Traumatic Brain Injury's Effect on PTSD: (TBI + PTSD)

From: Traumatic injury center of excellence (updated August 2023) — "Research review on mild traumatic brain injury and post-traumatic stress disorder.":

- "As an example of combat-induced TBI, "[I]n the military population, 5%–35% of service members who deployed to Iraq and Afghanistan sustained a mild TBI (mTBI), also known as concussion, during their deployment.[1] This is the most common form of TBI, accounting for 82.3% of the nearly ***473,000 service members diagnosed with a TBI between 2000 and 2022***.[2] Regardless of the origin, experiencing one mTBI nearly doubles the risk of sustaining subsequent mTBIs.[3] Therefore, a prophylactic pretreatment of active military personnel is required for maximum prevention of subsequent TBIs.
- "…[T]he Department of Defense Health Related Behaviors Survey found that 10.5% of Army, 9.1% of Marines, 9.7% of Navy, and 3.9% of Air Force active-duty service members had PTSD in 2015.[4] The prevalence of PTSD in the **veteran population is estimated** to be between 10% and 15% with a **lifetime prevalence ranging from 12% to 30%**.[5]
- "PTSD is one of the most commonly diagnosed psychiatric disorders associated with mTBI. In fact, the **risk of PTSD is *elevated two-to-threefold after mTBI*** **according to studies** of veterans, service members, and civilians.[6]
- Uncomplicated mTBIs are characterized by the presence of diffuse injuries that ***cannot be detected via CT***. They tend to involve areas of damage scattered in various seemingly intact structures throughout the brain. This damage often presents as diffuse neuronal damage, axonal (white matter) perturbation, and changes in vasculature, which are difficult to detect with conventional imaging modalities."[7]

FROM: Vasterling, JJ, et al., "Traumatic brain injury and posttraumatic stress disorder: Conceptual, diagnostic, and therapeutic considerations in the context of co-occurrence," *J Neuropsychiatry Clin Neurosci* 2018; 30:91–100; doi: 10.1176/appi.neuropsych.17090180:

- "The scientific community once believed that alterations of consciousness associated with TBI precluded formation of a trauma memory, making it improbable for PTSD to develop following TBI. **Experts, however, now recognize that PTSD may develop following TBI due to several factors**…. Epidemiological data confirm that PTSD indeed develops following TBI, and, within the general population, in particular following mild TBI.

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[1] Lindberg MA, Moy Martin EM, Marion DW. **Military** Traumatic Brain Injury: The History, Impact, and Future. *J Neurotrauma.* Sep 2022;39(17-18):1133-1145. doi:10.1089/neu.2022.0103

[2] **Department of Defense**. DOD TBI Worldwide Numbers https://health.mil/Military-Health-Topics/Centers-of-Excellence/Traumatic-Brain-Injury-Center-of-Excellence/DOD-TBI-Worldwide-Numbers

[3] Van Pelt KL, Allred D, Cameron KL, et al. A cohort study to identify and evaluate concussion risk factors across multiple injury settings: findings from the CARE Consortium. *Injury epidemiology*. 2019;6(1):1-11.

[4] Meadows SO, Engel CC, Collins RL, et al. 2015 Department of Defense Health Related Behaviors Survey (HRBS). ***Rand*** *health quarterly*. 2018;8(2)

[5] Stefanovics EA, Potenza MN, Pietrzak RH. PTSD and obesity in U.S. military veterans: Prevalence, health burden, and suicidality. *Psychiatry research*. Sep 2020;291:113242. doi:10.1016/j.psychres.2020.113242

[6] Miller SC, Whitehead CR, Otte CN, et al. Risk for broad-spectrum neuropsychiatric disorders after mild traumatic brain injury in a cohort **of US Air Force personnel**. *Occup Environ Med*. Aug 2015;72(8):560-6. doi:10.1136/oemed-2014-102646; Stein MB, Kessler RC, Heeringa SG, et al. Prospective Longitudinal Evaluation of the Effect of Deployment-Acquired Traumatic Brain Injury on Posttraumatic Stress and Related Disorders: Results From the **Army Study** to Assess Risk and Resilience in Servicemembers (Army STARRS). *The American journal of psychiatry*. Sep 4 2015:appiajp201514121572. doi:10.1176/appi.ajp.2015.14121572

[7] McGinn MJ, Povlishock JT. Pathophysiology of Traumatic Brain Injury. *Neurosurg Clin N Am*. Oct 2016;27(4):397-407. doi:10.1016/j.nec.2016.06.002

- "The medical records of over 500,000 U.S. Air Force service members revealed increased risk of PTSD shortly following mild TBI **and months later**.[8] [Note: **Therefore, the delay may offer the opportunity for interim treatment before the onset of PTSD**.]

FROM: Bryant, R., State of the art: "Post-traumatic stress disorder vs traumatic brain injury," *Dialogues Clin Neurosci.* 2011;13:251-262:

- "Post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) often coexist because brain injuries are often sustained in traumatic experiences. This review outlines the significant overlap between PTSD and TBI by commencing with a critical outline of the overlapping symptoms and problems of differential diagnosis. The impact of TBI on PTSD is then described, with increasing evidence suggesting that mild TBI can increase risk for PTSD.
- "Intriguingly, both case studies and cohort studies have noted the existence of PTSD developing following severe TBI. In many of the latter cases, these individuals suffer very significant periods of retrograde and anterograde amnesia, such that they do not recall any episodes of the traumatic experience.
- "One of the intriguing findings in recent years is that MTBI appears to increase the risk for PTSD. For example, Fann and colleagues reported from a large-scale study of 939 health plan members that patients with a history of mild TBI were 2.8 times more likely to develop a psychiatric disorder than patients with no TBI history. ***In a large military survey, whereas 16% of troops who sustained a bodily injury indicated PTSD, 44% of those with MTBI screened positive for PTSD***.[9] [Note: This development is in stark contrast to incorrect, previously held views that TBI was "protective" of PTSD development.]
- Delayed-onset PTSD refers to cases of PTSD in which the condition develops at least 6 months after the trauma. Most studies indicate that delayed-onset PTSD is rare. Although [delayed onset PTSD] uncommon following civilian trauma, it has been reported to occur more frequently in troops returning home from deployment. A review of delayed-onset PTSD studies found that it was rare for PTSD to develop outside military samples**, with up to one third of military cases** ***presenting as*** **delayed-onset; specifically, it is reported in 38% of military cases** ***compared with 15% in civilian cases***.[10]

FROM: Larsen, SE and Vasterling, JJ, "Traumatic brain injury and PTSD," PTSD: National center for PTSD
https://www.ptsd.va.gov/professional/treat/cooccurring/tbi_ptsd_v…y%20of%20the%20contexts%20in,those%20without%20a%20TBI%2

- "Many of the contexts in which a TBI occurs may also be psychologically traumatic, so it is **not uncommon for someone to have both TBI-related symptoms and PTSD from the same event**. **Indeed, injured patients with a TBI (and with multiple TBIs) are more likely to develop PTSD than those without a TBI history**.[11] This correlation may be particularly relevant, for

[8] Miller SC, Whitehead CR, Otte CN, et al: Risk for broad-spectrum neuropsychiatric disorders after mild traumatic brain injury in a cohort of **US Air Force** personnel. *Occup Environ Med* 2015; 72:560–566.
[9] Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in **US Soldiers** returning from Iraq. *N Engl J Med*. 2008;358:453-463.
[10] Andrews B, Brewin CR, Philpott R, Stewart L. Delayed-onset posttraumatic stress disorder: a systematic review of the evidence. *Am J Psychiatry.* 2007;164:1319-1326.
[11] Loignon, A., Ouellet, M. C., & Belleville, G. (2020). A systematic review and meta-analysis on PTSD following TBI among **military/Veteran** and civilian populations. *The Journal of Head Trauma Rehabilitation*, 35(1), E21-E35. https://doi.org/10.1097/HTR.0000000000000514

instance, in military or interpersonal violence populations, where injuries may involve both physical and psychological trauma.

- "**When a patient has comorbid PTSD and mTBI-related symptoms**, they may attribute these symptoms to consequences of the TBI rather than PTSD. However, regardless of whether TBI is contributing to the symptoms, it is important to collaboratively identify with patients when PTSD is part of the clinical picture because PTSD is not likely to get better without treatment and can exacerbate or masquerade as many of the symptoms the patient might attribute to post-concussive symptoms (e.g., neurocognitive deficits). For this reason, the VA/DoD Clinical Practice Guideline for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury recommends setting expectations of recovery with patients and referring them to treatment for any comorbid conditions.
- "Research on treatment for patients with PTSD and post-concussive symptoms is somewhat limited….most of the research has involved those with a history of mTBI, with much less direct evidence for those with moderate to severe TBI.

PTSD: The INFLAMMATION / PTSD Connection

Kim, T, et al., "Inflammation in Post-Traumatic Stress Disorder (PTSD): A Review of Potential Correlates of PTSD with a Neurological Perspective," *Antioxidants* 2020, 9, 107; doi:10.3390/antiox9020107:

- "Post-traumatic stress disorder (PTSD) is a chronic condition characterized by symptoms of physiological and psychosocial burden. **While growing research demonstrated signs of inflammation in PTSD, specific biomarkers that may be representative of PTSD such as the detailed neural correlates underlying the inflammatory responses in relation to trauma exposure are *seldom discussed***. Here, we review recent studies that explored alterations in key inflammatory markers in PTSD, as well as neuroimaging-based studies that further investigated signs of inflammation within the brain in PTSD, as to provide a comprehensive summary of recent literature with a neurological perspective. A search was conducted on studies published from 2009 through 2019 in PubMed and Web of Science. **Fifty original articles were selected**. Major findings included **elevated levels of serum proinflammatory** cytokines in individuals with PTSD across various trauma types, as compared with those without PTSD. Furthermore, neuroimaging-based studies demonstrated that **altered inflammatory markers are associated with structural and functional alterations in brain regions that are responsible** for the regulation of stress and emotion, including the amygdala, hippocampus, and frontal cortex.
- "Growing research on PTSD recommends the development and promotion of early treatment strategies for PTSD prior to any clinical symptom development. [Note: New treatments are prophylactically needed.]
- "**Among the 50 articles selected for this review, 43 were studies that explored serum inflammatory cytokine markers as measures of inflammation**, 4 were studies exploring PTSD- and oxidative stress-related genes, while the remaining 3 were neuroimaging-based studies that explored the neural correlates of inflammation in PTSD. For studies investigating inflammation in PTSD according to peripheral inflammatory markers, the current review identified and selected 24 studies that explored serum levels of proinflammatory cytokines including one or more of IL-1β, IL-6, TNF-α, and IFN-γ as well as CRP, and 19 studies that explored serum levels of anti-inflammatory cytokines IL-4 and/or IL-10.
- "Through the current literature selection, studies have demonstrated that **individuals with PTSD have significantly elevated serum levels of proinflammatory cytokines** than the respective control group without PTSD. Specifically, individuals with PTSD demonstrated as having higher levels of serum IL-1β, IL-6, TNF-α, IFN-γ, and CRP than individuals who have been exposed to

trauma but have never developed PTSD. In the current review, IL-6 demonstrated to be the most documented proinflammatory cytokine in human models of PTSD, and the majority of studies demonstrated increased IL-6 levels in the serum sample of individuals diagnosed with PTSD as compared with their respective control group. **This may also be in alignment with previous research which noted IL-6 as the most considerable marker for inflammation**. [Note: CRP and homocysteine are excellent, too.] Specifically, studies have shown that IL-6 is crucial in the relationship between immune system and CNS in inflammatory states.

- "In addition, studies have also demonstrated elevated CRP levels which are known to be influenced by proinflammatory cytokines, where individuals with PTSD showed increased CRP levels compared to healthy controls, and PTSD symptom severity were positively associated with CRP levels.
- "**Among veterans all of whom have been exposed to similar combat**, those who are diagnosed *with* ***PTSD demonstrated significant imbalance in their inflammatory state*** as compared to those without PTSD, implicating that one's risk or resilience towards PTSD may be largely explained by biological factors and ***their ability to regulate their inflammatory state*****, as opposed to the nature or severity of the traumatic event**.[12]
- "Furthermore, two studies also explored the additional factor of traumatic brain injury (TBI) in PTSD and found significant alteration in proinflammatory cytokine levels in association with PTSD. The first is the study by Devoto and colleagues (2017) who found that TBI may have an additive effect to the alteration of proinflammatory cytokine levels in the case of PTSD, as individuals with PTSD as well as TBI had demonstrated greater elevation in proinflammatory cytokine levels than individuals with PTSD but without TBI.[13] [Note: again, the increased inflammatory connection in military personnel with both TBI & PTSD is noted.]
- "Given the current findings summarized, a potential pathway underlying inflammation in PTSD may be suggested. A major collective finding from this review was elevated serum IL-6 levels in all but one study among the studies reviewed for alteration in proinflammatory cytokines in association with PTSD across various trauma types."

FROM: Muhie, S.,et al., Molecular signatures of post-traumatic stress disorder in war-zone-exposed veteran and active-duty soldiers*, Cell Reports Medicine* 4, 101045 May 16, 2023:

- **"Post-traumatic stress disorder (PTSD) affects more than 12% of combat-exposed soldiers** and about 6% of the US population.[14]
- "The Systems Biology Consortium (SBC) and Fort Campbell Cohort (FCC) cohorts were composed of 340 veterans (300 males and 40 females) and 180 active-duty service members (159 males and 21 females) respectively. Twenty-six members of the active-duty group were followed longitudinally for an average of 13 ± 0.75 months. All participants (those with and without PTSD) were exposed to military-service-related PTSD criterion A events.
- "**Inflammation-related** immune responses **were consistently activated across cohorts** to include pathways involved in inflammatory responses.
- "Reported findings provide support for theoretical models that describe PTSD systemic pathogenesis associated with psychological trauma as an interconnected tetrad of *inflammatory* responses, oxidative stress….

[12] Wang, Z., et al., M.R.I. An exploratory approach demonstrating immune skewing and a loss of coordination among cytokines in plasma and saliva of **Veterans** with combat-related PTSD. *Hum. Immunol*. 2016, 77, 652–657.

[13] Devoto, C., et al., Inflammation relates to chronic behavioral and neurological symptoms in military personnel with traumatic brain injuries. *Cell Transplant*. 2017, 26, 1169–1177.

[14] PTSD N.C.f. How common is PTSD? 2022. https://www.ptsd.va.gov/understand/common/common_**veterans**.asp

- "**Stress** can dysregulate immediate and regenerative immune responses to **cause excessive inflammation with functional deterioration of multiple organ systems**, including the noninfectious injury to the heart, arterial inflammation, and cardiovascular disease. Inflammatory response after traumatic stress results in the recruitment and activation of leukocytes from the bone marrow and local cytokine production in the vasculature. [Note: Decreased inflammation will result in less deterioration of organ systems, too.]
- "However, numerous lines of evidence suggest that even peripheral oxidative, inflammatory, vascular, and **metabolomic dysregulation can affect brain function and perpetuate PTSD symptoms**.
- "We **speculate** that **vasculature damage and related physiological pathologies potentially due to inflammation** and oxidative stress may precede neurological sequelae (e.g., cognitive decline). Our findings **raise the possibility that tissue injury and aborted healing of the injured tissue may contribute to the onset, course, and persistence of PTSD** including important comorbidities (cardiovascular diseases, metabolic dysregulation, T2DM, chronic pain, and neuropsychiatric disorders). [Therefore, impeded healing of injured tissue may contribute to PTSD.]
- "However, numerous lines of evidence suggest **that even peripheral oxidative, inflammatory**, vascular, and metabolomic dysregulation **can affect brain function and perpetuate PTSD symptoms. Thus, PTSD is coming to be seen as a systemic disorder rather than as a purely psychological illness**."

FROM: Aliev, G, et al., Neurophysiology and Psychopathology Underlying PTSD and Recent Insights into the PTSD Therapies—A Comprehensive Review, *J. Clin. Med.* 2020, 9, 2951 http://dx.doi.org/10.3390/jcm9092951

- **"PTSD is associated with dysregulation of the immune response**, which is reflected by an **increase in pro-inflammatory cytokines**, namely interleukins viz., IL-6 and IL-17, and a decrease in IL-4. Further, there are findings that support links between IL-6 and hypothalamus-pituitary-adrenal (HPA) to foster PTSD symptoms. Glucocorticoid secretions **through HPA axis** typically inhibit the lymphocyte proliferation and reduce the secretion of pro-inflammatory cytokines viz., IL-6, IL-12, interferon, and tumor necrosis factor during stress conditions. **Dysregulation in the HPA axis is associated with pathophysiology of PTSD**. In addition, the **gut microbiome plays a vital role in programming endocrine HPA axis, a key stress response regulator**. [Note: Brivanta(tm)'s main ingredient directly is incorporated into the tissue lining the entire gut.]
- "Metabolic alterations and mitochondrial dysfunction in neurons foster the psychopathological and neurophysiological changes during PTSD. Balanced release of secretions through hypothalamus-pituitary-adrenal (HPA)-axis signaling is crucial for ameliorating the PTSD effects since HPA-axis dysregulation causes inflammation, insulin resistance, oxidative stress, and energy deficiency due to the increased levels of catecholamines and corticothropin release factor. [Note: Brivanta(tm) directly supports maximization of mitochondrial (cellular energy production) structure through cardiolipin support.]
- **[T]he dietary modalities rich in omega-3/omega-6 fatty acids may benefit PTSD patients by reducing traumatic memories and enhancing the cognitive or behavioral aspects through the modulation of metabolic cascades**. However, **further research is required** to ascertain the complete role of fatty acid mediated metabolic alterations in PTSD patients.
- "This report [Grady Trauma Project at Emory University in Atlanta, Georgia, USA] concluded that the **substantial rise in pro-inflammatory cascade and CRP levels** may be involved in the fear-related PTSD psychopathology and heightened arousal symptoms. **Therapeutic modalities**

to mitigate the pro-inflammatory cascades across neurons and neuroglia may benefit PTSD patients.

- Mitochondria play a role in the psychopathology and pathophysiology of PTSD. The mitochondria role is pertaining to the PTSD-mediated symptomatology such as avoidance, inflammation, fear, anxiety, synaptic plasticity, and steroidogenesis. Dysregulated energy metabolism in mitochondria progressively leads to bioenergetic impairment *during PTSD. In addition,* ***chronic low-grade inflammation can cause the development of PTSD***.
- **"Future research should focus on the development of therapeutic modalities to mitigate the inflammation-mediated mood changes during PTSD.**

FROM: Govindula, A, et al., Emphasizing the Crosstalk Between Inflammatory and Neural Signaling in Post-traumatic Stress Disorder (PTSD), *Journal of Neuroimmune Pharmacology* (2023) 18:248–266:

- "Besides the disruption of hypothalamus-pituitary-axis (HPA) axis, intensified immune status with **elevated pro-inflammatory cytokines** and arachidonic metabolites of COX-2 such as PGE2 creates a putative scenario in **worsening the neurobehavioral facet of PTSD**. This review aims to link the Diagnostic and Statistical Manual of mental disorders (DSM-V) symptomology to major neural mechanisms that are supposed to underpin the transition from acute stress reactions to the development of PTSD.
- "Case-control studies in PTSD patients showed high levels of chemokines and proinflammatory cytokines, indicating that these increased inflammatory markers could act as biomarkers of PTSD risk, resilience, and stress responses.[15] These upregulated proinflammatory markers imply that those suffering from PTSD may have an activated immune system, which might contribute to neuroinflammation.
- "For optimal cell membrane integrity and neurologic function, a balance of inhibitory and excitatory neurotransmission via GABA and glutamate is required. [Note: Brivanta$^{(tm)}$ further optimizes cell membrane structure / integrity through its use of LA and ALA in its composition.]
- "The pharmacological treatment of PTSD has been restricted due to the narrow focus on the monoamine system and a lack of efficacy with current treatment approaches, indicating a gap in translating basic research to clinical research. Thus, **future research on the pharmacological treatment of PTSD should not only concentrate on novel neurotransmitter pathways but also aim to enhance the understanding of the pathophysiology**…."

FROM: Lee, DH, et al., Neuroinflammation in Post-Traumatic Stress Disorder. *Biomedicines* 2022, 10, 953.https://doi.org/10.3390/biomedicines10050953

- "**The Marine Resiliency Study** reported that preexisting concentrations of **C-reactive protein (CRP)** were **directly correlated with the occurrence and severity of PTSD**, three months after a seven-month military deployment, and elevated levels of **interleukin (IL)-6**, IL-8, and transforming growth factor β (TGF-β) **during hospitalization predicted the development of PTSD one month later**. **These data suggest that immune dysregulation [inflammation] predisposes individuals to PTSD**. The elevation of inflammatory cytokines in PTSD has clinical significance, as **chronic inflammation can adversely affect cardiovascular and physical health**. In addition, **individuals with PTSD are significantly more likely to suffer autoimmune disorders compared with those with other psychiatric conditions**. [Note: Brivanta$^{(tm)}$ has

[15] Zhang L, et al., Potential chemokine biomarkers associated with PTSD onset, risk, and resilience as well as stress responses in **US military** service members. *Transl Psychiatry* 10:1–9. https://doi.org/10.1038/s41398-020-0693-1

clinically lowered both CPR and homocysteine inflammatory markers in humans suffering physical injury. Therefore, with its use, other associated diseases should be decreased, too.]

- "**Neuroinflammation occurs when inflammatory reactions affect the nerve tissues**. The brain was once considered an immune-privileged site except in certain cases of illness and injury, but it is now well known **that peripheral pro-inflammatory cytokines can affect the brain** through several mechanisms, including by crossing the blood–brain barrier.[16] **Inflammation in the central nervous system and surrounding areas** can contribute to **neuroinflammation** through the activation of microglia and astrocytes. ***Neuroinflammation, unlike acute inflammation of the central nervous system, is considered a type of chronic inflammation***. Acute inflammation of the central nervous system occurs immediately after damage, causing reactions such as activation of the inflammatory molecules, endothelial cells, and tissue edema. On the other hand, **neuroinflammation is when nerve cells are continuously activated**, and other immune cells are mobilized to the brain. [Note: Brivanta$^{(tm)}$ was specifically designed to combat chronic inflammation.]
- "Cytokines are small proteins that are important for cell signaling. **They can move across the cellular lipid bilayer** and are involved in autocrine and endocrine signals as immunomodulators, albeit being different from hormones. Patients with PTSD are reported to have **significantly higher** blood levels of **inflammatory markers**, such as IL-1β, IL-6, TNF-α, and C reactive protein (**CRP**).
- "**CRP is also a protein that responds to inflammation**. It is an acute protein that increases with the secretion of interleukin-6 and is used as an **inflammatory marker** by promoting apoptosis through complement systems and bacterial action by macrophages. ***One study revealed that plasma CRP levels in veterans are potentially associated with the onset of PTSD symptoms, suggesting that inflammation may be a risk factor for PTSD***.[17] One study even duplicated prior results:[18] "Sixty-one male war veterans (31 PTSD and 30 control subjects) were included in this **replication study**. **We replicated, in a new sample, our previous finding** of **increased inflammatory markers in combat-exposed PTSD subjects** compared to combat-exposed non-PTSD controls. ***These findings strongly add to the growing literature suggesting that immune activation may be an important aspect of PTSD pathophysiology***, although not directly correlated with current PTSD symptom levels in the PTSD group."
- "Various studies have suggested that inflammation may play an important role in the pathophysiology of PTSD, providing evidence of non-infectious inflammation caused by interactions between the immune system and the brain mediated by psychological stress. These findings in clinical and animal studies show that PTSD can be associated with systemic and CNS inflammation and is not a mere isolated psychological response.
- "In addition to the immune system, regulatory disorders in other stress-response systems, including the HPA axis and the SNS, have been shown to be involved in the pathophysiology of PTSD. There are complex interactions between these systems, and the confusion of these interactions can play an important role in the pathogenesis of PTSD. **However, studies on the**

[16] Dantzer, R. et al., From Inflammation to Sickness and Depression: When the Immune System Subjugates the Brain. *Nat. Rev. Neurosci.* 2008, 9, 46–56.

[17] Eraly, S.A., et al., **Marine** Resiliency Study Team. Assessment of Plasma C-Reactive Protein as a Biomarker of Posttraumatic Stress Disorder Risk. *JAMA Psychiatry* 2014, 71, 423–431; Wang, Z., et al., M.R.I. An Exploratory Approach Demonstrating Immune Skewing and a Loss of Coordination Among Cytokines in Plasma and Saliva of **Veterans** with Combat-Related PTSD. *Hum. Immunol*. 2016, 77, 652–657; Lindqvist, D., et al. Increased Circulating Blood Cell Counts in Combat-Related PTSD: Associations with Inflammation and PTSD Severity. *Psychiatry Res.* 2017, 258, 330–336

[18] Lindqvist, D. et al., Increased Pro-Inflammatory Milieu in **Combat Related** PTSD—A New Cohort Replication Study. *Brain Behav. Immun*. 2017, 59, 260–264

inflammation of PTSD and its association with HPA axis dysfunction are still limited. Further studies must be conducted to clarify the underlying mechanism."

FROM: Department of Veteran's Affairs, PTSD Research Quarterly, VOLUME 29/ NO. 4 • ISSN: 1050 - 1835 • 2019

- "**Veterans with posttraumatic stress disorder (PTSD) suffer from a high burden of diseases** typically associated with aging including cardiovascular disease, autoimmune disorders, and dementia. **A large literature demonstrates that PTSD is associated with a pro-inflammatory activation of the immune system**, which may contribute to accelerated aging. The current state of the science **suggests that there is a bidirectional causal relationship between PTSD and inflammation**, which has implications for the development of clinically useful biomarkers and novel treatments. PTSD is strongly associated with increased risk for autoimmune disorders and cardiovascular disease, and immune factors should be targeted in **novel therapeutics to prevent the accrual of this comorbid burden in patients who remain chronically symptomatic**. [Note: Minimize inflammation and associated risk of PTSD, and the risk of numerous diseases is decreased. Because of its targeted design, Brivanta(tm) is expected to be highly successful in this area.]
- **In aggregate, the weight of the evidence supports the concept that PTSD is associated with elevations in pro-inflammatory cytokines** such as interleukin 6 (IL-6)…. **Increased inflammation was associated with current PTSD but not PTSD in remission** in a large sample of **Veterans** (N = 735) who had participated in the Mind Your Heart Study (O'Donovan et al., 2017). Inflammatory markers in Veterans with PTSD in remission were no different than those in Veterans without PTSD. [Note: confirmation that inflammation is causal to PTSD.]
- "There are a growing number of studies demonstrating that immune factors measured pre-trauma exposure confer risk for developing PTSD following trauma. Eraly and colleagues (2014) measured plasma levels of the inflammatory marker CRP in participants in the **Marine Resiliency Study prior to deployment into combat in either Iraq or Afghanistan**. After adjusting for baseline PTSD symptom severity (assessed by the Clinician-Administered PTSD Scale; CAPS) pre-deployment, higher levels of CRP were associated with higher post-deployment CAPS scores. Conclusions and Relevance: **A marker of peripheral inflammation, plasma CRP may be prospectively associated with PTSD symptom emergence, suggesting that inflammation may predispose to PTSD**:[19] "Adjusting for the baseline CAPS score, trauma exposure, and other relevant covariates, we found baseline plasma CRP concentration to be a highly significant overall predictor of post-deployment CAPS. [Note: Brivanta(tm) is specifically designed to (prophylactically) help compensate for an impaired delta-6 desaturase pathway to minimize pre-trauma chronic inflammation.]

[19] Eraly, S. A., et al., (2014). Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. *JAMA Psychiatry*, 71, 423-431. **Additional References**: Groer, et al., Relationship of PTSD symptoms with combat exposure, stress, and inflammation in **American soldiers**. *Biological Research for Nursing*, 2015, 17, 303-310; Lindqvist, D., et al. (2014). Proinflammatory milieu in combat-related PTSD is independent of depression and early life stress. *Brain, Behavior, and Immunity*, 42, 81-88; Lindqvist, D., et al., (2017). Increased pro-inflammatory milieu in **combat related** PTSD - A new cohort replication study. *q*, 59, 260-264; Spitzer, C., et al., (2010). Association of posttraumatic stress disorder with low-grade elevation *of C-reactive protein*: Evidence from the general population. *Journal of Psychiatric Research*, 44, 15-21. "This is another population-based study (N = 3049) which examined the association of PTSD with CRP. *PTSD diagnosis was associated with a nearly twofold risk for elevated CRP even after controlling for socio-demographics, body mass index, blood pressure, lipids, physical disease burden, and history of trauma exposure*.

- "**They found a strong association between early trauma exposure and *elevated CRP*** but not IL-6. Overall, there is **strong evidence that PTSD is associated with a pro-inflammatory state that may account for the high comorbid disease burden associated with this disorder**."