Psychopharmacology (2011) 214:175–196
DOI 10.1007/s00213-010-2151-x

REVIEW

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

Nicole R. Nugent · Audrey R. Tyrka · Linda L. Carpenter · Lawrence H. Price

Received: 5 April 2010 / Accepted: 13 December 2010 / Published online: 12 January 2011

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

N. R. Nugent (✉)
Bradley/Hasbro Children's Research Center,
Rhode Island Hospital,
Coro West Building, One Hoppin Street, Suite 204,
Providence, RI 02903, USA
e-mail: Nicole_Nugent@brown.edu

N. R. Nugent · A. R. Tyrka · L. L. Carpenter · L. H. Price
Department of Psychiatry and Human Behavior,
Alpert Medical School of Brown University,
Providence, RI, USA

A. R. Tyrka · L. L. Carpenter · L. H. Price
Mood Disorders Research Program, Butler Hospital,
Providence, RI, USA

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

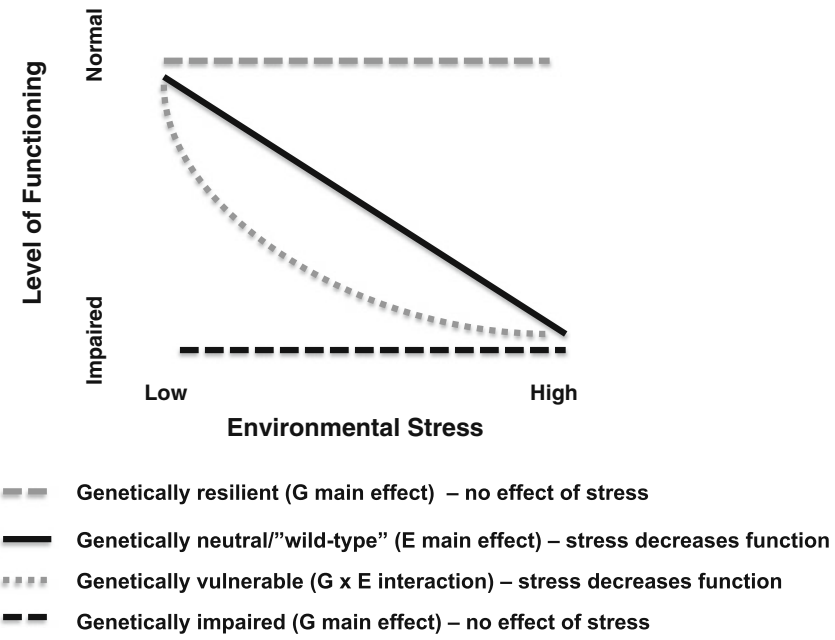

Fig. 1 Gene-environment interactions

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 cut-off" 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

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	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
	1,482 E							
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, c]
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]
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	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
	247 EA							
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 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]

Table 1 (continued)

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
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 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

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 *BDNFVal66Met* 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

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 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, 460 906 E	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 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

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

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

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								
Nelson et al. (2009)	259 NR	Childhood	"Adult"	Sexual abuse, physical abuse, emotional/physical partner maltreatment	Retrospective self-report	PTSD	Interview	Significant ELS × *GABRA2* 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

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 symp-

toms. 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.

Acknowledgment Manuscript preparation was supported, in part, by NIMH grants K01 MH087240 (NRN), R01 MH083704 and Department of Defense grant PR064771 (ART), and NIMH grant R01 MH068767 (LLC).

References

Adamec R, Burton P, Blundell J, Murphy DL, Holmes A (2006) Vulnerability to mild predator stress in serotonin transporter knockout mice. Behav Brain Res 170:126–140

Aguilera M, Arias B, Wichers M, Barrantes-Vidal N, Moya J, Villa H, van Os J, Ibanez MI, Ruiperez MA, Ortet G, Fananas L (2009) Early adversity and 5-HTT/BDNF genes: new evidence of gene× environment interactions on depressive symptoms in a general

population. Psychol Med 39:1425–1432. doi:10.1017/S0033291709005248
Alexander N, Kuepper Y, Schmitz A, Osinsky R, Kozyra E, Hennig J (2009) Gene-environment interactions predict cortisol responses after acute stress: implications for the etiology of depression. Psychoneuroendocrinology 34:1294–1303
Alleva E, Francia N (2009) Psychiatric vulnerability: suggestions from animal models and role of neurotrophins. Neurosci Biobehav Rev 33:525–536
Amat J, Baratta MV, Paul E, Bland ST, Watkins LR, Maier SF (2005) Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat Neurosci 8:365–371
Ansorge MS, Hen R, Gingrick JA (2007) Neurodevelopmental origins of depressive disorders. Current Opin Psychopharmacol 7:8–17
Araya R, Hu X, Heron J, Enoch M-A, Evans J, Lewis G, Nutt D, Goldman D (2009) Effects of stressful life events, maternal depression and 5-HTTLPR genotype on emotional symptoms in pre-adolescent children. Am J Med Genet B Neuropsychiatr Genet 150B:670–682
Åslund C, Leppert J, Comasco E, Nordquist N, Oreland L, Nilsson K (2009) Impact of the interaction between the 5HTTLPR polymorphism and maltreatment on adolescent depression. A population-based study. Behav Genet 39:524–531
Bagner DM, Pettit JW, Lewinsohn PM, Seeley JR (2010) Effect of maternal depression on child behavior: a sensitive period? J Am Acad Child Adolesc Psychiatry 49:699–707
Belsky J, Pluess M (2009) Beyond diathesis stress: differential susceptibility to environmental influences. Psychol Bull 135:885–908
Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R (2009) Vulnerability genes or plasticity genes? Mol Psychiatry 14:746–754
Bet PM, Penninx BWJH, Bochdanovits Z, Uitterlinden AG, Beekman ATF, NMv S, Deeg DJH, Hoogendijk WJG (2009) Glucocorticoid receptor gene polymorphisms and childhood adversity are associated with depression: new evidence for a gene-environment interaction. Am J Med Genet B Neuropsychiatr Genet 150B:660–669
Bhatnagar S, Sun LM, Raber J, Maren S, Julius D, Dallman MF (2004) Changes in anxiety-related behaviors and hypothalamic-pituitary-adrenal activity in mice lacking the 5-HT-3A receptor. Physiol Behav 81:545–555
Biederman J, Kim JW, Doyle AE, Mick E, Fagerness J, Smoller JW, Faraone SV (2008) Sexually dimorphic effects of four genes (COMT, SLC6A2, MAOA, SLC6A4) in genetic associations of ADHD: a preliminary study. Am J Med Genet B Neuropsychiatr Genet 147B:1511–1518
Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, Tang Y, Gillespie CF, Heim CM, Nemeroff CB, Schwartz AC, Cubells JF, Ressler KJ (2008) Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. J Am Med Assoc 299:1291–1305
Bradley RG, Binder EB, Epstein MP, Tang Y, Nair HP, Liu W, Gillespie CF, Berg T, Evces M, Newport DJ, Stowe ZN, Heim CM, Nemeroff CB, Schwartz A, Cubells JF, Ressler KJ (2008) Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. Arch Gen Psychiatry 65:190–200. doi:10.1001/archgenpsychiatry.2007.26
Bronfenbrenner U, Ceci SJ (1994) Nature-nuture reconceptualized in developmental perspective: a bioecological model. Psychol Rev 101:568–586
Brook JS, Cohen P, Brook D (1998) Longitudinal study of co-occurring psychiatric disorders and substance abuse. J Am Acad Child Adolesc Psychiatry 37:322–330
Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G (2001) Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives. Health Technol Assess 5:1–56
Brown GW, Harris TO (2008) Depression and the serotonin transporter 5-HTTLPR polymorphism: a review and a hypothesis concerning gene-environment interaction. J Affect Disord 111:1–12
Campbell-Sills L, Forde DR, Stein MB (2009) Demographic and childhood environmental predictors of resilience in a community sample. J Psychiatr Res 43:1007–1012
Carola V, Frazzetto G, Pascucci T, Audero E, Puglisi-Allegra S, Cabib S, Lesch KP, Gross C (2007) Identifying molecular substrates in a mouse mode of the serotonin transporter×environment risk factor for anxiety and depression. Biol Psychiatry 69:840–846
Caspi A, Sugden K, Moffitt T, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301:386–389
Caspi A, Hariri AR, Holmes A, Uher R, Moffit TE (2010) Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. Am J Psychiatry 167:509–527
Charney DS (2004) Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. Am J Psychiatry 161:195–216
Chipman P, Jorm AF, Prior M, Sanson A, Smart D, Tan X, Easteal S (2007) No interaction between the serotonin transporter polymorphism (5-HTTLPR) and childhood adversity or recent stressful life events on symptoms of depression: results from two community surveys. Am J Med Genet B Neuropsychiatr Genet 144B:561–565
Chipman P, Jorm AF, Tan X, Easteal S (2010) No association between the serotonin-1A receptor gene single nucleotide polymorphism rs6295C/G and symptoms of anxiety or depression, and no interaction between the polymorphism and environmental stressors of childhood anxiety or recent stressful life events on anxiety or depression. Psychiatr Genet 20(1):8–13
Chorbov V, Lobos E, Todorov A, Heath AC, Botteron K, Todd R (2007) Relationship of 5-HTTLPR genotypes and depression risk in the presence of trauma in a female twin sample. Am J Med Genet B Neuropsychiatr Genet 144B:830–833
Cicchetti D, Rogosch FA, Sturge-Apple ML (2007) Interactions of child maltreatment and serotonin transporter and monoamine oxidase a polymorphisms: depressive symptomatology among adolescents from low socioeconomic status backgrounds. Dev Psychopathol 19:1161–1180. doi:10.1017/S0954579407000600
Cohen RA, Hitsman BL, Paul RH, McCaffery J, Stroud L, Sweet L, Gunstad J, Niaura R, Macfarlane A, Bryant RA, Gordon E (2006) Early life stress and adult emotional experience: an international perspective. Int J Psychiatry Med 36:35–52
Coplan JD, Abdallah CG, Tang CY, Mathew SJ, Martinez J, Hof PR, Smith EL, Dwork AJ, Perera TD, Pantol G, Carpenter D, Rosenblum LA, Shungu DC, Gelernter J, Kaffman A, Jackowski A, Kaufman J, Gorman JM (2010) The role of early life stress in development of the anterior limb of the internal capsule in nonhuman primates. Neurosci Lett 480:93–96
Crayton JW, Joshi I, Gulati A, Arora RC, Wolf WA (1996) Effect of corticosterone on serotonin and catecholamine receptors and uptake sites in rat frontal cortex. Brain Res 728:260–262
Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, Poulton R, Caspi A (2009) Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med 163:1135–1143. doi:10.1001/archpediatrics.2009.214
De Kloet ER, Joels M, Holsboer F (2005) Stress and the brain: from adaptation to disease. Nature Rev Neuroscience 6:463–475
Dohrenwend BP, Levav I, Shrout PE, Schwartz S, Naveh G, Link BG, Skodol AE, Stueve A (1992) Socioeconomic status and psychiatric disorders: the causation-selection issue. Science 255:946–952

Dubow EF, Ippolito MF (1994) Effects of poverty and quality of the home environment on changes in the academic and behavioral adjustment of elementary school-age children. J Clin Child Psychol 23:401–412

Duman RS (2002) Pathophysiology of depression: the concept of synaptic plasticity. Eur Psychiatry 17(Suppl 3):306–310

Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59:1116–1127

Dunlop BW, Nemeroff CB (2007) The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 64:327–337

Eaves LJ (2006) Genotype×environment interaction in psychopathology: fact or artifact? Twin Res Hum Genet 9:1–8

Eaves LJ, Silberg JL, Meyer JM, Maes HH, Simonoff E, Pickles A, Rutter M, Neale MC, Reynolds CA, Erikson MT, Heath AC, Loeber R, Truett KR, Hewitt JK (1997) Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia twin study of adolescent behavioral development. J Child Psychol Psychiatry 38:965–980

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112:257–269

El Hage W, Powell JF, Surguladze SA (2009) Vulnerability to depression: what is the role of stress genes in gene×environment interaction? Psychol Med 39:1407–1411. doi:10.1017/S0033291709005236

Eley TC, Sugden K, Corsico A, Gregory AM, Sham P, McGuffin P, Plomin R, Craig IW (2004) Gene-environment interaction analysis of serotonin system markers with adolescent depression. Mol Psychiatry 9:908–915

Evans J, Xu K, Heron J, Enoch MA, Araya R, Lewis G, Timpson N, Davies S, Nutt D, Goldman D (2009) Emotional symptoms in children: The effect of maternal depression, life events, and COMT genotype. Am J Med Genet B 150(2):209–218

Fergusson DM, Horwood LJ (2002) Male and female offending trajectories. Dev Psychopathol 14:159–177

Fiscella K, Kitzman H (2009) Disparities in academic achievement and health: the intersection of child education and health policy. Pediatrics 123:1073–1080. doi:10.1542/peds.2008-0533

Fox NA, Hane AA, Pine DS (2007) Plasticity for affective neurocircuitry: how the environment affects gene expression. Current Directions in Psychological Science 16:1–5

Freisthler B, Gruenewald PJ, Ring L, LaScala EA (2008) An ecological assessment of the population and environmental correlates of childhood accident, assault, and child abuse injuries. Alcohol Clin Exp Res 32:1969–1975

Froger N, Palazzo E, Boni C, Hanoun N, Saurini F, Joubert C, Dutriez-Casteloot I, Enache M, Maccari S, Barden N, Cohen-Salmon C, Hamon M, Lanfumey L (2004) Neurochemical and behavioral alterations in glucocorticoid receptor-impaired transgenic mice after chronic mild stress. J Neurosci 24:2787–2796

Fu Q, Koenen KC, Miller MW, Heath AC, Bucholz KK, Lyons MJ, Eisen SA, True WR, Goldberg J, Tsuang MT (2007) Differential etiology of posttraumatic stress disorder with conduct disorder and major depression in male veterans. Biol Psychiatry 62:1088–1094

Gardner KL, Hale MW, Lightman SL, Plotsky PM, Lowry CA (2009) Adverse early life experience and social stress during adulthood interact to increase serotonin transporter mRNA expression. Brain Res 1305:47–63

Gatt JM, Nemeroff CB, Dobson-Stone C, Paul RH, Bryant RA, Schofield PR, Gordon E, Kemp AH, Williams LM (2009) Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol Psychiatry 14:681–695

Gibb BE, Uhrlass DJ, Grassia M, Benas JS, McGeary J (2009) Children, inferential styles, 5-HTTLPR genotype, and maternal expressed emotion-criticism: an integrated model for the intergenerational transmission of depression. J Abnorm Psychol 118:734–745

Gillespie CF, Phifer J, Bradley B, Ressler KJ (2009) Risk and resilience: genetic and environmental influences on development of the stress response. Depress Anxiety 26:984–992

Gotlib IH, Joormann J, Minor KL, Hallmayer J (2008) HPA axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression. Biol Psychiatry 63:847–851

Grahn RE, Willi MJ, Hammack SE, Maswood S, McQueen MB, Watkins LR, Maier SF (1999) Activation of serotonin-immunoreactive cells in the dorsal raphe nucleus in rats exposed to an uncontrollable stressor. Brain Res 826:35–43

Gross C, Hen R (2004) The developmental origins of anxiety. Nature Rev Neurosci 5:545–552

Gunnar M, Quevedo K (2007) The neurobiology of stress and development. Annu Rev Psychol 58:145–173. doi:10.1146/annurev.psych.58.110405.085605

Haeffel GJ, Getchell M, Koposov RA, Yrigollen CM, DeYoung CG, af Klinteberg B, Oreland L, Ruchkin VV, Grigorenko EL (2008) Association between polymorphisms in the dopamine transporter gene and depression. Evidence for a gene-environment interaction in a sample of juvenile detainees. Psychol Sci 19:62–69

Hammen C, Brennan PA, Keenan-Miller D, Hazel NA, Najman JM (2010) Chronic and acute stress, gender, and serotonin transporter gene×environment interactions predicting depression symptoms in youth. J Child Psychol Psychiatry 51:180–187

Handwerger K (2009) Differential patterns of HPA activity and reactivity in adult posttraumatic stress disorder and major depressive disorder. Harv Rev Psychiatry 17:184–205

Hardt J, Rutter M (2004) Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. J Child Psychol Psychiatry 45:260–273

Hariri AR, Holmes A (2006) Genetics of emotional regulation: the role of the serotonin transporter in neural function. Trends Cogn Sci 10:182–191

Harrington R (2001) Adolescent depression—same or different? Arch Gen Psychiatry 58:21–22

Hayden EP, Klein DN, Dougherty LR, Olino TM, Laptook RS, Dyson MW et al (2010) The dopamine D2 receptor gene and depressive and anxious symptoms in childhood: associations and evidence for gene-environment correlation and gene-environment interaction. Psychiatr Genet 20(6):304–310

Heim C, Nemeroff CB (2002) Neurobiology of early life stress: clinical studies. Semin Clin Neuropsychiatry 7:147–159

Heim C, Bradley B, Mletzko TC, Deveau TC, Musselman DL, Nemeroff CB, Ressler KJ, Binder EB (2009) Effect of childhood trauma on adult depression and neuroendocrine function: sex-specific moderation by CRH receptor 1 gene. Frontiers in Behavioral Neuroscience 3:1–10

Hemrick-Luecke SK, Evans DC (2002) Comparison of the potency of MDL 100, 907 and SB 242084 in blocking the serotonin (5HT) (2) receptor agonist-induced increases in rat serum corticosterone concentrations: evidence for 5-HT(2A) receptor mediation of the HPA axis. Neuropharmacology 42:162–169

Herman JP, Ostrander MM, Mueller NK, Figueiredo H (2005) Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry 29:12011–1213

Hicks BM, DiRago AC, Iacono WG, McGue M (2009) Gene×environment interplay in internalizing disorders: consistent findings across six environmental risk factors. J Child Psychol Psychiatry 50:1309–1317

Holmes A (2008) Genetic variation in cortico-amygdala serotonin function and risk for stress-related disease. Neurosci Biobehav Rev 32:1293–1314

Holmes A, Murphy DL, Crawley JN (2003) Abnormal behavioral phenotypes of serotonin transporter knockout mice: parallels with human anxiety and depression. Biol Psychiatry 54:953–959

Horowitz K, McKay M, Marshall R (2005) Community violence and urban families: experiences, effects, and directions for intervention. Am J Orthopsychiatry 75:356–368

Irish L, Kobayashi I, Delahanty DL (2009) Long-term physical health consequences of childhood sexual abuse: a meta-analytic review. J Pediatr Psychol 35:450–461. doi:10.1093/jpepsy/jsp118

Jaffee SR, Moffit TE, Caspi A, Fombonne E, Poulton R, Martin J (2002) Differences in early childhood risk factors for juvenile-onset and adult-onset depression. Arch Gen Psychiatry 59:215–222

Jinks JL, Fulker DW (1970) Comparison of the biometrical genetical, MAVA, and classical approaches to the analysis of the human behavior. Psychol Bull 73:311–349

Johnson JG, Cohen P, Dohrenwend BP, Link BG, Brook JS (1999) A longitudinal investigation of social causation and social selection processes involved in the association between socioeconomic status and psychiatric disorders. J Abnorm Psychol 108:490–499

Kaufman J, Yang BZ, Douglas-Palumberi H, Houshyar S, Lipschitz D, Krystal JH, Gelernter J (2004) Social support and serotonin transporter gene moderate depression in maltreated children. Proceedings of the National Academy of Sciences 101:17316–17321

Kaufman J, Yang BZ, Douglas-Palumberi H, Grasso D, Lipschitz D, Houshyar S, Krystal JH, Gelernter J (2006) Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. Biol Psychiatry 59:673–680

Kawachi I, Subramanian SV (2006) Measuring and modeling the social and geographic context of trauma: a multilevel modeling approach. J Trauma Stress 19:195–203

Kendler KS, Baker JS (2007) Genetic influences on measures of the environment: a systematic review. Psychol Med 37:615–626. doi:10.1017/S0033291706009524

Kendler KS, Kessler RC, Walters EE, MacLean CJ, Neale MC, Health AC, Eaves LJ (1995) Stressful life events, genetic liability and onset of an episode of major depression in women: evidence of genetic control of sensitivity to the environment. Am J Psychiatry 152:833–842

Kendler KS, Hettema JM, Butera F, Gardner CO, Prescott CA (2003) Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. Arch Gen Psychiatry 60:789–796

Kessing LV, Agerbo E, Mortensen PB (2003) Does the impact of major stressful life events on the risk of developing depression change throughout life? Psychol Med 33:1177–1184

Koenen KC, Galea S (2009) Gene-environment interactions and depression. JAMA 302:1859–1862. doi:10.1001/jama.2009.1575

Koenen KC, Fu QJ, Ertel K, Lyons MJ, Eisen SA, True WR, Goldberg J, Tsuang MT (2008) Common genetic liability to major depression and posttraumatic stress disorder in men. J Affect Disord 105:109–115

Kolber BJ, Boyle MP, Wieczorek L, Kelley CL, Onwuzurike CC, Nettles SA, Vogt SK, Muglia LJ (2010) Transient early-life forebrain corticotropin-releasing hormone elevation causes long-lasting anxiogenic and despair-like changes in mice. J Neurosci 30:2571–2581

Kraft P, Yen Y-C, Stram DO, Morrison J (2007) Exploiting gene-environment interaction to detect genetic associations. Hum Hered 63:111–119

Laaris N, Haj-Dahmane S, Hamon M, Lanfumey L (1995) Glucocorticoid receptor-mediated inhibition by corticosterone of 5-HT1A autoreceptor functioning in the rat dorsal raphe nucleus. Neuropharmacology 34:1201–1210

Laaris N, Le Poul E, Hamon M, Lanfumey L (1997) Stress-induced alterations of somatodendritic 5-HT1A autoreceptor sensitivity in the rat dorsal raphe nucleus-in vitro electrophysiological evidence. Fundam Clin Pharmacol 11:206–214

Lanfumey L, Pardon MC, Laaris N, Joubert C, Hanoun N, Hamon M, Cohen-Salmon C (1999) 5-HT1A autoreceptor desensitization by chronic ultramild stress in mice. NeuroReport 10:3369–3374

Laucht M, Treutlein J, Blomeyer D, Buchmann AF, Schmid B, Becker K, Zimmermann US, Schmidt MH, Gn E, Rietschel M, Banaschewski T (2009) Interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity for mood and anxiety psychopathology: evidence from a high-risk community sample of young adults. Int J Neuropsychopharmacol 12:737–747. doi:10.1017/S1461145708009875

Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Muller CR, Hamer DH, Murphy DL (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274:1527–1531

Li Q, Wichems C, Heils A, Van De Kar LD, Lesch KP, Murphy DL (1999) Reduction of 5-hydroxytryptamine (5-HT)(1A)-mediated temperature and neuroendocrine responses and 5-HT(1A) binding sites in 5-HT transporter knock-out mice. J Pharmacol Exp Ther 291:999–1007

Li Q, Holmes A, Ma L, Van de Kar LD, Garcia F, Murphy DL (2004) Medial hypothalamic 5-hydroxytryptamine (5-HT)1A receptors regulate neuroendocrine responses to stress and exploratory locomotor activity: application of recombinant adenovirus containing 5-HT1A sequences. J Neurosci 24:10868–10877

Li X, Inoue T, Abekawa T, Weng S, Nakagawa S, Izumi T, Koyama T (2006) 5-HT1A receptor agonist affects fear conditioning through stimulations of the postsynaptic 5-HT1A receptors in the hippocampus and amygdala. Eur J Pharmacol 532:74–80

Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN (2003) Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. Nat Genet 33:177–182

Luan JA, Wong MY, Wareham NJ (2001) Sample size determination for studies of gene-environment interaction. Int J Epidemiol 30:1035–1040

MacQueen GM, Ramakrishnan K, Ranasingan R, Chen B, Young LT (2003) Desipramine treatment reduces the long-term behavioral and neurochemical sequelae of early-life maternal separation. Int J Neuropsychopharmacol 6:391–396

Maercker A, Michael T, Fehm L, Becker ES, Margraf J (2004) Age of traumatisation as a predictor of post-traumatic stress disorder or major depression in young women. Br J Psychiatry 184:482–487. doi:10.1192/bjp.184.6.482

Marques AH, Silverman MN, Sternberg EM (2009) Glucocorticoid dysregulations and their clinical correlates. From receptors to therapeutics. Ann NY Acad Sci 1179:1–18

Mather K, Jinks JL (1982) Biometrical genetics: the study of continuous variation, 3rd edn. Chapman and Hall, London

McCart MR, Smith DW, Saunders BE, Kilpatrick DG, Resnick H, Ruggiero KJ (2007) Do urban adolescents become desensitized to community violence? Data from a national survey. Am J Orthopsychiatry 77:434–442

McCormick CM, Mathews IZ (2010) Adolescent development, hypothalamic-pituitary-adrenal function, and programming of adult learning and memory. Prog Neuro Psychopharmacol Biol Psychiatry 34:756–765

Mitchell SJ, Lewin A, Horn IB, Valentine D, Sanders-Phillips K, Joseph JG (2009) How does violence exposure affect the psychological health and parenting of young African-American mothers? Soc Sci Med 70:526–533

Moffit TE, Caspi A, Rutter M (2006) Measured gene-environment interactions in psychopathology: concepts, research strategies, and implications for research, intervention and public understanding of genetics. Perspect Psychol Sci 1:5–27

Moffitt TE, Caspi A, Rutter M (2005) Strategy for investigating interactions between measured genes and measured environments. Arch Gen Psychiatry 62:473–481

Monk C, McClure EB, Nelson EB, Zarahn E, Nilder RM, Leibenluft E, Charney DS, Ernst M, Pine DS (2003) Adolescent immaturity in attention-related brain engagement to emotional facial expressions. Neuroimage 20:420–428

Montag C, Weber B, Fliessbach K, Elger C, Reuter M (2009) The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: incremental support for a genetic risk factor for depression. Psychol Med 39:1831–1839. doi:10.1017/S0033291709005509

Munafo MR, Flint J (2009) Replication and heterogeneity in gene–environment interaction studies. Int J Neuropsychopharmacol 12:727–729. doi:10.1017/S1461145709000479

Munafo MR, Durrant C, Lewis G, Flint J (2009) Gene–environment interactions at the serotonin transporter locus. Biol Psychiatry 65:211–219

Murgatroyd C, Wu Y, Bockmuhl Y, Spengler D (2010) Genes learn from stress: how infantile trauma programs us for depression. Epigenetics 5:194–199

Musazzi L, Mallei A, Tardito D, Gruber SH, El Khoury A, Racagni G, Mathe AA, Popoli M (2010) Early-life stress and antidepressant treatment involve synaptic signaling and Erk kinases in a gene-environment model of depression. J Psychiatr Res 44:511–520

Nakamura M, Ueno S, Sano A, Tanabe H (2000) The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. Mol Psychiatry 5:32–38

Neale MC, Cardon LR (1992) Methodology for genetic studies of twins and families. Kluwer, Dordrecht

Nelson EC, Agrawal A, Pergadia ML, Lynskey MT, Todorov AA, Wang JC, Todd RD, Martin NG, Heath AC, Goate AM, Montgomery GW, Madden PA (2009) Association of childhood trauma exposure and GABRA2 polymorphisms with risk of posttraumatic stress disorder in adults. Mol Psychiatry 14:234–235

Nobile M, Rusconi M, Bellina M, Marino C, Giorda R, Carlet O, Vanzin L, Molteni M, Battaglia M (2009) The influence of family structure, the TPH2 G-703T and the 5-HTTLPR serotonergic genes upon affective problems in children aged 10–14 years. J Child Psychol Psychiatry 50(3):317–325

Nugent NR, Fyer A, Weissman M, Koenen KC (2010a) Genetics of anxiety disorders. In: Simpson HB, Neria Y, Lewis-Fernandez R, Schneier F (eds) Understanding anxiety: clinical and research perspectives from the Columbia University Department of Psychiatry. Cambridge University Press, New York, pp 139–155

Nugent NR, Amstadter AB, Koenen KC (2010b) Social support and interpersonal relationships following trauma. In: Horowitz LM, Strack S (eds) Handbook of interpersonal psychology: theory, research, assessment, and therapeutic interventions. Wiley, New York, pp 405–424

Paivio SC (2001) Stability of retrospective self-reports of child abuse and neglect before and after therapy for child abuse issues. Child Abuse Negl 25:1053–1068

Pariante CM, Lightman SL (2008) The HPA axis in major depression: classical theories and new developments. Trends Neurosci 31:464–468

Pehek EA, Nocjar C, Roth BL, Byrd TA, Mabrouk OS (2006) Evidence for the preferential involvement of 5-HT2A serotonin receptors in stress- and drug-induced dopamine release in the rat medial prefrontal cortex. Neuropsychopharmacology 31:265–277

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR (2005) 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci 8:828–834

Plomin R, Davis OSP (2009) The future of genetics in psychology and psychiatry: microarrays, genome-wide association, and non-coding RNA. J Child Psychol Psychiatry 50:63–71

Plomin R, DeFries JC, Loehlin JC (1977) Genotype-environment interaction and correlation in the analysis of human behavior. Psychol Bull 84:309–322

Polanczyk G, Caspi A, Williams B, Price TS, Danese A, Sugden K, Uher R, Poulton R, Moffitt TE (2009) Protective effect of CRHR1 gene variants on the development of adult depression following childhood maltreatment: replication and extension. Arch Gen Psychiatry 66:978–985. doi:10.1001/archgenpsychiatry.2009.114

Preece MA, Dalley JW, Theobald DE, Robbins TW, Reynolds GP (2004) Region specific changes in forebrain 5-hydroxytryptamine1A and 5-hydroxytryptamine2A receptors in isolation-reared rats: an in vitro autoradiography study. Neuroscience 123:725–732

Raine A (2002) Biosocial studies of antisocial and violent behavior in children and adults: a review. J Abnorm Child Psychol 30:311–326

Raison CL, Miller AH (2003) When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am J Psychiatry 160:1554–1565

Rao U, Hammen C, Daley SE (1999) Continuity of depression during the transition to adulthood: a 5-year longitudinal study of young women. J Am Acad Child Adolesc Psychiatry 38:908–915

Ressler KJ, Nemeroff (2000) Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety 12:2–19

Ressler KJ, Bradley B, Mercer KB, Deveau TC, Smith AK, Gillespie CF, Nemeroff CB, Cubells JF, Binder EB (2010) Polymorphisms in CRHR1 and the serotonin transporter loci: gene×gene×environment interactions on depressive symptoms. Am J Med Genet B Neuropsychiatr Genet 153b:812–824. doi:10.1002/ajmg.b.31052

Risch N, Herrell R, Lehner T, Liang K-Y, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR (2009) Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA 301:2462–2471. doi:10.1001/jama.2009.878

Ritchie K, Jaussent I, Stewart R, Dupuy A, Courtet P, Acelin M, Malafosse A (2009) Association of adverse chidhood environment and 5-HTTLPR genotype with late-life depression. J Clin Psychiatry 70:1281–1288

Roth S, Friedman MJ (1993) Prevalence and consequences of childhood trauma childhood trauma remembered: a report on the current scientific knowledge base and its applications. International society for traumatic stress studies. Northbrook, Illinois, pp 1–24

Rutter M (2008) Biological implications of gene–environment interaction. J Abnorm Child Psychol 36:969–975

Rutter M (2009) Gene-environment interactions: biologically valid pathway or artifact? Arch Gen Psychiatry 66:1287–1289

Rutter M (2010) Gene–environment interplay. Depress Anxiety 27:1–4

Rutter M, Kim-Cohen J, Maughan B (2006) Continuities and discontinuities in psychopathology between chidhood and adult life. J Child Psychol Psychiatry 47:276–295

Scaramella LV, Sohr-Preston SL, Callahan KL, Mirabile SP (2008) A test of the family stress model on toddler-aged children's adjustment among hurricane katrina impacted and nonimpacted low-income families. J Clin Child Adolesc Psychol 37:530–541

Schule C, Zill P, Baghai TC, Eser D, Zwanzger P, Wenig N, Rupprecht R, Bondy B (2006) Brain-derived neurotrophic factor

Val66Met polymorphism and dexamethasone/CRH test results in depressed patients. Psychoneuroendocrinology 31:1019–1025. doi:10.1016/j.psyneuen.2006.06.002

Silberg J, Pickles A, Rutter M, Hewitt J, Simonoff E, Maes H, Carbonneau R, Murrelle L, Foley D, Eaves L (1999) The influence of genetic factors and life stress on depression among adolescent girls. Arch Gen Psychiatry 56:225–232

Sjoberg RL, Nilsson KW, Nordquist N, Ohrvik J, Leppert J, Lindstrom L, Oreland L (2006) Development of depression: sex and the interaction between environment and a promoter polymorphism of the serotonin transporter gene. Int J Neuropsychopharmacol 9:443–449. doi:10.1017/S1461145705005936

Soliman F, Glatt CE, Bath KG, Levita L, Jones RM, Pattwell SS, Jing D, Tottenham N, Amso D, Somerville LH, Voss HU, Glover G, Ballon DJ, Liston C, Teslovich T, Van Kempen T, Lee FS, Casey BJ (2010) A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. Science 327:863–866

South SC, Krueger RF (2010) Genetic and environmental influences on internalizing psychopathology vary as a function of economic status. Psychol Med 41(1):107–117. doi:10.1017/S0033291710000279

Stein MB, Schork N, Gelernter J (2008) Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. Neuropsychopharmacology 33:312–319

Surtees PG, Wainwright NW, Willis-Owen SA, Luben R, Day NE, Flint J (2006) Social adversity, the serotonin transporter (5-HTTLPR) polymorphism and major depressive disorder. Biol Psychiatry 59:224–229

Takase LF, Nogueira MI, Baratta M, Bland ST, Watkins LR, Maier SF, Fornal CA, Jacobs BL (2004) Inescapable shock activates serotonergic neurons in all raphe nuclei of rat. Behav Brain Res 153:233–239

Tambs K, Mourn T (1993) Low genetic effect and age-specific family effect for symptoms of anxiety and depression in nuclear families, halfsibs and twins. Journal of Affect Disorders 27:183–195

Taylor SE, Way BM, Welch WT, Hilmert CJ, Lehman BJ, Eisenberger NI (2006) Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. Biol Psychiatry 60:671–676

Terr LC (1991) Childhood traumas: an outline and overview. Am J Psychiatry 148:10–20

Tjurmina OA, Armando I, Saavedra JM, Li Q, Murphy DL (2004) Life-long serotonin reuptake deficiency results in complex alterations in adrenomedullary responses to stress. Ann NY Acad Sci 1018:99–104

Tuvblad C, Grann M, Lichtenstein P (2006) Heritability for adolescent antisocial behavior differs with socioeconomic status: gene-environment interaction. J Child Psychol Psychiatry 47:734–743

Twitchell GR, Hanna GL, Cook EH, Stoltenberg SF, Fitzgerald HE, Zucker RA (2001) Serotonin transporter promoter polymorphism genotype is associated with behavioral disinhibition and negative effect in children of alcoholics. Alcohol Clin Exp Res 25:953–959

Tyrka AR, Carpenter LL, McDougle CJ, Kirwin PD, Owens MJ, Nemeroff CB, Strong DR, Price LH (2004) Increased CSF corticotropin-releasing factor during tryptophan depletion in healthy adults. Biol Psychiatry 56:531–534

Tyrka AR, Price LH, Gelernter J, Schepker C, Anderson GM, Carpenter LL (2009) Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor gene: effects on hypothalamic-pituitary-adrenal axis reactivity. Biol Psychiatry 66:681–685

Uher R (2008) Gene-environment interaction: overcoming methodological challenges. Novartis Found Symp 293:13–26

Uher R, McGuffin P (2010) The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. Mol Psychiatry 15:18–22

Vinkers CH, Oosting RS, van Bogaert MJ, Olivier B, Groenink L (2010) Early-life blockade of 5-HT(1A) receptors alters adult anxiety behavior and benzodiazepine sensitivity. Biol Psychiatry 67:309–316

Wichers M, Kenis G, Jacobs N, Mengelers R, Derom C, Vlietinck R, van Os J (2008) The BDNF Va66Met×5-HTTLPR×child adversity interaction and depressive symptoms: an attempt at replication. Am J Med Genet B Neuropsychiatr Genet 147B:120–123

Wust S, Federenko IS, van Rossum EF, Koper JW, Kumsta R, Entringer S, Hellhammer DH (2004a) A psychobiological perspective on genetic determinants of hypothalamus-pituitary-adrenal axis activity. Ann NY Acad Sci 1032:52–62

Wust S, Van Rossum EF, Federenko IS, Koper JW, Kumsta R, Hellhammer DH (2004b) Common polymorphisms in the glucocorticoid receptor gene are associated with adrenocortical responses to psychosocial stress. J Clin Endocrinol Metab 89:565–573

Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, BradyRD, Farrer L, Gelernter J (2009) Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. Arch Gen Psychiatry 66:1201–1209. doi:10.1001/archgenpsychiatry.2009.153

Yehuda R, Flory JD, Pratchett LC, Buxbaum J, Ising M, Holsboer F (2010) Putative biological mechanisms for the association between early life adversity and the subsequent development of PTSD. Psychopharmacol Berl 212:405–417

Zinzow HM, Ruggiero KJ, Hanson RF, Smith DW, Saunders BE, Kilpatrick DG (2009) Witnessed community and parental violence in relation to substance use and delinquency in a national sample of adolescents. J Trauma Stress 22:525–533