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Gene–environment interactions: early life stress and risk for depressive and anxiety disorders

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Abstract

Rationale—Prior reviews have examined how stress, broadly defined, interacts with genetic diathesis in the pathogenesis of internalizing (i.e., depressive and anxiety) disorders. Recent findings have suggested a unique role for early life stress (ELS) in the development of internalizing disorders, contributing to the rapid proliferation of research in this area.

Objective—This paper critically reviews studies in humans examining gene–environment interaction (GxE) effects of ELS on the risk for depression and anxiety, primarily from a candidate gene perspective. Major methodological challenges that are unique to such studies are considered.

Results—The majority of published studies have focused on candidates that regulate the serotonin system, especially the serotonin transporter. More recent work has addressed interactions of ELS with candidates from the hypothalamic-pituitary-adrenal axis and neurotrophin system. Available studies vary greatly with respect to definitions of ELS, examination of gene–gene interactions, consideration of gender effects, and attention to analytic limitations.

Conclusions—Overall, there is support for GxE effects of ELS on the risk for depressive and anxiety outcomes. Future studies of ELS in this context will require careful attention to methodologic considerations. Such studies would benefit from more systematic assessment of positive environmental factors (e.g., social support) and greater utilization of developmentally sensitive paradigms.

Keywords

Genetics; Trauma; Stress; Depression; Anxiety

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Early life stress and risk for depressive and anxiety disorders

Early life stress (ELS) is an established predictor of adverse outcomes across the lifespan encompassing neurocognitive, behavioral, health, and psychiatric domains (Danese et al. 2009; Gunnar and Quevedo 2007; Heim and Nemeroff 2002; Irish et al. 2009; Roth and Friedman 1993; Terr 1991). A substantially elevated risk of internalizing (i.e., depressive and anxiety) disorders following ELS is particularly well documented (Harrington 2001; Hicks et al. 2009; Kendler et al. 1995, 2003; Kessing et al. 2003). Preclinical models of ELS in laboratory animals have become increasingly popular in studies on the pathogenesis of mood and anxiety disorders and the development of novel pharmacological approaches to these conditions (Alleva and Francia 2009; Coplan et al. 2010; Gardner et al. 2009; Kolber et al. 2010; Musazzi et al. 2010; Vinkers et al. 2010).

Investigations of ELS in humans have examined a wide range of adverse life experiences. Whereas some studies have focused on discrete experiences such as natural disaster, others have examined the effects of such chronic experiences as childhood maltreatment (e.g., sexual/physical abuse, severe neglect) or adverse family environment (e.g., maternal depression, parental loss, divorce). The breadth of definitions of ELS reflects the reality that children are sensitive to a wide range of environmental influences, particularly to the degree that they impact the caregiving environment (Bronfenbrenner and Ceci 1994). However, this breadth introduces considerable between-and even within-study variability. Moreover, research suggests that differences in the chronicity and developmental timing of ELS may influence the nature and timing of outcomes (Maercker et al. 2004; McCormick and Mathews 2010), with further influences exerted by a host of moderating factors (Bagner et al. 2010; Brown and Harris 2008; Monk et al. 2003; Silberg et al. 1999).

For the purpose of this review, ELS will be defined as moderate-severe adversity experienced during childhood or adolescence. Stressors included in the studies reviewed range from traumatic events (e.g., war, abuse, and natural disaster) to family stressors (e.g., poverty, family conflict, and severe maternal criticism). This review focuses on “internalizing” psychopathological outcomes such as depression, posttraumatic stress disorder (PTSD), and other anxiety disorders, because of both the richness of the evidentiary base and the increasing recognition of the clinical significance of ELS in the course, treatment, and prognosis of these conditions.

Gene–environment interactions

Although it is well established that ELS is an important risk factor for several psychiatric disorders, ELS does not invariably lead to dysfunction, nor is it a specific risk factor for any particular disorder. Such divergent outcomes can be explained in part by gene-environment (GxE) interactions, in which genetic differences influence the likelihood that exposure to ELS will result in psychopathology. This is graphically depicted in Fig. 1, in which functioning is normal under conditions of low environmental stress, but impaired under conditions of high environmental stress (curved line). Although high environmental stress alone will degrade functioning (solid line), GxE interactions involve a genetically determined increase in vulnerability to such environmental effects. In contrast, genetically determined resilience (grey dashed line) or impairment (black dashed line) are associated with normal or impaired functioning, respectively, independent of levels of environmental stress. It is also possible for certain genes to confer environmentally sensitive “plasticity” such that the same genetic variant may confer risk under harmful environmental circumstances but provide benefit under auspicious conditions (Belsky et al. 2009; Belsky and Pluess 2009; Fox et al. 2007).

The relevance of the GxE model for understanding the pathogenesis of psychiatric illness has long been recognized. However, the recent introduction of methods for rapidly and inexpensively genotyping large numbers of individuals has shifted the focus of this area from traditional epidemiological and quantitative approaches to more precisely defined studies of the interactions of specific genetic and environmental risk factors. Against this backdrop, there has been a surge of interest in using genetic differences to inform understanding of how ELS exerts its pathogenic effects (Koenen and Galea 2009; Moffitt et al. 2005; Munafo and Flint 2009; Risch et al. 2009; Rutter 2009). The present paper reviews and critically evaluates the rapidly emerging literature in this area, with a focus on depressive and anxiety disorders.

Methodological considerations

Studies of candidate risk genes build upon findings from quantitative behavioral genetics studies using family, sibling, twin, and adoption designs, which show substantial heritability of depression and anxiety disorders. Candidate gene research is predicated on the assumption that common diseases are influenced by common genetic variants (Lohmueller et al. 2003). The selection of candidate genes for GxE studies usually reflects either prior implication of the gene product in the neurobiology of the disorder or prior identification of the gene through family linkage designs or genome wide association studies. The selection of environmental risk factors involves similar considerations. It is important that the study sample contains adequate numbers of subjects exposed and unexposed to the stressful environment to ensure adequate power, because only a main effect of genotype can be identified if nearly all participants have experienced high levels of the environmental factor (Munafo et al. 2009; Uher and McGuffin 2010). This is illustrated in Fig. 1, where the lines representing main effects for environment and gene converge with the line representing a GxE interaction. In the case of ELS, the nature and timing of the stress exposure may be a critical determinant of the sequelae, while the method of assessment (i.e., prospective, retrospective; interview, records, questionnaire) may be similarly critical in permitting detection of any moderation by candidate risk genes (Hardt and Rutter 2004; Moffitt et al. 2005; Paivio 2001).

Population stratification, or variation in allele frequency as a function of race/ancestry, is another major consideration, because if a mixed-ethnicity sample is used without control for population stratification, spurious GxE effects can result. The effects of genetic and environmental factors on symptoms of depression and anxiety have also been shown to differ as a function of age (Tambs and Mourn 1993) and gender (Eaves et al. 1997), so these factors should be considered in GxE analyses. Another important consideration is that individuals may shape their environments or elicit certain types of responses or stimuli in their environment, resulting in *gene–environment correlation* (*rGE*) (Plomin et al. 1977; Rutter 2009). A recent systematic review of genetic influences on environmental measures found estimated heritabilities of 39% for negative life events, 36% for trauma, and 27% across environmental measures (Kendler and Baker 2007). Accordingly, one of the challenges of GxE research is to distinguish between GxE and rGE effects.

Achieving sufficient statistical power presents a special challenge because interaction effects require larger numbers of subjects for adequate power (Brookes et al. 2001; Luan et al. 2001; Uher 2008), and power depends on allele frequencies in addition to exposure to ELS (Munafo et al. 2009). Yet another concern when testing for interaction effects is the potential for artifactual interactions that can occur secondary to subtle changes in definition and scaling of the variables (Jinks and Fulker 1970; Kraft et al. 2007; Mather and Jinks 1982; Moffit et al. 2006; Neale and Cardon 1992). For example, Eaves' (2006) simulation of GxE interactions in depression and antisocial behavior suggested that dichotomization (i.e., using a "clinical cutoff" to assign a yes/no diagnosis) and sampling from the extremes of a

distribution can significantly inflate the likelihood of potential spurious interactions. Caspi et al. (2010) highlight that for analyses of dichotomous variables, power to detect GxE interactions declines as the proportion of the sample with the risk allele or risk environment diverges from 50%. However, continuous measures of depression or anxiety disorders are also problematic in that they generally provide accurate assessments only of current symptoms, and therefore may miscategorize those individuals who have a history of such symptoms but are currently in remission.

Selecting candidate genes

Given the substantial overlap among depressive and anxiety disorders with respect to risk factors, clinical phenomenology, and treatment approaches, it is not surprising that these conditions also appear to share some genetic influences (Nugent et al. 2010a). Many of the polymorphisms with replicated effects are thought to be functional variants that influence relevant neurobiological systems (Fu et al. 2007; Koenen et al. 2008; Rutter 2008; Rutter 2010). Since these neurobiological pathways are influenced by multiple genes, a given gene may only account for a small amount of the variance in the risk for complex disorders.

Extensive research supports a role for the serotonin system in the development of both mood and anxiety disorders (for review, see Ressler and Nemeroff 2000). Moreover, there is strong evidence from human and animal studies that the stress response is modulated in part by serotonergic neurotransmission (for reviews, see El Hage et al. 2009; Holmes 2008). Animal models demonstrate increased serotonin neuronal activity, as indicated by increased gene expression and serotonin concentrations, in brain areas implicated in the stress response (e.g., Amat et al. 2005; Grahn et al. 1999; Takase et al. 2004). Differences in stress-induced alterations in serotonin function are affected by individual variability in dynamic responding across the serotonin pathway, including biosynthesis, intraneuronal transport and presynaptic release, postsynaptic receptor and second-messenger function, reuptake from the synapse, and catabolism. Genetically influenced variability at any point in this pathway can influence the timing, magnitude, and duration of stress-induced changes. Furthermore, there is ample evidence that many key components of the serotonin pathway (e.g., transporters and receptors) both influence and are influenced by the functioning of other stress systems in the brain and periphery (e.g., Adamec et al. 2006; Ansorge et al. 2007; Bhatnagar et al. 2004; Carola et al. 2007; Crayton et al. 1996; Froger et al. 2004; Gross and Hen 2004; Hariri and Holmes 2006; Hemrick-Luecke and Evans 2002; Herman et al. 2005; Laaris et al. 1995, 1997; Lanfumey et al. 1999; Li et al. 1999, 2004, 2006; Pehek et al. 2006; Pezawas et al. 2005; Preece et al. 2004; Tjurmina et al. 2004; Tyrka et al. 2004). Of note in the present review, evidence suggests that variation in the serotonin system (especially in the serotonin transporter and 1A receptor) may be particularly important during early development (Holmes et al. 2003; Ansorge et al. 2007).

Another promising source of GxE candidate genes is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is a neuroendocrine system involved in coordinating neural, hormonal, and behavioral responses to stressors, and there is extensive evidence documenting perturbed HPA function both as a result of ELS and in the context of depression and certain anxiety disorders (particularly PTSD) (Gillespie et al. 2009; Handwerger 2009; Marques et al. 2009; Pariante and Lightman 2008; Yehuda et al. 2010). Converging findings from preclinical and clinical studies indicate that exposure to excessive glucocorticoid concentrations impedes neuroprotection and neurogenesis in the hippocampus, effects linked to the pathogenesis of depression and anxiety disorders (De Kloet et al. 2005). Several studies have found evidence for GxE effects with genes involved in regulating corticotropin releasing hormone (CRH) and glucocorticoid function.

Brain-derived neurotrophic factor (BDNF), a nerve growth factor that supports neuronal survival and plasticity, has recently been strongly implicated in the pathophysiology of major depression (Duman and Monteggia 2006). Both stress and major depression are associated with neuronal atrophy and cell loss in the amygdala, prefrontal cortex, and hippocampus; there is evidence from preclinical studies in rodents that these effects are mediated through increases in glucocorticoids and decreases in BDNF (Duman and Monteggia 2006). Activation of the HPA axis has been proposed as a mechanism of BDNF down-regulation in response to stress and in association with depression. Reciprocal interactions between BDNF and serotonin have also been well documented (Duman 2002; MacQueen et al. 2003), underscoring the viability of genes that regulate BDNF as candidates for study.

Other neurotransmitters that have been implicated in the pathophysiology of major depression and anxiety disorders, such as dopamine, γ-amino-butyric acid (GABA), and glutamate, have also begun to serve as sources of candidate genes, as will be reviewed below.

Candidate genes and effects of early life stress

Serotonin system

Reflecting the wealth of research linking depression to serotonergic function, the majority of G×ELS studies to date have involved gene variants that regulate brain serotonin systems (Tables 1 and 2); in particular, numerous studies have focused on *5-HTTLPR*, a functional polymorphism in the promoter region of the serotonin transporter gene (*SLC6A4)*. The short (s) allele of this polymorphism confers lower transcriptional efficiency than the long (l) allele, and is associated with decreased transporter expression and serotonin reuptake (Lesch et al. 1996). A third functional allele has been identified for this gene, L_G, (Nakamura et al. 2000); this allele results in transcriptional capacity comparable to the s allele. Accordingly, recent studies typically categorize variants on the basis of function, with the L_G and s alleles grouped together as s', and the remaining l alleles labeled l'. Several investigators have suggested that the loss of function associated with the s' variant impairs cortical inhibition of the amygdala during stress, increasing sensitivity to the deleterious effects of stress on overall mood and anxiety (Hariri and Holmes 2006; Pezawas et al. 2005).

In 2003, Caspi et al. conducted the seminal candidate G×E investigation of risk for depression (Caspi et al. 2003). Their study involved careful prospective measurement of the environmental risk factor, selection of a gene with biological plausibility for interaction with the risk factor, testing for an interaction, and systematic examination of the specificity of the gene. In this longitudinal study of 847 young adults from a representative birth cohort in Dunedin, New Zealand, the 5-HTTLPR polymorphism was examined in relation to stress exposure and risk for depression. Stressful life events between ages 21–26 interacted with the *s* allele of this gene to predict the development of depressive symptoms, depression diagnoses, new-onset depression diagnoses, suicidality, and informants' reports of depressed behavior. The study also examined the contribution of ELS using an index comprised of both prospectively obtained measures (ratings of mother behavior, parental reports of harsh discipline, and changes in primary caregivers) and retrospective reports at age 26 (of sexual abuse and severe physical abuse occurring before age 11). ELS analyses also showed a significant GxE interaction, with the *s* allele of this gene predicting the subsequent development of major depression among those with ELS. This study catalyzed numerous investigations testing GxE effects in ELS and internalizing symptoms or disorders, with 21 published papers involving 22 samples to date (Aguilera et al. 2009; Araya et al. 2009; Åslund et al. 2009; Caspi et al. 2003; Chipman et al. 2007; Chorbov et al. 2007; Cicchetti et al. 2007; Eley et al. 2004; Gibb et al. 2009; Hammen et al. 2010; Kaufman et al. 2004, 2006;

Laucht et al. 2009; Nobile et al. 2009; Ritchie et al. 2009; Sjoberg et al. 2006; Stein et al. 2008; Surtees et al. 2006; Taylor et al. 2006; Wichers et al. 2008; Xie et al. 2009) (Table 1).

Findings from 15 of the 22 samples tested support increased risk for internalizing symptoms in participants with the low-expression short alleles and ELS in all participants (Aguilera et al. 2009; Åslund et al. 2009; Caspi et al. 2003; Cicchetti et al. 2007; Gibb et al. 2009; Kaufman et al. 2004, 2006; Nobile et al. 2009; Stein et al. 2008; Taylor et al. 2006; Xie et al. 2009) or in a subset of participants (Eley et al. 2004; Hammen et al. 2010, Sjoberg et al. 2006; Wichers et al. 2008). Of these studies, most used the biallelic definition of "short" allele applied by Caspi et al. (2003). Specifically, ten out of 13 studies using the biallelic definition found full or partial support for the *s* allele (Aguilera et al. 2009; Åslund et al. 2009; Caspi et al. 2003; Cicchetti et al. 2007; Eley et al. 2004; Kaufman et al. 2004, 2006; Sjoberg et al. 2006; Taylor et al. 2006; Wichers et al. 2008). Of the studies using the triallelic approach, five studies found full or partial support for deleterious GxE effects of the *s′* allele (Gibb et al. 2009; Hammen et al. 2010; Nobile et al. 2009; Stein et al. 2008; Xie et al. 2009), 3 studies found full or partial support for risk effects of the *l′* allele (Chorbov et al. 2007; Laucht et al. 2009; Ritchie et al. 2009), and 1 found no evidence for GxE effects (Araya et al. 2009).

5-HTTLPR: type of ELS—As discussed above, a critical methodological concern is the measurement of environmental risk. Nearly all of the studies (nine out of 11) that concluded that GxE interactions involved greater risk in *s/s′* carriers included some self-report of ELS experiences. Only 3 G×ELS studies relied entirely on parent report of ELS, with these studies finding no GxE effects (Araya et al. 2009), increased risk in *l/l′* youth with ELS (Laucht et al. 2009), and increased risk in *s′* carriers with ELS (Nobile et al. 2009). The validity of studies that do not supplement parent report with additional sources of information may be limited by the fact that parents may not be aware of all of their childs stressors.

Efforts to discern patterns whereby GxE effects may be specific to certain types of ELS have been complicated by the tendency for studies to conflate multiple forms of ELS. Of the 13 studies including physical abuse as an ELS, ten found support for GxE with risk associated with the *s/s′* allele (Aguilera et al. 2009; Åslund et al. 2009; Caspi et al. 2003; Cicchetti et al. 2007; Kaufman et al. 2006; Kaufman et al. 2004; Stein et al. 2008; Taylor et al. 2006; Wichers et al. 2008; Xie et al. 2009). Sexual abuse was included in nine studies, again with two thirds of these studies showing an interaction of ELS with the *s/s′* allele (Aguilera et al. 2009; Caspi et al. 2003; Cicchetti et al. 2007; Kaufman et al. 2006; Kaufman et al. 2004; Xie et al. 2009). However, physical and sexual abuses are low base-rate experiences in the general population, with only 5% of individuals endorsing a history of childhood physical or sexual abuse (Cohen et al. 2006). Accordingly, studies focusing on nonclinical samples would be grossly underpowered if the effect was driven by physical or sexual abuse exposures. Even emotional abuse is endorsed by only 12% of nonclinical populations (Cohen et al. 2006). Of 11 studies including emotional abuse, nearly all (n=10) reported GxE with increased risk conferred by *s/s′* allele (Aguilera et al. 2009; Åslund et al. 2009; Caspi et al. 2003; Cicchetti et al. 2007; Gibb et al. 2009; Kaufman et al. 2006; Kaufman et al. 2004; Stein et al. 2008; Taylor et al. 2006; Wichers et al. 2008). Neglect was found to interact with *s/s′* to increase risk for internalizing symptoms in six out of eight investigations (Aguilera et al. 2009; Cicchetti et al. 2007; Kaufman et al. 2006; Kaufman et al. 2004; Wichers et al. 2008; Xie et al. 2009).

Caspi et al. recently reviewed studies of stressful events experienced throughout the lifespan with respect to GxE with *5-HTTLPR* (Caspi et al. 2010). They concluded that whereas studies of specific stressors, such as childhood abuse or neglect, have generated consistent

GxE effects of the *s* allele, findings of studies examining less specific adverse events are more variable. Inspection of the studies in Table 1 shows that those finding a positive GxE effect with risk for the *s* allele tend to be focused on childhood maltreatment, whereas studies that did not clearly support this effect were more likely to use a compilation measure of several different types of early adversity, some of which included more widely experienced events, such as parental arguing/divorce, or qualitatively distinct circumstances, such as poverty or parent education levels.

As shown in Table 1, all of the samples that included parent mental health or substance abuse in their definition of ELS reported no effect (Araya et al. 2009; Chipman et al. 2007; Surtees et al. 2006). The study by Surtees et al. (2006) included factors such as "being sent away from home because of doing something wrong" and parent substance problems, which might also reflect important confounds such as risk for externalizing behavior problems or substance disorders. Research with children of alcoholics has reported increased levels of child aggressive behavior and increased anxious/depressed symptoms in children with the *l/l* genotype relative to other genotypes (Twitchell et al. 2001). The genetic and environmental pathways leading to internalizing symptoms may be different in families characterized by externalizing tendencies. This may be particularly problematic in studies of later-life internalizing, as research supports a progression of externalizing concerns to internalizing concerns, whereas the opposite is rarely seen (Brook et al. 1998; Fergusson and Horwood 2002; Rao et al. 1999; Rutter et al. 2006).

Poverty represents yet another type of ELS with an impact on both the developing child and the family as a whole. However, the influence of poverty or socioeconomic status may differ across psychiatric outcomes (Dohrenwend et al. 1992; Johnson et al. 1999). Consistent with early theory (Bronfenbrenner and Ceci 1994), twin models of both internalizing and externalizing have suggested that socioeconomically disadvantaged environments may obscure genetic effects (Raine 2002; South and Krueger 2010; Tuvblad et al. 2006). Poverty provides a context for numerous influences that can increase long-term risk for depression, such as exposure to neighborhood violence (Freisthler et al. 2008) and deviant peers (McCart et al. 2007; Zinzow et al. 2009), decreased academic and occupational opportunities (Dubow and Ippolito 1994; Fiscella and Kitzman 2009), decreased resiliency (Campbell-Sills et al. 2009), decreased adult monitoring (Horowitz et al. 2005), increased caregiver depression and aggression (Mitchell et al. 2009; Scaramella et al. 2008), and increased difficulty coping with trauma (Kawachi and Subramanian 2006). Accordingly, poverty may exert effects through qualitatively different mechanisms than some of the other types of ELS examined above. All but one (Chorbov et al. 2007) of the studies reporting GxE effects with increased risk conferred by *l/l*′ included socioeconomic status in their definition of ELS (Chipman et al. 2007; Laucht et al. 2009; Ritchie et al. 2009; Sjoberg et al. 2006). In their investigation, Laucht et al. (2009) suggested that adolescent-onset depression with prominent family adversity and externalizing symptoms, which characterized their depressed late-adolescent participants, could represent a phenotype that is distinct from depression with internalizing symptoms and onset at other ages.

5-HTTLPR: environmental moderators of GxE—Most studies have focused on the role of environment as either a *trigger* for expression of genetic vulnerability or a *potentiating* influence enhancing the main effect of *5-HTTLPR*. However, it is also possible that individuals with the "risk allele" are more sensitive to the presence of *compensating* influences, such as social support provided by significant others (Nugent et al. 2010b). Two related studies have explicitly examined the extent to which supportive environments may shape the impact of ELS. Kaufman et al. (2004) found that depressive symptoms were highest among maltreated children with the *s/s* genotype and low social support. In an expanded cohort, Kaufman et al. (2006) extended their finding in a four-way interactions

between *5-HTTLPR*, a polymorphism in the gene for BDNF, childhood maltreatment, and low social support in the prediction of depression.

5-HTTLPR: genetic moderators of GxE—Other genes directly regulating the serotonin system could enhance or attenuate *5-HTTLPR* effects. Furthermore, the serotonin system functions in concert with other neurobiological systems, which may also interact with ELS and/or serotonergic genes. In the study cited above, Kaufman et al. (2006) found that the *BDNF Val66Met* polymorphism moderated the GxE effect of the *s/s 5-HTTLPR* genotype such that the *s/s* effect in maltreated children was most pronounced among those with the *BDNF* met allele. The interaction of ELS×*5-HTTLPR*×*BDNF* was replicated in a study of adult female twins who reported on a history of childhood adversity (Wichers et al. 2008). However, Aguilera et al. (2009) did not find an effect of *BDNF Val66Met* in relation to their above-noted significant *5-HTTLPR*×ELS interaction.

Cicchetti et al. (2007) examined the effects of *5-HTTLPR* as well as the monoamine oxidase type A (*MAOA*) gene, which is involved in the degradation of serotonin. A significant interaction of *5-HTTLPR s/s* genotype with a history of sexual abuse in the prediction of internalizing symptoms was found primarily in adolescents with the low *MAOA* activity genotype. Eley et al. (2004) examined GxE effects on self-reported depressive symptoms as influenced by *5-HTTLPR* as well as two additional serotonin receptor genes (*HTR2A, HTR2C)*, the tryptophan hydroxylase gene (*TPH*, which codes for the rate-limiting enzyme involved in serotonin biosynthesis), and *MAOA*. Findings supported main effects for *HTR2A* and *TPH* and a trend toward a main effect of *5-HTTLPR*. The interaction of *5-HTTLPR* s/s genotype and environmental risk was not significant in the entire sample but was present in girls. The *MAOA* gene is located on the short arm of the X chromosome, and this is consistent with other evidence of gender-related effects of the *MAOA* polymorphism (Biederman et al. 2008).

5-HTTLPR: gender influences on GxE—There are substantial gender differences across internalizing disorders, raising the possibility that GxE interactions may operate differently in males and females. Gender-moderated effects, although infrequently tested, were identified in four studies (Åslund et al. 2009; Eley et al. 2004; Hammen et al. 2010; Sjoberg et al. 2006). Both Hammen et al. (2010) and Eley et al. (2004) found that female, but not male, *s′* and *s* carriers were at greater risk for depression under conditions of family problems. Similarly, a large study of adolescents identified an interaction between childhood abuse and family discord and the *s/s 5-HTTLPR* genotype in predicting depression in adolescent girls only (Åslund et al. 2009). Sjoberg et al. (2006) found that boys and girls with the *5-HTTLPR s* allele were sensitive to different types of stressors, with males affected by housing concerns and girls affected by traumatic family conflicts. Furthermore, the *s 5-HTTLPR* conferred risk for depression in girls but was protective in boys. The authors noted that these gender-related effects are consistent with both (1) findings from the stress and depression literature supporting gender differences in perceived stressors and (2) evidence that the *5-HTTLPR* may exert different influences on sex-varying stress hormones (i.e., gonadal and/or adrenocortical hormones).

5-HTTLPR: analytic considerations in GxE—The distribution of genotypes for a given gene should be in Hardy–Weinberg equilibrium (HWE), whereby the frequencies p and q of each allele are expected to approximate a distribution of $2pq$ for heterozygotes and q^2 and p^2 for the respective homozygotes. Divergence from HWE in GxE studies can arise from a number of sources, ranging from population stratification characteristics, to genotyping error, to aspects of sampling. In the first of two samples tested by Chipman et al. (2007), genotype frequencies were not in HWE, and no GxE interaction was detected. Although the replication sample did not show a departure from HWE, as the authors noted,

findings from the replication sample were limited by the fact that very few adolescents categorized as having persistent adversity had high levels of depressive symptoms. With respect to population stratification due to racial differences in allele frequency, most of the studies reviewed here have either comprised racially homogeneous groups or have adjusted their models for population stratification; however, some studies have not reported on this important issue (see Tables 1, 2, 3 and 4 for details).

The use of logistic regression techniques to identify interactions in GxE studies is widespread, but it is important to note that this technique can lead to both false-positive and false-negative findings (Eaves 2006; Moffit et al. 2006; Kraft et al. 2007; Munafo et al. 2009; Caspi et al. 2010). In addition, as shown in Table 1, many studies do not report whether they have tested for rGE between ELS and genotype. Studies that did observe rGE should be interpreted with caution, as it is possible that rGE can account for apparent GxE effects. For example, Wichers et al. (2008), identified a three-way interaction between ELS, *5-HTTLPR*, and *BDNF*, which the authors acknowledged must be qualified by the fact that they also found rGE between *BDNF* genotype and reported childhood adversity (with increased adversity reported by youth with Val/Met relative to Val/Val). Similarly, Aguilera et al. (2009) showed a GxE effect of the *5-HTTLPR s* allele and a history of childhood sexual abuse on depressive symptoms, but also observed rGE, in which the *l/l* genotype was more strongly associated with childhood sexual abuse than the *l/s* genotype.

TPH1 and TPH2—As noted above, the tryptophan hydroxylase genes *TPH1* and *TPH2* are involved in the synthesis of serotonin, and thus are excellent candidates for phenotypes related to alterations in the serotonin system. Eley et al. (2004) examined *TPH1*, in addition to other genes in the serotonin pathway, including *5-HTTLPR*, in their investigation of depressive symptoms in adolescents. Findings revealed a significant protective effect of *TPH1* on depressive symptoms in relation to ELS, which consisted of family problems, parent education, and adverse events occurring in adolescence. In another study (which also tested *5-HTTLPR*), Nobile et al. (2009) examined the effects of being in a single-parent family during childhood/adolescence, with a significant GxE identified with *TPH2* such that allele 5 decreased the risk of high depressive symptoms in single-parent youth.

5-HT1A, 5-HT2A, 5-HT2C receptors—Chipman et al. (2010) examined the potential interactive effects of the gene coding for the serotonin 1A receptor (*HTR1A*) and childhood adversity on symptoms of anxiety and depression in a large sample of adults. Childhood adversity (prior to age 16) was defined using a range of 17 potentially adverse experiences spanning maternal depression to sexual abuse, with endorsement of adversity subsequently grouped by number of experiences. No significant main effects or interactions were found in the prediction of depression or anxiety symptoms. Eley et al. (2004) examined polymorphisms of serotonin receptor 2A and 2C genes (*5-HT2A T102C*, *5-HT2C* VNTR) in their investigation of adolescent depression. Although no main or interaction effects for the *5-HT2C* VNTR were found, a significant main effect for increased depression in T allele carriers of the *5-HT2A T102C* was observed.

HPA axis

As discussed above, genes that regulate HPA axis function, including the CRH type I receptor (*CRHR1*), the glucocorticoid receptor, and FK506 binding protein 5 (*FKBP5*), are promising candidates for GxE interactions in the prediction of mood and anxiety disorders.

CRHR1—Bradley et al. found an interaction between reports of childhood maltreatment on the Childhood Trauma Questionnaire (CTQ) and *CRHR1* in predicting depressive symptoms in a sample of predominantly African-American and low socioeconomic status adults

(Bradley et al. 2008). Seven of ten single nucleotide polymorphisms (SNPs) spanning the gene showed significant interactions, with the rs110402 and rs7209436 SNPs significant even after correction for multiple tests. Participants with a history of childhood maltreatment who had the G/G rs110402 genotype had the highest depressive symptoms. In a replication sample, predominantly Caucasian and of higher socioeconomic status, the authors further examined common haplotypes of *CRHR1*, detecting a GxE protective effect on depression in individuals with a history of childhood maltreatment who possessed a TAT haplotype formed by three *CRHR1* variants (rs7209436, rs110402, and rs242924).

Polanczyk et al. (2009) examined this GxE interaction effect with the three most significant SNPs identified by Bradley et al. using data from two longitudinal cohort studies. Findings from their E-Risk cohort, a large study of women, replicated the interaction of retrospective reports of childhood maltreatment with the TAT haplotype (rs7209436, rs110402, and rs242924) in predicting depression diagnoses. However, results from the Dunedin cohort, comprised of both men and women, did not support the expected GxE interaction. Reinforcing the importance of how ELS is assessed when evaluating GxE interactions, the authors speculated that the inconsistency in their findings was due to the use of different measures of ELS in the two cohorts. Whereas the E-Risk cohort used the CTQ, a measure they argue elicits an affective component of appraisal of past maltreatment (e.g., “I felt that someone in my family hated me.”), the Dunedin study involved prospective multi-informant reports of events and an emotionally neutral assessment of ELS. Polanczyk et al. concluded that the GxE effect was supported, but with the effect specific to depression-relevant emotional memories assessed with the CTQ.

Tyrka et al. (2009) examined the interactions of two of these three polymorphisms in the *CRHR1* gene and childhood maltreatment, as measured by the CTQ, in predicting cortisol response to the dexamethasone/CRH test in healthy adults. For both polymorphisms, individuals with the G/G genotype and reported childhood maltreatment had an elevated cortisol response, suggesting that prior findings of elevated depressive symptoms in individuals with this genotype and childhood maltreatment could reflect alterations in neuroendocrine stress responding. These findings were partially replicated by Heim et al. (2009) in a Dex/CRH study of both men and women that examined *CRHR1* rs110402 and reported ELS in predicting cortisol response. Men, but not women, who were carriers of the A allele had decreased cortisol responses compared with men with the G/G genotype. In addition, there was a GxE interaction such that men reporting ELS with an A allele had decreased cortisol responses compared with women reporting ELS, but responses of men and women without ELS did not differ. Using an independent sample, these authors also examined the interaction between *CRHR1* rs110402 and ELS in predicting depression, again finding an interaction of ELS (particularly physical abuse) and *CRHR1* in men only. The authors suggested that the gender-related findings could partly reflect differences in the types of abuse (i.e., physical vs. sexual) reported by men and women.

One proposed mechanism of ELS interactions with serotonergic genes such as *5-HTTLPR* involves modulation of stress responses through HPA axis activity (El Hage et al. 2009). Consistent with this, the *s′* allele of *5-HTTLPR* has been associated with an exaggerated cortisol response to a standardized psychosocial stressor in children and adults (Alexander et al. 2009; Gotlib et al. 2008). Ressler et al. (2010) extended their prior GxE analyses of a *CRHR1* haplotype and childhood maltreatment (Bradley et al. 2008) by examining the triallelic *5-HTTLPR* as a further moderator of these interactions. The *s′* allele of *5-HTTLPR* enhanced the effects of the *CRHR1* risk haplotype, even under conditions of lower levels of abuse.

Glucocorticoid receptors—Modulation of the CRH response to stress and adversity relies on a complex feedback system that includes glucocorticoid receptors (GRs) and regulating genes (e.g., *FKBP5*). Since altered sensitivity of GRs is thought to mediate HPA axis dysregulation in depression and PTSD (Raison and Miller 2003), genes regulating components of this system are likely candidates for GxE investigations of the etiopathology of depression and anxiety (Charney 2004; Wust et al. 2004a; Wust et al. 2004b). Bet et al. (2009) examined polymorphisms of the GR gene *NR3C1* in 906 older adults who retrospectively reported on stressful life events in childhood. The *22/23 K* and *9beta* polymorphisms interacted with childhood adversity to predict depressive symptoms. Moreover, the *22/23EK* variant was associated with a lower morning free cortisol index in subjects reporting childhood adversity. Also in subjects reporting childhood adversity, heterozygotes for the *Bcl1* variant had lower serum cortisol binding globulin and less risk of depressive symptoms than either wild type or *Bcl1* homozygous subjects.

FKBP5—FKBP5 is a co-chaperone that regulates binding and nuclear translocation of GRs. Binder et al. (Binder et al. 2008) examined four SNPs of the *FKBP5* gene in a sample of predominantly low-income, urban, African American adult patients seeking medical care. *FKBP5* interacted with reported childhood maltreatment to predict PTSD symptoms. Moreover, these interaction effects remained significant even after controlling for potential confounds (i.e., depressive symptoms, age, sex, non-child abuse trauma, genetic ancestry). Xie et al. (2009) recently examined *FKBP5* SNPs in a large sample of African American and European American participants. Highlighting the importance of sample stratification effects, there was an interaction between childhood experiences of crime and abuse and *FKBP5* genotype in predicting PTSD in African Americans, but not European Americans.

Neurotrophins

As discussed above, BDNF and other neurotrophins, which support neuronal growth and survival, are thought to be important mediators of cellular alterations seen in major depression and other stress-related disorders. The Met allele of the functional *BDNF Val66Met* polymorphism confers abnormal intracellular packaging and secretion of BDNF (Egan et al. 2003), and has been implicated in impaired extinction of conditioned fear response and atypical frontoamygdala activity in humans (Soliman et al. 2010), as well as reduced amygdala and hippocampus volume (Montag et al. 2009). A study of depressed inpatients found that those with two copies of the Met allele of *BDNF Val66Met* had elevated adrenocorticotropic hormone and cortisol responses to the Dex/CRH text (Schule et al. 2006). Reciprocal interactions between *BDNF* and serotonin have also been well documented (Duman 2002; MacQueen et al. 2003). As discussed above, the studies by Kaufman et al. (2006) and Wichers et al. (2008) demonstrate that *BDNF Val66Met* acts as a moderator of *5-HTTLPR*×ELS interactions.

Two additional studies have examined interactions of *BDNF* variants with ELS in predicting internalizing outcomes. Aguilera et al. (2009) found that carriers of the Met allele of the *BDNF Val66Met* polymorphism with reported childhood abuse had greater risk for depressive symptoms than abused participants with the Val/Val genotype. Gatt et al. (2009) studied the relationship between ELS and *BDNF* in predicting depressive and anxiety symptoms, cognitive function, and heart rate in resting and arousal states in 374 healthy adults, with volumetric brain imaging in a subset of 89 participants. Significant interactions between *BDNF Val66Met* and ELS were observed, with *BDNF* Met carriers exposed to high ELS showing poorer working memory, elevated heart rate in resting and arousal conditions, and smaller hippocampus and amygdala volumes. In a path analysis, reduced gray matter in the hippocampus and lateral prefrontal cortex mediated the impact of the GxE interaction in predicting depressive symptoms. Similarly, startle-elicited heart rate mediated

the effects of *BDNF*×ELS on neuroticism, which predicted increased depressive and anxiety symptoms. In contrast, a specificity path analysis did not show similar effects with the *5-HTTLPR* gene.

Other candidate genes

Dopaminergic genes—Dopamine, which plays a central role in motivation and pleasure, has also been implicated in the pathophysiology of depression (Dunlop and Nemeroff 2007). Although several studies have examined whether stressful life events in adults interact with dopamine system genes, to our knowledge there is only 1 report examining interactions with ELS. In a study of 176 male juvenile detainees, the dopamine transporter gene (*DAT1*) interacted with reported maternal rejection in predicting both depression and suicidal ideation (Haeffel et al. 2008). This effect was specific to depression and did not predict anxiety symptoms.

GABRA2—GABA is the main inhibitory neurotransmitter in the mammalian brain, and it has frequently been implicated in the pathophysiology of depression and anxiety disorders. Nelson et al. (Nelson et al. 2009) examined 4 SNPs encoding $GABA_A$ receptors (*GABRA2)* in a subset of 259 participants in a family study of adult twins. ELS was measured by retrospective self-report and PTSD symptoms by structured telephone interview. Significant interactions were observed between ELS and three of the four *GABRA2* SNPs in predicting lifetime risk for PTSD.

Inconsistencies in the literature: methodological issues

Although extant research provides important insights into genes likely to be important in GxE studies of ELS, published studies are characterized by considerable differences in methodology, especially in terms of ELS measurement. ELS is difficult to assess, reflecting the subjectivity inherent to the experience of stress, biases involved in reporting and recall, and the developmental context in which such experiences occur. Studies yielding inconsistent findings have often relied on suboptimal timing of ELS assessment (ranging from a single measurement at 3 months of age to retrospective accounts of childhood provided by advanced-age participants). Another major source of inconsistency involves the type of early stress under study. Whereas some studies have focused on direct childhood maltreatment, such as abuse and neglect, others have included more broadly experienced events, such as parental arguing/divorce, or qualitatively distinct circumstances, such as poverty or parent education levels. Moreover, identified stressors may occur in the context of additional adversity that is not consistently identified or examined. Evidence from studies reviewed here supports the existence of differences in the impact of type of ELS, and these effects may be gender-specific (Cicchetti et al. 2007; Heim et al. 2009; Sjoberg et al. 2006). However, relatively few studies separately test for GxE effects within gender or type of ELS. A further complication is that some types of adversity commonly co-occur, while others, such as sexual abuse, may occur in isolation. If a particular form of adversity, such as childhood sexual abuse, is the critical environmental component, failure to adequately detect this could result in its unrecognized presence in both ELS and control groups.

Psychiatric disorders tend to co-occur, and are also heterogeneous, so that efforts to examine dichotomous diagnoses, a common approach in genetic research, are problematic (Eaves 2006). Examination of continuous measures affords greater statistical power and may decrease statistical error due to miscategorization of “subthreshold” individuals (Caspi et al. 2010; Plomin and Davis 2009). Consideration of the timing of onset and chronicity of illness may also influence findings of GxE investigations. Research supports differences in neurobiological and treatment-response characteristics of depression with onset in childhood, adolescence, and adulthood (Rutter et al. 2006), and there is evidence that the

ELS profiles of individuals with childhood- vs. adult-onset depression differ (Jaffee et al. 2002). Differences in both genetic and environmental determinants of childhood- vs. adult-onset disorders could be expected, limiting the validity of studies that combine these conditions. Developmentally sensitive longitudinal research is ideal for characterizing ELS, symptom onset, and course, but the challenges to longitudinal assessment are substantial.

Although no published meta-analyses have focused on gene by ELS interactions, a recent meta-analysis by Risch et al. (2009) examined GxE between stressful life events and *5-HTTLPR* on depression using 14 studies (*N*=14,250). Just under half of the included studies focused on the effects of ELS. The authors concluded that there was no support for an interaction effect, generating considerable controversy in the field. In a subsequent systematic review, the 14 studies (out of 34 possible studies) included in the Risch report were found to show a statistically significant bias toward negative findings (Uher and McGuffin 2010). Also informing this debate, Munafo et al. (2009) conducted a meta-analysis which led them to conclude that most of the available studies were underpowered, and that findings using logistic regression models were “compatible with chance.” They underscored the importance of analytic approach, sampling, and power in this area of research. Caspi et al. (2010), recently reviewing the role of *5-HTTLPR* in stress sensitivity from a broader perspective, asserted a prominent role for this gene in the neurobiological and behavioral responses to stress. However, it is important to note that these reviews included studies of life events occurring throughout the lifespan and did not formally address the potentially differential effects of ELS relative to adult stressors.

Conclusions and future directions

In spite of significant variability in methodology and findings, taken together these studies provide support for GxE effects of genes in the serotonin, HPA axis, and neurotrophin systems in predicting depressive and anxiety disorders. Several studies have notably failed to detect these effects. In addition to methodological factors (e.g., population stratification, measurement, rGE), studies reviewed here suggest that differences in findings may be attributable to: (1) type of ELS, (2) gender-related effects, (3) additional interactive or additive environmental influences, such as social support, and (4) additional moderating genes. Timing of ELS is likely also critically important, and may further explain inconsistencies in the literature. Although a survey of epigenetic methods and findings is outside the scope of this review, emerging epigenetic research suggests that timing of stress may be linked to functional alterations of genes implicated in depression (Murgatroyd et al. 2010).

Finally, an increasingly accepted GxE model assumes genes may interact with environmental influences on both ends of the spectrum, with risk and resilience resulting from exposure to negative and positive environments, respectively. If the same variants are serving to increase responsiveness to both positive and negative influences, as recently proposed (Belsky et al. 2009; Belsky and Pluess 2009; Fox et al. 2007), it may be especially important for future studies to also measure positive influences, and to assess functioning across a range of environmental circumstances.

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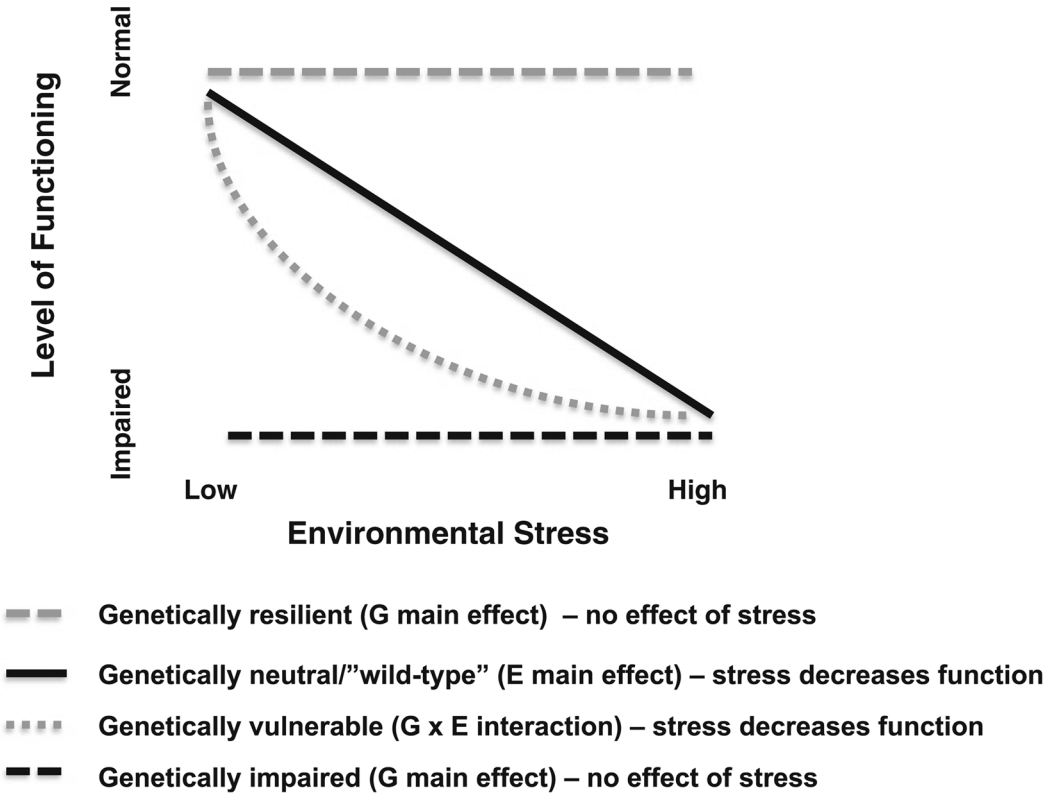

Fig 1.
Gene-environment interactions

Table 1

Studies of *5-HTTLPR* and GxE in early life stress

Author	Sample Gender (M, F); Ethnicity	Age of ELS	Age at outcome M (SD) or range	Type of ELS	ELS assessment	Outcome	Outcome assessment	Major findings
Studies reporting increased risk associated with s/s′								
Aguilera et al. (2009)	242, 292	Childhood	23 (5)	Emotional/physical/sexual abuse; neglect	Retrospective: self-report questionnaire	Depressive symptoms	Self-report questionnaire	Significant rGE: *5-HTTLPR* l/l predicted higher childhood sexual abuse than l/s
	534 E							Significant sex abuse×*5-HTTLPR*: sex abuse effects on depressive symptoms greater in s carriers
Åslund et al. (2009)	765, 717 1,482 E	Childhood and adolescence	17–18	Physical/emotional maltreatment, domestic violence, quarrels between parents	Concurrent: retrospective self-report on 4 single items	Self-report symptoms consistent with DSM-IV depression	Self-report questionnaire	Significant ELS×*5-HTTLPR*: increased self-report symptoms consistent with depression in girls with ELS and s/s genotype
Caspi et al. (2003)	432, 415 847 NZC	Childhood	26	Severe maternal rejection, harsh discipline, change in caregiver, physical abuse, sexual abuse	Longitudinal concurrent: combination of observation, parent-report and self-report	Depression diagnosis and symptoms	Clinical interview	Significant ELS×*5-HTTLPR*: significant dose-effects such probable and severe maltreatment groups evidenced highest depression in s/s and moderate depression in s/l
Cicchetti et al. (2007)	184, 155	Childhood and adolescence	17 (1)	Neglect, physical or sexual abuse, emotional abuse	DHS records	Depressive symptoms; anxious, depressed, and somatic symptoms	Clinical interview, self- report	Significant of sexual abuse×*5-HTTLPR*: sexually abused s/s genotype predicted increased depression/anxiety
	209 AA, 79 EA, 43 H, 8 other							Significant sexual abuse×*5-HTTLPR×MAOA*: sexually abused low *MAOA* activity, s carriers at greatest depression
Gibb et al. (2009)	41,59 82 EA	Childhood	10 (1)	Maternal critical expressed emotion	Maternal report; rating of videotaped interaction	Depressive symptoms; inferential style	Self-report; diagnostic interview	Significant ELS×*5-HTTLPR*× inferential style: dose response of genotype with depression increased in s′ carriers experiencing high levels of maternal criticism[a,b]
Kaufman et al. (2004)	46, 55 21 EA, 25 H, 32 AA, 23 BiR	Childhood	10 (2)	Sexual abuse, physical abuse, emotional abuse, neglect, domestic violence	Multi-informant (DCF records, caseworkers, youth, parents)	Depressive symptom scores	Self-report questionnaire	Significant ELS×*5-HTTLPR* & significant ELS×*5-HTTLPR*× social support: highest depression scores in ELS, s/s, low support[c]

Author	Sample Gender (M, F); Ethnicity	Age of ELS	Age at outcome M (SD) or range	Type of ELS	ELS assessment	Outcome	Outcome assessment	Major findings
Kaufman et al. (2006)	96, 100 55 EA, 47 H, 55 AA, 39 BiR	Childhood	9 (2)	Sexual abuse, physical abuse, emotional abuse, neglect, domestic violence	Multi-informant (DCF records, caseworkers, youth, parents)	Depressive symptom scores depression severity	Self-report questionnaire	Significant ELS×*5-HTTLPR*× *BDNF*: highest depression scores in *BDNF* met and s/s *5-HTTLPR*[c]
Nobile et al. (2009)	315, 292	Childhood and adolescence	12 (1)	"Family structure" (i.e., single- vs. two-parent families)	Parent report	Affective problems	Parent-report questionnaire	rGE trend: excess s/s in single-parent families
	E 592							Significant ELS×*5-HTTLPR*: single-parent s′ carriers greatest affective problems
Stein et al. (2008)	76, 171 247 EA	Childhood and adolescence	19 (2)	Emotional or physical abuse	Retrospective self- report questionnaire	Anxiety sensitivity	Self-report questionnaire	Significant ELS×*5-HTTLPR:* greatest anxiety sensitivity (especially physical sensitivity) in s/s or s′/s′ with emotional or physical abuse history
Taylor et al. (2006)	51, 67 45 AsianA, 40 EA, 33 NR	Childhood	18–29	Early family environment including physical and emotional maltreatment	Retrospective self-report questionnaire	Depressive symptoms	Self-report Questionnaires	Significant ELS×*5-HTTLPR*: s/s increased depressive symptoms under ELS
Xie et al. 2009	656, 596 582 EA, 670 AA	Before age 13	40 (10)	Violent crime, sexual abuse, physical abuse, neglect	Retrospective semi- structured interview	PTSD Diagnosis	Semi-structured interview	Significant ELS×*5-HTTLPR*: s′ carriers more likely to develop PTSD
Studies supporting increased risk associated with l/l′ alleles								
Chorbov et al. (2007)	0, 227 227 EA	Childhood and adolescence	22 (3)	Traumatic events (life- threatening accident/ disaster, physical abuse, sexual abuse, neglect)	Retrospective self-report questionnaire	Depressive diagnosis	Clinical interview	Significant ELS×*5-HTTLPR*: increased adolescent-onset depression diagnosis in l′
Laucht et al. (2009)	142, 167 309 E	Childhood	19	Family adversity (low parent education, unwanted pregnancy, overcrowding, etc.)	Parent interview at 3 months post-partum	Depressive symptoms & diagnosis; anxiety diagnosis	Clinical interview; self- report questionnaires	Significant ELS×*5-HTTLPR*: increased anxiety or depression diagnosis in youth with ELS and l′/l′ (or l/l) genotype
Studies with mixed GxE findings								
Chipman et al. (2007)	1,004, 1,091	Childhood and adolescence	20–24 15–18	Number of events ranging from maternal mental health concerns to physical/sexual abuse	Concurrent and retropective self-report items	Depressive symptoms	Self-report questionnaire	No significant ELS×*5-HTTLPR* in the first sample[b]
	2,095 AC 288, 296 584 AC			Number of family stressors over past 12 months and 6 years				No significant ELS×*5-HTTLPR* at 12–16 yo follow-up; significant only at 17–18 yo: l/l with high family adversity during past 6 years reported greatest depression[b]
Eley et al. (2004)	157, 220 NR	Adolescence	12–19	Combined index of family social problems, parent education, adverse events	Concurrent self-report questionnaire	High depressive symptom category	Self-report questionnaires	Significant ELS×*5-HTTLPR* in girls only: increased risk of

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Author	Sample Gender (M, F); Ethnicity	Age of ELS	Age at outcome M (SD) or range	Type of ELS	ELS assessment	Outcome	Outcome assessment	Major findings
								high depressive symptoms associated with s/s only in high ELS group[b]
Hammen et al. (2010)	132, 214	15–19	20	Negative life events (i.e., academic failure, divorce, victim of crime, etc.); chronic family stress at age 15	Interviews; multi-informant reports	Depressive symptoms		Significant rGE: s′/l′ genotype reported higher family discord[a]
	321 AC							No significant acute stress×*5-HTTLPR*[a] Significant family discord×*5-HTTLPR*, females only: s′ carriers with family discord evidenced more symptoms of depression[a]
Ritchie et al. 2009	395, 547 942 E	Childhood and adolescence	Mdn=72	Factors spanning physical/sexual abuse and maltreatment, illness, poverty, war, excess parent problem-sharing	Retrospective self- report with discussion opportunities	Depressive symptoms; depression diagnosis	Self-report questionnaire; interview	Significant ELS (poverty & excess parent problem-sharing)×*5-HTTLPR*: l′ carriers reporting poverty or parent problem sharing more likely to be depressed[b]
Sjoberg et al. (2006)	66, 114 180 E	Childhood and adolescence	19–22	Family residence, family conflicts, parental education and occupation, family finances	Concurrent and retrospective interview	Self-report symptoms consistent with DSM-IV depression	Self-report questionnaire	Significant ELS×*5-HTTLPR* interaction: s allele associated with depression category in girls reporting traumatic family conflict whereas s allele protective against depression category in boys reporting housing-related stress
Wichers et al. (2008)	0, 394	Childhood and adolescence	18–46	Emotional abuse, neglect	Retrospective self- report questionnaire	Depressive symptoms	Self-report questionnaire	Significant rGE: Increased childhood adversity in Val/Met *BDNF*
	394 E							Significant ELS×*5HTTLPR*×*BDNF*: among *BDNF* met carriers, increased depressive symptoms in s/l *5-HTTLPR* (trend in s/s)
Studies reporting no GxE effects								
Araya et al. (2009)	2,306,2,028 4,170 E	5–7	7	Maternal postnatal depression; 17 adverse life events	Maternal report	Emotionality symptoms	Parent-report questionnaire	No significant ELS×*5-HTTLPR* predicting emotional symptoms[a,b,c]
Surtees et al. (2006)	2,225, 1,950 NR	Childhood and adolescence	60 (9)	Separation from mother, divorce, frightening event, sent away from home due to behavior, parent unemployment, hospitalization, parent substance abuse, physical abuse	Retrospective self-report questionnaire	Self-report symptoms consistent with DSM-IV depression plus high neuroticism	Self-report questionnaire	No significant ELS×*5-HTTLPR* interaction predicting cases (self- report

Author	Sample Gender (M, F); Ethnicity	Age of ELS	Age at outcome M (SD) or range	Type of ELS	ELS assessment	Outcome	Outcome assessment	Major findings
								depression *and* high neuroticism)[a]

M male, *F* female; *AA* African American, *AsianA* Asian American, *AC* Australian White/Caucasian, *BiR* biracial, *EA* European American/white/Caucasian American, European *E*, *H* Hispanic, *NZC* New Zealand white/Caucasian, *NR* Not Reported

[a] No strategies to address population stratification reported

[b] No test of rGE reported

[c] Overlap between sample and other investigations reported herein

Table 2

Additional serotonin system candidate gene investigations of early life stress (ELS)

Author	Sample Gender (M, F) Ethnicity	Age of ELS	Age at outcome M (SD) or range	Type of ELS	ELS assessment	Outcome	Outcome assessment	Major findings
TPH2: G-703T								
Nobile et al. (2009)	315, 292 E 592	Childhood and adolescence	12 (1)	"Family structure" (i.e., single- vs. two-parent families)	Parent report	Affective problems	Parent-report questionnaire	Significant ELS× *TPH2* G-703T: single-parent G carriers greatest affective problems
TPH1: 3′ microsatellite allele 5								
Eley et al. (2004)	157, 220 NR	Adolescence	12–19	Combined index of family social problems, parent education, adverse events	Concurrent self-report questionnaire	High depressive symptom category	Self-report Questionnaires	Significant main effect of *TPH*: allele 5 protective such that it decreased risk of high depressive symptoms[b]
MAOA: uVNTR								
Cicchetti et al. (2007)	184, 155	Childhood and adolescence	17 (1)	Neglect, physical or sexual abuse, emotional abuse	DHS records	Depressive symptoms; anxious/depressed symptoms	Clinical interview, self-report	Significant *MAOA*×number of maltreatment subtypes: low activity variant at greatest risk for depression in 3–4 subtypes
	209 AA, 79 EA, 43 H, 8 other							Significant sexual abuse×*5-HTTLPR*×*MAOA*: sexually abused low *MAOA* activity, s carriers at greatest depression
5-HT1A receptor: rs6295 C/G								
Chipman et al. (2010)	3,177, 3,294 6,471 AC	Childhood and adolescence	20–24; 40–44; 60–64	17 adversities ranging from maternal mental health concerns to abuse	Self-report questionnaire	Depression and anxiety symptoms	Self-report questionnaire	No significant interaction or main effects
5-HT2A receptor*: T102C*								
Eley et al. (2004)	157, 220	Adolescence	12–19	Combined index of family social problems, parent education, adverse events	Concurrent self-report questionnaire	High depressive symptom category	Self-report Questionnaires	Significant main effect for *5HT2A*: increased depression risk associated with T alleles[b]
	NR							No significant *5HT2A*×ELS[b]
5-HT2C: promoter VNTR allele 1								
Eley et al. (2004)	157, 220 NR	Adolescence	12–19	Combined index of family social problems, parent education, adverse events	Concurrent self-report questionnaire	High depressive symptom category	Self-report Questionnaires	No significant main or interaction effects observed[b]

M male, *F* female; *AA* African American, *AsianA* Asian American, *AC* Australian White/Caucasian, *BiR* biracial, *EA* European American/white/Caucasian American, European *E, H* Hispanic, *NZC* New Zealand white/Caucasian, *NR* not reported

[a] No strategies to address population stratification reported

[b] No test of rGE reported

[c] Overlap between sample and other investigations reported herein

Table 3

HPA axis candidate gene investigations of early life stress (ELS)

Author	Sample Gender (M, F) Ethnicity	Age of ELS	Age at outcome M (SD) or range	Type of ELS	ELS assessment	Outcome	Outcome assessment	Major findings
CRHR1: rs11042, rs242924, rs4076452, rs12942300, rs7209436, rs4792887, rs242940, rs173365, rs242950, rs242948								
Bradley et al. (2008)	194, 303 484 AA, 4 EA, 2 H, 1 AsianA, 5 BiR, 3 other 0, 199 88% EA, 7% AA, 4% NA, 2%AsianA	Childhood	38 (13) 18–81	Physical/sexual/emotional abuse	Retrospective self-report questionnaire	Depression symptoms	Self-report questionnaire	Significant ELS×*CRHR1* on depressive symptoms: 7/10 SNPs in *CRHR1* significant GxE; rs110402 & rs7209436 remained significant after correction for multiple testing[b]
Heim et al. (2009)	424, 639	Childhood	18–77	Physical, sexual, emotional abuse	Retrospective self-report questionnaire	Depressive and PTSD symptoms; Cortisol response	Self-report questionnaire; DEX/CRH	Significant ELS×*CRHR1* on depressive symptoms in men: male abused rs110402 G carriers reported increased depressive symptoms[b]
	1,063 AA		18–45					Significant physical abuse×*CRHR1* on depressive symptoms: G/G genotype associated with depressive symptoms
	25, 53 NR							Significant ELS×*CRHR1* on DEX/CRH in men: male abused rs110402 G evidenced increased cortisol response[b]
Polanczyk et al. (2009)	0, 1,000 90% E	Childhood	26–55 32	Physical/sexual/emotional abuse, emotional/physical neglect; maltreatment	Retrospective self-report questionnaire; Concurrent behavioral observations, parent-report, self-report	Depression diagnosis	Clinical interview	rGE: trend in one of the two cohorts Significant ELS×*CRHR1* haplotype: rs7209436, rs110402, rs242924 TAT haplotype protective effect on maltreated participants
	476, 442 90% NZC							No replication found in second study with different measure of ELS
Ressler et al. (2010)	520, 855 1,375 AA	Childhood	18+	Physical/sexual/emotional abuse	Retrospective self-report	Depressive symptoms	Self-report questionnaire	Significant ELS×*CRHR1* haplotypes×*5-HTTLPR*: s′ allele enhanced CRHR1 risk haplotype effects on depressive symptoms at lower levels of abuse
Tyrka et al. (2009)	51, 78 129 EA	Childhood	18–61	Emotional/physical/sexual abuse; physical/emotional neglect	Retrospective self-report questionnaire	Cortisol response	Dexamethasone/corticotropin-releasing (DEX/CRH) hormone test	Significant ELS×*CRHR1*: rs110402 & rs242924 G/G genotypes associated with

Author	Sample Gender (M, F) Ethnicity	Age of ELS	Age at outcome M (SD) or range	Type of ELS	ELS assessment	Outcome	Outcome assessment	Major findings
								increased cortisol response only if reporting moderate to severe childhood maltreatment
Glucocorticoid Receptor *NR3C1:* 22/23EK (rs6189, rs6190); N363S A/G (rs6195); BclI C/G (rs41423247); exon 9beta A/G (rs6198)								
Bet et al. (2009)	446, 460	Childhood and adolescence	65+	War, impaired health, death/ separation of parents, sexual abuse	Retrospective self-report	Depressive symptoms	Self-report questionnaire	Significant ELS×22/23 EK×9beta predicting depressive symptoms
	906 E							Significant ELS×22/23EK predicting cortisol: lower cortisol in ELS
FKBP5: rs4713916, rs1360780, rs3800373, rs9470080, rs9296158								
Binder et al. (2008)	384, 516 855 AA, 20 EA, 1 AsianA, 8 BiR, 9 other, 2 NR	Childhood	41 (14)	Physical/sexual/emotional abuse	Retrospective self-report	PTSD symptoms	Self-report questionnaire	Significant ELS severity×*FKBP5* SNPs predicting PTSD symptoms[b]
Xie et al. (2009)	1,320, 1,107 1,284 AA, 1,143 EA	Prior to 13	39 (11)	Violent crime, sexual abuse, physical abuse	Retrospective self-report	PTSD diagnosis	Clinical interview	Significant ELS×*FKBP5* in AA

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[a] No strategies to address population stratification reported

[b] No test of rGE reported

[c] Overlap between sample and other investigations reported herein

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Table 4

Neurotrophic and other candidate gene investigations of early life stress (ELS)

Author	Sample Gender (M, F) Ethnicity	Age of ELS	Age at Outcome M (SD) or range	Type of ELS	ELS assessment	Outcome	Outcome assessment	Major findings
BDNF: Val66Met								
Aguilera et al. (2009)	242, 292 534 E	Childhood	23 (5)	Emotional/physical/sexual abuse; neglect	Retrospective self-report questionnaire	Depressive symptoms	Self-report questionnaire	Significant sexual abuse× *BDNF*: sexual abuse effects on depressive symptoms greater in met carriers
Gatt et al. (2009)	184, 190	Childhood and adolescence	36 (13)	Abuse, neglect, family conflict, illness/death, natural disasters	Retrospective self-report questionnaire	Severity of depressive and anxiety symptoms	Self-report questionnaire	Significant ELS× *BDNF:* ELS exposed Met carriers had smaller hippocampal and amygdala volume
	374 EA					Heart rate Brain gray matter		Structural Modeling: ELS exposure and Met carrier predict smaller gray matter in hippocampus and lateral prefrontal cortex which in turn predicts depressive symptoms
Wichers et al. (2008)	0, 464[a]	Childhood and adolescence	18–46	Emotional abuse, neglect	Retrospective self-report questionnaire	Depressive symptoms	Self-report questionnaire	Significant rGE: Increased childhood adversity in Val/Met *BDNF*
	464[a] E							Significant ELS× *BDNF*: childhood adversity associated with increased depression in Met carriers
*DAT1 (*also called *SLC6A3):* rs40184, rs6347, rs2652511								
Haeffel et al. (2008)	176, 0 176 E	Childhood and adolescence	16 (1)	Maternal rejection (e.g., physical punishment, hostility, disrespect, unjustified public criticism)	Retrospective self-report	Depressive symptoms, anxiety symptoms	Self-report questionnaire	Significant ELS×rs40184 predicting depressive symptoms and suicidal ideation[b]
DRD2 Taq1A: 1800497								
Hayden et al. (2010)	251,222	3 years of age or younger	3	Parenting practices and interaction styles	Ratings of parent supportiveness/ intrusiveness during standardized interaction task	Diagnoses of depression, anxiety, ODD; symptoms of internalizing, externalizing, anxious/ depressed	Diagnostic interview completed with parents; parent report questionnaire	Significant rGE between child DRD2 and parent behavior during task
	406 EA, 23 H							Marginally significant ($p = .05$) intrusiveness× *DRD2 Taq1A*: A2 homozygotes showed positive association between parent intrusiveness and symptoms while A1 carriers showed a negative association
COMT: Val158Met rs4680; rs2097603, rs6269, rs4818, rs165599								
Evans et al. (2009)	3,016, 5,838	5–7	7	Maternal postnatal depression; 17 adverse live events	Maternal report	Emotionality symptoms	Parent report	No significant ELS× *COMT*[d]
GABRA2: rs279836, rs279826, rs279858, rs279871								

Author	Sample Gender (M, F) Ethnicity	Age of ELS	Age at Outcome M (SD) or range	Type of ELS	ELS assessment	Outcome	Outcome assessment	Major findings
Nelson et al. (2009)	259 NR	Childhood	"Adult"	Sexual abuse, physical abuse, emotional/ physical partner maltreatment	Retrospective self-report	PTSD	Interview	Significant ELS×*GABRAA2* predicting PTSD[b,c]

M Male, *F* Female; *AA* African American, *AsianA* Asian American, *AC* Australian White/Caucasian, *BiR* Biracial, *EA* European American/White/Caucasian American, *E* European, *H* Hispanic, *NZC* New Zealand White/Caucasian, *NR* not reported

[a] Please note that these numbers differ from the three-way interactions with *5-HTTLPR* due to missing genotype information available for *5-HTTLPR* analyses

[b] No test of rGE reported

[c] No strategies to address population stratification reported

[d] Overlap between sample and other investigations reported herein