–626. doi:10.1016/j.addbeh.2012.01.009

Weiss, J. M., Goodman, P. A., Losito, B. G., Corrigan, S., Charry, J. M., & Bailey, W. H. (1981). Behavioral depression produced by an uncontrollable stressor: Relationship to norepinephrine, dopamine, and serotonin levels in various regions of rat brain. *Brain Research Reviews*, *3*, 167–205. doi:10.1016/0165-0173(81)90005-9

Williams, J., Spurlock, G., Holmans, P., Mant, R., Murphy, K., Jones, L., ... Owen, M. J. (1998). A meta-analysis and transmission disequilibrium study of association between the dopamine D3 receptor gene and schizophrenia. *Molecular Psychiatry*, *3*, 141–149. doi:10.1038/sj.mp.4000376

Wodarz, N., Bobbe, G., Eichhammer, P., Weijers, H. G., Wiesbeck, G. A., & Johann, M. (2003). The candidate gene approach in alcoholism: Are there gender-specific differences? *Archives of Women's Mental Health*, *6*, 225–230. doi:10.1007/s00737-003-0011-y

Wolf, E. J., Mitchell, K. M., Logue, M. W., Baldwin, C. T., Reardon, A. F., Humphries, D. E., & Miller, M. W. (2013). The corticotropin releasing hormone receptor 2 (CRHR-2) gene is associated with decreased risk and severity of posttraumatic stress disorder in women. *Depression & Anxiety*, *30*, 1161–1169. doi:10.1002/da.22176

Xi, Z.-X., Gilbert, J., Campos, A. C., Kline, N., Ashby, C. R., Hagan, J. J., ... Gardner, E. L. (2004). Blockade of mesolimbic dopamine D3 receptors inhibits stress-induced reinstatement of cocaine-seeking in rats. *Psychopharmacology*, *176*, 57–65. doi:10.1007/s00213-004-1858-y

Zhang, F., Fan, H., Xu, Y., Zhang, K., Huang, X., Zhu, Y., ... Liu, P. (2011). Converging evidence implicates the dopamine D3 receptor gene in vulnerability to schizophrenia. *American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics*, *156B*, 613–619. doi:10.1002/ajmg.b.31203