

Inflammation in Fear- and Anxiety-Based Disorders: PTSD, GAD, and Beyond

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The study of inflammation in fear- and anxiety-based disorders has gained interest as growing literature indicates that pro-inflammatory markers can directly modulate affective behavior. Indeed, heightened concentrations of inflammatory signals, including cytokines and C-reactive protein, have been described in posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), panic disorder (PD), and phobias (agoraphobia, social phobia, etc.). However, not all reports indicate a positive association between inflammation and fear- and anxiety-based symptoms, suggesting that other factors are important in future assessments of inflammation's role in the maintenance of these disorders (ie, sex, co-morbid conditions, types of trauma exposure, and behavioral sources of inflammation). The most parsimonious explanation of increased inflammation in PTSD, GAD, PD, and phobias is via the activation of the stress response and central and peripheral immune cells to release cytokines. Dysregulation of the stress axis in the face of increased sympathetic tone and decreased parasympathetic activity characteristic of anxiety disorders could further augment inflammation and contribute to increased symptoms by having direct effects on brain regions critical for the regulation of fear and anxiety (such as the prefrontal cortex, insula, amygdala, and hippocampus). Taken together, the available data suggest that targeting inflammation may serve as a potential therapeutic target for treating these fear- and anxiety-based disorders in the future. However, the field must continue to characterize the specific role pro-inflammatory signaling in the maintenance of these unique psychiatric conditions.

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INTRODUCTION

Fear- and anxiety-related psychiatric disorders are all associated with exaggerated fear reactions to stimuli specific to each disorder in the absence of any actual danger (Singewald *et al*, 2015). Indeed, posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), panic disorder (PD), and phobias (agoraphobia, social phobia, etc.) are all characterized by pathological fear and/or anxiety (APA, 2014). Furthermore, these fear and anxiety disorders are associated with impaired ability to extinguish learned fear and compromised capacity to learn safety behaviors (Singewald *et al*, 2015). Together, fear- and anxiety-based psychiatric disorders are at the same time the most prevalent (Kessler *et al*, 2005) and the most costly of mental health disorders (Gustavsson *et al*, 2011). As PTSD and other fear related disorders are associated with an array of other adverse mental and physical health outcomes (Boscarino,

2004; Kessler *et al*, 2005), ongoing translational and clinical research has focused on elucidating the neurobiological substrates underlying these conditions in order to inform the development of treatments and interventions that attenuate and/or prevent their associated adverse outcomes.

One biological process that has been increasingly interrogated over the last decade is the inflammatory system, as it has a clear role in the pathophysiology of chronic mental and physical illness. Immune signaling contributes to the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and other neurobiological processes that modulate affective behavior in the face of stressor exposure (Haroon *et al*, 2012). Indeed, exposure to traumatic and stressful events (including exposure to fear- and anxiety-provoking stimuli) results in HPA axis reactivity, activation of the immune system, and the release of pro-inflammatory cytokines (reviewed in Haroon *et al* (2012)). Over time and with continuous exposure to stressors, both HPA and immune function become dysregulated. Although extensive work has been done to characterize the role of endocrine dysfunction in the pathophysiology and maintenance of PTSD (Daskalakis *et al*, 2013; Hauger *et al*, 2012; O'Donovan *et al*, 2013; Yehuda and LeDoux, 2007), our understanding of the role of inflammation in the etiology and maintenance of

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fear- and anxiety-based disorders remains limited. Thus, in the current review, we will summarize significant findings that indicate that PTSD, and other fear- and anxiety-based disorders, are characterized by increased inflammatory processes associated with greater symptom severity. We focus specifically on alterations in pro- and anti-inflammatory signals, *in* and *ex vivo* stimulation of the immune cell responses and distribution, and immune transcription factors, gene expression and methylation in these disorders. We will also discuss the limited data available that suggest anxiety disorders are similarly associated with increased inflammation. For the purposes of this review, we will focus exclusively on anxiety disorders as defined by the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (APA, 2014), namely GAD, PD, and phobias. Finally, we will discuss the neurobiological mechanisms by which heightened inflammation occurs in these fear- and anxiety-related disorders and how inflammatory processes may work to exacerbate severity of these conditions. Understanding the role of inflammation in these highly prevalent and burdensome disorders has important translational and clinical implications, potentially offering new therapeutic targets for treatment upon future investigation.

PTSD and Inflammation

PTSD is a severe and heterogeneous psychiatric condition, often presenting with different re-experiencing, avoidance/numbing, and hyperarousal symptoms following exposure to a life-threatening event that results in psychological trauma (ie, exposure to an event including death or threatened death, actual or threatened serious injury, or actual or threatened sexual violence; Kessler *et al*, 1995). Underlying alterations in neuroendocrine, psychophysiological, and neurobiological systems have all been implicated in the etiology and maintenance of PTSD (for review see Michopoulos *et al* (2015b)). Importantly, although many will experience a traumatic event in their lifetime (70% of the general population), only 7.8% of the US population will go on to develop PTSD in the aftermath of trauma (Keane *et al*, 2009). PTSD is associated with significant co-morbidities including major depression, substance and alcohol abuse, PD, suicide, reduced life expectancy, as well as disability in daily activities, and increased health care utilization (Dedert *et al*, 2010; Khoury *et al*, 2010; Norrholm *et al*, 2011). Adverse physical health co-morbidities are also common in individuals with PTSD, including obesity, diabetes, cardiovascular disease (Boscarino, 2004; Coughlin, 2011; Heppner *et al*, 2009). These data in parallel with evidence indicating that PTSD is a chronic disorder with dysregulated stress axis function (Michopoulos *et al*, 2015b), have recently led to a burgeoning attempt to understand how inflammatory processes in the context of trauma exposure and PTSD are altered, and how they might drive changes in neurobiological pathways and affective behavior.

Alterations in basal concentrations of inflammatory signals in PTSD. Exposure to trauma is associated with pro-

inflammatory activity (Tursich *et al*, 2014). Specifically, increased circulating concentrations of interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α , and the acute phase reactant C-reactive protein (CRP) are all significantly associated with trauma exposure as shown in a recent meta-analysis (Tursich *et al*, 2014). The majority of these studies have specifically assessed the influence of childhood maltreatment and adversity on inflammation in adulthood (Baumeister *et al*, 2015; Lin *et al*, 2016). Indeed, individuals who were exposed to childhood maltreatment, as well as those exposed to difficult family and socio-economic circumstances in childhood (Taylor *et al*, 2006), show heightened levels of CRP in adulthood (Bertone-Johnson *et al*, 2012; Danese *et al*, 2007; Lin *et al*, 2016; Matthews *et al*, 2014; Rooks *et al*, 2012; Tietjen *et al*, 2012). Parental separation in early childhood is also associated with increased CRP in adulthood (Lacey *et al*, 2013; McDade *et al*, 2013). Concentrations of IL-6, IL-1 β , and TNF- α are elevated with childhood maltreatment (Gouin *et al*, 2012; Hartwell *et al*, 2013; Kiecolt-Glaser *et al*, 2011; Smith *et al*, 2011; Tietjen *et al*, 2012). Importantly, exposure to trauma in childhood is associated with increased risk for developing PTSD and other psychiatric conditions (Edwards *et al*, 2003).

Elevated concentrations of pro-inflammatory markers have been observed in individuals with PTSD (Guo *et al*, 2012; Hoge *et al*, 2009; Table 1, A). More specifically, circulating concentrations of IL-1 β (Oganesyan *et al*, 2009; Spivak *et al*, 1997; Tucker *et al*, 2004; von Kanel *et al*, 2007), IL-2 (Guo *et al*, 2012), and IL-6 (Bersani *et al*, 2016; Guo *et al*, 2012; Maes *et al*, 1999; Newton *et al*, 2014; Oganesyan *et al*, 2009) are elevated in PTSD. Central levels of IL-6 in cerebrospinal fluid have also been found to be elevated in PTSD (Baker *et al*, 2001). Concentrations of TNF- α are also increased in PTSD (Bersani *et al*, 2016; Oganesyan *et al*, 2009; Vidovic *et al*, 2011; von Kanel *et al*, 2007), and correlate positively with total PTSD symptomology, as well as all three DSM-IV-TR symptom sub-clusters (ie, avoidance, re-experiencing, and hyperarousal (von Kanel *et al*, 2007)). In addition, peripheral intercellular adhesion molecule-1 (Guo *et al*, 2012; Hoge *et al*, 2009; Plantinga *et al*, 2013) and interferon (INF)- γ (Hoge *et al*, 2009) are elevated in individuals with PTSD. Increased concentrations of CRP are also seen in individuals with PTSD (Bersani *et al*, 2016; Heath *et al*, 2013; Miller *et al*, 2001; Plantinga *et al*, 2013). More recently, heightened peripheral CRP concentrations were associated with higher PTSD symptoms and greater odds for a PTSD diagnosis (Michopoulos *et al*, 2015c). Furthermore, elevated CRP is also associated with impaired inhibition of fear-potentiated startle in the presence of a safety signal, a well-characterized biomarker of PTSD (Jovanovic *et al*, 2012). Combining concentrations of IL-1 β , IL-6, TNF- α , INF- γ , and CRP into a single pro-inflammatory score also indicated that inflammation is elevated in PTSD (Lindqvist *et al*, 2014b).

Although these data together collectively indicate that PTSD is associated with increases in pro-inflammatory markers, there are also data suggesting that there is no relationship between PTSD and heightened inflammation.

TABLE 1 Pro- (1A) and Anti- (1B) Immunological Factors Associated with PTSD

1A: Pro-inflammatory signals	Increased in PTSD	Opposite/no relationship in PTSD	Upheld in Passos <i>et al</i> (2015) meta-analysis
Interleukin-2	Guo <i>et al</i> (2012)	Tucker <i>et al</i> (2004) and Song <i>et al</i> (2007b)	—
Interleukin-6	Bersani <i>et al</i> (2016), Lindqvist <i>et al</i> (2014a), Maes <i>et al</i> (1999), Newton <i>et al</i> (2014), and Oganesyan <i>et al</i> (2009)	von Kanel <i>et al</i> (2007)	*
Interleukin-1 β	Lindqvist <i>et al</i> (2014a), Oganesyan <i>et al</i> (2009), Spivak <i>et al</i> (1997), Tucker <i>et al</i> (2004), and von Kanel <i>et al</i> (2007)	Smith <i>et al</i> (2011) and Hoge <i>et al</i> (2009)	*
C-reactive protein	Bersani <i>et al</i> (2016), Heath <i>et al</i> (2013), Lindqvist <i>et al</i> (2014a), Miller <i>et al</i> (2001), and Plantinga <i>et al</i> (2013)	McCanlies <i>et al</i> (2011), Muhtz <i>et al</i> (2011), Sondergaard <i>et al</i> (2004), and von Kanel <i>et al</i> (2007)	—
Interferon- γ	Hoge <i>et al</i> (2009) and Lindqvist <i>et al</i> (2014a)	—	*
Tumor necrosis factor- α	Bersani <i>et al</i> (2016), Lindqvist <i>et al</i> (2014a), Vidovic <i>et al</i> (2011), and von Kanel <i>et al</i> (2007)	—	*

1B: Anti-inflammatory signals	Decreased in PTSD	Opposite/no relationship in PTSD	Upheld in Passos <i>et al</i> (2015) meta-analysis
Interleukin-4	Smith <i>et al</i> (2011) and von Kanel <i>et al</i> (2007)	Guo <i>et al</i> (2012), Hoge <i>et al</i> (2009), and von Kanel <i>et al</i> (2007)	—
Interleukin-8	Song <i>et al</i> (2007a)	Guo <i>et al</i> (2012) and Hoge <i>et al</i> (2009)	—
Interleukin-10	—	Guo <i>et al</i> (2012), Hoge <i>et al</i> (2009), and von Kanel <i>et al</i> (2007)	—

Asterisks denote signals that were significantly different between PTSD cases and healthy controls in systematic meta-analysis conducted by Passos *et al* (2015).

For instance, studies have described decreased levels of CRP in individuals with PTSD (Sondergaard *et al*, 2004) or even a lack of association between PTSD and CRP levels (McCanlies *et al*, 2011; Muhtz *et al*, 2011; von Kanel *et al*, 2007), and PTSD and IL-6 (Song *et al*, 2007b) and IL-2 (Song *et al*, 2007b; Tucker *et al*, 2004). This same discrepancy in the literature also surrounds alterations in anti-inflammatory cytokines in individuals with PTSD (Table 1, B). In some studies, concentrations of IL-8 (Jergovic *et al*, 2015; Song *et al*, 2007b) and IL-4 (Smith *et al*, 2011; von Kanel *et al*, 2007) are lower in individuals with PTSD. IL-4 concentrations have also been correlated negatively with total hyperarousal symptoms (von Kanel *et al*, 2007). However, there are also reports of increased concentrations of IL-4, IL-8, and IL-10 in those with PTSD (Guo *et al*, 2012). The inconsistencies between these published reports on PTSD and inflammation may be related to small sample sizes, distinct study and ethnic populations, the presence of uncontrolled confounders (medication usage, presence of infection, co-morbidity with depression, and other chronic illnesses), and the use of different control groups for comparison.

A meta-analysis comparing individuals with PTSD and healthy, non-traumatized controls from 20 independent studies was recently conducted to systematically address whether PTSD is associated with alterations in inflammatory signals discussed above and outlined in Table 1 (Passos *et al*, 2015). The systematic meta-analysis revealed that levels of IL-1 β , IL-6, TNF- α , and IFN- γ are elevated in PTSD (Passos *et al*, 2015). Analyses also revealed that the duration of illness was associated positively with pro-inflammatory markers (Passos *et al*, 2015). Furthermore, the authors were able to conduct subgroup meta-analyses to disentangle to influence

of possible confounders, such as medication usage and comorbid major depression. TNF- α concentrations are still significantly associated with PTSD in unmedicated individuals, and TNF- α , IL-1 β , and IL-6 levels are still augmented significantly in those with PTSD and no co-morbid depression (Passos *et al*, 2015). Although this meta-analysis and coincident subgroup analysis move the field forward, future studies and analyses are necessary to determine how other factors (ie, smoking status, alcohol use, obesity, infection, and pulmonary and cardiovascular disease) influence the association between PTSD and inflammation.

Immune challenge response is altered in PTSD. Importantly, changes in circulating inflammatory markers are not the only alterations in inflammatory pathways reported in PTSD. The production of circulating cytokines in response to an immune challenge is also altered in individuals with PTSD such that production of pro-inflammatory markers is increased and production of anti-inflammatory markers is decreased. More specifically, endotoxin-induced increases in IL-6 are heightened in individuals with PTSD (Rohleder *et al*, 2004). *Ex vivo* administration of phytohemagglutinin (PHA), a potent inducer of cytokine production from T cells, to peripheral blood mononuclear cells (PBMCs) results in heightened increases in TNF- α and IL-6 secretion in individuals with PTSD compared with traumatized and non-traumatized controls (Gill *et al*, 2008). In contrast, production of anti-inflammatory IL-4 and the antiviral IFN- γ in blood following PHA stimulation in men with PTSD is attenuated compared with matched controls without PTSD (Kawamura *et al*, 2001). There has also been one report that increased spontaneous production of IL-1 and TNF- α in

PBMCs is present in individuals with PTSD compared with healthy controls (Gola *et al*, 2013). Finally, cell-mediated immunity, as assessed with a delayed-type hypersensitivity *in vivo* skin test, has also been shown to be enhanced in individuals with PTSD (Altemus *et al*, 2003; Masoudzadeh *et al*, 2012).

PTSD is associated with differential immune cell distribution and function. The above-described perturbations in the production and response of cytokines suggest that the function and distribution of immune cells may be altered in individuals with PTSD. Greater percentages and numbers of lymphocytes (Boscarino and Chang, 1999b; Vidovic *et al*, 2011), as well as greater T cells and leukocytes (Boscarino and Chang, 1999b) have been associated with the presence of PTSD. Individuals with PTSD also have reduced numbers of naive CD8(+) T lymphocytes and increases in the proportions of CD3(+) central and effector memory T lymphocytes compared with individuals without PTSD (Sommershof *et al*, 2009). Furthermore, higher levels of CD4 and CD5 expression (a marker of early immune response activation; Lemieux *et al*, 2008) on T cells is correlated positively with intrusive and negatively with avoidant symptoms in women with PTSD (Lemieux *et al*, 2008). Individuals with PTSD also exhibit increases in total PBMCs, pro-inflammatory Th1 and Th17 cells, and decreased T-regulatory (T-reg) cells that are correlated with increased peripheral concentrations of IFN- γ and IL-17 (Zhou *et al*, 2014). Because T-reg cells are critical for containing pro-inflammatory responses and Th1 and Th17 cells activate inflammatory responses (Afzali *et al*, 2007), these alterations in the composition of T-cell subsets may act in aggregate to direct systemic inflammatory tone into an overdrive state in PTSD (Jergovic *et al*, 2014). Finally, immunological aging of T-cell phenotypes has also been associated with PTSD (Aiello *et al*, 2016).

Immune gene transcription, expression, and methylation changes in PTSD. Alterations in the transcriptional patterns of expression for genes involved in inflammatory pathways have also been associated with PTSD (Segman *et al*, 2005; Yehuda *et al*, 2009; Zieker *et al*, 2007). Nuclear factor- κ B (NF κ B), signal transducer and activator of transcription 5B, and nuclear factor I/A are all critical transcription factors with substantive roles in the activation of cytokine responses to challenge whose activity is increased in the presence of PTSD (Guardado *et al*, 2016; O'Donovan *et al*, 2011; Pace *et al*, 2012; Sarapas *et al*, 2011). Gene expression of the pro-inflammatory cytokine IL-18 and its receptor IL-18R1 is decreased in individuals with PTSD (Mehta *et al*, 2011; Segman *et al*, 2005; Zieker *et al*, 2007). This decrease in IL-18 gene expression is consistent with epigenetic findings indicating that increased methylation in the promoter region of IL-18 is associated with the development of PTSD in soldiers following military deployment (Rusiecki *et al*, 2013). Gene expression of IL-16 is also downregulated, whereas expression of the IL-8 receptor is upregulated in chronic PTSD (Zieker *et al*, 2007). In addition, transcripts of genes

encoding enzymes involved in metabolism of reactive oxygen species (ROS) such as GSTM1 and GSTM2 (glutathione S-transferase mu 1 and 2) are altered in chronic PTSD (Neylan *et al*, 2011) and have been associated with risk for PTSD development in a prospective manner (Glatt *et al*, 2013; Tylee *et al*, 2015). Finally, the expression of the gene for thioredoxin (*TXNRD1*), a protein critical for responding to oxidative stress, is elevated in subjects with PTSD compared with traumatized controls (Logue *et al*, 2015).

The changes in inflammatory gene expression that have been described in individuals with PTSD are coincident with alterations in epigenetic markers, as immune-related methylation profiles are altered in PTSD (Heinzelmann and Gill, 2013). Methylation of mannosidase, alpha class 2C, member 1 (*MAN2C1*), acid phosphatase 5 (*ACP5*), and toll-like receptor (*TLR*) 8, which are genes involved in immune function, was found to be altered in PTSD (Smith *et al*, 2011; Uddin *et al*, 2011). Decreased methylation of immune-related genes *TLR1* and *TLR3* has also been described in individuals with PTSD in a manner related to the severity and burden of the traumatic event (Uddin *et al*, 2010). This epigenetic variability in immune function in PTSD is associated with exaggerated immune response to a cytomegalovirus challenge (Uddin *et al*, 2010). Furthermore, a recent analysis of microRNA expression in PBMCs from individuals with PTSD revealed that levels of microRNAs involved in immune signaling pathways are dysregulated (Zhou *et al*, 2014). Specifically, expression of microRNA-125a (MiR-125a) is downregulated in PTSD (Zhou *et al*, 2014). MiR-125a typically acts to decrease IFN- γ secretion from PBMCs, suggesting that lower levels of this microRNA in PTSD facilitate augmented IFN- γ levels.

Although a substantial amount of work has been done to characterize immune-related alterations in gene expression and methylation, there is a paucity of studies that address genomic markers that are associated with both heightened inflammation and PTSD severity. Results from a single genome-wide association study of PTSD indicate that PTSD in women is associated with an enrichment of genes involved in inflammatory pathways (Guffanti *et al*, 2013). Similarly, so far only one study, which we are aware of, has assessed the influence of single-nucleotide polymorphisms (SNPs) within an inflammatory genes that increases risk for inflammation and PTSD (Michopoulos *et al*, 2015c). This study determined that a single SNP in the *CRP* gene, rs1130864, was associated with heightened peripheral concentrations of CRP, augmented PTSD symptoms, and increased odds of a PTSD diagnosis in traumatized individuals (Michopoulos *et al*, 2015c). Overall, the discussed cross-sectional genetic and epigenetic studies indicate that higher inflammation is associated with increased PTSD severity. However, these genomic findings suggest that heightened baseline inflammatory markers due to genetic variability may serve as a biomarker of PTSD vulnerability.

The notion that augmented inflammation prior to trauma exposure increases individual risk for PTSD is supported by more recent prospective studies of PTSD risk. Indeed, higher

pre-deployment concentrations of CRP increase post-deployment risk for development of PTSD (Eraly *et al*, 2014). Elevated IL-6 concentrations immediately following exposure to motor vehicle collision in child trauma survivors are also predictive of elevated risk for PTSD development (Pervanidou *et al*, 2007). High IL-8 and low transforming growth factor- β (TFG- β , normally involved in immunosuppression) have also been shown to be predictors of PTSD in the acute aftermath of trauma (Cohen *et al*, 2011). Transcripts of genes involved in ROS metabolism, including *GSTM1* and *GSTM2*, have been associated with risk for PTSD development in a prospective manner (Glatt *et al*, 2013; Tylee *et al*, 2015). In addition, enriched expression of genes implicated in innate immunity and INF signaling at baseline (pre-deployment) is associated with increased risk for PTSD development post-deployment (Breen *et al*, 2015).

Overall, existing findings indicate that PTSD is associated with a pro-inflammatory state. Peripheral levels of cytokines and CRP are elevated in individuals with PTSD. Heightened expression of pro-inflammatory genes and coincident alterations in methylation patterns are also altered in PTSD. However, not all studies addressing this relationship have reported a positive association between increased inflammation and PTSD (McCanlies *et al*, 2011; Sondergaard *et al*, 2004; von Kanel *et al*, 2007). This discrepancy in the literature highlights the importance of other factors that may be influencing the association between inflammation and PTSD, such as type and chronicity of trauma exposure, clinician-administered *vs* self-reported measures of PTSD diagnosis, control group assessed (healthy *vs* trauma-exposed), and sociodemographics of individuals studied. The association between PTSD and inflammation is also impacted by other adverse mental and physical health outcomes, including depression (Gill *et al*, 2010; Maes *et al*, 1999) and cardiovascular disease (Spitzer *et al*, 2010; von Kanel *et al*, 2007), indicating that taking these co-morbid conditions into account when studying the relationship between PTSD and inflammation is critical in future studies. Furthermore, preclinical studies have suggested that stress-induced inflammatory responses can be causally related to hypertension and other cardiovascular risk factors secondary to T-lymphocyte and inflammatory effects on the vascular cellular architecture (Marvar *et al*, 2012).

Another important consideration is that the majority of studies examining the link between inflammation and PTSD have been cross-sectional in nature, and thus not able to address causation, or whether alterations in immune function precede trauma exposure or develop after trauma with chronic PTSD. Although no data as yet prospectively demonstrate that chronic PTSD results in augmented inflammation, prospective studies have begun to show that higher levels of inflammation prior to trauma exposure increases risk for subsequent development of PTSD following trauma exposure (Breen *et al*, 2015; Eraly *et al*, 2014; Glatt *et al*, 2013; Tylee *et al*, 2015). Continued accumulation of such prospective data is particularly important as it may aid in the identification of primary, and perhaps secondary

prevention strategies to reduce risk for PTSD, or its exacerbation, in populations at high risk of trauma exposure.

Fear- and Anxiety-Based Disorders and Inflammation

The primary anxiety disorders, based on the relatively new DSM-5 nosology of fear- and anxiety-based disorders include GAD (excessive anxiety and worry paired with physical symptoms), PD (recurrent, unexpected panic attacks coupled with fear of future attacks), agoraphobia (intense fear or anxiety triggered by anticipation of exposure to places from which escape would be difficult or help not readily available), social phobia (avoidance of social situations due to fear of negative evaluation), and specific phobia (excessive fear and avoidance of a circumscribed class of objects or contexts). Although each of these anxiety disorders has its own distinct set of diagnostic criteria, the disorders share underlying features of excessive fear and anxiety, and thus may also share neurobiological features. GAD, PD, agoraphobia, social phobia, and specific phobias are often found to be highly co-morbid with each other as well as other psychiatric disorders including depression, PTSD, and substance-use disorders (Conway *et al*, 2006; Kaufman and Charney, 2000; Regier *et al*, 1998). These anxiety disorders often emerge early in life and are associated with a long course of illness and significant functional impairment. In contrast to PTSD, the literature on inflammation in relation to anxiety disorders remains extremely limited. Findings are equivocal and significant variability in samples studied as well as the measures used makes adequate comparisons across studies challenging. The majority of published studies has examined individual anxiety disorders and has focused predominantly on GAD, PD, and agoraphobia. Our review of the literature did not identify any studies examining associations between social phobia or specific phobias and inflammation. Therefore, we will provide a brief overview of the findings on altered immune function from studies examining GAD and PD (both with and without agoraphobia), as well as agoraphobia.

Initial evidence indicates that anxiety disorders may be related to heightened pro-inflammatory markers, with one study that used a mixed anxiety disorder patient group finding increased levels of CRP among male anxiety disorder patients compared with controls (Vogelzangs *et al*, 2013). Other evidence in children with GAD (Copeland *et al*, 2012) and stable coronary heart disease patients with GAD (Bankier *et al*, 2008) also found higher rates of CRP in individuals with GAD compared with controls. In contrast, in a sample of patients with agoraphobia, no difference in mean level of CRP compared with controls was found, although agoraphobic patients did show a significant increase in CRP levels over time, whereas controls did not (Wagner *et al*, 2015). Findings have also been equivocal with regard to peripheral cytokine levels. For example, some studies have found increased circulating concentrations of TNF- α among GAD (Vieira *et al*, 2010) and PD patients (Hoge *et al*, 2009), whereas other research has found no

difference in TNF- α concentrations between anxiety disorders more generally (Vogelzangs *et al*, 2013), agoraphobia (Wagner *et al*, 2015) or PD patients and controls (Brambilla *et al*, 1999). Similarly, some studies have shown increased levels of IL-1 β (Brambilla *et al*, 1994; Hoge *et al*, 2009) and IL-6 (Hoge *et al*, 2009) in PD patients, whereas others have found no difference in IL-1 β and IL-6 between PD patients and controls (Rapaport and Stein, 1994; Tukul *et al*, 2012). Interestingly, lower levels of the pro-inflammatory cytokine IFN- γ have been found in both GAD and PD patients (Tukul *et al*, 2012; Vieira *et al*, 2010). Lower circulating concentrations of anti-inflammatory cytokines such as IL-2 and IL-4 have also been described in GAD patients (Vieira *et al*, 2010). However, IL-4 and IL-2 have also been found to be increased in PD (Hoge *et al*, 2009; Koh and Lee, 2004; Rapaport and Stein, 1994) or not different from controls in individuals with PD (Tukul *et al*, 2012).

Looking beyond inflammatory marker levels, evidence with regard to immune function or genetic mechanisms in relation to anxiety disorders remains unclear. Two studies examining immune function using circulating lymphocyte phenotypic markers in PD patients found evidence that individuals with PD may show alterations in circulating lymphocyte profiles or diminished cell activation (Manfro *et al*, 2000; Rapaport, 1998). Other evidence in a mixed anxiety disorder group found that those with anxiety disorders had lymphocyte and T-cell counts above the average range, as well as highly sensitized T-cell lymphocytes (Boscarino and Chang, 1999b). Similarly, studies of potential genetic and epigenetic alterations of immune function in relation to anxiety disorders are scarce. To our knowledge, only one study has been conducted on immune-related gene expression in GAD. Within a community sample of individuals with and without GAD, Wingo and Gibson (2015) found that only males with GAD showed changes in immune-related gene expression compared with controls (Wingo and Gibson, 2015).

Overall, the existing findings provide some preliminary evidence that GAD and PD in particular may be associated with a pro-inflammatory state, as evidenced by findings that peripheral concentrations of cytokines and CRP are elevated in these disorders. As not all studies addressing this relationship have reported a positive association between increased inflammation and these anxiety disorders, the importance of factors such as population assessed (community *vs* clinical), clinician-administered *vs* self-reported measures of anxiety disorder diagnosis, sociodemographic factors of individuals studied (eg, sex), and co-morbid mental and physical health problems must be considered. Looking more generally at anxiety and associations with pro-inflammatory markers in non-patient populations, researchers have found evidence that anxiety is related to higher concentrations of CRP and peripheral cytokines (Brennan *et al*, 2009; O'Donovan *et al*, 2010; Pitsavos *et al*, 2006) and predicts increased inflammatory response following acute stress (Carroll *et al*, 2011; Moons *et al*, 2010; Moons and Shields, 2015), demonstrating that anxiety and fear even at

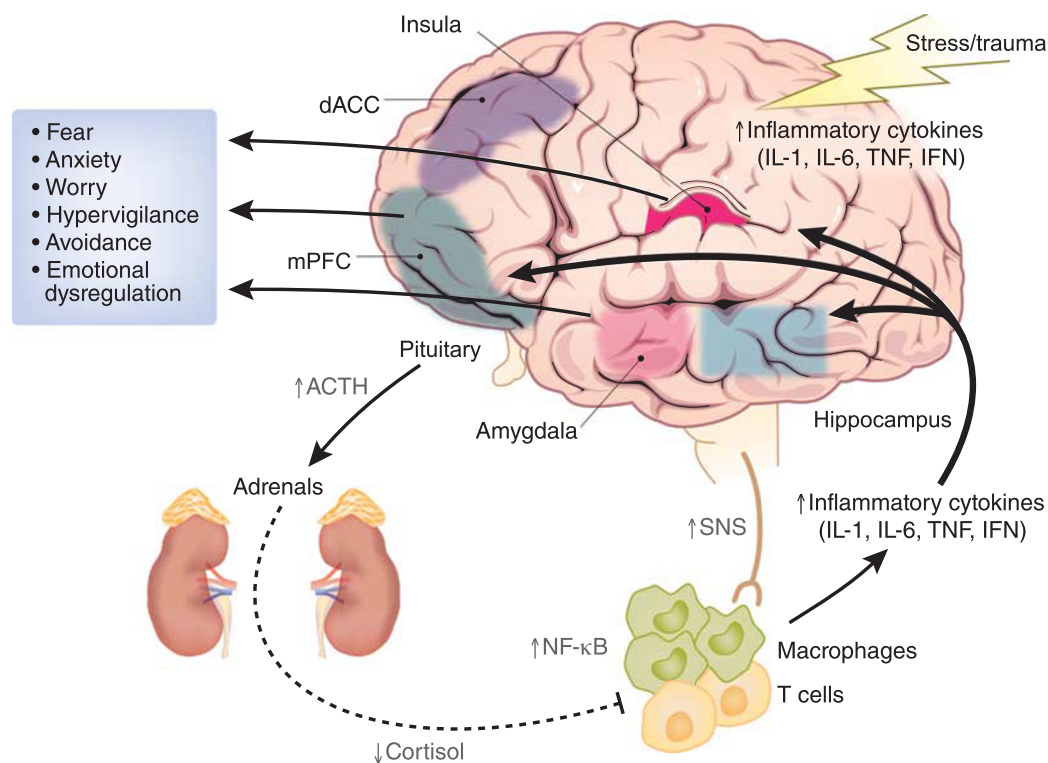
non-clinical levels impacts the immune response in important ways. There remains a great deal to understand about the association between anxiety disorders and inflammation, and more research is needed before any clear conclusions can be made.

Mechanisms of Increased Inflammation in Fear- and Anxiety-Based Disorders

The most parsimonious explanation of increased inflammation in fear- and anxiety-based disorders is via the activation of the stress response (Figure 1). Prolonged exposure to stressful stimuli that elicit fear and anxiety in PTSD, GAD, PD, and phobias activate both central and peripheral immune cells to release cytokines, such as IL-1 β (Koo and Duman, 2008; Maier and Watkins, 1998). For example, exposure to the laboratory Trier Social Stress Test activates the peripheral inflammatory response via increased NF κ B transcriptional activity that results in increased circulating concentrations of IL-6 (Bierhaus *et al*, 2003). On a cellular level, the release of danger-associated molecular patterns, such as heat-shock proteins and adenosine triphosphate, in response to stress exposure induces a NLRP3 inflammasome response that leads to the release of IL-1 β and other cytokines (Iwata *et al*, 2013; Maslanik *et al*, 2013). Although exposure to stressors can lead directly to increased inflammation through these aforementioned processes in the absence of pathogens, activation of the HPA axis and autonomic nervous system also modulate stress-induced inflammatory processes in a reciprocal manner.

HPA axis activation and subsequent secretion of glucocorticoids in response to stressor exposure typically acts to prevent pro-inflammatory activity via inhibition of NF κ B (Rhen and Cidlowski, 2005). In contrast, increased norepinephrine production following stressor exposure induces NF κ B activity that activates the immune system and increases cytokine production (Bierhaus *et al*, 2003). This sympathetic activation of the innate immune system acts via nerve fibers that innervate lymphoid organs that coordinate the innate immune responses to threat via alterations in adrenergic signaling (Nance and Sanders, 2007; Tan *et al*, 2007). Interestingly, evidence suggests that activation of the parasympathetic nervous system also can modulate the activity of the immune system via alterations in vagal release of acetylcholine from T cells (Tracey, 2009). For example, motor vagus nerve stimulation attenuates the activation of NF κ B following an immune challenge (Tracey, 2009). Taken together, these data suggest that any chronic condition that results in the diminished actions of glucocorticoids, and increased sympathetic and decreased parasympathetic activity should occur in tandem with increased inflammation. PTSD represents exactly such a chronic condition.

HPA axis dysregulation in PTSD facilitates a pro-inflammatory state. Exposure to trauma activates neuroendocrine responses and leads to long-lasting changes in the regulation of the HPA axis that compromise its ability to



Adapted from Felger *et al.* 2016

Figure 1. Inflammation in fear- and anxiety-based disorders: mechanisms and consequences. Exposure to trauma and acute stressors in individuals with fear- and anxiety-based may facilitate increased immune activity in both the periphery and the central nervous system (CNS) via stress and trauma effects on neuroendocrine systems and the sympathetic nervous system (SNS). The overactivity of the SNS and decreased activity of the parasympathetic nervous system in fear- and anxiety-based disorders increases the release of pro-inflammatory cytokines. Suppressed ability of glucocorticoids to inhibit inflammatory processes in these chronic stress states also contributes to a pro-inflammatory state that can influence neurotransmitter systems, neurocircuitry, and finally, affective behavior. Cytokines may contribute to the maintenance of fear- and anxiety-based symptoms by affecting the activity and connections of regions of the brain implicated in the etiology of these disorders, including the amygdala, hippocampus, insula, medial prefrontal cortex (mPFC), and the anterior cingulate (ACC). Figure adapted from Felger *et al.* (2016) and reproduced by permission of Oxford University Press (<http://global.oup.com/?cc=us>).

function appropriately. Decreased basal levels of circulating (Yehuda *et al.*, 2005) and urinary free cortisol (Mason *et al.*, 1986) have been described in individuals with PTSD. However, studies have also found increased or no differences in basal glucocorticoid levels (Meewisse *et al.*, 2007) and diurnal cortisol rhythms in individuals with PTSD (Freidenberg *et al.*, 2010; Maes *et al.*, 1998), suggesting that other factors maybe be contributing to HPA dysregulation in PTSD, such as sex (Freidenberg *et al.*, 2010), type and duration of trauma exposure, and severity of PTSD symptoms (Shea *et al.*, 2005). Regardless of the equivocal nature of findings describing differences in basal cortisol levels in individuals with PTSD, more consistent are the findings that PTSD is associated with enhanced glucocorticoid negative-feedback inhibition of the HPA axis as evidenced by increased suppression of cortisol levels following a dexamethasone-suppression test (Yehuda *et al.*, 1995). Heightened levels of peripheral and central corticotropin-releasing hormone (CRH; Baker *et al.*, 2005; de Kloet *et al.*, 2008) and elevated glucocorticoid receptor (GR) expression levels in lymphocytes (Matic *et al.*, 2013)

occur in tandem with enhanced glucocorticoid sensitivity in PTSD.

One critical modulator of HPA axis responsivity and glucocorticoid function is FKBP5, a heat-shock protein 90 co-chaperone that functions to negatively regulate the GR complex by inhibiting ligand binding and nuclear translocation of GR (reviewed in Binder (2009)). The expression of FKBP5 is induced by glucocorticoids, thus forming an ultra-short intracellular negative-feedback loop for GR activity in response to stressor exposure (Vermeer *et al.*, 2003), such that increased expression of FKBP5 following GR activation leads to the subsequent reduction in GR sensitivity (Binder, 2009). The reciprocal association between decreased levels of FKBP5-mRNA and enhanced GR sensitivity is characteristic of PTSD in trauma survivors (Yehuda *et al.*, 2009). Importantly, SNPs in the *FKBP5* gene that are associated with higher FKBP5-mRNA induction upon cortisol release (rs1360780, rs9296158, rs3800373, and rs9470080) are also associated with increased PTSD symptom severity in those with high levels of child abuse (Binder *et al.*, 2008). Interestingly, some alleles of these *FKBP5*-SNPs are

associated with enhanced glucocorticoid sensitivity, whereas other alleles of these SNPs are associated with GR resistance in individuals with PTSD (Binder *et al*, 2008).

Thus, the presence of these FKBP5 alleles can result in low levels of circulating cortisol and/or GR resistance in PTSD can lead to a pro-inflammatory state via decreases in anti-inflammatory GR signaling (Cohen *et al*, 2012). *FKBP5*-genotype status and trauma exposure history maybe also lead to increased inflammation, as exposure to childhood trauma is associated with epigenetic de-methylation near the rs1360780 *FKBP5*-SNP that is associated with GR dysregulation and increased expression of mRNA transcripts involved in T-cell receptor, TFG- β , and inflammatory response signaling pathways (Klengel *et al*, 2013). Together these data highlight the notion that both trauma exposure and PTSD can facilitate a pro-inflammatory state as described in Table 1. It is important to emphasize that this chronic low-grade inflammation characteristic of PTSD and other fear- and anxiety-based disorders can act to further impair GR signaling in a number of ways (reviewed in Pace *et al* (2007)). First, expression of GR is increased in whole-cell radioligand binding *in vitro* studies in response to challenge with pro-inflammatory cytokines (IL-6, TNF- α , and IFN- α ; Miller *et al*, 1999). Similar studies assessing cytosolic radioligand assays find GR expression to be decreased upon treatment with these same pro-inflammatory signals (Miller *et al*, 1999). Second, TNF- α or IL-1 administration *in vitro* alters the expression of the two GR isoforms, hGR α (active) and hGR β (non-active), via NF κ B activity (Webster *et al*, 2001). The proportion of hGR α (active) and hGR β directly influences the ability of glucocorticoids to activate GR-dependent genes by contributing to glucocorticoid resistance (Lewis-Tuffin and Cidlowski, 2006). Finally, cytokines can impair GR function by disrupting GR translocation and inhibiting downstream GR signaling, including NF κ B and mitogen-activated protein kinase cascades (Miller *et al*, 1999; Pace *et al*, 2007).

Autonomic nervous system and immune interactions in PTSD. Heightened sympathetic tone in the form of increased catecholamine secretion has been described consistently in individuals with PTSD (Southwick *et al*, 1999). Peripheral and central concentrations of norepinephrine are augmented in individuals with PTSD at baseline (Delahanty *et al*, 2005; Geraciotti *et al*, 2001; Southwick *et al*, 1999) and following exposure to threatening stimuli (Blanchard *et al*, 1991; Geraciotti *et al*, 2008). This increased norepinephrine production in PTSD in response to stressful or threatening stimuli can induce cytokine release (Bierhaus *et al*, 2003). The subsequent immune response occurs via NF κ B-dependent and -independent mechanisms (Bierhaus *et al*, 2003; Tan *et al*, 2007). More specifically, activation of adrenergic- β 2 receptors stimulates IL-6 and IL-1 β secretion from macrophages and monocytes via NF κ B and ERK signaling pathways, respectively (Bierhaus *et al*, 2003; Tan *et al*, 2007). Thus, the increased expression and function of adrenergic- β 2 receptors that has been described in

individuals with PTSD (Gurguis *et al*, 1999) can also contribute to increased inflammation in those with the disorder (Table 1). Finally, another robust phenotype characteristic of PTSD that may contribute to increased inflammation is decreased parasympathetic drive as evidenced by decreased heart rate variability (HRV; Blechert *et al*, 2007; Cohen *et al*, 2000).

HPA, autonomic nervous system, and immune interactions in other fear- and anxiety-based disorders. Hair cortisol levels are elevated in individuals with GAD and PD (Staufenbiel *et al*, 2013) and increased salivary cortisol concentrations have been associated with late-life GAD (Mantella *et al*, 2008). Higher cortisol awakening response has been described in individuals with PD with agoraphobia (Vreeburg *et al*, 2010) and cortisol nonsuppression in response to dexamethasone in those with agoraphobia and PD (Coryell *et al*, 1989). Although these data suggest that increased HPA axis functioning and GR dysregulation is present in these fear- and anxiety-based disorders, other reports have shown decreased cortisol levels or no differences in HPA axis function in those with GAD, PD, and phobia (Hek *et al*, 2013; van Veen *et al*, 2008). For instance, CRH levels in GAD and PD are not different from controls (Fossey *et al*, 1996; Jolkkonen *et al*, 1993). One factor that might account for these discrepancies is the onset of anxiety symptoms, as childhood anxiety disorder is associated with decreased basal HPA tone, increased sympathetic and attenuated parasympathetic activity (Dieleman *et al*, 2015). Increases in sympathetic tone, decreases in parasympathetic tone, and compromised vagal tone have also been described in PD (Blechert *et al*, 2007; Cohen *et al*, 2000). Similarly, studies have described decreased HRV in GAD (Thayer *et al*, 1996), social anxiety (Alvares *et al*, 2013), and specific phobia (Bornas *et al*, 2006). A recent meta-analysis concluded that all these anxiety disorders are all associated with reduced HRV (Chalmers *et al*, 2014). Taken together, the heightened sympathetic tone and reduction in parasympathetic activity, as well as the likely dysregulation of the HPA axis in anxiety disorders could lead to increased inflammation (Table 2) via similar pathways to those discussed above in the context of PTSD. However, future studies are necessary to better describe the effects of HPA axis and autonomic nervous system dysfunction on chronic low-grade inflammation in GAD, PD, social anxiety, and phobias.

Behavioral sources of inflammation in fear- and anxiety-based disorders. It is critical to keep in mind that there are many behavioral symptoms that also contribute to inflammatory response and functioning that often co-occur with PTSD and other fear- and anxiety-based disorders. These disorders cause intense distress and disrupt daily-life functioning, which in turn impacts general health habits and how individuals take care of themselves. For example, disruptions in regular sleep patterns can have a very detrimental effect on the immune system (Bryant *et al*, 2004) and persistent problems with sleep (eg, difficulty

TABLE 2 Immunological Factors Associated with Anxiety Disorders

Immune biomarkers	Relationship to anxiety disorders	References
Interleukin-6	Increased in PD	Hoge <i>et al</i> (2009)
Interleukin-1 β	Increased in PD	Brambilla <i>et al</i> (1994) and Hoge <i>et al</i> (2009)
Interleukin-2	Decreased in GAD Increased in PD	Koh and Lee (2004), Rapaport and Stein (1994), and Vieira <i>et al</i> (2010)
C-reactive protein	Increased in GAD Increases over time in agoraphobia	Bankier <i>et al</i> (2008), Copeland <i>et al</i> (2012), and Wagner <i>et al</i> (2015)
Tumor necrosis factor- α	Increased in GAD and PD Increases over time in agoraphobia	Hoge <i>et al</i> (2009), Vieira <i>et al</i> (2010), and Wagner <i>et al</i> (2015)

falling asleep, middle of the night awakenings) are a symptom of both PTSD and GAD. Severe sleep loss has been shown to increase circulating levels of CRP (Meier-Ewert *et al*, 2004) and IL-6 (Vgontzas *et al*, 1999). Even mild reductions in sleep quantity can increase inflammation levels (Vgontzas *et al*, 2004), suggesting that chronic problems with sleep, which is characteristic of PTSD and GAD, could contribute to a pro-inflammatory state.

Patients with PTSD or anxiety disorders may also be less likely to engage in healthy behavior, such as balanced eating and exercise, and more likely to engage in unhealthy behaviors, such as smoking. Indeed, individuals with PTSD and anxiety disorders are more likely to smoke (Fu *et al*, 2007; Morissette *et al*, 2007). PTSD and anxiety disorders are also associated with obesity, which may result in part from emotional eating behavior (Scott *et al*, 2008). Smoking has been linked to a pro-inflammatory state (Frohlich *et al*, 2003; Jamal *et al*, 2014). Obesity and high BMI are also associated with increased concentrations of inflammatory markers, such as CRP and IL-6 (Khaodhiar *et al*, 2004). However, at least with PTSD, increased inflammation levels have remained significant after adjusting for BMI in multiple studies (Heath *et al*, 2013; McCanlies *et al*, 2011; Spitzer *et al*, 2010). This suggests that although health risk factors such as smoking and BMI may contribute to inflammation, the relationship between inflammation and PTSD remains significant beyond these behavioral risk factors. Because of the strong impact of these behavioral symptoms on immune function, it will be important in future research to disentangle the particular effects of such behaviors from the effects of PTSD and anxiety disorders to better understand the unique contribution of fear- and anxiety-based disorders on inflammation.

Consequences of Increased Inflammation in Fear- and Anxiety-Based Disorders

Increased inflammation and cytokine activity in PTSD and other fear- and anxiety-based disorders can lead to an array of other adverse physical health and behavioral outcomes, including cardiovascular disease (CVD), diabetes, chronic fatigue syndrome, fibromyalgia, gastrointestinal disease, musculoskeletal disorders, and autoimmune disorders such as thyroiditis and rheumatoid arthritis, and irritable bowel

disease (Boscarino, 2004; O'Donovan *et al*, 2015b). A pro-inflammatory state may serve as an underlying biological mechanism by which PTSD and other fear- and anxiety-based disorders are highly co-morbid with CVD (Boscarino and Chang, 1999a) and metabolic syndrome (Weiss *et al*, 2011), as well as other physical illnesses (Boscarino, 2004). Furthermore, low-grade inflammation may also facilitate the expression of behavioral co-morbidities, such as depression, that are characterized by alterations in stress pathways and neurotransmitter systems (Haroon *et al*, 2012). Although inflammation can similarly facilitate changes in stress and metabolic systems in PTSD that may account for physical health co-morbidities associated with PTSD, those are out of the scope of the current review. We will next consider the effects of inflammation on neurocircuitry involved in the regulation of fear and anxiety that can contribute to the manifestation of fear and anxiety symptoms in PTSD, GAD, and other fear- and anxiety-based disorders.

Amygdala and hippocampus. The role of the amygdala in the etiology and maintenance of PTSD and other fear- and anxiety-based disorders has been very well characterized in translational neuroscience (Etkin and Wager, 2007). Specifically, amygdala activation in response to threatening stimuli is increased in PTSD, GAD, social anxiety disorder, specific phobia, and PD (Fonzo *et al*, 2015; Killgore *et al*, 2014; Monk *et al*, 2008). This heightened amygdala response to stress is associated with increased IL-6 production (Inagaki *et al*, 2012; Muscatell *et al*, 2015). Specifically, endotoxin administration in healthy controls increases IL-6 and TNF- α levels (Eisenberger *et al*, 2010) and amygdala response to socially threatening stimuli (Harrison *et al*, 2009b; Inagaki *et al*, 2012). Administration of typhoid vaccination also increases IL-6 response (Harrison *et al*, 2009a) and amygdala activity (Harrison *et al*, 2009b). Importantly, these increases in cytokine activity and amygdala responsivity to stress exposure are also associated with greater social disconnection and depressed mood (Muscatell *et al*, 2015), as well as cognitive disturbance and increased fatigue (Harrison *et al*, 2009b). Furthermore, this inflammation-induced amygdala response may also contribute to the association between increased CRP levels and heightened psychophysiological hyperarousal in traumatized individuals with PTSD (Michopoulos *et al*, 2015b).

The hippocampus is another brain structure within the medial temporal lobe whose function, structure, and functional connectivity with other regions is comprised in individuals with PTSD, GAD, and PD (Cui *et al*, 2016; Fani *et al*, 2012b; Woon *et al*, 2010). Hippocampal alterations, including smaller hippocampal volume, are associated with both emotional and cognitive deficits in individuals with PTSD (Bremner, 2006). Inflammatory processes may have a critical role in the etiology of hippocampal atrophy, as translational work in rodent models indicates that cytokines released from microglia inhibit neurogenesis within the dentate gyrus (Ekdahl *et al*, 2003) and promote neuronal apoptosis (Cunningham *et al*, 2005). In turn, reduced hippocampal volume is associated with increased inflammation and more severe PTSD symptoms in veterans (O'Donovan *et al*, 2015a). Cytokine actions can also facilitate cognitive and emotional deficits associated with PTSD, as IL-1 β blocks long-term potentiation in the hippocampus, and impairs spatial and contextual memory processing (Cunningham *et al*, 1996; Yirmiya and Goshen, 2011). Inflammatory challenges increase IL-1 in the medial temporal lobe (Ban *et al*, 1992) and also facilitate deficits in memory performance and contextual fear conditioning in rodents (Pugh *et al*, 1998; Yirmiya and Goshen, 2011). Finally, typhoid vaccination in healthy humans results in compromised spatial memory and decreased glucose metabolism in the perirhinal and entorhinal cortex (Harrison *et al*, 2014).

Medial prefrontal cortex and anterior cingulate. Regions of the medial prefrontal cortex (mPFC), including the rostral anterior cingulate cortex, subgenual ACC (sgACC, Brodmann's Area 25) and medial frontal gyrus, are all heavily connected to the amygdala and hippocampus, and critically involved in emotion regulation, attention bias, and fear extinction in individuals with PTSD and other anxiety disorders (Banich *et al*, 2009; Cui *et al*, 2016; Etkin and Wager, 2007; Fani *et al*, 2012a; Monk *et al*, 2008). Activation of the ventral mPFC (including the sgACC and the orbitofrontal cortex) due to a grief-elicitation task in women undergoing bereavement stress is associated with increased IL-1 β and TNF receptor II (TNF-II; O'Connor *et al*, 2009). Similarly, activation of the sgACC in response to typhoid vaccination is increased concurrently with mood deterioration (Harrison *et al*, 2009a). Functional connectivity between the sgACC and the amygdala and mPFC is also reduced upon typhoid vaccination in a manner that was associated with vaccine-induced increases in IL-6 (Harrison *et al*, 2009a). Similarly, increased CRP and IL-6 is associated with decreased functional connectivity between the ventral mPFC and the striatum (Felger *et al*, 2015). Finally, exposure to a laboratory stressor that increases IL-6 concentrations peripherally was associated with increased functional connectivity between the dorsomedial PFC and the amygdala in a manner that was correlated with IL-6 (Muscatell *et al*, 2015).

Another area that has been extensively studied in the context of inflammation effects of neurocircuitry is the

dorsal ACC (dACC, Brodmann's Area 24), as it is a target of central cytokine action and has a critical role in detecting and responding to threatening social and physical pain stimuli (Eisenberger and Lieberman, 2004). More specifically, the dACC serves as a stress-response system in both an emotional and physical way, as activation of the dACC leads to downstream stimulation of the autonomic nervous system (Critchley *et al*, 2005; Matthews *et al*, 2004). Neuroimaging studies in hepatitis C patients indicate that treatment with INF- α results in increased dACC activity that is correlated with visual-spatial-attention errors (Capuron *et al*, 2005). Typhoid vaccination also results in heightened activation of the dACC that is concurrent with increased blood flow during a Stroop task (Eisenberger and Lieberman, 2004; Harrison *et al*, 2009b). Similarly, endotoxin administration in healthy controls results in augmented social pain-related neural activity in the dACC that is associated with increases in IL-6 of females but not males (Eisenberger *et al*, 2005), corroborating previous reports of sex differences in inflammation in individuals with PTSD (Neylan *et al*, 2011).

Exaggerated activation of the dACC has been well described in individuals with PTSD (Felmingham *et al*, 2009; Milad *et al*, 2009; Pannu Hayes *et al*, 2009; Shin *et al*, 2007; Shin *et al*, 2001) and is associated with increased attention bias to threat (Fani *et al*, 2012a). Women with PTSD due to interpersonal trauma also show increased dACC activity in response to viewing threatening facing (Eisenberger *et al*, 2005). Individuals with neuroticism (Eisenberger *et al*, 2005) and high trait anxiety (Paulus *et al*, 2004) also show increased dACC activation. Augmented activity of the dACC has also been described as a mediator of hyperarousal symptoms in individuals with PTSD (Hamner *et al*, 1999), and has been associated with increased familial risk for PTSD development (Shin *et al*, 2011). Although most studies have focused on the role of mPFC and ACC in the etiology of PTSD, some studies indicate that the same regions are critical to the etiology of PD, GAD, social anxiety disorder, specific phobia, and agoraphobia. A meta-analysis indicates that reduced volume of the ventral ACC and the inferior frontal gyrus is common to anxiety disorders (social anxiety, GAD, PD, agoraphobia, and specific phobia; Shang *et al*, 2014). Finally, the dACC in the etiology of PD is suggested by data that indicate that surgery damage to the dACC can induce panic attacks (Shinoura *et al*, 2011). Overall these data indicate that inflammatory processes within the dACC may serve as a potent mechanism by which behavioral alterations may occur in individuals with fear- and anxiety-based disorders.

Insula. The insula is another brain area whose activity is associated with that of the amygdala and critical for the manifestation of emotional distress characteristic of PTSD and anxiety disorders. For instance, women with PTSD show decreased activation of the insula in response to shifts in interceptive responses (Simmons *et al*, 2009) and anxiety-prone individuals show heightened insula activity in anticipation of aversive visual stimuli (Simmons *et al*, 2006).

Women with PTSD from intimate partner violence show increased activation of the insula and amygdala, along with concurrent decreases in the functional connectivity between the insula, amygdala, and ACC (Fonzo *et al*, 2010). Increased activity of the insula has also been associated with other anxiety-based disorders (Paulus and Stein, 2006). Specifically, anxious individuals and those with PD (Fonzo *et al*, 2015) show increased insula activity (Alvarez *et al*, 2015). Importantly, peripheral inflammatory stimuli are capable of increasing the activity of the insula. Typhoid vaccination and endotoxin administration both increase insula activity (Eisenberger *et al*, 2009; Harrison *et al*, 2009b). Endotoxin administration also augmented glucose metabolism in the insula as determined by positron emission tomography neuroimaging (Hannestad *et al*, 2012).

Possible Mechanism by Which Inflammation Alters Brain and Behavior in Fear- and Anxiety-Based Disorders

It is clear that inflammatory processes influence neurobiological substrates underlying behavior and emotion characteristic of fear- and anxiety-based disorders (Figure 1). One biological mechanism by which inflammation influences neural networks critical for the regulation of emotional behavior and fear processes is by altering central neurotransmitter systems (reviewed in Dunn *et al* (1999)). For instance, administration of IFN- α for the treatment of hepatitis C increases glutamate to creatinine levels in the dACC that correlate with anhedonia and fatigue (Haroon *et al*, 2014). Increased CRP in depression is also associated with heightened glutamate levels within the basal ganglia (Haroon *et al*, 2016). Augmented release of glutamate from astrocytes has been shown to decrease brain-derived neurotrophic factor and increase excitotoxicity (Hardingham and Bading, 2010).

Cytokines can also lead to excitotoxicity by altering the function of indoleamine 2,3 dioxygenase, the enzyme that acts to convert tryptophan into kynurenine (Schwarcz, 2004). Kynurenine can be broken down by macrophages and microglia to form quinolinic acid, a *N*-methyl-*D*-aspartate receptor agonist that can directly simulate and block the reuptake of glutamate by astrocytes (Tavares *et al*, 2002). Although alterations in the kynurenine pathway have been described in major depression, there are currently no published accounts of alterations in this system in PTSD and other fear- and anxiety-based disorders. However, injections of TNF- α and IL-6 in the amygdala results in glutamate toxicity that is associated with impaired auditory fear conditioning in rodents (Hao *et al*, 2014; Jing *et al*, 2015). It is also important to note that levels of other neurotransmitters are altered in PTSD and other fear- and anxiety-based disorders that maybe related to inflammation-induced excitotoxicity (Crowley *et al*, 2016). Specifically, reduced GABA concentrations have been reported within the insula of individuals with PTSD (Rosso *et al*, 2014) and within the mPFC, ACC, and occipital cortex of those with

PD (Goddard *et al*, 2001; Long *et al*, 2013), and reductions in GABA signaling can contribute to glutamate excitotoxicity via inflammatory pathways (Crowley *et al*, 2016).

Treatment Implications and Future Directions

In sum, heightened inflammation and increased cytokine production in the face of HPA axis and autonomic nervous system dysregulation is characteristic of fear- and anxiety-based disorders. Although the majority of work has characterized a pro-inflammatory state in individuals with PTSD, the limited data available regarding the relationship between GAD, PD, phobias, and inflammation also point toward augmented inflammation. It is clear that more studies are necessary in these other anxiety disorders to further delineate the role of inflammation in their pathophysiology, as a state of chronic low-grade inflammation in fear- and anxiety-based disorders may lead directly to alterations in neurobiology critical for the control of emotional behavior and fear regulation that are perturbed in these disorders.

Future studies addressing these gaps in knowledge will also allow for meta-analyses to be conducted within fear- and anxiety-based disorders and across anxiety disorders as a whole. Overall, our non-systematic review is the first to synthesize available data on inflammation across fear- and anxiety-based disorders as defined by the DSM-5 (APA, 2014). The available data indicate a clear role for inflammation in the etiology and maintenance of fear- and anxiety-based disorders, increased inflammation is not specific to these disorders, as other mental health problems, such as depression, are also associated with a pro-inflammatory state (Dowlati *et al*, 2010). The lack of specificity in the era of the Research Domain Criteria marshaled in by the National Institutes of Mental Health (Cuthbert, 2014) suggests that inflammation may better serve as a biomarker of specific sub-domains of dysfunction (ie, negative- and positive-valence systems).

Regardless of specificity for DSM-based diagnoses, the presence of heightened inflammatory processes in these fear- and anxiety-disorders has important translational and clinical implications by providing the field with a range of new therapeutic targets that must be thoughtfully further investigated (Michopoulos and Jovanovic, 2015a). One possible therapeutic avenue that warrants further investigation is the use angiotensin-converting enzyme inhibitors (ACE-I) and blockers (ARBs) in the treatment of PTSD, as these classes of pharmacological agents are effective in managing cardio-metabolic disease that is highly co-morbid with PTSD. ACE-I/ARBs are typically prescribed to decrease blood pressure and sympathetic activity (Savoia and Schiffrin, 2007). However, these agents are also capable of reducing neuroinflammation (Benicky *et al*, 2011; Welty *et al*, 2015), as angiotensin-II activity increases CRP and IL-6 release (Sano *et al*, 2001; Zhao *et al*, 2013). The promise of using ACE-I/ARBs to alleviate PTSD symptoms in traumatized individuals is highlighted by evidence indicating that traumatized individuals using ACE-I/ARB medication have

decreased odds of PTSD diagnosis and fewer PTSD symptoms compared with traumatized individuals not taking these medications (Khouri *et al*, 2012). Thus, interventions that attenuate inflammatory processes in fear- and anxiety-based disorders may prove to be effective in mitigating the symptoms of these disorders, as well as decreasing associated adverse cardio-metabolic outcomes.

Although the promise of anti-inflammatory pharmacological agents for the treatment of chronic psychopathology has gained traction based on the work done with regard to depression (Raison *et al*, 2013; Uher *et al*, 2014), other forms of intervention could prove efficacious in dampening inflammatory processes in fear- and anxiety-based disorders. Cognitive and behavioral interventions, including prolonged exposure, are effective treatments for fear- and anxiety-based disorders (Butler *et al*, 2006; Powers *et al*, 2010), but it still remains unclear whether these treatments also reduce inflammation. Other forms of behavioral interventions that have been used for the treatment of fear- and anxiety-based disorder, such as community-based educational intervention, exercise, yoga, and meditation, have also been associated with decreases in inflammation (Bower and Irwin, 2016; Pace *et al*, 2009; Villablanca *et al*, 2015). Finally, it is important to note that dietary intake and the microbiome are potent modulators of inflammatory pathways (Kiecolt-Glaser, 2010; Petra *et al*, 2015), indicating that adherence to a Mediterranean diet or use of probiotics can also lead to a reduction in inflammation (Dai *et al*, 2008; Kekkonen *et al*, 2008).

Empirical evidence is still necessary to determine whether anti-inflammatory treatments are beneficial for all individuals with fear- and anxiety-based disorders. It may be the case that anti-inflammatory interventions are only efficacious in those individuals who show significantly elevated levels of inflammation, similar to what has been described in depression (Raison *et al*, 2013). Furthermore, acknowledging factors that are associated with systemic inflammation, such as obesity and exposure to childhood adversity, is critical for better informing treatment selection in individuals with fear- and anxiety-based disorders (Kiecolt-Glaser *et al*, 2015). This more personalized approach to therapeutic intervention may yield better therapeutic results. However, the field must continue to characterize factors that are associated with increased inflammation and adverse mental and physical health outcomes. For example, there is a clear sex difference in the prevalence of PTSD and other fear- and anxiety-based disorders (Kessler *et al*, 1995; McLean *et al*, 2011), and yet there is a paucity of data explaining the etiology of this sex difference. Recent work highlights the importance of considering sex as an important biological variable, as endotoxin-induced increases IL-6 and TNF- α are correlated with greater feelings of depressed mood and social disconnection only in women (Moieni *et al*, 2015). Thus, taking into consideration the whole range of biological and behavioral factors that influence inflammatory processes will ultimately improve the treatment and management of fear- and anxiety-based disorders, as well as better inform therapeutic strategies using anti-inflammatory agents.

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