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Review article

The centrality of fear extinction in linking risk factors to PTSD: A narrative review

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ABSTRACT

Recent prospective studies in emergency services have identified impaired fear extinction learning and memory to be a significant predictor of Posttraumatic Stress Disorder (PTSD), complementing a wealth of cross-sectional evidence of extinction deficits associated with the disorder. Additional fields of research show specific risk factors and biomarkers of the disorder, including candidate genotypes, stress and sex hormones, cognitive factors, and sleep disturbances. Studies in mostly nonclinical populations also reveal that the aforementioned factors are involved in fear extinction learning and memory. Here, we provide a comprehensive narrative review of the literature linking PTSD to these risk factors, and linking these risk factors to impaired fear extinction. On balance, the evidence suggests that fear extinction may play a role in the relationship between risk factors and PTSD. Should this notion hold true, this review carries important implications for the improvement of exposure-based treatments, as well as strategies for the implementation of treatment.

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1. Introduction

Epidemiological studies indicate that over half of the population in the United States will be exposed to a serious traumatic event in their lifetime (Kessler et al., 1995). One possible psychiatric outcome of trauma exposure is Posttraumatic Stress Disorder (PTSD), characterized by distressing re-experiencing, avoidance, negative (alterations in) cognitions and mood, and hyperarousal symptoms (American Psychiatric Association, 2013). Further, PTSD is associated with considerable psychological distress, elevated risk of suicide and comorbid psychiatric disorders. Despite high rates of trauma exposure, only 10–15% of individuals develop PTSD (Kessler et al., 1995; Ramchand et al., 2010), constituting approximately 3% of the population in the United States (Kessler et al., 2005). PTSD is unique among psychiatric disorders, as we know the triggering event; however it is unclear why the disorder develops in some but not in others. Research indicates that the majority of trauma survivors show severe PTSD symptoms in the weeks following trauma, however these rates drop dramatically in the following months (for a review, see Bryant, 2003). Therefore, the normative response to trauma is recovery. A significant body of scientific research has uncovered important neurobiological, cognitive, and psychological correlates of the disorder. A compelling and unresolved issue is *what discriminates those who develop PTSD from those who experience trauma but remain resilient?* This highlights the importance of identifying key risk and resilience factors, biomarkers, and underlying mechanisms that may mediate/moderate the relationship between a traumatic event and PTSD symptoms.

A prevailing model suggests that the impaired extinction of conditioned fear in the aftermath of trauma is critical in the development and maintenance of PTSD (e.g., Mineka and Oehlberg, 2008; Pitman et al., 2012). There is substantial evidence of greater fear conditioning and impaired fear extinction in patients with PTSD (Blechert et al., 2007; Norrholm et al., 2011; Zuj et al., 2016). However, to examine the role of fear extinction in the development of PTSD, longitudinal prospective studies are required that examine these processes prior to and following trauma exposure. Recent prospective studies have revealed that impaired fear extinction prior to trauma exposure predicts increased PTSD symptom severity (Guthrie and Bryant, 2006; Lommen et al., 2013; Orr et al., 2012). The use of prospective studies has allowed the identification of other key risk factors identified in PTSD development, including candidate genotypes (Matsuoka et al., 2013), stress and sex hormones (Bryant et al., 2011; Videlock et al., 2008), cognitive factors (Vasterling et al., 2012), and sleep disturbances (Bryant et al., 2010). Interestingly, the connection between these risk factors and impaired extinction learning in PTSD has not received much attention yet. To date, certain links have been identified between fear extinction and candidate genotypes (Johnson et al., 2012), stress and sex hormones (Milad et al., 2010; Mueller and Cahill, 2010), cognitive factors (Raes et al., 2009), and sleep disturbances (Spoormaker et al., 2010). On balance, the evidence points to impaired fear extinction as a shared factor that may link these biomarkers and risk factors to PTSD, although we acknowledge certain inconsistencies in the literature. In this review, we outline the evidence that suggests a fundamental role of fear extinction, and review an important question: is fear extinction the central factor that links known risk factors to PTSD?

1.1. Focus of this review

Impaired fear extinction learning and memory appear to be key variables that link risk factors to PTSD susceptibility, and the aim of this review is to highlight these convergences. This paper will address this issue by providing a comprehensive review of the pre-trauma risk and resilience factors of PTSD development, and the evidence linking these factors to impaired fear extinction processes. Classic PTSD signs and symptoms include fear and anxiety, catastrophic cognitions, anger, substance abuse, shame, and guilt. It is important to note that this review focuses on the fear-related symptoms of PTSD (e.g., intrusive memories and re-experiencing symptoms), which are often considered primary symptoms. First, an overview of the current fear conditioning and extinction model of PTSD will be provided, including a brief review of convergent animal and human research on the neural networks of fear extinction relating to PTSD, and a summary of emerging prospective studies in fear extinction and PTSD. Second, prospective and cross-sectional studies examining risk and resilience factors in PTSD across varying domains of genetics, stress and sex hormones, cognitive function, and sleep will be reviewed. Third, we highlight the converging literature bases of known risk factors and impaired fear extinction learning and/or its retention. Based on this, we propose a model in which extinction is the central variable linking risk factors to PTSD, and discuss the current empirical evidence for this model. Finally, we discuss considerations for future research to investigate this model. Should further investigations into the role of fear extinction as a mechanism between risk factors and PTSD hold true, these findings would carry important implications for further research and clinical practice. These implications include advances for theory building and the development of interventions aimed at boosting

PTSD resilience in susceptible populations (e.g., emergency services and military personnel).

1.2. The fear conditioning and extinction model of PTSD

The fear conditioning model is central in explaining the development of PTSD. This model is based on Pavlov's (1927) seminal work in classical conditioning, where a learned association between a previously neutral stimulus (e.g., a light, termed the conditioned stimulus; CS) and an aversive stimulus (unconditioned stimulus; US), leads to heightened US-expectancy of the CS. After learning, the CS alone generates a conditioned fear response in absence of the US. This principle operates when people experience trauma events. For example, an individual involved in a motor vehicle accident (US) is likely to experience a natural response of fear and heightened arousal (the unconditioned response; UCR). Following the event, aspects of the trauma that were not associated with the accident before (e.g., the car), may act as a trigger to activate the trauma memory, eliciting the CR.

While fear conditioning processes can explain the *acquisition* of conditioned fear, most traumatized individuals recover and do not go on to develop PTSD (reviewed in Bryant (2003)). Indeed, the majority of individuals report PTSD symptoms within the initial weeks following trauma in the form of acute stress disorder (Bryant, 2011), however only a small percentage of these do not recover, and go on to display persistent symptoms. This rapid reduction in PTSD symptoms may be attributed partially to fear extinction learning, which has led current models to emphasize fear extinction processes in the maintenance of PTSD (e.g., Mineka and Oehlberg, 2008; Pitman et al., 2012; VanElzakker et al., 2013). Fear extinction refers to a process of new learning in which repeated exposure to a CS in the absence of an aversive consequence (the US) leads to a reduction in conditioned fear responses. In the context of trauma, this typically involves experience of benign trauma reminders. In this sense, the minority of trauma survivors who experience persistent conditioned emotional responses and chronic PTSD can be regarded as suffering impaired fear extinction (Davis and Myers, 2002; Kolb and Mutalipassi, 1982). Therefore, a prevailing model of PTSD is that the disorder results from impaired fear extinction (Mineka and Oehlberg, 2008; Pitman et al., 2012; Shin and Liberzon, 2010).

1.3. Empirical evidence for impaired fear extinction in PTSD

Recently, research indicates that the persistence of PTSD symptoms nine months post-deployment in Dutch soldiers can be predicted by an impaired ability to inhibit learned fear, as indexed by an increased startle response to a CS in the presence of a safety signal (Sijbrandij et al., 2013). Compared to trauma-exposed controls without PTSD and healthy controls, participants with PTSD demonstrate a robust psychophysiological increase in arousal to the CS+ during the extinction phase, indicative of a reduced ability to extinguish conditioned fear (Blechert et al., 2007; Norrholm et al., 2011; Orr et al., 2000; Peri et al., 2000; Zuj et al., 2016). Further, participants with PTSD have also shown an impaired ability to inhibit conditioned fear responses to a CS that has not been reinforced by the US (Jovanovic et al., 2010, 2009). These findings suggest that PTSD symptoms are associated with impairment in regulating fear responses previously associated with an aversive stimulus, as well as responses to safety signals.

Participants often display over-expressed conditioned fear during the early stage of extinction learning, termed fear load (Norrholm et al., 2015). Fear load, as measured by fear-potentiated startle, has been observed in PTSD (Norrholm et al., 2011), and later identified to be significantly correlated with intrusive fear memories of a traumatic event (Norrholm et al., 2015). Importantly, the authors argue that fear load may be a quantifiable intermediate phenotype with a significant role in the etiology of fear-related psychopathology (Briscione et al., 2014; Norrholm et al., 2015).

Some studies have demonstrated little difference in within-session extinction learning between PTSD subjects and controls (Milad et al., 2008, 2009b) but rather found poor recall of extinction memories in PTSD 24 h after extinction learning (Milad et al., 2008, 2009b; Shvil et al., 2014). Shvil et al. (2014) used a two-day paradigm to assess fear conditioning and extinction learning on day one, and fear extinction recall on day two. The results showed impaired recall of fear extinction learning in PTSD, however this result was sex-specific, with men showing poorer extinction recall compared to women with PTSD (Shvil et al., 2014). Additional studies using a similar two-day paradigm have found further support for impaired fear extinction recall in PTSD, albeit without sex differences (Milad et al., 2008, 2009b). Together, these findings indicate that impairments may not be limited to extinction learning, but rather to the consolidation of extinction memories, or availability for recall. It is worth noting here, however, that there are certain methodological differences in the fear conditioning and extinction paradigms discussed here, compared to studies discussed in above paragraphs. For example, there are specific differences between paradigms regarding the use of partial or full CS-US reinforcement schedules, the addition of contextual contingencies, pharmacological challenge interventions, and the measurement of conditioned responses via skin conductance response (SCR), fear-potentiated startle, and self-report US-expectancy ratings (e.g., Milad et al., 2008; Norrholm et al., 2011; Soeter and Kindt, 2012). It is possible that these differences in experimental paradigms may account for alternate findings.

The continued expression of fear or spontaneous return of fear following extinction learning suggests that extinction is formed as a new memory that competes with the original conditioning memory, rather than overriding the conditioning trace (for a brief review, see Pace-Schott et al., 2015a). However, it remains unclear whether PTSD is associated with impairments in the learning, consolidation, or retrieval of extinction memories, or a combination of all of these processes. Nevertheless, evidence is clear that PTSD is associated with impaired mechanisms of fear extinction.

1.4. The neurobiology of fear conditioning and extinction

Research in rodent models and human neuroimaging has led to considerable advances in our understanding of the neural pathways involved in fear expression. This section will provide a brief discussion of the evidence from animal studies, followed by translational evidence in human neuroimaging studies (for a comprehensive review, see Pitman et al., 2012). Finally, this section will present convergent evidence for the role of this neural network in human neuroimaging studies using fear conditioning and extinction paradigms in PTSD subjects.

1.4.1. Animal studies

The amygdala has been referred to as the neural 'hub of fear' (Milad and Quirk, 2012), with different regions of the amygdala playing key roles in the acquisition of fear. Specifically, the basolateral amygdala (BLA) receives sensory information on the CS-US association, as well as the presence of contextual contingencies, and the central nucleus (CE) sends afferent projections to behavioral and endocrine systems to express fear (Holmes and Singewald, 2013; LeDoux, 2000; Pape and Pare, 2010; Pare and Duvarci, 2012; Pare et al., 2004). For example, the CE projects to the periaqueductal grey to regulate freezing behavior in rodents and the lateral hypothalamus to regulate blood pressure (Medina et al., 2002). Evidence also links the prelimbic system of the medial prefrontal cortex (mPFC) to the expression of conditioned fear. That is, freez-

ing behavior in rodents is correlated with neuronal activity in the prelimbic cortex (Burgos-Robles et al., 2009). Similarly, inactivation of the prelimbic cortex is associated with reduced expression of conditioned fear (Corcoran and Quirk, 2007), supporting the notion that the amygdala receives excitatory projections from the prelimbic cortex to express fear. Emerging evidence also suggests that activation of the basomedial amygdala (BMA) in mice plays a significant role in the reduction of freezing and anxiety behaviors (Adhikari et al., 2015). Furthermore, the ventral mPFC exerts top-down control over the BMA to regulate this process.

The amygdala sends afferent projections to sympathetic arousal centres to express fear, however the mPFC and the hippocampus play a larger role in mediating this process as the CS ceases to predict the US during fear extinction. Greater activation of the infralimbic cortex is associated with enhanced extinction recall (Milad and Quirk, 2002) and electrical stimulation of infralimbic neurons resulted in reduced conditioned fear responses (i.e., reduced freezing in rodents; Milad et al., 2004). In further support, lesions to the infralimbic cortex are associated with increased extinction recall (Laurent and Westbrook, 2009; Quirk et al., 2000). Presentation of a CS in an extinguished context has been associated with reduced conditioned freezing and enhanced cFos expression (an indicator of increased neuronal activity) in the infralimbic cortex (Hefner et al., 2008; Knapska and Maren, 2009). Alternatively, presentation of the CS in a non-extinguished context however, has resulted in high levels of conditioned freezing and greater cFos activity in the prelimbic cortex (Knapska and Maren, 2009). These findings suggest that the infralimbic cortex acts in opposition to the prelimbic cortex, with greater activity inhibiting the amygdala, and thereby inhibiting fear expression.

The hippocampus has been implicated in the contextual modulation of extinction learning. Corcoran and Maren (2001) found that when hippocampal activity went uninterrupted, rats showed context-specific freezing behavior. Fear expression was reduced in the extinction context, but elevated in non-extinguished contexts, supporting the notion that extinction learning is context specific. In a separate experiment, inactivation of the dorsal hippocampus resulted in reduced freezing to the CS when placed in either the extinguished or unextinguished context (Corcoran and Maren, 2001), indicating a role for the dorsal hippocampus in identifying safe versus threatening contexts. It is argued that the hippocampus projects directly to the BLA and indirect connections via the mPFC to relay contextual contingencies on the CS-US relationship (Orsini et al., 2011; Orsini and Maren, 2012). Therefore, when the CS no longer predicts the US, the hippocampus and infralimbic cortex send inhibitory projections to the amygdala, reducing the expression of conditioned fear and demonstrating successful fear extinction retention (for a comprehensive review on the hippocampus and contextual fear conditioning and extinction, see Maren et al., 2013).

1.4.2. Human studies

A remarkable aspect of fear conditioning and extinction is the potential for translational work from rodents to humans, with the goal of improving clinical interventions and treatment (Milad and Quirk, 2012; Quirk and Mueller, 2008). Activation of the amygdala is enhanced during the acquisition of fear (Cheng et al., 2003; Cheng et al., 2007; LaBar et al., 1998; Morris and Dolan, 2004). Consistent with animal studies, the BLA receives sensory information on the CS-US contingency during fear conditioning and projects this information to sympathetic arousal structures (for a comprehensive review, see LeDoux, 2000). Neuroimaging studies have found the dACC in humans to be the functional homologue of the prelimbic system in rodents (VanElzakker et al., 2013). Cortical thickness and activation of the dACC is positively correlated with SCR during the acquisition of fear, as well as presentations of the CS+ (Milad et al., 2007a). Further studies have also found increased dACC activation during fear conditioning (Buchel et al., 1998; Cheng et al., 2003; Knight et al., 2004; Linnman et al., 2011a; Phelps et al., 2004).

The ventromedial PFC (vmPFC) is suggested to be homologous to the rodent infralimbic cortex (Milad et al., 2006b; Milad et al., 2007b). Showing parallels with the proposition that the infralimbic cortex may inhibit the amygdala in rodents (e.g., Milad and Quirk, 2002), Motzkin et al. (2014) recently showed that vmPFC lesions in human subjects prevented the inhibition of amygdala activity in viewing aversive images, resulting in greater amygdala activity. Similarly, Milad et al. (2007b) found that the recall of extinction learning was positively correlated with activation of the vmPF Milad et al. (2007b) used an ABB conditioning and extinction design, whereby fear was acquired in context A, but extinguished in context B, with extinction recall also occurring in context B the next day. Extinction recall on day two was associated with increased hippocampal activation, suggesting an important role of the hippocampus in differentiating the acquisition versus extinction contexts (Milad et al., 2007b). Previous fMRI research using only one context for stimulus presentations found no evidence of hippocampal activation in association with vmPFC activation during extinction recall (Phelps et al., 2004). Milad et al. (2007b) speculate that this difference is due to contextual signaling in the hippocampus, with this signaling only occurring in instances of multiple contexts with different extinction contingencies. Indeed, Lang et al. (2009) identified increased hippocampal activation where multiple contextual conditioning/extinction contingencies were employed, supporting previous animal studies (Corcoran and Maren, 2001).

1.5. Neuroimaging of fear conditioning and extinction in PTSD

Neuroimaging studies in clinical PTSD samples provide additional support for the role of aforementioned neural structures in the acquisition and extinction of conditioned fear. During fear acquisition, participants with PTSD show significantly greater amygdala activation compared to trauma-exposed controls (Linnman et al., 2011b; Milad et al., 2009b) and trauma non-exposed controls (Bremner et al., 2005). Although increased amygdala activation is found during fear acquisition in healthy subjects (Cheng et al., 2003, 2007; LaBar et al., 1998; Morris and Dolan, 2004), it is possible the amygdala is hyperactive in PTSD. In support, increased avoidance symptoms correlate with increased amygdala, vmPFC, and hippocampus activity during both fear acquisition and extinction in United States military veterans with PTSD (Sripada et al., 2013).

PTSD is associated with hyperactivity in the dACC during fear acquisition and extinction learning (Rougemont-Bücking et al., 2011), and extinction recall 24 h later (Milad et al., 2009b; Rougemont-Bücking et al., 2011). Rougemont-Bücking et al. (2011) used a two-day paradigm measuring fear conditioning, extinction (day one), and extinction recall (day two) with fMRI scanning in PTSD subjects. PTSD subjects and healthy trauma-exposed controls acquired fear conditioned responses in context A, with extinction learning and recall occurring in context B. PTSD subjects showed greater dACC activation during conditioning, and reduced vmPFC activity during late extinction learning. A specific limitation of these findings, however, is that there were no between-group differences in SCR (a measure of conditioned responses) at any stage of conditioning or extinction. Although it is, therefore, difficult to attribute activation in these neural regions to greater conditioned responses, neural activity does support the proposed function of these regions at different stages of conditioning and extinction (Milad et al., 2007a,b). Further, Shvil et al. (2014) recently found that greater left rostral dACC activity was associated with poor fear extinction recall in men with PTSD, with no

effects in women with PTSD and trauma-exposed healthy controls.

Milad et al. (2009b) used a two-day paradigm (explained above, see Rougemont-Bücking et al., 2011) with fMRI scanning in PTSD subjects and trauma-exposed controls. PTSD was associated with greater amygdala activity during fear acquisition on day one, and decreased hippocampal and vmPFC activity during fear extinction recall on day two. Furthermore, extinction recall was associated with increased dACC activity in PTSD subjects, compared to trauma-exposed controls (Milad et al., 2009b). Importantly, these findings support previous research of hippocampal involvement when contextual contingencies are involved. That is, PTSD subjects showed lower hippocampal activation during recall of extinction memories in the extinction context, rather than the conditioning context (Milad et al., 2009b). In support, PTSD subjects show lower activity in the parahippocampal gyrus during extinction learning in a different context to an acquisition context (Rougemont-Bücking et al., 2011). Furthermore, a recent fMRI study found increased hippocampal activity during context presentations in extinction learning (Sripada et al., 2013). Alternatively, PET scans during fear conditioning and extinction have revealed increased blood flow in the left hippocampus during extinction learning in PTSD subjects compared to controls, although context was not manipulated in this study (Bremner et al., 2005). These findings implicate a role for the hippocampus in contextual contingencies in fear extinction learning and recall, however further research is required to shed light on whether this structure is only involved in contextual modulation, or other processes of conditioning and extinction.

1.6. Fear extinction learning in twin studies of PTSD

An important question regarding the neurobiology of PTSD is whether impaired neural signaling is a consequence of a traumatic event, or a biological risk factor that predisposes an individual to overly conditioned fear responding, an inability to extinguish conditioned fear, or both of these factors. An underlying vulnerability factor cannot be considered so, unless it precedes the onset of PTSD (Kremen et al., 2012). While this presents a particular issue in differentiating consequences from sequelae due to the unpredictable nature of trauma exposure, some studies have examined certain factors in twins discordant for combat-exposure, with some combat-exposed twins being diagnosed with PTSD and others reporting no symptoms. As monozygotic twins share 100% of their genetic makeup, it would be expected that both twins share specific risk factors (both cognitive and biological) with the only differentiating factor being trauma exposure and PTSD diagnosis. Specifically, it would be hypothesised that both twins show similar impairments in fear extinction learning, however trauma exposure mediates the display of PTSD symptoms.

One study has examined fear extinction learning in a monozygotic co-twin design. Milad et al. (2008) measured fear extinction learning and extinction recall in a sample of 14 monozygotic twin pairs discordant for PTSD diagnosis, and combat exposure from the Vietnam War. Seven twin pairs were discordant for PTSD diagnosis and combat exposure, and the remaining seven were only discordant for combat exposure with neither twin diagnosed with PTSD. This study revealed no between-group differences on psychophysiological arousal measures during fear acquisition and extinction recall one day later, compared with their co-twin, or twin pairs discordant for combat exposure. However, the authors revealed that PTSD diagnosis significantly interacts with combat exposure during extinction recall, suggesting that impaired extinction recall is a consequence of combat exposure, leading to PTSD, rather than a pre-trauma risk factor. As far as we are aware, this idea has not received any attention since.

1.7. Impaired fear extinction learning as a prospective risk factor of PTSD

While trauma-exposure is unpredictable in the general population, researchers have investigated fear extinction learning in people working in high-risk occupations. Despite evidence that impaired fear extinction learning may be a consequence of trauma (Milad et al., 2008), recent evidence has found impaired pre-trauma extinction learning to be a significant predictor of post-traumatic stress symptoms in trainee fire-fighters (Guthrie and Bryant, 2006). Guthrie and Bryant (2006) assessed trainee fire-fighters on PTSD symptoms and diagnosis, and a standardized fear conditioning and extinction task during cadetship (prior to trauma exposure), and reassessed within two years of commencing fire-fighting duties. This study revealed that greater EMG startle responses during extinction (reflecting impaired fear extinction learning) predicted higher PTSD symptoms following trauma exposure (Guthrie and Bryant, 2006). To our knowledge, this is the first study to examine pre-trauma fear extinction as a predictor of PTSD symptoms.

In support of pre-trauma fear extinction impairments predicting greater PTSD (Guthrie and Bryant, 2006), Orr et al. (2012) investigated fear conditioning and extinction in police and fire-fighter recruits. Participants underwent testing during training (prior to trauma exposure), and again several months after job-related trauma exposure. Psychophysiological measures during conditioning and extinction included SCR and electromyogram (EMG) responses to aversive stimuli. Logistic regression showed reduced extinction of forehead EMG responses to be a significant pre-trauma risk factor of greater post- traumatic stress symptoms (Orr et al., 2012). Additionally, at follow-up, psychophysiological assessments were conducted while participants recited the traumatic experience. Regression identified increased SCR to loud tones as a pre-trauma risk factor for higher physiological reactivity during the recital of the traumatic event (Orr et al., 2012). This second finding indicates that greater psychophysiological reactivity to aversive, or negative stimuli may be a trait-like factor in the development of negative trauma reactions. That is, individuals may have a predisposed tendency to display elevated psychophysiological reactions to aversive or negative stimuli. These findings add further support for the notion that impaired fear extinction learning can predict higher post-traumatic stress symptoms in at-risk populations.

Finally, a recent study extended previous findings to military populations by assessing pre-deployment Dutch military soldiers on a fear conditioning and extinction paradigm (Lommen et al., 2013). Consistent with the aforementioned studies (Guthrie and Bryant, 2006; Orr et al., 2012), Lommen et al. (2013) found impaired fear extinction to be significantly predictive of post-traumatic stress symptoms two months post-deployment to Afghanistan. Extinction performance was assessed by increased US-expectancy ratings to the CS+. A limitation of this study is the absence of a psychophysiological measure of arousal, however US-expectancy ratings are a commonly used measure of associative learning in fear conditioning and extinction paradigms (e.g., Blechert et al., 2007; Norrholm et al., 2011; Sijbrandij et al., 2013), are an externally valid measure of human fear conditioning (Boddez et al., 2013), and do not influence psychophysiological recordings (Blechert et al., 2008). Therefore, these findings indicate consistent results across several measures of arousal and threat expectancy, with impaired pre-trauma fear extinction as measured using elevated skin conductance response (Orr et al., 2012), elevated EMG corrugator responses (Guthrie and Bryant, 2006), and subjective expectancy ratings (Lommen et al., 2013) found to be predictive of

increased PTSD symptoms. While preliminary, these findings provide compelling evidence that an underlying pre-trauma deficit in extinguishing conditioned fear is an important variable in the etiology of PTSD symptoms.

2. Convergent PTSD risk factors in fear extinction

Here, the present review aims to demonstrate the apparent interactions between PTSD, biomarkers and risk factors, and impaired fear extinction. Previous comprehensive reviews (e.g., Bomyea et al., 2012; Zoladz and Diamond, 2013) have assessed evidence of multiple risk factors of PTSD, concluding there is significant variability due to gender, early trauma history, comorbidity, and dynamic biomarkers. The following sections discuss empirical evidence of the relationship between risk factors (genetics, neuroendocrine system, sex hormones, cognition and neuropsychological factors, and sleep) and PTSD, and their relation to impaired fear extinction learning and memory. It should be noted that due to the breadth of information presented here, specific references to recent reviews are provided where necessary for greater discussions of risk factors that cannot be discussed in the current review.

2.1. Genetics

With advances in understanding DNA methylation and epigenetic influences on gene expression, genetics is claimed to be one of the most promising fields of understanding PTSD susceptibility (Zoladz and Diamond, 2013). While research into genetic risk factors of PTSD is still in its infancy with limited genome-wide association studies, researchers have identified potential candidate genotypes involved in PTSD. Convergent translational findings are emerging from animal, epigenetic, and gene × environment studies in PTSD, focusing specifically on candidate genotypes such as BDNF, COMT, 5-HTTLPR, FKBP5, and PACAP. Furthermore, in many instances, genotype polymorphisms do not solely pose risk for PTSD, but rather interact with environmental factors to increase the likelihood of PTSD development. Bomyea et al. (2012) highlight the importance of studying gene × environment interactions, as stressors during childhood have the potential to reveal biological risk factors, with significant consequences on neural systems.

Research has identified that in some cases, PTSD development can be linked to familial factors (Gilbertson et al., 2006), with approximately one-third of the variability in PTSD symptoms explained by genetic factors (True et al., 1993). Similarly, twin studies have identified that between 35 and 45% of variability in fear conditioning and extinction can be explained by genetic influences (Hettema et al., 2003). Research has identified that candidate genotypes play a significant role in the cellular networks of fear memories, and are likely contributors to impaired extinction learning (see Johnson et al., 2012 for a review).

2.1.1. BDNF

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, playing a key role in synaptic plasticity. Specifically, BDNF is concentrated in regions of the central nervous system implicated in PTSD and fear extinction, such as the amygdala, prefrontal cortex, and hippocampus (Rakofsky et al., 2012). A recent prospective longitudinal study examined serum BDNF levels in motor vehicle accident survivors soon after trauma, and six-months post-trauma (Matsuoka et al., 2013). The results show a positive correlation between serum BDNF levels six-months post-trauma and PTSD severity. Furthermore, the PTSD group displayed significantly higher BDNF levels soon after hospital admission, indicating that increased BDNF levels soon after trauma could be a biomarker for greater PTSD symptoms.

Matsuoka et al. (2013) identified elevated serum BDNF levels post-trauma as a risk factor for increased PTSD symptoms six-months later. These findings have been supported in cross-sectional research showing higher serum BDNF levels in PTSD relative to controls (Hauck et al., 2009; Hauck et al., 2010). Further, Berger et al. (2010) examined the relationship between PTSD symptoms and serum BDNF over the course of a 12-week treatment program using the SSRI ecitalopram. The results of this study show low serum BDNF levels at baseline were associated with greater reduction of PTSD symptoms at the end of treatment. Alternatively, studies have identified lower BDNF levels (serum and plasma) in PTSD compared to trauma-exposed and healthy controls (Angelucci et al., 2014; Dell'Osso et al., 2009). It could be argued, however, that plasma BDNF levels do not accurately reflect cortical levels, as there is evidence that plasma BDNF follows a circadian rhythm, with greater levels early in the day (Begliuomini et al., 2008), and fluctuations with the menstrual cycle in females (Begliuomini et al., 2007).

Translational research shows an important role of BDNF in the fear network. In animal studies, BDNF knock-out mice, characterized by an approximate 50% reduction in BDNF levels, show impaired fear extinction (Psotta et al., 2013), and similarly infusing BDNF into the hippocampus increases neuronal activity in the infralimbic cortex during extinction training, and facilitates extinction learning (Rosas-Vidal et al., 2014). Additionally, Peters et al. (2010) injected BDNF into the infralimbic mPFC of rats, resulting in attenuated fear conditioned responses without undergoing extinction learning.

A single nucleotide polymorphism (SNP) with an amino acid change from a valine to a methionine at position 66 (val66met) in BDNF has recently been implicated in disorders of fear regulation (Frielingsdorf et al., 2010). Studies have identified carriers of the BDNF val66met met-allele show slow, impaired extinction learning ability (Soliman et al., 2010), and increased vmPFC and amygdala activity during extinction trials (Lonsdorf et al., 2015; Soliman et al., 2010). Further, Felmingham et al. (2013) identified that PTSD patients with the met66 allele show poorer response to exposure therapy (based on the processes of fear extinction learning) compared to val/val carriers. The role of the val66met SNP in fear extinction has been further reviewed in Notaras et al., 2015.

2.1.2. COMT

Catechol-O-methyltransferase (COMT) is a key enzyme in the prefrontal cortex and hippocampus, working in the degradation of synaptic dopamine levels, as well as epinephrine and norepinephrine (Bomyea et al., 2012). A common SNP coding at position 158 (val158met) is important in the activity of this enzyme. According to Chen et al. (2004), carriers of the val158 allele show increased COMT activity, resulting in greater elimination of dopamine and reduced prefrontal functioning. Alternatively, the met158 allele appears to be associated with reduced COMT activity, and therefore increased synaptic dopamine levels (Tunbridge et al., 2006). Val/met heterozygotes are believed to demonstrate intermediate levels of COMT activity (Tunbridge et al., 2006), and therefore may show balanced levels of dopamine within the synapse. Therefore, individuals homogenous for either the val or met allele of the COMT gene may be at an increased risk for PTSD, potentially caused by increased or decreased COMT activity in the synapse.

A prospective study by Clark et al. (2013) in members of the United States National Guard deployed to Iraq revealed that homozygous variants of COMT interact with trauma exposure to increase risk for PTSD development. Specifically, val/met allele carriers developed fewer PTSD symptoms under high trauma exposure compared with val/val or met/met carriers. All participants in this study were white males, potentially limiting generalization to females and other ethnic groups (Clark et al., 2013). Nevertheless, research in Ugandan refugees identified the met/met allele

to demonstrate a high risk for PTSD development independent of trauma severity (Kolassa et al., 2010). Further, Kolassa et al. (2010) revealed the val/val allele shows a dose-response relationship with trauma exposure to predict PTSD. These findings are supported by research in victims of urban violence, with carriers of the met allele showing increased PTSD symptoms (Boscarino et al., 2011; Valente et al., 2011). It is possible that reduced or increased levels of synaptic dopamine degradation in the prefrontal cortex confer risk for PTSD development by inhibiting prefrontal function during trauma exposure.

Risbrough et al. (2014) recently demonstrated that mice with the COMT met/met allele show increased cued fear, and impairments in the recall of extinction memories compared to val-carriers. In humans, met-carriers of the COMT val158met allele have been linked to impaired fear extinction learning. Lonsdorf et al. (2009) found extinction was associated with greater fear-potentiated startle to the CS+ in the met/met genotype, compared to val-carriers. Importantly, the met/met genotype in PTSD has been associated with an impairment to inhibit fear towards the CS-, which represents a safety signal compared to the CS+ (Norrholm et al., 2013; Wendt et al., 2014). Norrholm et al. (2013) demonstrated that performance in fear extinction learning was most impaired in met/met carriers with a current diagnosis of PTSD, compared with trauma-exposed controls. Furthermore, panic disorder patients with the met/met genotype also appear to show little symptom relief from exposure therapy, compared to val-carriers (Lonsdorf et al., 2010), indicating that exposure therapy may not be the most beneficial form of treatment for met-carriers.

2.1.3. Serotonin genes

Selective serotonin reuptake inhibitors (SSRIs) are a commonly used treatment method in PTSD, suggesting altered activity of genes encoding serotonin (5-HT) levels in PTSD (Thakur et al., 2009). The functional polymorphism of the serotonin transporter (5-HTTLPR) gene regulates the availability of 5-HT in the synapse, with carriers of the low expression ("short") allele showing reduced 5-HT transcription efficiency compared to the high expression ("long") allele (Lesch et al., 1996). In many instances, specific genotypes may not be directly involved in the etiology of a disorder (medical or psychiatric), but rather interact with environmental influences to increase the likelihood of an individual developing a specific condition. 5-HTTLPR appears to be one such gene, as the short allele of 5-HTTLPR has been shown to interact with trauma exposure and other factors to predict PTSD development.

Kilpatrick et al. (2007) interviewed 589 individuals affected by Florida hurricanes regarding hurricane exposure and social support, and collected DNA samples (including the 5-HTTLPR genotype). 5-HTTLPR showed no relationship with PTSD alone, however there was a significant interaction between the short allele, high hurricane exposure and low social support in predicting PTSD diagnosis. This link was not evident in participants with the long allele, low hurricane exposure and high social support. These findings have received further support, indicating that the 5-HTTLPR short allele interacts with environmental stressors to predict PTSD risk, including high crime and unemployment rates (Koenen et al., 2009). In a recent *meta*-analysis, it was revealed that the 5-HTTLPR short allele had a significant association with PTSD, but only in participants with high trauma-exposure (Gressier et al., 2013). Lee et al. (2005) also found a significantly higher occurrence of PTSD diagnosis in individuals with two short alleles, compared to carriers of at least one long allele.

A recent study in Israeli Defence Force soldiers involved the collection of prospective data before and during military deployment on the association between attentional threat bias, serotonin genes and PTSD risk (Wald et al., 2013). In opposition to the previous findings, the results show a significant interaction with the combination of high combat exposure, low expression 5-HTTLPR, and attentional threat bias as protective factors for PTSD, rather than risk factors. The relationship between 5-HTTLPR and threat bias may be evident only in military samples, due to attention to threat being considered a normal behavior in infantry soldiers (Wald et al., 2013). Alternatively, Mellman et al. (2009) found no association between 5-HTTLPR and PTSD, however, PTSD was significantly associated with the low expression (G) allele of the 5HT2 receptor antagonist, which is prominent in some pharmacological treatments. This presents an interesting possibility that PTSD risk may be due to the interaction of multiple genes involved in 5-HT activity.

The 5-HTTLPR-s allele has also been associated with a stronger conditioned fear trace. Findings are thus far consistent, with carriers of the 5-HTTLPR-s allele showing significantly stronger startle potentiation during the conditioning phase compared to carriers of the l/l-allele (Hermann et al., 2012; Lonsdorf et al., 2009; although see Lonsdorf et al., 2010). Similarly, studies have replicated these findings in healthy volunteers, but only in carriers of the risk allele (G-allele) for the corticotropin releasing hormone receptor 1 (CRHR1 rs878886; Heitland et al., 2013) and the risk allele (T-allele) for the NPS receptor gene (NPSR1 rs324981; Glotzbach-Schoon et al., 2013). These findings indicate that 5-HTTLPR-s interacts with other gene SNPs to promote a biological predisposition for impaired extinction of fear. Wendt et al. (2014) found that carriers of the short and long allele demonstrate comparable fear learning ability, however at re-conditioning, 5-HTTLPR-s allele carriers showed greater fear potentiated startle levels representing a stronger conditioning trace. These findings posit that carriers of the 5HTTLPR s-allele may develop a conditioning trace that increases in strength, and is resistant to extinction learning.

2.1.4. FKBP5

FK506 binding protein 5 (FKBP5) plays a significant role in the molecular networks of glucocorticoid receptor (GR) sensitivity and translocation, regulating cortisol activity and inhibiting negative feedback activity in the hypothalamic-pituitary-adrenal (HPA) axis (Bomyea et al., 2012). Specific SNPs of FKBP5 have been found to be important in gene × environment interactions, namely: rs9296158, rs3800373, rs1360780, and rs9470080 (Binder et al., 2008; Mehta et al., 2011; Xie et al., 2010). For example, Xie et al. (2010) found that the rs9470080 SNP interacts with early-life trauma to significantly predict PTSD development. Alone, FKBP5 SNPs show no direct effects on PTSD development or symptom severity (Binder et al., 2008; Xie et al., 2010), and appear to only interact with childhood trauma, with no G × E interactions with other forms of trauma (Binder et al., 2008). Research has, however, identified 12-weeks of cognitive behavior therapy for PTSD is associated with an increase in FKBP5 expression levels (Levy-Gigi et al., 2013; Szabo et al., 2014; Yehuda et al., 2013). Wilker et al. (2014) found that carriers of the SNP rs1360780T allele presented a significant risk of symptom relapse 10-months after exposure-therapy, with non-carriers showing a continuous reduction in symptoms. These findings highlight a significant role for FKBP5 in GR systems following childhood trauma, and in treatment outcome for PTSD.

To our knowledge, only one study has investigated FKBP5 in fear extinction and the retention of fear. Sawamura et al. (2016) recently used an animal model of PTSD to examine dexamethasone in extinction learning, and retention of extinction one day later. The authors found dexamethasone to be associated with a dose-dependent enhancement of extinction learning and retention. Furthermore, dexamethasone treatment was associated with reduced FKBP5 mRNA expression in the amygdala after extinction learning and retention. It was suggested that dexamethasone worked to enhance extinction learning and retention via dynamic FKBP5 regulation in the HPA axis. In support, the glucocorticoid receptor is critical in managing the stress response, and it is

believed that the glucocorticoid receptor is regulated via the FKBP5 gene (Zannas and Binder, 2014).

2.1.5. PACAP-PAC$_1$

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a protein encoded by the ADCYAP1 gene, and important in the activation of stress circuitry within the central and peripheral nervous systems (Uddin et al., 2013). The ADCYAP1 and ADCYAP1R1 (responsible for encoding the PAC$_1$ receptor) genes have recently been associated with sex-specific PTSD risk in women, but not men. Ressler et al. (2011) found that a single SNP (rs2267735) within the ADCYAP1R1 gene was a significant predictor of PTSD diagnosis and posttraumatic stress symptoms in highly traumatized African American women. A follow-up study by Almli et al. (2013) supported these findings with a significant genotype × trauma interaction, showing that the combination of ADCYAP1R1 gene and high trauma exposure predicted PTSD. Further, while Uddin et al. (2013) found no evidence of a direct effect of ADCYAP1R1 on PTSD development, they did find that ADCYAP1R1 interacts with high levels of childhood maltreatment to promote PTSD risk. Samples with relatively lower trauma-exposure have failed to find an association between the gene and PTSD (Chang et al., 2012), suggesting an underlying risk factor in the presence of high trauma exposure. On the basis of these preliminary findings, it is possible that the PACAP-PAC$_1$ pathway (and associated genes) may be used to confer risk for increased PTSD symptoms in women with increased trauma-exposure, however prospective longitudinal studies are required to test this hypothesis (Dias and Ressler, 2013).

Ressler et al. (2011) investigated mRNA changes in the ADCYAP1R1 allele of PACAP in the mouse brain during fear conditioning. The results show a significant increase in the amygdala ADCYAP1R1 mRNA during conditioning, with a similar relationship in the mPFC. Recently, Schmidt et al. (2015) infused PACAP-38 into the CA1 region of the hippocampus or the BLA of rats prior to a contextual fear extinction task. The results indicated that PACAP-38 infused in the amygdala resulted in a significantly greater percentage of freezing during a recall test (24 h after extinction learning). These results indicate that fear acquisition processes in the amygdala and consolidation/retrieval processes in the mPFC (Myers and Davis, 2007) and contextual extinction recall in the hippocampus (Schmidt et al., 2015) may be moderated by PACAP expression in these structures. Translating these findings to humans would further clarify the role of PACAP in fear memory.

2.1.6. Summary

Research in biomarkers of PTSD, and particularly genetic biomarkers, has been claimed to be the most promising field of advancing our understanding of PTSD risk (Zoladz and Diamond, 2013). Prospective and cross-sectional research has consistently linked increased serum BDNF to greater PTSD symptoms, and the BDNF val66met met-allele is associated with poorer therapeutic and experimental extinction learning. Homozygous variants of the COMT gene (i.e., met/met and val/val carriers) are associated with greater PTSD risk and significantly poorer fear extinction learning. There is consistent evidence that the 5-HTTLPR-s allele interacts with environmental stressors and high trauma-loads to increase risk for PTSD, and the s-allele is associated with stronger fear acquisition, however research in fear extinction is currently limited. FKBP5 SNPs appear to interact specifically with childhood trauma to promote PTSD risk, and dexamethasone administration enhances extinction learning and retention via FKBP5 mRNA regulation in the HPA axis. Research is currently consistent that PACAP-encoding genes interact with high-stress environments to promote PTSD risk, and animal research shows PACAP administration to the rat amygdala leads to a reduction in fear extinction recall.

2.2. Neuroendocrine system

As PTSD is a disorder primarily characterized by increased anxiety, stress and arousal, a logical assumption is that this disorder may involve irregularities in cycling hormones associated with the stress response. Specifically, stress hormones (i.e., cortisol and noradrenaline) are critical in the fear network and regulating fear responding. This assumption has led researchers to investigate neuroendocrine functioning in PTSD. Understanding neuroendocrine abnormalities in PTSD carries important implications for pharmacological treatments (for a comprehensive review on the pharmacological enhancement of exposure therapy, see Singewald et al., 2015).

2.2.1. Hypothalamic-pituitary-adrenal (HPA) axis and cortisol

The HPA axis is the mammalian brains premier neuroendocrine centre, which acts to regulate the release of hormones in different situations, including stress. Following stress exposure, the hypothalamus secretes a number of hormones and neuropeptides that stimulate the release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH facilitates cortisol release from the adrenal glands to promote a physiological environment for accommodating a stressful event. Cortisol release acts in a negative feedback loop to return the HPA axis to homeostasis in preparation for any subsequent activation (Munck and Guyre, 1986).

The assumption that the HPA axis is particularly sensitive to stressful responding in some situations has led to extensive research on the relationship between cortisol and PTSD diagnosis (Bomyea et al., 2012). With cortisol levels increasing synonymously with stress, investigators believed that PTSD might be associated with hyperactivity of naturally cycling cortisol levels (Zoladz and Diamond, 2013). Rather, PTSD has been associated with lower basal cortisol levels. Yehuda et al. (2009) found that after roughly 14 sessions of psychotherapy, cortisol levels differentiated non-responders to treatment from responders in survivors of the September 11 terrorist attack, with non-responders displaying reduced urinary cortisol levels. These findings indicate that lower cortisol levels may be used as a marker of treatment-resistant PTSD. Some studies have found results to support the notion that PTSD is associated with lower levels of naturally cycling cortisol levels compared to trauma-exposed and healthy controls (Bicanic et al., 2013; Wahbeh and Oken, 2013; Yehuda et al., 2007a,b; although see Groer et al., 2014; Shalev et al., 2008).

It is important to understand whether cortisol levels (a reflection of HPA axis activity) are an underlying biological risk factor for PTSD, or a product of trauma exposure (McFarlane et al., 1997), and hence require prospective investigation. A recent longitudinal study examined salivary cortisol levels in the morning and afternoon following hospital admission in 48 traumatic accident survivors (McFarlane et al., 2011). PTSD symptomatology was assessed six months post-trauma, revealing a significant, negative correlation between morning cortisol levels and PTSD symptoms six months later. Interestingly, afternoon cortisol levels were positively correlated with PTSD symptoms. These findings are in partial support of previous longitudinal studies in adults showing low *peri*-trauma cortisol levels to predict PTSD symptomatology at follow-ups (Delahanty et al., 2000; McFarlane et al., 1997), and that cortisol increases in the remission of PTSD symptoms in Holocaust survivors (Yehuda et al., 2007b). Interestingly, a prospective study in children found a sex-specific relationship between increased *peri*-trauma cortisol levels and increased PTSD symptoms six weeks later in boys, but not girls (Delahanty et al., 2005), thus presenting an interesting question regarding the differential effects of trauma exposure on the maturing sympathetic nervous system and HPA axis.

The above findings note some important implications for future research, notably regarding the inconsistency surrounding lower versus higher cortisol levels in PTSD samples, and in prospective prediction of PTSD. Indeed, some of these inconsistencies may be grounded in wide methodological variations in the collection and subsequent analysis of hormone samples (i.e., differences between blood, urine, and salivary collection methods). In addition, time-of-day is an important factor to take into account when measuring cortisol, which may explain differing morning versus afternoon levels in the recent prospective study by McFarlane et al. (2011). That is, cortisol experiences a surge shortly after waking, known as the cortisol awakening response (van Zuiden et al., 2011), which may bias findings.

Research suggests that increased cortisol enhances the formation of extinction memories (Bentz et al., 2013; Merz et al., 2014; Pace-Schott et al., 2013), although these findings are somewhat mixed (see Raio et al., 2014; Tabbert et al., 2010). Using a contextual fear conditioning task, Merz et al. (2014) found that following stress-induction (promoting an increase in cortisol levels), participants displayed reduced fear responses in the extinction context and attenuated responses in the acquisition context. Alternatively, Raio et al. (2014) found that following an acute stress task, participants displayed significantly worse recall of extinction memory compared to those who did not undergo the stress task. Evidence for the role of cortisol in the consolidation of extinction memories is somewhat mixed.

Studies have also examined the effect of acute stress tasks and cortisol administration on the efficacy of exposure-based treatments for specific phobias. Soravia et al. (2006) investigated oral cortisol consumption and response to exposure therapy in a sample of participants with a spider phobia. The results indicate that cortisol led to a reduction in spider fear that was maintained at retest two days later, compared to placebo treatment (Soravia et al., 2006). These findings suggest that cortisol administration facilitated and enhanced fear extinction learning, which has received further support in phobias of heights (de Quervain et al., 2011) and spiders (Soravia et al., 2014). To our knowledge, research has not yet examined these effects in a clinical PTSD sample.

2.2.2. Noradrenaline

Evidence suggests that noradrenaline (NA) interacts with cortisol during the presentation of emotional stimuli to enhance the consolidation of emotional memories (for a review, see McGaugh, 2004). Noradrenaline is a catecholamine playing important hormonal and neurotransmitter functions during the “fight or flight” stress response. Rat models of posttraumatic stress have revealed exaggerated NA utilisation levels in the locus coeruleus following stress (George et al., 2013), and increased NA levels in the rostral pons were related to the presence of trauma reminders (Terzioglu et al., 2013). In clinical studies in humans, PTSD has been linked to increased salivary, urinary, blood, and cerebrospinal fluid NA levels compared to trauma-exposed and healthy controls (Geracioti et al., 2001; Kosten et al., 1987; Nicholson et al., 2014; Pietrzak et al., 2013; Yehuda et al., 1998, 1992). A longitudinal study by Videlock et al. (2008) measured NA levels in emergency room admissions and again at 10 days, 1-month, and 5-months post-admission. Participants who developed PTSD at 5-months had significantly lower plasma NA levels at 10 days, 1-month, and 5-months post-trauma, contradicting findings of increased NA levels in cross-sectional research.

An additional method of measuring the impact of NA on PTSD symptoms is via pharmacological challenge studies with agents known to impact NA levels. Yohimbine and prazosin are two such drugs that have been assessed in PTSD. Yohimbine is an α-$_2$ adrenergic receptor antagonist that increases NA levels (Southwick et al., 1999), while prazosin is an α-$_1$ adrenergic receptor antagonist that reduces NA levels (Fuller et al., 1978). Studies of yohimbine administration have shown an increase in PTSD re-experiencing symptoms (Southwick et al., 1999). Prazosin administration, however, has been associated with a significant decrease in PTSD-related sleep disturbances and nightmares (Raskind et al., 2007, 2003), a significant increase in mean REM duration (Taylor et al., 2008), and a significant reduction of PTSD symptom severity and psychological distress (Raskind et al., 2003; Taylor et al., 2006, 2008). Further, propranolol administration (a β-adrenergic receptor antagonist) appears to block the effects of stress (Zoladz and Diamond, 2013), and shows promise in the treatment of PTSD (Brunet et al., 2011; Pitman, 2011; Pitman et al., 2002; Vaiva et al., 2003). These findings indicate that hyper-activity of the noradrenergic system, particularly NA release, is associated with greater severity of PTSD symptoms, and the blockade of NA release may be an effective strategy in PTSD treatment. To our knowledge, research has not yet investigated pre-trauma NA levels, and how these may interact with trauma and epigenetic processes to increase or reduce risk for PTSD.

In regards to fear extinction, mice that receive a post-extinction injection of epinephrine show an impaired ability to recall extinction learning, unless another injection is received immediately prior to extinction recall (Rosa et al., 2014). Additionally, increased NA into the amygdala of rats enhanced extinction learning (Berlau and McGaugh, 2006). Thus far, findings appear consistent, with greater NA levels influencing greater beta-receptor signaling which, in turn, strengthens memory formation (Mueller and Cahill, 2010). Greater activation of noradrenergic receptors during fear extinction is associated with better retrieval of extinction (Mueller et al., 2008). In further support, stimulation of noradrenergic beta-receptors in the amygdala following the retrieval of conditioned responses results in a stronger memory trace that is resistant to extinction (Debiec et al., 2011). These results posit that whether conditioning or extinction is being learned, enhanced noradrenergic receptor signaling results in a stronger memory trace.

A recently expanding body of literature is administering an α_2-adrenergic receptor antagonist (i.e., yohimbine) and a β-adrenergic receptor antagonist (i.e., propranolol) at select intervals during a fear conditioning paradigm to investigate their effects on reconsolidation and extinction learning. Thus far, studies are somewhat mixed with some studies showing that after fear acquisition, the use of propranolol attenuates fear responses when administered in close proximal timing with the conditioned stimuli (Kindt et al., 2014; Soeter and Kindt, 2012) while others note impairments in extinction learning (Bos et al., 2012, 2014; Soeter and Kindt, 2011). Further, Soeter and Kindt (2012) administered yohimbine immediately prior to fear acquisition, leading to an increase in NA release, and a fear conditioning trace that was broadly generalised and resistant to extinction. Importantly, the aim of these studies was to target the reconsolidation window for the original memory trace to prevent the return of fear (Kindt et al., 2014) rather than the formation of a new memory during extinction that is likely in constant competition with the original fear memory.

2.2.3. Summary

While the evidence suggests that PTSD is associated with hyperactive HPA axis activity (via reduced cortisol release, and therefore lower negative feedback of the HPA axis stress response), studies are inconsistent regarding the influence of cortisol levels (lower versus higher) on fear extinction learning and memory. Cross-sectional research suggests that PTSD is linked to increased saliva, urinary, blood, and cerebrospinal fluid levels of NA, however a longitudinal study found lower *peri*- trauma plasma NA levels predicted PTSD symptoms 5-months post-trauma. Further, the pharmacological enhancement of noradrenergic signaling during extinction learning appears to strengthen extinction. While

evidence indicates that cortisol and noradrenaline are involved in PTSD symptoms, and the regulation of fear responding, this research field appears to be marred by certain inconsistencies that require clarity.

2.3. Sex hormones: estrogen and progesterone

Women are twice as likely to develop PTSD compared to men (Glover et al., 2015; Kessler et al., 1995; Shansky, 2015) despite higher rates of trauma exposure in men. McLean et al. (2011) showed greater lifetime PTSD rates in women compared to men in the United States (8.5% vs. 3.4% respectively). Due to this increased prevalence in women compared to men, there has been a recent growth in research investigating sex differences in PTSD. In their review, Zoladz and Diamond (2013) highlight that greater PTSD risk in women is not considered to be due to factors such as trauma type, but may be due to biological differences, an idea that has been previously discussed by Cahill (2006). A recent prospective study found that women in the luteal phase of their menstrual cycle at the time of trauma were significantly more likely to experience flashbacks of the trauma compared to other women (Bryant et al., 2011). The luteal phase of the menstrual cycle is associated with an increase of estrogen and progesterone levels. In tandem with increasing sex hormones, the luteal phase involves an increase in glucocorticoid release (Handa et al., 1994), which is associated with greater emotional memory consolidation (Abercrombie et al., 2003). Bryant et al. (2011) hypothesise that greater consolidation of trauma memories may lead to an increase in flashback memories. Indeed, additional research has linked increased estrogen and progesterone levels, and the luteal phase with greater intrusive memories (Cheung et al., 2013; Ferree et al., 2011; Soni et al., 2013) and greater recall of threatening images (Felmingham et al., 2012). This evidence has implications for the menstrual cycle and associated hormone fluctuations as a key mechanism in the development of PTSD symptoms in women, but not men.

Considerable research examining sex differences in PTSD and disorders characterized by excessive fear has stimulated research examining sex differences in fear extinction (for a comprehensive review, see Lebron-Milad and Milad, 2012). Milad et al. (2010) investigated the effects of estradiol in a two-day fear extinction learning and recall paradigm. Healthy men and women underwent fear acquisition and extinction on day one and extinction recall on day two. Women with low levels of estradiol had significantly poorer extinction recall on day two, compared to women with higher levels of estradiol. Men had comparable extinction recall to high-estradiol women, which may speculatively be attributed to increased testosterone levels in men (Milad et al., 2010), although more research is needed on the relationship between testosterone and fear extinction. Further, Wegerer et al. (2014) recently found that healthy women with low estradiol demonstrate poorer fear extinction and more intrusive memories than women with higher estradiol. These findings support previous research indicating that higher estrogen levels result in stronger consolidation of fear extinction learning in rodents (Milad et al., 2009a) and humans (Glover et al., 2013; Milad et al., 2010; Zeidan et al., 2011). Further, Graham and Milad (2013) investigated the effects of hormone contraceptives on fear extinction learning in female rats and healthy women. The use of contraceptives results in a reduction of estrogen levels and, consistent with previous research, was associated with significantly impaired fear extinction recall. Importantly, women with PTSD and low estrogen levels show impaired fear extinction learning, compared with trauma-exposed controls with low estrogen levels (Glover et al., 2012), suggesting that other factors are involved.

With estrogen levels naturally fluctuating in women, researchers have identified that specific phases of the menstrual cycle may confer greater risk for poor consolidation of extinction memories. Recently, Glover et al. (2013) measured extinction recall in a sample of women currently in the follicular phase (lower estrogen) versus the luteal phase (high estrogen). The results indicated that the follicular phase was associated with poorer recall of extinction memories. Furthermore, lower estradiol levels in naturally cycling premenopausal women have been associated with lower extinction recall (Zeidan et al., 2011). Rodent studies similarly found the proestrus menstrual phase (characterized by high estrogen/progesterone) to be associated with greater consolidation of extinction learning (Milad et al., 2009a). Interestingly, Milad et al. (2006a) found that women in the late follicular phase (high estrogen) to show poorer extinction recall than early follicular phase women and men. While these findings go against the results of previous studies, the authors highlight that this menstrual phase is associated with lower activation of the vmPFC, which may account for poorer extinction recall due to the role that this structure plays in the consolidation and retrieval of extinction memories (Mueller and Cahill, 2010).

2.4. Cognitive factors

PTSD is reliably associated with deficits in attention and memory function, with impairments on these faculties included as diagnostic criteria of the DSM-IV (American Psychiatric Association, 2000; Vasterling and Brailey, 2005). Furthermore, PTSD has previously been characterized as a disorder of memory (McNally, 2006) due to hallmark re-experiencing symptoms such as distressing intrusive memories, and deficits in episodic and autobiographical memory. Longitudinal studies in combat veterans have identified that PTSD diagnosis at post-deployment has been associated with significant pre-deployment cognitive deficits in intellectual functioning, attention, learning, and memory (Gale et al., 2008; Kremen et al., 2007; Marx et al., 2009a; Thompson and Gottesman, 2008; Vasterling et al., 2012, 2006). Despite overwhelming and consistent evidence of cognitive deficits in PTSD, little research has investigated the relationship between cognitive factors and fear extinction. Due to this, here we review evidence of specific PTSD-related cognitive functioning in the areas of intellectual functioning, attention, and memory, followed by a section discussing the currently limited research in fear extinction and cognitive factors.

2.4.1. Intellectual functioning

While the measurement of "intelligence" in PTSD has been met with scepticism (Vasterling and Brailey, 2005), a number of studies have implicated a role for lower intellectual functioning in the development of PTSD (Breslau et al., 2013; Gilbertson et al., 2001; Macklin et al., 1998; Vasterling et al., 1997, 2002). A study in monozygotic twin pairs discordant for combat exposure and PTSD diagnosis indicated that lower intelligence was a familial risk factor for greater PTSD symptom severity (Gilbertson et al., 2006). Specific subscales of intelligence tests have identified verbal intellectual performance to be specifically impaired in PTSD (Vasterling and Brailey, 2005). Studies in children have revealed that those with PTSD show significantly lower verbal IQ on the WISC-III (Saigh et al., 2006; Samuelson et al., 2010). Further, Saigh et al. (2006) found no significant differences on performance IQ, with effects limited to verbal subtests (i.e., vocabulary and comprehension). These results have been supported in a study of combat veterans of the Gulf War, with poor performance on the WAIS-R being limited to verbal IQ in veterans with PTSD compared to veterans without PTSD (Vasterling et al., 1997). Additional research has identified verbal intellectual function (including verbal learning and memory) to be a primary cognitive complaint in PTSD (Barrett et al., 1996; Bremner et al., 2004; Gilbertson et al., 2006; Grigorovich et al., 2013; Jelinek et al.,

2006; Marx et al., 2009b; Parslow and Jorm, 2007; Samuelson et al., 2010; Vasterling et al., 2002).

2.4.2. Attention

Studies have identified that PTSD is associated with deficits in attentional resources. Recently, Flaks et al. (2014) found differences in processes of selective attention and short-term working memory capacity in a sample of urban violence victims with PTSD compared to trauma-exposed and non-exposed comparison groups. Patients with PTSD show significantly poorer performance than healthy controls on the digit span test, which is a measure of sustained attention and short-term memory (Horner et al., 2013). The findings of these studies are supported by numerous studies revealing PTSD-related attentional deficits in children (Beers and De Bellis, 2002; Samuelson et al., 2010) and veterans (Gilbertson et al., 2006; Marx et al., 2009a; Toomey et al., 2009; Vasterling et al., 2002, 2006). However, null findings of attentional deficits have been revealed in a community sample (Crowell et al., 2002) and well-educated combat veterans with PTSD (Neylan et al., 2004).

With hyperarousal to threat being a key diagnostic symptom of PTSD (American Psychiatric Association, 2013), studies have investigated attention biases to threatening stimuli in PTSD. Prospective studies have identified attentional biases to threat are significant predictors of PTSD development in combat veterans (Wald et al., 2013) and MVA survivors (Naim et al., 2013). Specifically, Wald et al. (2013) identified attentional threat biases at military recruitment (pre-trauma) to be a significant predictor of post-combat PTSD symptoms. These findings have been supported in cross-sectional studies indicating that veterans with PTSD show sustained attention to threatening stimuli, compared to comparison control groups (Armstrong et al., 2013; Olatunji et al., 2013).

2.4.3. Memory

Impaired attention in PTSD carries important implications for memory processes. As with verbal intelligence being the most consistent deficit in studies of PTSD- related intellectual functioning, a *meta*-analysis revealed verbal memory processes to be more consistently impaired in PTSD than nonverbal processes (Brewin et al., 2007). Improvements in verbal learning and memory have been associated with a reduction in PTSD symptom severity (Yehuda et al., 2006). Alternatively, a study by Wild and Gur (2008) found that poor response to eight sessions of cognitive behavioral therapy in PTSD was significantly predicted by poor verbal memory. These results are supported by growing research showing verbal learning and memory to be significantly impaired in PTSD (Barrett et al., 1996; Bremner et al., 2004; Gilbertson et al., 2006; Grigorovich et al., 2013; Jelinek et al., 2006; Marx et al., 2009b; Parslow and Jorm, 2007; Samuelson et al., 2010; Vasterling et al., 2002).

In a recent prospective study, Marx et al. (2009b) assessed neurocognitive functioning in a sample of pre-deployed U.S. Army soldiers, and assessed PTSD symptom severity at post-deployment. The results showed pre-deployment immediate visual recall was negatively correlated with PTSD symptoms at post-deployment (Marx et al., 2009b). Patients with PTSD have also shown poorer performance on working memory (Toomey et al., 2009; Vasterling et al., 2002), and visual recall memory (Samuelson et al., 2009). Further, veterans with chronic PTSD demonstrate poorer memory performance than veterans without PTSD (Yehuda et al., 2007a), which may be a consequence of prolonged secretion of stress hormones (Bomyea et al., 2012).

2.4.4. Fear extinction and cognitive factors

Despite consistent, and accumulating evidence of cognitive deficits in PTSD, the relationship between cognitive factors and fear extinction is a relatively new field. A recent study found that greater cognitive load during fear extinction resulted in impaired fear extinction learning (Raes et al., 2009). That is, preliminary evidence indicates that fear extinction learning relies on sufficient cognitive resources for efficient consolidation of extinction memories (akin to a dual-processing approach). The aforementioned cognitive processes of intelligence, attention, memory, and verbal functioning are impaired in PTSD, suggesting that these cognitive resources may be involved in fear extinction.

This notion—that fear extinction learning is a cognitive process relying on the use of multiple cognitive faculties—has received little attention, yet some relationships have been identified. Fear acquisition shares similarities to an attentional threat bias (Fani et al., 2012; Van Damme et al., 2006), with attentional threat biases increasing, decreasing, and returning in parallel with acquisition, extinction, and reinstatement phases of a differential fear conditioning paradigm (Van Damme et al., 2006). Additionally, Gazendam and Kindt (2012) found that engaging with a verbal task led to impaired fear extinction learning. Together, these early findings provide preliminary support for the idea that fear extinction is not an automatic process, but relies on cognitive resources for accurate consolidation (Raes et al., 2009). Fear extinction and generalization are inherently learning and memory processes, requiring the accurate consolidation and recall availability to reduce the likelihood of reinstatement or spontaneous recovery of conditioned fear responses (e.g., Milad and Quirk, 2012). Based on the research so far discussed, multiple factors affect memory processes required for the storage or generalization of extinction memories, however to our knowledge, a link between memory capacity and fear extinction learning ability has not yet been examined.

2.4.5. Summary

Studies in PTSD populations have consistently revealed lower levels of intelligence, attention, and memory to be associated with the disorder. Specifically, lower verbal intelligence, as well as verbal learning and memory appear to be primary complaints of the disorder. While still in its infancy, investigations of fear extinction and cognitive factors indicate that fear extinction ability is significantly hindered by increasing cognitive load, or by engaging in a verbal cognitive task. Therefore it can be assumed that fear extinction learning relies on sufficient cognitive resources for accurate consolidation, and the processing of an additional task reduces cognitive resources available for the consolidation of extinction.

2.5. Sleep disturbances

Sleep disturbances are widely considered to be a hallmark symptom of PTSD (Germain, 2013; Ross et al., 1989), and meet specific DSM-5 criteria relating to alterations in arousal and intrusive memories (American Psychiatric Association, 2013). Sleep is argued to be a central stage involved in emotional memory consolidation (reviewed in Pace-Schott et al., 2015a), and rapid eye movement (REM) sleep has been implicated in the consolidation of extinction memories (Spoormaker et al., 2010). Indeed, some studies have identified significant differences in REM sleep between clinical PTSD samples and comparison groups (Engdahl et al., 2000; Mellman et al., 1995; Mellman et al., 1997; Ross et al., 1994a,b), while other studies have revealed small to no differences (Breslau et al., 2004; Hurwitz et al., 1998). Importantly, studies examining specific sleep architecture disturbances in PTSD have revealed variable findings in relation to the specific disturbances in sleep stages (i.e., differences in REM density, duration and frequency; for a comprehensive review, see Pace-Schott et al., 2015b).

Prospective studies have found that objective and subjective sleep disturbances predict the development of PTSD. An early study tracked PTSD development and sleep difficulties of motor vehicle accident survivors over the course of one year (Koren et al.,

2002), finding increased excessive daytime sleepiness and insomnia symptoms at one month post-trauma significantly predicted PTSD development 11-months later. Furthermore, this difference became larger over the following 11-months, with the PTSD group reporting significantly poorer sleep quality. Additional studies have also found sleep disturbances at the time of the trauma to be a significant predictor of future PTSD diagnosis (Bryant et al., 2010; Mellman et al., 2002; Mellman and Hipolito, 2006; Mellman et al., 2004, 2007).

Nightmares are one of the most common symptoms reported in PTSD as a form of intrusive memory (Germain et al., 2008; Kobayashi et al., 2007; Levin and Nielsen, 2007). Pre-deployment nightmares have been found to predict PTSD development in soldiers (van Liempt et al., 2013), and a therapeutic reduction in nightmares using imagery rehearsal therapy led to an improvement in PTSD symptoms (Krakow et al., 2001). Together, these findings indicate that sleep disturbances may be an important variable in the maintenance of PTSD symptoms, and are an important factor to be considered during treatment.

There is considerable evidence that sleep quality is important for memory consolidation (Stickgold, 2005). The consolidation of fear extinction learning also requires sufficient sleep quality, with an emphasis on REM sleep (for a review, see Pace-Schott et al., 2015a). While only one study has identified impaired extinction learning in REM-deprived rats versus controls (Silvestri and Root, 2008), REM deprivation appears to consistently limit the consolidation of extinction learning, as evidenced by impaired extinction recall and/or generalization (Fu et al., 2007; Pace-Schott et al., 2012; Spoormaker et al., 2012). Participants deprived of sleep show greater SCR to the extinguished stimulus (Spoormaker et al., 2010), and poor generalization from an extinguished CS+, to an unextinguished CS+ (Pace-Schott et al., 2009). Recently, Spoormaker et al. (2014) found greater left vmPFC activity during fear conditioning to be associated with lower physiological expressions of fear during extinction learning the following day. Furthermore, greater left vmPFC activity was positively associated with REM sleep amount, which was also negatively associated with fear expression during extinction. The authors concluded that left vmPFC activity during fear conditioning is associated with greater extinction learning, and that this relationship is mediated by REM sleep quality (Spoormaker et al., 2014). This idea shows parallels with the finding that regions of the prefrontal cortex play specific roles in the consolidation of acquisition, extinction learning, and recall of extinguished fear memories (Milad et al., 2007b).

The aforementioned findings have important implications for the simultaneous treatment of sleep disturbances and avoidance symptoms in anxiety disorders. That is, there is some interplay between extinction learning and sleep quality, with each factor having enhancing effects on the other. So, while sleep appears to promote better consolidation of extinction memories (Pace-Schott et al., 2009), extinction training also appears to improve sleep quality (Sturm et al., 2013). These findings are supported by research in clinical populations showing that sleep following exposure therapy results in significant symptom reductions in spider phobia (Kleim et al., 2014). Furthermore, sleep disturbances have been improved with exposure therapy in clinical PTSD samples (Gutner et al., 2013; Long et al., 2011) and cognitive therapy for PTSD (Lommen et al., 2016). Despite these findings, however, Lommen et al. (2016) found that sleep quality and duration did not predict long-term treatment outcome in PTSD patients, and Datta and O'Malley (2013) found that greater sleep quantity is insufficient for extinction consolidation. Specifically, extinction learning was only recalled if post-extinction training REM sleep contained pontine-wave activity in the brainstem. These results show important implications for the quality of REM sleep in the consolidation of extinction memory, rather than the quantity of REM sleep. Furthermore, these findings suggest an important role of the brainstem in extinction memory consolidation (Datta and O'Malley, 2013). In summary, the role of sleep plays an integral role in the persistence of conditioned fear and consolidation of extinction memory, and should be paid close attention in the etiology and treatment of anxiety disorders.

2.5.1. Summary

Prospective studies are consistent that pre- and *peri*-trauma sleep disturbances predict future PTSD symptoms. Evidence is also consistent that sleep deprivation leads to poor extinction learning and generalization, with mixed findings for the role of physiological sleep stages, such as REM sleep. Further, clinical studies have shown that sleep disturbances and PTSD symptoms are reduced in tandem by exposure therapy and CBT for PTSD.

3. Summary and conclusions

The research presented in this review suggests that risk factors of PTSD may also share links with fear extinction. Although we acknowledge some inconsistences in the literature, the balance of evidence supports the notion that impaired fear extinction is a fundamental factor in PTSD etiology that is involved in, or influenced by, these additional risk factors. Substantial evidence shows impaired extinction learning, recall, and the generalization of extinction in PTSD populations compared to trauma-exposed and non-exposed groups, in addition to serving as a pre-trauma risk factor. The over-expression of conditioned fear during the early stages of extinction learning (termed fear load) has been significantly associated with the presentation of intrusive thoughts of trauma-related fear memories, and is argued to present a quantifiable intermediate phenotype underlying the etiology of fear-related psychopathologies (Norrholm et al., 2015). The extinction of a learned fear association is also the key concept driving exposure therapy, the first line treatment approach for PTSD and specific phobia. On this basis, the identification of fear extinction as a key variable of PTSD development provides specific clinical relevance, as well as theoretical relevance. Further enhancing our understanding of the processes of fear extinction can greatly improve our understanding of PTSD risk, and whether extinction learning potential can be improved for the purpose of preventing exaggerated fear responses that lead to significant health consequences.

Across a number of research fields, including genetics, hormonal (both stress and sex hormones), cognitive, and sleep disturbances, research is revealing important links between PTSD risk factors and fear extinction (see Table 1 for a concise summary of the relationship between risk factors and PTSD, and between risk factors and impaired fear extinction/response to exposure-based therapies). For example, women with low estrogen levels show significantly poorer fear extinction recall compared to women with high estrogen levels, and men (Milad et al., 2010), and that menstrual phase at the time of trauma is a significant risk factor for PTSD (Bryant et al., 2011). Similarly, verbal intelligence and memory are the most consistently impaired cognitive functions in PTSD (Brewin et al., 2007), and evidence indicates that extinction learning is impaired when individuals are required to perform tasks utilising verbal functioning (Gazendam and Kindt, 2012). Disturbed sleep is considered a hallmark symptom of PTSD (Germain, 2013), and growing evidence is implicating greater sleep quality to be a key mechanism in healthy extinction learning, recall, and generalization (Pace-Schott et al., 2015a). Indeed, recent reviews have acknowledged the important interaction between disturbed sleep and impaired fear extinction learning in the etiology of anxiety disorder symptoms (Pace-Schott et al., 2015a,b). The aforementioned factors are just a select few presented in this review to support the contribu-

Table 1
Risk factors of PTSD, and their relationship with impaired fear extinction/exposure therapy.

Risk factor	Relation to PTSD	Relation to impaired fear extinction/exposure therapy
Genotypes		
- BDNF	Increased BDNF levels soon after trauma predict greater PTSD symptoms.	Val66met associated with slow (impaired) extinction learning. Val66met associated with reduced response to exposure therapy.
- COMT	Homozygous variants (val/val and met/met) interact with trauma to predict PTSD.	Met/met carriers show poorer fear extinction learning compared to val carriers.
- 5-HTTLPR	s-allele interacts with trauma to promote increased PTSD symptoms.	s-allele associated with a stronger conditioned fear association that may be resistant to extinction.
- FKBP5	Shows exclusive interactions with early childhood trauma to predict PTSD.	Dexamethasone administration enhances extinction learning and retention via dynamic FKBP5 regulation in the HPA axis.
- PACAP	ADCYAP1R1 SNP (rs2267735) interacts with high trauma load to predict PTSD.	PACAP-38 administration results in impaired fear extinction recall in rodents.
Hormones		
- Cortisol	Cross-sectional research suggests reduced naturally cycling cortisol levels in PTSD, and as a marker for treatment-resistant PTSD. Low *peri*-trauma cortisol predicts increased PTSD symptoms.	Stress-induced cortisol increases associated with reduced fear expression in an extinction context and an acquisition context. Greater cortisol levels tend to be associated with more effective fear extinction learning. Oral cortisol consumption reduced spider fear following exposure therapy.
- Noradrenaline	Increased noradrenaline associated with greater PTSD symptoms and frequency of intrusive memories. Lower plasma noradrenaline levels predict PTSD symptoms 5-months post-hospitalization.	Enhanced noradrenergic signaling enhances memory formation; not limited to the formation of conditioning or extinction memories.
- Estrogen	Luteal phase (high estrogen) at time of trauma predicts greater PTSD symptoms, likely due to elevated glucocorticoid signaling during this phase of the menstrual cycle.	Follicular phase (low estrogen) associated with poorer fear extinction recall. Suggested that high estrogen enhances memory consolidation
Cognitive factors	PTSD associated with significant deficits in intellectual functioning, attention, learning, and memory. In particular, PTSD is most commonly associated with impairments in verbal learning and memory.	Poorer fear extinction learning ability while concurrently performing a verbal task, or under situations of greater cognitive load. Lower verbal learning and memory ability predicts poor responding to eight sessions of cognitive behavioral therapy.
Sleep disturbances	Sleep disturbances at the time of trauma significantly predict increased PTSD symptoms. Greater daytime sleepiness and insomnia post-trauma predicts increased PTSD symptoms.	Greater sleep deprivation associated with poorer fear extinction learning. Extinction learning ability best soon after waking, and declines throughout the day. Improved sleep quality enhances fear extinction learning and recall, and there is evidence for the reverse, that fear extinction learning improves sleep quality.

tion that impaired fear extinction processes play in PTSD etiology, with significant theoretical and clinical implications.

3.1. Theoretical implications

The current review highlights the need to establish a timeline or sequence of biological and environmental events that lead to the development of PTSD following a traumatic stressor. The development of such a timeline allows for the integration of multiple theories of PTSD development. For example, certain genotypes affect the regulation of the neuroendocrine system, and the negative feedback loop of the HPA axis, in some cases, via epigenetic interactions. These processes impair general fear extinction learning and retention ability. The occurrence of a traumatic event results in the acquisition of fear that is resistant to extinction via dysregulation of the HPA axis and neuroendocrine system, with contributions from the vmPFC, hippocampus and amygdala. Additionally, the occurrence of a new traumatic event may interact with the psychological consequences of previous trauma history to promote severe responding. Following trauma, fear extinction is hindered by the development of negative appraisals about the self and the trauma that exacerbate symptoms, and nightmares and sleep disturbances further prevent recovery. This is one of many possibilities by which a biological profile may confer risk for PTSD, and does not take into account the complexities of gene × environment interactions, or the countless influences of the environment (i.e., social support). Nevertheless, this review highlights an important need to understand the sequential "chain of events" that might lead to increased PTSD symptomatology.

The present review also carries important implications for well-established and empirically tested models of PTSD. One such theory is the cognitive model of PTSD (Ehlers and Clark, 2000), which proposed that PTSD symptoms persist as a result of negative appraisals of the self and the trauma, and due to fragmented and poorly elaborated autobiographical memories of the trauma. The avoidance of trauma reminders further exacerbates symptoms and affirms these negative appraisals. Fear extinction may be an important mechanism of this theory, with negative appraisals of the trauma and its sequelae providing an attentional bias to trauma reminders in the environment. These environmental and cognitive triggers result in intrusive and distressing memories of the trauma, which can be thought of as conditioned emotional/fear responses. These conditioned responses persist as a result of impaired extinction, and avoidance of these trauma reminders further facilitate ongoing fear responding, and hindering extinction. While these two well-respected and well-supported models (i.e., biological fear extinction, and Ehlers and Clark's cognitive model) are not mutually exclusive, little research has been conducted to examine the convergent aspects of these models.

3.2. Clinical implications

Should the ideas set forth in this review hold true, this model carries significant implications for various clinical and applied

settings. Specifically, further understanding these qualities may allow for interventions to boost extinction learning and consolidation, thereby increasing resilience to negative reactions following a trauma. This scenario could lead to the redirection of clinical resources to early interventions pre- and post-trauma to prevent PTSD onset, thereby reducing negative coping in the aftermath of trauma and increasing quality of life.

A recent review discusses important pharmacological evidence that fear extinction can be enhanced via manipulation of key neurochemical imbalances and the promotion of synaptic plasticity in neural regions involved in the fear response and associative learning (Singewald et al., 2015). Singewald et al. (2015) discuss the effects of manipulating some of the factors discussed in the current review, such as BDNF, serotonin, and noradrenaline. For example, in section 2.2.2 (noradrenaline) of the current review, we discuss the research that enhanced pharmacological activation of noradrenergic signaling resulted in more efficient retrieval of extinction learning (e.g., Mueller et al., 2008). Pharmacological agents show significant promise in boosting fear extinction learning ability and the retention of extinction (for a comprehensive review, see Singewald et al., 2015). Importantly, the combination of pharmacological intervention with exposure-based therapies may enhance fear extinction and prevent the return of fear.

The present review highlights the centrality of fear extinction memory in PTSD, and extinction as a possible mechanism linking risk factors to PTSD. At current, exposure-based treatments are among the most common treatment options for PTSD, based on the principles of extinction training to trauma-relevant stimuli. This review poses additional factors to be taken into account during treatment. Research suggests that fear extinction learning and memory are malleable constructs, with the potential for change. Time-of-day has revealed extinction learning, recall, and the generalization of extinction recall are significantly better in the morning compared to the evening in healthy participants (Pace-Schott et al., 2013). Similarly, healthy participants instructed with a verbal worrying task showed impaired fear extinction learning (as indexed by SCR and US-expectancy) compared to control groups (Gazendam and Kindt, 2012). Further, biological research has revealed that healthy women in the mid-follicular phase of the menstrual cycle display significantly poorer extinction memory compared to early-follicular healthy women and men (Milad et al., 2006a). To summarise, studies have identified that, in healthy populations, fear extinction memory can be altered as a function of time-of-day, cognitive resources devoted to a verbal task, and menstrual phase in women. While the target of exposure-based treatments is to extinguish the conditioned fear trace of the trauma memory, the above findings suggest that when treatment occurs, other factors should be taken into account. Indeed, our lab recently identified that extinction learning ability is significantly worse in participants with PTSD as they are awake for longer (Zuj et al., 2016), supporting the idea that exposure therapy would be more effective earlier in the day, rather than later (Pace-Schott et al., 2013). Further, extinction learning in women appears dynamic with menstrual phase (Milad et al., 2006a), and exposure therapy may be more effective during the luteal phase, characterized by higher levels of estrogen, which is shown to be involved in enhanced memory consolidation.

3.3. Directions for future research

Further research is required to explore the key links highlighted within this review. Should this conceptual model hold true, these findings carry important implications. In order to assess this extinction-based model of PTSD and other fear-related disorders, we suggest a number of research directions. First, longitudinal studies in first responder and military populations pre-trauma provide unique insights into the interplay between different factors (including fear extinction), and the role that each of these might play in the aftermath of trauma. In particular, the use of mediation and moderation analyses in such studies would allow the identification of causal relationships, as opposed to interactions between two or more variables to enhance PTSD risk. The findings of such designs would further our understanding of the temporal sequence of events that lead to PTSD development versus resilience. Currently, the temporal sequence beginning with trauma exposure and leading to increased PTSD symptoms is unknown, and improving our understanding of this sequence of events may greatly enhance the development of early interventions post-trauma to prevent the onset/persistence of symptoms.

Due to the expensive and time-consuming nature of prospective designs, cross-sectional research in PTSD compared to trauma non-exposed controls presents a unique opportunity to determine extinction learning and recall differences between trauma-exposed and non-exposed persons. Such designs that also include risk factors and biomarkers presented in the current review would increase our current understanding of PTSD risk, including the potential to shed light on certain inconsistencies (e.g., lower vs. higher cortisol levels conferring risk for PTSD). Third, a lack of genome-wide association studies demonstrates a considerable gap in the literature of genetic and heritable biomarkers for PTSD and fear extinction potential. In the current review, we discuss the role of only a small selection of candidate genotypes and their role in PTSD and fear extinction. The identification of additional genetic risk factors would aid in further understanding the genetic makeup that predisposes an individual to severe posttraumatic stress.

In addition to the select risk factors presented in the current review, prior trauma history may also play a key role. For example, previous evidence indicates that female rape victims show significantly lower cortisol levels and greater risk of PTSD if they have experience prior assaults (Resnick et al., 1995). More recently, Najavits and Walsh (2012) found that high dissociation symptoms in PTSD were associated with a history of early life trauma (see also Evren et al., 2011; Schafer et al., 2010). With the important role that previous trauma can play in responding to a current traumatic event, it is likely that trauma history may impair the ability to extinguish fear associated with new traumatic events. For example, as a person experiences more traumatic events, their inherent ability to extinguish a fearful association is reduced, resulting in greater PTSD risk. To our knowledge, however, no studies have examined this.

In this review, we have highlighted the centrality of fear extinction learning and memory, with influences from a number of biological and cognitive factors that also serve as risk factors for PTSD. Further, we note that the sequential manner by which fear extinction affects, or is affected by these biological and cognitive factors is unknown. Future research using moderation and mediation models may prove useful in identifying causal relationships and important interactions involving fear extinction and PTSD symptoms. Studies such as these carry important implications for treatment, and additional studies using mediation and moderation models may identify further variables that could aid or impair treatment outcome (e.g., stress and sex hormone levels at the time of treatment).

3.4. Final comment

In the present review, we discuss many of the risk factors for developing PTSD and their influence on fear extinction, carrying important implications for the centrality of fear extinction in PTSD. This notion has important clinical implications, with these risk factors potentially affecting exposure-based treatments of PTSD. However the influence of many of these variables on exposure

therapy outcome in PTSD is yet to be explored, and may aid in improving current treatment models, and in improving treatment itself. In short, research is consistent that risk factors of PTSD share an important relationship with fear extinction memory, and we suggest that fear extinction may be a central variable linking these risk factors to PTSD development and symptom persistence.

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