Inflammation and posttraumatic stress disorder

Hiroaki Hori, MD, PhD* and Yoshiharu Kim, MD, PhD

Department of Behavioral Medicine, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan

*Correspondence: Hiroaki Hori, MD, PhD, Department of Behavioral Medicine, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1, Ogawahigashi, Kodaira, Tokyo, 187-8553, Japan. *E-mail*: hori@ncnp.go.jp

Manuscript type: Review article (for "PCN Frontier Review")

Words: 5,008 words (250 words in abstract); 2 tables and 4 figures

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pcn.12820

Abstract

While posttraumatic stress disorder (PTSD) is currently diagnosed based solely on classic psychological and behavioral symptoms, a growing body of evidence has highlighted a link between this disorder and alterations in the immune and inflammatory systems. Epidemiological studies have demonstrated that PTSD is associated with significantly increased rates of physical comorbidities in which immune dysregulation is involved, such as metabolic syndrome, atherosclerotic cardiovascular disease, and autoimmune diseases. In line with this, a number of blood biomarker studies have reported that compared to healthy controls, individuals with PTSD exhibit significantly elevated levels of proinflammatory markers such as interleukin-1² , interleukin-6, tumor necrosis factor-±, and C-reactive protein. Moreover, various lines of animal and human research have suggested that inflammation is not only associated with PTSD but also can play an important role in its pathogenesis and pathophysiology. In this review, we first summarize evidence suggestive of increased inflammation in PTSD. We then examine findings that suggest possible mechanisms of inflammation in this disorder in terms of two different but interrelated perspectives: putative *causes* of increased proinflammatory activities and potential *consequences* that inflammation generates. Given that there is currently a dearth of treatment options for PTSD, possibilities of new therapeutic approaches using pharmacological and non-pharmacological treatments/interventions that have anti-inflammatory effects are also discussed. Despite the increasing attention given to the inflammatory pathology of PTSD, there remains much to be elucidated,

including more detailed mechanisms of inflammation, potential usefulness of inflammatory biomarkers as diagnostic and prognostic markers, and efficacy of novel treatment strategies targeting inflammation.

Keywords: Posttraumatic stress disorder (PTSD); Inflammation; Cytokine; Neuroinflammation; Treatment

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric condition that develops in a subset of individuals after a major traumatic event. Lifetime prevalence of PTSD is estimated at around 3.9% worldwide.[1] Diagnostic symptoms of PTSD include intrusion (or re-experiencing), avoidance, negative alterations in cognitions and mood, and hyperarousal.[2] Individuals with PTSD exhibit these symptoms for more than a month, with severe distress and functional impairment. Traditional cognitive theories of PTSD postulate that memory abnormalities manifested as dissociative flashback and intrusive memories are a key contributor to the development and persistence of the disorder.[3,4] The presence of these re-experiencing symptoms in individuals with PTSD implies that trauma-related fear can be easily activated in these individuals even in the absence of an actual threat.[5]

In addition to these classic psychobehavioral features, physical morbidities such as obesity, diabetes, and metabolic syndrome are common in individuals with PTSD.[6,7] Moreover, epidemiological studies have found a link between PTSD and an increased risk of serious physical diseases such as cardiovascular disease[8] and autoimmune disease.[9,10] Since these diseases have an inflammatory component, it is suggested that immune system is dysregulated in PTSD. With respect to therapeutics, the development of novel treatment strategies based on a deeper understanding of biological mechanisms underlying PTSD, such as inflammatory pathology, would be of particular significance.

In this review, we first summarize evidence suggestive of dysregulation in the

inflammatory system in (a subset of) individuals with PTSD, focusing on blood inflammatory markers. We then describe potential mechanisms linking PTSD with the dysregulated immune/inflammatory system by examining relevant findings from basic and clinical studies. To this end, 2 different (albeit interrelated) issues are distinguished and separately discussed: putative *causes* for inflammation in PTSD and possible *consequences* of inflammation in this disorder. Finally, we explore the possibility of treatment strategies that target inflammation in PTSD by introducing several different classes of pharmacological agents and non-pharmacological interventions.

Inflammation and PTSD

The notion that inflammation is involved in mental ill-health dates back at least to the observation of increased rates of depression among patients with chronic hepatitis C treated with interferon-±.[11] This original link between inflammation and depression has been supported by subsequent evidence that patients with major depressive disorder (MDD) show elevated levels of inflammatory markers, including pro-inflammatory cytokines such as interleukin-1² (IL-1²), interleukin-6 (IL-6) and tumor necrosis factor-± (TNF±) as well as acute-phase proteins such as C-reactive protein (CRP), in the blood[12,13] and in the cerebrospinal fluid.[14] Furthermore, studies have demonstrated that immune dysregulation and inflammation are associated with a range of psychiatric disorders beyond MDD, including schizophrenia,[15] bipolar disorder,[16] autism spectrum disorders,[17] and PTSD.[18]

As the evidence for an association between PTSD and inflammation derives primarily from studies on blood inflammatory markers, we focus on findings from these studies in this section. At the outset, however, it may be worth noting that besides these targeted investigations into inflammatory markers, hypothesis-free genome-wide,[19] blood DNA methylome,[20] and blood transcriptome[21,22] studies have identified immune/inflammatory-related genes and pathways as the most dysregulated in patients with PTSD compared to controls.

Inflammatory markers in PTSD

An increasing number of studies have shown that individuals with PTSD exhibit significantly elevated blood levels of inflammatory markers, such as IL-1², IL-6, TNF± and CRP, relative to healthy control subjects (Table 1). Among them, IL-6 is the best studied proinflammatory marker, for which a significant increase in patients with PTSD is almost consistently shown in a meta-analysis[18] and in most subsequent studies including ours;[23-25] in a Japanese female sample, we reported significantly higher serum IL-6 levels in women with PTSD than in healthy control women (Fig. 1).[25] In addition to the differences in basal levels of inflammatory markers, several studies have described altered production of proinflammatory cytokines in response to immune challenges in PTSD patients compared to controls.[26,27] On the other hand, some evidence suggests that trauma exposure itself, irrespective of the presence/absence of PTSD diagnosis, can lead to increased levels of proinflammatory markers.[28] Still, a number of studies comparing inflammatory markers between PTSD patients and trauma-exposed non-PTSD controls

have shown that PTSD is associated with elevated levels of these markers beyond the possible effect of trauma exposure.[23, 29-31]

Findings supporting the proinflammatory activity in PTSD are, however, not fully consistent; there are studies that have reported similar or even lower levels of inflammatory markers such as IL-6, TNF± and CRP in individuals with PTSD compared with controls.[32-34] Additionally, a few small studies have investigated cerebrospinal fluid levels of IL-6 in patients with PTSD, yielding conflicting results.[35,36] Perhaps in line with these mixed findings, IL-6 levels in our patients with PTSD showed considerable variation, overlapping substantially with those in controls (Fig. 1).[25] It is therefore conceivable that a significant subset of, but not all, individuals with PTSD exhibit increased inflammation. Such variations may be related to the heterogeneous nature of this disorder, as reflected, for example, in heterogeneity in concomitant psychiatric conditions. Indeed, it is reported that more than half of patients with PTSD have comorbid depressive disorders.[37,38] Moreover, early-life adversities such as childhood maltreatment are known to increase risk of PTSD in later life.[39,40] In particular, depression[12,41] and history of childhood maltreatment[42,43] have also been associated with increased inflammation; therefore, these conditions can confound the association between PTSD and inflammation. In the meta-analysis of Passos et al.,[18] however, IL-1² and IL-6 levels remained significantly increased in PTSD patients compared to controls in a subgroup analysis of studies that excluded patients with comorbid MDD.

Although smaller in number, there are studies that have examined anti-inflammatory

cytokines such as IL-4 and IL-10 in the blood of individuals with PTSD compared to controls.[23,24,44-47] However, their findings have been quite controversial. For IL-4, some studies have reported higher levels[45,47] while others have observed lower levels[46] or lower levels after controlling for several variables[44] in patients with PTSD compared to controls. Likewise, some have reported higher IL-10 levels in PTSD patients[24,45,47] whereas others have observed no significant difference[23,44] or lower levels.[48]

Temporal relationship between inflammation and PTSD

It is much less clear whether the increase in proinflammatory markers precedes or follows the onset of PTSD, which is essentially due to the scarcity of longitudinal data. Nonetheless, a few prospective studies have been conducted to address this issue. A study demonstrated that plasma CRP levels were prospectively associated with PTSD symptom emergence in male veterans, suggesting that inflammation may represent a risk factor for developing PTSD.[49] In addition, an RNA-seq based transcriptome study showed that dysregulated innate immune network at baseline (pre-deployment) was associated with the development of PTSD post-deployment.[50] Supporting this, evidence for an association of PTSD with genes (or gene variants) involved in the immune/inflammatory system such as the *CRP* gene[51] and the *ANKRD*55 gene[19] indicates that the increased inflammation constitutes a predisposing factor. Furthermore, it is postulated that chronic low-grade inflammation caused by early-life adversities will give rise to the pathogenesis of emotional and physical health problems.[52]

Conversely, another study utilizing longitudinal data reported that there were no

significant differences in pre-PTSD-onset levels of inflammatory/endothelial markers (including CRP, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1) between women with PTSD and control women.[53] Somewhat in agreement with this, several cross-sectional studies have reported that remitted patients with PTSD and healthy controls do not significantly differ in proinflammatory marker levels,[54,55] suggesting that heightened inflammation in these patients may not be a preexisting trait; however, the possibility cannot be ruled out that the increased proinflammatory activity that lasted from before PTSD onset is normalized after (or owing to) the treatment of the illness. Findings on correlations between PTSD severity and levels of inflammatory markers have been mixed, such that some studies observed significant positive correlation[44,56] whereas others reported absence of such significant correlation.[23,25]

These discrepant findings might collectively suggest that both directions of the temporal relationship between inflammation and PTSD onset are likely, perhaps depending on individuals and situations; it is also possible that preexisting inflammation becomes even worse after the development of PTSD.

Mechanisms underlying the link between inflammation and PTSD

Mechanism(s) that lies behind the association between increased proinflammatory activities and PTSD is unclear, yet likely to be complex. In this section, relevant findings from basic and clinical research are pulled together to make inferences about the mechanisms. For clarity purposes, we discuss such mechanisms from 2 different

perspectives, while recognizing that they are interlinked and have a lot in common: putative *causes* of increased inflammation in PTSD and potential *consequences* that the inflammation generates in this disorder.

Putative causes for increased inflammation in PTSD

It is generally accepted that severe or chronic stress can cause inflammation. This stress-related proinflammatory state represents "sterile inflammation", i.e., inflammation in the absence of pathogenic disease. Sterile inflammation can be triggered by the activation of pattern recognition receptors (PRRs) that detect endogenous ligands termed danger- (or damage-)associated molecular patterns (DAMPs).[57,58] DAMPs are host-derived, non-microbial endogenous molecules that are increased in response to physical and psychological stress, and are considered to include a variety of different molecules such as heat-shock proteins, S100 proteins, high mobility group box 1 (HMGB-1), uric acids, and adenosine triphosphate (ATP).[57,58] The binding of DAMPs to PRRs can lead to sterile inflammation in both inflammasome-independent and -dependent manners.[57] Therefore, a plausible explanation for the increased proinflammatory activity in PTSD would be that excessive stress associated with this disorder causes inflammation; incidentally, it should be noted here again that individuals with PTSD tend to experience chronic stress not only during the illness course but also prior to its onset (e.g., history of childhood maltreatment). In line with this, studies in PTSD animal models have shown that chronic stress can induce immunological changes associated with inflammation.[59,60]

Assuming this, the proinflammatory state in PTSD is considered to occur in the context of heightened stress responses, possibly in concert with alterations in the hypothalamic-pituitary-adrenal (HPA) axis function and autonomic nervous system activity. Notably, hypoactive HPA axis and hyperactive sympathetic nervous system (SNS) are among the most well established biological abnormalities in PTSD.[61,62] To briefly outline the HPA axis, it is a neuroendocrine system that plays a pivotal role in stress response and in the maintenance of homeostasis. It is activated in response to various stressors, resulting in an increased secretion of glucocorticoid (cortisol in humans) from the adrenal cortex. Glucocorticoid, in turn, regulates its own production through negative feedback by binding to glucocorticoid receptors (GRs) in the hypothalamus and pituitary. Glucocorticoid also exerts negative feedback via GRs and mineralocorticoid receptors (MRs) in the hippocampus.[63]

A putative scenario that explains how the stress-induced responses of these systems lead to increased inflammation is illustrated in Fig. 2. Cytokines (shown in red) are signaling molecules synthesized and secreted by multiple types of cells, including peripheral immune cells (e.g., macrophages, lymphocytes, etc.), vascular endothelial cells, and central nervous system (CNS) microglia, astrocytes and neurons.[64] Stress increases synthesis and release of corticotropin-releasing hormone (CRH) (and arginine vasopressin) in the paraventricular nucleus (PVN) of the hypothalamus. CRH stimulates SNS to produce catecholamines including norepinephrine (which leads to a number of PTSD symptoms such as hyperarousal). This increased norepinephrine release can

induce the production of proinflammatory cytokines such as IL-1 and IL-6 via nuclear factor-º B (NF-º B)-dependent[65] and other[66] mechanisms (although the interaction between autonomic nervous system and immune system can be much more complex). These cytokines, in turn, stimulate CRH secretion from the hypothalamic PVN. As for the HPA axis (re)activity, the increased CRH typically stimulates adrenocorticotropin (ACTH) secretion and consequently causes cortisol elevation; however, in PTSD, a large body of evidence shows *decreased* cortisol[61,67] in the face of *increased* CRH.[68,69] Since cortisol can decrease the synthesis and release of proinflammatory cytokines by suppressing NF-º B signaling[70] and by mediating cell type-specific regulation of apoptosis,[71] the reduced ability of cortisol to inhibit inflammatory responses in PTSD may exacerbate the proinflammatory state. In addition, given that cortisol is shown to inhibit the SNS activity[72] except when its elevation occurs in synchrony with noradrenaline release,[73] the persistent low cortisol levels in PTSD may contribute to SNS hyperactivity, thereby further accelerating inflammation.

It should be noted that the hypocortisolism coupled with greater GR sensitivity is a distinctive feature of PTSD. This direction of alteration may at first sight be paradoxical, given that heightened HPA axis activity is expected as a consequence of severe stress. In addition, depressive disorders, which are frequently comorbid with PTSD, are typically associated with hypercortisolism along with reduced GR sensitivity.[74] Therefore, if PTSD has a greater (or unique) inflammatory pathology than do other stress-related psychiatric disorders, the distinct pattern of alteration in HPA axis function might hold the key.

Importantly, it is suggested that low cortisol levels could be a risk factor for developing PTSD when exposed to traumatic events.[75,76] This hypoactive HPA axis prior to PTSD onset may represent genetic predisposition or allostatic change experienced during early life. For example, a polymorphism in the *FKBP5* gene, a co-chaperone of heat shock protein 90, is shown to confer susceptibility to PTSD[77] and to moderate GR sensitivity in PTSD.[78] This premorbid hypocortisolism may lead to failure in mobilizing adequate energy resources to cope with immediate serious stressors (e.g., traumatic experiences) and in restoring homeostasis after the challenge has subsided, thereby rendering the individual vulnerable to PTSD.

Another mechanism underlying elevated inflammation may relate to metabolic abnormalities. Recently, an increasing attention has been placed on the crosstalk between immune and metabolic pathways.[79] Of note, it is well recognized that obesity induces inflammation, leading to insulin resistance.[80] Findings from this line of research suggest that the increased proinflammatory activity in PTSD is due at least in part to metabolic abnormalities such as diabetes and dyslipidemia that are frequently seen in individuals with this disorder.[7] In addition, PTSD is associated with unhealthy lifestyles such as physical inactivity, unhealthy eating habits (e.g., binge eating and increased consumption of fast foods), and smoking.[81-83] These lifestyle variables can also contribute to inflammation.[84]

Possible consequences of increased inflammation in PTSD

Given the currently predominant definition of PTSD as a *brain* disorder, the key

concept here would be “neuroinflammation”, or inflammation of the nervous tissue. The brain was once considered an “immune-privileged” organ, which means that cells from the immune system do not enter the brain except for certain cases of disease and injury. A growing body of evidence in recent years, however, indicates that the brain and the immune system communicate routinely, both in sickness and in health. Indeed, it is now well known that peripheral proinflammatory cytokines can affect the brain via several mechanisms, including through active transport across the blood-brain barrier (BBB), through leaky regions in the BBB, or through the activation of neural pathways such as the vagal nerve.[85] Thus, inflammation in the periphery as well as in the CNS can both contribute to neuroinflammation via the activation of microglia and astrocytes (Fig. 2). In particular, IL-6, TNF±, and IL-1² are shown to influence the brain at the morphological, functional, and cognitive level, thereby affecting, for example, neurogenesis, synaptic plasticity, and memory/learning.[86]

Microglia, the primary innate immune cells in the CNS, are key mediators of neuroinflammatory processes. They exist in resting (quiescent) or activated states depending on the inflammatory milieu.[87] Microglia have several normal physiological functions including synaptogenesis, trophic support, chemotaxis, and neurogenesis.[87] However, microglia can lose these homeostatic functions during the course of many illnesses.[87] In diseased and stressed brains, microglia may persist in an activated state,[88] thereby overproducing cytotoxic molecules such as proinflammatory cytokines and glutamate.[89] In addition, these proinflammatory mediators produced by activated

microglia activate astrocytes that also release cytokines and further induce the activation of microglia; thus, communication between microglia and astrocytes can amplify proinflammatory signaling initiated by microglia.[90] These disease-associated responses of microglia and astrocytes may ultimately lead to functional/structural brain changes and behavioral changes associated with PTSD.

Another mechanism that has attracted considerable interest is the ability of proinflammatory cytokines to enhance the activity of the indoleamine 2,3-dioxygenase (IDO), the first and rate-limiting enzyme of the tryptophan degradation pathway, i.e., the kynurenine pathway (Fig. 3). Activation of IDO leads to decreased tryptophan concentrations and increased production of kynurenine. Kynurenine, in turn, is converted to several metabolites including quinolinic acid and kynurenic acid that subsequently activate and inhibit NMDA neurotransmission (respectively). In a proinflammatory state, there is a shift toward relatively more production of quinolinic acid than kynurenic acid, thereby contributing to NMDA receptor-elicited neurotoxicity.[91] Moreover, the increase in proinflammatory cytokines results in reduced production of serotonin by facilitating the breakdown of tryptophan, the primary substrate of serotonin. Glucocorticoids can also play a role in this inflammation-induced activation of the kynurenine pathway.[92]

As described earlier, a unique psychological manifestation of PTSD is the re-experiencing symptoms that include dissociative flashback and intrusive memories.[3,4] Numerous studies have investigated the neural basis of these characteristic symptoms, and functional neuroimaging studies have demonstrated hyperactivation of amygdala in

individuals with PTSD, particularly when exposed to traumatic and threat-related stimuli.[93,94] Importantly, several lines of work suggest that inflammation may be causally involved in the emergence and maintenance of these psychobehavioral symptoms of PTSD. In particular, a number of animal studies have shown that heightened inflammation impairs extinction of fear memory.[95-97] In humans, increased inflammation is shown to be related to enhanced amygdala activation in response to threatening stimuli.[98,99] In contrast, glucocorticoids are shown to reduce retrieval of aversive memories and enhance fear extinction.[100] It is also suggested in human neuroimaging studies that glucocorticoids can play a role in modifying amygdala responses to fearful stimuli and in altering functional connectivity between the amygdala and frontal cortices during emotional processing, in a time-dependent manner.[73,101] Thus, the heightened inflammation together with hypocortisolism could lead to the unique symptomatology of PTSD.

Besides these trauma-specific memory abnormalities and behavioral alterations, PTSD is associated with impairment in a range of cognitive functions including verbal memory/learning, working memory, attention, and executive functions, with particularly marked impairment in verbal memory/learning.[102,103] Epidemiological studies even suggest that individuals with PTSD are at an elevated risk of developing dementia.[104,105] Consistent with these cognitive impairments, neuroimaging studies have demonstrated that individuals with PTSD show structural and functional abnormalities in the brain regions that control cognitive function, including the hippocampus and prefrontal

cortex.[106-109] Notably, accumulated evidence suggests that increased inflammation can have detrimental effects on cognitive function.[110-112] In humans, for example, elevated levels of inflammatory markers have been shown to be associated with lower cognitive function in various diseases and conditions where cognitive dysfunction plays a role, such as depression,[113] schizophrenia,[114] cocaine addiction,[115] cerebrovascular disease,[116] and cognitive decline.[117] In line with this, we demonstrated that elevated serum IL-6 levels in PTSD patients was associated with worse cognitive function, suggesting that their cognitive dysfunction may be due at least partly to increased inflammation (Fig. 4).[25]

Potential anti-inflammatory treatment strategies

There is currently a dearth of pharmacological treatment options for PTSD, with only 2 selective serotonin reuptake inhibitors (SSRIs), paroxetine and sertraline, being approved by countries/organizations including the US Food and Drug Administration (FDA). Moreover, a substantial proportion of patients with PTSD do not adequately respond to these SSRIs.[118] Indeed, a meta-analysis[119] shows that the efficacy of these SSRIs is considerably lower than that of trauma-focused psychotherapies, which in turn have a problem of limited availability. Hence, the development of a novel pharmacotherapeutic approach for PTSD based on its underlying biological mechanisms, such as the inflammatory pathology, is a matter of great interest. Despite the abundant evidence suggesting the role of inflammation in PTSD, however, thus far this has rarely

been translated into treatment strategies. Still, several types of extant (off-label) pharmacological agents that have anti-inflammatory properties may represent a promising therapeutic option (Table 2).

First, nonsteroidal anti-inflammatory drugs (NSAIDs), which are used for the treatment and alleviation of various diseases and conditions, exert anti-inflammatory effects by inhibiting the enzyme cyclooxygenase 2 (COX-2) that is involved in cytokine production. These drugs, in particular the selective COX-2 inhibitor celecoxib, have demonstrated good efficacy and tolerability in depressed patients.[120] While their efficacy has not yet been examined in patients with PTSD, a study using a rat model of PTSD showed that treatment with ibuprofen reduced both inflammatory cytokine levels and behavioral symptoms.[121]

Treatment with monoclonal antibodies, which are approved for the treatment of autoimmune diseases and cancers, is a straightforward way to block cytokines. Among this class of agents, efficacy of infliximab, adalimumab (anti-TNF± antibodies) and tocilizumab (anti-IL-6 receptor antibody) in the treatment of depression has been reported,[122] although none has been tested in PTSD. These agents may be beneficial in a subset of patients with refractory PTSD who show increased inflammation.

Glucocorticoids, or steroids, have potent immunosuppressant effects among their diverse array of functions, as described earlier. Building on the findings of relatively low cortisol levels in individuals with PTSD, several studies have investigated the therapeutic effect of exogenous glucocorticoids. They have overall yielded favorable results,

indicating that these agents can alleviate PTSD symptoms when administered as a stand-alone treatment[123] or in combination with exposure-based psychotherapy.[124,125] In addition to these findings in patients who have already developed PTSD, glucocorticoid treatment given after traumatic experiences is shown to reduce risk of the subsequent development of this disorder.[126,127]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which are mainly used for the treatment of hypertension, are suggested to have anti-inflammatory properties.[128,129] Interestingly, a cross-sectional, observational study reported that, unlike other antihypertensive medications such as beta-blockers, calcium channel blockers and diuretics, the use of ACE inhibitors/ARBs was associated with significantly decreased PTSD symptoms.[130] Further, a rodent study showed that an ARB candesartan ameliorated the impaired fear extinction caused by lipopolysaccharide-induced activation of peripheral inflammation.[95]

Cannabis, a psychoactive substance, is demonstrated to have anti-inflammatory properties and might be beneficial in the treatment of PTSD.[131] The endocannabinoid system is shown to be involved in multiple aspects of the pathophysiology of PTSD including inflammatory processes,[131] and in line with this, several uncontrolled or small studies have reported the potential usefulness of cannabis (including whole plant marijuana and related cannabinoids) in the treatment of this disorder, particularly for the domains of sleep and nightmares.[132] At present, however, a balanced view would be that obvious risks of cannabis such as psychosis and substance misuse outweigh

unestablished benefits for PTSD.[132]

Another target that has been increasingly investigated in the treatment of PTSD is oxytocin, a neuropeptide best known for its role in parturition and lactation. Compelling evidence indicates that oxytocin also plays a role in many aspects of prosocial behaviors and affection[133] and as such can be associated with psychiatric disorders.[134] A number of studies have shown that oxytocin exerts favorable neurobiological and behavioral effects in individuals with PTSD.[135] In addition, oxytocin is reported to have anti-inflammatory properties in animals[136] and humans.[137]

It should also be noted that SSRIs are suggested to have some anti-inflammatory effects.[138,139] Although the specific molecular mechanisms by which SSRIs exert such effects are not clear, a variety of mechanisms have been proposed, including those mediated by the serotonin transporter, mediated by NF-º B, by IL-10, and via actions on cyclic adenosine monophosphate signaling.[138] Supporting this, a recent large-scale epidemiological study reported that persistent use of SSRIs during the first year after PTSD diagnosis was associated with attenuated risk of autoimmune disease.[10] Moreover, chronic PTSD patients who received SSRIs showed significant reduction in both clinical symptoms and serum IL-1² levels.[140] A meta-analysis demonstrated that PTSD patients receiving psychotropic medication including SSRIs did not significantly differ from control subjects in IL-1² or TNF± levels while patients who were medication-free showed significantly higher IL-1² and TNF± levels compared to controls;[18] still, the fact that PTSD patients on such medication had significantly elevated IL-6 levels compared

to controls[18,25] suggests that the SSRIs' effect of reducing inflammation is not sufficient, which justifies the necessity of investigating efficacy of other agents with anti-inflammatory properties in the treatment of PTSD.

Apart from pharmacological agents, studies have reported potentially beneficial effects of health-promoting behaviors (in contrast to the aforementioned unhealthy lifestyles), including exercise and specific dietary habits such as fish oil and lactobacillus drinks, in individuals with PTSD, although the findings are somewhat mixed especially with respect to sex differences.[82,102,141-143] Intriguingly, physical activity and exercise can reduce inflammation.[144,145] Dietary factors can also be associated with inflammation,[146] the effect of which may be mediated by the gut microbiota. Studies have shown that the gut microbiota play a critical role in the interplay between the gastrointestinal tract and the CNS, i.e., the gut-brain axis, in which the immune system acts as a key regulator.[147] Intestinal microbes influence the activation of peripheral immune cells that participate in neuroinflammation.[147] It is also shown that host microbiota control maturation and function of microglia in the CNS.[148] Given that several microbial phyla were reported to be altered in PTSD,[149] dysbiosis of gut microbiota may be involved in the increased inflammatory activity in PTSD. Thus, the possibly favorable effects of dietary and behavioral interventions in the treatment of PTSD may be attributable to their anti-inflammatory effects. As these interventions are generally better tolerated than medications, they can be an alternative therapeutic approach for PTSD.

Future directions

Mounting evidence from blood biomarker studies indicates that a considerable proportion of individuals with PTSD exhibit elevated proinflammatory activities. Moreover, various lines of research have suggested that inflammation can play an important role in the pathogenesis and pathophysiology of this disorder. Meanwhile, basic research in recent years has provided evidence of close interaction between the immune system and the brain and of sterile inflammation evoked by psychological stress, which has profoundly changed the notion of inflammation originally conceived as responses to harmful pathogens and irritants. These findings from clinical and basic studies together suggest that PTSD is not a simple psychological reaction to traumatic experiences, but can be associated with systemic and CNS inflammation. However, research on inflammation in PTSD is still quite limited, compared, for example, to the extensive work on the HPA axis dysfunction in this disorder; therefore, much needs to be done to elucidate mechanism(s) underlying increased inflammation in PTSD, mechanism(s) whereby inflammation contributes to the development and maintenance of this disorder, and potential usefulness, or the lack thereof, of novel treatment strategies targeting inflammation. In addition, evidence is lacking on inflammatory status in the brain, or neuroinflammation, in patients with PTSD, which should also be addressed in future research. In MDD, there is more direct evidence for this; for instance, brain microglial activation is suggested using positron emission tomography.[150]

Besides the inflammatory/immune system, dysregulation of other stress response

systems, including the HPA axis and SNS, is known to be involved in the pathogenesis and pathophysiology of PTSD. There is an intricate interplay between these systems, and importantly, the altered interaction between HPA axis and inflammatory system may play a key role in the etiology of PTSD. Therefore, it will be of significance to simultaneously investigate these systems in this disorder. This would also help in identifying phenotypic subgroups linked to different biological underpinnings within the current diagnosis of PTSD. To help get a bigger picture, genetic, epigenetic and transcriptional factors as well as environmental and life-style factors that increase or decrease inflammation need to be taken into account, as they are suggested to affect inflammation in PTSD.

Another issue that needs to be considered in PTSD research is potential sex differences. The prevalence of PTSD has been consistently shown to be higher in women than in men,[37,151] which cannot be accounted for by sex differences in the prevalence of the exposure to traumatic events.[152] Additionally, although the heritability of PTSD is estimated at around 30-40% by twin studies,[153] this estimate was reported to be as high as 72% when the sample was restricted to female patients.[154] The mechanism(s) underlying this sex difference in the PTSD etiology is not clear, while there is some evidence that suggests the involvement of ovarian hormones in memory abnormalities characteristic to this disorder.[155,156] Other potential mechanisms that explain sex differences in PTSD may include HPA axis (re)activity, oxytocin, as well as psychological factors such as differential threat perceptions and coping styles.[157] Inflammatory pathology in PTSD may also be different between sexes, which has been

poorly understood and therefore should be investigated in future research.

From a clinical viewpoint, it would be expected that inflammatory markers can serve as biomarkers for PTSD, although any diagnostic and prognostic markers need to have sufficiently high sensitivity and specificity. On the one hand, increased inflammation is not observed in all patients with PTSD, nor is it a unique feature of PTSD among psychiatric disorders. This suggests that inflammation may be better regarded as a transdiagnostic biomarker that will aid in subtyping psychiatric disorders based on different etiology, which is in accordance with the concept of the NIMH Research Domain Criteria.[158] In terms of treatment strategies, this implies that psychiatric patients with elevated inflammation, regardless of diagnosis, may benefit from drugs with anti-inflammatory properties. On the other hand, there is some evidence that PTSD, in particular, is closely associated with inflammation. For example, the association of autoimmune disorders with PTSD is shown to be even stronger than that with other psychiatric disorders.[9] Furthermore, animal studies of PTSD have shown that behavioral alterations mimicking the fear memory-related symptoms (e.g., conditioned fear responses) are associated with immune dysfunction and inflammation.[95,97] Taken together, it can be said that elevated proinflammatory markers may be useful in classifying (stress-related) psychiatric disorders in general, with PTSD possibly representing a model case in which heightened inflammation lies at the intersection where psychopathology meets pathoetiology.

With regard to intervention and treatment, it may seem premature to test the possibility

of inflammation-targeted therapeutic strategies before the mechanism of inflammation is fully clarified. Nonetheless, there is considerable evidence that shows the efficacy of these approaches in the treatment of patients with MDD. Furthermore, the findings of increased *peripheral* inflammatory markers themselves would deserve sufficient attention irrespective of causality or presence/absence of neuroinflammation, considering the increased risk of physical comorbidities of PTSD (e.g., metabolic syndrome and atherosclerotic cardiovascular disease) that are likely mediated by *systemic* inflammation.

The overall conclusion emerging from this review is that a substantial proportion of individuals with PTSD show increased inflammation and that a better understanding of causes and consequences of the altered inflammatory system will aid in elucidating the etiology of, and developing biologically-oriented diagnostics for, this disorder. In parallel with the mechanistic investigations, efforts should be directed toward searching for the possibility of new therapeutic avenues targeting inflammation in PTSD.

Acknowledgements

This study was supported in part by Health Labour Sciences Research Grant from the Japanese Ministry of Health, Labour and Welfare (201616028A), JSPS KAKENHI (16KT0198), and grants from the Takeda Science Foundation and the Japan Research Foundation for Clinical Pharmacology.

Disclosure Statement

The authors declare that they have no competing interests.

References

1. Koenen KC, Ratanatharathorn A, Ng L et al. Posttraumatic stress disorder in the World Mental Health Surveys. *Psychol Med.* 2017; **47**, 2260-2274.
2. APA. *Diagnostic and Statistical Manual of Mental Disorders, 5th edn*. American Psychiatric Publishing, Arlington, VA, 2013.
3. Brewin CR. A cognitive neuroscience account of posttraumatic stress disorder and its treatment. *Behav Res Ther*. 2001; **39**, 373-393.
4. McNally RJ. Cognitive abnormalities in post-traumatic stress disorder. *Trends Cogn Sci*. 2006; **10**, 271-277.
5. Ehlers A, Clark DM. A cognitive model of posttraumatic stress disorder. *Behav Res Ther.* 2000; **38**, 319–345.
6. Michopoulos V, Vester A, Neigh G. Posttraumatic stress disorder: a metabolic disorder in disguise? *Exp Neurol*. 2016; **284**, 220-229.
7. Mellon SH, Gautam A, Hammamieh R, Jett M, Wolkowitz OM. Metabolism, Metabolomics, and Inflammation in Posttraumatic Stress Disorder. *Biol Psychiatry*. 2018; **83**, 866-875.
8. Edmondson D, Kronish IM, Shaffer JA, Falzon L, Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. *Am Heart J*. 2013; **166**, 806-814.
9. O'Donovan A, Cohen BE, Seal KH et al. Elevated risk for autoimmune disorders in iraq and afghanistan veterans with posttraumatic stress disorder. *Biol Psychiatry.* 2015; **77**, 365-374.
10. Song H, Fang F, Tomasson G et al. Association of Stress-Related Disorders With Subsequent Autoimmune Disease. *JAMA*. 2018; **319**, 2388-2400.
11. Renault PF, Hoofnagle JH, Park Y et al. Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med.* 1987; **147**, 1577-80.
12. Dowlati Y, Herrmann N, Swardfager W et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry* 2010; **67**, 446-457.
13. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009; **71**, 171-186.
14. Sasayama D, Hattori K, Wakabayashi C et al. Increased cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder. *J Psychiatr Res.* 2013; **47**, 401-406.
15. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry*. 2011; **70**, 663-671.
16. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. *Biol Psychiatry.* 2013; **74**, 15-25.
17. Rossignol DA, Frye RE. A review of research trends in physiological abnormalities in

autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures. *Mol Psychiatry.* 2012; **17**, 389-401.

18. Passos IC, Vasconcelos-Moreno MP, Costa LG et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry*. 2015; **2**, 1002-1012.
19. Stein MB, Chen CY, Ursano RJ et al. Genome-wide Association Studies of Posttraumatic Stress Disorder in 2 Cohorts of US Army Soldiers. *JAMA Psychiatry.* 2016; **73**, 695-704.
20. Uddin M, Aiello AE, Wildman DE et al. Epigenetic and immune function profiles associated with posttraumatic stress disorder. *Proc Natl Acad Sci U S A.* 2010; **107**, 9470-9475.
21. Breen MS, Tylee DS, Maihofer AX et al. PTSD Blood Transcriptome Mega-Analysis: Shared Inflammatory Pathways across Biological Sex and Modes of Trauma. *Neuropsychopharmacology* 2018; **43**, 469-481.
22. Neylan TC, Sun B, Rempel H et al. Suppressed monocyte gene expression profile in men versus women with PTSD. *Brain Behav Immun.* 2011; **25**, 524-531.
23. Lindqvist D, Dhabhar FS, Mellon SH et al. Increased pro-inflammatory milieu in combat related PTSD - A new cohort replication study. *Brain Behav Immun*. 2017; **59**, 260-264.
24. de Oliveira JF, Wiener CD, Jansen K et al. Serum levels of interleukins IL-6 and IL-10 in individuals with posttraumatic stress disorder in a population-based sample. *Psychiatry Res*. 2018; **260**, 111-115.
25. Imai R, Hori H, Itoh M et al. Inflammatory markers and their possible effects on cognitive function in women with posttraumatic stress disorder. *J Psychiatr Res.* 2018; **102**, 192-200.
26. Rohleder N, Joksimovic L, Wolf JM, Kirschbaum C. Hypocortisolism and increased glucocorticoid sensitivity of pro-Inflammatory cytokine production in Bosnian war refugees with posttraumatic stress disorder. *Biol Psychiatry*. 2004; **55**, 745-751.
27. Gill J, Vythilingam M, Page GG. Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD. *J Trauma Stress*. 2008; **21**, 530-539.
28. Tursich M, Neufeld RW, Frewen PA et al. Association of trauma exposure with proinflammatory activity: a transdiagnostic meta-analysis. *Transl Psychiatry*. 2014; **4**, e413.
29. Bruenig D, Mehta D, Morris CP et al. Genetic and serum biomarker evidence for a relationship between TNF± and PTSD in Vietnam war combat veterans. *Compr Psychiatry*. 2017; **74**, 125-133.
30. O'Donovan A, Ahmadian AJ, Neylan TC, Pacult MA, Edmondson D, Cohen BE. Current posttraumatic stress disorder and exaggerated threat sensitivity associated with elevated inflammation in the Mind Your Heart Study. *Brain Behav Immun.* 2017; **60**, 198-205.
31. Miller MW, Maniates H, Wolf EJ et al. CRP polymorphisms and DNA methylation of the

AIM2 gene influence associations between trauma exposure, PTSD, and C-reactive protein. *Brain Behav Immun.* 2018; **67**, 194-202.

32. McCanlies EC, Araia SK, Joseph PN et al. C-reactive protein, interleukin-6, and posttraumatic stress disorder symptomology in urban police officers. *Cytokine*. 2011; **55**, 74-78.
33. Plantinga L, Bremner JD, Miller AH et al. Association between posttraumatic stress disorder and inflammation: a twin study. *Brain Behav Immun.* 2013; **30**, 125-132.
34. Sondergaard HP, Hansson LO, Theorell T. The inflammatory markers C-reactive protein and serum amyloid A in refugees with and without posttraumatic stress disorder. *Clin Chim Acta.* 2004; **342**, 93-98.
35. Baker DG, Ekhator NN, Kasckow JW et al. Plasma and cerebrospinal fluid interleukin-6 concentrations in posttraumatic stress disorder. *Neuroimmunomodulation.* 2001; **9**, 209-217.
36. Bonne O, Gill JM, Luckenbaugh DA et al. Corticotropin-releasing factor, interleukin-6, brain-derived neurotrophic factor, insulin-like growth factor-1, and substance P in the cerebrospinal fluid of civilians with posttraumatic stress disorder before and after treatment with paroxetine. *J Clin Psychiatry*. 2011; **72**, 1124-1128.
37. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry.* 1995; **52**, 1048-1060.
38. Perkonigg A, Kessler RC, Storz S, Wittchen HU. Traumatic events and post-traumatic stress disorder in the community: prevalence, risk factors and comorbidity. *Acta Psychiatr Scand*. 2000; **101**, 46-59.
39. McLaughlin KA, Koenen KC, Bromet EJ et al. Childhood adversities and post-traumatic stress disorder: evidence for stress sensitisation in the World Mental Health Surveys. *Br J Psychiatry* 2017; **211**, 280-288.
40. Scott KM, Smith DR, Ellis PM. Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults. *Arch Gen Psychiatry*. 2010; **67**, 712-719.
41. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016; **16**, 22-34.
42. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. *Mol Psychiatry*. 2016; **21**, 642-649.
43. Coelho R, Viola TW, Walss-Bass C, Brietzke E, Grassi-Oliveira R. Childhood maltreatment and inflammatory markers: a systematic review. *Acta Psychiatr Scand*. 2014; **129**, 180-192.
44. von Känel R, Hepp U, Kraemer B et al. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. *J Psychiatr Res.* 2007; **41**: 744-752.

45. Hoge EA, Brandstetter K, Moshier S, Pollack MH, Wong KK, Simon NM. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depress Anxiety*. 2009; **26**: 447-455.
46. Smith AK, Conneely KN, Kilaru V et al. Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2011; **156B**, 700-708.
47. Guo M, Liu T, Guo JC, Jiang XL, Chen F, Gao YS. Study on serum cytokine levels in posttraumatic stress disorder patients. *Asian Pac J Trop Med*. 2012; **5**, 323-325.
48. Teche SP, Rovaris DL, Aguiar BW et al. Resilience to traumatic events related to urban violence and increased IL10 serum levels. *Psychiatry Res*. 2017; **250**, 136-140.
49. Eraly SA, Nievergelt CM, Maihofer AX et al. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. *JAMA Psychiatry*. 2014; **71**, 423-431.
50. Breen MS, Maihofer AX, Glatt SJ et al. Gene networks specific for innate immunity define post-traumatic stress disorder. *Mol Psychiatry*. 2015; **20**, 1538-1545.
51. Michopoulos V, Rothbaum AO, Jovanovic T et al. Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. *Am J Psychiatry.* 2015; **172**, 353-362.
52. Nusslock R, Miller GE. Early-Life Adversity and Physical and Emotional Health Across the Lifespan: A Neuroimmune Network Hypothesis. *Biol Psychiatry*. 2016; **80**, 23-32.
53. Sumner JA, Chen Q, Roberts AL et al. Posttraumatic stress disorder onset and inflammatory and endothelial function biomarkers in women. *Brain Behav Immun*. 2018; **69**, 203-209.
54. Kawamura N, Kim Y, Asukai N. Suppression of cellular immunity in men with a past history of posttraumatic stress disorder. *Am J Psychiatry*. 2001; **158**, 484-486.
55. Gill JM, Saligan L, Lee H, Rotolo S, Szanton S. Women in recovery from PTSD have similar inflammation and quality of life as non-traumatized controls. *J Psychosom Res*. 2013; **74**, 301-306.
56. Gola H, Engler H, Sommershof A et al. Posttraumatic stress disorder is associated with an enhanced spontaneous production of pro-inflammatory cytokines by peripheral blood mononuclear cells. *BMC Psychiatry*. 2013; **13**, 40.
57. Fleshner M, Frank M, Maier SF. Danger Signals and Inflammasomes: Stress-Evoked Sterile Inflammation in Mood Disorders. *Neuropsychopharmacology*. 2017; **42**, 36-45.
58. Franklin TC, Xu C, Duman RS. Depression and sterile inflammation: Essential role of danger associated molecular patterns. *Brain Behav Immun.* 2018; **72**: 2-13.
59. Powell ND, Bailey MT, Mays JW et al. Repeated social defeat activates dendritic cells and enhances Toll-like receptor dependent cytokine secretion. *Brain Behav Immun*. 2009; **23**, 225-231.

60. Wei L, Simen A, Mane S, Kaffman A. Early life stress inhibits expression of a novel innate immune pathway in the developing hippocampus. *Neuropsychopharmacology* 2012; **37**, 567-580.
61. Daskalakis NP, Cohen H, Nievergelt CM et al. New translational perspectives for blood-based biomarkers of PTSD: From glucocorticoid to immune mediators of stress susceptibility. *Exp Neurol*. 2016; **284**, 133-140.
62. Hendrickson RC, Raskind MA. Noradrenergic dysregulation in the pathophysiology of PTSD. *Exp Neurol.* 2016; **284**, 181-195.
63. ter Heegde F, De Rijk RH, Vinkers CH. The brain mineralocorticoid receptor and stress resilience. *Psychoneuroendocrinology.* 2015; **52**, 92-110.
64. Galic MA, Riazi K, Pittman QJ. Cytokines and brain excitability. *Front Neuroendocrinol.* 2012; **33**, 116-125.
65. Bierhaus A, Wolf J, Andrassy M et al. A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci U S A*. 2003; **100**, 1920-1925.
66. Tan KS, Nackley AG, Satterfield K, Maixner W, Diatchenko L, Flood PM. Beta2 adrenergic receptor activation stimulates pro-inflammatory cytokine production in macrophages via PKA- and NF-kappaB-independent mechanisms. *Cell Signal*. 2007; **19**, 251-260.
67. Morris MC, Compas BE, Garber J. Relations among posttraumatic stress disorder, comorbid major depression, and HPA function: a systematic review and meta-analysis. *Clin Psychol Rev*. 2012; **32**, 301-315.
68. Bremner JD, Licinio J, Darnell A et al. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry*. 1997; **154**, 624-629.
69. Baker DG, West SA, Nicholson WE et al. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *Am J Psychiatry.* 1999; **156**, 585-588.
70. De Bosscher K, Vanden Berghe W, Haegeman G. The interplay between the glucocorticoid receptor and nuclear factor-kappaB or activator protein-1: molecular mechanisms for gene repression. *Endocr Rev.* 2003; **24**, 488-522.
71. Amsterdam A, Sasson R. The anti-inflammatory action of glucocorticoids is mediated by cell type specific regulation of apoptosis. *Mol Cell Endocrinol*. 2002; **189**, 1-9.
72. Gustavson SM, Sandoval DA, Ertl AC, Bao S, Raj SR, Davis SN. Stimulation of both type I and type II corticosteroid receptors blunts counterregulatory responses to subsequent hypoglycemia in healthy man. *Am J Physiol Endocrinol Metab.* 2008; **294**, E506-512.
73. Joëls M, Fernandez G, Roozendaal B. Stress and emotional memory: a matter of timing. *Trends Cogn Sci*. 2011; **15**, 280-288.
74. Holsboer F. The corticosteroid receptor hypothesis of depression.

Neuropsychopharmacology. 2000; **23**, 477-501.

75. Yehuda R, McFarlane AC, Shalev AY. Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. *Biol Psychiatry.* 1998; **44**, 1305-1313.
76. Yehuda R, Bierer LM, Schmeidler J, Aferiat DH, Breslau I, Dolan S. Low cortisol and risk for PTSD in adult offspring of holocaust survivors. *Am J Psychiatry.* 2000; **157**, 1252-1259.
77. Binder EB, Bradley RG, Liu W et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA.* 2008; **299**, 1291-1305.
78. Mehta D, Gonik M, Klengel T et al. Using polymorphisms in FKBP5 to define biologically distinct subtypes of posttraumatic stress disorder: evidence from endocrine and gene expression studies. *Arch Gen Psychiatry*. 2011; **68**, 901-910.
79. Lee YS, Wollam J, Olefsky JM. An Integrated View of Immunometabolism. *Cell*. 2018; **172**, 22-40.
80. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. *Nature*. 2017; **542**, 177-185.
81. van den Berk-Clark C, Secrest S, Walls J et al. Association between posttraumatic stress disorder and lack of exercise, poor diet, obesity, and co-occuring smoking: A systematic review and meta-analysis. *Health Psychol.* 2018; **37**, 407-416.
82. Hall KS, Hoerster KD, Yancy WS Jr. Post-traumatic stress disorder, physical activity, and eating behaviors. *Epidemiol Rev*. 2015; **37**, 103-115.
83. Hirth JM, Rahman M, Berenson AB. The association of posttraumatic stress disorder with fast food and soda consumption and unhealthy weight loss behaviors among young women. *J Womens Health (Larchmt).* 2011; **20**, 1141-1149.
84. O'Connor MF, Bower JE, Cho HJ et al. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. *Brain Behav Immun*. 2009; **23**, 887-897.
85. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008; **9**, 46-56.
86. Levin SG, Godukhin OV. Modulating Effect of Cytokines on Mechanisms of Synaptic Plasticity in the Brain. *Biochemistry*. 2017; **82**, 264-274.
87. Butovsky O, Weiner HL. Microglial signatures and their role in health and disease. *Nat Rev Neurosci.* 2018; **19**, 622-635.
88. Réus GZ, Fries GR, Stertz L et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience.* 2015; **300**, 141-154.
89. Takaki J, Fujimori K, Miura M, Suzuki T, Sekino Y, Sato K. L-glutamate released from

activated microglia downregulates astrocytic L-glutamate transporter expression in neuroinflammation: the 'collusion' hypothesis for increased extracellular L-glutamate concentration in neuroinflammation. *J Neuroinflammation*. 2012; **9**, 275.

90. Saijo K, Glass CK. Microglial cell origin and phenotypes in health and disease. *Nat Rev Immunol.* 2011; **11**, 775-787.
91. Myint AM, Schwarz MJ, Müller N. The role of the kynurenine metabolism in major depression. *J Neural Transm*. 2012; **119**, 245-251.
92. Dostal CR, Gamsby NS, Lawson MA, McCusker RH. Glia- and tissue-specific changes in the Kynurenine Pathway after treatment of mice with lipopolysaccharide and dexamethasone. *Brain Behav Immun.* 2018; **69**, 321-335.
93. Liberzon I, Taylor SF, Amdur R et al. Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry*. 1999; **45**, 817-826.
94. Fonzo GA, Simmons AN, Thorp SR, Norman SB, Paulus MP, Stein MB. Exaggerated and disconnected insular-amygdalar blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. *Biol Psychiatry*. 2010; **68**, 433-441.
95. Quiñones MM, Maldonado L, Velazquez B, Porter JT. Candesartan ameliorates impaired fear extinction induced by innate immune activation. *Brain Behav Immun.* 2016; **52**, 169-177.
96. Yu Z, Fukushima H, Ono C et al. Microglial production of TNF-alpha is a key element of sustained fear memory. *Brain Behav Immun.* 2017; **59**, 313-321.
97. Young MB, Howell LL, Hopkins L et al. A peripheral immune response to remembering trauma contributes to the maintenance of fear memory in mice. *Psychoneuroendocrinology*. 2018; **94**, 143-151.
98. Inagaki TK, Muscatell KA, Irwin MR, Cole SW, Eisenberger NI. Inflammation selectively enhances amygdala activity to socially threatening images. *Neuroimage.* 2012; **59**, 3222-3226.
99. Swartz JR, Prather AA, Hariri AR. Threat-related amygdala activity is associated with peripheral CRP concentrations in men but not women. *Psychoneuroendocrinology.* 2017; **78**, 93-96.
100. de Quervain D, Schwabe L, Roozendaal B. Stress, glucocorticoids and memory: implications for treating fear-related disorders. *Nat Rev Neurosci.* 2017; **18**, 7-19.
101. Henckens MJ, van Wingen GA, Joëls M, Fernández G. Time-dependent effects of corticosteroids on human amygdala processing. *J Neurosci*. 2010; **30**, 12725-12732.
102. Narita-Ohtaki R, Hori H, Itoh M et al. Cognitive function in Japanese women with posttraumatic stress disorder: Association with exercise habits. *J Affect Disord.* 2018; **236**,

306-312.

103. Scott JC, Matt GE, Wrocklage KM et al. 2015. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol Bull*. **141**, 105-140.
104. Flatt JD, Gilsanz P, Quesenberry CP Jr, Albers KB, Whitmer RA. Post-traumatic stress disorder and risk of dementia among members of a health care delivery system. *Alzheimers Dement.* 2017; **14**, 28-34.
105. Yaffe K, Vittinghoff E, Lindquist K et al. Posttraumatic stress disorder and risk of dementia among US veterans. *Arch Gen Psychiatry*. 2010; **67**, 608-613.
106. Aupperle RL, Allard CB, Grimes EM et al. Dorsolateral prefrontal cortex activation during emotional anticipation and neuropsychological performance in posttraumatic stress disorder. *Arch Gen Psychiatry* 2012; **69**, 360-371.
107. Bremner JD, Elzinga B, Schmahl C, Vermetten E. Structural and functional plasticity of the human brain in posttraumatic stress disorder. *Prog Brain Res*. 2008; **167**, 171-186.
108. Kuhn S, Gallinat J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. *Biol Psychiatry*. 2013; **73**, 70-74.
109. Li L, Wu M, Liao Y et al. Grey matter reduction associated with posttraumatic stress disorder and traumatic stress. *Neurosci Biobehav Rev*. 2014; **43**, 163-172.
110. Gruol DL. IL-6 regulation of synaptic function in the CNS. *Neuropharmacology* 2015; **96**, 42-54.
111. Spooren A, Kolmus K, Laureys G et al. Interleukin-6, a mental cytokine. *Brain Res Rev*. 2011; **67**, 157-183.
112. Trapero I, Cauli O. Interleukin 6 and cognitive dysfunction. *Metab Brain Dis*. 2014; **29**, 593-608.
113. Grassi-Oliveira R, Bauer ME, Pezzi JC, Teixeira AL, Brietzke E. Interleukin-6 and verbal memory in recurrent major depressive disorder. *Neuro Endocrinol Lett*. 2011; **32**, 540-544.
114. Misiak B, Stanczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: A systematic review. *Schizophr Res*. 2018; **192**, 16-29.
115. Levandowski ML, Hess AR, Grassi-Oliveira R, de Almeida RM. Plasma interleukin-6 and executive function in crack cocaine-dependent women. *Neurosci Lett*. 2016; **628**, 85-90.
116. Wada-Isoe K, Wakutani Y, Urakami K, Nakashima K. Elevated interleukin-6 levels in cerebrospinal fluid of vascular dementia patients. *Acta Neurol Scand*. 2004; **110**, 124-127.
117. Yang J, Fan C, Pan L et al. C-reactive protein plays a marginal role in cognitive decline: a systematic review and meta-analysis. *Int J Geriatr Psychiatry.* 2015; **30**, 156-165.
118. Hoskins M, Pearce J, Bethell A et al. Pharmacotherapy for post-traumatic stress disorder: systematic review and meta-analysis. *Br J Psychiatry.* 2015; **206**, 93-100.

119. Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. *Depress Anxiety*. 2016; **33**, 792-806.
120. Köhler O, Benros ME, Nordentoft M et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*. 2014; **71**, 1381-1391.
121. Lee B, Sur B, Yeom M, Shim I, Lee H, Hahm DH. Effects of systemic administration of ibuprofen on stress response in a rat model of post-traumatic stress disorder. *Korean J Physiol Pharmacol*. 2016; **20**, 357-366.
122. Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol Psychiatry*. 2018; **23**, 335-343.
123. Aerni A, Traber R, Hock C et al. Low-dose cortisol for symptoms of posttraumatic stress disorder. *Am J Psychiatry*. 2004; **161**, 1488-1490.
124. Surís A, North C, Adinoff B, Powell CM, Greene R. Effects of exogenous glucocorticoid on combat-related PTSD symptoms. *Ann Clin Psychiatry*. 2010; **22**, 274-279.
125. Yehuda R, Bierer LM, Pratchett LC et al. Cortisol augmentation of a psychological treatment for warfighters with posttraumatic stress disorder: Randomized trial showing improved treatment retention and outcome. *Psychoneuroendocrinology.* 2015; **51**, 589-597.
126. Schelling G, Roozendaal B, Krauseneck T, Schmoelz M, DE Quervain D, Briegel J. Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. *Ann N Y Acad Sci*. 2006; **1071**, 46-53.
127. Zohar J, Yahalom H, Kozlovsky N et al. High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: interplay between clinical and animal studies. *Eur Neuropsychopharmacol*. 2011; **21**, 796-809.
128. Kortekaas KE, Meijer CA, Hinnen JW et al. ACE inhibitors potently reduce vascular inflammation, results of an open proof-of-concept study in the abdominal aortic aneurysm. *PLoS One.* 2014; **9**, e111952.
129. Clancy P, Koblar SA, Golledge J. Angiotensin receptor 1 blockade reduces secretion of inflammation associated cytokines from cultured human carotid atheroma and vascular cells in association with reduced extracellular signal regulated kinase expression and activation. *Atherosclerosis*. 2014; **236**, 108-115.
130. Khoury NM, Marvar PJ, Gillespie CF et al. The renin-angiotensin pathway in posttraumatic stress disorder: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are associated with fewer traumatic stress symptoms. *J Clin Psychiatry*. 2012; **73**, 849-855.
131. Hill MN, Campolongo P, Yehuda R, Patel S. Integrating Endocannabinoid Signaling and

Cannabinoids into the Biology and Treatment of Posttraumatic Stress Disorder. *Neuropsychopharmacology.* 2018; **43**, 80-102.
132. Steenkamp MM, Blessing EM, Galatzer-Levy IR, Hollahan LC, Anderson WT. Marijuana and other cannabinoids as a treatment for posttraumatic stress disorder: A literature review. *Depress Anxiety*. 2017; **34**, 207-216.
133. Feldman R. Oxytocin and social affiliation in humans. *Horm Behav*. 2012; **61**, 380-391.
134. Cochran DM, Fallon D, Hill M, Frazier JA. The role of oxytocin in psychiatric disorders: a review of biological and therapeutic research findings. *Harv Rev Psychiatry*. 2013; **21**, 219-247.
135. Donadon MF, Martin-Santos R, Osório FL. The Associations Between Oxytocin and Trauma in Humans: A Systematic Review. *Front Pharmacol*. 2018; **9**, 154.
136. Garrido-Urbani S, Deblon N, Poher AL et al. Inhibitory role of oxytocin on TNF± expression assessed in vitro and in vivo. *Diabetes Metab*. 2018; **44**, 292-295.
137. Clodi M, Vila G, Geyeregger R et al. Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men. *Am J Physiol Endocrinol Metab*. 2008; **295**, E686-691.
138. Walker FR. A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? *Neuropharmacology*. 2013; **67**, 304-317.
139. Gałecki P, Mossakowska-Wójcik J, Talarowska M. The anti-inflammatory mechanism of antidepressants - SSRIs, SNRIs. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018; **80**, 291-294.
140. Tucker P, Ruwe WD, Masters B et al. Neuroimmune and cortisol changes in selective serotonin reuptake inhibitor and placebo treatment of chronic posttraumatic stress disorder. *Biol Psychiatry.* 2004; **56**, 121-128.
141. Nishi D, Koido Y, Nakaya N et al. Fish oil for attenuating posttraumatic stress symptoms among rescue workers after the great east Japan earthquake: a randomized controlled trial. *Psychother Psychosom.* 2012; **81**, 315-317.
142. Rosenbaum S, Vancampfort D, Steel Z, Newby J, Ward PB, Stubbs B. Physical activity in the treatment of post-traumatic stress disorder: a systematic review and meta-analysis. *Psychiatry Res.* 2015; **230**, 130-136.
143. Uemura M, Ohira T, Yasumura S et al. Association between psychological distress and dietary intake among evacuees after the Great East Japan Earthquake in a cross-sectional study: the Fukushima Health Management Survey. *BMJ Open*. 2016; **6**, e011534.
144. Nicklas BJ, Brinkley TE. Exercise training as a treatment for chronic inflammation in the elderly. *Exerc Sport Sci Rev.* 2009; **37**, 165-170.

145. Bower JE, Irwin MR. Mind-body therapies and control of inflammatory biology: A descriptive review. *Brain Behav Immun.* 2016; **51**, 1-11.
146. Calder PC, Ahluwalia N, Brouns F et al. Dietary factors and low-grade inflammation in relation to overweight and obesity. *Br J Nutr.* 2011; **106 Suppl 3**, S5-78.
147. Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. *Nat Neurosci.* 2017; **20**, 145-155.
148. Erny D, Hrab de Angelis AL, Jaitin D et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci.* 2015; **18**, 965-977.
149. Hemmings SMJ, Malan-Müller S, van den Heuvel LL et al. The Microbiome in Posttraumatic Stress Disorder and Trauma-Exposed Controls: An Exploratory Study. *Psychosom Med.* 2017; **79**, 936-946.
150. Holmes SE, Hinz R, Conen S et al. Elevated Translocator Protein in Anterior Cingulate in Major Depression and a Role for Inflammation in Suicidal Thinking: A Positron Emission Tomography Study. *Biol Psychiatry*. 2018; **83**, 61-69.
151. Kilpatrick DG, Resnick HS, Milanak ME, Miller MW, Keyes KM, Friedman MJ. National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria. *J Trauma Stress.* 2013; **26**, 537-547.
152. Blanco C, Hoertel N, Wall MM et al. Toward Understanding Sex Differences in the Prevalence of Posttraumatic Stress Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry.* 2018; **79**, 16m11364.
153. Stein MB, Jang KL, Taylor S, Vernon PA, Livesley WJ. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. *Am J Psychiatry.* 2002; **159**, 1675-1681.
154. Sartor CE, McCutcheon VV, Pommer NE et al. Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. *Psychol Med.* 2011; **41**, 1497-1505.
155. Ferree NK, Kamat R, Cahill L. Influences of menstrual cycle position and sex hormone levels on spontaneous intrusive recollections following emotional stimuli. *Conscious Cogn.* 2011; **20**, 1154-1162.
156. Wegerer M, Kerschbaum H, Blechert J, Wilhelm FH. Low levels of estradiol are associated with elevated conditioned responding during fear extinction and with intrusive memories in daily life. *Neurobiol Learn Mem.* 2014; **116**, 145-154.
157. Olff M, Langeland W, Draijer N, Gersons BP. Gender differences in posttraumatic stress disorder. *Psychol Bull.* 2007; **133**, 183-204.
158. Insel T, Cuthbert B, Garvey M et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010; **167**,

748-751.

Figure legends

Fig. 1. Serum interleukin (IL)-6 levels in patients with PTSD compared to healthy controls.

Combined dot- and box-plot showing IL-6 concentrations (pg/ml) of patients with PTSD (n = 40) and healthy controls (n = 65). There was a significant difference between groups (by Mann-Whitney *U* test). Adapted from Imai et al. (2018).

Fig. 2. Mechanisms of increased inflammation in PTSD.

Stress-induced interaction between the immune system, hypothalamic-pituitary-adrenal axis, and sympathetic nervous system is illustrated. *Abbreviations:* CRH, corticotropin-releasing hormone; AVP, arginine vasopressin; ACTH, adrenocorticotropin; GR, glucocorticoid receptor; NE, norepinephrine; NF-º B, nuclear factor-º B; IL-1, interleukin-1; IL-6, interleukin-6; TNF±, tumor necrosis factor ±.

Fig. 3. Proinflammatory cytokine-induced activation of the Kynurenine Pathway.

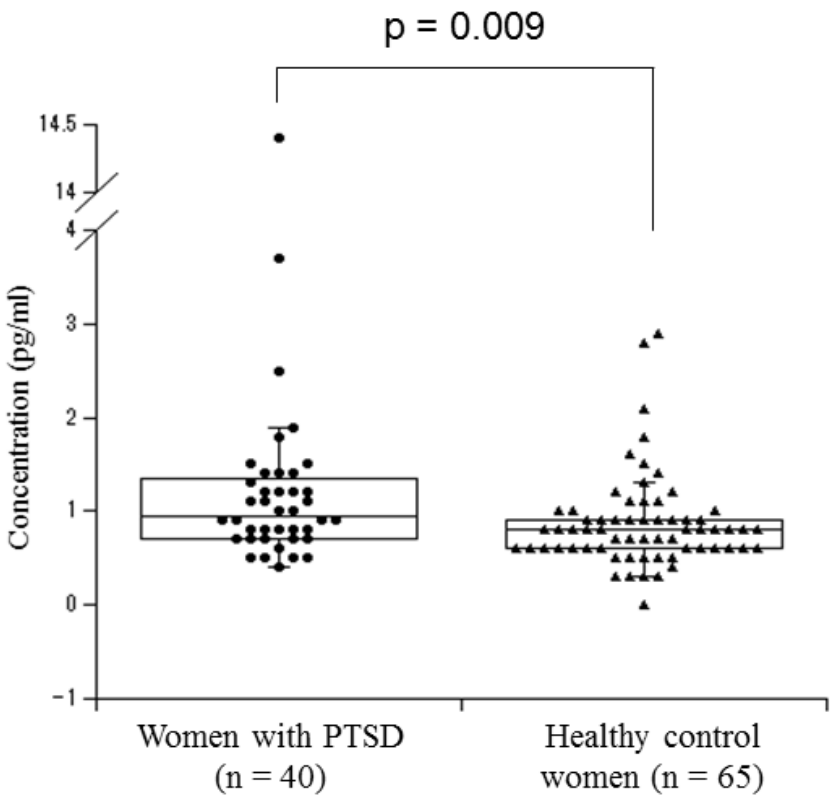
Only main branches of the Kynurenine Pathway are shown. *Abbreviations:* IDO, indoleamine-2,3-Dioxygenase; NMDA, N-methyl-D-aspartate.

Fig. 4. Association of serum interleukin (IL)-6 levels with cognitive function in patients with PTSD.

Neuropsychological functions are contrasted between PTSD patients with normal IL-6 levels (n = 22) and those with high IL-6 levels (n = 18). Patients were split into the normal and high IL-6 groups by the IL-6 level of 1.0 pg/ml (i.e., normal IL-6 group:

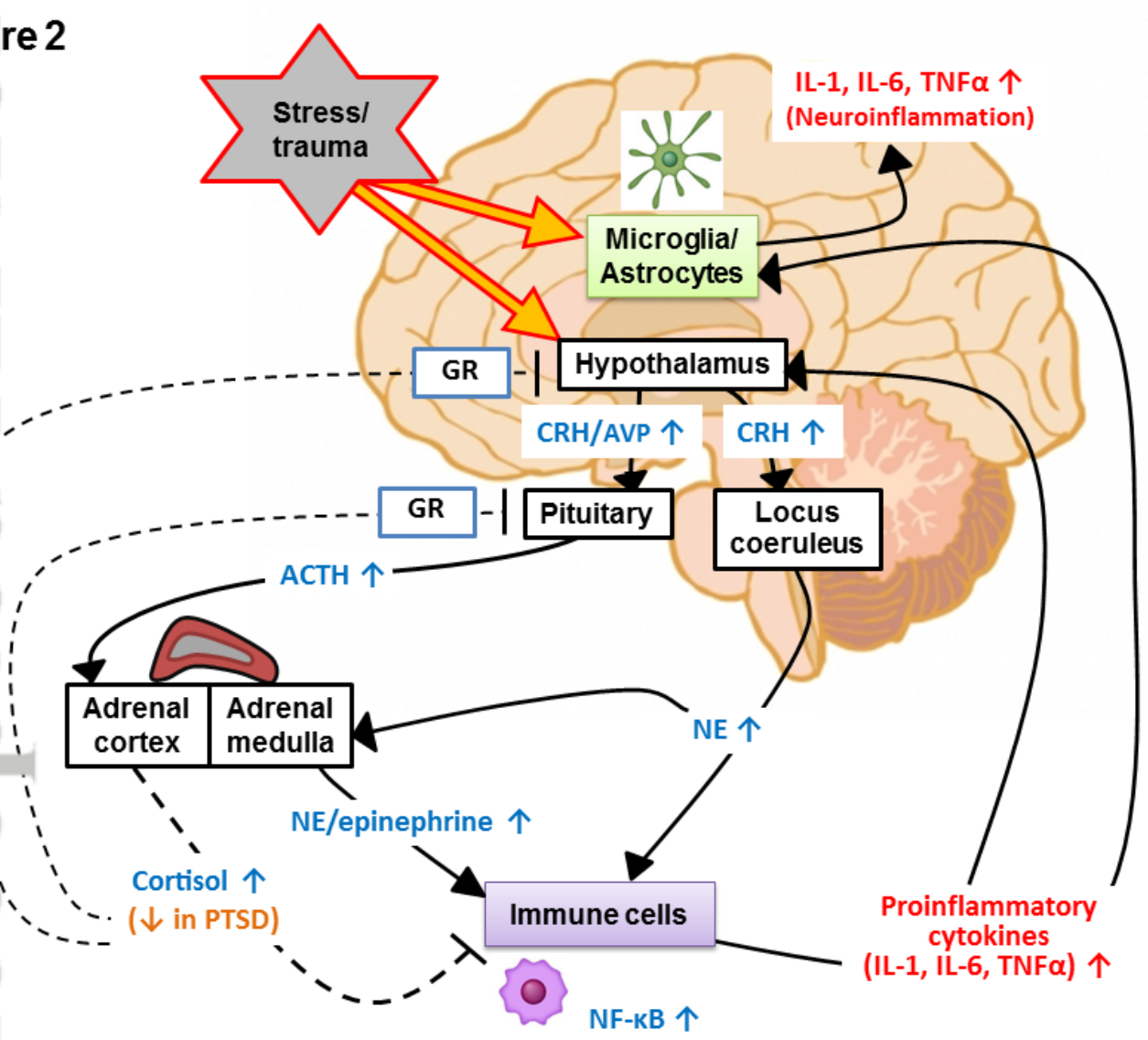
equal to or lower than 1.0 pg/ml; high IL-6 group: higher than 1.0 pg/ml). Error bars indicate SEM. *: $p < 0.05$; **: $p < 0.01$ (by t-test). *Abbreviation*: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status. Adapted from Imai et al. (2018).

Figure 1



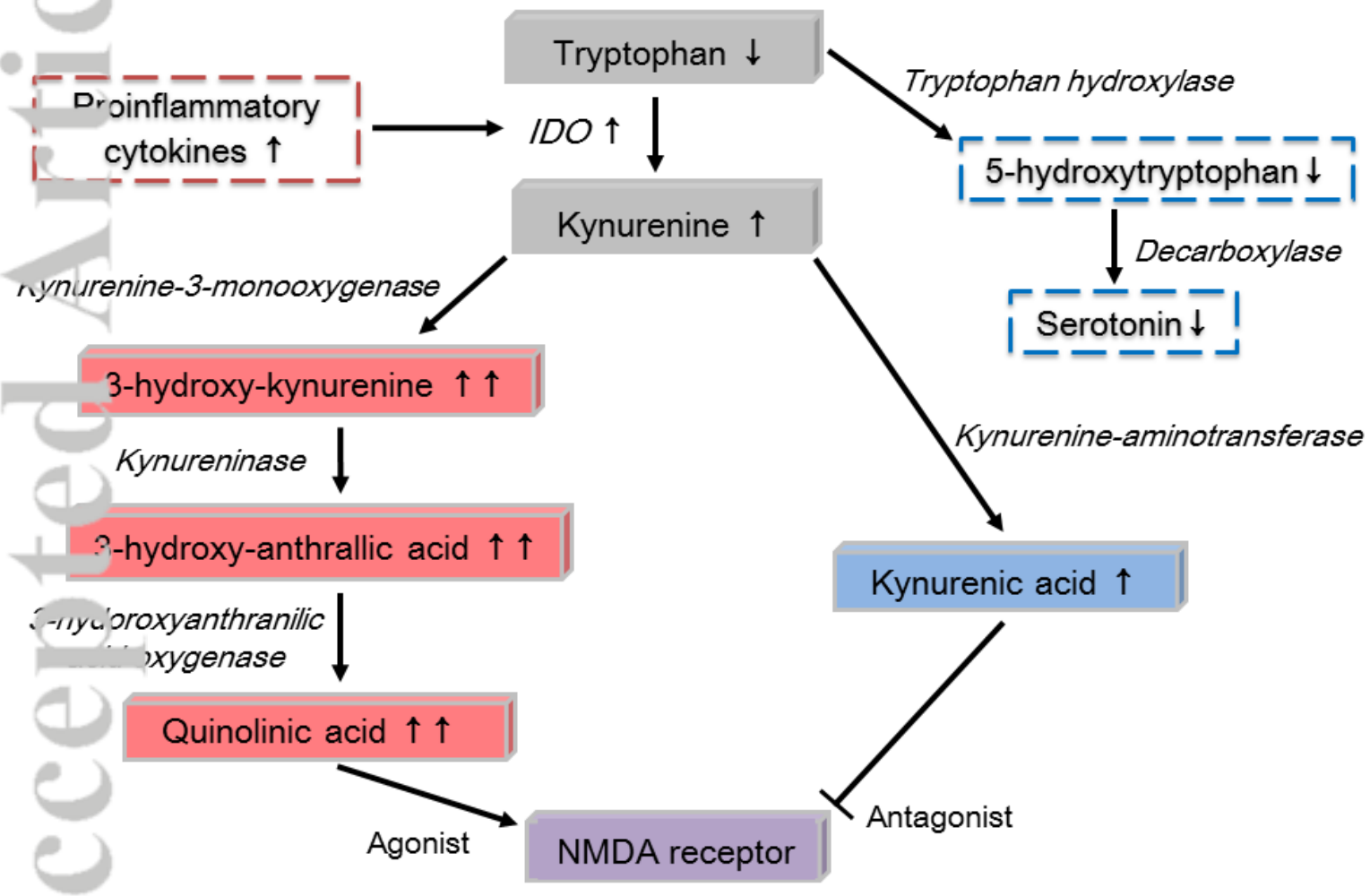
PCN_12820_Figure 1.TIF

Figure 2



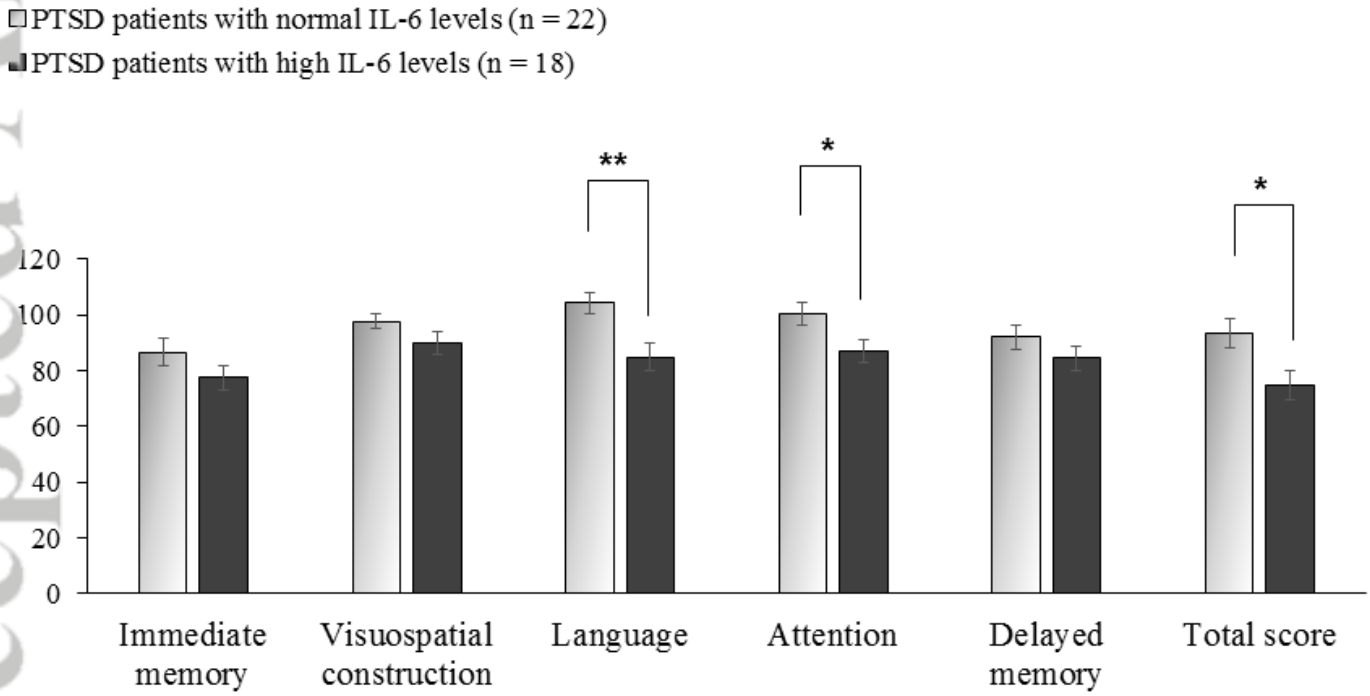
PCN_12820_Figure 2.TIF

Figure 3



PCN_12820_Figure 3.TIF

Figure 4



PCN_12820_Figure 4.TIF

Table 1. Pro- and anti-inflammatory markers associated with PTSD

	Increased in PTSD	No significant difference	Decreased in PTSD
Proinflammatory marker			
IL-1²	**Passos et al. (2015)**	Imai et al. (2018)[b]	(none)
IL-6	**Passos et al. (2015)** Lindqvist et al. (2017) de Oliveira et al. (2018) Imai et al. (2018)	Teche et al. (2017)	(none)
TNF±	Bruenig et al. (2017)	**Passos et al. (2015)**[c] Lindqvist et al. (2017)[d] Imai et al. (2018)[d]	(none)
CRP	O'Donovan et al. (2017) Miller et al. (2017) Lindqvist et al. (2017) Miller et al. (2018)	**Passos et al. (2015)** Imai et al. (2018)	(none)[e]
Anti-inflammatory marker			
IL-4	(none)[a]	**Passos et al. (2015)**	(none)[f]
IL-10	de Oliveira et al. (2018)	**Passos et al. (2015)** Lindqvist et al. (2017)	Teche et al. (2017)

Abbreviations : PTSD, posttraumatic stress disorder; IL-6, interleukin-6; IL-1² , interleukin-1² ; TNF±, tumor necrosis factor ±; CRP, C-reactive protein; IL-4, interleukin-4; IL-10, interleukin-10.

Notes : Only blood-based, baseline (without stimulation), case-control studies are listed. Included here are the meta-analysis of 20 studies (Passos et al., 2015; shown in bold) and studies published afterwards. Individual studies included in the meta-analysis of Passos et al. (2015) are not listed here.

[a] : Hoge et al. (2009) and Guo et al. (2012), which were included in the meta-analysis of Passos et al. (2015), reported significantly IL-4 levels in PTSD patients compared to controls.

[b] Levels of this cytokine fell below the detection limit in approximately half of the subjects.

[c] Significantly higher TNF± levels were seen in a subgroup of medication-free PTSD patients compared to controls.

[d] Trend toward higher levels in PTSD patients compared to controls.

[e] Sondergaard et al. (2004), which was not included in the meta-analysis of Passos et al. (2015) due to nonfulfillment of the inclusion criteria, reported significantly decreased CRP levels in PTSD patients compared to controls.

[f] Smith et al. (2011), which was included in the meta-analysis of Passos et al. (2015), reported significantly decreased IL-4 levels in PTSD patients compared to controls.

Table 2. Potential anti-inflammatory treatment for PTSD

	Typical drugs	Anti-inflammatory mechanism	Evidence of efficacy in PTSD
NSAIDs	Celecoxib Ibuprofen Naproxen	Reduce proinflammatory cytokine production by inhibiting COX-2	(none)
Monoclonal antibodies against cytokines	Infliximab (anti-TNF± antibody) Adalimumab (anti-TNF± antibody) Tocilizumab (anti-IL-6 receptor antibody)	Prevent cytokine from binding its receptor	(none)
Glucocorticoids (steroids)	Hydrocortisone Prednisolone Dexamethasone	Inhibit the expression of cytokines by a combination of genomic mechanisms	Aerni et al. (2004) Suris et al. (2010) Yehuda et al. (2015)
ACE inhibitors & ARBs	Captopril (ACE inhibitors) Candesartan (ARBs) Telmisartan (ARBs)	Prevent the synthesis of (ACE inhibitors), or block receptors of (ARBs), angiotensin II that increases inflammation	Khoury et al. (2012)
Cannabis	Nabilone (a synthetic analog of ” ^{9}-tetrahydrocannabinol)	Elevate endocannabinoid signaling that has anti-inflammatory effects	Fraser et al. (2009) Cameron et al. (2014) Jetly et al. (2015)

Abbreviations : PTSD, posttraumatic stress disorder; NSAIDs, nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; SSRIs, selective serotonin reuptake inhibitors; TNF±, tumor necrosis factor ±; IL-6, interleukin-6; COX-2, cyclooxygenase 2.