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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