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Dysregulation of inflammation, neurobiology, and cognitive function in PTSD: an integrative review

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Abstract

Compelling evidence from animal and human research suggest a strong link between inflammation and posttraumatic stress disorder (PTSD). Furthermore, recent findings support compromised neurocognitive function as a key feature of PTSD, particularly with deficits in attention and processing speed, executive function, and memory. These cognitive domains are supported by brain structures and neural pathways that are disrupted in PTSD and which are implicated in fear learning and extinction processes. The disruption of these supporting structures potentially results from their interaction with inflammation. Thus, the converging evidence supports a model of inflammatory dysregulation and cognitive dysfunction as combined mechanisms underpinning PTSD symptomatology. In this review, we summarize evidence of dysregulated inflammation in PTSD and further explore how the neurobiological underpinnings of PTSD, in the context of fear learning and extinction acquisition and recall, may interact with inflammation. We then present evidence for cognitive dysfunction in PTSD, highlighting findings from human work. Potential therapeutic approaches utilizing novel pharmacological and behavioral interventions that target inflammation and cognition also are discussed.

Keywords Posttraumatic stress disorder · Inflammation · Neurobiology · Cognition · Intervention

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychopathological consequence of exposure to a traumatic event and is associated with high rates of morbidity and mortality (Jakovljevic, Brajkovic, Loncar, & Cima, 2012; Roberge, Dupuis, & Marchand, 2010; Shalev, Liberzon, & Marmar, 2017). The disorder is characterized by symptoms of intrusion, avoidance, persistent negative alterations in cognitions and mood, and alterations in arousal and reactivity (American Psychiatry Association, 2013). Patients with PTSD show persistent and intense fear reactions when exposed to situations associated with a previous traumatic event or that are contextually inappropriate, interpreting threat despite a safe context (Steiger, Nees, Wicking, Lang, & Flor, 2015). In addition, persistent PTSD symptoms can be detrimental to physical and psychological health (McFarlane, 2010). Patients with PTSD report significantly more serious physical illnesses than their healthy counterparts, including more visits to the emergency department and primary care and higher rates of hospitalization and surgical procedures (Schnurr, 2015; Tuerk et al., 2013). Notably, comorbidity with other psychological diagnoses, such as depression and anxiety disorders, also tend to be higher with PTSD (Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). To further highlight the complexity of PTSD, it remains unknown why many patients continue to experience persistent, unremitting symptoms of PTSD following trauma-focused interventions (Bradley, Greene, Russ, Dutra, & Westen, 2005; Kearney & Simpson, 2015; Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008; Steenkamp, Litz, Hoge, & Marmar, 2015).

Compelling evidence suggests a strong link between inflammation and PTSD (Hori & Kim, 2019; Mellon, Gautman, Hammamieh, Jett, & Wolkowitz, 2018; Pace & Heim, 2011). Moreover, a key feature of PTSD is

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compromised neurocognitive function mainly ascribed to deficits in attention and processing speed, executive function, and verbal learning and memory (Scott et al., 2015). Notably, some of these cognitive deficits may impact fear learning and extinction (Hofmann, 2008). Evidence suggests that central and peripheral inflammation can negatively impact cognition (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Trapero & Cauli, 2014). Thus, inflammatory dysregulation together with cognitive dysfunction potentially contribute to PTSD symptomatology. Surprisingly, very limited work has explored the interplay among these mechanisms in PTSD human research. This is of particular significance, given that a deeper understanding of the inflammatory and neurocognitive mechanisms underlying PTSD could guide the development of novel and clinically relevant interventions for individuals with PTSD.

The purpose of this review is to provide insight into the links between inflammation and cognitive dysfunction that may underpin PTSD symptoms. First, we briefly summarize evidence that suggests inflammatory dysregulation in PTSD, because this pathway has been reviewed extensively elsewhere (Hori & Kim, 2019; Kim, Amidfar, & Won, 2019; Mellon et al., 2018; Speer, Upton, Semple, & McKune, 2018). We further explore the existing literature on the neurobiological alterations in PTSD, specifically neurobiological underpinnings of the fear network and how inflammation may interact with these pathways. Then, we present evidence for significant cognitive dysfunction in PTSD and expand on findings in human work. Based on the evidence, we provide a novel model of combined inflammatory dysregulation and cognitive dysfunction that potentially contributes to PTSD development, progression, and maintenance. Finally, we describe pharmacological approaches and nontrauma-focused behavioral interventions that potentially target these dysregulated inflammatory, learning, and cognitive mechanisms as novel treatments for PTSD.

Inflammation and PTSD

Inflammation has played a central role in the understanding of PTSD. We provide a brief overview of the evidence for a proinflammatory profile in PTSD and refer the reader to more in-depth reviews of the inflammation and PTSD link (Jones & Thomsen, 2013; Kim et al., 2019; Speer et al., 2018; Wang, Caughron, & Young, 2017). PTSD is described as a state of chronic stress or hyperarousal, accompanied by elevated levels of proinflammatory cytokines (Passos et al., 2015). Patients with PTSD show significantly higher levels of common proinflammatory cytokines relative to non-PTSD trauma-exposed or healthy individuals, including interleukin (IL)-1β, IL-6, tumor necrosis factor TNF-α, interferon gamma (IFN-γ), as well as the inflammation-stimulated acute phase protein, C-reactive protein (CRP) (Hussein, Dalton, Willmund, Ibrahim, & Himmerich, 2017; Wang & Young, 2016). Interestingly, peripheral levels of these proinflammatory markers have positively correlated with severity of PTSD symptoms and a greater probability to develop PTSD (Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017). The link between a proinflammatory state and PTSD is further supported by emerging studies demonstrating associations between early life trauma exposure and increased inflammation that negatively affects the development of immune, neural, and cognitive systems (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Danese & Lewis, 2017; Delpech et al., 2016).

The most common underlying mechanisms implicated in PTSD-related inflammatory dysregulation are altered HPA axis and autonomic nervous system (ANS) function (Speer et al., 2018). Dysregulation of the HPA axis and its link to inflammation has been extensively studied in the field of PTSD (Dunlop & Wong, 2019; Schumacher et al., 2019). Evidence suggests that the dysregulation occurs through increased sensitivity of the negative feedback mechanisms that regulate the HPA system, resulting in significantly lower levels of cortisol (Pan, Wang, Wu, Wen, & Liu, 2018; van Zuiden, Kavelaars, Geuze, Olff, & Heijnen, 2013). Of note, cortisol is a glucocorticoid (GC) with immunosuppressive and anti-inflammatory effects (Coutinho & Chapman, 2011). Dysregulation of cortisol secretion further points to vulnerability to develop PTSD, as evidenced by lower levels of circulating cortisol before exposure to a traumatic event (Luo et al., 2012; van Zuiden et al., 2013). With low circulating cortisol, the immune system is left in a state of increased inflammatory activation (Daskalakis et al., 2016; Hori & Kim, 2019). Thus, dysregulation of the HPA axis can contribute to a chronic low-grade inflammatory state in PTSD.

In the context of PTSD, dysregulation of the ANS is evidenced by a dominant sympathetic nervous system (SNS) and delayed reactivation of the parasympathetic nervous system (PNS) (Tan, Dao, Farmer, Sutherland, & Gevirtz, 2011), which, in turn, can increase inflammation (Marvar & Harrison, 2012). A promising area that has improved our understanding of ANS correlates of PTSD is the study of heart rate variability (HRV); yet, its link to inflammation has not been fully integrated into models of PTSD. HRV is the amount of change in heart rate across time and a key indicator of autonomic and physiological stress regulation (Kemp, Quintana, Felmingham, Matthews, & Jelinek, 2012; Lehrer & Gevirtz, 2014; Thayer, Yamamoto, & Brosschot, 2010). Emerging evidence demonstrates that decreased HRV is observed in PTSD and is likely indicative of a hyperarousal state supported by lower vagal tone, resulting in lower parasympathetic cardiac control (Bandelow et al., 2017; Dennis et al.,

2014; Shah et al., 2013; Williamson, Porges, Lamb, & Porges, 2014). Adequate vagal tone, as indexed by HRV, regulates inflammation (Pavlov & Tracey, 2012) and is associated with lower levels of proinflammatory markers (Bonaz, Sinniger, & Pellissier, 2016; Gerritsen & Band, 2018). Thus, a reduction in parasympathetic drive, resulting in decreased HRV activity, may be one source of inflammation in PTSD. Future studies employing a multi-modal approach including measures of HRV (i.e., electrocardiogram) and neuroimaging to explore inflammatory processes in patients with PTSD would significantly improve our understanding of the links between ANS regulation, inflammation, and PTSD. In all, the dysregulation between the ANS and the innate immune system can be detrimental to neurobiological systems involved in the behavioral, cognitive, and emotional regulation capacity in patients with PTSD.

Despite the strong evidence linking inflammation and PTSD, findings are not fully consistent (Jergovic et al., 2015; McCanlies et al., 2011; Plantinga et al., 2013). The discrepancies in studies can be mostly attributed to a lack of uncontrolled potential confounders, lack of uniformity in PTSD assessment and biomarker collection methods, small sample sizes, and variations in comparable control groups (Michopoulos et al., 2017). Another potential source of variance is the high comorbidity of PTSD with depression. Translational models suggest that increased inflammation is implicated in depression (Amodeo, Trusso, & Fagiolini, 2017; Lee & Giuliani, 2019; Miller & Raison, 2016), which could possibly confound associations between PTSD and inflammation. However, evidence also points to a distinct inflammatory profile when PTSD co-occurs with depression, that is, different from profiles observed in patients with PTSD alone (Gill, Luckenbaugh, Charney, & Vythilingam, 2010; Passos et al., 2015). Similarly, traumatic brain injuries (TBI) are highly prevalent among populations with history of PTSD (i.e., veterans, IPV survivors), and findings suggest that inflammation may be an underlying mechanism of both conditions (Devoto et al., 2017; Rathbone, Tharmaradinam, Jiang, Rathbone, & Kumbhare, 2015). Notably, findings further suggest that variability in TBI severity, such as presence or absence of LOC, may result in different proinflammatory profiles (Kanefsky et al., 2019). Thus, comorbidity of TBI and PTSD may also affect inflammatory trajectories in individuals with PTSD.

Overall, the previous findings support significantly elevated inflammation in PTSD. Despite the increasing support for a proinflammatory state in PTSD, it is important to note that inflammation is only one potential mechanism dysregulated in PTSD. Thus, we further consider how inflammation interacts with neurobiology in PTSD to suggest promising research avenues for elucidating the role of inflammation in PTSD.

Neurobiology of the fear network and inflammation

Fear conditioning and extinction is a useful model for understanding the intricate mechanisms involved in PTSD (Loayza Careaga, Neves Girardi, & Suchecki, 2016). For decades, animal models have shed light on these mechanisms, offering great insight into the role of these behavioral processes and their neurobiological underpinnings in PTSD. Importantly, accumulative evidence suggests that dysregulation of the inflammatory response contributes to the impaired fear extinction observed in patients with PTSD (Schelling et al., 2006). Evidence from animal studies demonstrates that exposure to acute or chronic stress can lead to significant changes in the central nervous system centers that regulate the stress response (i.e., hypothalamus) and fear memories (i.e., amygdala; Jones & Thomsen, 2013). Notably, upregulation of proinflammatory cytokines in these brain regions is observed following stress exposure (Johnson, Bernard, Kulp, & Mehta, 2019; Vecchiarelli et al., 2016). Moreover, peripheral injection of lipopolysaccharide (LPS) in rodents results in an increased inflammatory response in fear circuit areas in the brain, specifically the amygdala (Prager et al., 2013), the prefrontal cortex (Yang et al., 2013), and the hippocampus (Kranjac et al., 2012), which are critical structures in the extinction process. The fear network has been extensively studied in animal models, and emerging evidence supports the application of this network to individuals with PTSD. We will first summarize relevant findings from animal work on the fear network. Then, we will discuss the application of the fear network to PTSD by expanding on human neuroimaging studies and also present evidence of how inflammation potentially interacts with this neurocircuitry in PTSD.

Fear network in animal studies

Animal studies provided the foundational understanding of the structural and functional connectivity within the fear network, identifying critical roles for the amygdala, medial prefrontal cortex (mPFC), and the hippocampus in mediating fear-related processes. Animal models of fear have consistently linked the amygdala to fear learning and subsequent expression of fear memory and to the process of extinction (Davis, Zaki, Maguire, & Reijmers, 2017; Johansen et al., 2010). Given the complexity of the amygdala microcircuitry, studies with animals have identified differences in the activity of the amygdala subnuclei that are distinctly linked to fear processes. For example, interactions between the lateral (LA) and central (CeA) nuclei of the amygdala can increase or decrease fear responses, based on the centrolateral amygdala's inhibitory control of the centromedial amygdala (Hunt, Sun, Kucukdereli, Klein, & Sah, 2017; Maeng & Milad, 2017).

Within the amygdala's microcircuit, the CeA is predominantly involved in the behavioral expression of conditioned fear responses (Ciocchi et al., 2010). Supporting these findings, Duvarci, Popa, and Paré (2011) showed that fear conditioning caused neurons in the CeA to increase their response to a conditioned stimulus, and their findings further suggest that expression of conditioned fear behavior depends on increased activity within the subnuclei of the CeA. In addition, studies investigating neurons from the LA show potentiated responses to a tone that correlate with acquisition of fear and extinction learning (Herry et al., 2010; Pare & Collins, 2000). In this regard, the evidence suggests that the LA is involved in associative learning and the retrieval of fearful memories (Elrich, Bush, & LeDoux, 2012; Manassero, Renna, Milano, & Sacchetti, 2018).

Studies on fear extinction further provide evidence of a link between the amygdala and the mPFC that is necessary for the process of fear extinction memory (Bloodgood, Sugam, Holems, & Kash, 2018; Sotres-Bayon & Quirk, 2010). Medial prefrontal cortex neurons elicit larger evoked potentials after fear extinction training in animals, further supporting the role of the mPFC in extinction (Garcia, Spennato, Nilsson-Todd, Moreau, & Deschaux, 2008; Giustino & Maren, 2015). In rodents, the prelimbic (PL) and infralimbic (IL) regions of the mPFC show distinct roles in the acquisition, expression, and extinction of conditioned fear. For example, PL activity is essential for the regulation of fear expression (Giustino & Maren, 2015). Stimulation of the PL during exposure to a tone increased fear expression and impaired extinction learning (Vidal-Gonzalez, Vidal-Gonzalez, Rauch, & Quirk, 2006), whereas inactivating this region before extinction training reduced fear expression during early extinction training (Sierra-Mercado, Padilla-Coreano, & Quirk, 2011). In contrast, the IL region of the mPFC is consistently implicated in extinction learning (Godsil, Kiss, Spedding, & Jay, 2013; Sotres-Bayon & Quirk, 2010), with evidence also demonstrating that neuronal activity in IL further facilitates consolidation of extinction memory (Awad, Ferreira, & Maroun, 2015). Notably, inactivating the IL region impairs retrieval of fear extinction resulting in recovery of fear conditioning (Vollmer et al., 2016). This suggests a role of the mPFC in recall of extinction memory as well.

Increasing evidence demonstrates that the hippocampus is a critical structure in contextual fear conditioning and extinction. Connections between the hippocampus and the amygdala, specifically the LA, appear to be essential to the acquisition and consolidation of contextual fear (Chaaya, Battle, & Johnson, 2018). Models underscoring the acquisition of contextual fear memory suggest that fear memories are created when the hippocampus sends representations of contextual elements to the amygdala, which simultaneously receives somatosensory projections of aversive stimuli (Chaaya et al., 2018; Fanselow, 2010). In addition, fear extinction can be highly context dependent, with evidence suggesting further links to the hippocampus that support the recruitment of this region during extinction learning (Marek & Sah, 2018). At the structural level, evidence shows that projections from the hippocampus to the mPFC can innervate neurons in the IL and PL that are active during the extinction process (Parent, Wang, Su, Netoff, & Yuan, 2010). Notably, when communication between the hippocampus and the mPFC is disconnected, this can fully disrupt contextual fear extinction (Zelikowsky et al., 2013).

In all, animal studies of fear extinction, demonstrating the critical involvement of a neural circuit of amygdala-mPFC-hippocampus, support the translatability of the fear network to the study of PTSD in humans. These studies identify key brain regions and connections that, when disrupted, may contribute to the development, progression, and maintenance of PTSD.

Applying the fear network to human studies of PTSD

In line with the findings of the "fear network" of amygdala-mPFC-hippocampus from animal work, human neuroimaging studies also suggest critical roles for this network in PTSD. The amygdala, ventromedial prefrontal cortex (vmPFC), the anterior cingulate cortex (ACC), and the hippocampus have been identified as the key regions underlying the etiology, progression, and maintenance of PTSD (Fig. 1) (Linnman, Rougemont-Bücking, Beucke, Zeffiro, & Milad, 2011; Maeng & Milad, 2017; Milad & Quirk, 2012). These regions are anatomically aligned with the fear network identified in the animal studies. Importantly, structural and functional connectivity within these brain regions support fear acquisition and extinction processes in humans (Pietrzak et al., 2015; Selemon, Young, Cruz, & Williamson, 2019; Sherin & Nemeroff, 2011). Notably, there is emerging evidence demonstrating that these brain regions interact with inflammation, which suggests novel PTSD intervention targets.

Amygdala

In humans, the amygdala has a pivotal role in the encoding of emotional memories and in the perception and processing of fear (Hermans et al., 2014). Consistent with animal models, increased activity in the amygdala is implicated in acquisition, consolidation, and extinction of fear in humans (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Critchely, Mathias, & Dolan, 2002; Milad et al., 2009; Roozendaal, McEwen, & Chattarji, 2009). In studies using a conditioning and extinction paradigm, patients with PTSD relative to non-PTSD trauma-exposed individuals show greater amygdala activation during exposure to an aversive stimulus (fear conditioning phase), as

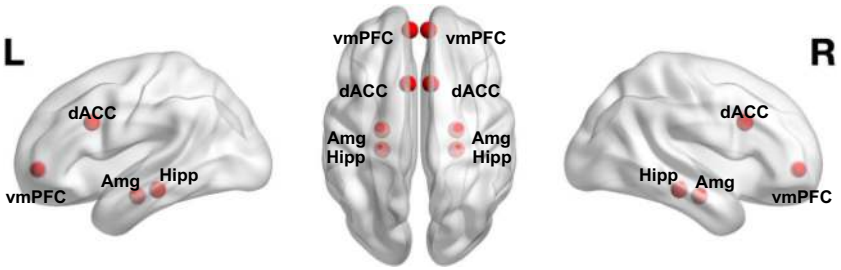

Fig. 1 Fear network in humans. The amygdala and the dACC exhibit robust activation during fear acquisition and expression. Extinction learning and recall of extinction memory are strongly associated with reduced activity of the vmPFC and the Hipp. vmPFC = ventromedial prefrontal cortex; dACC = dorsal anterior cingulate cortex; Amg = amygdala; Hipp = hippocampus

well as during extinction training (Linnman, Zeffiro, Pitman, & Milad, 2011). Supporting an active amygdala trend, patients with PTSD show greater resting amygdala activity before extinction training (Smith, Doran, Sippel, & Harpaz-Rotem, 2017). Interestingly, patients with PTSD continue to display increased amygdala activity following extinction training compared with trauma-exposed participants without PTSD and healthy controls, suggesting enhanced fear recall in PTSD (Wicking et al., 2016). The increased activity of the amygdala may indeed prevail in PTSD and could potentially be associated with treatment-resistance or relapse of PTSD symptoms following treatment (Hayes, Hayes, & Mikedis, 2012).

Of note, limited evidence in human studies show distinct changes within amygdala subnuclei related to PTSD. Recent findings show smaller lateral, paralaminar, and superficial amygdala nuclei volumes, but larger bilateral central, medial, and cortical nuclei in patients with PTSD relative to trauma-exposed individuals without PTSD (Morey et al., 2019; Stein et al., 2019; Veer et al., 2015). Similarly, PTSD symptom severity was associated with an indentation in the centromedial amygdala within a sample of combat-exposed veterans with PTSD (Akiki et al., 2017). These findings further align with animal work and suggest amygdala subregion-specific patterns that are consistent with fear learning and expression in PTSD.

More recently, evidence suggests a bi-directional influence between inflammatory processes and amygdala activity. Neuroimaging studies reveal that increased amygdala response to stress is associated with production of IL-6 (Muscatell et al., 2015). Endotoxin-induced IL-6 and TNF-α production can further elicit greater amygdala activity in response to socially threatening stimuli (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012). Notably, the inflammatory-induced increased activity of the amygdala potentially contributes to the increase in CRP production and hyperarousal in patients with PTSD (Michopoulos et al., 2015). More work is needed to directly examine the interactions between inflammation and the amygdala in the context of PTSD, as this area is presently understudied and may have further implications for PTSD interventions.

Ventromedial prefrontal cortex

Patients with PTSD also show distinct activity in the vmPFC (the human analog of the IL in rodents; Marek & Sah, 2018). Reduced volume and activity of the vmPFC is one of the most consistently reported biomarkers for PTSD (Kuhn & Gallinat, 2013). Typically, studies have focused on the contributions of the vmPFC to the extinction of conditioned fear, providing a direct correlation between the human vmPFC and the fear extinction process (Milad et al., 2005; Milad et al., 2009). While decreased regulatory activation of the vmPFC is linked to poor extinction learning, it also leads to deficient consolidation and recall of extinction memory (Phelps, Delgado, Nearing, & LeDoux, 2004; Rougemont-Bucking et al., 2011). Conversely, vmPFC activity also is altered during acquisition and expression of fear (Shvil et al., 2014), suggesting that disrupted vmPFC activity may preclude the development of PTSD symptoms. Evidence also demonstrates a distinct pattern of increased activation of the vmPFC during fear conditioning, yet reduced activity during extinction learning among individuals with PTSD (Brown et al., 2014; Sripada et al., 2012). Interestingly, studies using other tasks unrelated to fear conditioning and extinction demonstrate negative correlations between vmPFC activation and PTSD symptom severity (Hughes & Shin, 2011). This suggests that the reduced vmPFC activity may be more of a general functional property of this brain region in PTSD (VanElzakker, Dahlgren, Davis, Dubois, & Shin, 2014).

Notably, increased inflammation is also associated with disrupted activity of the vmPFC (Kim et al., 2019). A previous study demonstrated that activation of the vmPFC during a grief-eliciting task in women undergoing bereavement stress was associated with increased TNF-α receptor II and IL-1β (O'Connor, Irwin, & Wellisch, 2009). Although there is an existing gap in studies exploring the effects of inflammation on vmPFC activity in PTSD, it is possible that these inflammatory processes affect vmPFC activation, resulting in dysregulated emotional and cognitive processing in stress and trauma-related disorders (Felger, 2018).

Anterior cingulate cortex

In recent years, findings from PTSD studies in humans provide links to the anterior cingulate cortex (ACC) and, most commonly, the dorsal ACC (dACC; homologue to the rodent PL). The dACC is associated with the appraisal and regulation of emotions as well as with increased attention bias to threat, serving further as a stress response pathway leading to downstream stimulation of the ANS, increasing sympathetic activity (Fani et al., 2012; Giuliani, Drabant, & Gross, 2011; Tang et al., 2009). In humans, neuroimaging findings provide support that patients with PTSD exhibit smaller dACC volume, along with increased dACC activity being associated with the persistence of PTSD symptoms (Bromis, Calem, Reinders, Williams, & Kempton, 2018; van Rooij, Kennis, Vink, & Geuze, 2016). In addition, recent work shows that dACC task-related activity is also correlated with increased familial risk for PTSD development (Shin et al., 2011). Comparable to the activation of the amygdala, increased dACC activity is associated with the expression of fear and extinction processes (Bremner et al., 2005; Milad et al., 2009). During a fear conditioning trial, Rougemont-Bucking et al. (2011) found increased dACC activation in patients with PTSD, relative to a trauma-exposed control group without PTSD. Interestingly, the dACC showed sustained activity increases during fear conditioning (Linnman, Zeidan, Pitman, & Milad, 2012) while resting-state metabolism in dACC was negatively correlated with extinction recall in nontrauma-exposed healthy participants (Linnman et al., 2012). Therefore, dACC signaling may promote continued fear expression and thus impair inhibition of the expression of fear response during extinction recall (Linnman, Zeidan, Furtak, et al., 2012).

The dACC is also highly susceptible to inflammation-induced dysregulation. Increased soluble and stimulated cytokine production positively correlated with greater activation in the dACC, amygdala, and PFC following exposure to a laboratory stressor (Muscatell et al., 2016; Slavich, Way, Eisenberger, & Taylor, 2010). Earlier work in patients with hepatitis C virus showed that chronic administration of IFN-α resulted in increased dACC task-related activity and errors in a visuo-spatial attentional task (Capuron et al., 2005). Similarly, other studies have demonstrated associations among induced inflammation, poor cognitive outcomes, and dACC greater activity (Eisenberger, Lieberman, & Satpute, 2005; Harrison et al., 2009a). Overall, inflammation appears to increase dACC activity, and this interaction may further contribute to greater PTSD symptoms and impaired learning and recall of extinction.

Hippocampus

Evidence from earlier human studies on PTSD suggested that the hippocampus is critical in the encoding and recognition of environmental cues during fear acquisition and extinction learning (Corcoran & Maren, 2001; McEwen, 2000; Yehuda, 2002). Disrupted activity in hippocampal function can lead to failure to modulate contextual memories, thus rendering the individual with PTSD unable to distinguish between safe versus threatening contexts (Acheson, Gresack, & Risbrough, 2012; Flor & Wessa, 2010; Steiger et al., 2015). Indeed, the converging evidence proposes that deficient hippocampal function in PTSD at the time of trauma exposure can lead to a poor association of the context with the traumatic event (Acheson et al., 2012; Flor & Wessa, 2010). This, in turn, leads to impaired fear memory and subsequent generalization of the fear expression to different contexts. In this regard, prior reduced hippocampal activity may be a preexisting vulnerability to develop PTSD. In line with these findings, decreased activation of the hippocampus also was found in patients with PTSD who failed to recall extinction (Milad et al., 2009), and the reduced activity may be linked to reduced hippocampal volume (Bremner, Elzinga, Schmahl, & Vermetten, 2007). Patients with current PTSD have significantly smaller hippocampal volume (Apfel et al., 2011; Wang et al., 2010; Zhang et al., 2011), even when compared with trauma-exposed control individuals who do not have PTSD (Logue et al., 2018; Morey, Haswell, Hooper, & De Bellis, 2016). Notably, greater hippocampal volume is associated with PTSD treatment response. Patients with PTSD who evidenced greater baseline hippocampal volume demonstrated greater treatment gains following exposure therapy, suggesting that greater hippocampal volume potentially facilitates a more robust fear-extinction capacity (Rubin et al., 2016). The observed changes in hippocampal volume in PTSD, however, appear to be widespread and inconsistent as findings report reduced volume in posterior (Bonne et al., 2008), right and left (Woon, Sood, & Hedges, 2010) hippocampus.

Increased inflammation plays a pivotal role in hippocampal dysfunction and atrophy (Chesnokova, Pechnick, & Wawrowsky, 2016; Tsai, 2017). Positron emission tomography (PET) on healthy individuals demonstrated a reduction in parahippocampal and rhinal glucose metabolism following typhoid vaccination (Harrison, Doeller, Voon, Burgess, & Critchley, 2014). Additionally, in a study conducted with veterans, increased soluble receptor II for TNF-α was significantly associated with reduced hippocampal volume, and this association was stronger with greater PTSD severity (O'Donovan et al., 2015). Overall, the inflammatory-induced hippocampal atrophy and dysfunction has significant clinical implications for

patients with PTSD, as it potentially leads patients to fail to discriminate between dangerous and safe contexts following extinction training.

Functional connectivity of the amygdala-vmPFC-ACC-hippocampus circuit

Functional abnormalities in the fear network suggest a general neurocircuitry dysfunction in PTSD (VanElzakker et al., 2014). Evidence from neuroimaging studies provide a predominant framework of disrupted network connectivity, supporting a top-down regulation of temporal structures (i.e., amygdala and hippocampus) by frontal regions in PTSD (Phelps et al., 2004). Patients with PTSD show markedly reduced vmPFC activity that correlates with increased amygdala activity (Hayes, Hayes, & Mikedis, 2012), demonstrating the consistency of this brain activation pattern in the fear network in PTSD (Maeng & Milad, 2017). Exposure to fearful stimuli significantly decreased task-related functional connectivity between the right amygdala and the vmPFC among those with PTSD (Stevens et al., 2013). In healthy participants, activation of the dACC and deactivation of vmPFC metabolism significantly correlated with higher resting amygdala activity, further supporting an inhibitory role of the vmPFC on the amygdala's fear expression and the dACC's role in promoting it (Linnman, Zeidan, Furtak, et al., 2012). In addition, PTSD symptom severity, particularly hyperarousal, is associated with negative mPFC-amygdala coupling (Sadeh, Spielberg, Warren, Miller, & Heller, 2014). Few studies have examined brain functional connectivity during fear conditioning and extinction in PTSD samples. Evidence from healthy individuals suggests that concurrent activation of the amygdala and the hippocampus may be important for contextual fear learning (Baeuchl, Meyer, Hoppstadter, Diener, & Flor, 2015; Knight, Smith, Cheng, Stein, & Helmstetter, 2004). Notably, during extinction recall, brain activation patterns are consistent with vmPFC and hippocampal reduced activity, further demonstrating a role for these brain regions in the contextual modulation of fear extinction and thus contributing to contextual processing deficits (Garfinkel et al., 2014; Milad et al., 2007). The reduced activity of the vmPFC and hippocampus together with the increased activity of the amygdala and dACC may indeed underlie the impaired extinction processes observed in patients with PTSD (Sheynin & Liberzon, 2017).

Little is known about the contributions of inflammation to altered functional connectivity in PTSD; however, existing findings suggest possible implications for understanding psychiatric disorders. For example, IL-6 response to typhoid vaccination decreased mood in a sample of healthy men, and this inflammation-associated mood change correlated with reduced connectivity between the ACC and the amygdala and mPFC (Harrison et al., 2009b). Similarly, increased CRP predicted decreased functional connectivity between right amygdala and left vmPFC in patients with comorbid depression and anxiety (Mehta et al., 2018). Consistent with these findings, a recent study reported an indirect effect of IL-6 that partially mediated the association between childhood physical abuse and reduced adult amygdala-vmPFC connectivity (Kraynak, Marsland, Hanson, & Gianaros, 2019). The dissociation in frontotemporal activity coupled with increased inflammation could potentially result in difficulties with behavior and emotion regulation, and cognition in patients with PTSD and related comorbidities, such as depression.

Taken together, these findings support an interplay between inflammation and the amygdala-vmPFC-ACC-hippocampus circuit that further supports fear conditioning and extinction learning and recall. The recent advances in the field of PTSD suggest that the activity and functional connectivity of these brain regions also appears to be compromised in PTSD and vulnerable to the effects of inflammation. Thus, the emerging evidence may trace an inflammatory-neural pathway that is relevant for PTSD development, maintenance, and progression. Future studies are required using emerging cutting-edge imaging techniques (i.e., PET) to address this neuroinflammatory interplay and identify specific inflammation-associated neural biomarkers of PTSD. This would provide more direct evidence for the associations among inflammation and PTSD, and, in turn, it would advance the field by allowing to test the effects of novel interventions on central inflammatory-related processes in patients with PTSD.

Of note, the amygdala, PFC, ACC, and hippocampus are also central to cognition and consistently implicated in attention, processing speed, executive function, and memory. Notably, some of these cognitive processes also may impact fear conditioning and extinction (Hofmann, 2008). Thus, the potential dysregulation of inflammation, together with disrupted neural connectivity could have further detrimental implications for cognitive function and, subsequently, its contributions to persistent PTSD symptoms.

Cognitive deficits in posttraumatic stress disorder

In addition to an increased inflammatory response and altered neurobiological pathways, cognitive deficits are strongly linked to PTSD. Given the bi-directional links between cognition and emotions, cognitive deficits may play a central role in PTSD development, maintenance, or severity, and thus negatively impact treatment (Hayes, Vanelzakker, & Shin, 2012). Studies in PTSD provide strong evidence for memory dysfunction, while deficits in attention and processing speed and executive function have gained more recent empirical

attention (Koso & Hansen, 2006; Latack, Moyer, Simon, & Davila, 2017; Scott et al., 2015). The association between PTSD and cognition can be bi-directional, as cognitive deficits can result as part of the pathophysiology of PTSD, or they can potentially be a risk factor for PTSD (DiGangi et al., 2013; Sumner et al., 2017; Twamley et al., 2009).

Accumulating evidence shows that elevated central and peripheral inflammation can have detrimental effects on cognition (Gruol, 2015; Swardfager et al., 2010; Tangestani Fard & Stough, 2019; Trapero & Cauli, 2014; Walker et al., 2019). Increased inflammation is associated with poor cognitive function in mental health disorders, including depression (Charlton et al., 2018; Krogh et al., 2014) and anxiety (Salim, Chugh, & Asghar, 2012). Inflammation contributes to the regulation of neuronal, molecular, and cellular processes underlying cognitive function, including neuroplasticity, neurogenesis, and long-term potentiation (Yirmiya & Goshen, 2011). Conversely, inflammatory dysregulation can disrupt these immune-regulatory processes that support cognition and, in turn, affect cognitive function (Calabrese et al., 2014; Lin et al., 2018). Findings from animal work demonstrate that inflammation plays a central role in the neurocognitive underpinnings of PTSD symptoms, including fear learning and impaired extinction (Doenni, Song, Hill, & Pittman, 2017; Kranjac et al., 2012; Lisboa et al., 2018; Quinones, Maldonado, Velazquez, & Porter, 2016; Sparkman, Kohman, Garcia, & Boehm, 2005). There is very limited knowledge, however, about the interplay between inflammation and cognitive function in human studies of PTSD, leaving a critical gap in our understanding of this disorder. A recent cross-sectional study found that women with PTSD showed significantly higher levels of IL-6 and poor overall cognitive performance (Imai et al., 2018). Given that the evidence suggests that inflammation is a key component of PTSD and it further interacts with fear learning and extinction-related neural pathways, it is possible that these interactions also contribute to the reduced cognitive function in patients with this disorder.

Attention and processing speed of information

Recent evidence suggests that deficits in attention and processing speed are closely linked to the progression of PTSD (Aupperle, Melrose, Stein, & Paulus, 2012; Qureshi et al., 2011). Notably, inflammation has been associated with deficits in attention and slow processing speed (Beydoun et al., 2019), further underscoring the potential interplay of these inflammatory and cognitive mechanisms in PTSD etiology, progression, or severity. The severity of PTSD symptoms is strongly associated with poor performance on attention tasks (Dutra, Marx, McGlinchey, DeGutis, & Esterman, 2018), up to a year following exposure to a traumatic event (Marx et al., 2009). Most frequently, PTSD symptoms correlate with deficits in sustained and selective attention (Vasterling et al., 2002). Indeed, elevated symptoms of PTSD have correlated with a marked reduced ability to resist distractors (Esterman et al., 2013). Additionally, PTSD symptom severity can further impact the ability to maintain attention to task-relevant stimuli (Brownlow, Brown, & Mellman, 2014) and screen out irrelevant information, a difficulty that is not confined to specific trauma-related stimuli (Shucard, McCabe, & Szymanski, 2008). Together, these findings suggest deficits in the attentional control required to disengage attention from trauma-related stimuli in patients with PTSD (Ashley, Honzel, Larsen, Justus, & Swick, 2013).

Patients with PTSD also perform worse on timed tasks compared with their healthy counterparts, suggesting slow processing speed of information. One study showed that participants who met full criteria for PTSD scored significantly worse on processing speed, after adjusting for demographics (Cohen et al., 2013). However, when accounting for health behaviors, vascular risk factors, and depression, this association was reduced by 12% but remained significant nonetheless. Similar findings were previously reported when controlling for alcohol consumption, educational level, and depression, demonstrating that PTSD was independently associated with decreased performance on measures of attention and processing speed (Samuelson et al., 2006). While these studies suggest that PTSD may have independent links to poor cognition, others conclude that comorbidity of PTSD with inflammatory conditions (i.e., TBI) indeed worsens cognitive deficits, including processing speed and attention, further complicating cognitive outcomes in individuals with PTSD (Combs et al., 2015). Of note, in a sample of women who experienced intimate partner violence (IPV), severity of PTSD symptoms was associated with worse performance on speed tasks and, interestingly, on executive function tasks with only a time component, suggesting that slow processing speed confounded performance on measures of executive function (Twamley et al., 2009). Overall, this slowing of processing speed of information in patients with PTSD may be attributable to reduced attentional resources due to active cognitive efforts being directed toward coping with psychological distress (DePrince & Freyd, 2004).

Complementing these findings, attentional and information processing networks in patients with PTSD show disproportionate activation patterns in response to threat versus nonthreat-related content (Bryant et al., 2005). Recently, a study suggested a global brain network mechanism that traces both PTSD clinical symptoms and PTSD-related deficits in attention (Zhu et al., 2019). Their results demonstrated that increased functional segregation of the Default Mode Network and the occipital cortex are associated with sustained attention in patients with PTSD. Given that attention, processing speed, and learning may interact via frontocortical

pathways (Leong, Radulescu, Daniel, DeWoskin, & Niv, 2017; Woodward, Duffy, & Karbasforoushan, 2013) and frontal connectivity is highly sensitive to inflammation, the combined effects of inflammation and attentional and processing speed deficits potentially play a role in shaping traumatic memories.

Executive function

Consistent with a neurobiological profile of disrupted prefrontal connectivity and poor prefrontal-mediated task performance linked to inflammation (Marsland et al., 2006), PTSD also is associated with deficits in executive function (Polak, Witteveen, Reitsma, & Olff, 2012). Patients with PTSD show poor performance, with strong effects sizes, on measures of executive function compared with trauma-exposed individuals who do not develop PTSD (Hart Jr. et al., 2008). In a recent sample of individuals exposed to war and political violence, current levels of PTSD symptoms correlated with deficits in executive function 20 years after exposure to the trauma (Blanchette, Rutembesa, Habimana, & Caparos, 2019). The long-term effects of trauma exposure on executive function also are supported by evidence from survivors of natural disasters with a previous, but not current, diagnosis of PTSD. Individuals continued to show impaired cognitive flexibility and verbal fluency, further supporting sustained deficits in prefrontal organization (Eren-Kocak, Kilic, Aydin, & Hizli, 2009). Comorbidity with other psychiatric disorders can exacerbate these deficits, which can lead patients to become more treatment-resistant. For example, patients with PTSD with comorbid depression show greater impairment on multiple measures of executive function (Jurick et al., 2018). Interestingly, in depression coupled with childhood trauma, elevated levels of peripheral cytokines were distinctly associated with executive dysfunction (Peters et al., 2019). Given that executive function deficits, and inflammation, also are a hallmark of depression (Baune et al., 2018; Beblo, Sinnamon, & Baune, 2011; Bortolato, Carvalho, & McIntyre, 2015), comorbidity with PTSD can complicate a patients' clinical profile offering a very poor prognosis and little treatment gains.

Although there is ample evidence concerning impaired executive function in PTSD, it remains unclear which aspects of executive function become more compromised (Crowell, Kieffer, Siders, & Vanderploeg, 2002; Leskin & White, 2007; Twamley et al., 2009) or whether there is a global executive dysfunction in PTSD (Park et al., 2018). Previous findings further suggest that exposure to trauma itself, and not PTSD, suffices to develop deficits in executive function. For example, survivors of IPV evidenced worse performance on tasks of working memory and inhibition, regardless of the presence of a PTSD diagnosis (Stein, Kennedy, & Twamley, 2002). There is, however, converging evidence showing that PTSD is most strongly associated with deficits in inhibition, that is, difficulties with inhibiting automatic or inappropriate responses (Casada & Roache, 2005; Clausen et al., 2017; Contractor, Elhai, Ractliffe, & Forbes, 2013; Shucard et al., 2008; Sijbrandij, Engelhard, Lommen, Leer, & Baas, 2013; Wu et al., 2015). Studies with veterans demonstrate that higher PTSD symptoms strongly correlate with worse performance on inhibition tasks to a greater extent than other executive function domains, such as task switching, cognitive flexibility, and working memory (Campbell et al., 2009; DeGutis et al., 2015; Nelson, Yoash-Gantz, Pickett, & Campbell, 2009; Swick, Honzel, Larsen, Ashley, & Justus, 2012). In line with these findings, the stability of cognitive control processes—as indexed by variability in reaction time of behavioral responses—appears to be compromised in patients with PTSD as well. In a sample comparing individuals with and without PTSD, greater variability in response time during a response inhibition task was evidenced only among those with PTSD (Swick, Honzel, Larsen, & Ashley, 2013). This variability in reaction time was further associated with self-reported symptoms of PTSD and attentional impulsiveness. Notably, there is a possibility of a bi-directional relationship between deficits on inhibition and PTSD. Preexisting deficits with inhibitory control could lead to difficulties with disengaging from trauma-related memories and cues, increasing the likelihood of developing and maintaining PTSD (Aupperle et al., 2012). Conversely, symptoms of PTSD, such as intrusion and hypervigilance, further decrease the ability to inhibit behavioral and emotional responses. Overall, these findings support a model of impaired inhibitory control in PTSD, consistent with deficits in top-down cognitive control processes, which could potentially explain the observed difficulties in behavior and emotion regulation in patients with PTSD (Aupperle et al., 2012; Hayes, VanElzakker, & Shin, 2012).

Aside from its critical role in daily functioning, adequate executive function is required to benefit from interventions that rely on cognitive processes to facilitate emotion regulation and changing maladaptive thoughts and behaviors (Falconer, Allen, Felmingham, Williams, & Bryant, 2013; Jak et al., 2015). Thus, deficits in executive function or underlying inefficient inhibitory neural network connectivity could decrease the effectiveness of common trauma-focused, evidence-based interventions for PTSD. Executive function deficits also could damper the effects of pharmacological treatment on PTSD symptoms. For example, in patients with major depression, greater deficits in executive function predicted poorer treatment response to antidepressant medication (Pimontel et al., 2016; Sneed et al., 2010). Particularly, response inhibition appears to be a specific aspect of executive function that negatively impacts antidepressant response rate (Pimontel, Culang-Reinlieb, Morimoto, & Sneed, 2012; Sneed et al., 2007). Although some speculate that antidepressants, the pharmacological treatment of choice for PTSD,

exert anti-inflammatory effects (Galecki, Mossakowska-Wojcik, & Talarowska, 2018), these effects may not be sufficiently significant to mitigate the interaction between inflammation and executive dysfunction. Thus, executive deficits may persist, despite intervening on clinical mood and behavioral symptoms. In sum, unattended executive function deficits may lead to poor treatment response and outcomes.

Memory

Memory deficits in PTSD have been extensively studied both in animal and human work. A wealth of literature further supports a critical role of inflammatory signaling in learning and memory (Donzis & Tronson, 2014). Thus, inflammatory-related PTSD pathophysiology may play a key role in memory deficits, which are among the most common cognitive disturbances in PTSD. We provide only a brief review about relevant work attempting to clarify the associations between PTSD and memory function. Hippocampal dysfunction can lead to loss of context sensitivity of the fear conditioned response and result in memory deficits leading to poor integration of the traumatic event in patients with PTSD (Wolf, 2008). Earlier human and animal studies on the associations between memory dysfunction and PTSD reported impairments in both acquisition and recall related with a reduced ability to consolidate memory (Bremner, Vermetten, Afzal, & Vythilingam, 2004; Diamond, Fleshner, Ingersoll, & Rose, 1996; Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Golier, Harvey, Legge, & Yehuda, 2006; Luine, Villegas, Martinez, & McEwen, 1994). The most commonly reported deficits in memory function in patients with PTSD are deficits in episodic memory (Golier & Yehuda, 2002; Golier et al., 2006; Samuelson, 2011; Zlomuzica et al., 2018), with some evidence suggesting difficulties with visual (Aase et al., 2017; Sierk et al., 2019) and autobiographical memory (Dalgleish, Rolfe, Golden, Dunn, & Barnard, 2008; Wessel, Merckelbach, & Dekkers, 2002). Deficits in memory also may predict treatment outcomes with behavioral interventions. Patients with PTSD who did not respond to Cognitive Behavioral Therapy performed significantly worse on measures of verbal memory compared with responders and further demonstrated deficits in narrative encoding (Wild & Gur, 2008).

There is speculation that memory dysfunction can be attributable to deficits in other cognitive domains. For example, because difficulties in the ability to suppress involuntary thoughts in PTSD can reflect a general failure in executive control, it is possible that these deficits in turn confound results on specific memory tests involving organizational strategies and executive control (Johnsen & Asbjornsen, 2009). In addition, although several studies support deficits in learning and memory tasks in PTSD, minimal forgetting occurs over time, and individuals can typically recall information during a recognition trial, minimizing demands on retrieval (Cohen et al., 2013; Jenkins, Langlais, Delis, & Cohen, 1998; Johnsen, Kanagaratnam, & Asbjornsen, 2008). This further suggests that memory deficits in PTSD are associated with difficulties in strategic encoding and retrieval of information, showing that prefrontal pathways also contribute to memory deficits in PTSD (Brewin, Kleiner, Vasterling, & Field, 2007; Lagarde, Doyon, & Brunet, 2010; Samuelson et al., 2006; Twamley et al., 2009). Further supporting this proposition, recent evidence suggests that disruption of the PFC-hippocampal circuitry contributes to cognitive dysfunction, including memory, in depression and Alzheimer's disease (Sampath, Sathyanesan, & Newton, 2017), both of which are considered inflammatory-related neuropsychiatric conditions. Another assumption is that deficits in attention lead to the observed dysfunction in encoding. To address this, studies have controlled for attention and the effect of total learning in select memory tasks and have provided evidence suggesting that memory deficits in PTSD are not in fact secondary to attentional dysfunction (Gilbertson et al., 2001; Yehuda, Golier, Halligan, & Harvey, 2004; Yehuda, Golier, Tischler, Stavitsky, & Harvey, 2005). An additional concern raised from studies examining memory deficits in PTSD is that these have been conducted on groups with comorbid psychiatric disorders. While some studies controlling for comorbidity suggest that PTSD has an independent effect on memory (Bremner et al., 2004; Jelinek et al., 2006; Sierk et al., 2019), others have found that depression, in particular, contributes to the memory dysfunction and overall cognitive deficits in PTSD (Brandes et al., 2002; Burriss, Ayers, Ginsberg, & Powell, 2008; Johnsen & Asbjornsen, 2009; Johnsen et al., 2008).

Overall, these findings support a model of increased inflammation and compromised neurocognitive function in PTSD. Future longitudinal studies with comprehensive and standardized measures are needed to further elucidate the interplay among inflammation and cognition in PTSD. These longitudinal studies should further attempt to clarify the role of potential confounding factors in this interplay, such as depression considering its high comorbidity rates and its potential inherent inflammatory and cognitive dysregulation. Additionally, given the bi-directional influences between inflammation and cognition, it is worth exploring how lower cognitive function at the onset of PTSD moderates inflammatory trajectories and PTSD symptom progression. This would provide guidance for additional cognitive targets and strategies to address during intervention development.

Novel pharmacological and behavioral interventions for PTSD

The evidence presented thus far suggest that dysregulated inflammation and cognition may together contribute to the

development, progression, or severity of PTSD. In line with this proposition, targeting these mechanisms could offer novel treatment approaches for patients with PTSD. Current standard treatments for PTSD include both pharmacological and psychological interventions. We will briefly overview the support for novel pharmacological approaches (i.e., angiotensin receptor blockers and angiotensin-converting enzyme inhibitors) and behavioral interventions (i.e., mindfulness-based interventions, computerized cognitive training, heart rate variability biofeedback, and exercise) that may mitigate PTSD symptoms through their effects on inflammation and cognitive dysfunction. Notably, as described below, some of these interventions target inflammation and/or cognitive dysfunction. While inflammation can lead to structural and functional brain changes that impact cognitive function, inversely, poor cognitive function also can upregulate inflammation. Thus, targeting inflammation or cognitive function may potentially disrupt the bi-directional pathways contributing to PTSD symptoms and severity.

Novel pharmacological interventions for PTSD

The current evidence base for pharmacological treatment for PTSD is strongest for selective serotonin reuptake inhibitors (SSRIs), which are recommended as second-line treatment for patients who do not engage in or cannot access trauma-focused psychotherapies (Hoskins et al., 2015; Lee et al., 2016). Pharmacotherapy with SSRIs is most effective in decreasing hyperarousal and mood (irritability, anger, depression) symptoms of PTSD, but these have been less effective for the symptoms of reexperiencing, emotional numbing, and behavioral avoidance (Stein, Ipser, Seedat, Sager, & Amos, 2006). Here, we consider a novel pharmacological approach for PTSD to address underlying mechanisms that remain untargeted with current interventions. Recent evidence suggests that angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, which are common hypertensive medications, may exert anti-inflammatory properties and benefit cognitive function. The renin-angiotensin system (RAS) controls blood pressure and electrolyte balance, mainly by action of the octapeptide angiotensin II ([AngII]; Oliveira et al., 2007). AngII can induce cytokines and chemokines, possibly by activation of NF-κB (Pham, Chong, Vincenti, & Slice, 2008), that are important in recruiting leukocytes to sites of inflammation, thereby implicating AngII as a proinflammatory molecule (Benigni, Cassis, & Remuzzi, 2010; Chang & Wei, 2015). Treatment with ARBs and ACEs potentially prevents and reverses the neural and behavioral effects of inflammation. In an animal paradigm of PTSD, subchronic administration of candesartan, an ARB that centrally and peripherally blocks AngII activity at AngII receptor type 1 (AT1), prevented LPS-induced impairment of extinction learning and recall (Quinones et al., 2016). Evidence from human studies suggest protective effects of ARBs against cognitive impairment related to inflammatory diseases. Patients with Alzheimer's disease and vascular dementia taking ARBs showed a reduced progression of cognitive decline compared to patients not taking any ARBs (Chiu et al., 2014). Treatment with ARBs and ACEs also can improve PTSD symptoms among individuals exposed to trauma: lower symptoms of PTSD have been reported among individuals taking ARBs, and ACEs (Nylocks et al., 2015), specifically, reduced severity of intrusive and hyperarousal symptoms (Khoury et al., 2012). Overall, these findings suggest that targeting the RAS can have implications on inflammatory and cognitive outcomes and may well provide a novel pharmacological intervention for the treatment of PTSD.

Nontrauma-focused behavioral interventions for PTSD

Trauma-focused behavioral treatments have the strongest evidence of effectiveness, specifically cognitive processing therapy (CPT), prolonged exposure (PE), and eye movement desensitization and reprocessing ([EMDR]; Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Lee et al., 2016), and are recommended as the first-line treatment for PTSD. These behavioral interventions are based on the fear-learning model of PTSD, namely abnormalities in extinction of fear and safety learning (Shalev et al., 2017), and therefore target trauma-related beliefs, memories, and emotions. Despite their efficacy, these interventions have high rates of incompletion (up to 50%), and many patients continue to have residual symptoms following treatment (Bradley et al., 2005; Kearney & Simpson, 2015; Schottenbauer et al., 2008; Steenkamp et al., 2015). As such, researchers are increasingly investigating the use of nontrauma-focused behavioral interventions for PTSD. A handful of such interventions show particular promise for targeting the cognitive, neural, and inflammatory pathways underscored by this review.

As noted previously, deficits in executive control contribute to the development and maintenance of PTSD (LoSavio, Dillon, & Resick, 2017; Swick, Cayton, Ashley, & Turken, 2017). Recent findings also demonstrate that worse executive control predicts increased inflammatory reactivity to emotional distress (Shields, Kuchenbecker, Pressman, Sumida, & Slavich, 2016). This would suggest that targeting executive control may impact both cognitive and inflammatory pathways linked to PTSD. Mindfulness-based interventions (MBIs) may offer a novel approach to target these mechanisms. Mindfulness-based interventions train focused attention, which is the practice of sustaining attention on a chosen object, such as breath, while remaining attentive to the present

moment without judgment or emotional reactivity (Jha, Stanley, Kiyonaga, Wong, & Gelfand, 2010). Previous evidence demonstrates that mindfulness practice improves executive control ability (Fabio & Towey, 2018; Hofmann et al., 2019; Teper, Segal, & Inzlicht, 2013), possibly through attentional training-related changes in frontal, parietal, and temporal brain regions (Li, Liu, Zhang, Liu, & Wei, 2018; Taren et al., 2017). Indeed, MBIs can modulate PFC-amygdala connectivity (Holzel et al., 2011) and further improve attention and executive control in populations without PTSD (Desrosiers, Vine, Klemanski, & Nolen-Hoeksema, 2013; Goldin & Gross, 2010; Tang, Tang, Tang, & Lewis-Peacock, 2017). In addition, a recent study of an MBI for emotionally distressed adults showed reduced IL-6 levels from baseline to 4-month follow-up and that pretraining to posttraining changes in frontal brain cortices implicated in attention and executive control mediated the effects on IL-6 (Creswell et al., 2016). In general, randomized, clinical trials of MBIs provide empirical evidence of significant decreases in markers of inflammation and improved PTSD symptoms, including reductions in intrusion, avoidance, and arousal (Bergen-Cico, Possemato, & Pigeon, 2014; Black & Slavich, 2016; Davis et al., 2018; Gallegos, Crean, Pigeon, & Heffner, 2017; Heffner, Crean, & Kemp, 2016). These findings lend support for cognitive and inflammatory targets of MBIs that may shed light on how these interventions may be further developed and leveraged to treat PTSD symptoms.

Computerized cognitive training (CT) is a novel approach to potentially improve cognition, inflammation, and symptoms of PTSD. Computerized CT involves structured practice on standardized and cognitively challenging tasks (Lampit, Hallock, & Valenzuela, 2014). Currently, evidence shows that CT improves cognition and mood symptoms in depression (Morimoto, Wexler, & Alexopoulos, 2012; Motter et al., 2016; Owens, Koster, & Derakshan, 2013; Semkovska & Ahern, 2017; Wolinsky et al., 2009). In a randomized, controlled trial (RCT) of a computerized CT intervention for women with PTSD following exposure to sexual violence, training interference control improved working memory capacity and decreased reexperiencing symptoms (Bomyea, Stein, & Lang, 2015). In addition, improvements in cognitive flexibility—a domain implicated in executive control—resulting from 30 days of CT in trauma-exposed individuals were associated with lower PTSD symptoms 6 months after trauma exposure (Ben-Zion et al., 2018). It is possible that targeting cognition may strengthen connectivity of frontal regulatory areas in the brain leading efferent projections from frontal cortices to modulate subcortical cells known to trigger peripheral inflammatory responses (Cisler et al., 2013; Creswell et al., 2016; Gross, 2002; Irwin & Cole, 2011). Both computerized CT and MBIs potentially offer a top-down regulatory pathway for the modulation of circulating cytokines by strengthening functional connectivity of frontal regulatory areas associated with cognitive control and emotion regulation, and thus, warrant further research.

Heart rate variability is another promising target of behavioral intervention for PTSD. As noted previously, PTSD is associated with reduced HRV (Nagpal, Gleichauf, & Ginsberg, 2013; Tan et al., 2011). Importantly, there are links between HRV and cognitive-emotion processes that are relevant to PTSD. Evidence supports HRV as a peripheral index of the integrity of neural structures that underpin inhibitory control and more broadly regulate cognitive, emotion, and physiological responses to support goal-directed behavior. For example, the high-frequency domain of HRV (HF-HRV), reflecting vagal control of the heart, is positively related to working memory, sustained and selective attention, cognitive flexibility, and inhibition (Park, Vasey, Van Bavel, & Thayer, 2013; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Poor inhibition is a key mechanism by which individuals with PTSD produce context-inappropriate responses, including situationally inappropriate hypervigilance and interpreting threat despite a safe context (van Rooij, Geuze, Kennis, Rademaker, & Vink, 2015). Not surprisingly, poor inhibition is associated with reduced HRV in PTSD (Gillie & Thayer, 2014).

Given these links, heart rate variability biofeedback (HRVB) has received attention as an approach to modulating cognitive-emotional pathways in PTSD. HRVB entails breathing training to maximize respiratory sinus arrhythmia (RSA)—the synchronization of HR change (increases/decreases) with respiratory (inhalation/exhalation) patterns—and activity of the baroreflex, resulting in "bottom-up" modulation of autonomic response via the parasympathetic nervous system ([PNS]; Barlow, Lehrer, Woolfolk, & Sime, 2007; Lehrer, 2018). This activity supports regulation of cognition, physiological stress, and emotion (Beauchaine, Gatzke-Kopp, & Mead, 2007; Friedman, 2007; Goessl, Curtiss, & Hofmann, 2017; Lehrer et al., 2003).

Randomized, clinical trials of HRVB with PTSD populations have demonstrated significant reductions in PTSD symptom severity following HRVB (Tan et al., 2011; Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009). HRVB interventions with nontrauma populations have demonstrated beneficial effects on cognition, including improved attentional skills and executive function (Jester, Rozek, & McKelley, 2019; Prinsloo et al., 2011). However, results are less clear for its effects on inflammation. While HRVB appears to reduce inflammation-induced decline in HRV (Lehrer et al., 2010), possibly through PNS modulation of the cholinergic anti-inflammatory system (Gevirtz, 2013; Huston & Tracey, 2011), HRVB did not affect cytokine production. In all, HRVB may offer a novel bottom-up regulatory intervention to target these cognitive and inflammatory mechanisms that are dysregulated in patients with PTSD.

Physical exercise has beneficial effects for neural, cognitive, and inflammatory mechanisms linked to PTSD and is

receiving growing attention as a viable intervention for reducing PTSD symptoms. In non-PTSD samples, for example, acute aerobic exercise drives increased prefrontal oxygenation (Endo et al., 2013) and frontal and hippocampal activation (Chen et al., 2019; Yanagisawa et al., 2010). These exercise-induced changes, however, appear to be dependent on the intensity and duration of the exercise session (Fontes et al., 2018; Kao, Westfall, Soneson, Gurd, & Hillman, 2017; Ligeza, Maciejczyk, Kalamala, Szygula, & Wyczesany, 2018). Consistent with these neural changes, exercise can promote cognitive health as demonstrated by studies reporting improved cognitive function and neuroprotective effects following exercise regimes (Kirk-Sanchez & McGough, 2014; Mandolesi et al., 2018). Studies on the effects of exercise on cognition show improvements in aspects of executive function, including working memory (Chen et al., 2019) and inhibitory control (Kao et al., 2017; Oberste et al., 2019), as well as learning and memory (Austin & Loprinzi, 2019; Frith, Sng, & Loprinizi, 2017). The benefits of exercise can additionally extend to exerting anti-inflammatory effects.

Studies looking into the effects of high-intensity interval training in populations with chronic inflammatory-related diseases show reductions in circulating proinflammatory cytokines, including TNF-α and IL-6 (Alizadeh et al., 2019; Gyorkos et al., 2019). Interestingly, IL-6 and IL-10 can be both increased following exercise and exert anti-inflammatory effects through the inhibition of TNF-α and IL-1β (Pedersen, 2017). Although the underlying mechanisms in which exercise reduces inflammation are yet to be fully elucidated, findings suggest that it increases the production and release of anti-inflammatory cytokines reduces the expression of Toll-like receptors on monocytes and macrophages and reduces visceral fat mass (Collao, Rada, Francaux, Deldicque, & Zbinden-Foncea, 2019; Gleeson et al., 2011).

Empirical demonstration of PTSD symptom reduction after resistance and aerobic exercise is evidenced by several clinical studies. Results from RCTs, including aerobic exercise or broadly exercise training in PTSD samples, have demonstrated clinically significant improvements in PTSD symptoms following exercise regimes (Fetzner & Asmundson, 2015; Hall et al., 2019). Similarly, Whitworth, Nosrat, SantaBarbara, and Ciccolo (2019) tested the effects of a 3-week, high-intensity resistance exercise intervention on PTSD symptoms and found large beneficial effects on symptoms of avoidance and hyperarousal. Notably, another study reported a nonsignificant trend on PTSD symptom reduction following an 8-week exercise—described as a combination of weight and endurance training—and sports intervention with male refugees (Knappe, Colledge, & Gerber, 2019). Finally, a recent meta-analysis identified exercise as having positive effects on relevant aspects of PTSD, including exposure and desensitization to internal arousing cues, exercise-induced neuroplasticity, improved cognitive function, normalization of HPA function, and reductions in inflammatory markers (Hegberg, Hayes, & Hayes, 2019). Together, these findings suggest that exercise promotes cognitive and anti-inflammatory pathways, potentially resulting in improvements in PTSD symptoms, and thus, should be further developed as a novel treatment approach.

Conclusions and future directions

The mechanisms underpinning PTSD are complex. Nonetheless, accumulating evidence supports elevated inflammation and cognitive dysfunction as common features underlying this disorder. Biomarkers of inflammation, including proinflammatory cytokines, are consistently elevated in a significant proportion of patients with PTSD and thus may be driving PTSD symptoms. In addition, compelling evidence points to the detrimental effects of cognitive dysfunction on PTSD outcomes. In parallel with these findings, animal and human research demonstrate that PTSD, in the context of fear learning and extinction, is strongly linked to disrupted activity of brain networks that also support cognition. Translational work is beginning to elucidate how inflammation may impact these critical neural pathways in patients with PTSD, but the research remains limited. More evidence from human studies of PTSD is needed regarding how the interplay between inflammation and cognitive dysfunction contribute to PTSD trajectories. Given the consistent associations between inflammation and cognition, as well as the potential interaction of inflammation with critical neural pathways that support fear learning, extinction, and cognition, it is reasonable to hypothesize that these mechanisms in combination play a central role in PTSD.

The lines of evidence reviewed here for inflammatory, neurobiological, and cognitive interactions suggest avenues for more comprehensive measurement and integration of multiple systems into models of PTSD. Animal and human models should be leveraged to reveal the role of neuroinflammation in PTSD. Evidence is scarce regarding the neuroinflammatory processes involved in PTSD and how they contribute to the development, progression, and maintenance of the disorder. By addressing this gap, findings could provide direct evidence for the associations between inflammation, neurocircuitry, and PTSD to further identify central biomarkers that may facilitate diagnostic and intervention decision-making in PTSD. The study of brain microglia activation is a promising avenue to explore centrally the inflammatory activity and trajectories in patients with PTSD. Evidence demonstrates that increased cytokine production within the CNS results in higher microglia activation (Brown & Vilalta, 2015). Interestingly, recent findings show microglia activation using PET in major depression (Holmes et al., 2018), another inflammatory disorder

commonly comorbid with PTSD. Expanding the application of HRV measurement to neuroimaging research may help to shed light on the role of ANS dysregulation in neuroinflammation and PTSD. Notably, given that HRV is regulated by neural structures that also underpin cognitive-emotional processes, HRV measures in conjunction with neurocognitive testing and neuroimaging may provide a broader, integrative picture of cognitive and emotion regulation in PTSD. In general, more studies are needed that further examine explicitly and comprehensively cognitive function in PTSD. Utilization of standard and sensitive neurocognitive tests alongside physiological, neuroimaging, inflammation, and psychological markers will improve our growing understanding of the association between cognition and PTSD. Finally, further attention should be directed to better understand highly prevalent comorbidities in PTSD, including TBI. The mechanisms underlying PTSD and TBI comorbidity are not fully understood. More work is needed to elucidate the role of differences in TBI severity on PTSD symptom trajectories and inflammatory regulation. Considering the increased inflammatory response potentially ascribed to both conditions, their aggregated burden on neural and cognitive function can adversely affect emotional and behavioral regulation, as well as treatment and recovery. Thus, elucidating these integrative pathways in comorbid PTSD and TBI will have significant clinical implications. Given the devastating effects of PTSD on individuals, there is a critical need to better understand how inflammatory and cognitive regulatory systems together contribute to PTSD development, progression, and maintenance.

Considering that PTSD symptoms may persist in some patients following treatment with trauma-focused behavioral interventions or pharmacological approaches (Berger et al., 2010; Bradley et al., 2005; Schottenbauer et al., 2008; Steenkamp et al., 2015), it is likely that there are underlying mechanisms in PTSD that remain untargeted with the current interventions. The widespread effects of chronic elevated inflammation can have multiple repercussions in the CNS and therefore should not be the only targeted mechanism. Alternatively, targeting both inflammation and cognition, irrespective of whether inflammation leads to cognitive deficits or the inverse, may promote changes in the CNS that could lead to clinically meaningful improvements in PTSD symptoms. We speculate, based on the evidence, that the interventions described in this review could target both mechanisms in PTSD, and thus, deserve further research to test this assumption. Furthermore, there is considerable evidence showing the efficacy of these approaches in the treatment of neuropsychiatric conditions with altered inflammatory response and cognition (i.e., depression and Alzheimer's disease; Cavallo, Hunter, van der Hiele, & Angilletta, 2016; Chiu et al., 2014; Hofmann & Gomez, 2017; Lin et al., 2019; Motter et al., 2016).

Conclusions

The growing evidence for dysregulated inflammation and cognitive function in PTSD suggest that further research on the bidirectional interplay of these pathways will advance a deeper understanding of the etiology, progression, and maintenance of PTSD. In addition, elaborating on these underlying mechanisms can afford further development and testing of novel pharmacological approaches and behavioral interventions that effectively target inflammation and cognitive function and, in turn, meaningfully reduce PTSD symptomatology.

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