HHS Public Access

Author manuscript

Psychiatry Res. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

Psychiatry Res. 2021 April ; 298: 113801. doi:10.1016/j.psychres.2021.113801.

Dopamine transporter *(DAT1)* gene in combat veterans with PTSD: A case-control study

Zachary D. Zuschlag[a,b,1], **Ebele Compean**[c,1], **Paul Nietert**[d], **Steven Lauzon**[d], **Mark Hamner**[c,e], **Zhewu Wang**[c,e,*]

[a]Mental Health and Behavioral Sciences Service, James A. Haley Veterans' Hospital, Tampa, FL, USA

[b]Department of Psychiatry and Behavioral Neurosciences, University of South Florida, Tampa, FL, USA

[c]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

[d]Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC USA

[e]Mental Health Services, Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC, USA

Abstract

The dopamine transporter (*DAT1*) gene has been postulated to be involved in PTSD; however, existing studies have shown inconsistencies when examining genotypic and allelic associations. The primary objective of this study was to examine whether *DAT1–40bp-VNTR* (*DAT1)* 9R polymorphism might increase the risk of PTSD development in combat veterans, utilizing a case-control gene association study with both control and PTSD cases having previous exposure to combat traumas. Participants with PTSD *(N = 365)* and combat-exposed controls without PTSD *(N = 298)* were included in analysis. After controlling for race, sex and age, when dichotomized, absence of *DAT1* 10R/10R genotypes was associated with PTSD diagnosis compared to no PTSD diagnosis; these results were not statistically significant when trichotomized 10R/10R, 10R/X, 9R/9R. Similarly, odds ratio for absence of 10R/10R genotype showed a statistically significant increase in the risk of developing PTSD. *DAT1* genotype was also associated with statistically significant mean total CAPS scores, both when dichotomized and trichotomized. In conclusion,

*Corresponding author: Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 109 Bee Street, Charleston, SC 29401, USA. wanzh@musc.edu (Z. Wang).

[1] Shared first authorship

Author statement

This material is the result of work supported with resources and the use of Veterans' Hospital facilities. The contents of this publication do not represent the views of the Department of Veterans Affairs or the United States Government. The article is the authors' original work, hasn't received prior publication, and isn't under consider for publication elsewhere.

Declaration of Competing Interest

Mark Hamner has been the recipient of a research grant from Otusuka Pharmaceuticals; although, this conflict is not relevant for this manuscript. All other authors report no relevant financial conflicts.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

our results indicate that the absence of 10R/10R is associated with an increased risk of PTSD and higher CAPS total scores.

Keywords

PTSD; Genetics; Veterans; *DAT1*; CAPS; Combat; Trauma

1. Introduction

Posttraumatic stress disorder (PTSD) is a common and debilitating psychiatric illness. The majority of individuals in the general population (40–90%) endorse lifetime exposure to at least one traumatic event, and the lifetime prevalence of PTSD has been reported to be 7–12% (Broekman et al., 2007). Among military veterans, rates of trauma exposure and PTSD are substantially higher, with almost 90% of military veterans endorsing exposure to at least one traumatic event, and up to 32% meeting criteria for lifetime PTSD (Wisco et al., 2014). Although the majority of civilians and veterans are exposed to traumatic events, most do not subsequently develop PTSD. Thus, identification of predictors of the development of PTSD following exposure to trauma is critically needed to further advance prevention and treatment interventions.

Genetic influences have been a target of investigation as previous research suggests involvement of gene-environmental (GXE) interactions, including showing that approximately 30% of variance in PTSD can be accounted for by genetic factors (Stein et al., 2002; True et al., 1993). The dopaminergic system has been a focused target of interest in PTSD research. Dopamine has been implicated in learning, fear and stress response (Graham et al., 2014; Li et al., 2016) and is associated with the hypothalamic-pituitary-adrenal (HPA) axis via its conversion to norepinephrine (NE) by dopamine β hydroxylase (DBH) (Li et al., 2016). Abnormal dopamine-associated biological and molecular processes have been correlated with PTSD diagnosis, including symptoms such as poor concentration, flashbacks and hyperarousal (Hamner and Diamond, 1993; Hamner and Gold, 1998; Yehuda et al., 1992). Dopamine transporters are involved in the reuptake process through regulation of dopamine levels at the synapses (Li et al., 2016; Segman et al., 2002) and are regulated by the *DAT1* (SLC6A3) gene.

DAT1 gene is located on chromosome 5q15.3 and has a 40 base pair variable number tandem repeat (VNTR) in the 3′ untranslated region (*DAT1–40bp-VNTR*); the associated VNTR can vary from 3–11 copies (Vandenbergh et al., 1992). The two most common alleles of *DAT1* VNTR polymorphisms are: 10 repeats (10R) and 9 repeats (9R). The three main genotypes, which are 9/9R, 9/10R and 10/10R (Kang et al., 1999; Vandenbergh et al., 1992), may play a role in susceptibility to PTSD. Previous studies conducted among civilians, however, have yielded mixed results (Bailey et al., 2010; Chang et al., 2012; Drury et al., 2009; Valente et al., 2011). Additionally, to the authors' knowledge, there have been no prior studies examining *DAT1* as a candidate gene for PTSD among military Veterans.

Existing studies of *DAT1* gene in the general population contain moderate sample sizes (e.g. 200–300 participants) with skewed PTSD case-to-control ratios (Bailey et al., 2010; Chang

et al., 2012; Segman et al., 2002; Valente et al., 2011). Furthermore, these studies are limited by inclusion of participants with heterogenous trauma types (e.g. sexual assault, serious car accidents, domestic violence, robbery and others) (Chang et al., 2012; Segman et al., 2002; Valente et al., 2011). Studies with larger sample sizes and homogenous trauma types may help advance the research on candidate gene studies for PTSD. Combat veterans are unique and ideal candidates given the relative homogeneity of the trauma type and quantification of the trauma event (i.e. via the Combat Exposure Scale). In addition, given that not all combat veterans develop PTSD, a comparable control group is available.

Although there is a need for research examining *DAT1* in Veterans exposed to combat trauma, there is currently a paucity of literature in this regard. The current study aimed to meet this need by investigating the association between *DAT1* and PTSD among military veterans with uniformed trauma type (i.e. combat), utilizing a balanced ratio of case-to-control design. The primary objective was to examine whether *DAT1* (*DAT1–40bp-VNTR)* 9R polymorphism might increase the risk of PTSD development in combat veterans; to the authors' knowledge, this is the first *DAT1* candidate gene study conducted in Veterans with PTSD.

2. Methods

2.1. Recruitment and participants

365 veterans with PTSD and 298 combat exposed veterans without PTSD were recruited from two Veterans Affairs Medical Centers (VAMC) from April 1st, 2002 to September 30th, 2016: one in Charleston, SC and one in Cincinnati, OH. Inclusion criteria included: age 18 to 80 years old; history of combat exposure with DD214 (a Certificate of Release or Discharge from Active Duty provided to service members after leaving active service); a score≥10 on the Combat Exposure Scale (CES). The CES is a validated assessment scale which has been found to have good internal consistency and test-retest reliability (Keane et al., 1989). The U.S. Department of Veterans Affairs and the VA National Center for PTSD identifies it as a preferred assessment scale for clinical and research purposes. The score >=10 was used as a threshold for inclusion to reflect a minimum of greater than "light" exposure. Exclusion criteria included: current or lifetime DSM-IV diagnoses of bipolar disorder, primary psychotic disorder and substance use in the six months prior to study enrollment.

2.2. Measures

After collecting the demographic and deployment information, the participants were assessed by a trained research assistant for the presence of PTSD or other psychiatric disorders with either Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) or Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). SCID was used at the Cincinnati VAMC from April 2002 through March 2007 (n = 320), and MINI was used at the Charleston VAMC from April 2007 through September 2016 (n = 343). Diagnoses were confirmed by study team members who are board certified psychiatrists (M.H. and Z.W.) Both the SCID (First et al., 2007) and MINI (Sheehan et al., 1998); have been to show to have good validity and reliability parameters.

In addition, further assessments were also performed at the initial interview. The Clinician Administered PTSD Scale (CAPS-IV), a structured and diagnostic interview, was used to evaluate PTSD including symptom severity. The CAPS assess frequency and intensity of PTSD symptoms, as well as assesses for functional impairment, subjective distress, and other parameters (Weathers et al., 2001). The Combat Exposure Scale (CES) (Keane et al., 1989), a 7-item, self-report measure, was used to gather information about combat-related stressors and exposure. CES total scores range from 1 to 41 with lower scores reflecting lower combat exposure severity. A CES total score ≥10 was required for inclusion in order to control for trauma exposure levels when evaluating the PTSD group versus the combat-exposed control group. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) is a self-report item that measures quality of life. Q-LES-Q has good reliability and validity psychometric parameters (Stevanovic, 2011; Endicott et al., 1993). Q-LES-Q was initially obtained, but later removed from study protocol to decrease assessment burden on participants.

2.3. Genotyping

Participants provided venous blood samples with standard genomic DNA isolation performed according to the protocol of the Puregene kit (Gentra Systems Inc., Minneapolis, MN). The SLC6A3 3′ VNTR polymorphisms were studied using methods described by Vandenbergh (Vandenbergh et al., 1992). The PCR for *DAT1–40 base pair-VNTR* was carried out in a 15 μl reaction containing: 50 ng DNA, 10 picomoles of each primer, 200 μM dNTP, 0.1 u of Pfx DNA polymerase, 1x PCR buffer. The reaction was heated with multiple cycles. The PCR products were separated by 3% agarose gel stained with ethidium bromide. The gels were scored by a laboratory assistant and Z.W., who were blinded to case-control status and other clinical assessments.

2.4. Ethical considerations

The study was approved by the Institutional Review Boards (IRB) of both the Medical University of South Carolina and the University of Cincinnati. Written IRB-approved informed consent was obtained prior to the occurrence of any study-related procedures.

2.5. Statistical analysis

Data were analyzed from April 10, 2018, through September 27, 2018. The sample size provided 80% power to detect odds ratios (ORs) ranging from 1.6 to 2.0 when comparing categorical variables (e.g., genotype) between groups, assuming 2-sided hypothesis testing and an alpha level of 0.025. Additionally, the PTSD case sample provides sufficient power to detect subtle differences (effect sizes of 0.33) in CAPS scores between genotype groups. Further, these sample sizes also provided 80% power for the secondary outcomes, allowing, for example, the detection of subtle differences in continuous measures (effect sizes of 0.24) when comparing PTSD cases to controls and when comparing one genotype to another.

Descriptive statistics are presented as mean (standard deviation) and n (%) for continuous and categorical variables, respectively. The *DAT1* genotype was categorized in two ways: (1) using a dichotomous variable indicating whether or not 10 repeats (10R) were present on both alleles, and (2) using a trichotomous variable indicating whether a) at least 10R were

present on both alleles (10R/10R), (b) 10R were present on only 1 allele (10R/X), or c) exactly 9R were present on both alleles (9R/9R). These three gene categories covered all combinations in our population. The Hardy-Weinberg equilibrium (HWE) was verified prior to any formal analysis. Student's *t*-test and chi-square test were used for continuous and categorical variables, respectively. To compare measures across the 3-category genotype groupings, one-way ANOVA and chi-square tests were used for continuous and categorical variables, respectively. To identify subject characteristics associated with PTSD, a multivariable logistic regression was utilized with PTSD status as the dependent variable, genotype as the independent variable, and race, sex, and age as covariates. To identify characteristics associated with the CAPS total and subscale scores, general linear regression models were utilized and included genotype, race, sex, and age in the models. The analysis of CAPS scores included only participants with a diagnosis of PTSD. Statistical significance was assessed with an α-level of 0.05 unless otherwise specified. In order to account for the fact that genotype was categorized and tested two separate ways, we adjusted the alpha level to 0.025 for analyses involving genotype, meaning that only *P*-values <0.025 are considered statistically significant. For the same reason, 97.5% confidence intervals (Cis) are presented as opposed to 95% Cis. Analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics

The demographic and clinical characteristics of the final sample of 663 veterans (45.1 years old [SD 14.1], 556 males [83.9%], 107 females [16.1%]) after removing records with missing values ($n = 13$), are included in Table 1. On average, participants with PTSD were significantly younger, had higher CES scores and had lower quality of life scores than combat-exposed controls. In addition, participants with PTSD were more likely to be African Americans and were more likely to have a substance use or depression diagnosis, as compared to combat-exposed controls.

3.2. DAT1 genotypes

Table 2 provides information on demographic and clinical variables of interest, stratified by the three genotypes. As noted in the multivariable model presented in Table 3, genotype was significantly associated with PTSD diagnosis after controlling for age, sex, and ethnicity, when using dichotomized genotype 10R/10R compared to 10R/X and 9R/9R *(OR, 1.60: 97.5% CI, 1.01–2.07; P = 0.022)*. When using the trichotomized genotype, there was not a statistically significant association with PTSD after controlling for demographic variates. In the trichotomized genotype model, the odds of having PTSD for those with 10R/X vs 10R/10R was 1.4 *(97.5% CI, 0.97–2.04, P = 0.041)*, and for those with 9R/9R vs 10R/10R was 1.*80 (97.5% CI 0.77–4.23, P = 0.12)*.

In the total sample, significant differences across genotypes were noted in total CAPS scores in a dose-dependent relationship; this finding did not depend on whether genotype was dichotomized (10R/10R vs. other) or trichotomized, as illustrated by Table 2. The CAPS D subscale score exhibited significant *(P = 0.02)* differences when genotype was dichotomized,

but not when genotype was trichotomized *(P = 0.06).* For the comorbidities and other measures, there was no association between the *DAT1* genotypes and: substance use *(P = 0.88* for dichotomized genotype; *P = 0.84* for trichotomized genotype); CES (*P = 0.46* for dichotomized genotype; *P = 0.76* for trichotomized genotype); depression (*P = 0.33* for dichotomized genotype; *P = 0.06* for trichotomized genotype); and Q-LES-Q (*P = 0.20* for dichotomized genotype; *P = 0.39* for trichotomized genotype).

4. Discussion

4.1. Major findings and discussion of previous studies

To our knowledge, this is the first study to examine *DAT1* genotypes in a Veteran population with PTSD. In this study of military Veterans with combat exposures, we found that absence of 10R/10R alleles were associated with PTSD diagnosis after controlling for covariates, suggesting the present of 9R may be a risk factor for developing PTSD. In the Veterans with PTSD group, *DAT1* genotypes were not associated with PTSD symptom severity as measured by the CAPS. This suggests that the *DAT1* gene may increase Veteran's risk of PTSD developing post combat exposure, however, once PTSD develops, the current findings suggest that *DAT1* may not influence the severity of PTSD symptoms. The increased likelihood of PTSD diagnosis with 9R/10R heterozygotes and 9R/9R homozygotes is consistent with findings from a recent meta-analysis examining *DAT1* with PTSD, which found that the 9R allele was associated with PTSD with an OR of 1.62 (Li et al., 2016). In the current study, the genotypic and allelic association with PTSD symptom severity (i.e. total CAPS score) replicates the finding in a Hurricane Katrina's study by Drury and colleagues (Drury et al., 2009) . However, two community studies did not find a *DAT1* association with PTSD symptom severity (Bailey et al., 2010; Valente et al., 2011). While we found that the *DAT1* genotype is associated with hyperarousal symptoms for dichotomized genotype, previous literature is mixed (Drury et al., 2009; Valente et al., 2011). Yet, conceptually, the association between hyperarousal symptoms and *DAT1* supports the dopaminergic theory that correlates with certain PTSD symptoms such as reactivity and hyperarousal symptoms (Lee et al., 2016). No association between the PTSD intrusion or avoidance subscale scores was observed, which is consistent with prior community studies (Bailey et al., 2010; Drury et al., 2009; Valente et al., 2011). Interestingly, intrusive symptoms have been shown to be the most heritable PTSD cluster category (Bailey et al., 2010).

Genotype frequencies of the *DAT1* 9th alleles in patients with PTSD were: *non 9R* alleles in 51.2%, one 9R allele in 59.5%, two 9R alleles in 63.6%. This stepwise increase provides a possible gene dose effect, which supports our finding that the 9R alleles may be a potential risk factor for development of PTSD after trauma exposure among veterans. In addition, the 9R/9R homozygote individuals presented with the most severe PTSD symptoms indicated by highest CAPS scores (58.6), followed by 9R/10R heterozygote (50.6), then 10R/10R homozygote (43.4). This provides further evidence supporting our hypothesis that the 9R allele may have negative impacts on Veterans' response to combat trauma.

4.2. Baseline characteristic differences

Examination of baseline demographics revealed age and ethnicity differences between Veterans with PTSD as compared to combat-exposed controls without PTSD. One community *DAT1* candidate gene study for PTSD found a statistical difference in age between participants with and without PTSD; in that particular study, participants with PTSD were on average six years younger than those without PTSD (Valente et al., 2011). For our sample, this could also reflect recruitment bias, particularly selection bias as participants are subjectively referred to the research study via another provider/clinic. This age difference could also be reflective of the Veteran population at the time of recruitment given the demographics of Veterans who were deployed for the Afghanistan and Iraq wars. Given the start of study recruitment and of recent deployments, there were disproportionately more Vietnam veterans recruited at the start of the study; however, at later dates, more Afghanistan and Iraq combat veterans, who are younger, entered the study. Baseline ethnicity difference between the two groups could also be from recruitment bias. It is unclear if African Americans, who are considered minorities in the U.S., are at increased risk of having/being diagnosed with PTSD (Dohrenwend et al., 2008; Kaczkurkin et al., 2016; Monnier et al., 2002; Rosenheck and Fontana, 1996; Steenkamp et al., 2017), however, younger age and ethnic minorities have previously been shown to be potential risk factors for PTSD in Veterans (Wisco et al., 2014).

4.3. Strengths and limitations

The strengths of this study include: large sample size, more balanced case-to-control ratio, uniform trauma with verification in Veterans' records, and the inclusion of comorbidities. The current study has several limitations to consider. First, the findings only apply to Veterans, specifically combat trauma-exposed Veterans, and thus may not be generalizable to non-Veteran or heterogenous-trauma PTSD populations. Second, we did not have a healthy, non-combat exposed, control Veteran group for comparison. Lastly, recruitment bias could account for two baseline covariate differences between the PTSD cases and combat-exposed controls which may have skewed our findings. Despite these limitations, the current study is novel and is the first to show the association between *DAT1* genotype and PTSD among Veterans.

Notably, *DAT1* genotypes or alleles do not necessarily translate to changes in the intrinsic function of the *DAT1* protein, epigenetics or its density in the brain (Abdolmaleky et al., 2008; Cimino et al., 2018; Jasiewicz et al., 2014). Even so, several studies report that 10R allele has a differential affinity and/or expression compared to the 9R allele (Michelhaugh et al., 2001; Mill et al., 2002; van Dyck et al., 2005). Moreover, the *DAT1* genotype presented pertains mostly to the 9R and 10R alleles as these are the predominant alleles in the general population (Kang et al., 1999; Vandenbergh et al., 1992), as well as, in our sample. Nonetheless, it is unclear if the DAT VNTR polymorphism is associated with *DAT1* gene expression.

4.4. Implications

These findings are clinically relevant. First, the *DAT1* gene may serve as a biomarker for combat-exposed Veterans. As these Veterans return from their tour, the first encounter with a

clinician might include determining their *DAT1* genotype. If the combat-exposed Veterans do not have 10R/10R allele, in addition to any other relevant clinical factors, then providers may choose to closely monitor for PTSD development and may allow for earlier intervention with mental health care. Second, there is evidence that individuals with the 9R allele are slow responders to antidepressant medications (Kirchheiner et al., 2007), which are also the pharmacological treatments recommended for PTSD (Courois et al., 2017). Thus, knowing the Veteran's *DAT1* genotype may be instrumental to the therapeutic management decisions between the provider and Veteran. Lastly, these findings suggest that pharmacological agents that modulate the dopamine system may be of interest in PTSD. For example, a recent study of the second generation antipsychotic quetiapine suggested efficacy for the treatment of PTSD in a Veteran population (Villarreal et al., 2016); a finding which may be attributable to quetiapine's modulating dopaminergic action in particular brain regions (Silverstone et al., 2012). Another pharmacological agent with growing interest for the treatment of PTSD is atomoxetine, a selective norepinephrine reuptake inhibitor, which also has evidence for dopaminergic modulation (Akay et al., 2015). This agent is being investigated as a potential treatment for PTSD (Daud and Rydelius, 2009; Adler et al., 2004). Thus, *DAT1* could be a pharmacotherapeutic target as well as a potential biomarker for susceptibility to PTSD after trauma exposure. In addition to being the first candidate gene study in Veterans, our study is consistent with results found in non-Veteran community studies (Chang et al., 2012; Drury et al., 2009; Segman et al., 2002;Valente et al., 2011; Li et al., 2016).

4.5. Conclusion

To the authors' knowledge, the current study represents the largest sample for a single, non-twin, non-familial, *DAT1* PTSD candidate gene association study to date. Results show that the presence of the 9R allele may be a risk factor for Veterans developing PTSD following combat exposure. In addition, we found an association between *DAT1* genotypes and total CAPS scores, in both dichotomized and trichotomized genotype models. For the CAPS subscale scores, only CAPS D showed a linear relationship with decrease scores for the 10R allele in dichotomized but not trichotomized genotypes. These results replicate previous findings of *DAT1* genotypes with PTSD in the general population and add to the growing body of literature implicating 9R alleles with increased risk of developing PTSD. While these findings are significant, future studies are needed to replicate the results. The authors concur with Segman and colleagues that the best replication of a *DAT1* association with PTSD should include a transmission disequilibrium design which will limit ethnic confounds and false negative diagnoses (Segman et al., 2002). The clinical implications of this study warrant further research to explore *DAT1* as a potential target to improve PTSD management for Veterans.

Acknowledgments

The authors would like to thank Michael Madson and the Center for Academic Excellence.

Funding

This work was supported in part by Veterans Affairs merit grants 1I01CX000487–01A1 and 1R34MH078854–01, NIDA grants R25 DA020537 and K02 DA039229, and NIH/NCATS CTSA grant UL1 TR001450.

References

Abdolmaleky HM, Smith CL, Zhou JR, Thiagalingam S, 2008. Epigenetic alterations of the dopaminergic system in major psychiatric disorders. Methods Mol. Biol 448, 187–212. [PubMed: 18370235]

Adler LA, Kunz M, Chua HC, Rotrosen J, Resnick SG, 2004. Attention-deficit/hyperactivity disorder in adult patients with posttraumatic stress disorder (PTSD): is ADHD a vulnerability factor? J. Atten Disord 8, 11–16. [PubMed: 15669598]

Akay AP, Kaya GC, Baykara B, Demir Y, Ozek H, Alsen S, Eren MS, Emiroglu NI, Ertay T, Ozturk Y, Miral S, Durak H, Tufan E, 2015. Atomoxetine treatment may decrease striatal dopaminergic transporter availability after 8 weeks: pilot SPECT report of three cases. Neuropsychiatr. Dis. Treat 11, 2909–2912. [PubMed: 26640376]

Bailey JN, Goenjian AK, Noble EP, Walling DP, Ritchie T, Goenjian HA, 2010. PTSD and dopaminergic genes, DRD2 and DAT, in multigenerational families exposed to the Spitak earthquake. Psychiatry Res. 178, 507–510. [PubMed: 20554017]

Broekman BF, Olff M, Boer F, 2007. The genetic background to PTSD. Neurosci. Biobehav. Rev 31, 348–362. [PubMed: 17126903]

Chang SC, Koenen KC, Galea S, Aiello AE, Soliven R, Wildman DE, Uddin M, 2012. Molecular variation at the SLC6A3 locus predicts lifetime risk of PTSD in the Detroit Neighborhood Health Study. PLoS ONE 7, e39184. [PubMed: 22745713]

Cimino S, Cerniglia L, Ballarotto G, Marzilli E, Pascale E, D'Addario C, Adriani W, Tambelli R, 2018. DNA Methylation at the DAT promoter and risk for psychopathology: intergenerational transmission between school-age youths and their parents in a community sample. Front. Psychiatry 8, 303. [PubMed: 29375406]

Courois C, Sonis J, Brown L, Cook J, Fairbank J, Friedman M, Gone J, Jones R, Greca A, Mellman T, Roberts J, Schulz P, 2017. Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults.

Daud A, Rydelius PA, 2009. Comorbidity/overlapping between ADHD and PTSD in relation to IQ among children of traumatized/non-traumatized parents. J. Atten Disord 13, 188–196. [PubMed: 19395643]

Dohrenwend BP, Turner JB, Turse NA, Lewis-Fernandez R, Yager TJ, 2008. War-related posttraumatic stress disorder in Black, Hispanic, and majority White Vietnam veterans: the roles of exposure and vulnerability. J. Trauma. Stress 21, 133–141. [PubMed: 18404630]

Drury SS, Theall KP, Keats BJ, Scheeringa M, 2009. The role of the dopamine transporter (DAT) in the development of PTSD in preschool children. J. Trauma. Stress 22, 534–539. [PubMed: 19960520]

Endicott J, Nee J, Harrison W, Blumenthal R, 1993. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol. Bull 29, 321–326. [PubMed: 8290681]

First M, Spitzer R, Gibbon M, Williams J, 2007. Structured clinical interview for DSM-IV axis I disorders.

Graham DP, Nielsen DA, Kosten TR, Davis LL, Hamner MB, Makotkine I, Yehuda R, 2014. Examining the utility of using genotype and functional biology in a clinical pharmacology trial: pilot testing dopamine beta-hydroxylase, norepinephrine, and post-traumatic stress disorder. Psychiatr. Genet 24, 181–182. [PubMed: 24983834]

Hamner MB, Diamond BI, 1993. Elevated plasma dopamine in posttraumatic stress disorder: a preliminary report. Biol. Psychiatry 33, 304–306. [PubMed: 8471687]

Hamner MB, Gold PB, 1998. Plasma dopamine beta-hydroxylase activity in psychotic and non-psychotic post-traumatic stress disorder. Psychiatry Res 77, 175–181. [PubMed: 9707300]

Jasiewicz A, Grzywacz A, Jablonski M, Bienkowski P, Samochowiec A, Samochowiec J, 2014. The analysis of the polymorphic variations of the dopamine gen transporter (DAT1) and the serotonin transporter (5-HTTLPR) in patients with alcohol dependence syndrome with inclusion of the phenotypic feature of sweet liking preference. Psychiatr. Pol 48, 89–103. [PubMed: 24946437]

Kaczkurkin AN, Asnaani A, Hall-Clark B, Peterson AL, Yarvis JS, Foa EB, STRONG STAR Consortium, 2016. Ethnic and racial differences in clinically relevant symptoms in active duty

military personnel with posttraumatic stress disorder. J. Anxiety Disord 43, 90–98. [PubMed: 27639110]

Kang AM, Palmatier MA, Kidd KK, 1999. Global variation of a 40-bp VNTR in the 3′-untranslated region of the dopamine transporter gene (SLC6A3). Biol. Psychiatry 46, 151–160. [PubMed: 10418689]

Keane T, Fairbank J, Caddell J, Zimering R, Taylor K, Mora C, 1989. Clinical evaluation of a measure to assess combat exposure. Psychol. Assess 1, 53.

Kirchheiner J, Nickchen K, Sasse J, Bauer M, Roots I, Brockmoller J, 2007. A 40-basepair VNTR polymorphism in the dopamine transporter (DAT1) gene and the rapid response to antidepressant treatment. Pharmacog. J 7, 48–55.

Lee JC, Wang LP, Tsien JZ, 2016. Dopamine rebound-excitation theory: putting brakes on PTSD. Front. Psychiatry 7, 163. [PubMed: 27729874]

Li L, Bao Y, He S, Wang G, Guan Y, Ma D, Wang P, Huang X, Tao S, Zhang D, Liu Q, Wang Y, Yang J, 2016. The association between genetic variants in the dopaminergic system and posttraumatic stress disorder: a meta-analysis. Medicine (Baltimore) 95, e3074. [PubMed: 26986136]

Michelhaugh SK, Fiskerstrand C, Lovejoy E, Bannon MJ, Quinn JP, 2001. The dopamine transporter gene (SLC6A3) variable number of tandem repeats domain enhances transcription in dopamine neurons. J. Neurochem 79, 1033–1038. [PubMed: 11739616]

Mill J, Asherson P, Browes C, D'Souza U, Craig I, 2002. Expression of the dopamine transporter gene is regulated by the 3′ UTR VNTR: evidence from brain and lymphocytes using quantitative RT-PCR. Am. J. Med. Genet 114, 975–979. [PubMed: 12457396]

Monnier J, Elhai JD, Frueh BC, Sauvageot JA, Magruder KM, 2002. Replication and expansion of findings related to racial differences in veterans with combat-related PTSD. Depress. Anxiety 16, 64–70. [PubMed: 12219337]

Rosenheck R, Fontana A, 1996. Race and outcome of treatment for veterans suffering from PTSD. J. Trauma. Stress 9, 343–351. [PubMed: 8731552]

Segman RH, Cooper-Kazaz R, Macciardi F, Goltser T, Halfon Y, Dobroborski T, Shalev AY, 2002. Association between the dopamine transporter gene and posttraumatic stress disorder. Mol. Psychiatry 7, 903–907. [PubMed: 12232785]

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC, 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl 20), 22–33 quiz 34.

Silverstone PH, Lalies MD, Hudson AL, 2012. Quetiapine and buspirone both elevate cortical levels of noradrenaline and dopamine in vivo, but do not have synergistic effects. Front. Psychiatry 3, 82. [PubMed: 23049514]

Steenkamp MM, Schlenger WE, Corry N, Henn-Haase C, Qian M, Li M, Horesh D, Karstoft KI, Williams C, Ho CL, Shalev A, Kulka R, Marmar C, 2017. Predictors of PTSD 40 years after combat: findings from the National Vietnam Veterans longitudinal study. Depress. Anxiety 34, 711–722. [PubMed: 28489300]

Stein MB, Jang KL, Taylor S, Vernon PA, Livesley WJ, 2002. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. Am. J. Psychiatry 159, 1675–1681. [PubMed: 12359672]

Stevanovic D, 2011. Quality of life enjoyment and satisfaction questionnaire-short form for quality of life assessments in clinical practice: a psychometric study. J. Psychiatr. Ment. Health Nurs 18, 744–750. [PubMed: 21896118]

True WR, Rice J, Eisen SA, Heath AC, Goldberg J, Lyons MJ, Nowak J, 1993. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Arch. Gen. Psychiatry 50, 257–264. [PubMed: 8466386]

Valente NL, Vallada H, Cordeiro Q, Miguita K, Bressan RA, Andreoli SB, Mari JJ, Mello MF, 2011. Candidate-gene approach in posttraumatic stress disorder after urban violence: association analysis of the genes encoding serotonin transporter, dopamine transporter, and BDNF. J. Mol. Neurosci 44, 59–67. [PubMed: 21491204]

van Dyck CH, Malison RT, Jacobsen LK, Seibyl JP, Staley JK, Laruelle M, Baldwin RM, Innis RB, Gelernter J, 2005. Increased dopamine transporter availability associated with the 9-repeat allele of the SLC6A3 gene. J. Nucl. Med 46, 745–751. [PubMed: 15872345]

Vandenbergh DJ, Persico AM, Hawkins AL, Griffin CA, Li X, Jabs EW, Uhl GR, 1992. Human dopamine transporter gene (DAT1) maps to chromosome 5p15.3 and displays a VNTR. Genomics 14, 1104–1106. [PubMed: 1478653]

Villarreal G, Hamner MB, Canive JM, Robert S, Calais LA, Durklaski V, Zhai Y, Qualls C, 2016. Efficacy of quetiapine monotherapy in posttraumatic stress disorder: a randomized, placebo-controlled trial. Am. J. Psychiatry 173, 1205–1212. [PubMed: 27418378]

Weathers FW, Keane TM, Davidson JR, 2001. Clinician-administered PTSD scale: a review of the first ten years of research. Depress. Anxiety 13, 132–156. [PubMed: 11387733]

Wisco BE, Marx BP, Wolf EJ, Miller MW, Southwick SM, Pietrzak RH, 2014. Posttraumatic stress disorder in the US veteran population: results from the National Health and Resilience in Veterans Study. J. Clin. Psychiatry 75, 1338–1346. [PubMed: 25551234]

Yehuda R, Southwick S, Giller EL, Ma X, Mason JW, 1992. Urinary catecholamine excretion and severity of PTSD symptoms in Vietnam combat veterans. J. Nerv. Ment. Dis 180, 321–325. [PubMed: 1583475]

Table 1

Demographic and clinical characteristics of veterans with combat-related PTSD by study group.

Variable	No PTSD (*n* = 298)	PTSD (*n* = 365)	*P* Value
Age, mean (SD)	46.8(13.8)	44.0(14.3)	0.01
Male, No (%)	247 (82.9)	310 (85.2)	0.46
Race, No. (%)			0.003
Caucasian	224 (75.2)	247 (67.7)	
African American	49 (16.4)	98 (26.8)	
Other	25 (8.4)	20 (5.5)	
CES, mean (SD)[a]	19.6(9.1)	21.6(8.8)	0.02
Q-LES-Q, mean (SD)[b]	61.3(12.4)	40.6(8.9)	<0.001
Alcohol diagnosis, No. (%)	17 (8.9)	105 (30.9)	<0.001
Substance use diagnosis, No. (%)	21 (7)	124 (34)	<0.001
Depressive disorder diagnosis, No. (%)	14 (4.7)	240 (65.8)	<0.001

[a]CES: Combat Exposure Scale from 436 veterans.

[b]Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire from 107 veterans.

Table 2

Comparison of demographic and clinical characteristics by genotype.

	Genotype		
Variable	10R, 10R (*n* = 378)	10R, X (*n* = 252)	9R, 9R (*n* = 33)
Age, mean (SD), y	45.1 (13.9)	45.1 (14.7)	48.3 (12.9)
Male, No (%)	314 (83.3%)	220 (87.3%)	23 (69.7%)
Race, No. (%)			
Caucasian	268 (70.9%)	180 (71.4%)	23 (69.7%)
African American	81 (21.4%)	57 (22.6%)	9 (27.3%)
Other	29 (7.7%)	15 (6%)	1 (3%)
PTSD diagnosis, No. (%)	194 (51.2%)	150 (59.5%)	21 (63.6%)
‡CAPS total score, mean (SD)	43.4 (38.4) *,#	50.6 (37.4) *,#	58.6 (36.7) *,#
CAPS subscale B score, mean (SD)	12.0 (11.6)	13.9 (12.0)	13.79 (12.0)
CAPS subscale C score, mean (SD)	16.9 (16.0)	19.0 (15.7)	16.42 (14.6)
CAPS subscale D score, mean (SD)	15 (12.5) #	17.4 (12.6) #	18.95 (12.2) #
Depression, No. (%)	139 (36.7)	96 (38.1)	19 (57.6)
Alcohol Use Disorder, No. (%)	61 (20.6)	57 (27)	4 (16)
Substance Use Disorder, No. (%)	82 (21.6)	57 (22.6)	6 (18.2)
[a]CES, mean (SD)	21.2 (8.9)	20.6 (8.9)	20.4 (9.1)
[b]Q-LES-Q, mean (SD)	46.5 (12.0)	43.4 (13.9)	37.0 (0)

‡CAPS: Clinician Administered PTSD Scale on 638 veterans.

[a]CES: Combat Exposure Scale.

[b]Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire.+Tested on only genotypes 10R/10R vs. 10R/X due to an $n = 1$ in genotype 9R/9R.

*p-value < 0.025 for trichotomized genotype.

#p-value < 0.025 for dichotomized genotype.

Table 3

Logistic regression results examining factors associated with PTSD diagnosis.

Variable	Odds Ratio	97.5% CI	*P* Value
Genotype			
(10R,X or 9R,9R)	1.60	(1.01, 2.07)	0.022 *
10R,10R	Reference		
Race			
Non-white	7.25	(0.96, 2.11)	0.047
White	Reference		
Sex			
Male	1.42	(0.72, 1.89)	0.48
Female	Reference		
Age	0.99	(0.97, 1.00)	0.009 *

* *p*-value < 0.025.