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Gene-Environment Interaction in Posttraumatic Stress Disorder: An Update

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The authors provide a detailed review of the extant gene–environment interaction (GxE) research in the etiology of posttraumatic stress disorder (PTSD). They begin with a discussion of why PTSD is uniquely fitting for the innovative framework of GxE methodology, followed by a review of the heritability and main effect molecular genetics studies of PTSD. Next, they discuss the six GxE investigations to date on PTSD. They end with a discussion of future directions and significance of this research, with an emphasis on the expansion of psychosocial factors that may be fitting environmental variables for inclusion in this new research area. The authors posit that GxE research is vital to elucidating risk and resilience following exposure to a potentially traumatic event.

Although the majority of individuals have been exposed to at least one potentially traumatic event (PTE) during their lifetime, trauma-exposed individuals evidence heterogeneous responses, including resilience, rapid recovery, or the development of psychopathology (e.g., posttraumatic stress disorder [PTSD], depressive and anxiety disorders, and a range of comorbidities; Copeland, Keeler, Angold, & Costello, 2007; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Differential responding to environmental pathogens is perhaps one of the most important indicators of a gene–environment interaction (GxE), in which the effects of environmental exposure are moderated by genotype (Moffitt, Caspi, & Rutter, 2005). In the present article, we discuss the compatibility of the GxE paradigm with research on PTSD, review the six published GxE investigations of PTSD, and briefly highlight strategies for future studies.

Posttraumatic Stress Disorder as an Ideal Candidate for GxE Methodology

In a seminal article outlining strategies for examining interactions between candidate genes and measured environments, Moffitt and colleagues (Moffitt et al., 2005) provide an overview of the GxE paradigm, recommend steps for conducting GxE research, and highlight the benefits of GxE strategies for understanding the etiology of common mental disorders. PTSD, as one of the few psychiatric diagnoses requiring exposure to an environmental pathogen (e.g., exposure to a PTE), is particularly suited to GxE research.

Potentially Traumatic Events as Candidate Environmental Pathogens

PTEs are excellent candidates for GxE research according to the criteria set out by Moffitt et al. (2005). First, there is variability in response even to the most severe PTEs; most exposed individuals do not develop PTSD. Second, PTEs as reviewed in detail elsewhere (Delahanty, 2008), appear to exert measurable and causal effects on neurobiological pathways relevant to the development of PTSD. Third, evidence from epidemiologic and twin studies suggest severity of PTEs, such as combat exposure, are causally related to the development of PTSD (Dohrenwend et al., 2006; Goldberg, True, Eisen, & Henderson, 1990).

However, it is not merely the occurrence of PTEs that confers risk for PTSD, but also important contextual and descriptive

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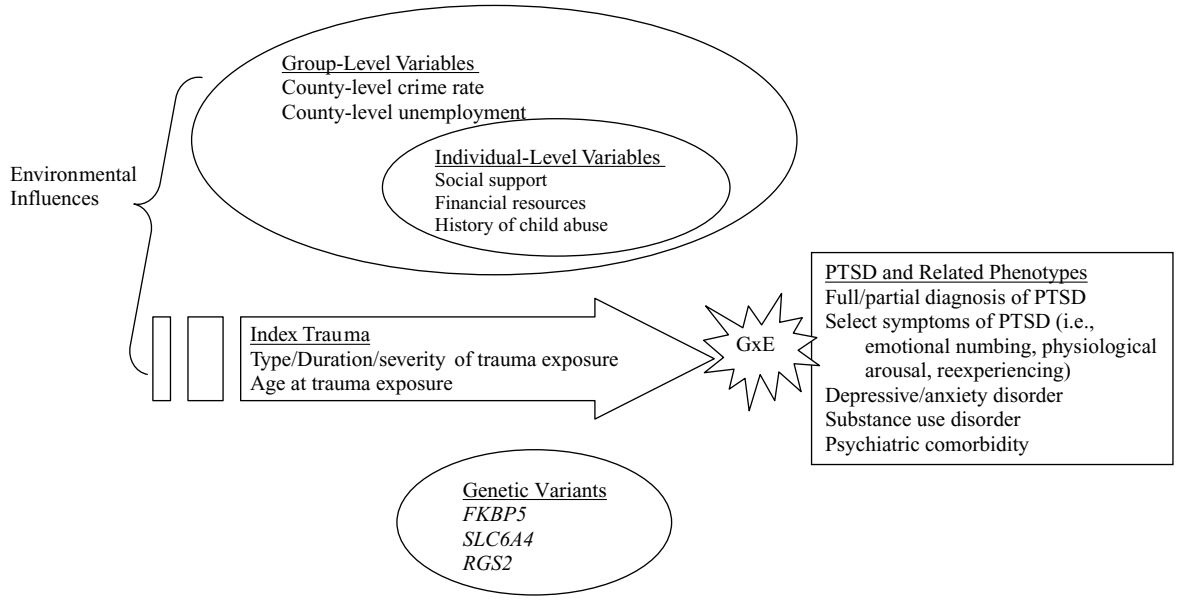

Figure 1. A thematic overview of GxE studies of posttraumatic stress disorder.

aspects of the trauma. As shown in Figure 1, specific aspects of the trauma (e.g., extent of exposure such as level of hurricane exposure) may be important for understanding the degree and nature of influence of the environmental pathogen. Identifying relevant aspects of the traumatic experience can be somewhat informed by the expected neurobiological mechanisms of effect on subsequent PTSD. For example, emergent research suggests that maternal hormones and concomitant pre- and perinatal environment may influence glucocorticoid functioning in offspring (de Kloet, Sibug, Helmerhorst, & Schmidt, 2005; Yehuda et al., 2005). Given this evidence for possible developmentally sensitive processes, GxE studies examining aspects of the glucocorticoid system may need to carefully quantify age-related factors such as age at index trauma, age at first trauma, or maternal peripartum symptoms.

Genetic Investigations of Posttraumatic Stress Disorder

Evidence for genetic influences on posttrauma development of PTSD comes from both family and twin studies (see Koenen, 2007, for a review of genetic methodology pertaining to PTSD). Offspring whose parents have PTSD evidence higher rates of PTSD as adults (Yehuda, Halligan, & Bierer, 2001) and during childhood (Hall et al., 2005). Similarly, twin studies of PTSD suggest that genetic influences account for about one third of the variance in risk of developing PTSD (Stein, Jang, Taylor, Vernon, & Livesley, 2002; True et al., 1993). However, familial risk of developing PTSD may be partly mediated by genetic influences on exposure to trauma (Koenen et al., 2002), referred to as the gene-environment correlation, and twin studies of both veteran and civilian samples have supported a role for genetic factors in exposure to PTEs (Lyons et al., 1993; Stein et al., 2002). Nonetheless, genetic influences on exposure to PTEs do not fully account for genetically conferred risk for PTSD, as 30% of the variance in PTSD in the Vietnam Era Twin Registry was associated with genetic factors even after controlling for combat exposure (True et al., 1993).

Reviewed in detail elsewhere (Amstadter, Nugent, & Koenen, 2009; Broekman, Olff, & Boer, 2007; Koenen, 2007; Nugent, Amstadter, & Koenen, 2008), 17 candidate gene studies of PTSD have been conducted, most of which have focused on the dopaminergic system (i.e., *DRD2, DAT*). Other neurobiological systems have been studied, including the serotonergic system (i.e., *SLC6A4, 5-HTR2A*), markers of the hypothalamic pituitary adrenal axis (i.e., *GCCR, FKBP5, CNR1*), components of the locus coeruleus/noradrenergic system (i.e., *NPY, DBH*), and neurotrophins (i.e., *BDNF*). Reviews detailing the hypothesized underlying neurobiological mechanisms whereby these genes are believed to exert their effects are available elsewhere (Amstadter et al., 2009; Broekman et al., 2007). Of brief note, however, apparent discrepancies in this literature may be partly resolved by attention to environmental factors (such as whether control participants were trauma-exposed) by careful and neurobiologically informed characterization of the PTSD-related phenotype (such as comorbid concerns such as harmful drinking in PTSD cases). However, beyond the diagnostically-inherent inclusion of trauma exposure in most investigations, only six of these investigations (reviewed below) have formally tested GxE interactions.

Nonetheless, published candidate gene studies can inform selection of genes for GxE investigations. Perhaps most notably, many of the published genetic variants are ideal candidates for GxE investigations according to Moffitt and colleagues (2005). More specifically, some of the aforementioned genes have putative functional effects on neurobiological systems affected by exposure to PTEs (Amstadter et al., 2009), appear to be associated with PTSD or PTSD-related phenotypes, and are common polymorphisms. Studies may also benefit from consideration of the combined environmental effects of PTEs and additional environmental constructs (e.g., social support) on neurobiological systems believed to influence development of PTSD. For example, nonhuman animal models have shown interactions between the promoter region of the serotonin transporter gene and early rearing environment (peer rearing vs. maternal rearing), suggesting a possible role for early or possibly peritrauma social relationships in models involving the promoter region of the serotonin transporter gene (Suomi, 2006).

Moreover, as neurobiological mechanisms are unlikely to show effects on "diagnostic status" as a construct, careful consideration of the PTSD-related phenotype is also warranted. For example, a series of studies first noted that a deletion variant of *ADRA2B,* the gene coding for the alpha2b-adrenergic receptor was associated with enhanced memory for emotional information in a sample of young adults (de Quervain et al., 2007). A subsequent study examined *ADRA2B* in trauma-exposed Rwandan refugees, with higher reexperiencing found in deletion carriers than in noncarriers, though no differences were found in hyperarousal, avoidance, or diagnostic status. In this case, given the mechanism whereby *ADRA2B* influences posttraumatic phenotypes, the role for *ADRA2B* would have been missed if PTSD, instead of the refined phenotype of reexperiencing symptoms, had been measured.

GxE Posttraumatic Stress Disorder Investigations

Although the phenotype of PTSD is uniquely well-suited for GxE research (Koenen, Nugent, & Amstadter, 2008), only six GxE studies of PTSD have been published or are in press (see Table 1). Consistent with recommended GxE methodology, these investigations have generally examined common polymorphic variants that have shown prior support for gene-disorder associations. Further, these studies selected environmental risks that (a) have been previously shown to buffer/exacerbate the potentially deleterious effects of PTEs, and (b) may be plausibly expected to interact with the candidate genes investigated.

The Florida Hurricanes Study. Three of the six published GxE investigations have come from our research team using data from the 2004 Florida Hurricanes Study (Amstadter et al., 2009; Kilpatrick et al., 2007; Koenen et al., 2009), a National Institute of Mental Health funded project designed to assess hurricane-related outcomes in a representative sample of older adults ($n = 1{,}130$, age 60 and over) and a comparison sample of younger adults ($n = 413$, age 21–59) residing in Florida disaster sites. This household probability sample of adults was interviewed 6–9 months after the hurricanes about demographic variables, exposure to the hurricane(s), PTSD status, prior exposure to potentially traumatic events (PTEs), and social support (Acierno, Ruggiero, Kilpatrick, Resnick, & Galea, 2006). The study design included collecting saliva samples via mail from adults who had been interviewed about their exposure to the 2004 hurricanes, and over 600 participants returned saliva samples. Comparisons of participants who did and did not return saliva samples found that there were no significant differences on any major variables (Galea, Acierno, Ruggiero, Resnick, & Kilpatrick, 2006), underscoring the viability of biologic data collection via U.S. mail for the purposes of genetic analyses. The saliva collection kits used in the Florida Hurricanes Study obtained approximately 10–30 μg of DNA from each sample, with a failure rate of about 3% (no higher than found in studies in which samples are not mailed to the laboratory prior to DNA extraction), which is an adequate yield to support a plethora of genetic assays.

The first article published from this project, and notably, the first published GxE PTSD study, tested the hypothesis that the polymorphism in the serotonin transporter gene (also known as 5-HTTLPR or *SLC6A4*) would modify the risk of posthurricane PTSD under the high environmental risk conditions (Kilpatrick et al., 2007). This commonly studied polymorphism is a variable number tandem repeat (VNTR) located in the promoter region of the gene. The 5-HTTLPR is a functional polymorphism, with the short, "s" allele being less transcriptionally efficient than the long, "l" allele (Lesch et al., 1996). This polymorphism has since been found to be triallelic, in that a third functional allele, "L_G" has been identified (Nakamura, Ueno, Sano, & Tanabe, 2000); L_G is characterized by an A>G substitution at nucleotide 6 of the first of two extra 22-bp repeats in the l allele, resulting in transcriptional capacity comparable to the s′ allele. In this study, the L_G and s′ alleles were coded as s′ alleles; L_A alleles were coded as l′ alleles. Environmental stress conditions were dichotomized into high versus low hurricane exposure, and high versus low social support. As illustrated by Figure 2, the low expression (s′) variant of the 5-HTTLPR increased risk of posthurricane PTSD, but only under the high stress conditions of high hurricane exposure and low social support. At highest risk ($n = 27$) were those with the s′/s′ genotype and high stress exposure. Medium risk ($n = 54$) were those with the l′/s′ genotype and high stress exposure. All others ($n = 498$) were considered low risk. There was a strong association between risk group and prevalence of PTSD, $\chi^2(2,\ N = 579) = 19.94$, $p < .001$. High-risk individuals (high hurricane exposure, the low expression 5-HTTLPR variant, low social support) were at 4.5 times (95% CI = 1.2–17.9) the risk of developing PTSD as compared to low-risk individuals.

Table 1. Review of Published GxE Studies of Posttraumatic Stress Disorder

First author	Year	Trauma-exposed controls?	Trauma type	Gene name (symbol)	Environmental variables	Finding
Binder et al.	2008	Yes	Various	FKBinding protein 5*(FKBP5)*	Childhood trauma exposure and adult trauma exposure. The Trauma Events Inventory was used to measure trauma exposure. A three-level variable was used for childhood events (no abuse, physical or sexual abuse, physical and sexual abuse). A four-level nonchild abuse variable was created (no adult trauma, one type, two types, three or more types).	Four SNPs in *FKBP5* significantly interacted with severity of child abuse in prediction of adult PTSD symptoms
Kilpatrick et al.	2007	Yes	Hurricane	Serotonin transporter (*SLC6A4*)	Hurricane exposure and social support. Five hurricane exposure characteristics were assessed; endorsement of two or more was dichotomized as high hurricane exposure. Social support was measured via a modified Medical Outcomes Study Module (five items on a 4-point scale); a score of 15 and below was dichotomized into low social support.	Significant association between s/s genotype and PTSD in adults with high hurricane exposure and low social support
Koenen et al.	2009	Yes	Hurricane; various	Serotonin transporter (*SLC6A4*)	County crime rate and county level-unemployment. Both variables were dichotomized into high vs. low, where high was defined as above the mean of studied counties.	Significant interaction between genotype and both county-level environmental variables. s′ allele was associated with decreased risk of PTSD in low-risk environments (low crime/unemployment), and increased risk of PTSD in high-risk environments

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Table 1. Continued

First author	Year	Trauma-exposed controls?	Trauma type	Gene name (symbol)	Environmental variables	Finding
Kolassa et al.	In press	Yes	War	Serotonin transporter (*SLC6A4)*	Number of traumatic events. Number of trauma experiences assessed using a structured interview administration of a checklist of 36 war- and nonwar-related trauma events (e.g., rape, bombing, or shelling).	The fitted probability of PTSD in s homozygotes, regardless of number of traumas reported. However, participants with the s'/l' and l'/l' genotypes showed an S-shaped dose-response, with increasing rates of PTSD reported as a function of number of traumatic experiences. Little difference for genotype was observed in participants reporting 15+ traumas.
Amstadter et al.	2009	Yes	Hurricane; various	Regulator of G-protein signaling 2 (*RGS2*)	Hurricane exposure, prior trauma, and social support. Five hurricane exposure characteristics were assessed; endorsement of two or more was dichotomized as high hurricane exposure. Five Criterion A events were assessed, dichotomized into prior trauma positive or negative. Social support was measured via a modified Medical Outcomes Study Module (five items on a 4-point scale); a score of 15 and below was dichotomized into low social support.	Significant association between CC genotype and posthurricane PTSD in adults with high hurricane exposure and low social support; significant association between CC genotype and lifetime PTSD in adults with prior trauma exposure and low social support

(*Continued*)

Table 1. Continued

First author	Year	Trauma-exposed controls?	Trauma type	Gene name (symbol)	Environmental variables	Finding
Nelson et al.	2009	No	Various	Gamma-aminobutyric acid receptor, alpha-2 (*GABRA2)*	Childhood trauma exposure assessed via a modified version of the Christchurch Trauma Inventory. Five types of childhood trauma were assessed: sexual abuse; physical abuse by mother, father, or other adult household member; emotional and physical partner maltreatment by a parent. A single second-order childhood trauma factor score was created for analyses.	Three SNPs in *GABRA2* significantly interacted with the childhood factor score in prediction of adult PTSD. Elevated risk was found only for homozygous individuals.

Note. PTSD = posttraumatic stress disorder; SNPs = single nucleotide polymorphisms; s′ allele = short version (vs. long) of the serotonin transporter promoter polymorphism.

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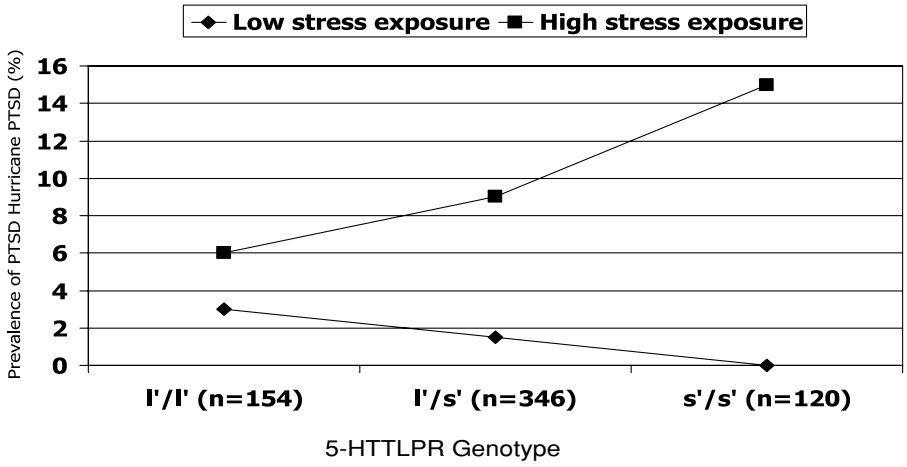

Figure 2. Level of stress exposure modifies the association between the 5-HTTLPR genotype and posthurricane posttraumatic stress disorder. Note: Low stress exposure was defined as low hurricane exposure and high social support. High stress exposure was defined as high hurricane exposure and low social support. 5-HTTLPR genotypes were triallelic with lg categorization.

A second article was published by our team that examined the 5-HTTLPR gene and PTSD (Koenen et al., 2009). Whereas previous GxE investigations of psychiatric phenotypes have only examined individual-level environmental variables (e.g., Caspi et al., 2003; Kilpatrick et al., 2007), this study investigated the role of group-level social environment. Specifically, crime rate (taken from the Serious Crimes Known to Police, U.S. Federal Bureau of Investigation, Uniform Crime Reporting Program unpublished data from 1999 [Federal Bureau of Investigation, 2002], high crime counties were defined as counties in which the crime rate was above the mean crime rate of the counties in our study) and percent unemployment (taken from the 2000 U.S. Census Summary File 3 [U.S. Census Bureau, 2000], high unemployment was defined as counties in which the unemployment rate was above the mean of the studied counties) were the examined environmental variables. Of particular note, county-level crime rate data provide an example of an environmental variable that may be objectively observed. Results indicated that county-level crime rate and percent unemployment modified the association between the 5-HTTLPR genotype and PTSD; low expression allele carries (s′ allele) were at increased risk for PTSD in high environmental stress conditions (high unemployment, high crime), and were at decreased risk for PTSD in low-risk environments (low unemployment, low crime). Here we underscore the importance of investigation of not just individual-level variables, but also group-level factors of the overall social environment.

The third PTSD GxE article using Florida Hurricane Study data examined a polymorphism that had not previously been studied in the context of PTSD (Amstadter et al., 2009). Polymorphisms in the *RGS2* (regulator of G-protein signaling 2) gene were found to be associated with anxious behavior in mice (Leygraf et al., 2006) and anxiety in humans (Smoller et al., 2008). We examined whether rs4606, a single nucleotide polymorphism (SNP) of *RGS2*, and social support moderated risk for posthurricane and lifetime PTSD. Rs4606 (C allele was the risk allele) was associated with increased symptoms of posthurricane PTSD symptoms under conditions of high hurricane exposure and low social support ($p < .05$). Further, this polymorphism was associated with lifetime PTSD symptoms under conditions of lifetime exposure to a PTE (other than the current hurricane), and low social support ($p < 0.001$). These GxE interactions remained significant after adjustment for sex, ancestry, and age, indicating that *RGS2* rs4606 modifies risk of postdisaster and lifetime PTSD under conditions of high stressor exposure.

GxE Under Conditions of High Trauma Exposure. The 5-HTTLPR polymorphism of *SLC6A4* was recently examined in 408 Rwandan refugees (Kolassa et al., in press). Participants endorsed extremely high levels of trauma exposure, reporting an average of 12.6 different traumas. Given the rates of traumatic experiences, 81% of participants met full criteria for lifetime PTSD and the probability of PTSD was nonlinearly associated with number of traumas, asymptotically approaching a probability of 1 for participants reporting 15 or more traumatic events. Findings supported a main effect for genotype, with the resiliency associated with the presence of an l′ allele diminishing across exposure to increasing numbers of traumatic events. More specifically, whereas the fitted probability of lifetime PTSD for participants homozygous for the low expression allele (s′/s′) was 100% regardless of the number of traumatic experiences, carriers of the l′ alleles evidenced lower levels of PTSD following exposure to few trauma experiences, but showed significantly increased risk associated with

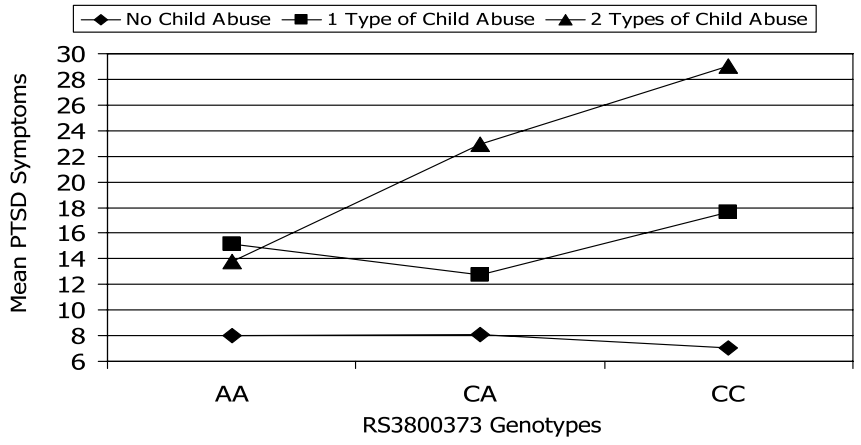

Figure 3. Severity of child abuse modifies the association between *FKBP5* polymorphisms and adult posttraumatic stress disorder symptoms. Created based on data presented in "Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults," by E. B. Binder, R. G. Bradley, W. Liu, M. P. Epstein, T. C. Deveau, K. B. Mercer, et al. 2008, Journal of the American Medical Association, 299, pp. 1291–1305. Copyright 2008 by the American Medical Association.

increasing numbers of traumatic experiences. The extremely high levels of trauma exposure and concomitant high rates of PTSD found in this sample demonstrate the overwhelming effects of trauma under conditions of extreme exposure and highlight the importance of careful characterization of trauma exposure in GxE research.

Child Abuse as a GxE Moderator. A recent study by Ressler's research team at Emory University (Atlanta, GA) also tested GxE models for PTSD (Binder et al., 2008). The sample ($n = 762$) consisted predominately of low-income African American patients who presented to general medical clinics at a large urban hospital. Current PTSD was assessed, as well as a retrospective assessment of exposure to child abuse. Fine mapping of the *FKBP5* locus was undertaken, as *FKBP5* is a glucocorticoid-regulating gene, and has been previously found to be related to peritraumatic dissociation (a potent predictor of PTSD; Koenen et al., 2005). Hence, it was a fitting candidate gene. No main effects of polymorphisms in *FKBP5* were identified, but a significant GxE interaction between severity of child abuse (but not adult traumatic events) and *FKBP5* polymorphisms was found for PTSD. Figure 3 illustrates the interaction findings for one of the *FKBP5* polymorphisms that remained significant after correction for multiple testing. The results show that the C allele was associated with higher levels of PTSD symptoms, but only among individuals exposed to two or more types of child abuse. There was no effect of genotype for individuals who experienced only one type of child abuse or no child abuse. Dexamethasone suppression test data also demonstrated that these polymorphisms have functional consequences for glucocorticoid system response sensitivity. They concluded that variation in *FKBP5*, in the presence of child abuse, may alter sensitivity of this stress-response pathway, "placing those individuals who have had significant child abuse at significant risk for PTSD in the face of other traumatic experiences" (p. 1304).

Finally, Nelson et al. (2009) examined the interaction of gamma-aminobutyric acid receptor, alpha-2 (*GABRA2)* polymorphisms and childhood trauma in risk of lifetime PTSD diagnosis in adults ($n = 259$). The authors found significant ($p < .05$) interactions between three SNPs and childhood abuse; only homozygous individuals were at significantly increased risk of PTSD. Findings remained similar after controlling for nicotine and alcohol dependence. No evidence for significant GxE interactions were found for major depression.

Novel Environmental Variables

An important direction for PTSD GxE research to advance in is not only the expansion of studied genetic (G) variables, but also the broadening of environmental (E) variables that are investigated. Environmental variables previously found to moderate the relationship between genetic variants and PTSD include individual-level variables (e.g., social support, level of trauma exposure), and group-level environmental variables (i.e., county-level crime rate, county-level unemployment rate). Although the studied E variables have been promising, they likely only represent a small fraction of the possible E characteristics that may play a role in the etiology and maintenance of PTSD, leaving a wide-open field of research in need of being conducted. Expansion of both individual-level and group-level environmental variables is warranted.

Extant psychosocial studies of PTSD may help to inform the selection of E variables for inclusion in GxE studies. A number of

psychosocial risk factors for PTSD have been identified (Brewin, Andrews, & Valentine, 2000) that may be fitting E variables for use in future research (e.g., education, general childhood adversity, current life stressors, female gender). Further, aspects of an individuals' trauma history (e.g., PTE severity, duration, interpersonal victimization, age of onset, multiple victimization history) have been related to increased risk for the disorder (Brewin et al., 2000), and could also be studied in the context of a GxE study of PTSD. Additionally, findings from the nonhuman primate literature may help inform novel E variable selection, particularly for pediatric PTSD, as early rearing environment has also been shown to moderate the relationship between serotonin transporter variation and central nervous system function (Bennett et al., 2002), as well as hypothalamic adrenal axis response to stress (Barr et al., 2004). PTSD GxE studies may also benefit from findings in other areas of psychiatric genetic study. For example, a recent GxE study of depression found that parenting style, specifically perceived maternal rejection, moderated the relationship between genetic variants and depression in juvenile detainees (Haeffel et al., 2008), suggesting that family environment variables (e.g., family cohesion, communication, conflict) may be fitting E variables in the study of child and adolescent PTSD.

Limitations/Challenges in GxE Research in Posttraumatic Stress Disorder

Our review of the literature identified only six GxE investigations of PTSD, three of which report findings from the same larger study. Thus, few conclusions may be drawn about the complicated interplay of genes and environment in PTSD. Because psychiatric genetic research requires large samples and has a history of multiple failed attempts at replication, quantitative reviews of the literature have been critical for thorough appraisal of candidate genes in more extensively studied disorders (i.e., schizophrenia, depression, etc.). The scarcity of published GxE investigations of PTSD prevents quantitative examination at this time. Moreover, the large number of plausible candidate genes and environmental variables present a further challenge to the field both through the risk of type I error and through the reduced likelihood that comparable genetic and, in particular, environmental variables will be examined across investigations. For example, Kilpatrick and colleagues (2007) examined only two environmental risk factors, including level of hurricane exposure and of social support, with genotype risk varying as a function of both environmental influences. Further, to the degree that environmental risk factors rely on self-report, particularly retrospective self-report, the presence of PTSD may color reported environmental risks and inflate associations between environment and PTSD. The effect of PTSD symptoms on retrospective recall of trauma exposure has been well documented in veteran samples (Koenen, Stellman, Dohrenwend, Sommer, & Stellman, 2007; Roemer, Litz, Orsillo, Ehlich, & Frieman, 1998; Southwick, Morgan, Nicolaou, & Charney, 1997). Hence, researchers interested in GxE research with PTSD are encouraged to consider objective measures of risk (such as county crime/unemployment rates) or to conduct longitudinal investigations that attenuate recall biases. Finally, it is important to note that PTSD is only one possible outcome of trauma exposure. As we have discussed elsewhere, research supports considerable genetic overlap between PTSD and other psychiatric disorders (Koenen, Nugent, & Amstadter, 2008) and our own work with trauma-exposed populations has identified posttrauma GxE effects on depression similar to those for PTSD (Kilpatrick et al., 2007).

Significance and Future Directions

PTSD is a prevalent disorder that represents a significant public health burden to adults, adolescents, and children. GxE research in PTSD has the potential to substantially improve our understanding of the specific genetic variants that are associated with PTSD, as well as the environmental conditions that influence these effects. Of note, only one of the six GxE studies of PTSD identified a significant main effect for genotype (Kolassa et al., in press). Thus, the potential role of these specific genes in PTSD etiology would not have been detected without testing for their interaction with specific stressor variables. Understanding both genetic and environmental influences, as well as their interactions, has the potential to inform neurobiological models of PTSD and to inform treatment efforts. For example, given the consistently identified interactions between social environment and the S-HTTLPR as well as evidence that posttraumatic adjustment may be partly predicted by the S-HTTLPR, genetically informed interventions may benefit from the incorporation of family members or other sources of social support in individuals with low-transcription alleles. This is particularly promising as family environment and social supports have been shown to be modifiable in the context of ecologically based approaches to early intervention (Dadds, Spence, Holland, Barrett, & Laurens, 1997) and psychosocial treatment (Henggeler, Clingempeel, Brondino, & Pickrel, 2002). GxE research in PTSD is in its infancy and many important lines of research warrant study (e.g., developmental trajectories, various neurobiological systems as G variables, expansion of E variables, possible sex differences, examination of endophenotypes of PTSD). These lines of research have clear public health significance and will be able to inform primary prevention of the disorder among those at risk, secondary prevention of PTSD development among trauma-exposed individuals, and the allocation of limited treatment resources to those who are most likely to be affected.

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