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Genetic pathways to posttraumatic stress disorder and depression in children: Investigation of catechol-O-methyltransferase (COMT) Val158Met using different PTSD diagnostic models

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ABSTRACT

The catechol-O-methyltransferase (COMT) Val158Met polymorphism has been linked to PTSD, although findings have been inconsistent. Recently, different diagnostic criteria for PTSD have been introduced by ICD-11 and DSM-5, including separate criteria for adults and for young children (i.e., the preschool criteria). The preschool criteria may be applicable to older children as well. This study is the first to examine COMT associations with depression and PTSD, using new diagnostic models, in school-age children (7–11 years) exposed to a natural disaster. Children (n = 115) provided saliva samples for genotyping and completed measures assessing disaster exposure, posttraumatic stress, and depressive symptoms. COMT Met allele carriers were at risk for PTSD, but only when using ICD-11 (*OR* = 6.99) or the preschool criteria (*OR* = 4.77); there was a trend for DSM-IV and no association for DSM-5 (adult criteria). However, all children agreed upon as having PTSD by both DSM-5 and ICD-11 were Met allele carriers. The genetic association between the COMT Met allele and PTSD seemed primarily driven by arousal symptoms, as a significant relationship emerged only for the PTSD arousal symptom cluster. In contrast, COMT Val allele homozygosity was associated with depression (*OR* = 4.34). Thus, findings suggest that opposing COMT genotypes increased vulnerability to depressive versus arousal-based clinical presentations following trauma exposure. As a result, the heterogeneity of the DSM-5 PTSD criteria and its inclusion of depressive symptoms may mask COMT associations with DSM-5 PTSD. Future research should consider how the use of different diagnostic models of PTSD may influence genetic findings.

1. Introduction

Genetic variation is considered a key factor in determining risk for posttraumatic stress disorder (PTSD), with genetic contributions to PTSD vulnerability estimated to be around 30–40% (Sartor et al., 2012; Voisey et al., 2014). Children are a vulnerable population for developing PTSD following trauma exposure (Silverman and La Greca, 2002); yet little research has investigated genetic risk for PTSD in trauma-exposed children.

Catechol-O-methyltransferase (COMT) has received increasing attention as playing a role in several psychiatric disorders, including PTSD. The COMT enzyme is involved in the catalysis and inactivation of catecholamines, such as dopamine. The widely-studied rs4680 variant within the COMT gene substitutes the amino acid valine (Val) to methionine (Met) at codon 158, which is commonly known as the Val158Met polymorphism. Met allele carriers have a 40% reduction in enzyme activity, resulting in higher levels of dopamine in the brain (Chen et al., 2004).

The COMT Val158Met polymorphism has been linked to PTSD, although findings have been mixed. The Met allele has been associated with PTSD in many studies (Boscarino et al., 2011; Clark et al., 2013; Humphreys et al., 2014; Kolassa et al., 2010; Valente et al., 2011), whereas the Val allele also has been linked to PTSD in some studies (Clark et al., 2013; Humphreys et al., 2014). A study of earthquake-exposed adults that examined genetic associations with PTSD using DSM-5 criteria did not find an association for the Val158Met polymorphism (Goenjian et al., 2014).

The broader literature, taken together, indicates that both alleles may confer advantages and vulnerabilities. From an evolutionary perspective, Goldman's “warrior/worrier” model (Goldman et al., 2005) posits that there may be tradeoffs between stress resiliency (“warrior” allele Val) and cognitive functioning (“worrier” allele Met) that contribute to the persistence of both alleles in the population. The disadvantages conferred by either Val158Met allele can influence mechanisms that increase vulnerability to different psychiatric disorders.

This point is illustrated by research indicating that Val homozygotes

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have greater risk for depression (Drury et al., 2010; Massat et al., 2005; Sheikh et al., 2013), even though the Met allele is most commonly identified as the risk allele for PTSD. Depression is highly comorbid with PTSD, and co-occurs in half of individuals with PTSD (Rytwinski et al., 2013); this comorbidity may be partially responsible for findings linking Val to PTSD. The high degree of variability in PTSD presentations is an important factor to consider when investigating genetic associations (Young et al., 2014).

Importantly, diagnostic conceptualizations of PTSD recently have been evolving, with the release of DSM-5 in 2013 and the upcoming ICD-11 release in 2018 (American Psychiatric Association, 2013; World Health Organization, 2017). A major difference between the DSM-5 and ICD-11 criteria for PTSD is the amount of symptoms overlapping with other disorders, especially depression. DSM-5 added a new symptom cluster for problems with cognitions and mood to the PTSD criteria, which now share many symptoms in common with depression (e.g., anhedonia, negative beliefs, insomnia, concentration problems). In contrast, ICD-11 reduces PTSD criteria by focusing on a few "core" symptoms, which do not overlap with depressive symptoms (Maercker et al., 2013). Unsurprisingly, given these differences, DSM-5 PTSD has greater comorbidity with depression in youth than does ICD-11 PTSD (La Greca et al., 2017). Research on the COMT gene has not investigated associations with these different diagnostic models of PTSD; given the differences in how the COMT gene influences psychopathology, the Val158Met polymorphism may be differentially related to DSM-5 versus ICD-11 PTSD.

In addition to being the first to investigate genetic associations with different diagnostic models of PTSD, this study contributes to the literature by investigating COMT in school-age children (ages 7–11). Very few studies have investigated genetic risk for PTSD in children. The only study of youth examining COMT genetic risk for PTSD used younger children (ages 3–6), finding that COMT Val158Met was associated with increased arousal symptoms, and that the association with PTSD was moderated by race (Humphreys et al., 2014). Several studies have examined COMT and depression in very young children, finding that children with homozygous Val158 alleles were at greater risk for depression (Drury et al., 2010; Sheikh et al., 2013).

It is important to investigate genetic risk for PTSD specifically in school-age children, because children may present with different PTSD symptoms than adults (Danzi and La Greca, 2016). In fact, recognizing the developmental differences in PTSD presentations in children, DSM-5 introduced separate PTSD criteria specifically intended for children ages six and younger (i.e., the preschool criteria; American Psychiatric Association, 2013). The preschool criteria also may capture the trauma reactions of many school-age children (Danzi and La Greca, 2017).

The purpose of this study was to investigate the association between COMT Val158Met and different diagnostic models of PTSD (ICD-11, DSM-IV, DSM-5, and DSM-5 preschool criteria) and PTSD symptom clusters. We also investigated the relationship between COMT Val158Met and depression.

2. Methods

2.1. Participants

Participants were children (n = 115) exposed to Hurricane Ike, a devastating natural disaster that was responsible for 103 deaths and was one of the most damaging hurricanes in U.S. history, costing $29.5 billion (Berg, 2008; Blake et al., 2011). The children were school-age (7–11 years), 54% female, and ethnically/racially diverse (37% White, 30% Hispanic, 20% Black, 13% Other/Mixed). Children with genetic data were part of a larger sample (n = 327); there were no differences in age, gender, life threat, stressors, PTSD, or depression between children with genetic data and the larger sample, although a greater percentage of White children participated in genetic testing (La Greca et al., 2013).

2.2. Procedure

The study protocol was approved by Internal Review Boards for the University of Miami, University of Texas-Medical Branch, and Galveston Independent School District. Children were recruited from all six elementary schools in Galveston, TX, which sustained a direct hit from Hurricane Ike. After obtaining parental informed consent and child assent, questionnaire measures were administered to children 8 months postdisaster. At the time of assessment, additional parental consent forms were distributed for the ancillary genetic testing study. After obtaining consent and assent, children's saliva samples were collected using Oragene DNA collection kits. Additional details are provided in La Greca et al. (2013).

2.3. Measures

2.3.1. Trauma exposure and stress

Hurricane exposure, including life threat and postdisaster stressors, was assessed using the Hurricane Related Traumatic Experiences–Revised (HURTE-R; La Greca et al., 1996). The HURTE-R includes four scales: Actual life threat (e.g., windows breaking; six *Yes/No* items; range of 0–6), perceived life threat (thinking you might die during the hurricane; one *Yes/No* item), immediate loss/disruption (e.g., home damage; ten *Yes/No* items; range of 0–10), and ongoing loss/disruption (e.g., home still damaged; six *Yes/No* items; range of 0–6).

Additional stressful life events (e.g., death of family member) were assessed using a short version of the Life Events Checklist (LEC; Johnson and McCutcheon, 1980), which consists of 14 *Yes/No* items. LEC items were summed to yield a score that could range 0–14.

Both the HURTE-R and LEC have been widely used to assess disaster exposure and postdisaster stressors in other studies of children (La Greca et al., 2010; Weems et al., 2010; Yelland et al., 2010).

2.3.2. Depression

The Children's Depression Inventory (CDI) is a commonly-used measure of depressive symptoms (Kovacs, 1981). The CDI has 27 items; however, one item on suicidal ideation was not administered due to IRB concerns. The items have three levels of severity (scored 0, 1, or 2), with a score of 1 or 2 indicating symptom endorsement; thus, higher scores indicate greater depression. Internal consistency was acceptable ($\alpha = 0.84$).

2.3.3. PTSD

The Posttraumatic Stress Disorder-Reaction Index, Revision 1 (PTSD-RI-R) is one of the most widely-used measures for assessing PTSD symptoms in children (Steinberg et al., 2013, 2004). The PTSD-RI-R has strong psychometric properties (Elhai et al., 2013; Steinberg et al., 2013); in this sample, internal consistency was excellent ($\alpha = 0.90$). The PTSD-RI-R includes 22 items on a 3-point scale (0 = *None of the time*, 2 = *Some of the time*, 4 = *Most of the time*); 17 items are used to assess DSM-IV criteria, per standard scoring procedures (Steinberg et al., 2004). A score of 4 was used to indicate symptom presence, consistent with recommendations (Steinberg et al., 2004).

The methodology for assessing ICD-11, DSM-5, and the DSM-5 preschool criteria for PTSD has been described in detail elsewhere, including the item text used for individual symptoms (Danzi and La Greca, 2016; La Greca et al., 2017; Danzi and La Greca, 2017). ICD-11 consists of six symptoms across three symptom clusters (re-experiencing, avoidance, and arousal); at least one symptom per cluster is required for diagnosis (World Health Organization, 2017). DSM-5 contains 20 symptoms across four clusters, with the minimum requirement of one symptom from the re-experiencing cluster, one symptom from the avoidance cluster, two symptoms from the cognitions/mood cluster, and two symptoms from the arousal cluster (American Psychiatric

Association, 2013). The DSM-5 preschool criteria have 16 symptoms across three clusters, with at least one symptom required from the re-experiencing cluster, one symptom reflecting either avoidance or changes in cognitions/mood, and two arousal symptoms (American Psychiatric Association, 2013). The PTSD-RI-R was used to assess all ICD-11 symptoms and most DSM-5 and DSM-5 preschool criteria symptoms; two DSM-5 symptoms and one preschool criteria symptom were not captured by the PTSD-RI-R, and so two items from the Revised Children's Manifest Anxiety Scale (RCMAS; Reynolds and Richmond, 1985) and one item from the CDI were used to approximate these symptoms (Danzi and La Greca, 2016; Danzi and La Greca, 2017; La Greca et al., 2017). The DSM-5 symptom of reckless/self-destructive behavior was not assessed; this symptom was based on adult-orientated behaviors that are unlikely to be relevant for school-age children (Friedman et al., 2011).

2.3.4. Genotyping

Analysis of genetic variance was conducted by the Center for Genome Technology Genotyping Core Facility at the John P. Hussman Institute for Human Genomics at the University of Miami Miller School of Medicine. DNA was extracted from saliva samples using Qiagen PureGene reagents. Taqman allelic discrimination assays were performed for rs4680 (Val158Met) using established protocols and quality control procedures. The genotypic distribution for Val158Met was in Hardy-Weinberg equilibrium ($\chi^2[1] = 0.137$, $p > .05$), with genotypes Val/Val (n = 40), Val/Met (n = 54), and Met/Met (n = 21).

2.4. Analyses

All analyses were conducted using SPSS (IMB Version 24). Missing questionnaire data (< 3% for study variables) were handled using multiple imputation, specifically an iterative Markov chain Monte Carlo method of 20 imputations with 100 burn-in iterations at item-level; results were pooled across imputations (Graham et al., 2007).

Analyses of variance, chi-square tests, and Pearson correlations were conducted to determine relationships between study variables, as appropriate. There were several variables expected to be associated with outcome variables (PTSD and depression) based on prior research. Specifically, gender and race/ethnicity are well-established predictors of PTSD and depression (Banks and Weems, 2014; Pfefferbaum et al., 2015). Life threat (objective and perceived), hurricane-related loss/disruption (immediate and ongoing), and other stressful life events are also important to the development of PTSD and depression (Banks and Weems, 2014; La Greca et al., 1996; Pfefferbaum et al., 2015; Yelland et al., 2010). Thus, relationships between these variables and the dependent variables were evaluated to determine whether these variables should be included as covariates in regression models.

To investigate genetic associations with PTSD, logistic regression analyses were conducted separately with each diagnostic model (DSM-IV, DSM-5, DSM-5 preschool, and ICD-11) as a binary outcome (1 = diagnosis, 0 = no diagnosis). Regression analyses were conducted controlling for demographics (gender, race/ethnicity), trauma exposure and stress (actual life threat, perceived life threat, immediate and ongoing loss/disruption, stressful events), and comorbidity (depression) by entering these variables in a step prior to entering the COMT genotype. To test for gene-environment interactions, interaction terms were created for COMT and the trauma exposure and stress variables; these were entered individually in a later step. Additional logistic regressions were used to investigate associations between COMT and PTSD symptom clusters (controlling for the same variables). Symptom clusters were defined according to DSM-5 criteria, because that definition is the broadest and mostly encompasses the clusters defined by the other diagnostic models.

The relationship between COMT and depression also was investigated. Logistic regression was used to allow for direct comparison to the PTSD odds ratios. The clinical cutoff score of 19 or higher on the CDI was used to indicate depression (Kovacs, 1981). In order to be analogous to the PTSD analyses, the same logistic regression model (1 = depression, 0 = no depression) was used to evaluate genetic associations with depression, controlling for the same demographic and stress exposure variables, as well as comorbidity (PTSD-RI-R total severity scores).

Overall, the analyses were conducted with the COMT genotypes modeled as Met dominant and Met recessive. The Met dominant model compared Met allele carriers to Val homozygotes (Met/Met and Met/Val versus Val/Val). The Met recessive model compared Val allele carriers to Met homozygotes (Val/Val and Met/Val versus Met/Met).

3. Results

3.1. Preliminary analyses

There were no significant differences in genotypic distribution for gender ($\chi^2[2] = 1.47$, $p > .05$) or race/ethnicity ($\chi^2[6] = 9.92$, $p > .05$). Study analyses initially were conducted separately within each racial/ethnic group, but no significant findings emerged; thus, the full sample was used instead. In the full sample, Black children reported higher PTSD-RI-R severity scores than White children ($F[3111] = 4.55$, $p < .01$) and girls had higher PTSD severity than boys ($F[1113] = 5.28$, $p < .05$). There were no gender differences for depressive symptoms; however, Hispanic and Black children reported more depressive symptoms than White children (*Welch's* $F[3, 44.07] = 3.46$, $p < .05$), although Games-Howell post hoc tests only indicated trends. PTSD and depression scores each were correlated with perceived life threat, actual life threat, immediate loss/disruption, ongoing loss/disruption, and stressful life events (for PTSD, Pearson correlation coefficients ranged from 0.27 to 0.48, $ps < .01$; for depression, coefficients ranged from 0.19 to 0.36, $ps < .05$). PTSD and depression were also correlated ($r = 0.57$, $p < .001$). Given these associations, all of these variables were controlled when examining genetic associations with PTSD and depression.

3.2. COMT Val158Met

3.2.1. Risk for PTSD and depression

Met dominant and Met recessive genetic models were tested using logistic regression, for each diagnostic model of PTSD and depression. No significant findings emerged for the Met recessive model. Results for the Met dominant model are provided in Table 1. To aid in the comparison of odds ratios, the left side of Table 1 displays results with Met carriers as the reference group (coding of 1 = Met/Met and Val/Met; coding of 0 = Val/Val) and the right side displays analogous results with Val homozygotes as the reference group (coding of 1 = Val/Val; coding of 0 = Met/Met and Val/Met). Met carriers were at greater risk for PTSD as defined by ICD-11 (*OR* = 6.99) and the DSM-5 preschool

Table 1
COMT Val158Met associations with PTSD diagnostic models and depression using the Met dominant model.

	Met carriers		Val homozygotes		*p-value*
	OR	*95% CI*	*OR*	*95% CI*	
PTSD					
DSM-IV	4.41†	0.83–23.43	0.23†	0.04–1.20	.081
DSM-5	2.94	0.48–17.95	0.34	0.06–2.07	.242
DSM-5 Preschool	4.77*	1.08–21.14	0.21*	0.05–0.93	.040
ICD-11	6.99*	1.34–36.57	0.14*	0.03–0.75	.021
Depression	0.23*	0.06–0.85	4.34*	1.17–16.02	.028

Met carriers: coding of 1 = Met/Met and Val/Met, 0 = Val/Val.
Val homozygotes: coding of 1 = Val/Val, 0 = Met/Met and Val/Met.
†$p < .1$, *$p < .05$.

Table 2
Associations between PTSD symptom clusters and COMT Met carriers.

	OR	*95% CI*	*p-value*
PTSD			
Re-experiencing	1.00	0.32–3.14	.996
Avoidance	2.18	0.77–6.14	.140
Cognitions/Mood	1.43	0.45–4.60	.547
Arousal	4.49*	1.07–18.86	.040

*$p < .05$.

criteria (*OR* = 4.77). In addition, there was a trend for DSM-IV and no association for DSM-5 (adult criteria).

There was a significant association between COMT and depression (see Table 1). However, in contrast to PTSD, odds ratios revealed that the opposing COMT genotype conferred risk for depression. Specifically, Val homozygotes were at greater risk for depression (*OR* = 4.34).

3.2.2. PTSD symptom clusters

PTSD symptom clusters were investigated for associations with COMT Val158Met, using the Met dominant genetic model. Logistic regression results for Met carriers (1 = Met/Met and Val/Met; 0 = Val/Val) for each PTSD symptom cluster are displayed in Table 2. Only the arousal symptom cluster was associated with COMT Val158Met (*OR* = 4.49). The other PTSD symptom clusters were not associated with the COMT polymorphism.

3.2.3. Comparison of PTSD diagnostic models

We compared genotypic frequencies in the soon-to-be current diagnostic models recommended for children of this age group: DSM-5 and ICD-11. These two diagnostic models are also the most divergent. In this sample, there was a 33% overlap in cases between DSM-5 and ICD-11. There were discrepancies in the genetic frequencies ($\chi^2 = 9.40$, $p < .05$). All children (100%) who met criteria for both ICD-11 and DSM-5 had the Met allele. For children identified only by ICD-11 (but not DSM-5), 73% had the Met allele. However, for children identified only by DSM-5 (but not ICD-11), only 20% had the Met allele.

3.2.4. Gene-environment interactions

Each PTSD diagnostic model and depression were investigated for interactions between COMT and indicators of trauma exposure and stress. Specifically, interactions were investigated for life threat (actual and perceived), hurricane-related loss/disruption (immediate and ongoing), and major life stressors. No significant gene-environment interactions emerged for perceived life threat, actual life threat, or ongoing loss/disruption. A gene-environment interaction emerged for immediate loss/disruption, but only for the ICD-11 PTSD criteria; Met carriers with greater post-hurricane loss/disruption (e.g., home damaged, possessions ruined, food scarcity) were at heightened risk for ICD-11 PTSD than those with less loss/disruption (OR = 3.73, $p < .01$). Similarly, a gene-environment interaction emerged for major life stress, but only for the ICD-11 criteria; Met carriers with more stressful life events were at heightened risk for ICD-11 PTSD than those with fewer stressful events (OR = 14.34, $p < .05$). No significant gene-environment interactions emerged for depression or for the DSM-IV, DSM-5, or the DSM-5 preschool criteria for PTSD.

4. Discussion

PTSD and depression occur frequently in youth following natural disasters (Jia et al., 2010; Lai et al., 2013; Norris et al., 2002; Pfefferbaum et al., 2015). In this study, opposing COMT genotypes influenced risk for PTSD versus depression. Children who were Met allele carriers had greater PTSD, as defined by ICD-11 or the DSM-5 preschool criteria, whereas children with homozygous Val alleles had greater depression. These findings may reveal a potential pathway through which trauma-exposed individuals are influenced towards a PTSD versus depressogenic response to trauma.

Investigation of symptom clusters revealed that the genetic association with PTSD was primarily driven by arousal symptoms, as the arousal cluster was the only PTSD symptom cluster associated with Met allele carriers. This relationship with arousal fits with the role of COMT Met158 in increasing dopamine levels in the synaptic cleft via reduced enzyme activity (Chen et al., 2004). Heightened dopamine levels have been linked to increased arousal (Monti and Monti, 2007; Vermetten and Bremner, 2002).

These findings suggest that COMT Met allele carriers may be at increased risk for an arousal-based presentation of PTSD, whereas Val homozygotes may be at increased risk for a presentation that has more in common with depression. Arousal symptoms are a substantial component of the ICD-11 criteria for PTSD (2 out of 6 symptoms). Children who were carriers of the Met allele were almost seven times more likely to be diagnosed with ICD-11 PTSD than the non-carriers.

No relationship emerged between COMT Val158Met and DSM-5 PTSD. This result is consistent with findings from another study that did not obtain an association between Val158Met and DSM-5 PTSD in disaster-exposed adults (Goenjian et al., 2014). The DSM-5 criteria allow for a great deal of heterogeneity in PTSD presentations, with over 600,000 possible symptom combinations (Galatzer-Levy and Bryant, 2013). DSM-5 criteria contain many shared symptoms with depression, and has higher comorbidity with depression (La Greca et al., 2017). Given that opposing COMT genotypes increased risk for depression versus an arousal-based PTSD presentation (i.e., ICD-11), the heterogeneity in DSM-5 PTSD may have masked associations with COMT. This will be an important issue for researchers to consider since the use of DSM-5 criteria for assessing PTSD in genetic studies will likely become more prominent over the next decade.

We also compared genetic frequencies between ICD-11 and DSM-5, as these diagnostic models will soon be the current criteria recommended for use in this age group (7–11 years) and yet have major differences in terms of factor structure (three factors in ICD-11 versus four in DSM-5) and number of symptoms (six versus 20). Interestingly, all children agreed upon as having PTSD by both ICD-11 and DSM-5 were Met allele carriers. This adds credence to the argument that Met158 is associated with a "pure" presentation of PTSD. For children identified only by ICD-11, 73% were Met allele carriers. For children identified only by DSM-5, 80% were Val homozygotes. These children identified only by DSM-5 may represent the subset with a depressive presentation, given the relationship between Val homozygosity and depression.

In addition to ICD-11, a significant association with COMT also emerged for the DSM-5 preschool criteria, with Met allele carriers being over four times more likely to be diagnosed using the preschool criteria than non-carriers. The preschool criteria share much in common with ICD-11, such as a three-factor structure and fewer symptoms compared to DSM-5. The preschool criteria were designed to exclude highly internalized or cognitively-advanced symptoms that may be difficult for young children to report (Scheeringa et al., 2011); as a result, the DSM-5 preschool criteria share less in common with depression compared to DSM-5 adult criteria. For example, the preschool criteria omit symptoms such as negative beliefs or distorted cognitions about guilt or blame.

This study found a trend in the association between DSM-IV and COMT. DSM-IV criteria reflect an intermediary between DSM-5 and the preschool criteria. DSM-IV has three symptom clusters, as does the preschool criteria, and also lacks a cognitions/mood cluster (where most of the depressive symptoms reside in DSM-5). However, the DSM-IV criteria still includes many symptoms that are common in depression (e.g., anhedonia), as is true for DSM-5.

Gene-environment interactions only emerged for ICD-11 PTSD, for the stressors of immediate hurricane-related loss/disruption and major life events. No gene-environment interactions emerged when using the

other diagnostic models. It is interesting that significant main effects and interactions were obtained for ICD-11, given that the ICD-11 criteria are more parsimonious and simpler to assess compared to the more expansive DSM models. When compared descriptively, the odds ratio for ICD-11 was higher than for the other diagnostic models (see Table 1), so the emergence of significant interactions for ICD-11 may be a product of the stronger relationship between ICD-11 and COMT. Given the differences in findings depending on which diagnostic model was used, future research on PTSD should consider utilizing multiple criteria, as this approach may provide more nuanced insight into how etiological factors contribute to vulnerability for PTSD. Understanding how risk factors differentially predict different models of PTSD will improve the overarching conceptualization of the disorder.

Although this study makes several novel contributions, including being the first to examine COMT associations with PTSD in school-age children and to examine genetic associations with new diagnostic models, several limitations should be noted. First, this study only had child-report of PTSD and depressive symptoms. Even though parents may have difficulty identifying children's internalizing PTSD symptoms (Stover et al., 2010), future research would benefit from using multiple informants, including parents, teachers, and clinicians, to assess child PTSD. Further, because the data were collected prior to the advent of new PTSD diagnostic models, the criteria had to be approximated using measures available at the time. This methodology is described in detail elsewhere (e.g., Danzi and La Greca, 2016; Danzi and La Greca, 2017; La Greca et al., 2017); the DSM-5 symptom of reckless/self-destructive behavior was unable to be assessed. Future research should investigate genetic associations with different diagnostic models using measures designed and validated to assess them once such measures become available. Finally, this study focused on children exposed to a hurricane. While this is a strength for reducing confounding variability (Voisey et al., 2014), these findings may not generalize to other trauma types, especially complex traumas such as child maltreatment. Future research should investigate these issues in children exposed to other types of trauma.

Taken together, the findings illustrate the importance of 1) considering how PTSD is being defined when investigating genetic relationships; and 2) investigating genetic associations with PTSD symptom clusters. This approach may provide insight into the mechanisms through which genetic risk is conferred and thereby contribute to understanding the biological basis underlying broad variations in clinical presentations, especially in highly heterogeneous disorders such as PTSD. Future research linking genetic vulnerability to specific clinical presentations may also help with refining and improving the diagnosis of PTSD in children.

Conflicts of interest

B.A. Danzi has no conflicts of interest to disclose.
A.M. La Greca has no conflicts of interest to disclose.

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Contributors

A.M. La Greca obtained funding to support the project and was the Principal Investigator for the data collection. Both authors contributed to the study design, aims, and hypotheses presented in this paper. B.A. Danzi conducted statistical analyses and manuscript preparation. Both authors have approved the final article.

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