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Invited review

Gene × environment vulnerability factors for PTSD: The HPA-axis

Divya Mehta [a], Elisabeth B. Binder [a,b,*]

[a] Max Planck Institute of Psychiatry, Kraepelinstrasse 2-10, 80804 Munich, Germany
[b] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, USA

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a severely debilitating psychiatric condition. Although a lifetime trauma incidence of 40–90% has been reported in the general population, the overall lifetime prevalence for PTSD ranges between 7–12%, suggesting individual-specific differences towards the susceptibility to PTSD. While studies investigating main genetic effects associated with PTSD have yielded inconsistent findings, there is growing evidence supporting the role of gene–environment (G × E) interactions in PTSD. The hypothalamus pituitary adrenal (HPA) axis is one of the main systems activated after exposure to a trauma and perturbations in this system are one of the more consistent neurobiological abnormalities observed in PTSD. Genes regulating the HPA-axis are therefore interesting candidates for G × E studies in PTSD. This article will review the concept and initial results of G × E interactions with polymorphisms in these genes for PTSD. In addition, the use of alternate phenotypes and more complex interaction models such as G × G × E or G × E × E will be explored. Finally, putative molecular mechanisms for these interactions will be presented. The research presented in this article indicates that a combined analysis of environmental, genetic, endophenotype and epigenetic data will be necessary to better understand pathomechanisms in PTSD.

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1. Introduction

The multifactorial nature of psychiatric traits imply that individual genes are likely to exert only a modest effect and that the interaction of several genes with each other and with the environment determine the end phenotype (Newton-Cheh and Hirschhorn, 2005). Studies investigating gene–environment (G × E) interactions aim at assessing the joint contribution of genetic and environmental factors for developing a specific disorder. Unlike other genetic approaches which assume a direct relationship between genes and the psychiatric disease, G × E studies incorporate information about the environment and assume that the susceptibility to environmental pathogens is moderated by genetic factors.

In the broad sense, G × E interactions indicate any form of interplay between genetic and environmental components. This includes true statistical and biological G × E interactions in which genetic or environmental effects are moderated by each other, additive G + E models with independent contributions of environmental as well as genetic factors and finally G–E correlations, in which genetic factors influence the exposure to but not the consequences of trauma. Among these different models, studies of G × E interactions have gained the most interest since epidemiological studies suggest that for multifactorial traits the relationships between risk factors are always likely to be greater than additive. For these complex disorders usually none of the risk factors are either essential or sufficient to cause the phenotype by itself and additive patterns of established risk factors have been shown to be prevalent in psychiatric disorders (Clarke et al., 2009; van Os et al., 2008).

Twin, family and adoption studies suggest an interplay between genetic and environmental factors for the pathogenesis of psychiatric disorders, especially mood and anxiety disorders (Merikangas and Swendsen, 1997). This is reflected by the absence of strong main genetics effects for these disorders as apparent from the latest large meta-analyses of genome-wide association data for major depression (Wray et al., 2010). While epidemiological and family data have long advocated the importance of G × E in psychiatric disorders (Cadoret et al., 1995; Kendler and Eaves, 1986), studies investigating these interactions on a molecular level have only been published since 2003.

The first study evaluating specific G × E interactions in psychiatric disorders investigated a functional polymorphism in the promoter region of the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) (Caspi et al., 2002). The authors reported that maltreated children with a MAOA genotype conferring low levels of the MAOA enzyme and

* Corresponding author. Max Planck Institute of Psychiatry, Kraepelinstrasse 2-10, 80804 Munich, Germany. Tel.: +49 89 30622 301; fax: +49 89 30622 605.
E-mail address: binder@mpipsykl.mpg.de (E.B. Binder).

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thus higher monoamine activity developed conduct disorder, antisocial personality, and violent criminality in adulthood more often than maltreated children with a high-activity MAOA genotype. Most importantly, no main effect of this polymorphism was found. This report highlighted the importance of assessing gene–environment interactions in psychiatry and was followed by a plethora of gene–environment studies in a range of psychiatric disorders including depression, suicide, antisocial behaviour and post-traumatic stress disorder (PTSD) (Caspi and Moffitt, 2006).

2. Relevance of gene–environment (G × E) interactions in PTSD

Post-traumatic stress disorder is a severely debilitating psychiatric condition characterised by persistent symptoms of intrusive re-experiencing, avoidance and hyperarousal following exposure to a traumatic event. PTSD is an ideal candidate for G × E studies: first, PTSD is the only disorder within the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) which requires the exposure to an environmental trigger in the form of a trauma as a prerequisite for its diagnosis. Second, although a lifetime trauma incidence of 40–90% has been reported in the general population, the overall lifetime prevalence for PTSD ranges between 7–12%, indicating a high variability in the long term effects of trauma (Breslau, 2001; Kessler et al., 1995). Third, the dysregulation of neurobiological pathways activated following exposure to a traumatic event is thought to contribute to the pathophysiology of PTSD, offering a number of candidate genes for G × E studies (Delahanty, 2008). Finally, the heterogeneity of the biological response to and the long term effects of trauma could in part be mediated by pre-existing individual differences in personality, cognitive abilities and other autonomic physiological factors which are all known to be under genetic influence (Koenen et al., 2003a, b; Plomin et al., 2001; Stein et al., 2002b; True et al., 1993).

In addition to requiring exposure to a traumatic event, several studies have now shown that the type, timing, intensity and duration of the trauma are important in determining the susceptibility for this disorder. Among war soldiers, a dose-response relationship of longer combat duration or higher combat intensity was associated with increased PTSD risk (Goldberg et al., 1990; Green et al., 1990). Furthermore, victims of sexual assault and violent crimes have a higher risk of developing PTSD compared to victims of accidents and natural disasters (Breslau et al., 1998; Prigerson et al., 2001). In addition, exposure to early trauma has also been shown to strongly increase the susceptibility to develop PTSD as adults (Yehuda et al., 2010), further underlining the complex interaction of environment exposures and the importance of a detailed assessment of trauma exposure in PTSD research and by extension in G × E studies in this disorder.

Twin and family studies conducted mostly in war veterans showed that PTSD is influenced by genetic factors and demonstrated a genetic vulnerability to PTSD independent of the effects of combat exposure and the genetic influences determining that exposure (Stein et al., 2002a). Overall, the heritability of PTSD has been estimated to be around 30% (True et al., 1993).

So far a number of studies have investigated main effects of genetic polymorphisms in candidate genes within several neurobiological systems including the hypothalamic pituitary adrenal (HPA) axis, dopaminergic system, serotonergic system, noradrenergic system and neurotrophic system on the development of PTSD (Broekman et al., 2007). Most of these associations have however not been consistently replicated or were only reported in single studies with relatively small sample sizes (Caspi et al., 2003; Gillespie et al., 2005; Hamet and Tremblay, 2005; Kendler et al., 2005; Lasky-Su et al., 2005). In contrast to these studies in which cases and controls were at most matched to exposure to a certain general traumatic event (war, natural disaster etc.), G × E studies in PTSD take a more detailed account of trauma types, timing and intensity in interaction with the genetic variant.

This article will concentrate on these G × E studies, with a focus on the role of genes within the HPA-axis in these interactions.

3. The role of the HPA-axis in stress regulation and PTSD

The HPA-axis is one of the main systems to regulate the physiological stress response in mammals (Sapolsky et al., 2000). Exposure to a stressor induces the release of corticotrophin releasing hormone (CRH) from the paraventricular nucleus in the hypothalamus, which stimulates the release of adrenocorticotrophin hormone (ACTH) from the anterior pituitary, in turn increasing the release of glucocorticoids (mainly cortisol in humans) from the cortex of the adrenal glands. Glucocorticoids act through two mostly intracellular receptors, the mineralocorticoid and glucocorticoid receptors (MR and GR, respectively). The high affinity MR is mainly implicated in the appraisal process and the acute onset of the stress response, whereas the lower affinity GR promotes adaptation to and recovery from stress. One of the main roles of activation of the GR is to promote negative feedback of the HPA-axis at each level to terminate the stress response once the exposure to the stressor has ended.

Glucocorticoid receptor signaling additionally requires numerous chaperones, accessory proteins, co-regulators and interacting transcription factors within a large molecular complex to allow transcriptional regulation of target genes (Pratt and Toft, 1997). Furthermore, the activity of CRH as well as cortisol is regulated by binding proteins, limiting the amount of free and thus active ligand.

This complex system plays a central role in the ability of an organism to cope with stress (de Kloet et al., 2005). A dysregulation of this response at any level may contribute to an enhanced vulnerability or compromised resilience to stress and thus an increased susceptibility to develop stress- and trauma-related psychiatric disorders, including PTSD.

Alterations of the HPA-axis are one of the most consistent neurobiological findings in PTSD. PTSD has been associated with a range of changes in this system, including increased activity of the CRH/CRH type 1 receptor (CRHR1) system, altered baseline cortisol levels and an increased sensitivity of the GR. Several converging studies have suggested that the alterations of GR sensitivity observed in PTSD could reflect a pre-existing vulnerability which increases the probability of developing PTSD following trauma exposure (Yehuda, 2009). In fact in a recent study, higher pre-deployment GR expression in peripheral blood cells was associated with an increased risk to suffer from PTSD after exposure to combat trauma (van Zuiden et al., 2010). These biological differences in the set-point regulation of the HPA-axis could be related to genetic factors altering the baseline response of this system or long term effects of other environmental exposures, including *in utero* environment, early life events or previous trauma exposure. The latter are most likely mediated by epigenetic modifications impacting the activity of genes regulating the HPA activity (Epstein et al., 1997; Yehuda, 2002).

3.1. Long term effects of environment on HPA-axis regulation

Altered HPA-axis reactivity during pregnancy has been shown to have long lasting effects on the programming of this axis in the offsprings and these effects are mediated by epigenetic modifications in key genes regulating this axis including the GR (Meaney and Ferguson-Smith, 2010; Zhang and Meaney, 2009). This also seems to be an important factor for children of women suffering from

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PTSD (or exposed to trauma) during pregnancy. Reduced salivary cortisol levels were observed in mothers who developed PTSD after experiencing the 9/11 tragedy while they were pregnant compared to pregnant women who did not develop PTSD after experiencing the event (Yehuda et al., 2005). In addition to the mothers, the one-year old offspring of the mothers with PTSD also displayed lower salivary cortisol and the effects seemed to be more pronounced if the traumatic event had occurred before the third trimester of pregnancy. This is in line with data from descendants of Holocaust survivors with PTSD who have significantly lower urinary cortisol excretion compared to descendants of Holocaust survivors who did not develop PTSD (Yehuda et al., 2002). These descendents are also more prone to develop PTSD symptoms themselves, suggesting that *in utero* programming of the stress hormone system by PTSD related endocrine changes increase the risk to suffer from this disorder. Exposure to postnatal early adverse events is also an important risk factor for developing PTSD (Yehuda et al., 2010, 2007). Similar to prenatal stress, early life trauma has been shown to lead to long term effect on HPA-axis reactivity (Heim and Nemeroff, 2009; Tyrka et al., 2009) most likely via epigenetic mechanisms (McGowan et al., 2009; Murgatroyd et al., 2009).

3.2. Genetic effects on HPA-axis regulation

In addition to environmental factors, a number of polymorphisms in HPA-axis genes have also been shown to alter the reactivity of this axis, and by that could predispose to the risk to develop PTSD after trauma exposure. HPA-axis reactivity has been shown to be moderated by a number of genetic polymorphisms, including variants in the genes encoding the GR – NR3C1, the MR – NR3C2, the CRH binding protein – CRHBP, the CRH type 1 receptor -CRHR1 as well as FKBP5, a co-chaperone of the GR.

In the gene encoding the GR itself, a number of functional polymorphisms have been reported including the TthIII I, ER22/23EK – , N363S, BclI and GR-9β variants which have been shown to be associated with changes in GR sensitivity or altered cortisol levels (Manenschijn et al., 2009). In addition to physiological effects, these variants have also been associated with the development of psychiatric disorders. BclI carrier status, related to GR-supersensitivity, was found to be overrepresented in depressed patients in one study and associated with higher ACTH responses using a combined dexamethasone-CRH test together with significantly lower treatment response rates in another study (Brouwer et al., 2006; van Rossum et al., 2006). ER22/23EK, conferring relative GR resistance was found to be associated with major depression in a Swedish and a German cohort (van Rossum et al., 2006; van West et al., 2006).

A non-synonymous coding SNP in NR3C2 (I180V), encoding the MR has been shown to alter the response to acute psychosocial stress as measured by the Trier social stress test (DeRijk et al., 2006). In another study, the -2G/C SNP within the MR was found to be associated with lower morning plasma cortisol levels (Kuningas et al., 2007). The I180V and -2G/C SNPs are linked within a multi-SNP haplotype in the MR gene promoter region and are thought to confer differences in transcriptional activity and protein regulation (Klok et al., unpublished observations).

Polymorphisms in the gene encoding the CRH binding protein are associated not only with higher baseline ACTH levels (Binder et al., 2010) but also decreased antidepressant response to citalopram treatment, especially in patients with anxious depression. Polymorphisms in CRH type 1 receptor (CRHR1), the main receptor for HPA-axis activation have been shown to be associated with a higher reactivity in the combined dex-CRH test (Heim and Nemeroff, 2009; Tyrka et al., 2009). These polymorphisms were also shown to interact with child abuse to predict adult depression (Bradley et al., 2008; Grabe et al., 2010).

Several lines of evidence suggest that the FK506 binding protein 51 or FKBP5 is an important functional regulator of the GR-complex (Pratt and Toft, 1997; Grad and Picard, 2007). During maturation of the GR-complex, FKBP5 binds to the GR chaperone hsp90 and in this conformation, the receptor complex has lower affinity for cortisol and is less likely to translocate to the nucleus (Wochnik et al., 2005). In addition, FKBP5 may also promote the nuclear translocation of the non-active beta-isoform of the GR, thereby decreasing overall GR signalling (Zhang et al., 2008). FKBP5 expression is induced by steroids via intronic steroid response elements (Hubler et al., 2003; Hubler and Scammell, 2004; Magee et al., 2006), including glucocorticoids as part of an intracellular ultra-short negative feedback loop for GR activity (Vermeer et al., 2003). Increased transcription and translation of FKBP5 following steroid receptor activation would then reduce GR sensitivity as part of an ultra-short feedback loop. Functional polymorphisms in the FKBP5 gene have been associated with GR resistance and decreased negative feedback of the axis after exposure to a psychological stressor (Binder et al., 2008; Ising et al., 2008). All the above-mentioned polymorphisms altering HPA-axis reactivity are thus prime candidates to moderate the risk to develop PTSD.

4. Gene–environment interactions in PTSD

4.1. Gene – environment interactions on PTSD symptoms

While a number of studies have investigated the genetic underpinnings of PTSD, only 9 have formally tested gene–environmental interactions and three have tested G × E interactions on alternate PTSD phenotypes. This has recently been reviewed by Koenen et al. (2009) and is summarized in Table 1. Only two of the nine G × E studies in PTSD performed so far have reported a main effect of the interacting polymorphisms, reinforcing the importance of considering G × E interactions in PTSD.

Two of the nine G × E reports studied variants within HPA-axis candidates including FKBP5 and CRHR1. Our group assessed current PTSD and retrospective child abuse exposure in a predominantly African–American sample recruited in general medical clinics at a large urban hospital in the United States (Binder et al., 2008). In this cohort, we tested whether SNPs within the CRHR1 gene (rs110402, rs242924, and rs7209436) that had been reported to increase risk for depression after child abuse would also moderate the risk for PTSD. However, none of the 3 SNPs showed a significant main effect or interaction effect with child abuse or non–child abuse trauma exposure on PTSD symptom severity, indicating that the interaction with these polymorphisms might be specific to the development of depression (Bradley et al., 2008; Binder et al., 2004). In the same study, we identified a significant interaction of four polymorphisms within the FKBP5 gene (rs9296158, rs3800373, rs1360780 and rs9470080) with severity of child abuse to predict adult PTSD symptoms. These SNPs were all part of a previously defined functional haplotype (Binder, 2009) and the alleles associated with GR resistance and decreased negative feedback of the HPA-axis in healthy adults were the ones that conferred risk for PTSD after exposure to child abuse. These G × E interactions remained significant after controlling for non–child abuse trauma level, and severity of depressive symptoms. The moderating effects of these functional FKBP5 polymorphisms on PTSD are also supported by an earlier report, in which the same polymorphisms were shown to predict symptoms of peritraumatic dissociation in children following acute medical injury. The extent of dissociative symptoms has been shown to be a predictor for the development of post-traumatic stress disorder (Koenen et al., 2005). The significant interactions between the FKBP5 polymorphisms with child abuse to predict PTSD symptoms were

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Table 1
List of nine published G × E studies on PTSD and three published G × E studies on alternate PTSD phenotypes.

No	Year	1st author	Gene	Genetic variants	Trauma type	Environmental variables	Population	Sample size	Main genetic effects
1	2007	Kilpatrick	SLC6A4	5HTTLPR	Florida Hurricane	Hurricane and social support	Primarily Caucasian	589	No
2	2008	Binder*	FKBP5	rs4713916, rs1360780, rs3800373, rs992105, rs9296158, rs737054, rs1334894, rs9470080	Various traumas	Childhood and adult trauma	Primarily African Americans	900	No
			CHRH1	rs110402, rs242924, rs7209436					
3	2009	Koenen	SLC6A4	5HTTLPR	Florida Hurricane	Country crime rate, umemployment	Primarily Caucasian	651	No
4	2009	Xie	SLC6A4	5HTTLPR	Various traumas	Childhood adversity, adult trauma	African American, European American	1252	No
5	2009	Grabe	SLC6A4	5HTTLPR, rs25531	Various traumas	Various traumas	Caucasian	3045	No
6	2009	Xie	FKBP5	rs3800373, rs9296158, rs1360780, rs9470080	Child abuse	Childhood maltreatment	African American, European American	2427	No
7	2009	Amstadter	RGS2	rs4606	Florida Hurricane	Hurricane, social support	Primarily Caucasian	607	Yes
8	2009	Nelson	GABRA2	rs279836, rs279826, rs279858, rs279871	Various traumas	Childhood trauma	Australian	2594	Yes
9	2010	Kolassa	SLC6A4	5HTTLPR	Rwandan genocide	War and non-war related events	African	408	No

No	Year	1st author	Gene	Genetic variants	Trauma type	Alternate PTSD phenotypes	Population	Sample size
10	2005	Koenen	FKBP5	rs3800373, rs1360780	Acute medical injury	Peritraumatic dissociation (Peritraumatic Dissociative Experiences Questionnaire and PTSD Reaction Index)	African American, Caucasian	46
11	2005	Bachmann	GR	N363S, BclI, E22E, R23K, F29L, L112F, D233N, K293K	War	GR sensitivity (low dose dexamethasone suppression test and dermal vasoconstrictor assay)	Vietnamese	118
12	2008	Binder*	FKBP5	rs4713916, rs1360780, rs3800373, rs992105, rs9296158, rs737054, rs1334894, rs9470080	Various traumas	GR sensitivity (low dose dexamethasone suppression test)	Primarily African Americans	900

* Indicates same study.

recently replicated by Xie and colleagues in an independent African American cohort while the same associations were not significant in European Americans (Xie et al., 2010). While this might be related to ethnicity-specific genetic linkage disequilibrium, this could also be linked to the different severity of exposure to early trauma in the two groups. For example, the level of sexual abuse was higher in European Americans in all the genotype groups while the number of crimes witnessed or experienced was consistently higher among the African Americans. The importance of the level of trauma exposure for the interaction was already observed in our initial report, in which the interaction effects were only seen in individuals exposed to at least two types of moderate to severe child abuse, but not in individuals exposed to one type of child abuse. We have observed a parallel importance of the type and severity of early trauma exposure for interactions of CRHR1 polymorphisms on depression. In fact, interactions were strongest with physical abuse and less pronounced with sexual abuse (Heim et al., 2009). The findings underline the importance of a careful characterization of the environmental exposure in G × E studies, which will be discussed in more detail below.

Another important factor to take into account in G × E interactions are disorders with shared risk factors. PTSD and depression are often comorbid and early trauma has been shown to be a risk factor for both. PTSD and depression symptoms were highly correlated in our cohort ($R \sim 0.6$). While we did not observe significant interaction of FKBP5 SNPs with early trauma to predict depression symptoms, this has been observed in other cohorts (Worthman et al., 2010; Zimmermann et al., 2009) and would fit the hypothesis that these polymorphisms alter stress hormone response in general and are not specific to a given psychiatric disorder. It is therefore likely that other genetic or environmental risk factors contribute to define the predominance of specific psychiatric symptoms after trauma exposure in FKBP5 risk allele carriers.

Only a handful of studies have so far specifically investigated candidate genes within the HPA-axis in G × E studies for PTSD, and this certainly needs to be expanded. Furthermore, as mentioned in the introduction, G × G × E but also G × E × E effects need to be explored. Both have been reported for a functional polymorphisms in the promoter region of the serotonin transporter gene, the serotonin transporter linked polymorphic region (5-HTTLPR) which has been shown to moderate the risk for PTSD (see Table 1).

Both, social support as well as crime rate and unemployment rate modified the association between the 5-HTTLPR genotype and PTSD in victims of hurricane Kathrina. Carriers of the short risk allele were at increased risk for developing PTSD in the aftermath of hurricane Kathrina only when lacking social support (Kilpatrick et al., 2007) or in conditions of high environmental stress such as high unemployment and high neighbourhood crime (Koenen et al., 2009). These results highlight the importance of assessing not only individual-level but also group-level environmental factors in G × E studies.

The 5-HTTLPR has also been associated with G × G × E interactions, including interactions with a functional variant in the BDNF gene and the above-mentioned CRHR1 variants (Gatt et al., 2010; Yang et al., 2010). We have reported that only in absence of a protective CRHR1 haplotype, the 5-HTTLPR S allele is associated with increased depressive symptoms after exposure to moderate levels of child abuse (Ressler et al., 2009). Among individuals carrying both risk variants lower levels of child abuse severity were sufficient to cause clinically relevant symptoms of depression as compared to individuals with no risk variants or only one of the two risk variants. While G × G × E interactions have not yet been reported for PTSD, they are likely to play an important role this disorder.

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4.2. Gene – environment interactions on alternate PTSD phenotypes

Behavioural phenotypes including psychiatric disorders are complex, influenced by a number of genetic and environmental factors and sometimes difficult to measure. Therefore a number of researchers have suggested using more reliable and possibly heritable intermediate phenotypes or endophenotypes for genetic analyses of psychiatric diseases. The assumption is that such intermediate phenotypes are biologically closer to the level of gene action than the end phenotype. They are usually more reliably measured than psychiatric phenotypes and could have greater predictive power due to their quantitative nature (Gottesman and Gould, 2003). There is, however, an ongoing debate about the use of endophenotypes in psychiatric diseases and recently several assumptions about endophenotypes and criteria for evaluating the validity and utility of putative endophenotypic markers have been questioned (Bearden and Freimer, 2006). For example, the issue of specificity of endophenotypes could be a concern as a number of biological phenotypes are common to different psychiatric disorders, including changes in hippocampal volume or stress hormone reactivity. On the other hand, these shared biological abnormalities might point to the fact that our current diagnostic algorithms fail to capture biologically similar patients and using intermediate phenotype, would bring us closer to a true disease category. In addition, for a number of these biological phenotypes, it is not entirely clear whether they represent a true endophenotype in the sense of a trait marker or are a correlate of the disorder. However, it has been argued that endophenotypes that are an epiphenomenon of the trait could still be valuable in identifying risk factors for the trait although the term "biomarker" might be more appropriate for such measures (Walters and Owen, 2007).

Several alternate phenotypes have been proposed for PTSD, including increased startle response, hippocampal volume abnormalities, endocrine measures and gene expression profiles (Broekman et al., 2007; Segman and Shalev, 2003). Two studies have reported effects of HPA-axis polymorphisms on GR sensitivity in PTSD using the low-dose dexamethasone suppression test. Bachmann et al reported that only individuals suffering from PTSD and carrying the GR polymorphism Bcl1 GG genotype showed increased glucocorticoid sensitivity (Bachmann et al., 2005). This is in line with previous reports showing an enhanced GR sensitivity in GG carriers of the BclI polymorphism also in the absence of a psychiatric disorder (Bachmann et al., 2005; Panarelli et al., 1998). Similar findings were also reported for FKBP5 polymorphisms (Binder et al., 2008). Only individuals with PTSD and also carrying the FKBP5 risk alleles displayed GR super-sensitivity, while this was not the case for individuals with PTSD carrying the other FKBP5 genotype. In contrast to the findings with BclI – where the same alleles is consistently associated with GR-supersensitivity in all samples, the FKBP5 alleles associated with supersensitivity in PTSD are associated with GR resistance in healthy controls (Binder et al., 2008; Ising et al., 2008; Mehta et al., accepted).

In an ongoing study, we assessed the interaction between FKBP5 SNPs and PTSD symptoms on gene expression profiles in peripheral blood as several groups have reported peripheral blood gene expression levels to correlate with PTSD symptoms (Segman et al., 2005; Yehuda et al., 2009; Zieker et al., 2007). We identified 41 transcripts whose expression levels were significantly associated with the genotype × PTSD symptom interaction term (Mehta et al., accepted) and often showed opposite correlations with symptom severity in the different genotype groups. Their association with PTSD symptoms would thus not have been detected in the overall sample. In the genes encoding these transcripts, we could also observe an over-representation of steroid/glucocorticoid response elements, suggesting that the differential response pattern could be driven by the different endocrine findings in PTSD in individuals with opposite functional FKBP5 genotypes. In FKBP5 risk allele carriers, PTSD is associated with GR-supersensitivity (Binder et al., 2008) and thus possibly a stronger induction of GR-responsive genes. This is not the case in carriers of the opposite genotype. In fact, one of the transcripts affected by this interaction is FKBP5 itself which is a sensitive marker of GR sensitivity (Scammell et al., 2001) and had previously been reported to be differentially expressed in PTSD (Yehuda et al., 2009).

5. Possible molecular mechanism of G × E interactions within the HPA-axis in PTSD

5.1. Epigenetic mechanisms in psychiatric diseases

One important mechanism through which environmental factors can leave long term marks on DNA function is epigenetic modification (Meaney, 2010). These include DNA methylation, chromatin modification and histone deacetylation, RNA editing, RNA interference and DNA rearrangements (Costello and Plass, 2001; Hmadcha et al., 1999).

DNA methylation involves the methylation of cytosines in cytosine-guanine (CpG) dinucleotides. By DNA methylation, access of transcription factors to regulatory elements is reduced and DNA methylation is most often associated with transcriptional repression by decreasing the binding of specific transcriptional enhancers (Murgatroyd et al., 2010). DNA methylation is interpreted by a family of methyl CpG-binding domain (MBD) proteins (including MeCP2, and MBD1-4), which interact with histone deactylases as well DNA-methyltransferases to confer gene silencing. The binding of these proteins to methylated DNA also appears to be critical to maintain the DNA methylation status, as the dissociation of this complex and specifically MeCP2 has been associated with site specific de-methylation (Murgatroyd et al., 2009; Chen et al., 2003; Martinowich et al., 2003).

Recent evidence suggests that DNA methylation is one important mechanism of translating long term effects of exposure to stressful life events and could also mediate G × E interactions as allele-specific DNA methylation is a common phenomenon in a number of human tissues (Mill and Petronis, 2007).

Early experiences have been shown to induce long lasting changes in gene expression and thereby neuronal functioning (Ladd et al., 2000). In the last years, it has become clear that on a molecular level, long term effects of such environmental exposures are mediated by epigenetic changes, including most prominently DNA methylation. Early negative experience has been associated with the hyper-methylation as well as de-methylation of specific regulatory sites in key genes for stress processing including the GR as well as the neuropeptide AVP (McGowan et al., 2009; Murgatroyd et al., 2009; Weaver et al., 2004). Several mechanisms have been proposed as to how environmental stimuli can mechanistically lead to DNA methylation changes. One is the dissociation of the MBD protein MeCP2 from methylated DNA by calcium-influx dependent phosphorylation of MeCp2 as shown for the BDNF and AVP locus (Murgatroyd et al., 2009; Chen et al., 2003; Martinowich et al., 2003). The other could be related to increased cortisol release in response to negative stressors. In fact, the group of T. Grange has shown that binding of the GR to glucocorticoid response element (GRE) can lead to demethylation of CpGs around these GREs and by that to changes in transcriptional regulation. This GR-activation mediated de-methylation is an active process involving DNA-repair mechanisms. The associated transcriptional regulation is likely mediated by inducing chromatin-structure changes of the locus in question (Kress et al., 2006; Thomassin

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et al., 2001). In fact, a recent publication has shown that trauma burden in patients with PTSD is negatively associated with DNA methylation in whole blood in a number of genes related to immune-function (Uddin et al., 2010). Trauma or PTSD-related epigenetic changes are therefore likely to affect a number of genes.

5.2. Possible role of epigenetic modifications as a mediator of G × E interactions in PTSD: FKBP5 as an example

As stated above, FKBP5 is a negative regulator of GR activity and FKBP5 mRNA and protein are induced after GR activation, providing an ultra-short negative feedback loop on GR-activity. FKBP5 induction by GR activation and the regulation of GR sensitivity by FKBP5 seem to be present in a number of tissues, including the brain (Scharf et al., 2011). Given the central importance of negative feedback of the HPA-axis to recover from stress, genetic polymorphisms that affect this interaction, such as functional polymorphisms in FKBP5, could be important moderators of the impact of stress exposure. Several years ago, common single nucleotide polymorphisms (SNPs) in FKBP5 have been identified that are associated with FKBP5 protein expression as well as a differential induction of FKBP5 mRNA by GR activation in peripheral blood cells (Binder et al., 2004). In line with the described function of FKBP5, these polymorphisms are also linked to differences in GR sensitivity most likely by altering the described ultra-short feedback loop. In fact, in healthy controls, the alleles associated with a stronger induction of FKBP5 by GR-activation are also associated with a relative GR resistance (Binder et al., 2008). This baseline difference in GR sensitivity seems to lead to differential activation of the stress hormone axis when confronted by a stressor. In fact, healthy controls homozygous for the high induction alleles show significantly slower recovery of stress-related increases in cortisol levels as well as more anxiety symptoms in the recovery phase than healthy controls with the other genotypes (Ising et al., 2008). In addition, the same alleles are also associated with higher cortisol reactivity in infants and interact with parent-child attachment in early life to predict stress hormone activity in infants (Luijk et al., 2010). Infants with insecure attachment and the high-induction alleles show higher cortisol reactivity than infants with insecure attachment and homozygous for the other allele.

The FKBP5 alleles associated with higher risk for PTSD symptoms following exposure to early trauma are also the ones associated with stronger induction of FKBP5 by GR activation and lead to an impaired negative feedback of the stress response by increasing GR resistance via an ultra-short negative feedback loop. One could therefore speculate that FKBP5 alleles increase the risk for stress-related psychiatric disorders due to a slower return to base-line of stress-induced cortisol levels and thus a prolonged exposure to glucocorticoids. It has been shown that glucocorticoid receptor activation as well as early trauma can induce long-term epigenetic changes (Meaney, 2010). In fact, Lee and colleagues (Lee et al., 2010) have shown de-methylation of intronic GREs within the mouse *fkbp5* locus following chronic corticosterone exposure. Interestingly, these changes were seen both in DNA from peripheral blood as well as brain tissue. These changes in GRE DNA methylation could then lead to chromatin structure changes and alter the proposed tri-dimensional interaction which involves the several GREs within the *FKBP5* locus and thereby GR-induction of FKBP5 transcription. The pattern of DNA-demethylation in CG dinucleotides surrounding steroid response elements after glucocorticoid exposure fits well with the above described epigenetic changes following GR activation (Kress et al., 2006; Flavin et al., 2004). One could hypothesize that risk allele carriers exposed to early trauma experience a prolonged activation of the GR as more FKBP5 is induced. This could then lead to specific epigenetic changes that are seen to a greater extent in risk allele carriers. These epigenetic changes could then in turn interfere with the GR/FKBP5 ultra short feedback loop and thus the regulation of the stress hormone system following environmental stimuli (Fig. 1). This might explain why we observe relative GR resistance in healthy risk allele carriers but GR-

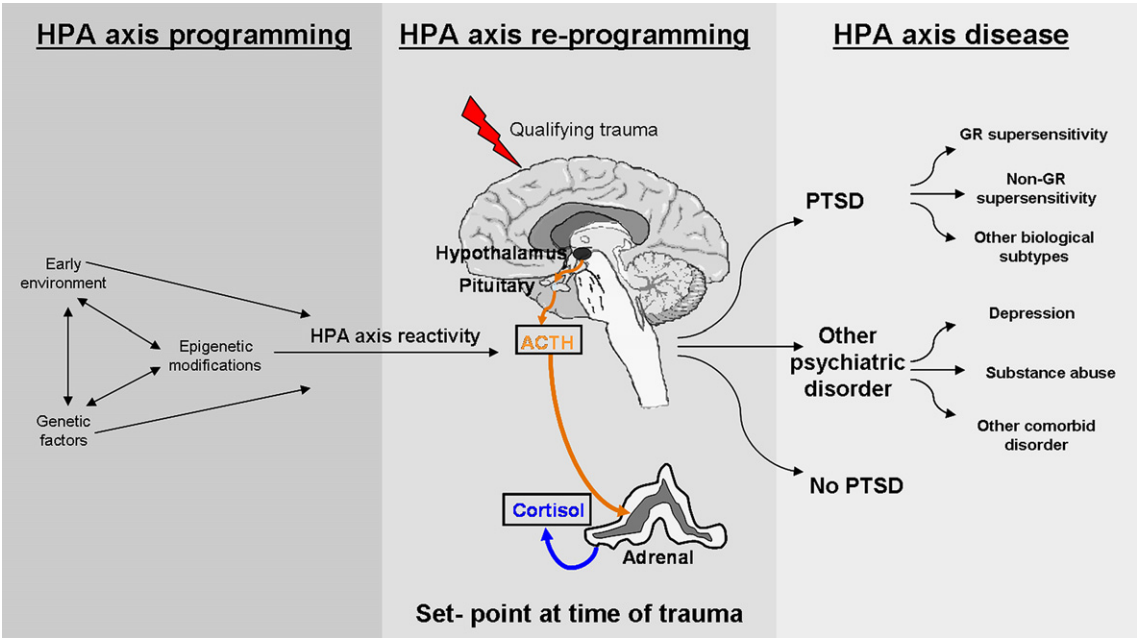

Fig. 1. Genetic susceptibility factors (such as FKBP5 polymorphisms), early environment (such as child abuse) and epigenetic modifications influence HPA-axis reactivity either directly or in interaction with each other. This baseline HPA-axis reactivity would then determine the long-term impact of exposure to additional traumatic events. This impact will also be modulated by the number, type, duration and intensity of the traumatic event(s). These additional trauma exposures might also result in re-programming of HPA-axis reactivity. Depending on the pre-existing vulnerability and the type of additional trauma exposure, long-term effects can include a spectrum of psychiatric symptoms and symptom severity. Furthermore, individuals who develop a certain symptom pattern, such as PTSD may not be biologically identical and might exhibit distinct biological dysregulation with different underlying pathophysiological disturbances.

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supersensitivity in PTSD risk allele carriers. This prolonged cortisol exposure likely not only induces epigenetic changes in the FKBP5 locus but possibly also in a number of other GR-regulated genes. Such allele-specific differences in trauma-related methylation could also be present for other polymorphisms that alter the stress hormone response.

6. Challenges in G × E research in PTSD

There are several challenges to be considered in G × E research in PTSD. It is important to note that the G × E interactions which have been identified to date in psychiatric genetics often do occur independent of main genetic effects. In G × E interactions where no main genetic effects exist, specific environmental pathogens act as a "switch" and only in the presence of this environmental switch, the genetic component remains operative and G × E interaction occurs.

Detection of G × E interactions require larger sample sizes that the detection of main genetic effects. The identification of an interaction is reported to require at least a fourfold larger sample size than the identification of a main genetic effect of comparable magnitude (Smith and Day, 1984). Larger and well characterized samples will therefore increase the probability of detecting true G × E effects. Detection of G × G × E or G × E × E interactions will require even larger sample sizes to reach adequate power for such analyses with even smaller cell sizes. Research on the genetics of PTSD will have to follow the example of other psychiatric disorders, in which international consortia, such as the psychiatric GWAS consortium (Sullivan, 2010) cooperate to detect genetic associations in very large samples.

Meta-analyses of all published PTSD G × E interaction data might provide sufficient statistical power to uncover true interactions. These meta-analyses might, however, be challenged by heterogeneity in the types, levels and measurements of trauma exposure and other environmental variables, as previous studies have indicated the presence of interaction only with specific types and levels of trauma exposures or trauma assessment methods (Kaufman, 2010; Munafo et al., 2009). For example, a recent meta-analysis has shown that the 5-HTTLPR robustly interacts with childhood trauma and medical illness to predict depression, while this is not the case for more general life events (Karg et al., 2011). This would also explain negative results from a previous meta-analysis investigating this issue (Risch et al., 2009). Meta-analyses of G × E data might be further confounded by publication bias as negative G × E associations will usually not be considered for first publication and published G × E studies report only statistically significant interactions rather than listing additional interactions showing a trend towards significance.

Expansion of both genetic as well as environmental variables in G × E studies and inclusion of studies with different trauma types will facilitate the search for a broader range of G × E interactions in PTSD. Several environmental risk factors for PTSD including race, age, education, gender and general childhood adversity and post-trauma social support have been proposed (Brewin et al., 2000). However, unlike the reasonably well documented genome, the number and type of environmental influences or 'environome' is not well understood. Environmental factors can be complex, measured on continuous scales or might be dichotomous, time-dependent, state-dependent or multidimensional (Thomas, 2010). Uncertainties in trauma exposure assignments and other environmental factors can lead to unpredictable biases, including spurious interactions. Strategies to maximize the sensitivity and specificity of environmental factor measurements and distinguishing between group-level environmental factors and individual environmental variables could improve the likelihood of detecting a true G × E interaction (Wong et al., 2003). As with other genetic studies, replication of G × E interactions are essential to prove that the results are robust and true positives. Non-replication of G × E results might reflect true heterogeneity owing to differences in the distribution of exposures, probable individual or group-level confounders in the environmental variables or differences in exposure measurement error across studies, population stratification, inadequate sample sizes or multiple testing. For instance, Caspi and colleagues reviewed all published studies investigating the extensively studied interaction between the S allele of 5-HTTLPR and stressful environment resulting in depressive symptoms (Caspi et al., 2010). The authors noted that all studies using objective indicators or personal interviews to assess stress exposure yielded positive replications of the G × E interaction while almost all non-replications were based on brief self-reported measures of stress.

Some G × E interactions might be population-specific and validation in other cohorts is preferable. Population stratification needs to be controlled for to ensure that reported G × E interactions are not false positives due to systematic differences in ancestry.

Confounding due to a correlation between the genetic and environmental risk factors might be misinterpreted if the factors are considered as independent. This so-called gene–environment correlation is a fundamental issue in behavioural genetic research and might impede proper interpretation of G × E interactions if not accounted for (Eaves et al., 2003). For example, a GABRA2 gene polymorphism was found to be associated with alcohol dependence and marital status (Edenberg et al., 2004). Individuals carrying the high-risk GABRA2 variant were less likely to be married, partly because they were at higher risk for antisocial personality disorder and were less likely to be motivated by a desire to please others (Dick et al., 2006).

Comorbidity between PTSD and other psychiatric diseases as well as a shared genetic risk for these disorders can be a major confounder in G × E interaction studies. The use of biological measures specific to a psychiatric disorder, if present, could help to discern whether associations are specific to a disorder or shared among disorders with a set of common risk factors. For instance, Ressler et al., (2011) have recently shown that SNPs within the receptor for pituitary (PACAP) were significantly associated with PTSD symptoms only but not with the severity of depression symptoms or life-time substance abuse. Furthermore these same SNPs were also associated with impaired fear inhibition as measured in a startle paradigm which has previously been shown to be a specific biomarker of PTSD but not depression symptoms (Jovanovic et al., 2010).

Finally, one must keep in mind that no inference towards biological causality can be made from G × E interactions as these are based on statistical observations only. Additional functional studies are required to confirm biological mechanisms of G × E actions.

7. Conclusions and future perspectives

The long-standing assumption that gene–environment interactions were so rare or so marginal that they could safely be ignored in behavioural genetic analyses was found to be unrealistic (Zammit et al., 2010). Compared to other complex traits, search for vulnerability factors for psychiatric diseases has been more challenging. In the context of psychiatric diseases, G × E interactions present a new frontier for identification of risk factors. Gene-environment interactions can shed light on fundamental biological processes and aid in risk prediction and evaluation of beneficial changes in adaptable environmental exposures. In addition, the knowledge of specific G × E interactions in PTSD would allow targeting preventions and therapeutic interventions in high-risk groups.

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G × E studies of PTSD will help to uncover specific genetic and environmental conditions that influence the susceptibility to PTSD and to unravel neurobiological pathways which will allow better understanding of the different biological mechanisms underlying development of PTSD. In addition to traditional candidate gene approaches for G × E studies in PTSD, genome-wide, pathway-driven and systems biology approaches will be future tools for testing biological hypothesis and inferring causal pathways involved in the aetiology of PTSD. Moreover, the use of intermediate processes or endophenotypes such as gene expression profiling, neuroimaging, electrophysiology or neuroendocrinology in PTSD might facilitate discovery of additional G × E effects which otherwise might not be captured. This may allow the identification of biologically distinct subsets of patients with PTSD which could provide a valuable tool for improving our mechanistic, diagnostic, and therapeutic approaches to PTSD.

Epigenetic modulations of gene expression changes in PTSD are one possible mechanism of G × E actions and will certainly be a central component of PTSD research. Epigenetic pattern in peripheral blood, together with other biomarkers may also allow an integrated view of the combined risk due to genetic predisposition and environmental exposure. These molecular, physiological and biological patterns can then help to find optimal individualized treatment and prevention options.

Conflict of interest statement

The authors declare no conflicts of interest. There were no commercial sponsors or commercial relationships related to the current work. All additional past and present financial ties of the investigators are disclosed herein.

Mehta, Divya – nothing to disclose.

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