Gene × Environment Interactions: From Molecular Mechanisms to Behavior

Thorhildur Halldorsdottir[1] and Elisabeth B. Binder[1,2]

[1]Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich 80804, Germany; email: binder@psych.mpg.de

[2]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia 30322

Annu. Rev. Psychol. 2017. 68:215–41

First published online as a Review in Advance on September 30, 2016

The *Annual Review of Psychology* is online at psych.annualreviews.org

This article's doi: 10.1146/annurev-psych-010416-044053

Keywords

psychopathology, genomics, epigenetic, gene-by-environment interactions, stress, trauma

Abstract

Gene-by-environment interactions (G × Es) can provide important biological insights into psychiatric disorders and may consequently have direct clinical implications. In this review, we begin with an overview of the major challenges G × E studies have faced (e.g., difficulties replicating findings and high false discovery rates). In light of these challenges, this review focuses on describing examples in which we might begin to understand G × Es on the molecular, cellular, circuit, and behavioral level and link this interaction to altered risk for the development of psychiatric disorders. We also describe recent studies that utilize a polygenic approach to examine G × Es. Finally, we discuss how gaining a deeper understanding of G × Es may translate into a therapeutic practice with more targeted treatments.

Contents

INTRODUCTION

G × E: gene-by-environment interaction

It is widely accepted that psychiatric disorders are multifactorial diseases that emerge through the interplay between environmental factors and genetic predisposition. Gene-by-environment interaction (G × E) studies address the extent to which genetic predisposition in combination with environmental determinants shapes the risk for psychiatric disorders (see the sidebar G × E Terminology; **Figure 1**). G × E studies examine the main effects of environmental and genetic determinants as predictors of phenotypes or pathology, as well as whether their joint effects differ from the product of their individual effects. A significant interaction indicates that both independent variables together influence the dependent variable.

Several theoretical models have been proposed to describe G × Es. Among the most prominently used is the diathesis-stress model, which stipulates that genetic vulnerability predisposes an individual to the development of a psychiatric disorder when exposed to adversity. In other words, an individual may be genetically susceptible to a psychiatric disorder, but the disorder

G × E TERMINOLOGY

Before discussing G × Es, it is worthwhile to review commonly used terminology. Genes are small sections of the chromosome that code for RNA molecules and, in consequence, proteins. The human genome is composed of 46 chromosomes, which are long sequences of DNA. The DNA sequence is composed of a chain of the nucleotide bases adenine (A), cytosine (C), guanine (G), and thymine (T). An allele is a variant form of a gene in a specific genetic locus on a chromosome. Humans have two alleles at each genetic locus, one from each parent. Each pair of alleles represents the genotype of a specific gene. Genotypes can be either homozygous, with two identical alleles at a particular locus, or heterozygous, with two differing alleles at a locus. Most G × E studies examine single-nucleotide polymorphisms (SNPs) (see **Figure 1*a***). A haplotype is a set of SNPs in close proximity to each other with alleles that are inherited together.

Another important aspect of genetic studies is gene expression, i.e., the way in which DNA is read (see **Figure 1*b***). Gene expression occurs via two steps, called transcription (DNA to RNA) and translation (RNA to proteins), within the cell. Cells respond to changes in their environment through these two processes.

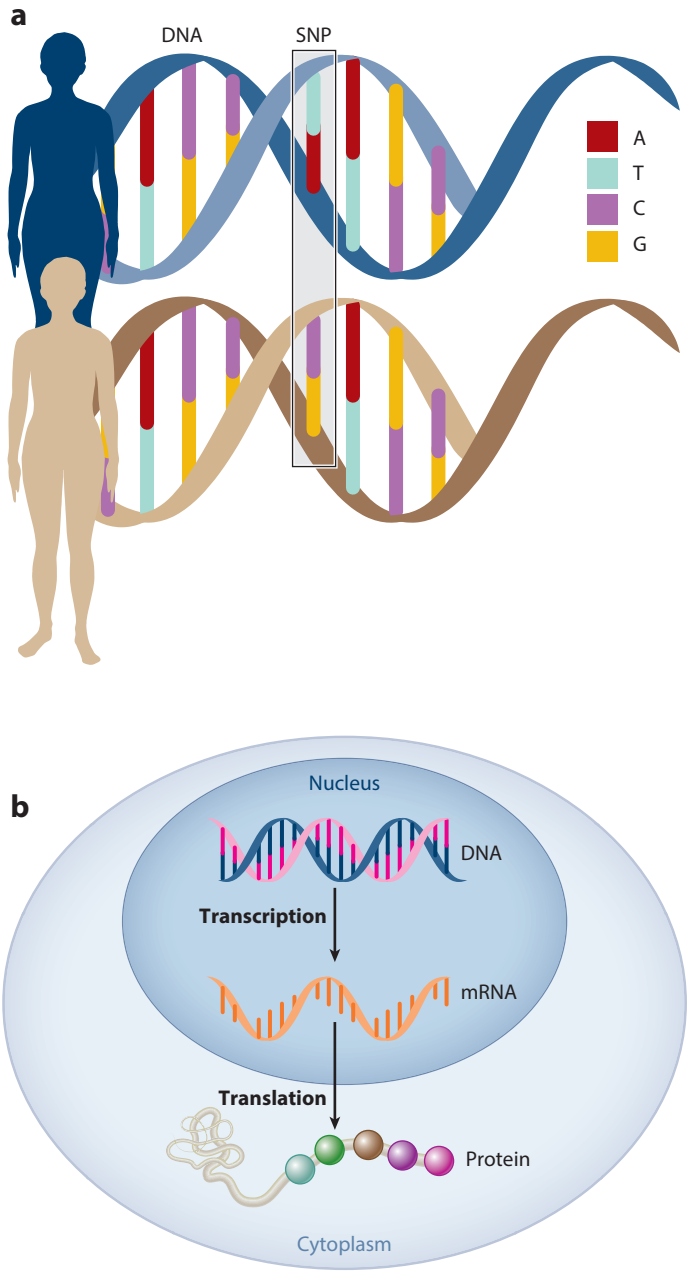

Figure 1

(*a*) The DNA sequence is composed of a chain of the nucleotide bases adenine (A), cytosine (C), guanine (G), and thymine (T). A single-nucleotide polymorphism (SNP) is a variation in a single nucleotide occurring at a certain position, or genetic locus, on a chromosome. Variations at the SNP level account for many of the differences seen across individuals. (*b*) Schematic representation of transcription and translation. Transcription occurs within the nucleus when DNA is copied into RNA and then messenger RNA (mRNA). During translation, information from the mRNA is used to create a protein.

does not develop unless triggered by an environmental stressor. Conversely, individuals without this genetic predisposition do not develop a psychiatric disorder when confronted with adversity. This model has proven very fruitful in stimulating research, and the majority of conducted G × E studies adhere to this model. However, the diathesis-stress model has been criticized for disproportionately focusing on stressors and negative life events and ignoring positive environments (Belsky & Pluess 2009). Among the critics of this model, Belsky and colleagues (2007, Belsky & Pluess 2009) argue that the diathesis-stress model risks misclassifying environmental influences by focusing mainly on negative environmental influences; thus, they propose an alternative, the differential-susceptibility perspective (Belsky et al. 2007, Belsky & Pluess 2009). This model proposes that individuals vary in their susceptibility to environmental influences (both negative and positive) rather than claiming that specific genotypes are inherently good or bad (Belsky et al. 2007, Belsky & Pluess 2009). That is, the genotype can either exacerbate an individual's risk of psychopathology in negative environmental conditions or mitigate the risk of psychopathology in positive environmental conditions. Thus, it is more appropriate to refer to variants for such environmentally dependent genotypes as plasticity variants rather than risk or vulnerability variants because they appear to make individuals more susceptible to both negative and positive environmental influences (see **Figure 2**). As noted above, most G × E studies have limited their analyses to negative environmental risk factors. To represent both perspectives, we point out in this review any G × E studies depicting the differential-susceptibility framework.

G × E studies can provide important biological insights into psychiatric disorders and may consequently have direct clinical implications. It is currently an exciting time for research on the

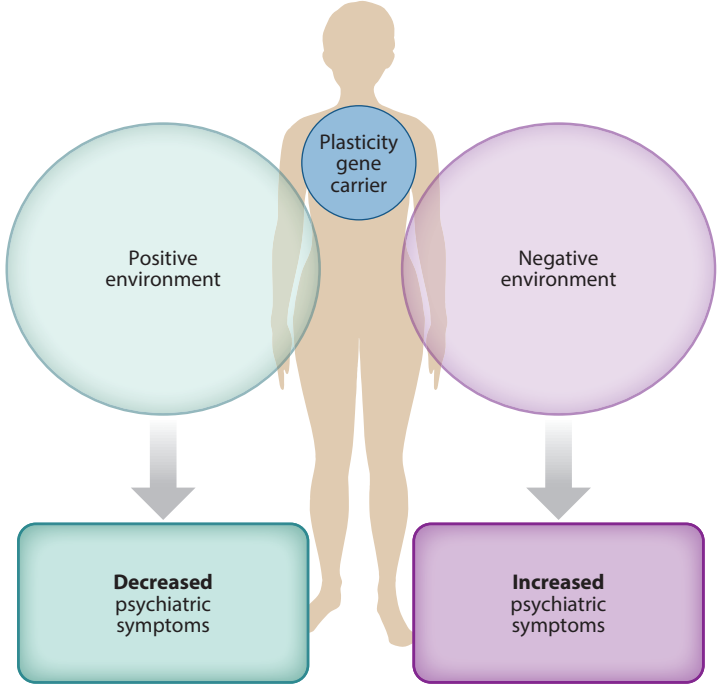

Figure 2

The differential-susceptibility model proposes that genetic predisposition makes an individual more susceptible to both negative and positive environmental conditions and thereby either exacerbates or mitigates the risk of psychiatric symptoms in accordance with the environmental conditions.

genetic underpinnings of psychiatric disorders. New genotyping technologies and analytical tools are emerging, enabling the examination of the effects of genetic variants in multinational collaborations with large sample sizes. At the same time, it is important to view the current literature in light of the methodological challenges that G × E studies have faced. Toward this end, this review begins by discussing some of these challenges associated with G × E studies, namely difficulties replicating findings and high false discovery rates. Due to these challenges, we have selected G × E studies for this review that have moved beyond candidate gene association testing and offer multilevel validation for the interactions detected, including corroborating neuroimaging, endocrine, and molecular findings. Among the new analytical tools, we describe recent studies utilizing a polygenic approach to examine G × Es. Finally, we discuss how gaining a deeper understanding of G × Es may translate into a therapeutic practice with more targeted treatments.

G × E CHALLENGES

As with research in any other field, G × E studies are faced with a number of criticisms and limitations (Dick et al. 2015). In this section, we discuss the major challenges facing the field at present and some of the proposed solutions.

To date, most G × E studies have relied on candidate-gene approaches. In these studies, researchers choose a specific gene of interest on the basis of its biological function in a psychiatric disorder and test whether the association between variation in this gene and the disorder differs across environments. In spite of the hundreds of candidate G × E publications on psychiatric outcomes, few findings are generally accepted by the genetics community because only a small number of interactions have been robustly associated with a psychiatric disorder across multiple studies. This lack of reproducibility is in part because of the small sample sizes (mostly <1,000 participants) in these studies and the resulting lack of power to detect interactions with small effect sizes.

Variation in heritability estimates of psychiatric disorders in different environmental contexts is another complicating factor that increases the difficulty of replication. High heritability indicates that genetic factors account for a large portion of the susceptibility to a particular psychiatric disorder. However, this does not mean that genes cause the disorder. Similarly, it does not imply that the same genetic factors will account for the same amount of variance under all circumstances. Indeed, when environmental or genetic conditions change, so do heritability estimates (Rutter et al. 2006). This poses a methodological challenge to G × E studies, given that heritability is likely to differ across studies when the samples vary in terms of level or range of environmental risk. However, this same variation in heritability estimates underscores the need to examine genetic and environmental determinants jointly. Similarly, findings may also differ on the basis of the operationalization and scaling of measures. Thus, there is a need for high-quality measurement of genetic and environmental factors, along with transparency in the operationalization of variables, to enhance the probability of study findings being replicated (Rutter et al. 2006, Rutter & Pickles 2015).

Candidate-gene approaches have also been criticized for their simplification of genetic models. These studies typically rely on one individual single-nucleotide polymorphism (SNP) or other types of genetic variants such as repeat polymorphisms or a set of variants that explain only a small portion of the genetic variation in psychiatric disorders (Duncan & Keller 2011). Research from both epidemiological and genetic studies, however, indicates that the genetic architecture of psychiatric disorders is highly complex and that psychiatric disorders are polygenic (i.e., involve multiple genes). This combination of low likelihood that a candidate gene accounts for a large portion of the variance, low power, and small effect sizes can lead to high false discovery rates (Duncan & Keller 2011). In addition, G × E studies often account only for confounds using main

SNP: single-nucleotide polymorphism

effects but not their interaction terms, which may also contribute to spurious associations (Duncan & Keller 2011).

SERT: serotonin transporter

SSRI: selective serotonin reuptake inhibitor

***5-HTTLPR*:** *serotonin transporter promoter*

Despite these challenges, we are not claiming that G × Es have only yielded erroneous findings. These challenges do, however, highlight the need to replicate findings and validate them on a mechanistic level. As a starting point for navigating this challenging field, Rutters and colleagues' (2006) recommended strategy has been to focus hypotheses on potential biological pathways that incorporate both genetic and environmental determinants rather than to use an open-ended search for statistical interactions, which would likely result in a high number of false positive findings. They recommend examining genes found to be susceptible to environmental factors rather than genes associated directly with a psychiatric disorder. Hypotheses must be built on the empirical evidence of biological information about the gene and the environmental determinants. The combination of risk-increasing genes and risk-increasing environmental influences likely results in specific pathophysiological disturbances in molecular pathways, which may in turn impact the neural circuits associated with psychopathology. Toward that end, this review focuses on illustrating examples in which we might begin to understand G × E on the molecular, cellular, circuit, and behavioral level and link this interaction to altered risk for the development of psychiatric disorders.

GENE-BY-ENVIRONMENT INTERACTIONS VALIDATED ACROSS MULTIPLE LEVELS

Serotonin Transporter Promoter Polymorphism

Following its initial discovery by Lesch et al. (1996), a polymorphism in the promoter of the serotonin transporter gene (*5-HTTLPR*) has become one of the most studied polymorphisms in psychological and psychiatric research, including in G × E studies (for an overview of *5-HTTLPR* studies, see Caspi et al 2010, Karg et al. 2011, Munafo et al. 2009). The *5-HTTLPR* polymorphism is a variation of repeats in the promoter region of the serotonin transporter (the *SLC6A4* gene encoding the SERT protein), which is involved in the reuptake of serotonin by brain synapses and is the target of the selective serotonin reuptake inhibitor (SSRI) medications commonly used to treat depression and anxiety disorders. *5-HTTLPR* polymorphisms are categorized into short (S) alleles with 14 repeats and long (L) alleles with 16 repeats; the short alleles are associated with lower transporter expression and serotonin uptake (Lesch et al. 1996). Although these are the most common alleles, others have been described and are often specific to certain ethnicities (e.g., Xie et al. 2009). In addition, an SNP within the repeat region has been shown to moderate the functionality of *5-HTTLPR* alleles (Hu et al. 2006). A handful of studies have related this polymorphism to the actual binding capacity of SERT in positron emission tomography (PET)-ligand studies or to the abundance of the transporter in postmortem studies, but with inconsistent results (e.g., Cannon et al. 2006, Frankle et al. 2005, Mann et al. 2000).

In the first G × E study involving *5-HTTLPR*, Caspi et al. (2003) demonstrated that individuals with one or two copies of the low-expressing S allele of *5-HTTLPR* were at greater risk for depression (measured at both the symptomatic and diagnostic level) and exhibited greater suicidality after exposure to stressful life events (both in childhood and adulthood) compared to individuals not carrying this risk allele. In the absence of adverse life events, the polymorphism did not alter risk, a result that is consistent with a large number of studies finding no case/control differences of this polymorphism with the diagnosis of depression per se (for a review, see Karg et al. 2011). This influential article was one of the first to demonstrate genetically driven

individual differences in the response to environmental stress and vulnerability to psychopathology. Since this study, *5-HTTLPR* has been found to moderate the relationship between various other environmental stressors and various psychiatric problems, including anxiety, posttraumatic stress disorder (PTSD), suicide attempts, alcohol consumption, eating disorders, substance use, and attention-deficit/hyperactivity disorder (ADHD) (Gibb et al. 2006, Kilpatrick et al. 2007, Koenen et al. 2009, Kranzler et al. 2012, Laucht et al. 2009, Liu et al. 2015, Roy et al. 2007, Stein et al. 2008, Stoltenberg et al. 2012, van der Meer et al. 2014).

PTSD: posttraumatic stress disorder

ADHD: attention deficit hyperactivity disorder

Consistent with the differential-susceptibility perspective, the same genotype (S-allele carriers) has also been found to decrease the risk of psychopathology in enriched environments (Belsky & Pluess 2009, Hankin et al. 2011, Pluess et al. 2010). Specifically, carriers of the *5-HTTLPR* S allele are at greater risk of psychopathology when exposed to stressors, but they display the fewest depressive symptoms when they grew up in a supportive environment or experienced recent positive events (Eley et al. 2004, Taylor et al. 2006).

What mechanisms could confer such differential susceptibility? As described above, *5-HTTLPR* in its environmentally sensitive short form has been associated with lower efficiency of SERT in cell systems compared to its long form. The way this relates to serotonergic signaling in neural circuits is much less clear. Functional brain imaging studies suggest that the polymorphism is associated with an inherently different neural circuit activation during emotion processing. Specifically, differential brain activity in regions involved in emotion processing (e.g., amygdala, cingulate cortex, hypothalamus) has been observed in individuals following exposure to emotional stimuli based on the *5-HTTLPR* genotype (Alexander et al. 2012; Canli et al. 2006; Dannlowski et al. 2007, 2008; Fortier et al. 2010; Hariri et al. 2005; Munafo et al. 2008; Pezawas et al. 2005). For instance, Fortier et al. (2010) found greater regional brain activation in children with the S-allele genotype when watching a sad movie compared to children with the alternate genotype. This altered processing of emotional stimuli may emerge on the behavioral level due to a differential systemic response to stress. In fact, increased neuroticism has been observed in individuals carrying the S allele compared to L-allele carriers (Munafo et al. 2009).

At the endocrine level, enhanced cortisol secretion following an acute stressor has been observed in healthy S-allele carriers with a history of stressful life events but not in individuals homozygous for the L allele with a similar history of stressful events (Alexander et al. 2009). Differences between *5-HTTLPR* genotypes have also been reported in the autonomic nervous system. Specifically, children carrying the L allele have a higher stress-induced increase in salivary α-amylase, which is elicited by the autonomic nervous system, compared to S-allele carriers. This finding suggests differential stress-related autonomic changes in the body based on genotype and an overall sharper recovery following stressor exposure in the L-allele carriers than in the S-allele carriers (Mueller et al. 2012). Taken together, the putative differences in serotonergic neurotransmission, which drive altered activation in various brain regions and differences in stress reactivity, may lead to dysregulated emotional processing of stressors in S-allele carriers and thus cause increased vulnerability to the development of a psychiatric disorder. In-depth knowledge about these mechanisms may also allow more individualized therapeutic interventions, as discussed in the section Implications for Treatment.

Despite the large number of studies conducted on *5-HTTLPR*, the moderating effect of this polymorphism remains controversial. Two meta-analyses have yielded a negative result for the moderation effect of *5-HTTLPR* on the relationship between stressful life events and depression (Munafo et al. 2009, Risch et al. 2009), whereas two more recent meta-analyses supported the moderation findings (Karg et al. 2011, Sharpley et al. 2014). Researchers have explained such incongruent findings in several ways, including heterogeneity of both the measurement of the environmental

determinants and phenotypes across studies (Caspi et al. 2010, Uher & McGuffin 2008). For example, early-life stress and childhood abuse have consistently been shown to interact with *5-HTTLPR* polymorphisms in predicting depression (Karg et al. 2011). When stressors at other stages of life are examined, the results are less consistent. Other studies indicate that aggregated life stressors at the group level (e.g., living in a dangerous neighborhood), not just the individual level, can moderate G × E findings but are often not accounted for (Kilpatrick et al. 2007, Koenen et al. 2009). Findings have also varied depending on how depression is operationalized. For instance, Uher and colleagues (2011) showed that *5-HTTPLR* moderated the relationship between stressful life events and depression only in patients with persistent depression and not in patients with a single episode of depression. In sum, these findings highlight the importance of careful characterization of the environmental determinant in G × Es, as well as the outcome measure.

HPA: hypothalamic-pituitary-adrenal

***FKBP5*:** *FK506 binding protein-5*

GR: glucocorticoid receptor

mRNA: messenger RNA

FK506 Binding Protein-5 Polymorphisms

Gene variants moderating the stress response and the regulation of the hypothalamic-pituitary-adrenal (HPA) axis are among the most promising candidates for G × E studies in psychiatry (see sidebar The Hypothalamic-Pituitary-Adrenal Axis; **Figure 3**). Among these genes, one of the most comprehensively studied is *FK506 binding protein-5* (*FKBP5*), encoding the protein FKBP51. Within the cell, FKBP51 is a central regulator of stress responsivity because it is part of the steroid receptor complex (Grad & Picard 2007). Glucocorticoid receptor (GR) function, an important part of the stress system (**Figure 3**), is regulated by a large molecular complex that includes chaperones as well as co-chaperones such as FKBP51. When FKBP51 is bound to the GR complex, the receptor has low affinity to cortisol and does not translocate readily to the nucleus (Davies et al. 2002, Wochnik et al. 2005). Importantly, *FKBP5* is also a target of GR activation, and its messenger RNA (mRNA) and protein are induced by cortisol. This creates an ultrashort negative feedback loop in which GR induces FKBP51, which then limits GR activity (Vermeer et al. 2003). This induction of *FKBP5* mRNA and the resulting intracellular regulation of GR activity are moderated by common genetic variants in the *FKBP5* locus. The associated changes in GR sensitivity during the feedback regulation of the HPA axis lead to prolonged stress-related cortisol release in individuals carrying the variant that is associated with higher *FKBP5* mRNA induction

THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis in psychiatric patients has been well documented (Baumeister et al. 2014), making genes associated with the axis attractive targets for G × E researchers.

The HPA axis is central to stress response. When confronted with a stressor, corticotropin-releasing hormone (CRH) is excreted from the paraventricular nucleus of the hypothalamus. CRH acts on the pituitary gland, resulting in the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. This induces the release of cortisol from the adrenal cortex. Subsequently, ACTH acts on the adrenal glands, stimulating the production and release of glucocorticoids by the adrenal cortices (Vale et al. 1981) (**Figure 3**). Glucocorticoids bind to glucocorticoid receptors (GRs), which inhibit the synthesis and release of CRH in the hypothalamus and of ACTH in the pituitary. This enables a negative feedback regulation, allowing the reduction of HPA axis activation and the restoration of homeostasis once the threat has subsided (Holsboer 2000).

Disruption of this feedback regulation can have long-lasting effects on brain activity and the regulation of the stress hormone system (Bale & Vale 2004). Among the HPA axis–associated genes, *FK506 binding protein-5* (*FKBP5*) and *corticotropin-releasing hormone receptor 1* (*CRHR1*) have received the most attention in G × E studies.

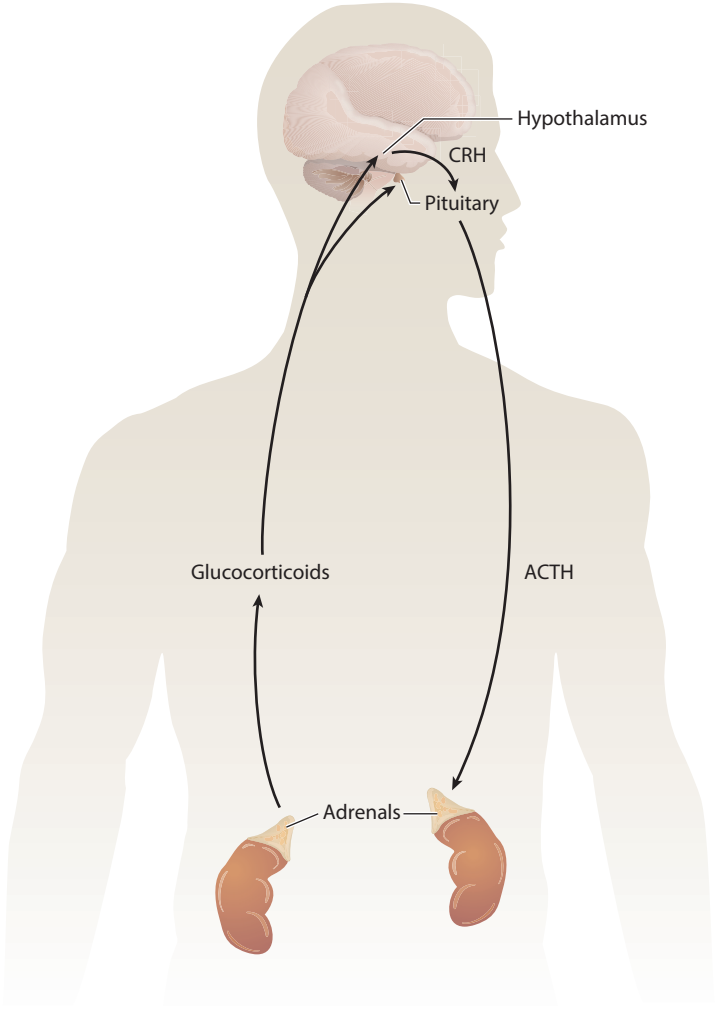

Figure 3

In the hypothalamic-pituitary-adrenal axis, corticotropin-releasing hormone (CRH) is excreted from the paraventricular nucleus of the hypothalamus within minutes of being confronted with a stressor. CRH acts on the pituitary gland, resulting in the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which further induces the release of cortisol from the adrenal cortex. Subsequently, ACTH acts on the adrenal glands, stimulating the production and release of glucocorticoids by the adrenal cortices. Of note, CRH and its receptors are also important regulators of the stress response in other, mainly limbic, brain regions.

(Binder et al. 2004, Buchmann et al. 2014, Klengel et al. 2013). This genetic change in the physiologic stress response is associated with an altered risk for psychiatric disorders.

In the case of *FKBP5*, genetic and epigenetic changes must come together (**Figure 4**). Specifically, changes in the DNA methylation of *FKBP5* locus glucocorticoid response elements (GREs; short DNA motifs that can bind to GRs) have been implicated in this additional disinhibition (Klengel et al. 2013). DNA methylation refers to the transfer of a methyl group (CH_3) to any of the millions of cytosine-phosphate-guanosine dinucleotide sites in the human genome. This alters

GRE: glucocorticoid response element

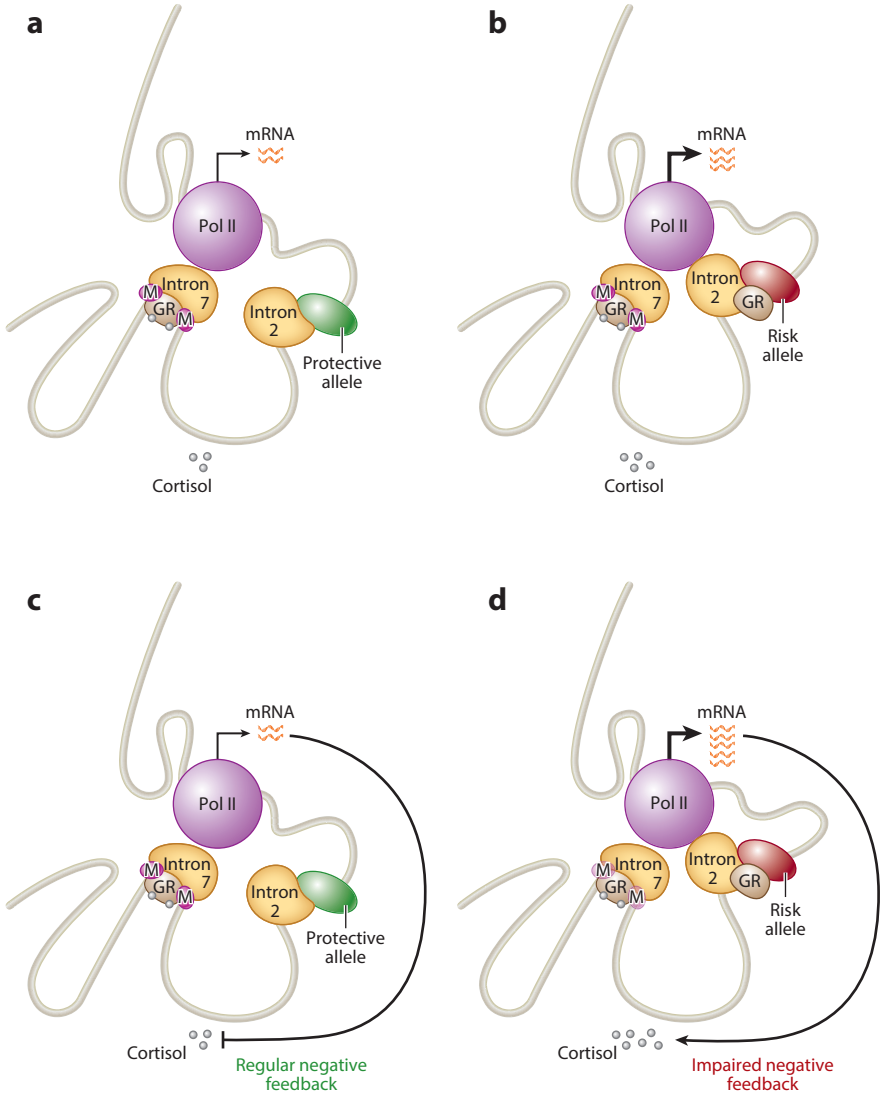

Figure 4

Schematic representation of the interaction of glucocorticoid receptor elements (GREs) in introns 2 and 7 in the rs1360780 single-nucleotide polymorphism of *FKBP5* at the genetic level (*a*,*b*) and epigenetic level (*c*,*d*) following exposure to early trauma. (*a*) The protective rs1360780 major allele reduces the interaction between GRE intron 2 and the RNA polymerase II (Pol II), thereby decreasing the production of *FKBP5* messenger RNA (mRNA) in response to glucocorticoid receptor (GR) activation. (*b*) The risk rs1360780 minor allele increases the interaction between GRE intron 2 and the promoter, resulting in increased *FKBP5* induction. In other words, risk-allele carriers have genetically determined higher *FKBP5* mRNA expression and GR resistance. (*c*) When exposed to early trauma, the negative feedback of *FKBP5* in protective allele carriers remains stable. Regular transcriptional activation of *FKBP5* results in the GR terminating the stress response and in regular normalization of cortisol levels once the threat has subsided. (*d*) In contrast, the negative feedback loop is impaired in risk-allele carriers following exposure to childhood trauma. Specifically, early trauma leads to increased activation of *FKBP5*, which in turn results in the reduction of DNA methylation (M) around intron 7 and higher and prolonged cortisol levels. Figure adapted from Klengel & Binder (2015) with permission.

the three-dimensional structure of the DNA and leads to a reduced accessibility of methylated sites to transcriptional regulators (Novik et al. 2002). The likely causal *FKBP5* SNP, rs1360780, is in close proximity to a GRE in intron 2 of the gene (**Figure 4*a*,*b***). Introns are noncoding sections of an RNA transcript that are removed before the RNA molecule is translated into protein but often harbor regions that are important for gene transcription regulation. In the risk-allele conformation, this transcriptional enhancer is in close proximity to the promoter and thus enhances GR signaling in *FKBP5* transcription. This has been associated with an enhanced short feedback on GR sensitivity and a delayed systemic negative feedback on the cortisol response to stress (Klengel et al. 2013). This leads to longer cortisol exposure following stress and, consequently, active demethylation of another GRE (see **Figure 4*d***). In fact, binding of the GR to GREs can lead to active demethylation, sensitizing the target to future exposure (Thomassin et al. 2001). The demethylation further derepresses the transcriptional response of *FKBP5* to GR (Klengel & Binder 2015, Sharma et al. 2016). This disruption in regulatory homeostasis is thought to result in long-lasting changes in the neural circuits involved in stress and anxiety regulation via both changes in GR tone and a direct downstream effect of FKBP51 on additional pathways that are highly relevant for neuronal function and synaptic plasticity (Zannas et al. 2016).

GWAS: genome-wide association study

Interactions between *FKBP5* and stressful life events have been found to be associated with a variety of psychiatric disorders and traits, including PTSD, depression, aggression, suicidality, and psychosis, by many studies that include well over 12,000 individuals (for a review, see Zannas et al. 2016). The majority of these studies report a general vulnerability to psychopathology in individuals carrying alleles associated with higher *FKBP5* induction following stress exposure. These findings have largely been proven robust across studies and in different ethnic groups. Importantly, genome-wide association studies (GWASs) and candidate gene case-control association studies have not found a main effect for the gene in predicting psychopathology, indicating that the effect is dependent on environmental influences (Binder et al. 2008, Nievergelt et al. 2015, Solovieff et al. 2014). This suggests that additional mechanisms besides the genetic regulation of *FKBP5* are necessary to trigger the stress interaction effect.

A wealth of evidence from animal and human studies supports the association of high FKBP51 function and psychiatric disorders. In animals, increased FKBP51 function has been associated with increased anxiety, decreased stress coping, delayed fear extinction, and a more dysregulated stress response (Albu et al. 2014, Attwood et al. 2011, Hartmann et al. 2012, O'Leary et al. 2011, Sawamura et al. 2016, Touma et al. 2011). In humans, the alleles with high *FKBP5* reactivity are associated with behavioral risk phenotypes, such as increased dissociation following trauma, increased bias toward threat, and increased intrusions (Cheung & Bryant 2015, Fani et al. 2013, Koenen et al. 2005), as well as a prolonged cortisol response following stress exposure (Buchmann et al. 2014, Ising et al. 2008).

At the circuit level, brain regions associated with emotion processing, inhibition, and memory, including the amygdala and hippocampus, are thought to be involved in *FKBP5*-related vulnerability to psychopathology. Overall, the hippocampus is the brain region with the highest baseline levels of FKBP51 expression, yet it shows little transcriptional reactivity to stress. Other brain regions, such as the amygdala and the hypothalamus, have low baseline levels but show dramatic increases in expression following stress (Scharf et al. 2011). Animal studies have shown that overexpression of FKBP51 in the amygdala increases anxiety behavior and decreases stress coping, and the opposite is true when FKBP51 is blocked in this brain area (Attwood et al. 2011, Hartmann et al. 2015).

Human structural and functional neuroimaging studies also indicate that the *FKBP5* genotype has a major effect on these brain regions (Fani et al. 2013, 2014, 2016; Hirakawa et al. 2016; Holz et al. 2015) and that the interaction with early adversity compounds this effect (Grabe et al.

CRHR1: *corticotropin-releasing hormone receptor 1*

CRH: corticotropin-releasing hormone

2016, Holz et al. 2015, Tozzi et al. 2016, White et al. 2012). Increased hippocampal and amygdala activity in response to threat and white matter abnormalities in the posterior cingulum have been observed in risk-allele carriers compared to alternative genotypes (Fani et al. 2013, 2014, 2016; Hirakawa et al. 2016; Holz et al. 2015). Two studies have found that the *FKBP5* risk genotypes interact with childhood neglect to predict increased threat-related activity in the amygdala (Holz et al. 2015, White et al. 2012). Specifically, both studies found that the right amygdala activity increased in parallel with the level of childhood neglect reported by homozygote *rs1360780* risk-allele carrier young adults during an emotional face-matching task, whereas the opposite was true for homozygotes of the protective allele. Heterozygotes exhibited intermediate levels of activity. Holz et al. (2015) also found that homozygote *rs1360780* risk-allele carriers displayed increased amygdala-hippocampus coupling, indicating that *FKBP5* may play a role in emotional memory formation, which may result in the negative emotional memory often seen in depressed patients (Hamilton & Gotlib 2008). Another study indicated that the combination of the *FKBP5* risk allele with a history of childhood abuse may predispose an individual to more widespread structural brain changes in other subcortical and cortical emotion-processing brain regions in addition to the amygdala and hippocampus (Grabe et al. 2016). In particular, Grabe and colleagues (2016) found that minor allele carriers of *FKBP5* rs1360780 exposed to child abuse had reduced gray matter volumes in the bilateral insula, the superior and middle temporal gyrus, and the bilateral anterior cingulate cortex, as well as the hippocampus and amygdala, compared to abused major allele carriers. Although the findings have been less consistent, postmortem studies have shown that *FKBP5* gene and protein expression are reduced in the amygdala of suicide victims compared to controls (Pérez-Ortiz et al. 2013) but increased in the prefrontal cortex of schizophrenia and bipolar patients compared to healthy controls (Sinclair et al. 2013).

These collective multilevel neurobiological findings suggest that an inherent genetic disinhibition of *FKBP5* in several emotion-processing brain regions is associated with increased bias toward threat, enhanced cortisol response, and altered amygdala and hippocampal response to threat. In combination with exposure to trauma in childhood, this genotype results in additional GR-mediated epigenetic disinhibition, which pushes this regulatory circuit over a threshold and leads to disease phenotypes. This result may be due to altered stress-related synaptic plasticity, possibly mediated by the effects of *FKBP5* on relevant pathways (Zannas et al. 2016). In support of this hypothesis, a recent postmortem study comparing PTSD patients and controls suggested that high FKBP51 levels in the orbitofrontal cortex were associated with a decrease in overall dendritic spine density (Young et al. 2015).

Corticotropin-Releasing Hormone Receptor 1

Corticotropin-releasing hormone receptor 1 (*CRHR1*) is another well-studied gene involved in the regulation of the stress response via the HPA axis. CRHR1 is a guanine nucleotide-binding protein (G-protein) receptor that binds corticotropin-releasing hormone (CRH) and is consequently a major physiological regulator of the HPA axis. The encoded protein plays a key role in the activation of signal transduction pathways involved in the regulation of the stress response (Koob 1999).

The link between genetic variants of both CRH and *CRHR1* and psychopathology has been extensively studied (for a review, see Binder & Nemeroff 2010). In terms of G × Es, *CRHR1* polymorphisms have been shown to predict both risk of and resilience to depressive symptoms in adults who have endured child abuse. More specifically, a haplotype composed of intronic SNPs in the *CRHR1* gene was found to protect against the development of depression in adults with a history of abuse across different ethnic groups (Bradley et al. 2008, Polanczyk et al. 2009). This indicates that genetically determined differences in CRH-mediated neurotransmission may increase or decrease

the detrimental effects of child abuse on the stress hormone system and thus influence an individual's susceptibility to developing depressive symptoms in adulthood. Replication of these findings in larger samples is still necessary to rule out false positive associations. Additionally, the ways in which early adversity is assessed may be relevant in the context of this G × E finding given that retrospective self-report of childhood abuse has been found to interact significantly with the gene whereas the prospective assessment of maltreatment has not (Bradley et al. 2008, Polanczyk et al. 2009).

COMT: *catechol-O-methyltransferase*

Further support for the *CRHR1* findings has come from endocrine and neuroimaging studies. In healthy adults with a history of childhood trauma, Tyrka et al. (2009) showed that individuals carrying the *CRHR1* risk haplotype experienced an increased cortisol response to combined dexamethasone/CRH stimulation but no differences across the genotypes were observed in adults with no history of early trauma. These findings were supported by Heim et al. (2009). Similarly, the *CRHR1* haplotype was found to interact with maltreatment in predicting diurnal regulation of cortisol levels in children (Cicchetti et al. 2011). These findings suggest that *CRHR1* risk-haplotype carriers have a genetic vulnerability to early trauma exposure, which may contribute to a long-lasting increase in CRHR1 signaling and dysregulation in the stress hormone system.

On a circuit level, preclinical studies in rodents have observed altered *CRHR1* mRNA expression and CRH binding in the hypothalamus, amygdala, and other brain regions associated with emotion response (Potter et al. 1994). It is thought that CRH activity at the CRHR1 in extrahypothalamic regions contributes to anxiety and depressive symptoms (Binder & Nemeroff 2010). *CRHR1* risk variants have also been shown to predict differential activation of limbic and cortical areas in emotion paradigms. For example, increased activity in the subgenual cingulate has been observed in depressed homozygote risk-allele carriers (i.e., G carriers) compared to depressed resilience allele carriers (i.e., A carriers) and controls when viewing negative versus neutral words (Hsu et al. 2012). Moreover, deactivation in the hypothalamus, amygdala, and nucleus accumbens was found in the depressed A carriers compared to controls during the same experiment. These findings may suggest biologically different types of depression depending on *CRHR1* genotype (Hsu et al. 2012). Interestingly, both depression and early-life stress were associated with changes in brain activity depending on genotype. Specifically, early-life stress and hypothalamus activation were negatively correlated only in A carriers (Hsu et al. 2012). These findings further support the notion that exposure to early-life stress can differentially impact emotional processing based on *CRHR1* genotype. *CRHR1* genotype–dependent differences have also been observed on a behavioral level with *CRHR1* risk-allele carriers exhibiting increased fear and stress sensitization compared to carriers of the alternative genotype (Starr et al. 2014, Weber et al. 2016).

Catechol-O-Methyltransferase

Although environmental stressors, such as early trauma, are the most common environmental determinant used in G × E studies, several studies suggest genotypic differences in outcomes based on cannabis use. In this and the following section, we review genes found to moderate the relationship between cannabis use and psychotic symptoms and schizophrenia.

Dysregulation in dopaminergic function has been implicated in the pathogenesis of schizophrenia (e.g., Kapur 2003). Cannabis use may also impact dopamine circuits (Colizzi et al. 2016), interacting with genetic variants associated with this system to predict risk for schizophrenia. The *catechol-O-methyltransferase* (*COMT*) gene, located on chromosome 22, encodes an enzyme that metabolizes dopamine and has been linked to schizophrenia.

Caspi and colleagues (2005) reported that a functional *COMT* gene polymorphism had a moderating effect on the increased risk for psychosis in adulthood following cannabis use during

CNR1: *cannabinoid receptor type 1*

THC: tetrahydrocannabinol

adolescence. They examined a G-to-A missense variation (i.e., one amino acid is altered in the protein product) in which the amino acid valine (Val) substitutes methionine (Met) at codon 158 ($Val^{158}Met$). This variation has been shown to decrease COMT's enzymatic activity and result in a slower breakdown of dopamine. The homozygous Met genotype has been found to have the lowest COMT activity and the homozygous Val genotype the highest, with heterozygous carriers displaying intermediate activity (Männistö & Kaakkola 1999). Caspi et al. (2005) reported that homozygous Val genotype carriers were more likely to develop psychotic symptoms in adulthood after using cannabis during adolescence compared to the homo- and heterozygous Met genotype carriers. These associations have since been replicated, although some studies have yielded null findings for this interaction (Costas et al. 2011; Funke et al. 2005; van Winkel 2011; Zammit et al. 2007, 2011). These findings were further extended by the discovery that the effects of cannabis were dependent on the proportion of THC and cannabidiol (another type of cannabinoid found in cannabis) in the cannabis (Niesink & van Laar 2013, Schubart et al. 2011). A higher concentration of cannabidiol in the cannabis mitigated the risk of the psychotic symptoms associated with cannabis use. Interestingly, two additional studies found a three-way interaction between adolescent cannabis use, the *COMT* gene, and childhood maltreatment (Alemany et al. 2014, Vinkers et al. 2013). In particular, cannabis use and a history of childhood abuse together were associated with increased psychotic symptoms in Val carriers compared to heterozygous or homozygous Met carriers. These genetic differences may increase the impact of cannabis use on dopamine circuits and, consequently, increase the risk for psychotic disorders (Sami et al. 2015).

The cellular and molecular mechanisms by which cannabis use contributes to vulnerability to psychotic symptoms remain unclear (for a review, see Malone et al. 2010). However, neuroimaging studies have provided further support for the relationship between *COMT* Val status and psychotic symptoms (for a review, see Lawrie et al. 2008). For instance, greater activation in the dorsolateral prefrontal cortex and reduced volumes of the prefrontal cortex and temporal lobes have been observed in Val carriers compared to Met carriers (Egan et al. 2001, Ohnishi et al. 2006). In accordance with these brain anomalies, the *COMT* gene variation may also increase cognitive vulnerability to other psychiatric disorders, including depression (Antypa et al. 2013, Craddock et al. 2006). Indeed, the *COMT* gene has been linked to heightened risk of broader personality traits associated with various psychopathologies (Hettema et al. 2015). For example, Val carriers tend to score higher on both introversion and extraversion measures than Met carriers (Hettema et al. 2008, 2015). Furthermore, the *COMT* genotype has been found to moderate the relationship between stressful life events and pathologies other than psychotic symptoms, including aggression, ADHD, and depression (Antypa et al. 2013, Hettema et al. 2015, Hygen et al. 2015, Thapar et al. 2005).

Cannabinoid Receptor Type 1 and *Mitogen-Activated Protein Kinase 14*

Two other genes, *cannabinoid receptor type 1* (*CNR1*) and *mitogen-activated protein kinase 14* (*MAPK14*), have also been found to moderate the relationship between cannabis use and schizophrenia. The main active component in cannabis, tetrahydrocannabinol (THC), activates cannabinoid receptors such as *CNR1* in the brain. Activation of *CNR1* has been found to induce apoptosis (i.e., the process of programmed cell death) through a complex cascade of kinases (i.e., an enzyme that adds phosphate groups to other molecules) and caspases (i.e., enzymes involved in apoptosis) (Chan et al. 1998, Downer et al. 2003), including *MAPK14* (Derkinderen et al. 2001, Powles et al. 2005). *CNR1* has also been implicated in the regulation of striatal dopamine (Pazos et al. 2005).

The G × E studies involving these gene variants have focused on their moderating effect on cannabis use and brain structure differences in individuals with and without schizophrenia.

Specifically, *CNR1* and *MAPK14* genetic variants have been found to predict greater deficits in white matter volume and cognitive impairment in a subset of patients with schizophrenia and marijuana abuse or dependence compared to individuals with schizophrenia without co-occurring marijuana abuse or dependence (Ho et al. 2011, Onwuameze et al. 2013). Interestingly, one study observed a significant gene–gene (i.e., *CNR1–MAPK14*) interaction influencing brain volume abnormalities in patients with both schizophrenia and a history of cannabis use during adolescence (Onwuameze et al. 2013). This interaction was additive: Patients with co-occurring schizophrenia and marijuana misuse who were carriers of both *CNR1* and *MAPK14* risk-alleles had the greatest deficit in white matter compared to the alternative genotypes. Although these findings are promising, this interaction remains to be expanded to and validated on other biological levels.

PRS: polygenic risk score

MDD: major depressive disorder

Polygenic Approaches

In accordance with Rutter and colleagues' (2006) recommendations, most G × E studies have been conducted using hypothesis-driven candidate genes. However, multiple gene variants likely work together to shape the risk for a psychiatric disorder (Kraft & Aschard 2015). As such, polygenic risk score (PRS) analyses provide an exciting framework for G × E studies. In contrast to hypothesis-driven candidate-gene approaches, polygenic approaches incorporate the contributions of many common genetic variants of small magnitude across the genome. A PRS for an individual is typically calculated by summing the number of alleles for each SNP; this sum is then weighted by the effect size derived from a GWAS. A GWAS involves a systematic examination of whether genotype frequencies for variants across the genome differ between individuals affected with a specific disorder and those who are unaffected. Thus, the PRS represents the additive effect of multiple SNPs, with a higher PRS typically suggesting a greater genetic predisposition toward the psychiatric disorder. Such scores give a much better representation of the genetic risk profile than a single candidate gene. Polygenic analyses have already demonstrated much larger cumulative effect sizes and greater predictive power than single-variant predictors (Bulik-Sullivan et al. 2015, Maier et al. 2015). Additionally, PRSs are not limited to examining disease risk: They also have the potential to investigate behavioral phenotypes, brain activity, and physiological and molecular measures relevant to environmental responses. This will allow a much more detailed exploration of the ways in which the environment interacts with genetic predisposition on different molecular and behavioral levels. This field is rapidly expanding, and new computational advances are emerging to construct PRSs with improved predictive and statistical abilities (e.g., Bulik-Sullivan et al. 2015, Maier et al. 2015). By design, polygenic studies do not point directly to specific genes associated with disease. However, complementary methods, such as gene-set analyses or subsetting using functionally relevant variants that alter gene transcription or DNA methylation or are located in relevant enhancer regions, can be employed to further dissect the potential biological mechanisms underlying such G × Es.

Three studies have examined the interaction between PRSs [based on data from the international Psychiatric Genomics Consortium (PGC) for major depressive disorder (MDD)] and childhood trauma in predicting MDD in independent adult samples (Mullins et al. 2016, Musliner et al. 2015, Peyrot et al. 2014). All three studies reported that the PRS had a significant main effect and examined its interaction with stressful life events. To briefly summarize their findings, Peyrot et al. (2014) and Mullins et al. (2016) reported a significant interaction between the PRS for MDD and childhood trauma in predicting depression. Peyrot and colleagues (2014) found that individuals with a high PRS and a history of childhood trauma were more likely to develop MDD than those with a low PRS and no exposure to trauma. Conversely, Mullins and colleagues (2016) found that individuals with a history of moderate-to-severe childhood trauma had lower

GWEIS: genome-wide by environment interaction study

PRSs for MDD than other cases or controls. In explaining their findings, Mullins and colleagues (2016) suggested that childhood trauma is such a strong risk factor that it may override to some extent genetic liability for the disorder. In addition to childhood trauma, Mullins et al. (2016) also examined the interaction between the PRS and stressful life events in adulthood in predicting MDD, which was nonsignificant. In the third study, Musliner et al. (2015) examined the interaction between the PRS for MDD and the occurrence of stressful life events during the previous 2 years in older adults. As in Mullins et al.'s (2016) study, the interaction between stressful life events in adulthood and the PRS was not significant (Musliner et al. 2015). These somewhat discrepant findings highlight the need to further examine both the type and timing of stressful life events in combination with genetic risk for psychopathology.

The studies above investigated PRSs derived from case/control associations but without functional annotation. Investigating PRSs that lead to functional differences in the response to environmental risk factors may, as pointed out by Rutter et al. (2006), be even more likely to lead to promising G × Es. As described in the section *FK506 Binding Protein-5* Polymorphism, the GR plays an important role in regulating gene expression. When an individual is confronted with a stressor, activation of the GR initiates adaptive physiological changes in the body through genome-wide transcriptional changes. As such, genetically determined differences in the transcriptional response to GR activation may contribute to individual differences in response to stressors and thus in susceptibility to psychiatric disorders (Lee & Sawa 2014, Shirazi et al. 2015). Using a stimulated expression quantitative trait locus approach, Arloth et al. (2015) constructed a genetic risk profile score based on genetic variants moderating the immediate transcriptional response to GR activation. The authors identified over 3,000 genetic variants that significantly altered the glucocorticoid-induced transcriptional changes of close to 300 transcripts. The genetic variants that altered the cellular response to stress were significantly enriched among variants associated with MDD and schizophrenia in the large meta-analyses published by the PGC (Ripke et al. 2013, 2014). In an independent sample, the cumulative score of genetic variants associated with both functional changes in the GR response of the transcriptome and risk for MDD predicted abnormal amygdala reactivity during a threat-related task. The findings suggest that genetic variants moderating the immediate cellular response to stress may also be associated with differences in the stress-processing neural circuit and an increased risk for stress-related psychiatric disorders (Arloth et al. 2015).

In addition to polygenic scores in G × E studies, genome-wide gene by environment interaction studies (GWEISs) are another possible unbiased analytical approach and elegant way to preserve power. Dunn and colleagues (2016) recently conducted a GWEIS analysis using social support and stressful life events as environmental determinants of depressive symptoms in over 10,000 women belonging to ethnic minorities. The findings pointed to interesting possible differences between minority groups. Specifically, increased depressive symptoms were observed to co-occur with both higher levels of reported stressful life events and more copies of the major allele of the gene *CEP350* in African American women. However, the same result was not found in a smaller independent replication sample, underscoring the need for large samples in GWEISs. In addition to requiring large sample sizes, GWEISs are based on GWASs in conjunction with environmental determinants and are thus fraught with a number of statistical complexities (e.g., Almli et al. 2014, Aschard et al. 2012). For instance, studies composed of large cohorts incorporating measures of environmental exposure carry the risk of overt and hidden differences in these measures.

IMPLICATIONS FOR TREATMENT

In this section, we discuss how G × E findings may be incorporated into clinical practice. We first define personalized treatment and then describe the current status of treatments for psychiatric

disorders and the need to establish neurobiological profiles to advance personalized medicine. We outline G × Es that significantly predict treatment outcomes and discuss how they can be utilized to improve outcomes.

The goals of personalized treatment are to predict an individual's risk of developing a psychiatric disorder, obtain an accurate diagnosis, and determine the most effective and favorable treatment option (Ozomaro et al. 2013). Personalized medicine builds on the assumption that unique characteristics, including clinical presentation, history of environmental influences, and genetic alterations, influence how (and whether) an individual will respond to a certain treatment. This concept has gained considerable attention, likely due to the limitations of our current treatment options and recent advances in genomics. Despite the identification of a number of evidence-based treatments, treatment efficacy for most disorders remains unsatisfactory. As an illustration, approximately 60% of treatment-seeking individuals with depression achieve remission after an initial trial of psychotherapy, pharmacotherapy, or a combination of the two (Gaynes et al. 2009, Holtzheimer & Mayberg 2011, Trivedi et al. 2006). That leaves a staggering 40% of patients who continue to have clinically significant symptoms following the intervention. These relatively low remission rates cause serious individual and public health concerns due to the individual's continued distress, loss of productivity, and heightened risk of suicide.

In an effort to improve treatment outcomes, researchers have sought predictors and moderators to determine what treatment works best for whom. Several studies have examined genetic markers as predictors of response to antidepressants (Garriock et al. 2010, Ising et al. 2009, Keers & Aitchison 2011, Licinio et al. 2004, Porcelli et al. 2012, Uher et al. 2010, Zou et al. 2010) and psychotherapy (Eley et al. 2012, Knuts et al. 2014, Lester et al. 2012, Lonsdorf et al. 2010). However, these findings have been inconsistent (Garriock et al. 2010, GENDEP Investig. et al. 2013, Ising et al. 2009, Uher et al. 2010). Additionally, when a genetic variant has been found to predict treatment outcomes, the effect size of the finding tends to be small and thus not suitable for clinical prediction (Keers & Aitchison 2011). Demographic and clinical characteristics have also proved relatively weak predictors of treatment response (Johnstone et al. 2009, Nanni et al. 2012, Nemeroff et al. 2003). There is, however, evidence suggesting that exposure to stressful life events may differentially predict treatment outcomes (Agnew-Blais & Danese 2016, Nemeroff et al. 2003). For instance, depressed individuals with a history of childhood trauma have been found to respond more favorably to psychotherapy compared to pharmacotherapy (Nemeroff et al. 2003). The collective findings suggest differences in the etiology and pathogenesis of depressed individuals based on their developmental history. These findings also indicate that treatment response may be determined by a combination of factors, such as G × Es.

Several pharmacogenetic G × E studies have been conducted to predict treatment response to antidepressants. Relevant to the genetic variants discussed above, two studies (Keers et al. 2011, Mandelli et al. 2009) found that *5-HTTLPR* moderated the relationship between recent life stress and treatment with SSRIs but not tricyclic antidepressants for depression. In fact, recent life stress predicted poorer treatment outcomes in S-allele carriers compared to L-allele carriers. Conversely, no genotype differences were noted in individuals not exposed to recent life stress. G × Es that are significant for treatment response have also been reported for the *FKBP5* and *CRHR1* polymorphisms (Keers & Uher 2012). However, these findings differ from the *5-HTTLPR* results in that individuals with the risk genotype for depression showed better treatment outcomes than alternative genotypes when exposed to stressors. Homo- or heterozygote minor allele carriers of *FKBP5* or *CRHR1* who had recently been exposed to stressful life events were more likely to respond to antidepressant treatment than individuals with this genotype who had not been exposed to recent life stressors. On the contrary, stressful life events had little effect on treatment response in the respective alternative genotypes. The authors speculated that serotonin signaling and HPA

axis dysfunction are two distinct etiological pathways to depression. This might explain why the G × E studies involving the *5-HTTLPR*, *FKBP5*, and *CRHR1* polymorphisms yielded opposite findings in terms of treatment response (Keers & Uher 2012). This hypothesis remains to be tested in future studies.

Interestingly, different genotypes may predict treatment response to psychotherapy than to pharmacotherapy. For instance, Eley and colleagues (2012) found that the S allele of *5-HTTLPR* predicted good cognitive behavioral therapy outcomes in depressed patients, whereas this genotype has been found to negatively predict response to antidepressants (Niitsu et al. 2013, Porcelli et al. 2012). These findings may be in line with the differential-susceptibility model (Belsky & Pluess 2009) mentioned in the Introduction. Individuals with the S allele may be more susceptible to environmental influences and could therefore respond better to changes in the environment brought about by psychotherapy. Indeed, experimental evidence indicates that S-allele carriers benefit more from a supportive environment than do individuals with other genotypes (Brody et al. 2009). Specifically, Brody et al. (2009) examined the differential response of youth to a community-based intervention aimed at increasing nurturing parenting practices and children's compliance and goal-setting. They found that youths carrying the S allele (both homozygote and heterozygote carriers) benefitted more from a family-based intervention designed to reduce risk behaviors in rural African American youths than did L-allele carriers.

Another interesting and potentially clinically relevant study may have identified differential usage of coping strategies as a mechanism for increased internalizing symptoms in children carrying the *5-HTTLPR* S allele (Cline et al. 2015). Specifically, homozygote S-allele carriers exhibited higher levels of internalizing symptoms compared to L-allele carriers. S-allele carriers were also less likely to use distraction coping strategies, particularly after exposure to stressful life events, such as traumatic events and hostile relationships with caregivers. This tendency may, in part, explain the elevated internalizing symptoms in S-allele carriers. In the absence of these distraction strategies, the authors hypothesized that the homozygous S-allele carriers perseverated on negative thoughts about their problems instead of engaging in problem-solving techniques or enlisting social support, thus increasing their risk of developing depressive or anxiety symptoms. Findings such as these can help personalize psychotherapeutic treatment approaches. In particular, identifying skills that individuals are lacking on the basis of genetic and environmental determinants may have important clinical implications for developing effective prevention strategies and interventions.

The current G × E findings highlight the potential clinical utility of environmentally focused preventions and interventions in overcoming genetic predisposition toward developing a psychiatric disorder. These interventions could target specific behavioral domains, as suggested by Cline et al. (2015), but could also target specific neural circuits whose activation is altered in a G × E context. This targeting may be achieved by a combination of diagnostic neuroimaging, genetics, and neurofeedback (Hamilton et al. 2016, Linden et al. 2012, Young et al. 2014). Research suggests that neurofeedback using functional magnetic resonance imaging may be a useful therapeutic option for psychiatric disorders in the future.

CONCLUSIONS

G × Es can shed light on the pathophysiology of psychiatric disorders. These studies describe differing subpopulations within psychiatric disorders on the basis of genotypes and environmental influences, with possibly different molecular pathways and neural circuits mediating risk. This deeper understanding of the underlying pathobiology may allow more targeted prevention and treatment strategies. However, to be successful, several limitations must be overcome and studies in larger cohorts or consortia will be necessary. Importantly, G × E analyses need to be carried

out more systematically in longitudinal cohorts with careful mapping of environmental factors so that complex G × Es with multiple environmental factors can be performed. In such studies, deep phenotyping, including endophenotypes at several levels of investigation, and biosampling over several points in time should be performed. We also lack sufficient tools for more mechanistic investigations. Although humanized animal models may allow investigation of specific human variants, models for polygenic risk interactions are needed. For modeling effects on the molecular and cellular level, neurons and brain organoids derived from induced pluripotent stem cells may represent attractive tools. These may allow investigation of the impact of genetic risk factors and environmental mediators (glucocorticoids, monoamines, etc.) in the context of neuronal differentiation and connectivity. In the end, such in-depth G × E analyses may reveal more homogeneous neurobiological diagnostic categories than are provided by our current diagnostic framework, which, in turn, may improve an individual's prognosis through personalized medicine and targeted therapeutic interventions.

DISCLOSURE STATEMENT

E.B. is co-inventor on *FKBP5: a novel target for antidepressant therapy*, European Patent No. EP 1687443 B1, and receives a research grant from Böhringer-Ingelheim for a collaboration on functional investigations of *FKBP5*. T.H. has nothing to disclose.

ACKNOWLEDGMENTS

This review was supported by a European Research Council starting grant, G × E-MOLMECH grant 281338, to E.B.

LITERATURE CITED

Agnew-Blais J, Danese A. 2016. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry* 3:342–49

Albu S, Romanowski CP, Letizia Curzi M, Jakubcakova V, Flachskamm C, et al. 2014. Deficiency of FK506-binding protein (FKBP) 51 alters sleep architecture and recovery sleep responses to stress in mice. *J. Sleep Res.* 23:176–85

Alemany S, Arias B, Fatjó-Vilas M, Villa H, Moya J, et al. 2014. Psychosis-inducing effects of cannabis are related to both childhood abuse and COMT genotypes. *Acta Psychiatr. Scand.* 129:54–62

Alexander N, Klucken T, Koppe G, Osinsky R, Walter B, et al. 2012. Interaction of the serotonin transporter-linked polymorphic region and environmental adversity: increased amygdala-hypothalamus connectivity as a potential mechanism linking neural and endocrine hyperreactivity. *Biol. Psychiatry* 72:49–56

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* 34:1294–303

Almli LM, Duncan R, Feng H, Ghosh D, Binder EB, et al. 2014. Correcting systematic inflation in genetic association tests that consider interaction effects: application to a genome-wide association study of posttraumatic stress disorder. *JAMA Psychiatry* 71:1392–99

Andréasson S, Engström A, Allebeck P, Rydberg U. 1987. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. *Lancet* 330:1483–86

Antypa N, Drago A, Serretti A. 2013. The role of COMT gene variants in depression: bridging neuropsychological, behavioral and clinical phenotypes. *Neurosci. Biobehav. Rev.* 37:1597–610

Arloth J, Bogdan R, Weber P, Frishman G, Menke A, et al. 2015. Genetic differences in the immediate transcriptome response to stress predict risk-related brain function and psychiatric disorders. *Neuron* 86:1189–202

Aschard H, Lutz S, Maus B, Duell EJ, Fingerlin TE, et al. 2012. Challenges and opportunities in genome-wide environmental interaction (GWEI) studies. *Hum. Genet.* 131:1591–613

Attwood BK, Bourgognon JM, Patel S, Mucha M, Schiavon E, et al. 2011. Neuropsin cleaves EphB2 in the amygdala to control anxiety. *Nature* 473:372–75

Bale TL, Vale WW. 2004. CRF and CRF receptors: role in stress responsivity and other behaviors. *Annu. Rev. Pharmacol. Toxicol.* 44:525–57

Baumeister D, Lightman SL, Pariante CM. 2014. The interface of stress and the HPA axis in behavioural phenotypes of mental illness. *Curr. Top. Behav. Neurosci.* 18:13–24

Belsky J, Bakermans-Kranenburg MJ, Van IJzendoorn MH. 2007. For better and for worse: differential susceptibility to environmental influences. *Curr. Dir. Psychol. Sci.* 16:300–4

Belsky J, Pluess M. 2009. Beyond diathesis stress: differential susceptibility to environmental influences. *Psychol. Bull.* 135:885–908

Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, et al. 2008. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA* 299:1291–305

Binder EB, Nemeroff CB. 2010. The CRF system, stress, depression and anxiety-insights from human genetic studies. *Mol. Psychiatry* 15:574–88

Binder EB, Salyakina D, Lichtner P, Wochnik GM, Ising M, et al. 2004. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nat. Genet.* 36:1319–25

Bradley RG, Binder EB, Epstein MP, Tang Y, Nair HP, et al. 2008. Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. *Arch. Gen. Psychiatry* 65:190–200

Brody GH, Beach SRH, Philibert RA, Chen YF, Murry VM. 2009. Prevention effects moderate the association of 5-HTTLPR and youth risk behavior initiation: gene × environment hypotheses tested via a randomized prevention design. *Child Dev.* 80:645–61

Buchmann AF, Holz N, Boecker R, Blomeyer D, Rietschel M, et al. 2014. Moderating role of FKBP5 genotype in the impact of childhood adversity on cortisol stress response during adulthood. *Eur. Neuropsychopharmacol.* 24:837–45

Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, et al. 2015. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* 47:291–95

Canli T, Qiu M, Omura K, Congdon E, Haas BW, et al. 2006. Neural correlates of epigenesis. *PNAS* 103:16033–38

Cannon DM, Ichise M, Fromm SJ, Nugent AC, Rollis D, et al. 2006. Serotonin transporter binding in bipolar disorder assessed using [^{11}C]DASB and positron emission tomography. *Biol. Psychiatry* 60:207–17

Caspi A, Hariri AR, Holmes A, Uher R, Moffitt 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* 167:509–27

Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, et al. 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene × environment interaction. *Biol. Psychiatry* 57:1117–27

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, et al. 2003. Influence of life stress on depression: moderation by a polymorphism in the *5-HTT* gene. *Science* 301:386–89

Chan GC, Hinds TR, Impey S, Storm DR. 1998. Hippocampal neurotoxicity of Δ^9-tetrahydrocannabinol. *J. Neurosci.* 18:5322–32

Cheung J, Bryant RA. 2015. FKBP5 risk alleles and the development of intrusive memories. *Neurobiol. Learn. Mem.* 125:258–64

Cicchetti D, Rogosch FA, Oshri A. 2011. Interactive effects of *corticotropin releasing hormone receptor 1*, serotonin transporter linked polymorphic region, and child maltreatment on diurnal cortisol regulation and internalizing symptomatology. *Dev. Psychopathol.* 23:1125–38

Cline JI, Belsky J, Li Z, Melhuish E, Lysenko L, et al. 2015. Take your mind off it: coping style, serotonin transporter linked polymorphic region genotype (5-HTTLPR), and children's internalizing and externalizing problems. *Dev. Psychopathol.* 27:1129–43

Colizzi M, McGuire P, Pertwee RG, Bhattacharyya S. 2016. Effect of cannabis on glutamate signalling in the brain: a systematic review of human and animal evidence. *Neurosci. Biobehav. Rev.* 64:359–81

Costas J, Sanjuán J, Ramos-Ríos R, Paz E, Agra S, et al. 2011. Interaction between COMT haplotypes and cannabis in schizophrenia: a case-only study in two samples from Spain. *Schizophr. Res.* 127:22–27
Craddock N, Owen MJ, O'Donovan MC. 2006. The catechol-O-methyl transferase (*COMT*) gene as a candidate for psychiatric phenotypes: evidence and lessons. *Mol. Psychiatry* 11:446–58
Dannlowski U, Ohrmann P, Bauer J, Deckert J, Hohoff C, et al. 2008. 5-HTTLPR biases amygdala activity in response to masked facial expressions in major depression. *Neuropsychopharmacology* 33:418–24
Dannlowski U, Ohrmann P, Bauer J, Kugel H, Baune BT, et al. 2007. Serotonergic genes modulate amygdala activity in major depression. *Genes Brain Behav.* 6:672–76
Davies TH, Ning YM, Sánchez ER. 2002. A new first step in activation of steroid receptors: hormone-induced switching of FKBP51 and FKBP52 immunophilins. *J. Biol. Chem.* 277:4597–600
Derkinderen P, Ledent C, Parmentier M, Girault JA. 2001. Cannabinoids activate p38 mitogen-activated protein kinases through CB1 receptors in hippocampus. *J. Neurochem.* 77:957–60
Dick DM, Agrawal A, Keller MC, Adkins A, Aliev F, et al. 2015. Candidate gene-environment interaction research: reflections and recommendations. *Perspect. Psychol. Sci.* 10:37–59
Downer EJ, Fogarty MP, Campbell VA. 2003. Tetrahydrocannabinol-induced neurotoxicity depends on CB1 receptor-mediated c-Jun N-terminal kinase activation in cultured cortical neurons. *Br. J. Pharmacol.* 140:547–57
Duncan LE, Keller MC. 2011. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am. J. Psychiatry* 168:1041–49
Dunn EC, Wiste A, Radmanesh F, Almli LM, Gogarten SM, et al. 2016. Genome-wide association study (GWAS) and genome-wide by environment interaction study (GWEIS) of depressive symptoms in African American and Hispanic/Latina women. *Depress. Anxiety* 33:265–80
Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, et al. 2001. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *PNAS* 98:6917–22
Eley TC, Hudson JL, Creswell C, Tropeano M, Lester KJ, et al. 2012. Therapygenetics: the 5HTTLPR and response to psychological therapy. *Mol. Psychiatry* 17:236–37
Eley TC, Sugden K, Corsico A, Gregory AM, Sham P, et al. 2004. Gene–environment interaction analysis of serotonin system markers with adolescent depression. *Mol. Psychiatry* 9:908–15
Fani N, Gutman D, Tone EB, Almli L, Mercer KB, et al. 2013. FKBP5 and attention bias for threat: associations with hippocampal function and shape. *JAMA Psychiatry* 70:392–400
Fani N, King TZ, Reiser E, Binder EB, Jovanovic T, et al. 2014. FKBP5 genotype and structural integrity of the posterior cingulum. *Neuropsychopharmacology* 39:1206–13
Fani N, King TZ, Shin J, Srivastava A, Brewster RC, et al. 2016. Structural and functional connectivity in post-traumatic stress disorder: associations with FKBP5. *Depress. Anxiety* 33:300–7
Fortier E, Noreau A, Lepore F, Boivin M, Pérusse D, et al. 2010. Early impact of 5-HTTLPR polymorphism on the neural correlates of sadness. *Neurosci. Lett.* 485:261–65
Frankle WG, Narendran R, Huang Y, Hwang DR, Lombardo I, et al. 2005. Serotonin transporter availability in patients with schizophrenia: a positron emission tomography imaging study with [^{11}C]DASB. *Biol. Psychiatry* 57:1510–16
Funke B, Malhotra AK, Finn CT, Plocik AM, Lake SL, et al. 2005. COMT genetic variation confers risk for psychotic and affective disorders: a case control study. *Behav. Brain Funct.* 1:1–19
Garriock HA, Kraft JB, Shyn SI, Peters EJ, Yokoyama JS, et al. 2010. A genomewide association study of citalopram response in major depressive disorder. *Biol. Psychiatry* 67:133–38
Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. 2009. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr. Serv.* 60:1439–45
Investig GENDEP., Investig MARS., Investig STAR*D. 2013. Common genetic variation and antidepressant efficacy in major depressive disorder: a meta-analysis of three genome-wide pharmacogenetic studies. *Am. J. Psychiatry* 170:207–17
Gibb BE, McGeary JE, Beevers CG, Miller IW. 2006. Serotonin transporter (5-HTTLPR) genotype, childhood abuse, and suicide attempts in adult psychiatric inpatients. *Suicide Life Threat. Behav.* 36:687–93
Grabe HJ, Wittfeld K, Van der Auwera S, Janowitz D, Hegenscheid K, et al. 2016. Effect of the interaction between childhood abuse and rs1360780 of the *FKBP5* gene on gray matter volume in a general population sample. *Hum. Brain Mapp.* 37:1602–13

Grad I, Picard D. 2007. The glucocorticoid responses are shaped by molecular chaperones. *Mol. Cell. Endocrinol.* 275:2–12

Habets P, Marcelis M, Gronenschild E, Drukker M, van Os J. 2011. Reduced cortical thickness as an outcome of differential sensitivity to environmental risks in schizophrenia. *Biol. Psychiatry* 69:487–94

Hamilton JP, Glover GH, Bagarinao E, Chang C, Mackey S, et al. 2016. Effects of salience-network-node neurofeedback training on affective biases in major depressive disorder. *Psychiatry Res. Neuroimaging* 249:91–96

Hamilton JP, Gotlib IH. 2008. Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biol. Psychiatry* 63:1155–62

Hankin BL, Nederhof E, Oppenheimer CW, Jenness J, Young JF, et al. 2011. Differential susceptibility in youth: evidence that 5-HTTLPR × positive parenting is associated with positive affect 'for better and worse'. *Transl. Psychiatry* 1:e44

Hariri AR, Drabant EM, Munoz KE, Kolachana BS, Mattay VS, et al. 2005. A susceptibility gene for affective disorders and the response of the human amygdala. *Arch. Gen. Psychiatry* 62:146–52

Hartmann J, Wagner KV, Gaali S, Kirschner A, Kozany C, et al. 2015. Pharmacological inhibition of the psychiatric risk factor *FKBP51* has anxiolytic properties. *J. Neurosci.* 35:9007–16

Hartmann J, Wagner KV, Liebl C, Scharf SH, Wang XD, et al. 2012. The involvement of FK506-binding protein 51 (FKBP5) in the behavioral and neuroendocrine effects of chronic social defeat stress. *Neuropharmacology* 62:332–39

Heim C, Bradley B, Mletzko T, Deveau TC, Musselmann DL, et al. 2009. Effect of childhood trauma on adult depression and neuroendocrine function: sex-specific moderation by CRH receptor 1 gene. *Front. Behav. Neurosci.* 3:1–10

Hettema JM, An SS, Bukszar J, Van den Oord EJ, Neale MC, et al. 2008. Catechol-O-methyltransferase contributes to genetic susceptibility shared among anxiety spectrum phenotypes. *Biol. Psychiatry* 64:302–10

Hettema JM, Chen X, Sun C, Brown TA. 2015. Direct, indirect and pleiotropic effects of candidate genes on internalizing disorder psychopathology. *Psychol. Med.* 45:2227–36

Hirakawa H, Akiyoshi J, Muronaga M, Tanaka Y, Ishitobi Y, et al. 2016. FKBP5 is associated with amygdala volume in the human brain and mood state: a voxel-based morphometry (VBM) study. *Int. J. Psychiatry Clin. Pract.* 20:1–10

Ho BC, Wassink TH, Ziebell S, Andreasen NC. 2011. Cannabinoid receptor 1 gene polymorphisms and marijuana misuse interactions on white matter and cognitive deficits in schizophrenia. *Schizophr. Res.* 128:66–75

Holsboer F. 2000. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology* 23:477–501

Holtzheimer PE, Mayberg HS. 2011. Stuck in a rut: rethinking depression and its treatment. *Trends Neurosci.* 34:1–9

Holz NE, Buchmann AF, Boecker R, Blomeyer D, Baumeister S, et al. 2015. Role of FKBP5 in emotion processing: results on amygdala activity, connectivity and volume. *Brain Struct. Funct.* 220:1355–68

Hsu DT, Mickey BJ, Langenecker SA, Heitzeg MM, Love TM, et al. 2012. Variation in the corticotropin-releasing hormone receptor 1 (*CRHR1*) gene influences fMRI signal responses during emotional stimulus processing. *J. Neurosci.* 32:3253–60

Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, et al. 2006. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *Am. J. Hum. Genet.* 78:815–26

Hygen BW, Belsky J, Stenseng F, Lydersen S, Guzey IC, Wichstrom L. 2015. Child exposure to serious life events, COMT, and aggression: testing differential susceptibility theory. *Dev. Psychol.* 51:1098–104

Ising M, Depping AM, Siebertz A, Lucae S, Unschuld PG, et al. 2008. Polymorphisms in the *FKBP5* gene region modulate recovery from psychosocial stress in healthy controls. *Eur. J. Neurosc.* 28:389–98

Ising M, Lucae S, Binder EB, Bettecken T, Uhr M, et al. 2009. A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. *Arch. Gen. Psychiatry* 66:966–75

Johnstone JM, Luty SE, Carter JD, Mulder RT, Frampton C, Joyce PR. 2009. Childhood neglect and abuse as predictors of antidepressant response in adult depression. *Depress. Anxiety* 26:711–17

Kapur S. 2003. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am. J. Psychiatry* 160:13–23
Karg K, Burmeister M, Shedden K, Sen S. 2011. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Arch. Gen. Psychiatry* 68:444–54
Keers R, Aitchison KJ. 2011. Pharmacogenetics of antidepressant response. *Expert Rev. Neurother.* 11:101–25
Keers R, Uher R. 2012. Gene–environment interaction in major depression and antidepressant treatment response. *Curr. Psychiatry Rep.* 14:129–37
Keers R, Uher R, Huezo-Diaz P, Smith R, Jaffee S, et al. 2011. Interaction between serotonin transporter gene variants and life events predicts response to antidepressants in the GENDEP project. *Pharmacogenomics J.* 11:138–45
Kilpatrick DG, Koenen KC, Ruggiero KJ, Acierno R, Galea S, et al. 2007. The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. *Am. J. Psychiatry* 164:1693–99
Klengel T, Binder EB. 2015. *FKBP5* allele-specific epigenetic modification in gene by environment interaction. *Neuropharmacol. Rev.* 40:244–46
Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, et al. 2013. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat. Neurosci.* 16:33–41
Knuts I, Esquivel G, Kenis G, Overbeek T, Leibold N, et al. 2014. Therapygenetics: 5-HTTLPR genotype predicts the response to exposure therapy for agoraphobia. *Eur. Neuropsychopharmacol.* 24:1222–28
Koenen KC, Aiello AE, Bakshis E, Amstadter AB, Ruggiero KJ, et al. 2009. Modification of the association between serotonin transporter genotype and risk of posttraumatic stress disorder in adults by county-level social environment. *Am. J. Epidemiol.* 169:704–11
Koenen KC, Saxe G, Purcell S, Smoller JW, Bartholomew D, et al. 2005. Polymorphisms in FKBP5 are associated with peritraumatic dissociation in medically injured children. *Mol. Psychiatry* 10:1058–59
Koob GF. 1999. Corticotropin-releasing factor, norepinephrine, and stress. *Biol. Psychiatry* 46:1167–80
Kraft P, Aschard H. 2015. Finding the missing gene-environment interactions. *Eur. J. Epidemiol.* 30:353–55
Kranzler HR, Scott D, Tennen H, Feinn R, Williams C, et al. 2012. The 5-HTTLPR polymorphism moderates the effect of stressful life events on drinking behavior in college students of African descent. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 159:484–90
Laucht M, Treutlein J, Blomeyer D, Buchmann AF, Schmid B, et al. 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.* 12:737–47
Lawrie SM, Hall J, McIntosh AM, Cunningham-Owens DG, Johnstone EC. 2008. Neuroimaging and molecular genetics of schizophrenia: pathophysiological advances and therapeutic potential. *Brit. J. Pharmacol.* 153:S120–24
Lee RS, Sawa A. 2014. Environmental stressors and epigenetic control of the hypothalamic-pituitary-adrenal axis. *Neuroendocrinology* 100:278–87
Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, et al. 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 274:1527–31
Lester KJ, Hudson JL, Tropeano M, Creswell C, Collier DA, et al. 2012. Neurotrophic gene polymorphisms and response to psychological therapy. *Transl. Psychiatry* 2:e108
Licinio J, O'kirwan F, Irizarry K, Merriman B, Thakur S, et al. 2004. Association of a corticotropin-releasing hormone receptor 1 haplotype and antidepressant treatment response in Mexican-Americans. *Mol. Psychiatry* 9:1075–82
Linden DE, Habes I, Johnston SJ, Linden S, Tatineni R, et al. 2012. Real-time self-regulation of emotion networks in patients with depression. *PLOS ONE* 7:e38115
Liu Y, Garrett ME, Dennis MF, Green KT, Ashley-Koch AE, et al. 2015. An examination of the association between 5-HTTLPR, combat exposure, and PTSD diagnosis among US veterans. *PLOS ONE* 10:e0119998
Lonsdorf TB, Rück C, Bergström J, Andersson G, Öhman A, et al. 2010. The COMTval158met polymorphism is associated with symptom relief during exposure-based cognitive-behavioral treatment in panic disorder. *BMC Psychiatry* 10:99–107

Maier R, Moser G, Chen GB, Ripke S, Coryell W, et al. 2015. Joint analysis of psychiatric disorders increases accuracy of risk prediction for schizophrenia, bipolar disorder, and major depressive disorder. *Am. J. Hum. Genet.* 96:283–94

Malone DT, Hill MN, Rubino T. 2010. Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models. *Br. J. Pharmacol.* 160:511–22

Mandelli L, Marino E, Pirovano A, Calati R, Zanardi R, et al. 2009. Interaction between SERTPR and stressful life events on response to antidepressant treatment. *Eur. Neuropsychopharmacol.* 19:64–67

Mann JJ, Huang YY, Underwood MD, Kassir SA, Oppenheim S, et al. 2000. A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch. Gen. Psychiatry* 57:729–38

Männistö PT, Kaakkola S. 1999. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. *Pharmacol. Rev.* 51:593–628

Mueller A, Strahler J, Armbruster D, Lesch KP, Brocke B, Kirschbaum C. 2012. Genetic contributions to acute autonomic stress responsiveness in children. *Int. J. Psychophysiol.* 83:302–8

Mullins N, Power RA, Fisher HL, Hanscombe KB, Euesden J, et al. 2016. Polygenic interactions with environmental adversity in the aetiology of major depressive disorder. *Psychol. Med.* 46:759–70

Munafo MR, Brown SM, Hariri AR. 2008. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biol. Psychiatry* 63:852–57

Munafo MR, Freimer NB, Ng W, Ophoff R, Veijola J, et al. 2009. 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 150:271–81

Musliner KL, Seifuddin F, Judy JA, Pirooznia M, Goes FS, Zandi PP. 2015. Polygenic risk, stressful life events and depressive symptoms in older adults: a polygenic score analysis. *Psychol. Med.* 45:1709–20

Nanni V, Uher R, Danese A. 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *Am. J. Psychiatry* 169:141–51

Nemeroff CB. 1989. Clinical significance of psychoneuroendocrinology in psychiatry: focus on the thyroid and adrenal. *J. Clin. Psychiatry* 50(Suppl. 13–20):21–22

Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, et al. 2003. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *PNAS* 100:14293–96

Niesink RJ, van Laar MW. 2013. Does cannabidiol protect against adverse psychological effects of THC? *Front. Psychiatry* 4:1–8

Nievergelt CM, Maihofer AX, Mustapic M, Yurgil KA, Schork NJ, et al. 2015. Genomic predictors of combat stress vulnerability and resilience in US Marines: a genome-wide association study across multiple ancestries implicates *PRTFDC1* as a potential PTSD gene. *Psychoneuroendocrinology* 51:459–71

Niitsu T, Fabbri C, Bentini F, Serretti A. 2013. Pharmacogenetics in major depression: a comprehensive meta-analysis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 45:183–94

Novik KL, Nimmrich I, Genc B, Maier S, Piepenbrock C, et al. 2002. Epigenomics: genome-wide study of methylation phenomena. *Curr. Issues Mol. Biol.* 4:111–28

Ohnishi T, Hashimoto R, Mori T, Nemoto K, Moriguchi Y, et al. 2006. The association between the Val158Met polymorphism of the catechol-O-methyl transferase gene and morphological abnormalities of the brain in chronic schizophrenia. *Brain* 129:399–410

O'Leary JC III, Dharia S, Blair LJ, Brady S, Johnson AG, et al. 2011. A new anti-depressive strategy for the elderly: ablation of FKBP5/FKBP51. *PLOS ONE* 6:e24840

Onwuameze OE, Nam KW, Epping EA, Wassink TH, Ziebell S, et al. 2013. *MAPK14* and *CNR1* gene variant interactions: effects on brain volume deficits in schizophrenia patients with marijuana misuse. *Psychol. Med.* 43:619–31

Ozomaro U, Wahlestedt C, Nemeroff CB. 2013. Personalized medicine in psychiatry: problems and promises. *BMC Med.* 11:132–67

Pazos MR, Nunez E, Benito C, Tolon RM, Romero J. 2005. Functional neuroanatomy of the endocannabinoid system. *Pharmacol. Biochem. Behav.* 81:239–47

Pérez-Ortiz JM, García-Gutiérrez MS, Navarrete F, Giner S, Manzanares J. 2013. Gene and protein alterations of *FKBP5* and glucocorticoid receptor in the amygdala of suicide victims. *Psychoneuroendocrinology* 38:1251–58

Peyrot WJ, Milaneschi Y, Abdellaoui A, Sullivan PF, Hottenga JJ, et al. 2014. Effect of polygenic risk scores on depression in childhood trauma. *Br. J. Psychiatry* 205:113–19

Pezawas L, Meyer-Lindenberg A, Drabant EM, Verchinski BA, Munoz KE, et al. 2005. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat. Neurosci.* 8:828–34

Pluess M, Belsky J, Way BM, Taylor SE. 2010. 5-HTTLPR moderates effects of current life events on neuroticism: differential susceptibility to environmental influences. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 34:1070–74

Polanczyk G, Caspi A, Williams B, Price TS, Danese A, et al. 2009. Protective effect of *CRHR1* gene variants on the development of adult depression following childhood maltreatment: replication and extension. *Arch. Gen. Psychiatry* 66:978–85

Porcelli S, Fabbri C, Serretti A. 2012. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. *Eur. Neuropsychopharmacol.* 22:239–58

Potter E, Sutton S, Donaldson C, Chen R, Perrin M, et al. 1994. Distribution of corticotropin-releasing factor receptor mRNA expression in the rat brain and pituitary. *PNAS* 91:8777–81

Powles T, te Poele R, Shamash J, Chaplin T, Propper D, et al. 2005. Cannabis-induced cytotoxicity in leukemic cell lines: the role of the cannabinoid receptors and the MAPK pathway. *Blood* 105:1214–21

Ripke S, Neale BM, Corvin A, Walters JT, Farh KH, et al. 2014. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511:421–27

Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, et al. 2013. A mega-analysis of genome-wide association studies for major depressive disorder. *Mol. Psychiatry* 18:497–511

Risch N, Herrell R, Lehner T, Liang KY, Eaves L, et al. 2009. Interaction between the serotonin transporter gene (*5-HTTLPR*), stressful life events, and risk of depression: a meta-analysis. *JAMA* 301:2462–71

Roy A, Hu XZ, Janal MN, Goldman D. 2007. Interaction between childhood trauma and serotonin transporter gene variation in suicide. *Neuropsychopharmacology* 32:2046–52

Rutter M, Moffitt TE, Caspi A. 2006. Gene–environment interplay and psychopathology: multiple varieties but real effects. *J. Child Psychol. Psychiatry* 47:226–61

Rutter M, Pickles A. 2015. Annual research review: threats to the validity of child psychiatry and psychology. *J. Child Psychol. Psychiatry* 57:398–416

Sami MB, Rabiner EA, Bhattacharyya S. 2015. Does cannabis affect dopaminergic signaling in the human brain? A systematic review of evidence to date. *Eur. Neuropsychopharmacol.* 25:1201–24

Sawamura T, Klengel T, Armario A, Jovanovic T, Norrholm SD, et al. 2016. Dexamethasone treatment leads to enhanced fear extinction and dynamic Fkbp5 regulation in amygdala. *Neuropsychopharmacology* 41:832–46

Scharf SH, Liebl C, Binder EB, Schmidt MV, Müller MB. 2011. Expression and regulation of the *Fkbp5* gene in the adult mouse brain. *PLOS ONE* 6:e16883

Schubart CD, Van Gastel WA, Breetvelt EJ, Beetz SL, Ophoff RA, et al. 2011. Cannabis use at a young age is associated with psychotic experiences. *Psychol. Med.* 41:1301–10

Sharma S, Powers A, Bradley B, Ressler KJ. 2016. Gene × environment determinants of stress- and anxiety-related disorders. *Annu. Rev. Psychol.* 67:239–61

Sharpley CF, Palanisamy SK, Glyde NS, Dillingham PW, Agnew LL. 2014. An update on the interaction between the serotonin transporter promoter variant (*5-HTTLPR*), stress and depression, plus an exploration of non-confirming findings. *Behav. Brain Res.* 273:89–105

Shirazi SN, Friedman AR, Kaufer D, Sakhai SA. 2015. Glucocorticoids and the brain: neural mechanisms regulating the stress response. In *Glucocorticoid Signaling*, ed. J-C Wang, C Harris, pp. 235–52. New York: Springer

Sinclair D, Fillman SG, Webster MJ, Weickert CS. 2013. Dysregulation of glucocorticoid receptor co-factors FKBP5, BAG1 and PTGES3 in prefrontal cortex in psychotic illness. *Sci. Rep.* 3:1–10

Solovieff N, Roberts AL, Ratanatharathorn A, Haloosim M, De Vivo I, et al. 2014. Genetic association analysis of 300 genes identifies a risk haplotype in *SLC18A2* for post-traumatic stress disorder in two independent samples. *Neuropsychopharmacology* 39:1872–79

Starr LR, Hammen C, Conway CC, Raposa E, Brennan PA. 2014. Sensitizing effect of early adversity on depressive reactions to later proximal stress: moderation by polymorphisms in serotonin transporter and corticotropin releasing hormone receptor genes in a 20-year longitudinal study. *Dev. Psychopathol.* 26:1241–54

Stein MB, Schork NJ, Gelernter J. 2008. Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders. *Neuropsychopharmacology* 33:312–19

Stoltenberg SF, Anderson C, Nag P, Anagnopoulos C. 2012. Association between the serotonin transporter triallelic genotype and eating problems is moderated by the experience of childhood trauma in women. *Int. J. Eat. Disord.* 45:492–500

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* 60:671–76

Thapar A, Langley K, Fowler T, Rice F, Turic D, et al. 2005. Catechol O-methyltransferase gene variant and birth weight predict early-onset antisocial behavior in children with attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiatry* 62:1275–78

Thomassin H, Flavin M, Espinas ML, Grange T. 2001. Glucocorticoid-induced DNA demethylation and gene memory during development. *EMBO J.* 20:1974–83

Touma C, Gassen NC, Herrmann L, Cheung-Flynn J, Büll DR, et al. 2011. FK506 binding protein 5 shapes stress responsiveness: modulation of neuroendocrine reactivity and coping behavior. *Biol. Psychiatry* 70:928–36

Tozzi L, Carballedo A, Wetterling F, McCarthy H, O'Keane V, et al. 2016. Single-nucleotide polymorphism of the *FKBP5* gene and childhood maltreatment as predictors of structural changes in brain areas involved in emotional processing in depression. *Neuropsychopharmacology* 41:487–97

Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, et al. 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am. J. Psychiatry* 163:28–40

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* 66:681–85

Uher R, Caspi A, Houts R, Sugden K, Williams B, et al. 2011. Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: replications and implications for resolving inconsistent results. *J. Affect. Disord.* 135:56–65

Uher R, McGuffin P. 2008. The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. *Mol. Psychiatry* 13:131–46

Uher R, Perroud N, Ng MY, Hauser J, Henigsberg N, et al. 2010. Genome-wide pharmacogenetics of antidepressant response in the GENDEP project. *Am. J. Psychiatry* 167:555–64

Vale W, Spiess J, Rivier C, Rivier J. 1981. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and β-endorphin. *Science* 213:1394–97

van der Meer D, Hartman CA, Richards J, Bralten JB, Franke B, et al. 2014. The serotonin transporter gene polymorphism *5-HTTLPR* moderates the effects of stress on attention-deficit/hyperactivity disorder. *J. Child Psychol. Psychiatry* 55:1363–71

van Winkel R. 2011. Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: sibling analysis and proband follow-up. *Arch. Gen. Psychiatry* 68:148–57

Vermeer H, Hendriks-Stegeman BI, van der Burg B, van Buul-Offers SC, Jansen M. 2003. Glucocorticoid-induced increase in lymphocytic FKBP51 messenger ribonucleic acid expression: a potential marker for glucocorticoid sensitivity, potency, and bioavailability. *J. Clin. Endocrinol. Metab.* 88:277–84

Vinkers CH, Van Gastel WA, Schubart CD, Van Eijk KR, Luykx JJ, et al. 2013. The effect of childhood maltreatment and cannabis use on adult psychotic symptoms is modified by the COMT $Val^{158}Met$ polymorphism. *Schizophr. Res.* 150:303–11

Weber H, Richter J, Straube B, Lueken U, Domschke K, et al. 2016. Allelic variation in CRHR1 predisposes to panic disorder: evidence for biased fear processing. *Mol. Psychiatry* 21:813–22

White MG, Bogdan R, Fisher PM, Munoz KE, Williamson DE, Hariri AR. 2012. FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. *Genes Brain Behav*. 11:869–78

Wochnik GM, Rüegg J, Abel GA, Schmidt U, Holsboer F, Rein T. 2005. FK506-binding proteins 51 and 52 differentially regulate dynein interaction and nuclear translocation of the glucocorticoid receptor in mammalian cells. *J. Biol. Chem.* 280:4609–16

Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, et al. 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* 66:1201–9

Young KA, Thompson PM, Cruz DA, Williamson DE, Selemon LD. 2015. BA11 FKBP5 expression levels correlate with dendritic spine density in postmortem PTSD and controls. *Neurobiol. Stress* 2:67–72

Young KD, Zotev V, Phillips R, Misaki M, Yuan H, et al. 2014. Real-time FMRI neurofeedback training of amygdala activity in patients with major depressive disorder. *PLOS ONE* 9:e88785

Zammit S, Owen MJ, Evans J, Heron J, Lewis G. 2011. Cannabis, COMT and psychotic experiences. *Br. J. Psychiatry* 199:380–85

Zammit S, Spurlock G, Williams H, Norton N, Williams N, et al. 2007. Genotype effects of *CHRNA7*, *CNR1* and *COMT* in schizophrenia: interactions with tobacco and cannabis use. *Br. J. Psychiatry* 191:402–7

Zannas AS, Wiechmann T, Gassen NC, Binder EB. 2016. Gene-stress-epigenetic regulation of *FKBP5*: clinical and translational implications. *Neuropsychopharmacology* 41:261–74

Zou YF, Wang F, Feng XL, Li WF, Tao JH, et al. 2010. Meta-analysis of *FKBP5* gene polymorphisms association with treatment response in patients with mood disorders. *Neurosci. Lett.* 484:56–61