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Risk and Resilience: Genetic and Environmental Influences on Development of the Stress Response

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Abstract

Exposure to stressful events during development has consistently been shown to produce long-lasting alterations in the hypothalamic-pituitary-adrenal (HPA) axis, which may increase vulnerability to disease, including PTSD and other mood and anxiety disorders. Recently reported genetic association studies indicate that these effects may be mediated, in part, by gene x environment (GxE) interactions involving polymorphisms within two key genes, *CRHR1* and *FKBP5*. Data suggest that these genes regulate HPA axis function in conjunction with exposure to child maltreatment or abuse. In addition, a large and growing body of preclinical research suggests that increased activity of the amygdala-HPA axis induced by experimental manipulation of the amygdala mimics several of the physiological and behavioral symptoms of stress-related psychiatric illness in humans. Notably, interactions between the developing amygdala and HPA axis underlie critical periods for emotional learning which are modulated by developmental support and maternal care. These translational findings lead to an integrated hypothesis: high levels of early life trauma lead to disease through the developmental interaction of genetic variants with neural circuits that regulate emotion, together mediating risk and resilience in adults.

Keywords

Post-traumatic Stress Disorder; Depression; socioeconomic status; Trauma; Child Abuse; Childhood Maltreatment; amygdala

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Epidemiological and clinical research studies have consistently identified exposure to trauma and neglect during early life as a major adverse influence on adult risk for mood and anxiety disorders (Chapman et al 2004; Dube et al 2001; Felitti et al 1998; Gladstone et al 2004; McCauley et al 1997). The parallel study of individuals who emerge from such adverse environments without significant mood or anxiety disorder (Rutter 2006) has resulted in the identification of psychosocial and biological variables associated with psychological resilience (Feder et al 2009). As with, environmental variables, predisposing genetic factors also influence vulnerability (Stein et al 2002; Sullivan et al 2000) and resilience (Rijsdijk et al 2003) in terms of aggregate risk for mood and anxiety disorders such as post-traumatic stress disorder (PTSD) and depression. However, the relationship

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between individual genetic variability and exposure to positive and negative life events as translated to risk for depression and PTSD remains unclear (Figure 1).

To examine the relationship between genetic and environmental risk factors for depression and PTSD in more depth, our research group has recently focused on candidate genes related to the hypothalamic-pituitary-adrenal (HPA) axis, a collection of neural and endocrine structures that facilitate the adaptive response to stress. Briefly, parvocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus project to the median eminence where they secrete corticotrophin-releasing hormone (CRH) into the primary plexus of blood vessels that comprise the hypothalamo-hypophyseal portal system (Swanson et al 1983). The secreted CRH is subsequently transported to the anterior pituitary gland where it activates CRH_1 receptors on pituitary corticotrophs resulting in increased secretion of adrenocorticotrophic hormone (ACTH). ACTH released from the anterior pituitary into the systemic circulation stimulates the production and release of cortisol from the adrenal cortex. Feedback inhibition, mediated in part by activity of cortisol on mineralocorticoid and glucocorticoid receptors at the hippocampus, PVN, and pituitary (de Kloet et al 1991) reduces stress-induced activation of the HPA axis and limits excess secretion of glucocorticoids effectively dampening the stress response (Jacobson and Sapolsky 1991).

Elements of the HPA axis have previously been implicated in the physiological and pathological regulation of stress reactivity (Heinrichs and Koob 2004) and elevated cerebrospinal fluid (CSF) concentrations of CRH have repeatedly been reported in patients with depression (see e.g., Hartline et al 1996; Nemeroff et al 1984), as well as in combat veterans with PTSD (Baker et al 1999; Bremner et al 1997). In addition, several studied have found data indicating that the transcription (Raadsheer et al 1995) as well as expression (Raadsheer et al 1994) of CRH may be increased in postmortem tissue in patients with depression. Further, postmortem studies of individuals who have committed suicide have revealed elevated concentrations of CSF CRH (Arato et al 1989), decreased expression of CRH_1 receptor mRNA within the frontal cortex (Merali et al 2004), increased CRH concentrations and decreased density of CRH receptors within the frontal cortex in comparison to controls (Merali et al 2006; Nemeroff et al 1988).

Developmental Trauma, CRH, and Depression

The experience of child abuse appears to pathologically alter the function of the HPA axis (Heim et al 2008b). Depressed patients who have a history of childhood adversity show elevated secretion of adrenocorticotrophic hormone (ACTH) and cortisol in response to a laboratory stress test (Heim et al 2000), as well as with neuroendocrine challenge tests including the dexamethasone-CRF test (Heim et al 2008a; Heim et al 2001). More recently reported data (McGowan et al 2009) identified epigenetic regulation of glucocorticoid receptors (GR) in post-mortem tissue from individuals with a history of child abuse. These data indicate that trauma exposure during childhood persistently alters the endogenous stress response, acting principally upon CRH and its downstream effectors, suggesting that a gene x environment (GxE) interaction at this locus may be important in mediating the effects of childhood trauma exposure on adult risk for depression. To examine whether the effects of child abuse on adult depressive symptoms (Figure 2A) are moderated by genetic polymorphisms within the CRH receptor (CRHR1) gene, our research group recently performed an association study examining GxE interaction between genetic polymorphisms at the *CRHR1* locus and measures of child abuse on adult depressive symptomatology (Bradley et al 2008). This study was cross-sectional in design and participants were primarily low-income, African-American (>95%), men and women seeking care in the general medical care and obstetrics-gynecology clinics of an urban public hospital. The studied population reported high levels of exposure to childhood physical, sexual and

emotional abuse. Fifteen single nucleotide polymorphisms (SNPs) spanning 57kb of the *CRHR1* were examined (n = 422). We identified significant GxE interactions with multiple individual SNPS as well as with a common haplotype spanning intron 1 of the *CRHR1* locus that modify adult risk of depression in the presence of childhood trauma exposure (Figure 2B,C,D). Specific *CRHR1* polymorphisms appeared to moderate the effect of child abuse on the risk for adult depressive symptomatology but did not influence risk for adult post-traumatic stress symptomatology. These protective effects were supported with similar findings in a second independent sample (n=199). These data suggest that a GxE interaction is important for the expression of depressive symptoms in adults with *CRHR1* risk or protective alleles who have a history of child abuse.

In addition to the above findings, there have been several additional reports of *CRHR1* polymorphisms associated with depression and suicidality (Licinio et al., 2004; Liu et al., 2006; Wasserman et al., 2007; and Utge et al., 2009). Although these reports have not all used the same SNPs, several have found main effects for depressive symptomatology or antidepressant response. Licinio et al., (2004) examined the association of *CRHR1* genotypes with the phenotype of antidepressant treatment response in 80 depressed Mexican-Americans in Los Angeles who completed a prospective randomized, placebo lead-in, double-blind treatment of fluoxetine or desipramine, with active treatment for 8 weeks. They found that a haplotype consisting of single-nucleotide polymorphisms rs1876828, rs242939 and rs242941 was associated with a greater antidepressant treatment response. These findings were generally supported by Liu and colleagues (2007), who also found a main effect of *CRHR1* haplotype status with major depression frequency in a Chinese cohort (Liu et al., 2006). Wasserman and colleagues (2008–9) demonstrated in family trios with suicide attempter offspring (N=672) that *CRHR1* polymorphisms (particularly rs4792887) were associated with suicide attempt history as a function of depression. Child abuse history was not reported in these studies. However, the extremely strong predictive value of history of child maltreatment for adult depression, suicide risk, and response to treatment suggests that stratification of these cohorts for child abuse may reveal interesting additional effects of *CRHR1* on depressed phenotypes.

Fear Learning and CRH: Rodent Studies

Classical fear learning (Pavlovian fear conditioning) in animals has provided great insight into the mammalian fear response and the hypothesized role of the amygdala in patients with PTSD is complemented by two decades of work demonstrating the amygdala's role in the learning and expression of fear in rodents (Davis, 1989; LeDoux, 2000; Maren, 2008). Within the brain, the amygdala appears to function as one component of a threat-responsive comparator system that acts to differentiate threatening from non-threatening environmental stimuli in real time on the basis of prototype matching to fear memories and initiate adaptive behavior to deal with any perceived threat (Bishop, 2008; Rodigues et al., 2009). Preclinical studies indicate that persistent hyperactivity of the HPA axis following developmental stress exposure is mediated, at least in part, by a hyperactive CRHR1 system (Ladd et al 2000; Lupien et al 2009; Plotsky et al 2005). In conjunction with data from functional brain imaging studies demonstrating increased activity of the amygdala in patients with depression (Drevets 2000) and PTSD (Hull 2002), these findings raise the question of whether developmental trauma exposure and fear-learning might adversely impact function of the HPA axis through effects at the level of the amygdala.

A persistent finding in patients with depression is the elevation in the numbers of CRH and arginine-vasopressin neurons in the PVN in comparison to control subjects (Purba et al 1995; Raadsheer et al 1994). Recently experiments conducted to examine CRH function in the amygdala may provide insight into these findings (Keen-Rhinehart et al 2009).

Genetically modified lentiviral vectors were introduced into the Central Nucleus of the amygdala (CeA) resulting in overexpression of CRH and arginine-vasopressin within the CeA as well as the PVN. Overexpression of CRH in these structures was accompanied physiologically by decreased glucocorticoid negative feedback, and behaviorally by increased anxiety-like behavior (acoustic startle) and depressive-like behavior (forced swim). These data suggest that unrestrained CRH synthesis in the CeA may produce dysregulation of the HPA axis, which is associated with many of the behavioral, physiological, and reproductive consequences associated with stress-related disorders.

Developmental Trauma, FKBP5, and PTSD

Increased HPA axis reactivity (Yehuda 2001; Yehuda et al 1991) and elevated GR sensitivity (Yehuda et al 2004a; Yehuda et al 2004b) are recurrent findings in patients with post-traumatic stress disorder (PTSD). FKBP5 (Figure 3) is a co-chaperone component of the GR heterocomplex (Schiene-Fischer and Yu, 2001; Binder, 2009) that plays a key role in the regulation of GR sensitivity and hence the expression of glucocorticoid-responsive genes by virtue of its participation in an ultra-short, intracellular negative feedback loop regulating GR activity (Vermeer et al 2003). Several lines of data suggest a role for *FKBP5* in the pathophysiology of PTSD. Overexpression of *FKBP5* reduces the hormone binding affinity (Denny et al 2000) and nuclear translocation of GR (Wochnik et al 2005). New world monkeys with naturally-occurring overexpression of *FKBP5* experience increased GR resistance and hypercortisolemia (Denny et al 2000; Scammell et al 2001). In addition, clinical research has identified *FKBP5* alleles associated with variation in GR resistance in depressed patients (Binder et al 2004) that are also associated with elevated peri-traumatic dissociation in medically-injured children (Koenen et al 2005), a psychological response to trauma which is predictive of PTSD risk in adults (Ozer et al 2003). Finally, level of *FKBP5* expression in peripheral blood mononuclear cells at four months post-trauma exposure is predictive of PTSD diagnosis in trauma survivors (Segman et al 2005). Most recently, gene expression analysis from a study of subjects with PTSD following the World Trade Center Attacks found that *FKBP5* showed reduced expression in PTSD, consistent with enhanced GR responsiveness (Yehuda et al., 2009).

To further evaluate the role of *FKBP5* in the etiology of PTSD, our research group examined *FKBP5* polymorphisms in association with level of adult PTSD symptomatology (Binder et al 2008). This cross-sectional study examined genetic and psychological risk factors for PTSD using a verbally-presented survey, combined with SNP genotyping, in a randomly-chosen sample of non-psychiatric clinic patients. Participants were primarily low-income, African-American (>95%), men and women seeking care in the general medical care and obstetrics-gynecology clinics of an urban public hospital. We found that this population had experienced significant levels of childhood abuse as well as non-child abuse trauma. 900 total participants were included in the overall analyses and 762 participants were included for all genotype studies. The primary outcome measure was severity of adult PTSD symptomatology, as measured with the modified PTSD Symptom Scale (mPSS). Independent factors included in the analyses were non-child abuse (primarily adult) trauma exposure and child abuse measured using the traumatic events inventory (TEI) and eight single nucleotide polymorphisms (SNPs) spanning the *FKBP5* locus.

As expected based on prior research, we found that level of child abuse (Figure 4A) and non-child abuse trauma (Figure 4B) exposure separately predicted level of adult PTSD symptoms. Although *FKBP5* SNPs did not directly predict PTSD outcome, or interact with level of non-child abuse trauma to predict PTSD, 4 SNPs in the *FKBP5* locus significantly interacted with the severity of child abuse to predict level of adult PTSD (Figure 5). This gene x environment interaction remained significant when controlling for depression

severity scores, age, gender, levels of non-child abuse trauma exposure and genetic ancestry. This genetic interaction was also paralleled by *FKBP5* genotype- and PTSD-dependent effects on glucocorticoid receptor sensitivity as measured by the dexamethasone suppression test. Collectively, these data suggest a potential gene-childhood environment interaction for adult PTSD.

Integration of Data on Variations of *CRHR1* and *FKBP5* and Childhood Abuse in Predicting Adult Mood and Anxiety Disorders

As described above, data from several genetic association studies indicate that variation in *CRHR1* and *FKBP5* may influence risk for depressive and post-traumatic stress symptoms contingent on the experience of child abuse. One possible explanation for this finding is that a critical period exists for the normative development of an emotional regulatory system. The existence of such a system would not be unprecedented as other neurobiological systems such as the visual system have critical periods whereby normal development and functioning of the system is contingent on input from the environment (Wiesel and Hubel 1963).

In support of this hypothesis, preclinical data suggest that the quality of maternal care influences an emotional critical period in rodents (Moriceau and Sullivan 2005; Moriceau and Sullivan, 2006a). Rat pups have a sensitive period during which they have an increased capacity to learn preferences for novel odors, a decreased capacity to develop odor aversion, and a generalized hypo-responsiveness to environmental stress and corticosterone release. This phenomenon is thought to facilitate close maternal attachment during the period of early postnatal development when rat pups are maximally dependent on maternal care and proximity for survival (Sevelinges et al., 2007). During the sensitive period, odor-shock pairing produces either odor preference or odor aversion depending upon the presence or absence of the mother during conditioning. Maternal absence during odor-shock pairing results behaviorally in odor avoidance and physiologically in amygdala activation and corticosterone secretion. Conversely, maternal presence during odor-shock pairing results behaviorally in odor preference without amygdala activation or corticosterone secretion (Moriceau et al., 2006b). The effect of maternal presence on preference for the shock-paired odor and suppression of corticosterone secretion and amygdala activation following odor-shock pairing may be blocked by infusion of corticosterone into the amygdala of rat pups during odor-shock pairing suggesting that corticosterone (*the rat equivalent of cortisol*) plays a central role in facilitating and defining the temporal boundaries of such an emotional critical period as it relates to fear-learning (Moriceau and Sullivan 2006a).

In relation to the *FKBP5* and *CRHR1* GxE effects discussed above, it is important to note that these two studies were obtained with subjects that were primarily impoverished, highly traumatized populations (Bradley et al., 2008; Binder et al., 2008; Gillespie et al., in press). It has been previously reported that inner-city minority populations appear to be exposed to extreme amounts of trauma (Alim et al 2006; Breslau et al 1998). In particular, economically disadvantaged African Americans living within urban environments experience high levels of trauma (Breslau et al 1991; Breslau et al 1998; Fitzpatrick and Boldizar 1993; Selner-O'Hagan et al 1998; Shakoor and Chalmers 1991) and a very large amount of this exposure occurs during youth (Fitzpatrick and Boldizar 1993; Selner-O'Hagan et al 1998; Shakoor and Chalmers 1991).

Recently, McEwen and colleagues reported that higher cortisol levels were found in children of low socioeconomic status compared to children of high socioeconomic status. Most interestingly, among this group, the child's cortisol levels correlated with the extent of maternal depressive symptomatology (Lupien et al 2000). These combined data suggest that

children of low socioeconomic status residing in urban areas with high trauma exposure are at increased risk for dysregulation of cortisol levels beginning at an early age (Shonkoff et al., 2009).

The data described above suggest that a critical period exists during which brain exposure to corticosterone affects fear learning that is modulated by the quality of maternal care. Together, this convergent series of data suggest the following hypothesis (Figure 6): During a sufficiently supported development, there develops an amygdala-dependent emotional circuit that is able to *appropriately* differentiate threatening from non-threatening environmental stimuli. In contrast, when child abuse is combined with these biological risk factors, amygdala development may be altered through interactions of elevated stress / cortisol and genetic risk / resilience factors such as described with variation in *FKBP5* or *CRHR1*. This developmental interaction may lead to an amygdala-dependent emotional circuit is altered and always *primed* for stress responsiveness. In the case of child maltreatment with combined genetic risk, this emotion circuit is *unable* to differentiate threat appropriately. Thus, in the presence of an adult trauma these individuals may be at a higher risk for PTSD or other trauma-related psychopathology, such as depression.

In summary, heritability accounts for 30–40% of the variance contributing to risk for PTSD and for other mood and anxiety disorders. It is also well known that childhood exposure to abuse and other early life adverse events increases risk for the later development of these disorders. Recent research from a number of areas suggests that childhood experiences in combination with genetic factors appear to contribute to alterations in biologically based stress response systems. Taken together, these data suggest that a greater understanding of risk, resiliency, and stress-related illness will rely on further progress in dissecting the interactions between genes and the environment during the developmental critical periods of neural circuits that underlie emotion.

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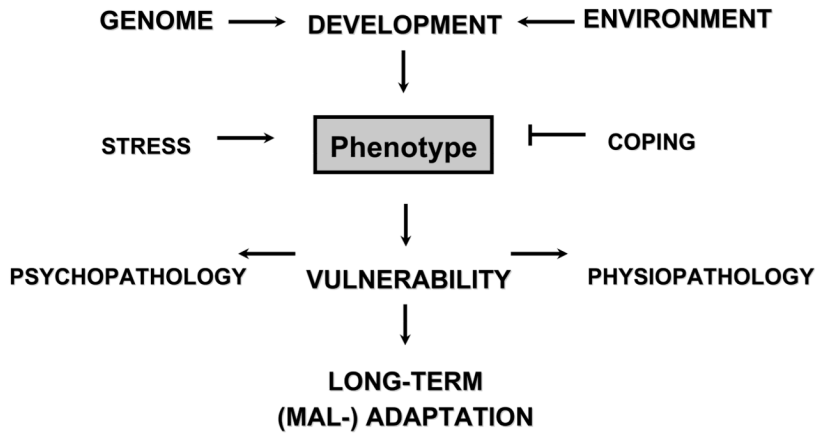

Figure 1. Schematic Diagram of Genetic and Environmental Effects on Development
Gene x environment interactions affect critical periods of emotional neural system development, differentially mediating vulnerability and resilience.

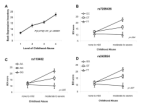

Figure 2. CRHR1 Polymorphisms Strongly Interact with Level of Childhood Abuse in the Prediction of Adult Depression

A) Level of childhood abuse by self report very strongly associates with current depressive symptoms measured with the Beck Depression Inventory. CRHR1 polymorphisms rs7209436 (B), rs110402 (C), and rs242924 (D) interact with level of reported child abuse. For all of these polymorphisms within the CRHR1 gene, at low levels of child abuse, there are similar levels of BDI-based depressive symptoms, but at moderate to severe levels of abuse, the CRHR1 SNPs separately associate with differential levels of depressive symptoms. (adapted from Bradley et al., 2008)

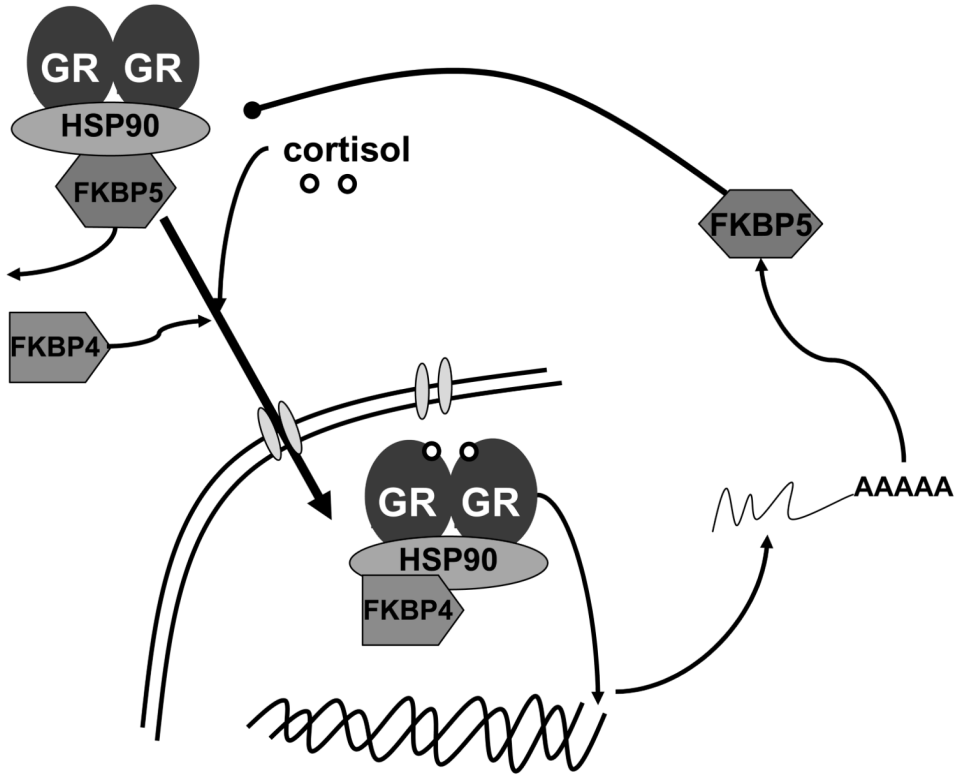

Figure 3. Schematic of FKBP5 cellular function

Schematic diagram depicting the function of FKBP5 as a co-chaperone which regulates glucocorticoid receptor (GR) binding and translocation within the nucleus. When sufficient cortisol is present leading to GR dimerization and FKBP4 binding, FKBP5 is displaced allowing GR translocation and transcriptional activation. However, one of the gene targets of GR is the FKBP5 gene, which when increased in expression is thought to act as a negative intracellular feedback on the GR system within the cell. *(figure courtesy of Elisabeth Binder, PhD)*

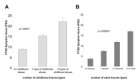

Figure 4. Child Abuse and Adult Trauma Predict PTSD symptoms

Both level of childhood abuse (number of types of physical, sexual or emotional abuse) (A) and number of types of adult non-childhood trauma (B) each predict level PTSD symptoms in the adult. (adapted from Binder et al., 2008)

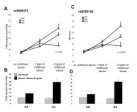

Figure 5. FKBP5 genotype interacts with level of child abuse to predict level of adult PTSD symptoms

FKBP5 polymorphisms rs3800373 (A–B), and rs9296158 (C–D) interact with level of reported child abuse to predict level of adult PTSD symptoms. For these polymorphisms within the *FKBP5* gene, at low levels of child abuse, there are similar levels of mPSS-based PTSD symptoms, but at moderate to severe levels of abuse, the *FKBP5* SNPs separately associate with differential levels of PTSD symptoms. (adapted from Binder et al., 2008)

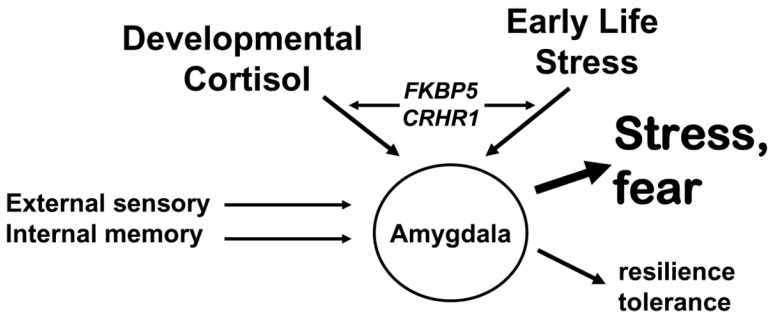

Figure 6. Early Life Stress – HPA axis Gene Interaction

This diagram represents the function of the adult *amygdala*. It continually compares neural inputs containing *external sensory* information with emotion-related *internal memory* to rapidly activate systems leading to *tolerance to aversion* and resilience vs. the fight or flight, *fear and stress* reaction. The data reviewed here suggests that with sufficiently supportive development, a dynamic amygdala-dependent emotional circuit is created allowing proper interpretation of threat responses. In contrast, child abuse combined with biological risk factors (e.g. increased stress-dependent cortisol interacting with *FKBP5* or *CRHR1* polymorphisms) may lead to an adult amygdala-dependent emotional circuit that is always 'primed' for stress responsiveness. It is hypothesized that this latter hyper-active stress response may, in the presence of adult trauma, lead to a higher risk for trauma-related psychopathology.