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A consideration of select pre-trauma factors as key vulnerabilities in PTSD

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Abstract

Posttraumatic stress disorder (PTSD) is a pathological response to a traumatic event. A number of risk and vulnerability factors predicting PTSD development have been identified in the literature. Many of these variables are specific factors occurring during and after exposure to a traumatic event or are not measured prospectively to assess temporal sequence. Recent research, however, has begun to focus on pre-trauma individual differences that could contribute to risk for developing PTSD. The present review proposes that a number of biological and cognitive vulnerability factors place individuals at risk for PTSD development prior to the actual experience of trauma. Accordingly, this review provides a summary of evidence for a select number of these factors as pre-trauma vulnerabilities to PTSD. Included is a discussion of biological factors, including molecular genetic studies of systems regulating serotonin, catecholamines, and glucocorticoids as well as aspects of the neuroendocrine system. Specific cognitive factors are also considered, including intelligence, neuropsychological functioning and cognitive biases such as negative attributional style and appraisals. For each factor, the present review summarizes evidence to date regarding PTSD vulnerability and highlights directions for future research in this area.

Keywords

PTSD; trauma; vulnerability factors; risk factors

1. Introduction

Posttraumatic stress disorder (PTSD) is a pathological response to a traumatic event such as combat, natural disasters, or physical or sexual assault. PTSD occurs in approximately eight percent of the general population in America and seven percent in Europe, with higher rates in women than in men (de Vries & Olff, 2009; Glynn, Marshall, Schell, & Shetty, 2006; Kessler, Chiu, Demler, & Walters, 2005; see Kessler & Üstün, 2008 for international prevalence estimates). PTSD results in significant social and economic burden and puts

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individuals at increased risk for physical and mental health difficulties including depression and suicide (e.g., Hidalgo & Davidson, 2000). Although epidemiological investigations indicate that as many as 74% of women and 81% of men will experience a stressful event that qualifies as a traumatic stressor according to the APA diagnostic criteria (Kessler et al., 2005; Stein, Walker, & Hazen, 1997), only a relative minority of trauma-exposed individuals goes on to develop PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; McNally, Bryant & Ehlers, 2003). This suggests that individual differences present before, during, or after trauma may be important in understanding why some individuals go on to develop PTSD while others recover naturally.

Theoretical models describing the etiology and maintenance of PTSD emphasize cognitive and affective reactivity during and after trauma exposure. For example, schema-based theories posit that incompatibility of trauma-related information with pre-existing schemas leads to the affective and cognitive symptoms of PTSD until this information can be successfully incorporated into the individual's prior conceptualization of the world (e.g., Janoff-Bulman, 1989). Associative network models such as Emotional Processing Theory (Foa, Steketee & Rothbaum, 1989) describe dysregulation in the activation, connectivity, and responsiveness of fear-related representations in memory after traumatic experiences, leading to overgeneral and hyper-activated fear reactivity (e.g., fear structures). Other cognitive theories propose that maladaptive negative beliefs emerge after trauma about the self and symptoms, the world, and others, as do problems regulating memory systems that access sensory and autobiographical memory representations (e.g., perceptual priming in Ehlers & Clark, 2000; situationally and verbally accessible memories in Dual Representation Theory, Brewin, Dalgleish, & Joseph, 1996). Each of these models can account for the relationship between PTSD and many of the known risk factors for PTSD present during and after the traumatic event. These include characteristics of the event such as trauma severity (e.g., degree of life threat) as well as personal and environmental characteristics including peri-traumatic panic and dissociation, appraisals of symptoms, and post-trauma stress and social support (e.g., Brewin, Andrews, & Valentine, 2000; Ozer, Best, Lipsey, & Weiss, 2003).

Each of these models also point to factors that exist *before* trauma that may make some individuals more prone to developing PTSD than others. For example, in schema theories, the pre-existing schema held by an individual before trauma is critical to determining whether or not trauma will lead to psychopathology. In Emotional Processing Theory some individuals are thought to have a "potentiated" fear network, making them more inclined to develop symptoms. In cognitive models such as Ehlers and Clark's cognitive model and Dual Representation Theory, there are cognitive dysfunctions that presumably have some degree of pre-trauma etiology (e.g., pre-existing beliefs about safety; inability to inhibit sensory memory). Consistent with these models, empirical data also indicate that certain pre-trauma factors increase risk for psychopathology after trauma. Pre-trauma risk factors documented in extant literature include factors such as female gender, family history of psychopathology and prior trauma exposure (e.g., Brewin et al., 2000; Ozer et al., 2003).

This proposed interplay between pre-existing characteristics, traumatic experiences, and subsequent PTSD symptoms is consistent with a diathesis-stress conceptualization of PTSD. That is, certain constitutional factors pertaining to the individual (diatheses) are thought to predispose some individuals to developing psychopathology (PTSD) in the context of severe environmental stress (trauma; McKeever & Huff, 2003). Diatheses can be categorized into biological characteristics as well as ecological characteristics. Biological components may include factors such as genetic makeup or physiological reactivity, while ecological characteristics include environmental factors (e.g., social and developmental history), as

well as psychological factors (e.g., cognitive variables, personality, pre-existing psychopathology).

Researchers evaluating risk factors for psychopathology propose that examination of *vulnerability* diathesis factors is especially critical (e.g., Ingram & Price, 2000). A vulnerability factor can be defined as an enduring, endogenous trait inherent in the individual that serves to increase the likelihood of developing a particular disorder such as PTSD (Ingram & Price, 2009). By definition, then, vulnerability factors are typically characteristics observed in the individual before the onset of stress, and exclude characteristics found in the environment or otherwise outside the individual. Vulnerability factors are thought to point to mechanisms leading to the disordered state, in contrast to general risk diathesis factors that are associated with increased probability of psychopathology without indicating a direct causal relationship. Although a substantial body of evidence documents *risk* factors for PTSD (e.g., gender), growing empirical evidence also points to a number of characteristics that may be *vulnerabilities* to PTSD. Given the role of vulnerabilities as potential mechanisms of psychopathology development, critical examination of potential vulnerability factors in PTSD may point the etiology of problematic forms of cognitive and emotional processing outlined in current models of the disorder.

The present review describes research on a subset of factors that increase the likelihood that an individual will develop PTSD. In contrast to prior reviews discussing general risk factors, we focus on evidence for vulnerabilities in PTSD. That is, the present review focuses exclusively on a number of features that are stable (i.e., existing in the individual *prior* to trauma exposure), and endogenous (i.e., individual-level characteristics, rather than environmental factors). Consistent with diathesis stress model of the disorder, we differentiate between biological and ecological vulnerabilities. Within biological vulnerabilities, we provide a review of genetic factors related to systems regulating serotonin, catecholamines, and glucocorticoids, in addition to factors related to the neuroendocrine system. Moreover, within ecological vulnerabilities we focus specifically on cognitively-based psychological factors given the emphasis of conceptual (and treatment) models on cognitions. We specifically describe extant literature on intelligence, neuropsychological functioning, and cognitive biases as potential vulnerabilities for PTSD. Thus, the following sections will provide an overview of literature on the biological and cognitive factors existing *prior* to trauma exposure that may be implicated in the etiology and maintenance of PTSD.

2. Biological Vulnerability Factors

In this section we review a number of biologically-based characteristics that are observable in the individual prior to trauma exposure (or are not mutable by on trauma exposure, such as genetic factors) and subsequently associated with increased rates of PTSD development. We discuss research examining the role of genetic factors and heritability of PTSD risk and potential gene candidates thought to confer risk for diagnosis and/or increased symptom severity. In addition, work examining the physiological stress response is discussed, including potential pathways by which more distal biological dispositions turn into dysfunctional stress response after trauma.

2.1 Heritability of PTSD risk

Family studies indicate that risk for PTSD development after trauma exposure does appear to be genetically conferred. For example, twin studies report approximately 30% of the risk for developing PTSD is accounted for by genetic factors (Koenen et al., 2008; Skre, Onstad, Torgersen, & Lygren, 1993; Stein, Jang, Taylor, Vernon & Livesly, 2002; True et al., 2003;

Xian et al., 2000, although see Sartor et al., 2011 for higher estimates). In addition, studies of offspring of parents with PTSD indicate that prevalence of PTSD is higher in these individuals than in the general population (Yehuda, Schmeidler, Giller, Siever, & Binder-Brynes, 1998; Yehuda, Schmeidler, Wainberg, Binder-Brynes, & Duvdevani, 1998). This corpus of research suggests that genetic factors confer vulnerability to the development of PTSD after a traumatic stressor at a moderate level. These studies do have important caveats, such as the overlap of genetic factors accounting for PTSD and trauma exposure and the potential role of the environment in observed effects in family studies. Moreover, these general genetic vulnerabilities do not point to the mechanisms by which risk may be conferred.

2.2. Molecular genetics studies

The molecular genetics approach evaluates the effect of specific genes on variability in an observable trait, providing more specific information about potential mechanisms of action than general family studies. Consistent with a diathesis-stress approach to understanding PTSD, recent research specifically addresses the impact of genetic influence within the context of environmental stressors, including the experience of traumatic events and stressors during development (i.e., gene x environment interactions (GxE); Koenen et al., 2009; Mehta & Binder, in press). GxE research in PTSD is proposed to be essential to understanding vulnerability and resilience after exposure to a traumatic event because it allows for direct examination of biological factors accounting for variability in response to a discrete identified stressor (Koenen, Nugent, & Amstadter, 2008). For example, one way that GxEs may confer vulnerability to PTSD is if certain genetic risk factors are “unmasked” by challenges to the individual during key developmental periods, hence altering the maturation of neural systems that control physiological and behavioral responses to stress and trauma. Here we will review the most recent findings, with an emphasis on replications of prior work when available (see also Amstadter, Nugent, & Koenen, 2009; Broekman, Olff, & Boer, 2007 for a full review of genes associated with PTSD).

2.2.1 Serotonin genes—Based on the link between monoamine and catecholamine signaling with anxiety behaviors and the efficacy of drugs facilitating release of serotonin (5-HT) and norepinephrine to treat anxiety disorders, researchers have focused on a number of genes that regulate these systems (Millan, 2003). The most well studied gene encodes the 5-HT transporter (5-HTT), which tightly regulates synaptic 5-HT levels via active reuptake at the presynaptic membrane. A common variant with differential numbers of repeats in the promoter region of this gene (termed “5HTTLPR”) alters mRNA expression levels and thus function, with carriers of the “short” form (fewer repeats) exhibiting reduced expression and in some studies showing higher risk for PTSD compared to carriers of the long version (Afifi, Asmundson, Taylor, & Jang, 2010; Kilpatrick et al., 2007; Koenen, Amstadter, & Nugent, 2009; Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010; Lee et al., 2005; although see Grabe et al., 2009; Mellman et al., 2009; Thakur, Joobar, & Brunet, 2009). Carriers of the low expression variant also exhibit reduced response to both pharmacological interventions (e.g., selective serotonin reuptake inhibitors; Lesch & Gutknecht, 2005) and cognitive behavioral therapy in PTSD (Bryant et al., 2010).

Consistent with diathesis-stress models, a number of studies demonstrate that having the low-expression variant of 5HTTLPR is associated with greater rates of PTSD, but only after exposure to high levels of stress (e.g., low social support; Kilpatrick et al., 2007 or stressful life events; Xie et al., 2009). However, the relationship between 5HTTLPR and trauma is complex, and epigenetic modification of 5HTT gene may modulate PTSD risk. One form of epigenetic modification is DNA methylation, in which the promoter region of a given gene is methylated and gene expression is thus inhibited. One study found that high methylation

(and thus less expression) potentially confers *protection* from PTSD in cases of high trauma burden (Koenen et al., 2011). This result is in opposition to the finding that carriers of the low expression 5HTTPLR allele show greater risk for development of PTSD. The 5HTTPLR variant is a fixed genetic mutation, whereas methylation changes can occur during development or even later in the life span. Thus, genetic vs. epigenetic modification of 5-HTT expression may have very different consequences on neural development and subsequent trauma risk. Taken together, there is evidence that genetic and epigenetic modulation of 5-HTT expression modifies risk for development of PTSD and this effect is dependent upon level of trauma exposure.

How reduction of 5-HTT expression alters PTSD risk is unclear, and may involve changes in maturation and 5-HT signaling in a number of brain circuits. Mice exposed to 5-HTT inhibitors exhibit increased anxiety-like behaviors in adulthood and mimicked stress-response phenotypes of mice lacking the 5-HTT gene (Ansorge, Zhou, Lira, Hen, & Gingrich, 2004). These data suggest that loss of 5-HTT function during development may be an important factor in the role of 5HTTPLR in risk for stress disorders. The low expression variant of 5HTTPLR is also associated with high reactivity in circuits underlying stress response and emotional learning, including prefrontal cortex circuits, the orbitofrontal cortex, and amygdala (Southwick, Rasmusson, Barron, & Arnsten, 2005, Milad et al., 2005, Southwick et al., 2005). Thus, hyperactivity of emotional circuits in adulthood may also play a role in increasing risk for PTSD.

2.2.2. COMT gene—Another gene that has been shown to be associated with PTSD risk is the gene encoding catechol-o-methyltransferase (COMT). COMT is an enzyme involved in the degradation of catecholamines: epinephrine, norepinephrine and dopamine. COMT mRNA is highly expressed in both prefrontal cortex and hippocampus, but has relatively low expression in striatum (Matsumoto et al., 2003). A single nucleotide polymorphism (SNP) was found in the human COMT gene (COMT-Met; Lachman et al., 1996; Tunbridge, Harrison, & Weinberger, 2006) that decreases COMT enzymatic activity by 40% in prefrontal cortex tissue (Chen et al., 2004). This diminished activity reduces the dopamine clearance in the cortex and thus increases dopamine tone (Tunbridge et al., 2006). A number of studies suggest that the effects of this COMT-Met polymorphism may be a vulnerability for PTSD. In a Ugandan refugee sample (N=424) carriers homozygous for the Met allele were found to be significantly more likely to develop PTSD after relatively few trauma exposures compared to carriers of the Val allele (Kolassa et al., 2010). This study did not find that Met carriers were any more likely to experience trauma, suggesting that this finding is not an artifact of risk for trauma exposure. This finding was recently replicated in a smaller study of urban violence victims (Valente et al., 2011) as well as in a larger study (N=502) of PTSD associated with malignant pain (Boscarino, Erlich, Hoffman, Rukstalis, & Stewart, 2011).

Although a causal link for this polymorphism with PTSD has yet to be established, carriers of the Met allele have been shown to exhibit increased brain activation in the frontal cortex, amygdala and hippocampus in response to emotional or painful stimuli (Drabant et al., 2006, Smolka et al., 2005). The COMT Met allele has also been associated with poorer fear extinction than Val carriers in healthy controls, as well as reduced response to exposure therapy in a small sample of panic disorder patients (Lonsdorf et al., 2009, 2010). Thus, one might speculate that Met carriers may have altered or “increased” function of neural circuits underlying emotion processing and memory, which could act as a vulnerability for PTSD symptoms via impaired fear extinction processes.

2.2.3 FKBP5 genes—A number of studies have begun to show that both genetic and epigenetic differences in the FKBP5 gene interact with childhood trauma to effect

vulnerability to PTSD (Binder et al., 2008; Boscarino et al., 2011; Yehuda et al., 2009, Xie et al., 2010). FKBP5 is a co-chaperone peptide that negatively regulates bound glucocorticoid receptor translocation to the nucleus, thus inhibiting glucocorticoid signaling pathways including negative feedback. Polymorphisms in the FKBP5 gene have been linked to PTSD in trauma exposed individuals (Binder, 2009; Binder et al., 2008; Xie et al., 2010). Although the specific function of these mutations is unknown, they are associated with increased glucocorticoid resistance and increased FKBP5 expression in healthy controls, which is a logical consequence of increased inhibition of glucocorticoid signaling by FKBP5 (Binder et al., 2004, 2008, Ising et al., 2008). In PTSD subjects, however, these polymorphisms are associated with increased glucocorticoid sensitivity and reduced FKBP5 expression (Binder, 2009; Mehta et al., 2011). These data suggest that trauma, perhaps via epigenetic mechanisms that alter expression of FKBP5 or other HPA axis genes, change HPA function differently across FKBP5 genotype. The only way to test such a hypothesis is via a prospective study, predicting that carriers of the FKBP5 polymorphisms will reverse to low expression following trauma exposure. A recent prospective study in the Dutch military was unable to test this hypothesis due to a low number of PTSD cases; however, they did find that *low* plasma FKBP5 expression predicted high PTSD symptoms after combat (van Zuiden, Geuze, Willemen, Vermetten, Maas, Amarouchi, Kavelaars, & Heijnen, 2011). These data are similar to findings that PTSD subjects exhibit low peripheral FKBP5 expression (Mehta et al., 2011, Yehuda et al., 2009).

Taken at face value these data suggest low FKBP5 expression predicts PTSD symptom development. One potential mechanism is through FKBP5 genotype altering HPA axis signaling and thereby impacting the maturation of key limbic circuits and/or the HPA axis directly. Or the reverse may occur, with trauma leading to developing circuits undergoing epigenetic changes in FKBP5 and related HPA axis genes that are already functionally at risk due to genetic variation, resulting in long term alteration of HPA axis signaling in these circuits.

2.2.4 Summary—Findings using genetic methodology indicate that genetic and epigenetic factors (particularly in stress response gene pathways) existing prior to the experience of traumatic stress may influence the development of PTSD. Studies of the 5-HTT, COMT and FKBP5 gene variants are the most numerous with replications of at least some findings. Importantly variance in 5-HTT, COMT and FKBP5 may not only confer risk, but also modify pharmacologic or behavioral treatment responses; however, more studies in PTSD specific populations are needed to address this important question.

How and when these genes affect stress response systems during and after trauma, or how they may act via interactions with developmental traumas is unknown. For example, it is not yet clear how differences in FKBP5 levels may interact with childhood trauma to “direct” a developmental trajectory toward increased risk. Given the plasticity of the hippocampus (which develops significantly during early childhood) and prefrontal cortex (which develops heavily during adolescence), it is possible that experiencing early life trauma at a number of developmental periods could impact the function of these circuits, with the strength of this impact being modified by certain genotypes in the stress pathway. Alternatively these genetic factors may directly increase or decrease function of a particular circuit important for fear learning or emotional regulation (e.g. COMT and 5-HTT modulation of amygdala/ frontal cortex activation and function). Animal models of 5-HTT and COMT function have been particularly helpful in establishing causal relationships between functional variants and related stress phenotypes as well as how these gene variants may alter neurocircuit development (Harrison & Tunbridge, 2008, Homberg & Lesch, 2011). Establishing functional mechanisms of these polymorphisms will be critical to understanding how these polymorphisms alter gene function and ultimately response to trauma.

2.3 Neuroendocrine Response and Vulnerability to PTSD

The hypothalamic-pituitary-adrenal (HPA) axis allows the body to respond to the experience of stress. In this system, the paraventricular nucleus of the hypothalamus secretes corticotropin releasing factor (CRF), which activates CRF receptors at the pituitary. The pituitary subsequently releases adrenocorticotrophic hormone into the blood stream, which induces the adrenal glands to induce peripheral release of cortical glucocorticoids (e.g., cortisol). Glucocorticoids act to mobilize physiological changes such as release of glucose and lipid stores and increasing immune response (Breedlove, Rosenzweig, & Watson, 2007). They are also transported to the central nervous system and act to modify neural plasticity and behavior, as well as to shut off CRF release (negative feedback). Although this response is useful for mobilizing the body's resources to cope with threat and typically terminates to return the body to homeostasis, chronic or particularly severe stressors, such as trauma, may lead to disruptions in this system. As a result, the body may be exposed to prolonged release of stress hormones and cortisol, leading to chronic inflammation and other negative consequences that can be conceptualized as "wear and tear" (referred to as allostatic load; McEwen, 2004).

Given that trauma is an extreme stressor, functioning of HPA components that regulate physiological reactions to stress may be a vulnerability to PTSD. Specifically, individuals with pre-existing tendency toward more sensitive or reactive HPA systems may demonstrate disruptions in the excretion of stress hormones or the negative feedback loop during and after the traumatic event, as well as increased hyperarousal and cognitive consequences of prolonged secretion of stress hormones. Cross-sectional literature on cortisol alterations in PTSD has been complex and somewhat inconsistent, but many findings demonstrate hypocortisolism in PTSD, such that individuals with PTSD experience lower resting levels of peripheral cortisol and enhanced negative feedback mechanisms (see Handwerger, 2009; Meewisse, Reitsma, De Vries, Gersons, & Olff, 2007; Mehta et al., 2011; Yehuda, 2006; Yehuda, Golier, Halligan, & Harvey, 2004). These reduced basal cortisol levels in PTSD may be a consequence of specific genetic backgrounds associated with PTSD discussed previously (e.g. glucocorticoid receptor and FKBP5 genotypes, see Mehta et al., 2011, van Zuiden, Geuze, Willemen, Vermetten, Maas, Amarouchi, Kavelaars, & Heijnen, 2011).

A number of longitudinal studies characterized the time course of cortisol adaptation soon after trauma to determine if cortisol response to trauma represents a vulnerability to subsequent PTSD development. These studies generally suggest that low cortisol responses early after trauma predicted increased risk for PTSD symptoms, potentially because this diminished response reflects the body's attempt to down-regulate high peri-trauma cortisol (Delahanty, Raimonde, & Spoonster, 2000; McFarlane, Barton, Yehuda, & Wittert, 2011; although see Shalev et al., 2008). Data from prospective studies also suggest that higher morning cortisol (presumably reflecting greater cortisol reactivity) prior to trauma predicts higher levels of peri-traumatic dissociation and acute stress symptoms after traumatic stress (Inslicht et al., 2011), although this finding is not consistently replicated (van Zuiden, Geuze, Willemen, Vermetten, Maas, Heijnen, & Kavelaars, 2011; van Zuiden, Kavelaars, et al., 2011; Heinrichs et al., 2005). A recent prospective study in Dutch military found that individuals with increased glucocorticoid binding capacity in leukocytes prior to military deployment were more likely to develop PTSD symptoms after combat exposure (van Zuiden, Geuze, Willemen, Vermetten, Maas, Heijnen, & Kavelaars, 2011). This same group found that reduced levels of FKBP5 also predicted PTSD symptoms (see FKBP5 section above - van Zuiden, Geuze, Willemen, Vermetten, Maas, Amarouchi, et al., 2011), suggesting that increased sensitivity to glucocorticoid signaling either via increased receptor levels or reduced negative modulation by FKBP5 confers risk for development of PTSD. Thus, although findings are still equivocal in some respects, pre-trauma features of the

individuals' HPA functioning appear to comprise one potential vulnerability factor for PTSD after experiencing trauma.

The processes involved in HPA axis alteration development are not fully understood, but the resiliency of this system is likely a function of genotype, childhood trauma, trauma burden or an interaction between these factors (Kearney, Wessler, Kaur & Lemos-Miller, 2010; McCrory, De Brito, & Viding, 2010; Meaney et al., 1996; Tarullo & Gunnar, 2006). Indeed some studies suggest that HPA axis function may change in response to trauma depending on specific genotype and past trauma history (Mehta et al., 2011). Because of the clear interaction of multiple factors on these markers, careful evaluation of genetic polymorphisms, their functional effects across subjects with and without trauma and PTSD symptoms will be the standard for future studies in the field.

How HPA axis disruption might increase risk for PTSD is another open question with an extensive animal and human literature (for review see Yehuda, 2009; Mehta & Binder, 2011). Glucocorticoid signaling facilitates fear conditioning as well as fear extinction (Steckler and Risbrough, 2011), and excess glucocorticoid signaling can severely disrupt cortical and hippocampal structure and function, which may in turn disrupt emotional regulation (Acheson, Gresack, & Risbrough, 2012; Conrad, 2008). Again, large prospective studies that cut across multiple lines of inquiry (imaging, HPA markers, cognitive assessments, stress reactivity) will be needed to untangle which markers of dysfunction precede trauma-induced PTSD symptoms and other related disruptions (e.g. cognitive function, stress response). Moreover, these studies will need to evaluate whether or not stress effects on HPA development and subsequent alterations in HPA function actually *mediates* predisposition to psychopathology in adulthood, or if other effects, such as epigenetic changes in response to developmental stress play a larger role (Yehuda et al., 2009).

3. Cognitive Vulnerability Factors

Theoretical models of PTSD suggest that biases in cognitive processing are implicated in the maintenance of symptoms (e.g., Brewin et al., 1996; Ehlers & Clark, 2000; Foa et al., 1989). Cognitive correlates of PTSD can be divided into two domains: general cognitive functioning, which includes intelligence and neuropsychological performance on non-valenced tasks, and cognitive biases, which refer to distortions in the processing of emotional information. An emerging body of literature suggests that these cognitive characteristics may exist prior to the occurrence of the traumatic event and may be implicated in the etiology of the disorder. Below we review the extant evidence for the role of general cognitive functioning and biased cognitive processing as pre-trauma vulnerabilities for PTSD.

3.1 General Cognitive Functioning

3.1.1 Intelligence—Extant data suggest a link between intelligence and PTSD symptoms after trauma (e.g., McNally & Shin, 1995; Vasterling, Brailey, Constans, & Borges, 1997). A review by Brewin and colleagues (2000) concludes that intelligence may be a vulnerability above and beyond other pre-morbid conditions that accounts for a relatively small but significant portion of the variance in PTSD development (weighted average effect size of $r = .18$). Studies consistently demonstrate that lower intelligence prior to trauma exposure predicts subsequent PTSD development. One commonly used methodology for obtaining intelligence data on individuals before trauma exposure is the use of records from military personnel who were subsequently exposed to combat or other service-related traumatic events. In these studies, pre-trauma intelligence predicted PTSD diagnosis after exposure to trauma (Boscarino, 2006; Kaplan et al., 2002; Macklin et al., 1998; Pitman, Orr,

Lowenhagen, & Macklin, 1991), even when adjusting for the extent of combat exposure (Macklin et al., 1998). The link between pre-trauma intelligence and PTSD is also supported in longitudinal studies that assess children over the course of development; these demonstrate that intelligence assessed early in childhood is subsequently associated with PTSD in adolescent (Breslau, Lucia, & Alvarado, 2006) and adulthood (Koenen, Moffitt, Poulton, Marin, & Caspi, 2007).

Evidence for the link between intelligence and PTSD is also available indirectly from studies using samples of individuals with intellectual disability. If individuals with relatively diminished intellectual functioning are more likely to develop PTSD after trauma, this group will likely have greater rates of PTSD relative to individuals with average intelligence. Consistent with this hypothesis, a recent review suggested that PTSD may be more prevalent in individuals with intellectual disability (Mevisen & de Jongh, 2010), although as the authors note environmental factors and stressors may account for this relationship. For example, daily stressors associated with lower psychosocial functioning may lead to altered stress reactivity that also differentiate those with and without disability and may be differentially associated with PTSD development after trauma.

In summary, research using diverse samples and methodologies documents intelligence as a pre-trauma vulnerability factor for PTSD, although the effect size for this relationship is modest. The mechanisms by which intelligence confers risk for PTSD have yet to be empirically examined. One hypothesis is that those with higher intelligence are better able to use effective problem solving strategies to cope with symptoms (Macklin et al., 1998). Alternatively, the relationship between intelligence and PTSD may be accounted for by executive functioning abilities (i.e., cognitive systems that allow for planning and regulating goal directed behavior, including inhibition and working memory). That is, because intelligence is highly associated with executive functioning ability (Engle, Tuholski, Laughlin, & Conway, 1999), executive functioning may actually be the underlying vulnerability. By this account, an individual's executive functioning abilities may promote more efficient cognitive reactivity to trauma, thus modulating PTSD risk (e.g., Verwoerd, Wessel, & de Jong, 2009; see section 3.1.2 below). We next turn to specific research utilizing neuropsychological assessment to examine aspects of executive functioning as potential vulnerabilities.

3.1.2 Neuropsychological Performance—PTSD is characterized by deficiencies on neuropsychological assessments of executive functioning in individuals with PTSD. For example, individuals with PTSD demonstrate diminished ability to maintain focused attention (Vasterling et al., 1998; Vasterling et al., 2002), poorer working memory performance (e.g., Leskin & White, 2007; Stein, Kennedy, & Twamley, 2002), and poorer inhibitory control (Falconer et al., 2008; Yehuda, Keefe, Harvey, & Levengood, 1995) relative to healthy individuals (for a review of cognitive functioning differences see Buckley, Blanchard, & Neil, 2000; Constans, 2005; Mathews & MacLeod, 2005).

Relative deficits in cognitive functioning in those with PTSD appear to pre-date trauma exposure. Twin studies have found that performance on neuropsychological tests in non-trauma exposed twins predicted cognitive performance in the twin with PTSD, suggesting that poor cognitive functioning is pre-existing vulnerability factor (Gilbertson et al., 2006; Kremen et al., 2007). Moreover two studies to date found that cognitive functioning assessed prior to trauma predicts PTSD. In the first, Parslow and Jorm (2007) administered a battery of neuropsychological tests to a random sample of young adults before and after the occurrence of a natural disaster. Results indicated that those with lower performance on neuropsychological assessments, including memory, working memory, and attention, assessed during the first time point prior to the disaster independently predicted greater

PTSD symptoms after the disaster. In a second study, Marx, Doron-Lamarca, Proctor, and Vasterling (2009) administered a neuropsychological assessment battery to active duty Army personnel prior to deployment and subsequently assessed psychopathology symptoms post-deployment. Results indicated that better immediate visual recall performance predicted more severe PTSD symptoms after combat exposure. Thus, in both cases neuropsychological performance predicted PTSD symptoms after trauma, although results differed in terms of the specific type of cognitive functioning that was predictive of PTSD.

Evidence using analogue methodologies also suggests that cognitive deficits may be pre-trauma vulnerability factors. In particular, the ability to control proactive interference (i.e., interference in memory for recently learned stimuli from previously learned stimuli) appears to be associated with re-experiencing symptoms after stress. For example, Verwoerd, Wessel, de Jong, Nieuwenhuis, and Huntjens (2011) demonstrated that performance on the proactive interference control index of the California Verbal Learning Test predicts re-experiencing symptoms following analogue traumatic stressors (i.e., a distressing film). Similar effects are documented in studies using other forms of proactive interference tasks in analogue samples (Verwoerd et al., 2009; Wessel, Overwijk, Verwoerd, & de Vrieze, 2008). Thus, difficulty with proactive interference control may reflect a general failure of inhibitory control processes, which may lead to greater frequency of intrusive symptoms following trauma exposure.

In summary, data from longitudinal and analogue studies to date suggests that performance on neuropsychological assessments before trauma predicts PTSD symptom severity. Although studies differed in terms of which neuropsychological tests were predictive of PTSD, methodological differences, such as sample selection and statistical procedures, may have influenced this discrepancy (e.g., analogue versus actual traumatic events, use of full neuropsychological batteries versus single tests). Nonetheless, these studies together support the hypothesis that lower neuropsychological performance, including aspects of executive functioning, is a vulnerability factor for PTSD. Moreover, this relationship may be driven by inability to regulate re-experiencing symptoms such as intrusive memories after trauma.

Recent theoretical models of cognitive functioning in PTSD propose that deficits in aspects of executive functioning may be a neurobiological vulnerability for PTSD (e.g., Koenen, 2006; Verwoerd, Wessel, & de Jong, 2009). Specifically, relatively diminished executive functioning may reflect poor prefrontal cortex functioning leading to decreased inhibition of amygdala reactivity to threat (Koenen, 2006). From a cognitive perspective, diminished executive functioning may lead to an inability to exert cognitive control over emotionally distressing thoughts and memories, reflected in greater re-experiencing symptoms (Verwoerd et al., 2009).

3.2 Cognitive biases

Another cognitive mechanism thought to contribute to PTSD is cognitive biases, including distorted or inaccurate beliefs, thoughts about one's self, the world, and others, and fear of emotional reactions. According to cognitive models, individuals with PTSD demonstrate cognitive biases that increase one's subjective sense of threat (e.g., perceptions of lack of safety in the environment) and prompt bias-consistent behavioral actions (e.g., avoidance; Foa et al., 1989; Ehlers & Clark, 2000). These biases are hypothesized to arise because individuals experience difficulty with adaptively integrating information from the traumatic experience with their understanding of the world, themselves, and other people. For example, trauma-related information may be inconsistent with positive beliefs about the safety and predictability of the world, or may be consistent with and confirm overly negative beliefs (Feeny & Foa, 2006). Cognitive biases including attributions, rumination, anxiety sensitivity, and looming cognitive style have been proposed to be vulnerability factors for

PTSD (Elwood, Hahn, Olatunji, & Williams, 2009). Guided this earlier review, below we describe evidence for cognitive biases as vulnerabilities in each of the aforementioned domains. We also describe data regarding fear of emotions more generally, in addition to negative appraisals, based on the presence of empirical studies suggesting these may constitute vulnerabilities. As part of this review we specifically discuss evidence for each bias as a pre-trauma factor, emphasizing data from prospective designs assessing each bias prior to trauma exposure when available.

3.2.1 Negative attributional style and rumination—Negative attributional style refers to an individual's likelihood of explaining events by attributing them to "internal, stable, and global" causes (Elwood et al., 2009). Rumination, or the tendency to mentally dwell on negative emotions and events, is theorized to serve an avoidance functioning by preventing the individual from cognitively processing the details of the actual traumatic stressor. Tendencies toward negative attributional style and rumination, assessed via participant self-report, have been identified in numerous cross-sectional studies of adults and children with PTSD. These studies indicate that individuals with posttraumatic stress symptoms tend to endorse less perceived control, and more global and/or stable attributions for negative events relative to those who experience no or few symptoms in adult (e.g., Ginzburg, Solomon, Dekel, & Neria, 2003) and child samples (Runyon & Kenny, 2002). The extent of this type of attributional style appears to be positively associated with symptom severity (e.g., Falsetti & Resick, 1995; Gray, Pumphrey, & Lombardo, 2003; Greening, Stoppelbein, & Docter, 2002; Joseph, Brewin, Yule & Williams, 1991; Palker-Corell & Marcus, 2004). Similarly, the tendency toward rumination about trauma-relevant information is associated with PTSD symptoms (e.g., Clohessy & Ehlers, 1999; Michael, Halligan, Clark, & Ehlers, 2007).

Longitudinal studies also suggest a relationship between cognitive biases and PTSD. Mikulincer and Solomon (1988) found that changes in attributional style after trauma (i.e., participant's self-reported increased attribution of negative personal events to stable, external and uncontrollable causes) were associated with increases in PTSD symptoms over time in a sample of war veterans. Moreover, high levels of rumination occurring after trauma predict later PTSD symptoms in adults (Kleim, Ehlers, & Glucksman, 2007; Mayou, Ehlers, & Bryant, 2002) and children (Ehlers, Mayou, & Bryant, 2003). This methodology (i.e., administering assessments closely following a traumatic event) provides additional information relative to a cross-sectional approach but is limited because it does not allow for an examination of the role of trauma exposure on the development of these types of negative attributions. To date, no published studies utilized pre-trauma assessment of these biases. In spite of this limitation, this body of evidence suggests that these types of cognitions merit further study as potential vulnerabilities, including examination of whether these biases are latent traits that are activated by trauma or stable traits present in the individual before trauma exposure.

Researchers have begun to use experimental designs to better elucidate the causal role of rumination. In these studies, the authors encourage participants to use a particular cognitive style in response to an analogue stressor to examine the effect on PTSD symptoms. Ehring, Fuchs, and Käsner (2009) asked participants to think about a negative personal experience and assigned participants to use rumination or distraction in response to that stressor (by priming rumination or distraction using items from a rumination questionnaire or distraction questionnaire, respectively). Results indicated that those using rumination continued to be distressed and have intrusive images after the stressor relative to the distraction condition. Zetsche, Ehring, and Ehlers (2009) obtained similar results using a distressing film rather than a negative personal memory. The results from these studies indicate that increasing or decreasing reliance on this type of cognitive process increases or decreases intrusive thoughts, respectively, and thus implies that rumination may be a causal factor in PTSD.

Although future work is needed in clinical samples, these data indicate that one's tendency toward rumination may be a vulnerability factor that is activated by experiencing trauma, leading to increased tendencies toward recurrent intrusive cognitions.

3.2.2 Negative appraisals—Cognitive models specifically emphasize appraisals about the self, others, and world in understanding problematic post-trauma reactions. Consistent with these theories, cross sectional studies confirm a relationship between negative appraisals and PTSD and suggest that PTSD is associated with negative beliefs about the individuals reactions during the trauma, the meaning of continued symptoms of PTSD, and subjective sense of current threat in the environment (e.g., Dunmore, Clark, & Ehlers, 1999; Engelhard, Macklin, McNally, van den Hout, & Arntz, 2001; Smith & Bryant, 2000). Longitudinal studies assessing appraisals soon after trauma also suggest that these traits increase risk for PTSD in adult (Dunmore, Clark, & Ehlers, 2001; Ehlers, Mayou, & Bryant, 1998; Ehling, Ehlers, & Glucksman, 2008; Halligan et al., 2003) and youth samples (Bryant, Salmon, Sinclair, & Davidson, 2007; Meiser-Stedman, Dalgleish, Glucksman, Yule, & Smith, 2009).

Data from studies assessing appraisals prior to trauma support the role of this factor as a vulnerability. Specifically, appraisals about the self (e.g., beliefs about one's inability to cope) prior to experiencing trauma predicted PTSD at four-year follow-up in a sample of firefighters (Bryant & Guthrie, 2007). Conversely, relatively higher evaluation of self worth prior to trauma has been associated with lower PTSD in a prospective study of police officers (Yuan et al., 2011). Taken together, these studies suggest that beliefs about the self, including appraisals about one's value or ability to cope, appear to predict PTSD symptoms even when assessed prior to the actual traumatic event. This is consistent with the proposed role of appraisals as a vulnerability factor. For example, an individual with negative beliefs about themselves may react to traumatic experiences with exaggerated predictions regarding the effects of trauma and subsequent symptoms (e.g., "I can't handle this", "if I don't control my symptoms I will go crazy"). These predictions likely drive an ongoing perception of threat combined with a sense of inability to cope, thus perpetuating anxiety symptoms (e.g., Bryant & Guthrie, 2007).

3.2.3 Fear of emotions—Recent studies document an association between PTSD and fear of emotions. Specifically, increased fear of the experience or consequences of having or expressing emotions generally is associated with greater PTSD severity (Farnsworth & Sewell, 2011; Jacupcak, Farnsworth & Sewell, 2011; Price et al., 2006; Tull et al. 2007). Specific forms of fear of emotion studied in PTSD include anxiety and disgust sensitivity (i.e., high reactivity and aversion to the experience of consequences of feeling anxiety or disgust, respectively). Anxiety sensitivity has been linked to PTSD in a number of studies in adults (for a review see Elwood et al., 2009) and children (Kiliç, Kiliç, & Yilmaz, 2008; Storr, Jalongo, Anthony, & Breslau, 2007). Elevated disgust has also been associated with PTSD in combat samples (Foy, Sippelle, Rueger, & Carroll, 1984). At least one study has indicated that disgust sensitivity interacts with peri-traumatic reactions to predict PTSD development in combat exposed military personnel (Engelhard, Olatunji, & de Jong, 2010).

Fear of emotions may also be a pre-trauma vulnerability to PTSD, rather than a cross-sectional correlate of the disorder. Koegh and colleagues (2002) assessed anxiety sensitivity before childbirth and PTSD symptoms two weeks postpartum. Results indicated that anxiety sensitivity at the prenatal assessment predicted subsequent PTSD symptoms. Marshall, Miles, and Stewart (2010) assessed the time course of anxiety sensitivity and PTSD to determine the reciprocal relationship of the two constructs after trauma. The authors assessed each variable immediately after trauma then at 6- and 12-month follow-up points in a sample of individuals with physical trauma. Results revealed that these two factors

reciprocally predict one another, suggesting that anxiety sensitivity at early time points predicts subsequent PTSD when controlling for earlier PTSD symptoms (although similar to the studies of negative appraisals and rumination, this study is limited due to the assessment of anxiety sensitivity immediately after trauma). Evidence for the role of disgust sensitivity in PTSD is more limited. However, one study using an analogue sample found that greater disgust reactivity assessed prior to viewing a distressing film predicted more re-experiencing symptoms immediately after the film (Bomyea & Amir, in press). Thus, preliminary evidence suggests that these variables may be pre-trauma factors increasing risk of PTSD development after trauma.

Continued research using longitudinal designs is needed to demonstrate that constructs pertaining to fear of emotion are present before trauma and to describe how these factors confer risk for PTSD. Nonetheless, researchers theorize that greater reactivity and aversion to bodily sensations may facilitate avoidance behaviors that exacerbate pathology after trauma (e.g., Elwood et al., 2009). In addition, negative appraisals about the ability to cope with physical sensations related to emotions (described above) may also contribute to patterns of avoidance that exacerbate symptoms (e.g., experiential avoidance; Boeschen, Koss, Figueredo, & Coan, 2001; Shenck, Putnam, & Noll, 2012).

3.2.4 Looming cognitive style—Looming cognitive style refers to the tendency for individuals to pervasively predict threat in the environment combined with the sense that this threat is rapidly increasing (e.g., Reardon & Williams, 2007). Two studies indicate that self-report of greater looming cognitive style is modestly associated with PTSD symptoms (Reardon & Williams, 2007; Williams, Shahar, Riskind & Joiner, 2005). Research documenting information processing biases in PTSD also supports the looming cognitive style hypothesis. For example, individuals with PTSD endorse interpretations of ambiguous information as relatively more threatening support the contention that a threat-biased, negative schema consistent with the looming cognitive style may be present in these individuals (e.g., Amir, Coles, & Foa, 2002; Elwood, Williams, Olatunji, & Lohr, 2007). Similarly, individuals with PTSD demonstrate attention and memory biases toward threatening information (e.g., Constans, 2005; Yehuda, Stavitsky, Tischler, Golier, & Harvey, 2005), which is consistent with the presence of a threat-biased looming cognitive style (Riskind, Williams, Gessner, Chrosniak, & Cortina, 2000).

To date, one published study suggests that information processing manifestations of a looming cognitive style may be a vulnerability factor for PTSD. Beevers and colleagues (2011) assessed attention bias using eye tracking technology in a sample of military personnel prior to combat exposure to examine whether or not attentional bias may be a vulnerability to PTSD. In the initial assessment session participants were asked to attend to pictures of emotional faces while their gaze was monitored. These participants subsequently returned completed assessments of combat exposure, PTSD, and other mental health problems while deployed. Results revealed that those who demonstrated an attentional bias away from threatening information were more likely to develop PTSD symptoms after combat. Additional evidence for attentional avoidance as a vulnerability for PTSD comes from a study by Wald and colleagues (2011), demonstrating that attentional avoidance soon after experiencing trauma predicted subsequent PTSD at 1 year follow-up.

This evidence suggests that patterns of attentional bias may constitute a vulnerability to PTSD. Although further research is needed to understand how this bias confers risk to PTSD, it is proposed that attention bias may reflect a cognitive manifestation of avoidance symptoms that are problematic in exacerbating and maintaining PTSD symptoms (e.g., Wald et al., 2011). Thus, individuals who are predisposed to use avoidance coping at the level of attention may also tend to use behavioral coping based on avoidance of perceived

threat or negative emotion. Alternatively, difficulty attending to trauma stimuli may disrupt processing of trauma-related stimuli during the event, thus leading to disruptions in memory coherence and organization that proposed to contribute to PTSD development (Brewin, 2011). However, findings require further replication and other aspect of looming cognitive style have yet to be examined empirically as a pre-trauma predictor of PTSD,

4. Summary and Conclusions

A number of intrinsic and stable traits related to an individual's biology and cognitive functioning appear to increase the likelihood of developing PTSD. Evidence to date suggests that heritable biological factors may be vulnerability factors for subsequently developing PTSD. Although the exact mechanisms of transmission of this vulnerability are not known at this time, candidates include the 5-HTT, COMT, and FKBP5 genes. There is evidence suggesting that dysregulation in HPA axis function, particularly glucocorticoid sensitivity and reduced FKBP5 expression, may be a pre-trauma vulnerability factor for PTSD. General cognitive factors including intelligence and neuropsychological functioning also appear to be pre-trauma variables that are implicated in PTSD development. Moreover, forms of cognitive biases (i.e., negative attributions, rumination, negative appraisals, fear of emotion, and looming cognitive style) appear to interact with trauma exposure to predict PTSD symptoms. Table 1 presents a summary of reviewed studies that include prospective assessment of the purported vulnerability factor of interest (or assess a factor that is not altered by trauma exposure such as genetic makeup).

One question raised by empirical data in this area is *how* these particular factors confer vulnerability to PTSD. It is important to understand the mechanisms by which each vulnerability (or vulnerabilities jointly) lead to symptoms. Based on the evidence reviewed here, a model accounting for the effect of the vulnerability factors reviewed might specify two potential pathways to PTSD development. First, many of the vulnerability factors reviewed here are directly implicated in increased anxiety reactivity. These include variables such as molecular genetic variables that modulate neurobiological bases of anxiety (e.g., amygdala reactivity), as well as neuroendocrine responses that lead to chronic hormone-based stress reactivity and autonomic arousal, and cognitive biases that perpetuate a sense of current threat (e.g., negative appraisals). Second, other vulnerability factors appear to operate in part via decreased cognitive control over trauma-related cognitions. These include factors such as proactive interference control and rumination, which appear to confer risk for PTSD by increasing the frequency of re-experiencing symptoms such as intrusive memories. In conjunction, these two pathways contribute directly to the increased anxiety reactivity and cognitive symptoms observed in those with PTSD, and may also lead to avoidance symptoms via operant conditioning processes (e.g., situations are avoided because this diminishes anxiety and triggered cognitive symptoms). Although these two pathways may be partially distinct, anxiety reactivity and cognitive control are likely interrelated and reciprocal, and some factors like operate via both mechanisms. Though plausible, empirical evidence is needed to explicitly test the hypotheses of this model and develop it further based on empirical evidence.

Moreover, research examining the interplay of the vulnerability diatheses described here with peri-traumatic factors is needed to more comprehensively model PTSD using a diathesis-stress conceptualization. Given that an individuals' response during trauma significantly impacts PTSD development (for a review of peri-traumatic risk factors see Ozer, et al., 2003), this approach may further integrate our knowledge of vulnerability factors with models of PTSD development that focus on peri- and post-traumatic reactivity. For example, biological predispositions may lead to greater anxiety and panic during trauma, leading to negative evaluations about one's reactions during trauma and more

intrusive thoughts in the aftermath of the trauma. These consequences may then contribute to negative beliefs about the world on one's coping ability as outlined by models such as Ehlers and Clark's cognitive model (2000). Alternatively, greater intrusive thoughts as a result of diminished cognitive functioning may contribute to the development and over-accessibility of fear structures noted in Foa and colleagues (1989). Similarly, understanding the interaction of vulnerability factors may allow for more accurate conceptual models of PTSD given that each individual vulnerability is like to play only a small role in overall risk for PTSD (Elwood et al., 2009). Thus, research designed to examine competing models regarding the role of various vulnerability factors is also needed to better understand the pathways to PTSD development.

From a methodological perspective, further research is critically needed in this area using prospective, longitudinal study designs. Without proper sequential sequencing of assessment points it is impossible to disentangle effects of trauma exposure on assessments of factors such as HPA axis functioning or cognitive performance. The paucity of research in this area is undoubtedly due in part to the difficulties associated with identifying a large group of individuals to assess a disorder with relatively low prevalence. Without an adequate baseline group, lack of statistical power precludes analyzing potential relationships between baseline factors and PTSD. However, identifying high risk populations who are more likely to experience trauma (e.g., police officers) offers a viable alternative, with the caveat that these populations are likely to be different from a typical representative sample on many characteristics. For example, these groups differ on characteristics such as personality (e.g., Salters-Pedneault Rueff, & Orr, 2010) that may influence development of PTSD or other psychopathology after traumatic events. Evidence supporting and generating theoretical hypotheses may also be derived from experimental and analogue study designs, particularly when conducted in conjunction with studies in clinical populations.

In spite of potential limitations in our understanding of these factors, existing research in this area provides useful clinical information. Biological and cognitive vulnerability factors known to date may be useful in identifying those at risk for developing PTSD after trauma exposure. For example, those with relatives with PTSD may have a genetic "loading" predisposing them to PTSD under intense stress through neurotransmitter regulation or altered HPA reactivity. Similarly, those with lower intelligence or neuropsychological impairments appear more prone to PTSD development. Awareness of these factors may alert clinicians to those potentially most in need of preventative efforts or early intervention after exposure to trauma.

An understanding of the pre-trauma vulnerabilities outline here may also suggest intervention approaches, particularly once the mechanisms of the vulnerabilities are established. For example, identifying vulnerability factors within a specific individual may lead to greater personalized treatment (e.g., those with strong cognitive bias vulnerabilities may be amenable to cognitive approaches). In addition, understanding how risk for PTSD is conferred by vulnerability factors has the potential to improve current treatment approaches by distilling the critical components of physiological and cognitive change necessary for treatment success. Moreover, understanding these vulnerabilities may inform development of novel treatment approaches. For example, based on data suggesting cognitive functioning may be implicated in PTSD, a number of research groups have begun examining cognitive training programs as interventions for PTSD (see author notes in this manuscript and also Schweizer & Dalgleish, 2011).

In summary, a greater understanding of vulnerability factors that exist pre-trauma are critical to better develop theoretical accounts of PTSD and, eventually, for the development of prevention programs. Though further research is needed, the extant findings suggest that

characteristics that pre-date trauma exposure operate to increase PTSD for specific individuals.

References

- Acheson DT, Gresack JE, Risbrough VB. Hippocampal dysfunction effects on context memory: Possible etiology for posttraumatic stress disorder. *Neuropharmacology*. 2012; 62(2):674–685. [PubMed: 21596050]
- Afifi TO, Asmundson GJG, Taylor S, Jang KL. The role of genes and environment on trauma exposure and posttraumatic stress disorder symptoms: A review of twin studies. *Clinical Psychology Review*. 2010; 30(1):101–112. doi:10.1016/j.cpr.2009.10.002. [PubMed: 19892451]
- Amir N, Coles ME, Foa EB. Automatic and strategic activation and inhibition of threat-relevant information in posttraumatic stress disorder. *Cognitive Therapy and Research*. 2002; 26(5):645–655. doi:10.1023/A:1020309326976.
- Amstadter AB, Nugent NR, Koenen KC. Genetics of PTSD: Fear conditioning as a model for future research. *Psychiatric Annals*. 2009; 39(6):358–367. doi:10.3928/00485713-20090526-01. [PubMed: 19779593]
- Ansorge MS, Zhou M, Lira A, Hen R, Gingrich JA. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science*. 2004; 306(5697):879–881. doi:10.1126/science.1101678. [PubMed: 15514160]
- Beevers CG, Lee H, Wells TT, Ellis AJ, Telch MJ. Association of predeployment gaze bias for emotion stimuli with later symptoms of PTSD and depression in soldiers deployed in Iraq. *The American Journal of Psychiatry*. 2011; 168(7):735–741. doi:10.1176/appi.ajp.2011.10091309. [PubMed: 21454916]
- Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology*. 2009; 34(Suppl 1; Supplement):S186–S195. doi:10.1016/j.psycheneu.2009.05.021. [PubMed: 19560279]
- Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA: Journal of the American Medical Association*. 2008; 299(11):1291–1305. doi:10.1001/jama.299.11.1291.
- Binder EB, Salyakina D, Lichtner P, Wozniak GM, Ising M, Putz B, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. *Nature Genetics*. 2004; 36(12):1319–1325.
- Boeschen LE, Koss MP, Figueredo AJ, Coan JA. Experiential avoidance and post-traumatic stress disorder: A cognitive mediational model of rape recovery. *Journal of Aggression, Maltreatment & Trauma*. 2001; 4:211–245. doi:10.1300/J146v04n02_10.
- Bomyea J, Amir N. Disgust propensity as a predictor of intrusive cognitions following a distressing film. *Cognitive Therapy and Research*. (in press). DOI: 10.1007/s10608-010-9331-1.
- Boscarino JA. External-cause mortality after psychologic trauma: The effects of stress exposure and predisposition. *Comprehensive Psychiatry*. 2006; 47(6):503–514. doi:10.1016/j.comppsy.2006.02.006. [PubMed: 17067875]
- Boscarino JA, Erlich PM, Hoffman SN, Rukstalis M, Stewart WF. Association of FKBP5, COMT and CHRNA5 polymorphisms with PTSD among outpatients at risk for PTSD. *Psychiatry Research*. 2011; 188(1):173–174. doi:10.1016/j.psychres.2011.03.002. [PubMed: 21440309]
- Breedlove, SM.; Rosenweig, MR.; Watson, NV. *Biological Psychology*. 5th ed. Sunderland, MAUSA: 2007. p. 496-498.
- Breslau N, Lucia VC, Alvarado GF. Intelligence and other predisposing factors in exposure to trauma and posttraumatic stress disorder. *Archives of General Psychiatry*. 2006; 63(11):1238–1245. doi:10.1001/archpsyc.63.11.1238. [PubMed: 17088504]
- Brewin CR. The nature and significance of memory disturbance in posttraumatic stress disorder. *Annual Review of Clinical Psychology*. 2011; 7:203–227. doi:10.1146/annurev-clinpsy-032210-104544.

- Brewin CR, Dalgleish T, Joseph S. A dual representation theory of posttraumatic stress disorder. *Psychological Review*. 1996; 103(4):670–686. doi:10.1037/0033-295X.103.4.670. [PubMed: 8888651]
- Broekman BFP, Olff M, Boer F. The genetic background to PTSD. *Neuroscience and Biobehavioral Reviews*. 2007; 31(3):348–362. doi:10.1016/j.neubiorev.2006.10.001. [PubMed: 17126903]
- Bryant RA, Felmingham KL, Falconer EM, Pe Benito L, Dobson-Stone C, Pierce KD, Schofield PR. Preliminary evidence of the short allele of the serotonin transporter gene predicting poor response to cognitive behavior therapy in posttraumatic stress disorder. *Biological Psychiatry*. 2010; 67(12):1217–1219. doi:10.1016/j.biopsych.2010.03.016. [PubMed: 20434135]
- Bryant RA, Guthrie RM. Maladaptive self-appraisals before trauma exposure predict posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*. 2007; 75(5):812–815. doi:10.1037/0022-006X.75.5.812. [PubMed: 17907863]
- Bryant RA, Salmon K, Sinclair E, Davidson P. A prospective study of appraisals in childhood posttraumatic stress disorder. *Behaviour Research and Therapy*. 2007; 45(10):2502–2507. doi:10.1016/j.brat.2007.04.009. [PubMed: 17560541]
- Buckley TC, Blanchard EB, Neill WT. Information processing and PTSD: A review of the empirical literature. *Clinical Psychology Review*. 2000; 20(8):1041–1065. doi:10.1016/S0272-7358(99)00030-6. [PubMed: 11098399]
- Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. *American Journal of Human Genetics*. 2004; 75:807–21. [PubMed: 15457404]
- Clohessy S, Ehlers A. PTSD symptoms, response to intrusive memories and coping in ambulance service workers. *British Journal of Clinical Psychology*. 1999; 38(3):251–265. doi:10.1348/014466599162836. [PubMed: 10532147]
- Conrad CD. Chronic stress-induced hippocampal vulnerability: The glucocorticoid vulnerability hypothesis. *Reviews in the Neurosciences*. 2008; 19(6):395–411. Retrieved from www.csa.com. [PubMed: 19317179]
- Constans, JI. Information-processing biases in PTSD. In: Vasterling, JJ.; Brewin, C., editors. *Neuropsychology of PTSD: Biological, Cognitive, and Clinical Perspectives*. Guilford Press; New York: 2005. p. 105-129.
- Delahanty DL, Raimonde AJ, Spoonster E. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. *Biological Psychiatry*. 2000; 48(9):940–947. [PubMed: 11074232]
- de Vries G, Olff M. The lifetime prevalence of traumatic events and posttraumatic stress disorder in the Netherlands. *Journal of Traumatic Stress*. 2009; 22(4):259–267. doi:10.1002/jts.20429. [PubMed: 19645050]
- Drabant EM, Hariri AR, Meyer-Lindenberg A, Munoz KE, Mattay VS, Kolachana BS, et al. Catechol-O-methyltransferase Val158Met genotype and neural mechanisms related to affective arousal and regulation. *Archives of General Psychiatry*. 2006; 63:1396–1406. [PubMed: 17146014]
- Dunmore E, Clark DM, Ehlers A. Cognitive factors involved in the onset and maintenance of posttraumatic stress disorder (PTSD) after physical or sexual assault. *Behaviour Research and Therapy*. 1999; 37(9):809–829. [PubMed: 10458046]
- Dunmore E, Clark DM, Ehlers A. A prospective investigation of the role of cognitive factors in persistent posttraumatic stress disorder (PTSD) after physical or sexual assault. *Behaviour Research and Therapy*. 2001; 39(9):1063–1084. doi:10.1016/S0005-7967(00)00088-7. [PubMed: 11520012]
- Ehlers A, Clark DM. A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy*. 2000; 38(4):319–345. doi:10.1016/S0005-7967(99)00123-0. [PubMed: 10761279]
- Ehlers A, Mayou RA, Bryant B. Psychological predictors of chronic posttraumatic stress disorder after motor vehicle accidents. *Journal of Abnormal Psychology*. 1998; 107(3):508–519. doi:10.1037/0021-843X.107.3.508. [PubMed: 9715585]

- Ehlers A, Mayou RA, Bryant B. Cognitive predictors of posttraumatic stress disorder in children: Results of a prospective longitudinal study. *Behaviour Research and Therapy*. 2003; 41(1):1–10. doi:10.1016/S0005-7967(01)00126-7. [PubMed: 12488116]
- Ehring T, Ehlers A, Glucksman E. Do cognitive models help in predicting the severity of posttraumatic stress disorder, phobia, and depression after motor vehicle accidents? A prospective longitudinal study. *Journal of Consulting and Clinical Psychology*. 2008; 76(2):219–230. doi: 10.1037/0022-006X.76.2.219. [PubMed: 18377119]
- Ehring T, Fuchs N, Kläsener I. The effects of experimentally induced rumination versus distraction on analogue posttraumatic stress symptoms. *Behavior Therapy*. 2009; 40(4):403–413. doi:10.1016/j.beth.2008.10.001. [PubMed: 19892085]
- Elwood LS, Hahn KS, Olatunji BO, Williams NL. Cognitive vulnerabilities to the development of PTSD: A review of four vulnerabilities and the proposal of an integrative vulnerability model. *Clinical Psychology Review*. 2009; 29(1):87–100. doi:10.1016/j.cpr.2008.10.002. [PubMed: 19008028]
- Elwood LS, Williams NL, Olatunji BO, Lohr JM. Interpretation biases in victims and non-victims of interpersonal trauma and their relation to symptom development. *Journal of Anxiety Disorders*. 2007; 21(4):554–567. doi:10.1016/j.janxdis.2006.08.006. [PubMed: 16963221]
- Engelhard IM, Macklin ML, McNally RJ, van den Hout MA, Arntz A. Emotion- and intrusion-based reasoning in vietnam veterans with and without chronic posttraumatic stress disorder. *Behaviour Research and Therapy*. 2001; 39(11):1339–1348. doi:10.1016/S0005-7967(00)00101-7. [PubMed: 11686268]
- Engelhard IM, Olatunji BO, de Jong PJ. Disgust and the development of posttraumatic stress among soldiers deployed to Afghanistan. *Journal of Anxiety Disorders*. 2010 doi:10.1016/j.janxdis.2010.08.003.
- Engle RW, Tuholski SW, Laughlin JE, Conway ARA. Working memory, short-term memory, and general fluid intelligence: A latent-variable approach. *Journal of Experimental Psychology: General*. 1999; 128(3):309–331. doi:10.1037/0096-3445.128.3.30. [PubMed: 10513398]
- Falconer E, Bryant R, Felmingham KL, Kemp AH, Gordon E, Peduto A, Olivieri G, Williams LM. The neural networks of inhibitory control in posttraumatic stress disorder. *Journal of Psychiatry & Neuroscience*. 2008; 33(5):413–422. Retrieved from www.csa.com. [PubMed: 18787658]
- Falsetti SA, Resick PA. Causal attributions, depression, and post-traumatic stress disorder in victims of crime. *Journal of Applied Social Psychology*. 1995; 25(12):1027–1042. doi:10.1111/j.1559-1816.1995.tb00615.x.
- Farnsworth JK, Sewell KW. Fear of emotion as a moderator between PTSD and firefighter social interactions. *Journal of Traumatic Stress*. 2011; 24(4):444–450. doi:10.1002/jts.20657. [PubMed: 21780188]
- Feeny, NC.; Foa, EB. Cognitive vulnerability to PTSD. In: Alloy, LB.; Riskind, JH., editors. *Cognitive vulnerability to emotional disorders*. Lawrence Erlbaum Associates Publishers; Mahwah, NJ, US: 2006. p. 285-301.
- Foa EB, Steketee G, Rothbaum BO. Behavioral/cognitive conceptualizations of post-traumatic stress disorder. *Behavior Therapy*. 1989; 20(2):155–176. doi:10.1016/S0005-7894(89)80067-X.
- Foy DW, Sippelle RC, Rueger DB, Carroll EM. Etiology of posttraumatic stress disorder in vietnam veterans: Analysis of premilitary, military, and combat exposure influences. *Journal of Consulting and Clinical Psychology*. 1984; 52(1):79–87. doi:10.1037/0022-006X.52.1.79. [PubMed: 6699251]
- Gilbertson MW, Paulus LA, Williston SK, Gurvits TV, Lasko NB, Pitman RK, Orr SP. Neurocognitive function in monozygotic twins discordant for combat exposure: Relationship to posttraumatic stress disorder. *Journal of Abnormal Psychology*. 2006; 115(3):484–495. doi: 10.1037/0021-843X.115.3.484. [PubMed: 16866589]
- Ginzburg K, Solomon Z, Dekel R, Neria Y. Battlefield functioning and chronic PTSD: Associations with perceived self-efficacy and causal attribution. *Personality and Individual Differences*. 2003; 34(3):463–476. doi:10.1016/S0191-8869(02)00066-1.
- Grabe HJ, Spitzer C, Schwahn C, Marcinek A, Frahnow A, Barnow S, et al. Serotonin transporter gene (SLC6A4) promoter polymorphisms and the susceptibility to posttraumatic stress disorder.

- The American Journal of Psychiatry. 2009; 166(8):926–933. doi:10.1176/appi.ajp.2009.08101542. [PubMed: 19487392]
- Gray MJ, Pumphrey JE, Lombardo TW. The relationship between dispositional pessimistic attributional style versus trauma-specific attributions and PTSD symptoms. *Journal of Anxiety Disorders*. 2003; 17(3):289–303. doi:10.1016/S0887-6185(02)00205-0. [PubMed: 12727123]
- Greening L, Stoppelbein L, Docter R. The mediating effects of attributional style and event-specific attributions on postdisaster adjustment. *Cognitive Therapy and Research*. 2002; 26(2):261–274. doi:10.1023/A:1014530021675.
- Halligan SL, Michael T, Clark DM, Ehlers A. Posttraumatic stress disorder following assault: The role of cognitive processing, trauma memory, and appraisals. *Journal of Consulting and Clinical Psychology*. 2003; 71(3):419–431. doi:10.1037/0022-006X.71.3.419. [PubMed: 12795567]
- Handwerker K. Differential patterns of HPA activity and reactivity in adult posttraumatic stress disorder and major depressive disorder. *Harvard Review of Psychiatry*. 2009; 17(3):184–205. [PubMed: 19499418]
- Harrison PJ, Tunbridge EM. Catechol-o-methyltransferase (COMT): A gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. *Neuropsychopharmacology*. Special Issue: Catechol-O-Methyl Transferase (COMT), Recent Findings. 2008; 33(13):3037–3045. doi:10.1038/sj.npp.1301543.
- Heinrichs M, Wagner D, Schoch W, Soravia LM, Hellhammer DH, Ehler U. Predicting posttraumatic stress symptoms from pretraumatic risk factors: A 2-year prospective follow-up study in firefighters. *The American Journal of Psychiatry*. 2005; 162(12):2276–2286. doi:10.1176/appi.ajp.162.12.2276. [PubMed: 16330591]
- Hidalgo RB, Davidson JRT. Posttraumatic Stress Disorder: Epidemiology and health-related considerations. *Journal of Clinical Psychiatry*. 2000; 61:5–13. [PubMed: 10795604]
- Homberg JR, Lesch K. Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry*. 2011; 69(6):513–519. doi:10.1016/j.biopsych.2010.09.024. [PubMed: 21047622]
- Ingram, RE.; Price, JM. Understanding psychopathology: The role of vulnerability. In: Ingram, R.; Price, JM., editors. *Vulnerability to psychopathology: Risk across the lifespan*. 2nd Edition. Guilford press; New York: 2009. p. 3-17.
- Inslicht SS, Otte C, McCaslin SE, Apfel BA, Henn-Haase C, Metzler T, et al. Cortisol awakening response prospectively predicts peritraumatic and acute stress reactions in police officers. *Biological Psychiatry*. 2011; 70(11):1055–1062. doi:10.1016/j.biopsych.2011.06.030. [PubMed: 21906725]
- Ising M, Depping A, Siebertz A, Lucae S, Unschuld PG, Kloiber S, et al. Polymorphisms in the FKBP5 gene region modulate recovery from psychosocial stress in healthy controls. *European Journal of Neuroscience*. 2008; 28(2):389–398. doi:10.1111/j.1460-9568.2008.06332.x. [PubMed: 18702710]
- Jakupcak M, Osborne TL, Michael S, Cook JW, McFall M. Implications of masculine gender role stress in male veterans with posttraumatic stress disorder. *Psychology of Men & Masculinity*. 2006; 7(4):203–211. doi:10.1037/1524-9220.7.4.203.
- Janoff-Bulman R. Assumptive worlds and the stress of traumatic events: Applications of the schema construct. *Social Cognition*. 1989; 7:113–136. Retrieved from www.csa.co.
- Joseph SA, Brewin CR, Yule W, Williams RM. Causal attributions and psychiatric symptoms in survivors of the herald of free enterprise disaster. *British Journal of Psychiatry*. 1991; 159:542–546. doi:10.1192/bjp.159.4.542. [PubMed: 1751865]
- Kaplan Z, Weiser M, Reichenberg A, Rabinowitz J, Caspi A, Bodner E, Zohar J. Motivation to serve in the military influences vulnerability to future posttraumatic stress disorder. *Psychiatry Research*. 2002; 109(1):45–49. doi:10.1016/S0165-1781(01)00365-1. [PubMed: 11850050]
- Kearney CA, Wechsler A, Kaur H, Lemos-Miller A. Posttraumatic stress disorder in maltreated youth: A review of contemporary research and thought. *Clinical Child and Family Psychology Review*. 2010; 13(1):46–76. doi:10.1007/s10567-009-0061-4. [PubMed: 20012361]
- Keogh E, Ayers S, Francis H. Does anxiety sensitivity predict post-traumatic stress symptoms following childbirth? A preliminary report. *Cognitive Behaviour Therapy*. 2002; 31(4):145–155. doi:10.1080/165060702321138546.

- Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*. 2005; 62:617–27. [PubMed: 15939839]
- Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry*. 1995; 52:1048–1060. [PubMed: 7492257]
- Kessler, RC.; Üstün, TB., editors. *The WHO World Mental Health Surveys: global perspectives on the epidemiology of mental disorders*. Cambridge University Press; New York: 2008. p. 1-580.
- Kiliç EZ, Kiliç C, Yilmaz S. Is anxiety sensitivity a predictor of PTSD in children and adolescents? *Journal of Psychosomatic Research*. 2008; 65(1):81–86. doi:10.1016/j.jpsychores.2008.02.013. [PubMed: 18582616]
- Kilpatrick DG, Koenen KC, Ruggiero KJ, Acierno R, Galea S, Resnick HS, et al. The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. *The American Journal of Psychiatry*. 2007; 164(11):1693–1699. doi:10.1176/appi.ajp.2007.06122007. [PubMed: 17974934]
- Kleim B, Ehlers A, Glucksmann E. Early predictors of chronic post-traumatic stress disorder in assault survivors. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences*. 2007; 37(10):1457–1467. doi:10.1017/S0033291707001006.
- Koenen, KC. Developmental epidemiology of PTSD: Self-regulation as a central mechanism. In: Yehuda, R., editor. *The psychobiology of post-traumatic stress disorder*. Mount Sinai School of Medicine; Blackwell Publishing; New York, NY, US: Malden: 2006. p. 255-266.
- Koenen KC, Amstadter AB, Nugent NR. Gene-environment interaction in posttraumatic stress disorder: An update. *Journal of Traumatic Stress*. 2009; 22(5):416–426. doi:10.1002/jts.20435. [PubMed: 19743189]
- Koenen KC, Fu QJ, Ertel K, Lyons MJ, Eisen SA, True WR, et al. Common genetic liability to major depression and posttraumatic stress disorder in men. *Journal of Affective Disorders*. 2008; 105(1-3):109–115. doi:10.1016/j.jad.2007.04.021. [PubMed: 17540456]
- Koenen KC, Moffitt TE, Poulton R, Martin J, Caspi A. Early childhood factors associated with the development of post-traumatic stress disorder: Results from a longitudinal birth cohort. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences*. 2007; 37(2):181–192. doi:10.1017/S0033291706009019.
- Koenen KC, Nugent NR, Amstadter AB. Gene-environment interaction in posttraumatic stress disorder: review, strategy and new directions for future research. *Eur Archives of Psychiatry and Clinical Neuroscience*. 2008; 258(2):82–96.
- Koenen KC, Uddin M, Chang S-C, Aiello AE, Wildman DE, Goldmann E, et al. SLC6A4 methylation modifies the effect of the number of traumatic events on risk for posttraumatic stress disorder. *Depression and Anxiety*. 2011; 28(8):639–647. DOI: 10.1002/da.20872. [PubMed: 21608084]
- Kolassa I, Kolassa S, Ertl V, Papassotiropoulos A, De Quervain DJ. The risk of posttraumatic stress disorder after trauma depends on traumatic load and the catechol-methyltransferase polymorphism. *Biological Psychiatry*. 2010; 67(4):304–308. doi:10.1016/j.biopsych.2009.10.009. [PubMed: 19944409]
- Kremen WS, Koenen KC, Boake C, Purcell S, Eisen SA, Franz CE, et al. Pretrauma Cognitive Ability and Risk for Posttraumatic Stress Disorder: A Twin Study. *Archives of General Psychiatry*. 2007; 64(3):361–368. [PubMed: 17339525]
- Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics*. 1996; 6:243–50. [PubMed: 8807664]
- Lee HJ, Lee MS, Kang RH, Kim H, Kim SD, Kee BS, et al. Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. *Depression and Anxiety*. 2005; 21(3):135–139. [PubMed: 15965993]
- Lesch KP, Gutknecht L. Pharmacogenetics of the serotonin transporter. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2005; 29(6):1062–1073. doi:10.1016/j.pnpbp.2005.03.012. [PubMed: 15951088]

- Leskin LP, White PM. Attentional networks reveal executive function deficits in posttraumatic stress disorder. *Neuropsychology*. 2007; 21(3):275–284. doi:10.1037/0894-4105.21.3.275. [PubMed: 17484590]
- Lonsdorf TB, Rück C, Bergström J, Andersson G, Öhman A, Lindefors N, Schalling M. The COMTval158met polymorphism is associated with symptom relief during exposure-based cognitive-behavioral treatment in panic disorder. *BMC Psychiatry*. 2010; 10 doi: 10.1186/1471-244X-10-99.
- Lonsdorf TB, Weike AI, Nikamo P, Schalling M, Hamm AO, Öhman A. Genetic gating of human fear learning and extinction: Possible implications for gene-environment interaction in anxiety disorder. *Psychological Science*. 2009; 20(2):198–206. doi:10.1111/j.1467-9280.2009.02280.x. [PubMed: 19175757]
- Marshall GN, Miles JNV, Stewart SH. Anxiety sensitivity and PTSD symptom severity are reciprocally related: Evidence from a longitudinal study of physical trauma survivors. *Journal of Abnormal Psychology*. 2010; 119(1):143–150. doi:10.1037/a0018009. [PubMed: 20141251]
- Marx BP, Doron-LaMarca S, Proctor SP, Vasterling JJ. The influence of pre-deployment neurocognitive functioning on post-deployment PTSD symptom outcomes among iraq-deployed army soldiers. *Journal of the International Neuropsychological Society*. 2009; 15(6):840–852. doi: 10.1017/S1355617709990488. [PubMed: 19891817]
- Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology*. 2005; 1(1):167–195. doi:10.1146/annurev.clinpsy.1.102803.143916.
- Matsumoto M, Weickert CS, Akil M, Lipska BK, Hyde TM, Herman MM, et al. Catechol O-methyltransferase mRNA expression in human and rat brain: evidence for a role in cortical neuronal function. *Neuroscience*. 2003; 116:127–37. [PubMed: 12535946]
- Mayou RA, Ehlers A, Bryant B. Posttraumatic stress disorder after motor vehicle accidents: 3-year follow-up of a prospective longitudinal study. *Behaviour Research and Therapy*. 2002; 40(6):665–675. doi:10.1016/S0005-7967(01)00069-9. [PubMed: 12051485]
- McCrory E, De Brito SA, Viding E. Research review: The neurobiology and genetics of maltreatment and adversity. *Journal of Child Psychology and Psychiatry*. 2010; 51(10):1079–1095. doi:10.1111/j.1469-7610.2010.02271.x. [PubMed: 20546078]
- McEwen BS. Protection and Damage from Acute and Chronic Stress: Allostasis and Allostatic Overload and Relevance to the Pathophysiology of Psychiatric Disorders. *Annals of the NY Academy of Science*. 2004; 1032(1):1–7.
- McFarlane AC, Barton CA, Yehuda R, Wittert G. Cortisol response to acute trauma and risk of posttraumatic stress disorder. *Psychoneuroendocrinology*. 2011; 36(5):720–727. [PubMed: 21093988]
- McKee VM, Huff ME. A diathesis-stress model of posttraumatic stress disorder: Ecological, biological, and residual stress pathways. *Review of General Psychology*. 2003; 7(3):237–250. doi: 10.1037/1089-2680.7.3.237.
- McNally NJ, Bryant RA, Ehlers A. Does early psychological intervention promote recovery from post-traumatic stress? *Psychological Science in the Public Interest*. 2003; 4:45–79.
- McNally RJ, Shin LM. Association of intelligence with severity of posttraumatic stress disorder symptoms in Vietnam combat veterans. *The American Journal of Psychiatry*. 1995; 152(6):936–938. Retrieved from www.csa.com. [PubMed: 7755129]
- Meaney MJ, Diorio J, Francis D, Widdowson J, LaPlante P, Caldji C, et al. Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. *Developmental Neuroscience*. 1996; 18(1-2):49–72. [PubMed: 8840086]
- Meewisse M, Reitsma JB, De Vries G, Gersons BPR, Olff M. Cortisol and post-traumatic stress disorder in adults: Systematic review and meta analysis. *British Journal of Psychiatry*. 2007; 191(5):387–392. doi:10.1192/bjp.bp.106.024877. [PubMed: 17978317]
- Mehta D, Binder EB. Gene × environment vulnerability factors for PTSD: The HPA-axis. *Neuropharmacology*. 2011 doi:10.1016/j.neuropharm.2011.03.009.
- Mehta D, Gonik M, Klengel T, Rex-Haffner M, Menke A, Rubel J, et al. Using Polymorphisms in FKBP5 to Define Biologically Distinct Subtypes of Posttraumatic Stress Disorder: Evidence

- From Endocrine and Gene Expression Studies. *Archives of General Psychiatry*. 2011; 68(9):901–910. [PubMed: 21536970]
- Meiser-Stedman R, Dalgleish T, Glucksman E, Yule W, Smith P. Maladaptive cognitive appraisals mediate the evolution of posttraumatic stress reactions: A 6-month follow-up of child and adolescent assault and motor vehicle accident survivors. *Journal of Abnormal Psychology*. 2009; 118(4):778–787. doi:10.1037/a0016945. [PubMed: 19899847]
- Mellman TA, Alim T, Brown DD, Gorodetsky E, Buzas B, Lawson WB, et al. Serotonin polymorphisms and posttraumatic stress disorder in a trauma exposed African American population. *Depression and Anxiety*. 2009; 26(11):993–997. [PubMed: 19842167]
- Mevissen L, de Jongh A. PTSD and its treatment in people with intellectual disabilities: A review of the literature. *Clinical Psychology Review*. 2010; 30(3):308–316. doi:10.1016/j.cpr.2009.12.005. [PubMed: 20056303]
- Michael T, Halligan SL, Clark DM, Ehlers A. Rumination in posttraumatic stress disorder. *Depression and Anxiety*. 2007; 24:307–317. doi:10.1002/da.20228. [PubMed: 17041914]
- Mikulincer M, Solomon Z. Attributional style and combat-related posttraumatic stress disorder. *Journal of Abnormal Psychology*. 1988; 97(3):308–313. doi:10.1037/0021-843X.97.3.308. [PubMed: 3192823]
- Milad MR, Quinn BT, Pitman RK, Orr SP, Fischl B, Rauch SL. Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *PNAS*. 2005; 102(30):10706–10711. [PubMed: 16024728]
- Millan MJ. The neurobiology and control of anxious states. *Progress in Neurobiology*. 2003; 70(2):83–244. doi:10.1016/S0301-0082(03)00087-X. [PubMed: 12927745]
- Ozer EJ, Best SR, Lipsey TL, Weiss DS. Predictors of posttraumatic stress disorder and symptoms in adults: A meta-analysis. *Psychological Bulletin*. 2003; 129(1):52–73. doi:10.1037/0033-2909.129.1.52. [PubMed: 12555794]
- Palker-Corell A, Marcus DK. Partner abuse, learned helplessness, and trauma symptoms. *Journal of Social and Clinical Psychology*. 2004; 23(4):445–462. doi:10.1521/jscp.23.4.445.40311.
- Parslow RA, Jorm AF. Pretrauma and posttrauma neurocognitive functioning and PTSD symptoms in a community sample of young adults. *The American Journal of Psychiatry*. 2007; 164(3):509–515. doi:10.1176/appi.ajp.164.3.509. [PubMed: 17329477]
- Pitman RK, Orr SP, Lowenhagen MJ, Macklin ML. Pre-Vietnam contents of posttraumatic stress disorder veterans' service medical and personnel records. *Comprehensive Psychiatry*. 1991; 32(5):416–422. doi:10.1016/0010-440X(91)90018-8. [PubMed: 1743012]
- Price JL, Monson CM, Callahan K, Rodriguez BF. The role of emotional functioning in military-related PTSD and its treatment. *Journal of Anxiety Disorders*. 2006; 20(5):661–674. doi:10.1016/j.janxdis.2005.04.004. [PubMed: 16139471]
- Reardon JM, Williams NL. The specificity of cognitive vulnerabilities to emotional disorders: Anxiety sensitivity, looming vulnerability and explanatory style. *Journal of Anxiety Disorders*. 2007; 21:625–643. doi:10.1016/j.janxdis.2006.09.013. [PubMed: 17070666]
- Riskind JH, Williams NL, Gessner TL, Chrosniak LD, Cortina JM. The looming maladaptive style: Anxiety, danger, and schematic processing. *Journal of Personality and Social Psychology*. 2000; 79(5):837–852. doi:10.1037/0022-3514.79.5.837. [PubMed: 11079245]
- Runyon MK, Kenny MC. Relationship of attributional style, depression, and posttrauma distress among children who suffered physical or sexual abuse. *Child Maltreatment*. 2002; 7(3):254–264. doi:10.1177/1077559502007003007. [PubMed: 12139192]
- Salter-Pedneault K, Ruef AM, Orr SP. Personality and psychophysiological profiles of police officer and firefighter recruits. *Personality and Individual Differences*. 2010; 49(3):210–215. doi:10.1016/j.paid.2010.03.037.
- Sartor CE, McCutcheon VV, Pommer NE, Nelson EC, Grant JD, Duncan AE, et al. Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences*. 2011; 41(7):1497–1505. doi:10.1017/S0033291710002072.

- Schweizer S, Dagleish T. Emotional working memory capacity in posttraumatic stress disorder (PTSD). *Behaviour Research and Therapy*. 2011; 49(8):498–504. doi:10.1016/j.brat.2011.05.007. [PubMed: 21684525]
- Shalev AY, Videlock EJ, Peleg T, Segman R, Pitman RK, Yehuda R. Stress hormones and post-traumatic stress disorder in civilian trauma victims: a longitudinal study. Part I: HPA axis responses. *International Journal of Neuropsychopharmacology*. 2008; 11(3):365–372. [PubMed: 17971262]
- Shenck CE, Putnam FW, Noll JG. Experiential avoidance and the relationship between child maltreatment and PTSD symptoms: Preliminary evidence. *Child Abuse and Neglect*. 2012; 36:118–126. doi:10.1016/j.chiabu.2011.09.01. [PubMed: 22398300]
- Skre I, Onstad S, Torgersen S, Lygren S. A twin study of DSM-III—R anxiety disorders. *Acta Psychiatrica Scandinavica*. 1993; 88(2):85–92. doi:10.1111/j.1600-0447.1993.tb03419.x. [PubMed: 8213211]
- Smith K, Bryant RA. The generality of cognitive bias in acute stress disorder. *Behaviour Research and Therapy*. 2000; 38(7):709–715. doi:10.1016/S0005-7967(99)00096-0. [PubMed: 10875192]
- Smolka MN, Schumann G, Wrase J, Grusser SM, Flor H, Mann K, et al. Catechol-*O*-methyltransferase Val158Met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. *Journal of Neuroscience*. 2005; 25:836–842. [PubMed: 15673663]
- Southwick, SM.; Rasmusson, A.; Barron, J.; Arnsten, A. Neurobiological and neurocognitive alterations in PTSD: A focus on norepinephrine, serotonin, and the hypothalamic-pituitary-adrenal axis. In: Vasterling, JJ., Brewin, CR., editors. *Neuropsychology of PTSD: Biological, cognitive, and clinical perspectives*. Guilford Press; New York, NY, US: 2005. p. 27–58.
- Steckler T, Risbrough V. Pharmacological treatment of PTSD—Established and new approaches. *Neuropharmacology*. 2012; 62(2):617–627. doi:10.1016/j.neuropharm.2011.06.012. [PubMed: 21736888]
- Stein MN, Jang KL, Taylor S, Vernon PA, Livesley WJ. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: A twin study. *American Journal of Psychiatry*. 2002; 159:1675–1681. [PubMed: 12359672]
- Stein MB, Kennedy CM, Twamley EW. Neuropsychological function in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biological Psychiatry*. 2002; 52(11):1079–1088. doi:10.1016/S0006 3223(02)01414-2. [PubMed: 12460691]
- Stein MB, Walker JR, Hazen AL. Full and partial posttraumatic stress disorder: findings from a community survey. *American Journal of Psychiatry*. 1997; 154:1114–1119. [PubMed: 9247398]
- Storr CL, Ialongo NS, Anthony JC, Breslau N. Childhood antecedents of exposure to traumatic events and posttraumatic stress disorder. *The American Journal of Psychiatry*. 2007; 164(1):119–125. doi:10.1176/appi.ajp.164.1.119. [PubMed: 17202553]
- Tarullo AR, Gunnar MR. Child maltreatment and the developing HPA axis. *Hormones and Behavior*. 2006; 50(4):632–639. doi:10.1016/j.yhbeh.2006.06.010. [PubMed: 16876168]
- Thakur GA, Joobar R, Brunet A. Development and persistence of posttraumatic stress disorder and the 5-HTTLPR polymorphism. *Journal of Traumatic Stress*. 2009; 22(3):240–243. [PubMed: 19444877]
- True WR, Rice J, Eisen SA, Dphil ACH, Goldberg J, Lyons MJ, Nowak J. A twin study of genetic and environmental contributions to liability for Posttraumatic Stress Symptoms. *Archives of General Psychiatry*. 1993; 50:257–264. HPA axis functioning. [PubMed: 8466386]
- Tull MT, Jakupcak M, McFadden ME, Roemer L. The role of negative affect intensity and the fear of emotions in posttraumatic stress symptom severity among victims of childhood interpersonal violence. *Journal of Nervous and Mental Disease*. 2007; 195(7):580–587. doi:10.1097/NMD.0b013e318093ed5f. [PubMed: 17632248]
- Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-*o*-methyltransferase, cognition, and psychosis: Val¹⁵⁸Met and beyond. *Biological Psychiatry*. 2006; 60(2):141–151. doi:10.1016/j.biopsych.2005.10.024. [PubMed: 16476412]
- Valente N, Vallada H, Cordeiro Q, Bressan R, Andreoli S, Mari J, et al. Catechol-*O*-methyltransferase (COMT) val158met Polymorphism as a Risk Factor for PTSD After Urban Violence. *Journal of Molecular Neuroscience*. 2011; 43:516–23. [PubMed: 21080103]

- van Zuiden M, Geuze E, Willemen HL, Vermetten E, Maas M, Amarouchi K, et al. Glucocorticoid Receptor Pathway Components Predict Posttraumatic Stress Disorder Symptom Development: A Prospective Study. *Biological Psychiatry*. 2011 in press.
- van Zuiden M, Geuze E, Willemen H, Vermetten E, Maas M, Heijnen CJ, Kavelaars A. Pre-existing high glucocorticoid receptor number predicting development of posttraumatic stress symptoms after military deployment. *The American Journal of Psychiatry*. 2011; 168(1):89–96. doi:10.1176/appi.ajp.2010.10050706. [PubMed: 21078706]
- van Zuiden M, Kavelaars A, Rademaker AR, Vermetten E, Heijnen CJ, Geuze E. A prospective study on personality and the cortisol awakening response to predict posttraumatic stress symptoms in response to military deployment. *Journal of Psychiatric Research*. 2011; 45(6):713–719. doi: 10.1016/j.jpsychires.2010.11.013. [PubMed: 21185572]
- Vasterling JJ, Brailey K, Constans JI, Borges A. Assessment of intellectual resources in gulf war veterans: Relationship to PTSD. *Assessment*. 1997; 4(1):51–59. doi: 10.1080/0969594970040104,
- Vasterling JJ, Duke LM, Brailey K, Constans JI, Allain AN, Sutker PB. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology*. 2002; 16(1):5–14. doi:10.1037/0894-4105.16.1.5. [PubMed: 11853357]
- Verwoerd J, Wessel I, de Jong PJ. Individual differences in experiencing intrusive memories: The role of the ability to resist proactive interference. *Journal of Behavior Therapy and Experimental Psychiatry*. 2009; 40(2):189–201. doi:10.1016/j.jbtep.2008.08.002. [PubMed: 18929357]
- Verwoerd J, Wessel I, de Jong PJ, Nieuwenhuis MMW, Huntjens RJC. Pre-stressor interference control and intrusive memories. *Cognitive Therapy and Research*. 2011; 35(2):161–170. doi: 10.1007/s10608-010-9335-x. [PubMed: 21475619]
- Wald I, Shechner T, Bitton S, Holoshitz Y, Charney DS, Muller D, et al. Attention bias away from threat during life threatening danger predicts PTSD symptoms at one-year follow-up. *Depression and Anxiety*. 2011; 28(5):406–411. doi:10.1002/da.20808. [PubMed: 21381159]
- Wessel I, Overwijk S, Verwoerd J, de Vrieze N. Pre-stressor cognitive control is related to intrusive cognition of a stressful film. *Behaviour Research and Therapy*. 2008; 46(4):496–513. doi: 10.1016/j.brat.2008.01.016. [PubMed: 18328465]
- Williams NL, Shahar G, Riskind JH, Joiner TE. The looming maladaptive style predicts shared variance in anxiety disorder symptoms: Further support for a cognitive model of vulnerability to anxiety. *Journal of Anxiety Disorders*. 2005; 19(2):157–175. doi:10.1016/j.janxdis.2004.01.003. [PubMed: 15533702]
- Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Brady K, et al. Interactive effect of stressful life events and the serotonin transporter genotype on posttraumatic stress disorder diagnosis in 2 independent populations. *Archives of General Psychiatry*. 2009; 66(11):1201–1209. doi:10.1001/archgenpsychiatry.2009.153. [PubMed: 19884608]
- Xian H, Chantarujikapong SI, Scherrer JF, Eisen SA, Lyons MJ, Goldberg J, et al. Genetic and environmental influences on posttraumatic stress disorder, alcohol and drug dependence in twin pairs. *Drug and Alcohol Dependence*. 2000; 61(1):95–102. doi:10.1016/S0376-8716(00)00127-7. [PubMed: 11064187]
- Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Farrer LA, et al. Interaction of FKBP5 with Childhood Adversity on Risk for Post-Traumatic Stress Disorder. *Neuropsychopharmacology*. 2010; 35(8):1684–1692. [PubMed: 20393453]
- Yehuda R. Advances in understanding neuroendocrine alterations in PTSD and their therapeutic implications. *Annals of the New York Academy of Science*. 2006; 107:137–166.
- Yehuda R, Cai G, Golier JA, Sarapas C, Galea S, Ising M, et al. Gene Expression Patterns Associated with Posttraumatic Stress Disorder Following Exposure to the World Trade Center Attacks. *Biological Psychiatry*. 2009; 66(7):708–711. [PubMed: 19393990]
- Yehuda R, Keefe RSE, Harvey PD, Levengood RA. Learning and memory in combat veterans with posttraumatic stress disorder. *The American Journal of Psychiatry*. 1995; 152(1):137–139. Retrieved from www.csa.com. [PubMed: 7802106]

- Yehuda R, Schmeidler J, Giller EL, Siever LJ, Binder-Brynes K. Relationship between Posttraumatic Stress Disorder characteristics of Holocaust survivors and their adult offspring. *American Journal of Psychiatry*. 1998b; 155:841–843. [PubMed: 9619162]
- Yehuda R, Schmeidler J, Wainberg M, Binder-Brynes K, Duvdevani T. Vulnerability to posttraumatic stress disorder in adult offspring of holocaust survivors. *The American Journal of Psychiatry*. 1998; 155(9):1163–1171. Retrieved from www.csa.com. [PubMed: 9734537]
- Yehuda, R.; Stavitsky, K.; Tischler, L.; Golier, JA.; Harvey, PD. Learning and memory in aging trauma survivors with PTSD. Vasterling, JJ.; Brewin, CR., editors. Guilford Press; New York, NY, US: 2005. p. 208-229. Retrieved from www.csa.com
- Yuan C, Wang Z, Inslicht SS, McCaslin SE, Metzler TJ, Henn-Haase C, et al. Protective factors for posttraumatic stress disorder symptoms in a prospective study of police officers. *Psychiatry Research*. 2011; 188(1):45–50. doi:10.1016/j.psychres.2010.10.034. [PubMed: 21095622]
- Zetsche U, Ehrling T, Ehlers A. The effects of rumination on mood and intrusive memories after exposure to traumatic material: An experimental study. *Journal of Behavior Therapy and Experimental Psychiatry*. 2009; 40(4):499–514. doi:10.1016/j.jbtep.2009.07.001. [PubMed: 19665693]

Highlights

- Vulnerability factors for PTSD may exist prior to experiencing trauma.
- Biological factors include genetics and physiological stress reactivity.
- Cognitive factors include neuropsychological ability and cognitive biases.
- Prospective research will further elucidate pre-trauma vulnerability factors.

Table 1

List of reviewed studies that include assessment of vulnerability factor isolated from effects trauma exposure

Vulnerability	Subtype	Research Articles
Biological	Genetic Twin Studies	Twin: True et al. (1993); Stein et al. (2002); Skre et al., (1993)
	Molecular G x E Interaction (reviewed by Koenen et al., 2009; Mehta & Binder, in press)	5HTTLPR variations: Binder et al. (2008); Grabe et al., (2009); Kilpatrick et al., (2007); Koenen et al., (2009); Kolassa et al. (2010); Xie et al. (2009). COMT: Kolassa et al 2010; valente et al. 2011, Boscarino et al. 2011 FKBP5 genotype: van Zuiden, Geuze, Willemen, Vermetten, Maas, Amarouchi, Kavelaars, & Heijnen, 2011
	HPA Functioning	Amstadter et al. (2011 [CRF1]); Amstadter, Koenen et al., (2009 [NPY]); Binder et al. (2008 [FKBP5]); Mehta et al. (2011); van Zuiden, Geuze, Willemen, Vermetten, Maas, Heijnen, & Kavelaars (2011); van Zuiden, Kavelaars, et al., (2011); Yehuda et al. (2009)
Cognitive	Intelligence	Boscarino (2006); Breslau et al., (2006); Kaplan et al., (2002); Koenen et al. (2007) Macklin et al., (1998); Pitman et al., (1991)
	Neuropsychological Performance	Parslow & Jorm (2007); Marx et al., (2009); Verwoerd, Wessel, & de Jong, 2009; Verwoerd, Wessel, de Jong, Nieuwenhuis, & Huntjens (2011); Wessel, Overwijk, Verwoerd, & de Vrieze (2008)
	Cognitive Biases	Beevers et al. (2011); Bomyea & Amir (2011); Bryant & Guthrie (2007); Koegh et al. (2002); Yuan et al., 2011