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Oxidative Stress, Inflammation, and Neuroprogression in Chronic PTSD

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Abstract

Posttraumatic stress disorder is a serious and often disabling syndrome that develops in response to a traumatic event. Many individuals who initially develop the disorder go on to experience a chronic form of the condition that in some cases can last for many years. Among these patients, psychiatric and medical comorbidities are common including early onset of age-related conditions such as chronic pain, cardiometabolic disease, neurocognitive disorders, and dementia. The hallmark symptoms of posttraumatic stress—recurrent sensory-memory reexperiencing of the trauma(s)—are associated with concomitant activations of threat- and stress-related neurobiological pathways that occur against a tonic backdrop of sleep disturbance and heightened physiological arousal. Emerging evidence suggests that the molecular consequences of this stress-perpetuating syndrome include elevated systemic levels of oxidative stress and inflammation. In this paper, we review evidence for the involvement of oxidative stress and inflammation in chronic PTSD and the neurobiological consequences of these processes including accelerated cellular aging and neuroprogression. Our aim was to update and expand upon previous reviews of this rapidly-developing literature and discuss magnetic resonance spectroscopy as an imaging technology uniquely-suited to measuring oxidative stress and inflammatory markers *in vivo*. Finally, we highlight future directions for research and avenues for the development of novel therapeutics targeting OXS and inflammation in patients with PTSD.

Introduction

Posttraumatic stress disorder is a serious and often disabling condition that affects approximately 8 percent of individuals in the general population at some point during their lifetime.[1] Estimates suggest that as many as one-third of those who develop PTSD go on to experience a chronic form of the disorder that, in many cases, lasts for years.[2,3] Among these patients, psychiatric and medical comorbidities are common with many presenting with early onset of age-related conditions such as cardiometabolic disease,[4] neurocognitive disorders,[5] and dementia.[6] The hallmark features of PTSD are recurrent sensory-memory episodes of reexperiencing the trauma(s) which can be spontaneous or cued by exposure to

stimuli reminiscent of the trauma, anniversaries of the event, or other adverse life events. These episodes are accompanied by phasic activations of stress-related neurobiology that occur in the context of tonic symptoms of hypervigilance, heightened negative affect, and arousal. Together, these symptoms constitute a stress-perpetuating syndrome that maintains the individual in a chronic state of sustained stress.[7,8] Emerging evidence suggests that the biological consequences this include elevated systemic levels of oxidative stress (OXS) and inflammation (INF), accelerated cellular aging and neuroprogression—the pathological remodeling of neural circuitry that occurs over the course of a chronic mental illness.

The purpose of this paper was to provide a qualitative review of the scientific literature on the relationship of PTSD to OXS and INF and to discuss magnetic resonance spectroscopy (MRS) as a neuroimaging approach that is uniquely suited to studying the processes *in vivo*. The studies we reviewed were identified through a search of the PUBMED database spanning the years 1980 (the date of the first appearance of PTSD in the DSM-III) through early 2017 using the search terms “PTSD and [oxidative stress]” (40 hits), “PTSD and inflammation” (163 hits) and “PTSD and [magnetic resonance spectroscopy]” (61 hits) and through examination of the citations contained in the papers identified through this search. The search did not access unpublished studies or include published abstracts. Our specific aims were to (1) update and expand upon our previous review of this rapidly-developing topic[7] with a new emphasis on the involvement of inflammatory processes, (2) provide a qualitative summary of studies that have examined associations between PTSD and biomarkers of OXS and INF, and (3) offer a review and summary of published MRS studies of PTSD. Finally, we highlight directions for future research and avenues for the development of novel therapeutics targeting OXS and INF in patients with PTSD.

Mechanisms and Impacts of OXS and INF

OXS is a cellular status that occurs when pro-oxidant molecules (e.g., reactive oxygen/nitrogen species; ROS/NOS) exceed the capacity of available antioxidants (e.g., glutathione [GSH], superoxide dismutase [SOD] and related enzymes) to counteract their effects. Under acute OXS, antioxidants increase in response to the presence of pro-oxidant molecules. When OXS is prolonged, antioxidants become depleted leading to cell degeneration and apoptosis.[9] OXS is a molecular mechanism fundamental to aging and widely implicated in many common diseases. The brain is particularly vulnerable to its deleterious effects due to its high metabolic demand and dense composition of oxidation-susceptible lipid cells. Studies have linked OXS to blood-brain barrier disruptions, altered patterns of neural growth, and changes in brain morphology.[10, 11]

INF is a similarly ubiquitous cellular reaction implicated in many common diseases and initiated by cell injury. Its primary function is to destroy injurious agents and/or protect injured tissue though the proliferation of inflammatory cells such as neutrophils, monocytes, and lymphocytes. At the site of INF, these cells trigger the release of various enzymes, including ROS/NOS, pro-inflammatory cytokines and other chemical mediators, and in doing so, induce OXS. Thus, OXS and INF tend to co-occur and are intertwined in such a way that one process can readily induce the other and vice versa.[12] Emerging evidence suggests that both conditions can be triggered by chronic psychological stress and/or stress-

related mental illnesses, including PTSD, and their separate and interactive effects, when chronic, may exert destructive effects on the brain and peripheral organ systems.

OXS and PTSD

Preliminary clinical evidence for the involvement of OXS in the pathophysiology of PTSD comes from cross-sectional studies that have found significant differences in blood antioxidant enzyme concentrations and OXS-related gene expression between PTSD patients and controls (see Table 1). For example, Atli et al.[13] reported elevated levels of serum lipid peroxidation (reflecting the breakdown and oxidation of polyunsaturated fatty acids) and depleted antioxidant enzymes in earthquake survivors with PTSD compared to earthquake-exposed controls. Similarly, Stefanovic et al.[14] measured blood levels of SOD and glutathione transferase in Croatian war veterans and found depleted levels of both antioxidants in veterans with PTSD compared to controls. Gene expression studies have found similar alterations in antioxidant gene RNA transcription in patients with PTSD. For example, Zieker et al.[15] observed down-regulated expression of the antioxidant genes SOD and thioredoxin reductase (which interacts with glutathione to detoxify ROS) in patients with PTSD who witnessed a catastrophic air show disaster. In conjunction with these effects, Zieker et al. reported that transcripts for the pro-inflammatory cytokines genes Interleukin (IL)-16 and -18 were downregulated as well suggesting that the patients were immunocompromised.

Several studies point to the presence of depleted levels of glutathione transferases (which interact with glutathione to detoxify pro-oxidant molecules) in the pathophysiology of PTSD. For example, in one of the few longitudinal studies that have been conducted on this topic, Glatt et al.[16] reported that levels of glutathione S-transferase mu 1(GSTM1) measured prior to deployment predicted the subsequent development of PTSD symptoms in U.S. Marines deployed to Iraq and/or Afghanistan. Subsequently, in a follow-up study based on the same cohort, Tylee et al.[17] showed that PTSD diagnostic status could be predicted with 80% accuracy using an algorithm based entirely on the expression of GSTM1 and its counterpart GSTM2.

Findings from studies of patients with depression and other anxiety disorders suggest a similar pattern. Specifically, studies have found depression to be associated with oxidative damage to DNA and suppressed antioxidant activity.[18,19] Similarly, studies of patients with anxiety disorders have shown elevated levels of lipid peroxidation in generalized anxiety disorder[20] and suppressed antioxidant activity in panic disorder.[21]

Indirect evidence also pointing to the possible involvement of OXS-related biology in PTSD came from the first genome-wide association study of PTSD.[22] In that study, Logue et al. found a genome-wide-significant association between a single nucleotide polymorphism (SNP) in the Retinoic Acid Orphan Receptor Alpha gene (*RORA*; rs8042149) and a diagnosis of PTSD among veterans. Though subsequent PTSD GWASs have not replicated this association at GWAS-significant levels, one independent research group published a replication of the rs8042149-PTSD association[23] and Miller et al.[24] found that another *RORA* SNP, rs17303244, was significantly associated with the severity of symptoms in the fear spectrum of psychopathology (i.e., defined by panic, agoraphobia, specific phobia, and

obsessive-compulsive disorder). Similarly, Lowe et al.[25] reported an association between *RORA* SNP rs893290 and PTSD symptom trajectories over time.

RORA is expressed in the prefrontal cortex, hippocampus, and hypothalamus. It is activated during OXS and serves to protect neurons by increasing the expression of other genes involved in the clearance of ROS (Gpx1 and Prx6). Based on this, Miller et al.24 hypothesized that individuals carrying *RORA* risk variant(s) may mount an inadequate response to OXS placing them at risk for neurodegeneration and functional abnormalities in regions of the brain involved in modulating fear and anxiety. Other evidence pointing to the role of OXS in the neurobiology of PTSD came from a recent study that examined the *ALOX12* and *ALOX15* genes in relationship to PTSD and measures of neural integrity.[8] The enzyme 12/15-lipoxygenase, transcribed by the genes *ALOX12* and *ALOX15*, is involved mechanisms of oxidative damage to the brain. Specifically, when levels of GSH become depleted during OXS, 12/15-LOX attacks mitochondria and produces pro-oxidant reactive oxygen species. Given this characteristic, this enzyme as has been referred to as “the central executioner in an OXS-related neuronal death program” (Pallast et al., 2009 p882).[26] Based on this reasoning, Miller et al. tested the hypothesis that genetic variants within *ALOX12* and/or *ALOX15* would moderate the association between PTSD and cortical thickness. Analyses identified a novel *ALOX12* locus (rs1042357/rs10852889) that interacted with maximum lifetime PTSD severity to predict reduced thickness of the right prefrontal cortex with this effect explaining seven percent of the variance of cortical thickness in that region. Collectively, these findings point to the involvement of OXS in the pathophysiology of PTSD and underscore the role of individual differences in OXS resistance in conferring resilience/vulnerability to traumatic stress.

INF and PTSD

Findings from blood biomarker, genetic association, and DNA methylation studies have also found evidence for the role of inflammatory processes in the pathophysiology of PTSD. A recent meta-analysis of plasma and serum studies incorporating the results of 20 such studies found the diagnosis to be reliably associated with elevated levels of circulating peripheral IL-6, IL-1β, TNFα, and interferon ϒ.[27] Genetic association studies have also implicated inflammation-related genes in the etiology of PTSD and a recent network analysis of 83 candidate genes previously associated with the disorder showed that genes involved in INF, including *TNFα* and *IL-1b*, were also involved in regulation of the PTSD-associated genes. [28] Similarly, differential DNA methylation (DNAm) and/or differential gene expression has been reported for INF and immune system genes in several PTSD studies.[29,30,15]

One of the most widely-studied and extensively-validated markers of INF is ***C-reactive protein*** **(CRP)**, a protein that can be measured in plasma or serum that responds to inflammatory stimuli by triggering cellular responses that lead to their clearance. CRP is the most sensitive of the body’s inflammatory reactants and capable of proliferating up to 1000-fold in response to triggering stimuli. Because CRP is produced primarily in the liver, it was long assumed to be expressed solely in the periphery. However, recent studies have documented the presence of CRP in stroke lesions[31] and cortical and subcortical tissue from patients with various neurodegenerative disease[32,33]. Emerging evidence also suggests that

CRP is produced in microvessel endothelial cells that form the blood-brain-barrier[34] and that peripheral CRP can affect central nervous system via blood-brain barrier disruption.[35,36]

Studies of blood CRP levels in PTSD patients have yielded somewhat mixed results. Passos et al., (2015) meta-analyzed results of five studies (131 cases; 136 controls total) but found no significant differences between cases and controls.[27] However, several larger and more recent studies that were not included in that analysis have reported positive associations between PTSD symptom severity and plasma CRP levels (see Table 2), but again, not all additional findings have been uniform (cf., Baumert et al. [2013], Dennis et al., 2016).[37,38]

One often cited, but as yet understudied, source of variability in findings across studies is unmeasured genetic variation in relevant genes such as the *CRP* gene. Twin studies of blood CRP levels have estimated its heritability to be between 25–40%[39,40,41] and large-scale GWAS studies with Ns > 10,000 have identified individual *CRP* polymorphisms to be associated with up to 64% differences in blood CRP levels (e.g., rs3091244, AA versus CC genotype[42]). To our knowledge, however, only one published study has examined the association of *CRP* genetic variation with CRP levels and PTSD. In that study, Michopoulos et al. (2015) found *CRP* SNP rs1130864 to be significantly associated with PTSD symptom severity in their full sample (N = 2,692) and with plasma CRP levels in a subsample (n = 137).[43] Plasma CRP was also positively correlated with impaired inhibition to a safety cue in the context of a fear-potentiated startle study (n = 135) suggesting a link between inflammatory status and fear circuitry.

Possible Mechanisms for the Association between PTSD and Elevated OXS & INF

One possible mechanism for the associations between PTSD, OXS and INF is via chronic and repeated activation of the hypothalamic-pituitary-adrenal (HPA) axis which occurs during reexperiencing the trauma. Such activation has been identified as a primary mechanism of stress-related damage to the brain. Specifically, the glucocorticoid-hippocampal atrophy model[44] posits that stress-induced glucocorticoids exert neurotoxic effects on the brain, especially on regions with a high density of glucocorticoid receptors such as the hippocampus and pre-frontal cortex.

Animal studies have found evidence consistent with a causal association between elevated glucocorticoids and increased levels of ROS and markers of oxidative damage.[45] In a meta-analysis of 19 studies, Costantini et al.[46] found a mean effect size of $r = 0.55$ for the effect of glucocorticoid administration on OXS parameters as well as an association between the duration of glucocorticoid administration and extent of oxidative damage. Another study showed that subcutaneous corticosterone administration was associated with increased oxidation and reduced antioxidant enzyme activity in the rat hippocampus.[47] Furthermore, paralleling results of clinical neuroimaging studies of PTSD, these effects, in turn, were linked to hippocampal cell death and memory impairment on a learning task.

The HPA-axis is also reciprocally coupled with the immune system.[45,48] Glucocorticoids generally restrict the inflammatory process by inhibiting synthesis and release of proinflammatory cytokines,[49] however, under conditions of excitotoxicity, elevated levels of glucocorticoids may induce pro-inflammatory cytokine expression.[50] Furthermore,

cytokines released from microglia inhibit neurogenesis and promote neural apoptosis[51,52] and these processes have been implicated in the neuroprogression associated with PTSD and related disorders.[53]

Sleep disturbance, a common symptom of PTSD, is another possible mechanism for the link between PTSD, OXS and INF. Sleep is essential to cellular processes in the brain involved in detoxification and restoration[54]. Its restorative properties are based on the reduction of the neural activity (including glucose metabolism and oxidation processes) which allows antioxidant and anti-inflammatory processes to catch-up with the metabolic by-products of the waking hours. In the domain of OXS, clinical studies have found increased levels of OXS markers following laboratory-induced sleep deprivation[55] and in patients with primary insomnia.[56] Additional support comes from animal studies that have found evidence of OXS in the hippocampus, cortex, and amygdala after sleep deprivation[57] as well as blocking of these effects with antioxidant agents.[58] Similarly, sleep deprivation has been shown to cause increases in levels of proinflammatory molecules such as tumor necrosis factor-α (TFN- α), the interleukins (e.g., IL-1β, IL-6) and C-reactive protein.[59] Chronic sleep loss may induce blood-brain barrier disruption via the regulatory effect of inflammatory molecules on tight junction proteins.[60] Furthermore, a recent study of military personnel who were diagnosed with insomnia and underwent cognitive behavioral therapy for insomnia showed that individuals who responded to treatment with improved sleep showed reduced expression of the inflammatory cytokines IL-1β, IL-6, IL-8 and IL-13. These changes were also associated with a reduction in depression symptoms.[61]

Consequences of PTSD-related OXS and INF: Neuroprogression and Accelerated Aging

Imaging studies have linked PTSD to reduced volume and/or thickness of the anterior cingulate cortex, left temporal pole/middle temporal gyrus, and ventromedial prefrontal cortex.[62] Similarly, in the subcortex, a recent meta-analysis[63] supported the association between PTSD and smaller volumes in the hippocampus (36 studies, n=1,623), and amygdala (14 studies, n=682). However, the functional significance of these differences remains unclear and a controversy exists over whether these differences reflect pre-existing vulnerabilities, consequences of trauma exposure, or signs of neuroprogression. One possibility suggested by the foregoing evidence for the effects of chronic OXS and neuroinflammation on neural integrity from *in vitro* studies, animal models, and the study of other neurodegenerative disorders is that observed differences in brain morphology are primarily a consequence, as opposed to a cause, of PTSD. That said, the types of longitudinal clinical neuroimaging studies that would be necessary to provide more definitive answers to these questions have yet to be completed.

A related line of recent research suggests that PTSD is also associated with accelerated cellular aging. One paradigm for this type of investigation makes use of epigenetic indices of cellular age derived from genome-wide DNA methylation algorithms (DNAm) that are highly correlated chronological age (*r*s = .96; 1,2). Investigators have recently begun to apply these algorithms to examine factors that contribute to accelerated aging and have found accelerated DNAm age to be associated with various age-related health conditions and PTSD. For example, Wolf et al.[64] examined associations between PTSD, DNAm age, and

measures of neural integrity in a sample of veterans with a high prevalence of PTSD and found that advanced DNAm age was associated with decline in the microstructural integrity of the genu of the corpus callosum, a region important for communication across the prefrontal cortices. Mediation analyses further showed that through this neuronal deficit, accelerated DNAm age was associated with poorer performance on tests of executive function and working memory. Similarly, evidence from epidemiological studies suggests that accelerated DNAm age estimates are associated with mortality such that every 5 year increase in DNAm age beyond chronological age is associated with 11% – 21% increased odds of all-cause mortality.[65] Though the biological mechanisms linking PTSD to accelerated aging remain to be identified, OXS and inflammatory processes are strong candidates for future investigation.

Magnetic Resonance Spectroscopy Neuroimaging of OXS and INF

Recent advances in clinical magnetic resonance spectroscopy (MRS) technology now make it possible to visualize *in vivo* concentrations of OXS and INF-related molecules in the brain. Using a standard MR scanner, MRS acquires a spectrum of various neurometabolites, or brain chemicals, from a single cubic region of interest (ROI). Each chemical has distinct resonance frequencies that can be identified by their chemical shift and are indicative of the concentration of that metabolite within the ROI. The metabolites that MRS visualizes exist in close mechanistic proximity to the genes that regulate them. By virtue of this characteristic, when MRS parameters are analyzed in relationship to molecular genetic data there is unprecedented potential to gain insight into the biological pathways and genetic sources of individual differences that moderate the effects of traumatic stress on neural health and function. Furthermore, investigators have also suggested that MRS can be used to detect the precursors of neuroprogression before it can be detected through standard approaches to structural morphology.[66]

Table 3, provides a summary of the 22 MRS studies of PTSD that we included in this review. The most commonly studied regions have been the hippocampus and anterior cingulate cortex with the majority of focusing on N-acetyl aspartate (NAA), creatine (CR; or the NAA/CR ratio), glutamate, and/or gamma-aminobutyric acid (GABA). *NAA* is an amino-acid synthesized in neurons and transported along axons[67]. It is considered a marker of neuronal viability and depleted levels are commonly associated with neuronal loss. Reduced concentration of this molecule has been the most reliable finding across PTSD studies, particularly within the hippocampus and the anterior cingulate (for a meta-analysis, see Karl & Werner, 2010).[66] Though the underlying mechanism for reduced density and viability is not entirely clear, preliminary evidence suggests that it may be due to down regulation of brain derived neurotrophic factor (BDNF) mRNA[68] and/or glutamate excitotoxicity.[69]

Glutamate is the primary *excitatory* neurotransmitter in the cortex and its coupling with glutamine is essential to normal brain function. Differentiating glutamate from glutamine using MRS has historically been challenging because the resonances of the two molecules are strongly coupled and overlap with each other in the proton spectrum. As a result, conventional one-dimensional MRS studies can only measure their combined resonances,

termed “Glx”. As shown in Table 3, previous studies of Glx in PTSD samples have yielded mixed results with several studies finding elevated levels in the cortex and hippocampus while others showing reduced Glx in the anterior cingulate cortex. More recent two dimensional methods and higher field strength scanners can now make it possible to disaggregate the signature of these two molecules. Using this approach, Rosso et al. [69]examined glutamate metabolism in the hippocampus and found elevated glutamate in the right hippocampus of PTSD patients and lower NAA on both sides, suggesting that lower NAA co-occurs with excess glutamate.

GABA is the chief *inhibitory* neurotransmitter in the nervous system and its actions are mediated by two classes of receptors ($GABA_A$ and $GABA_B$). $GABA_A$ receptors are targets of many anxiolytic, anticonvulsant, and sedative/hypnotic drugs and have been studied extensively in relationship to mechanisms of fear and anxiety. Previous MRS studies have found reduced levels of GABA in various brain regions involved in emotional processes in patients with anxiety disorders. However, PTSD studies conducted to date have yielded mixed results (Table 3). Given the fact that the $GABA_A$ receptor is modulated by OXS-related mechanisms[70] and that $GABA_A$ receptor responses are potentiated in the presence of GSH while inhibited by oxidized GSH,[71] future studies examining GABA and GSH levels simultaneously could shed new light on the interplay between OXS and mechanisms of fear and anxiety.

Myo-inositol (mI) is present primarily in the inter-cellular solution of glial cells which are are activated during INF with these changes accompanied by increased volume of mI in the cell. MRS studies measuring MI in conjunction with NAA have provided evidence for its role of INF (indexed by MI) and loss of neuronal integrity (indexed by NAA) in a variety of psychiatric and neurodegenerative conditions.[72,73] In addition, consistent with the hypothesis that sleep disturbance potentiates OXS and INF, one noteworthy MRS study of healthy older adults found strong positive correlation between poorer self-reported sleep quality and mI in the hippocampus ($r = .42$).[74] For this review, we were able to locate five MRS studies that have examined MI in samples of individuals with PTSD. Results were mixed with one study reporting positive associations between MI concentrations and a diagnosis of PTSD,[75] one finding reduced MI in PTSD patients with comorbid alcohol use disorders, and three studies finding no significant differences between PTSD cases and controls.[76,77,78] Unfortunately, the small size of the samples that have been studied, substantial differences between studies in sample characteristics, differences in regions of interest examined, and varying methods of computing mI concentrations complicate interpretation of these findings. Additional studies are needed to clarify the nature of the relationship of mI levels to PTSD.

Thus far, the metabolites discussed have been shown to play a role in neuroinflammation but none directly measure OXS. However, recent technical developments now permit visualization of the brain’s most abundant anti-oxidant molecule: *glutathione (GSH).* GSH is biologically synthesized through enzymatic reactions, exerts its antioxidant effects by detoxifying ROS, and the maintenance of adequate levels of GSH is essential for preventing oxidative damage to the brain. To maintain redox homeostasis, GSH increases in response to elevated ROS. However, when OXS becomes prolonged, and cellular mechanisms fail to

counteract these processes, the amount of free GSH becomes depleted leading to irreversible cell degeneration and cell death.[9] Depleted GSH has been observed in post-mortem prefrontal cortex tissue from patients with a variety of psychiatric and neurodegenerative diseases.[79] Historically, its detection in the brain has been technically challenging due to its overlap with many other resonances as well as its low concentration. However, new spectral editing methods as well as more advanced post-processing methods now allow for the direct measurement of this important metabolite with MRS. To our knowledge only prior study has used MRS to examine GSH concentrations in PTSD patients.[80] In that study Michels et al.[80] measured the GSH concentrations in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) of PTSD patients (n=12) and controls (n=17). Analyses revealed GSH concentrations to be 23% higher in PTSD cases in both ROIs, suggesting the presence of acute OXS in these regions. Similarly, Duffy et al.[81] found elevated levels of GSH in the anterior cingulate cortex of older adults with lifetime histories of depression.

Implications for the Development of Novel Therapeutics

The foregoing review points to the potential value of research and development on antioxidant and/or anti-inflammatory compounds in the treatment of PTSD. The use of antioxidant supplements is supported by evidence from *in vitro* studies examining antioxidant efficacy, nutrition studies of antioxidant-rich diets (e.g., in reducing risk for Alzheimer's disease[82]) and animal studies demonstrating the use of antioxidant supplements to reduce OXS.[83] Some clinical studies have supported the use of anti-oxidant compounds. For example, Dysken et al.[84] showed that vitamin E significantly reduced the rate of functional decline in veterans with mild to moderate Alzheimer's disease and decreased caregiver burden compared to placebo. Unfortunately, many human clinical trials of antioxidant therapeutics have been less successful, with the majority of studies showing minimal or inconclusive benefits.[85]

One possible explanation for the lack of more promising findings of antioxidant therapeutics in clinical trials is that that not all patients benefit equally from antioxidant therapeutics, as there are substantial genetic individual differences in OXS reactivity. Another consideration is that although OXS damage may be limited to specific brain regions, cells types, or cell membranes, most of the antioxidant therapies are global with poor target specificity. Therefore, an antioxidant compound that is more targeted may be better suited for the study of antioxidant therapeutics. One such compound is the antioxidant SS31, which targets the mitochondria and has been shown to protect neurons from neurotoxins.[86] Similarly, L-carnitine, which is a free radical scavenger[87] has been found to reduce OXS damage and improve outcomes in patients with mood and neurodegenerative disorders.[88,89] Another relevant compound is N-acetylcysteine, a liposome encapsulated with GSH that can cross the blood-brain barrier and promote GSH levels in the brain.[79] N-acetylcysteine has shown positive clinical outcomes in disorders such as Alzheimer's disease, schizophrenia, and depression and has been shown to protect against OXS.[90]

Research on the development of anti-inflammatory treatments for PTSD to date has been limited to animal models. For example, administration of ibuprofen to mice subjected to a substantial stressor showed reduced anxious behavior and reduced expression of

inflammatory markers in the hippocampus compared to rats not administered the drug.[91] Similarly, rats fed a diet enriched for curcumin, a component in the turmeric spice with anti-inflammatory properties, showed reduced consolidation of fear-related memories during a conditioning paradigm as well as reduced reconsolidation of an existing fear memory,[92] suggesting a possible role for anti-inflammatories in fear memory formation and retention. In a separate study, rats fed a diet enriched with blueberries, which have anti-inflammatory properties, and subjected to a trauma-like paradigm (including repeated and extended exposure to a cat) showed reduced anxiety behavior and decreased expression of a number of inflammatory proteins in the prefrontal cortex.[93] Though human studies have yet to be conducted, a substantial number of individuals with PTSD are likely to be regular users of anti-inflammatories, given the comorbidity between PTSD and chronic pain[94] and the common recommendation for use of prescription and over-the-counter anti-inflammatories to treat pain-related conditions.[95] This suggests that it may be possible make use of existing archived or medical record data to begin to examine if and how anti-inflammatory use is related to PTSD severity.

In contrast to the nascent research concerning anti-inflammatory compounds and PTSD, there is a far more developed literature regarding anti-inflammatory agents and neurodegeneration. Polyphenols (e.g., curcumin and compounds founds in vegetables, spices, and fruits) exert both anti-oxidant and anti-inflammatory effects and are associated with decreased risk for dementia and Alzheimer's disease (Molino et al.,[96]; Davinelli et al.[97]; Venigalla et al.[98]). Beyond pharmacological treatment to reduce INF and neuroinflammation, exercise may also lead to reduced INF and improved neuronal health (Bertram et al.[99]; Svensson et al.[100]), suggesting a potential alternative behavioral approach to moderating INF. As well, many drugs that exert direct effects on homeostatic and metabolic functions, OXS processes, and the glucocorticoid system may have downstream effects on inflammatory parameters and therefore may play a role in reducing the burden of peripheral and neuroinflammation.

Conclusion

We have reviewed evidence from *in vitro* studies, animal models, clinical and neuroimaging and genetic studies consistent with the hypothesis that chronic PTSD is associated with elevated systemic OXS and INF. However, many of the clinical findings have been based on peripheral biomarkers which are, at best, indirect indicators of the OXS and INF in the brain. Post-mortem PTSD brain tissue studies are notably absent from this literature but could provide important insights into the presence and location of inflammatory markers and oxidative damage in the brain and would offer the opportunity to cross-validate findings across tissue, neuroimaging, and blood-based investigations. Given that OXS and INF are involved both in normal aging and a wide variety of diseases, it is untenable to conceptualize there processes as specific to stress-related disorders or PTSD. Rather, these processes are best approached as ubiquitous disease phenomena that are potentiated by traumatic stress, chronic PTSD and related conditions. As such, markers of these phenomena remain potentially fruitful candidates for future PTSD-related biomarker and treatment development.

References

1. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry. 1995; 52(12):1048–60. [PubMed: 7492257]
2. Kessler RC. Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry. 2000; 61(Suppl 5):4–12. discussion 13–4.
3. Solomon SD, Davidson JR. Trauma: prevalence, impairment, service use, and cost. J Clin Psychiatry. 1997; 58(Suppl 9):5–11.
4. Wolf EJ, Schnurr PP. PTSD-Related Cardiovascular Disease and Accelerated Cellular Aging. Psychiatric Ann. 2016; 46:527–532.
5. Burri A, Maercker A, Krammer S, Simmen-Janevska K. Childhood trauma and PTSD symptoms increase the risk of cognitive impairment in a sample of former indentured child laborers in old age. PLoS One. 2013; 8(2):e57826. [PubMed: 23469076]
6. Yaffe K, Vittinghoff E, Lindquist K, et al. Posttraumatic stress disorder and risk of dementia among US veterans. Arch Gen Psychiatry. 2010; 67(6):608–13. [PubMed: 20530010]
7. Miller MW, Sadeh N. Traumatic stress, oxidative stress and posttraumatic stress disorder: neurodegeneration and the accelerated-aging hypothesis. Mol Psychiatry. 2014; 19(11):1156–62. [PubMed: 25245500]
8. Miller MW, Wolf EJ, Sadeh N, et al. A novel locus in the oxidative stress-related gene *ALOX12* moderates the association between PTSD and thickness of the prefrontal cortex. Psychoneuroendocrinology. 2015; 62:359–65. [PubMed: 26372769]
9. Aquilano K, Baldelli S, Ciriolo MR. Glutathione: new roles in redox signaling for an old antioxidant. Front Pharmacol. 2014; 5:196. [PubMed: 25206336]
10. Schiavone S, Jaquet V, Trabace L, Krause KH. Severe life stress and oxidative stress in the brain: from animal models to human pathology. Antioxid Redox Signal. 2013; 18(12):1475–90. [PubMed: 22746161]
11. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Curr Neuropharmacol. 2009; 7(1):65–74. [PubMed: 19721819]
12. Biswas SK. Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? Oxid Med Cell Longev. 2016:e569831.
13. Atli A, Bulut M, Bez Y, et al. Altered lipid peroxidation markers are related to post-traumatic stress disorder (PTSD) and not trauma itself in earthquake survivors. Eur Arch Psychiatry Clin Neurosci. 2016; 266(4):329–36. [PubMed: 26324882]
14. Štefanović L, Kalinić D, Mimica N, et al. Oxidative status and the severity of clinical symptoms in patients with post-traumatic stress disorder. Ann Clin Biochem. 2015; 52(1):95–104. [PubMed: 24707007]
15. Zieker J, Zieker D, Jatzko A, et al. Differential gene expression in peripheral blood of patients suffering from post-traumatic stress disorder. Mol Psychiatry. 2007; 12(2):116–8. [PubMed: 17252001]
16. Glatt SJ, Tylee DS, Chandler SD, et al. Blood-based gene-expression predictors of PTSD risk and resilience among deployed marines: a pilot study. Am J Med Genet B Neuropsychiatr Genet. 2013; 162B(4):313–26. [PubMed: 23650250]
17. Tylee DS, Chandler SD, Nievergelt CM, et al. Blood-based gene-expression biomarkers of post-traumatic stress disorder among deployed marines: A pilot study. Psychoneuroendocrinology. 2015; 51:472–94. [PubMed: 25311155]
18. Forlenza MJ, Miller GE. Increased serum levels of 8-hydroxy-2′-deoxyguanosine in clinical depression. Psychosom Med. 2006; 68(1):1–7. [PubMed: 16449405]
19. Irie M, Asami S, Ikeda M, Kasai H. Depressive state relates to female oxidative DNA damage via neutrophil activation. Biochem Biophys Res Commun. 2003; 311(4):1014–8. [PubMed: 14623283]
20. Bulut M, Selek S, Bez Y, et al. Reduced PON1 enzymatic activity and increased lipid hydroperoxide levels that point out oxidative stress in generalized anxiety disorder. J Affect Disord. 2013; 150(3):829–33. [PubMed: 23706841]

21. Ozdemir O, Selvi Y, Ozkol H, Tuluce Y, Besiroglu L, Aydin A. Comparison of superoxide dismutase, glutathione peroxidase and adenosine deaminase activities between respiratory and nocturnal subtypes of patients with panic disorder. Neuropsychobiology. 2012; 66(4):244–51. [PubMed: 23095458]
22. Logue MW, Bauver SR, Knowles JA, et al. Multivariate analysis of anxiety disorders yields further evidence of linkage to chromosomes 4q21 and 7p in panic disorder families. Am J Med Genet B Neuropsychiatr Genet. 2012 Apr; 159B(3):274–80. [PubMed: 22253211]
23. Amstadter AB, Sumner JA, Acierno R, et al. Support for association of RORA variant and posttraumatic stress symptoms in a population-based study of hurricane exposed adults. Mol Psychiatry. 2013; 18(11):1148–9. [PubMed: 23319003]
24. Miller MW, Wolf EJ, Logue MW, Baldwin CT. The retinoid-related orphan receptor alpha (RORA) gene and fear-related psychopathology. J Affect Disord. 2013; 151(2):702–8. [PubMed: 24007783]
25. Lowe SR, Meyers JL, Galea S, et al. RORA and posttraumatic stress trajectories: main effects and interactions with childhood physical abuse history. Brain Behav. 2015; 5(4):e00323. [PubMed: 25798337]
26. Pallast S, Arai K, Wang X, Lo EH, van Leyen K. 12/15-Lipoxygenase targets neuronal mitochondria under oxidative stress. J Neurochem. 2009; 111(3):882–9. [PubMed: 19737346]
27. 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(11):1002–12. [PubMed: 26544749]
28. Pollard HB, Shivakumar C, Starr J, et al. “Soldier’s Heart”: A Genetic Basis for Elevated Cardiovascular Disease Risk Associated with Post-traumatic Stress Disorder. Front Mol Neurosci. 2016; 9:87. [PubMed: 27721742]
29. Breen MS, Maihofer AX, Glatt SJ, et al. Gene networks specific for innate immunity define post-traumatic stress disorder. Mol Psychiatry. 2015 Dec; 20(12):1538–45. [PubMed: 25754082]
30. 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(6):700–8. [PubMed: 21714072]
31. Di Napoli M, Godoy DA, Campi V, et al. C-reactive protein in intracerebral hemorrhage: time course, tissue localization, and prognosis. Neurology. 2012; 79(7):690–9. [PubMed: 22855859]
32. Yasojima K, Schwab C, McGeer EG, McGeer PL. Human neurons generate C-reactive protein and amyloid P: upregulation in Alzheimer’s disease. Brain Res. 2000; 887(1):80–9. [PubMed: 11134592]
33. Strang F, Scheichl A, Chen YC, et al. Amyloid plaques dissociate pentameric to monomeric C-reactive protein: a novel pathomechanism driving cortical inflammation in Alzheimer’s disease? Brain Pathol. 2012; 22(3):337–46. [PubMed: 21951392]
34. Alexandrov PN, Kruck TP, Lukiw WJ. Nanomolar aluminum induces expression of the inflammatory systemic biomarker C-reactive protein (CRP) in human brain microvessal endothelial cells (hBMECs). J Inorg Biochem. 2015; 152:210–3. [PubMed: 26265215]
35. Elwood E, Lim Z, Naveed H, Galea I. The effect of systemic inflammation on human brain barrier function. Brain Behav Immun. 2016; (16):S0889–1591. 30488–3.
36. Kuhlmann CR, Librizzi L, Closhen D, et al. Mechanisms of C-reactive protein-induced blood-brain barrier disruption. Stroke. 2009; 40(4):1458–66. [PubMed: 19246692]
37. Baumert J, Lukaschek K, Kruse J, et al. No evidence for an association of posttraumatic stress disorder with circulating levels of CRP and IL-18 in a population-based study. Cytokine. 2013; 63(2):201–8. [PubMed: 23706403]
38. Dennis PA, Weinberg JB, Calhoun PS, et al. An investigation of vago-regulatory and health-behavior accounts for increased inflammation in posttraumatic stress disorder. J Psychosom Res. 2016; 83:33–9. [PubMed: 27020074]
39. Dupuis J, Larson MG, Vasan RS, et al. Genome scan of systemic biomarkers of vascular inflammation in the Framingham Heart Study: evidence for susceptibility loci on 1q. Atherosclerosis. 2005; 182(2):307–14. [PubMed: 16159603]

40. Pankow JS, Folsom AR, Cushman M, et al. Familial and genetic determinants of systemic markers of inflammation: the NHLBI family heart study. Atherosclerosis. 2001; 154(3):681–9. [PubMed: 11257270]
41. Retterstol L, Eikvar L, Berg K. A twin study of C-reactive Protein compared to other risk factors for coronary heart disease. Atherosclerosis. 2003; 169(2):279–82. [PubMed: 12921979]
42. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG. Genetically elevated C-reactive protein and ischemic vascular disease. N Engl J Med. 2008; 359(18):1897–908. [PubMed: 18971492]
43. 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(4):353–62. [PubMed: 25827033]
44. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry. 2000; 57(10):925–35. [PubMed: 11015810]
45. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its behavioral and metabolic correlates: from HPA axis to glucocorticoid receptor dysfunction. Ann N Y Acad Sci. 2012; 1261:55–63. [PubMed: 22823394]
46. Costantini D, Marasco V, Møller AP. A meta-analysis of glucocorticoids as modulators of oxidative stress in vertebrates. J Comp Physiol B. 2011; 181(4):447–56. [PubMed: 21416253]
47. Sato H, Takahashi T, Sumitani K, Takatsu H, Urano S. Glucocorticoid Generates ROS to Induce Oxidative Injury in the Hippocampus, Leading to Impairment of Cognitive Function of Rats. J Clin Biochem Nutr. 2010; 47(3):224–32. [PubMed: 21103031]
48. Haroon E, Raison CL, Miller AH. Psychoneuroimmunology Meets Neuropsychopharmacology: Translational Implications of the Impact of Inflammation on Behavior. Neuropsychopharmacology. 2012; 37(1):137–162. DOI: 10.1038/npp.2011.205. [PubMed: 21918508]
49. Sapolsky RM, Romero LM, Munk AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory and preparative actions. Endocr Rev. 2000; 21:55–89. [PubMed: 10696570]
50. MacPherson A, Dinkel K, Sapolsky R. Glucocorticoids worsen excitotoxin-induced expression of pro-inflammatory cytokines in hippocampal cultures. Exp Neurol. 2005; 194(2):376–83. [PubMed: 16022865]
51. Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. J Neurosci. 2005; 25(40):9275–84. [PubMed: 16207887]
52. Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O. Inflammation is detrimental for neurogenesis in adult brain. Proc Natl Acad Sci USA. 2003; 100(23):13632–7. [PubMed: 14581618]
53. Michopoulos V, Powers A, Gillespie CF, Ressler KJ, Jovanovic T. Inflammation in Fear- and Anxiety-Based Disorders: PTSD, GAD, and Beyond. Neuropsychopharmacology. 2016 [Epub ahead of print].
54. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science. 2013; 342(6156):373–7. [PubMed: 24136970]
55. Alzoubi KH, Khabour OF, Salah HA, Abu Rashid BE. The combined effect of sleep deprivation and Western diet on spatial learning and memory: role of BDNF and oxidative stress. J Mol Neurosci. 2013; 50(1):124–33. [PubMed: 22956188]
56. Gulec M, Ozkol H, Selvi Y, et al. Oxidative stress in patients with primary insomnia. Prog Neuropsychopharmacol Biol Psychiatry. 2012; 37(2):247–51. [PubMed: 22401887]
57. Vollert C, Zagaar M, Hovatta I, et al. Exercise prevents sleep deprivation-associated anxiety-like behavior in rats: potential role of oxidative stress mechanisms. Behav Brain Res. 2011; 224(2): 233–40. [PubMed: 21621560]
58. Silva RH, Abilio VC, Takatsu AL, et al. Role of hippocampal oxidative stress in memory deficits induced by sleep deprivation in mice. Neuropharmacology. 2004; 46(6):895–903. [PubMed: 15033349]

59. Hurtado-Alvarado G, Pavón L, Castillo-García SA, et al. Sleep loss as a factor to induce cellular and molecular inflammatory variations. Clin Dev Immunol. 2013; 2013:018341.
60. Hurtado-Alvarado G, Dominquez-Salazar E, Pavon L, Velazquez-Moctezuma J, Gomez-Gonzalez B. Blood-brain barrier disruption induced by chronic sleep loss: low-grade inflammation may be the link. J Immunol Res. 2016; 2016:4576012. [PubMed: 27738642]
61. Livingston WS, Rusch HL, Nersesian PV, Baxter T, Mysliwiec V, Gill JM. Improved sleep in military personnel is associated with changes in the expression of inflammatory genes and improvement in depression symptoms. Front Psychiatry. 2015; 6:59. [PubMed: 25983695]
62. Kühn S, Gallinat J. Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. Biol Psychiatry. 2013; 73(1):70–4. [PubMed: 22840760]
63. O'Doherty DC, Chitty KM, Saddiqui S, Bennett MR, Lagopoulos J. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatry Res. 2015; 232(1):1–33. [PubMed: 25735885]
64. Wolf EJ, Logue MW, Hayes JP, et al. Accelerated DNA methylation age: associations with PTSD and neural integrity. Psychoneuroendocrinology. 2016; 63:155–162. [PubMed: 26447678]
65. Marioni RE, Shah S, McRae AF, et al. DNA methylation age of blood predicts all-cause mortality in later life. Genome Biol. 2015; 16:25. [PubMed: 25633388]
66. Karl A, Werner A. The use of proton magnetic resonance spectroscopy in PTSD research – meta-analyses of findings and methodological review. Neurosci Biobehav Rev. 2010; 34(1):7–22. [PubMed: 19559046]
67. Moffet JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM. N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. Prog Neurobiol. 2007; 81(2):89–131. [PubMed: 17275978]
68. Rasmusson AM, Shi L, Duman R. Downregulation of BDNF mRNA in the hippocampal dentate gyrus after re-exposure to cues previously associated with footshock. Neuropyschopharmacology. 2002; 27(2):133–42.
69. Rosso IM, Crowley DJ, Silveri MM, Rauch SL, Jensen JE. Hippocampus Glutatmate and N-Acetyl Aspartate Markers of Excitotoxic Neuronal Compromise in Posttraumatic Stress Disorder. Neuropyschopharmacology. 2017; doi: 10.1038/npp.2017.32
70. Calvo DJ, González AN. Dynamic Regulation of the GABAA Receptor Function by Redox Mechanisms. Mol Pharmacol. 2016; 90(3):326–33. [PubMed: 27439531]
71. Tartaglia MC, Narayanan S, De Stefano N, et al. Choline is increased in pre-lesional normal appearing white matter in multiple sclerosis. J Neurol. 2002; 249(10):1382–90. [PubMed: 12382153]
72. Zahr NM, Mayer D, Rohlfing T, Sullivan EV, Pfefferbaum A. Imaging neuroinflammation? A perspective from MR spectroscopy. Brain Pathol. 2014; 24(6):654–64. [PubMed: 25345895]
73. Chang L, Munsaka SM, Kraft-Terry S, Ernst T. Magnetic resonance spectroscopy to assess neuroinflammation and neuropathic pain. J Neuroimmune Pharmacol. 2013; 8(3):576–93. [PubMed: 23666436]
74. Cross NE, Lagopoulos J, Duffy SL, et al. Sleep quality in healthy older people: relationship with ^{1}H magnetic resonance spectroscopy markers of glial and neuronal integrity. Behav Neurosci. 2013; 127(5):803–10. [PubMed: 24128367]
75. Seedat S, Videen JS, Kennedy CM, Stein MB. Single voxel proton magnetic resonance spectroscopy in women with and without intimate partner violence-related posttraumatic stress disorder. Psychiatry Res. 2005; 139(3):249–58. [PubMed: 16055312]
76. Pennington DL, Abé C, Batki SL, Meyerhoff DJ. A preliminary examination of cortical neurotransmitter levels associated with heavy drinking in posttraumatic stress disorder. Psychiatry Res. 2014; 224(3):281–7. [PubMed: 25444536]
77. Ham BJ, Chey J, Yoon SJ, et al. Decreased N-acetyl-aspartate levels in anterior cingulate and hippocampus in subjects with post-traumatic stress disorder: a proton magnetic resonance spectroscopy study. Eur J Neurosci. 2007; 25(1):324–9. [PubMed: 17241294]
78. Yang ZY, Quan H, Peng ZL, Zhong Y, Tan ZJ, Gong QY. Proton magnetic resonance spectroscopy revealed differences in the glutamate + glutamine/creatine ratio of the anterior cingulate cortex

between healthy and pediatric post-traumatic stress disorder patients diagnosed after 2008 Wenchuan earthquake. Psychiatry Clin Neurosci. 2015; 69(12):782–90. [PubMed: 26171979]

79. Gu F, Chauhan V, Chauhan A. Glutathione redox imbalance in brain disorders. Curr Opin Clin Nutr Metab Care. 2015; 18(1):89–95. [PubMed: 25405315]
80. Michels L, Schulte-Vels T, Schick M, et al. Prefrontal GABA and glutathione imbalance in posttraumatic stress disorder: preliminary findings. Psychiatry Res. 2014; 224(3):288–95. [PubMed: 25448399]
81. Duffy SL, Lagopoulos J, Cockayne N, et al. Oxidative stress and depressive symptoms in older adults: A magnetic resonance spectroscopy study. J Affect Disord. 2015; 180:29–35. [PubMed: 25881278]
82. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. JAMA. 2002; 287(24):3223–9. [PubMed: 12076218]
83. Dumont M, Lin MT, Beal MF. Mitochondria and antioxidant targeted therapeutic strategies for Alzheimer's disease. J Alzheimers Dis. 2010; 20:633–43.
84. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA Cooperative Randomized Trial. JAMA. 2014; 311(1):33–44. [PubMed: 24381967]
85. Firuzi O, Miri R, Tavakkoli M, Saso L. Antioxidant therapy: current status and future prospects. Curr Med Chem. 2011; 18(25):3871–88. [PubMed: 21824100]
86. Reddy TP, Manczak M, Calkins MJ, et al. Toxicity of neurons treated with herbicides and neuroprotection by mitochondria-targeted antioxidant SS31. Int J Environ Res Public Health. 2011; 8(1):203–21. [PubMed: 21318024]
87. Nałęcz KA, Miecz D, Berezowski V, Cecchelli R. Carnitine: transport and physiological functions in the brain. Mol Aspects Med. 2004; 25(5–6):551–67. [PubMed: 15363641]
88. Pettegrew JW, Levine J, McClure RJ. Acetyl-L-carnitine physical-chemical, metabolic, and therapeutic properties: relevance for its mode of action in Alzheimer's disease and geriatric depression. Mol Psychiatry. 2000; 5(6):616–32. [PubMed: 11126392]
89. Ribas GS, Vargas CR, Wajner M. l-carnitine supplementation as a potential antioxidant therapy for inherited neurometabolic disorders. Gene. 2014; 533(2):469–76. [PubMed: 24148561]
90. Unnithan AS, Jiang Y, Rumble JL, et al. N-acetyl cysteine prevents synergistic, severe toxicity from two hits of oxidative stress. Neurosci Lett. 2014; 560:71–6. [PubMed: 24361774]
91. 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(4):357–66. [PubMed: 27382352]
92. Monsey MS, Gerhard DM, Boyle LM, Briones MA, Seligsohn M, Schafe GE. A diet enriched with curcumin impairs newly acquired and reactivated fear memories. Neuropsychopharmacology. 2015; 40(5):1278–88. [PubMed: 25430781]
93. Ebenezer PJ, Wilson CB, Wilson LD, Nair AR, J F. The Anti-Inflammatory Effects of Blueberries in an Animal Model of Post-Traumatic Stress Disorder (PTSD). PLoS One. 2016; 11(9):e0160923. [PubMed: 27603014]
94. Higgins DM, Kerns RD, Brandt CA, et al. Persistent pain and comorbidity among Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn veterans. Pain Med. 2014; 15(5):782–790. [PubMed: 24548466]
95. Wong JJ, Côté P, Sutton DA, et al. Clinical practice guidelines for the noninvasive management of low back pain: A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur J Pain. 2016 [Epub ahead of print].
96. Molino S, Dossena M, Buonocore D, et al. Polyphenols in dementia: From molecular basis to clinical trials. Life Sci. 2016; 161:69–77. [PubMed: 27493077]
97. Davinelli S, Maes M, Corbi G, Zarrelli A, Willcox DC, Scapagnini G. Dietary phytochemicals and neuro-inflammaging: from mechanistic insights to translational challenges. Immun Ageing. 2016; 13:16. [PubMed: 27081392]
98. Venigalla M, Sonego S, Gyengesi E, Sharman MJ, Münch G. Novel promising therapeutics against chronic neuroinflammation and neurodegeneration in Alzheimer's disease. Neurochem Int. 2016; 95:63–74. [PubMed: 26529297]

99. Bertram S, Brixius K, Brinkmann C. Exercise for the diabetic brain: how physical training may help prevent dementia and Alzheimer's disease in T2DM patients. Endocrine. 2016; 53(2):350–63. [PubMed: 27160819]
100. Svensson M, Lexell J, Deierborg T. Effects of Physical Exercise on Neuroinflammation, Neuroplasticity, Neurodegeneration, and Behavior: What We Can Learn From Animal Models in Clinical Settings. Neurorehabil Neural Repair. 2015; 29(6):577–89. [PubMed: 25527485]
101. Attari A, Asgary S, Naderi G, Rezayat A. Lipid peroxidation and antioxidant capacity in posttraumatic stress disorder. Journal of Isfahan Medical School. 2002; 20(65):4–6.
102. Čeprnja M, Derek L, Unic A, et al. Oxidative stress markers in patients with post-traumatic stress disorder. Coll Antropol. 2011; 35(4):1155–60. [PubMed: 22397253]
103. Şimşek Ş, Yuksel T, Kaplan I, Uysal C, Aktas H. The Levels of Cortisol and Oxidative Stress and DNA Damage in Child and Adolescent Victims of Sexual Abuse with or without Post-traumatic Stress Disorder. Psychiatry Investig. 2016; 13(6):616–621.
104. Tezcan E, Atmaca M, Kuloglu M, Ustundag B. Free radicals in patients with post-traumatic stress disorder. Eur Arch Psychiatry Clin Neurosci. 2003; 253(2):89–91. [PubMed: 12799747]
105. Bersani FS, Wolkowitz OM, Lindqvist D, et al. Global arginine bioavailability, a marker of nitric oxide synthetic capacity, is decreased in PTSD and correlated with symptom severity and markers of inflammation. Brain Behav Immun. 2016; 52:153–60. [PubMed: 26515034]
106. 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(4):423–31. [PubMed: 24576974]
107. Gill J, Lee H, Barr T, et al. Lower health related quality of life in U.S. military personnel is associated with service-related disorders and inflammation. Psychiatry Res. 2014 Apr 30; 216(1): 116–22. [PubMed: 24559851]
108. Heath NM, Chesney SA, Gerhart JI, et al. Interpersonal violence, PTSD, and inflammation: potential psychogenic pathways to higher C-reactive protein levels. Cytokine. 2013; 63(2):172–8. [PubMed: 23701836]
109. Lindqvist D, Dhabhar FS, Mellon SH, et al. Increased pro-inflammatory milieu in combat related PTSD - A new cohort replication study. Brain Behav Immun. 2016 [Epub ahead of print].
110. McCanlies EC, Araia SK, Joseph PN. C-reactive protein, interleukin-6, and posttraumatic stress disorder symptomology in urban police officers. Cytokine. 2011; 55(1):74–8. [PubMed: 21493089]
111. Miller RJ, Sutherland AG, Hutchinson JD, Alexander DA. C-reactive protein and interleukin 6 receptor in post-traumatic stress disorder: a pilot study. Cytokine. 2001; 13(4):253–5. [PubMed: 11237435]
112. Muhtz C, Godemann K, von Alm C, et al. Effects of chronic posttraumatic stress disorder on metabolic risk, quality of life, and stress hormones in aging former refugee children. J Nerv Ment Dis. 2011; 199(9):646–52. [PubMed: 21878777]
113. Plantinga L, Bremner JD, Miller AH, et al. Association between posttraumatic stress disorder and inflammation: a twin study. Brain Behav Immun. 2013; 30:125–32. [PubMed: 23379997]
114. Rosen, Rl, Levy-Carrick, N., Reibman, J., et al. Elevated C-reactive protein and posttraumatic stress pathology among survivors of the 9/11 World Trade Center attacks. J Psychiatr Res. 2017; 89:14–21. [PubMed: 28135632]
115. Sőndergaard 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(1–2):93–8. [PubMed: 15026269]
116. Spitzer C, Barnow S, Völzke H, et al. Association of posttraumatic stress disorder with low-grade elevation of C-reactive protein: evidence from the general population. J Psychiatr Res. 2010; 44(1):15–21. [PubMed: 19628221]
117. 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(9):744–52. [PubMed: 16901505]

118. von Känel R, Begre S, Abbas CC, Saner H, Gander ML, Schmid JP. Inflammatory biomarkers in patients with posttraumatic stress disorder caused by myocardial infarction and the role of depressive symptoms. Neuroimmunomodulation. 2010; 17(1):39–46. [PubMed: 19816056]
119. Brown S, Freeman T, Kimbrell T, Cardwell D, Komoroski R. In vivo proton magnetic resonance spectroscopy of the medial temporal lobes of former prisoners of war with and without posttraumatic stress disorder. J Neuropsychiatry Clin Neurosci. 2003; 15(3):367–70. [PubMed: 12928515]
120. De Bellis MD, Keshavan MS, Spencer S, Hall J. N-Acetylaspartate concentration in the anterior cingulate of maltreated children and adolescents with PTSD. Am J Psychiatry. 2000; 157(7): 1175–7. [PubMed: 10873933]
121. Eckart C, Kaufmann J, Kanowski M, et al. Magnetic resonance volumetry and spectroscopy of hippocampus and insula in relation to severe exposure of traumatic stress. Psychophysiology. 2012; 49(2):261–70. [PubMed: 22092224]
122. Freeman TW, Cardwell D, Karson CN, Komoroski RA. In vivo proton magnetic resonance spectroscopy of the medial temporal lobes of subjects with combat-related posttraumatic stress disorder. Magn Reson Med. 1998; 40(1):66–71. [PubMed: 9660555]
123. Freeman T, Kimbrell T, Booe L, et al. Evidence of resilience: neuroimaging in former prisoners of war. Psychiatry Res. 2006; 146(1):59–64. [PubMed: 16361087]
124. 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(4):323–5. [PubMed: 22449527]
125. Kimbrell T, Leulf C, Cardwell D, Komoroski RA, Freeman TW. Relationship of in vivo medial temporal lobe magnetic resonance spectroscopy to documented combat exposure in veterans with chronic posttraumatic stress disorder. Psychiatry Res. 2005; 140(1):91–4. [PubMed: 16169712]
126. Li L, Chen S, Liu J, Zhang J, He Z, Lin X. Magnetic resonance imaging and magnetic resonance spectroscopy study of deficits in hippocampal structure in fire victims with recent-onset posttraumatic stress disorder. Can J Psychiatry. 2006; 51(7):431–7. [PubMed: 16838824]
127. Lim MK, Suh CH, Kim HJ, et al. Fire-related post-traumatic stress disorder: brain 1H-MR spectroscopic findings. Korean J Radiol. 2003; 4(2):79–84. [PubMed: 12845302]
128. Mahmutyazicioğlu K, Konuk N, Ozdemir H, Atasoy N, Atik L, Gündoğdu S. Evaluation of the hippocampus and the anterior cingulate gyrus by proton MR spectroscopy in patients with post-traumatic stress disorder. Diagn Interv Radiol. 2005; 11(3):125–9. [PubMed: 16206051]
129. Menon M, Nasrallah H, Lyons J, Scott M, Liberto V. Single-voxel proton MR spectroscopy of right versus left hippocampi in PTSD. Psychiatry Res. 2003; 123(2):101–8. [PubMed: 12850249]
130. Meyerhoff DJ, Mon A, Metzler T, Neylan TC. Cortical gamma-aminobutyric acid and glutamate in posttraumatic stress disorder and their relationships to self-reported sleep quality. Sleep. 2014; 37(5):893–900. [PubMed: 24790267]
131. Rosso IM, Weiner MR, Crowley DJ, Silveri MM, Rauch SL, Jensen JE. Insula and anterior cingulate GABA levels in posttraumatic stress disorder: preliminary findings using magnetic resonance spectroscopy. Depress Anxiety. 2014; 31(2):115–23. [PubMed: 23861191]
132. Schuff N, Neylan TC, Lenoci MA, et al. Decreased hippocampal N-acetylaspartate in the absence of atrophy in posttraumatic stress disorder. Biol Psychiatry. 2001; 50(12):952–9. [PubMed: 11750891]
133. Neylan TC, Schuff N, Lenoci M, Yehuda R, Weiner MW, Marmar CR. Cortisol levels are positively correlated with hippocampal N-acetylaspartate. Biol Psychiatry. 2003; 54(10):1118–21. [PubMed: 14625155]
134. Schuff N, Neylan TC, Fox-Bosetti S, et al. Abnormal N-acetylaspartate in hippocampus and anterior cingulate in posttraumatic stress disorder. Psychiatry Res. 2008; 162(2):147–57. [PubMed: 18201876]
135. Shu XJ, Xue L, Liu W, et al. More vulnerability of left than right hippocampal damage in right-handed patients with post-traumatic stress disorder. Psychiatry Res. 2012; 212(3):237–44. [PubMed: 23149034]

136. Villareal G, Petropoulos H, Hamilton DA, et al. Proton magnetic resonance spectroscopy of the hippocampus and occipital white matter in PTSD: preliminary results. Can J Psychiatry. 2002; 47(7):666–70. [PubMed: 12355679]

Table 1

Studies of OXS-related Biomarker Associations with PTSD

First author (year)	Cohort	Marker	Ns	PTSD Association
Atli (2016)[13]	M&F, disaster	PON1, MDA	32/70	↑ MDA, ↓PON1
Attari (2002)[101]	M, military	MDA, RBCH	30/30	↑ MDA, ↓RBCH
Borovac-Štefanović (2015)[14]	M, military	GPx, SOD	50/30	↓ GPx, ↓ SOD
Čeprnja (2011)[102]	M, military	8-OHdG *	46/28	*ns*
Glatt (2013), Tylee (2015)[16,17]	M, military	RNA (microarray)	25/25	↓ GSTM1&2
Michels (2014)[80]	M&F, mixed	GSH (MRS cortex)	12/17	↓ GSH
Şimşek (2016)[103]	M&F, children	GPx, SOD, 8-OHdG	31/30	*ns*
Tezcan (2003)[104]	M &F, mixed	GSH, SOD	14/14	*ns*
Zieker (2007)[15]	disaster †	RNA (microarray)	8/8	↓ SOD1, ↓ TXR1

Note: Ns listed are for cases/controls, respectively. Unless otherwise noted (i.e., MRS), all studies were based on blood samples.

* = From urine;

† = sex breakdown not reported; GSH = glutathione; GPx = glutathione peroxidase; GSTM = glutathione s-transferase mu; MDA = malondialdehyde; ns = non-significant; MRS = magnetic resonance spectroscopy; PON1 = paraoxonase; RBCH = rate of blood cell hemolysis; SOD = superoxide dismutase; TXR = thioredoxin reductase; 8-OHdG = 8-hydroxy-2-deoxyguanosine.

Table 2

Studies of C-reactive Protein (CRP) Associations with PTSD

First author (year)	Cohort	Ns	PTSD Association
Baumert (2013)[37]	M&F, mixed	51/2698	*ns*
Bersani (2016)[105]	M, military	56/65	*ns*
Dennis (2016)[38]	M&F, mixed	85/82	*ns*
Eraly (2014)[106]	M, military	117/1744	+
Gill (2013)[p107]	F, mixed	26/51	+
Heath (2013)[108]	F, IPV	17/122	+
Lindqvist (2014)[p109]	M only, military	51/51	*ns*
McCanlies (2011)[110]	M&F, police	32/79	*ns*
Michopoulos (2015)[43]	M&F, mixed	187*	+
Miller (2001)[111]	M&F, mixed	17/8	*ns*
Muhtz (2011)[p112]	M&F refugees	25/25	*ns*
Plantinga (2013)[113]	M&F, twins	59/476	+
Rosen (2017)[114]	M&F, 9/11 WTC	641*	+
Sőndergaard (2004)[115]	M&F, refugees	32/54	−
Spitzer (2010)[116]	M&F, mixed	55/294	+
von Känel (2007)[p117]	M&F, mixed	14/14	*ns*
von Känel (2010)[p118]	M&F, MI	15/29	*ns*

Note: Italics denotes papers included in the Passos et al (2015) meta-analysis; Ns listed are for cases/controls, respectively;

* = number of cases versus controls not reported; IPV = interpersonal violence; MI = myocardial infarction; M/W = men/women; *ns* = nonsignificant; WTC = World Trade Center.

Table 3

Summary of PTSD-MRS Studies

First author (year)	Cohort	Ns	ROI	Primary PTSD Finding
Brown (2003)[119]	M, military	9/12	temporal	↓NAA/Cr
De Bellis (2000)[120]	M&F, children	11/11	ACC	↓ NAA/Cr
Eckart (2012)[121]	M&F, refugee	20/16	hippo, insula	↓ NAA with child trauma
Freeman (1998)[122]	M, military	21/8	temporal	↓ NAA/Cr
Freeman (2006)[123]	M, military	20/6	hippo	*ns*
Guo (2012)[124]	M&F, mixed	50/50	hippo, ACC	↓ NAA/Cr in both
Ham (2007)[77]	M&F, disaster	26/25	hippo, ACC	↓ NAA in both
Kimbrell (2005)[125]	M, military	47/21	temporal	↓ NAA/Cr
Li (2006)[126]	M&F, disaster	12/12	hippo	↓ NAA/Cr
Lim (2003)[127]	M&F, children	16/8	BG, FWM, PWM	↓ NAA/Cr in BG
Mahmutyazicioglu (2005)[128]	M&F, mixed	10/6	hippo, ACC	↓ NAA/Cr in both;↑Cho/Cr in hippo
Menon (2003)[129]	M&F, mixed	14/7	hippo	↓ NAA/Cr
Meyerhoff (2014)[130]	M, mixed	28/20	cortex, ACC	↑glx in cortex; ↓ GABA in ACC
Michels (2014)[80]	M&F, mixed	12/17	DLPFC, ACC	↑ GABA and GSH in both
Pennington (2014)[76]	M, mixed	28/19	ACC, cortex	↓ GABA in POC; ↑Glu in temporal
Rosso 2014[131]	M&F, mixed	13/13	insula and ACC	↓GABA in insula
Rosso 2017[69]	M&F, mixed	24/34	hippo	↑Glu; ↓NAA
Schuff 2001[132] *Neylan (2003)*[133]	*M, military*	18/19	hippo	↓NAA ↓Cr
Schuff 2008[134]	M&F, mixed	55/49	hippo, ACC	↓ NAA/Cr in hippo, ↓ NAA in ACC
Seedat 2005[75]	W, IPV	16/11	ACC	↑Cho/Cr, ↑mI/Cr
Shu 2013[135]	M&F, mixed	11/11	hippo	↓ NAA/cr; ↑Cho/Cr;
Villareal 2002[136]	M&F, mixed	8/5	hippo, WM	↓NAA, ↓Cr in hippo; ↓CR in WM
Yang 2015[77]	M&F, children	33/21	ACC	↓ Glx and ↓ Glx/Cr

Note: Italics denotes papers included in Karl & Werner's (2010) meta-analysis. Ns listed are for cases/controls, respectively. ACC = anterior cingulate cortex; BG = basal ganglia; CSV = centrum semiovale; Cr = creatine; DLPFC = dorsolateral prefrontal cortex; FWM = frontal white matter; GABA = gamma-aminobutyric acid; Glu = glutamate; Glx = glutamate/glutamine; GSH = glutathione; hippo = hippocampus; mI = myo-Inositol; NAA = N-acetyl aspartate; ns = nonsignificant; POC = parieto-occipital cortices; PWM = parietal white matter; WM = white matter.