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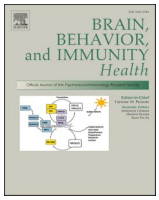

Post traumatic stress disorder associated hypothalamic-pituitary-adrenal axis dysregulation and physical illness

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ABSTRACT

Conventional human stress responses are mediated by the sympathetic adrenal medullar (SAM) axis and the hypothalamic pituitary adrenal (HPA) axis. The SAM axis mediates the immediate response to stress through norepinephrine and epinephrine while the HPA axis mediates the slow response through corticosteroids, primarily cortisol, to effect systemic changes. Post Traumatic Stress Disorder (PTSD), a psychiatric disorder that develops in a small subset of people exposed to a traumatic event, may dysregulate these systems and result in increased risk of various clinical conditions. These conditions include but are not limited to cardiovascular disease, metabolic conditions, autoimmune diseases, neurocognitive disorders, and women's health complications such as preterm birth, polycystic ovarian syndrome, and endometriosis to name a few. This review focuses on how PTSD dysregulates the HPA axis, and further, how these alterations affect the immune system and physical health outcomes.

1. Introduction

Comorbidities associated with post traumatic stress disorder (PTSD) have been heavily researched over the last several years as has the role of neuroendocrine systems. However, current literature lacks a comprehensive review detailing alterations in the hypothalamic pituitary adrenal (HPA) axis and its role in the development of physical comorbidities in PTSD patients. This review begins with an overview of PTSD and a description of normal HPA axis function, followed by a discussion of current research in neuroendocrine alterations in PTSD patients. We then propose a mechanism of HPA axis dysfunction in PTSD development and its relation to immunological alterations, specifically changes that may lead to the development of major comorbidities associated with PTSD. Lastly, we discuss future directions in the field of PTSD and somatic illness research.

2. Post traumatic stress disorder

As a result of a traumatic event, some individuals may develop post traumatic stress disorder, a psychiatric disorder characterized by reliving the traumatic event, avoidance of stimuli that are reminiscent of the traumatic event, negative cognitions or feelings, and hyperarousal and reactivity. Not everybody exposed to a traumatic event will develop PTSD; individuals who experience traumatic events but do not develop PTSD are said to be resilient. Similar to other psychiatric disorders, there is not a distinct biomarker that defines disease diagnosis, instead PTSD is diagnosed by a psychologist or psychiatrist based on history. Risk factors for PTSD include sex, dose-dependency, and genetics. Women are 2–3 times more likely to develop PTSD than their male counterparts (Pooley et al., 2018). Dose-dependent responses are also believed to play a role in PTSD development as longer traumatic events increase the disease development risk (Kaysen et al., 2010). One genetic factor associated with PTSD is a single nucleotide polymorphism tagging FK506 Binding Protein (FKBP5), a molecule involved in glucocorticoid signaling (Binder, 2009). Epigenetic factors may also play a role in disease protection or risk factors. Interestingly, previous exposure to traumatic events may sensitize the immune system as well as alter epigenetic markers, further conferring disease risk. This lack of clarity in risk factors as well as many PTSD studies being retrospective, make it difficult to discern risk factors from physiological results. Despite this lack of definitive biomarkers and clear risk factors, there is extensive research detailing biological alterations in PTSD patients including immune responses and neuroendocrine function, specifically the hypothalamic pituitary adrenal (HPA) axis.

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3. The hypothalamic pituitary adrenal axis

A normal stress response includes activation of the sympathetic adrenal medullar (SAM) axis for the initial fast response, which is mediated by epinephrine and norepinephrine, as well as the simultaneous but slower hypothalamic pituitary adrenal (HPA) response. The hormones released due to HPA activation can then induce systemic change including, but not limited to, immune responses, digestion and energy consolidation/expenditure, and autonomous functions including regulation of heart rate and blood pressure (Herman et al., 2016).

Specifically, the limbic system stimulates the amygdala, which subsequently activates the hypothalamus. The hypothalamus releases corticotropin releasing hormone (CRH) which travels through portal circulation to the anterior pituitary (Dunlop and Wong, 2019). CRH type 1 receptors then bind CRH, which stimulates the release of adrenocorticotropin (ACTH) into systemic circulation (Dunlop and Wong, 2019). This circulating ACTH then is bound by its cognate receptors in the adrenal cortex to stimulate the release of corticosteroids, such as cortisol, which is the main effector molecule of the HPA axis. Cortisol is then able to limit HPA activity at both the hypothalamic and pituitary level through negative feedback.

Cortisol is the primary glucocorticoid in humans and is only biologically active when not bound to various proteins such as corticosteroid binding globulin (CBG) (Choi, 2022). This free cortisol is able to elicit biological effects by crossing the cellular membrane and interacting with glucocorticoid receptors within the cytosol. Once bound, the GR/cortisol complex migrates to the nucleus and interacts with glucocorticoid response elements to alter transcription (Dunlop and Wong, 2019). GR are located within virtually every tissue and organ, allowing action on virtually every system within the body. It is important to note that extra-hypothalamic GR are also involved in HPA axis regulation, specifically in the prefrontal cortex and hippocampus ((Zhu et al., 2014); (McKlveen et al., 2013)). Thus, HPA regulation of cortisol is critical for system homeostasis. However, PTSD has been associated with dysregulation of this system, shown by altered levels of CRH, ACTH, and cortisol, as well as altered number and sensitivity of GR.

4. Neuroendocrine and HPA alterations in PTSD

Current research in neuroendocrine alterations in PTSD patients has produced a variety of conclusions, some of which are conflicting. A general review of this research shows that serum CRH is high, there is no clear trend in ACTH, and cortisol is low in PTSD patients when compared to controls. The difficulties in reproducing this type of study as well as the variability of conclusions may be due to the transient nature of these biological components. Within circulation, CRH has a half-life of approximately 4 min, ACTH has a half-life of approximately 22 min, and cortisol has a half-life of approximately 1 h ((Nezi et al., 2000); (Veldhuis et al., 2001; McKay and Cidlowski, 2003))). Protease activity plays a role in the short half-life of these molecules. As a result, blood samples must be placed on ice immediately after collection to protect against protease activity. Additionally, each of these proteins have a natural diurnal pattern, thus making the timing and collection of such measurements extremely important.

4.1. CRH

CRH is the first effector molecule involved in the HPA stress response and has been found to be elevated in the cerebrospinal fluid and plasma in PTSD patients (Baker et al., 1999); (Bremner et al., 1997)). Additionally, overexpression of CRH in rodents has been shown to increase anxiety behaviors (van Gaalen et al., 2002). Based on these data, it was hypothesized that CRH antagonists could be a therapeutic target, however most clinical trials were discontinued due to adverse effects including symptom exacerbation (Spierling and Zorrilla, 2017).

4.2. ACTH

Whereas CRH concentrations in PTSD patients are well defined, this is not the case for ACTH. Since ACTH is produced as a result of CRH stimulation at the pituitary, there should be a positive correlation between CRH and ACTH concentrations, however this has not been consistently demonstrated. For example, in one study of sexually assaulted women, ACTH concentrations were found to be elevated in the PTSD group when compared to controls, however this conclusion is complicated by the presence of comorbid depression in all but 2 PTSD participants (D'Elia et al., 2021). Thus, the effects of PTSD and depression on ACTH concentration could not be separated.

Conversely, in a study of adolescent sexual assault victims with and without PTSD, baseline ACTH and cortisol were measured and found to have no significant difference (Duval et al., 2004). After using the dexamethasone suppression test to measure the amount of negative feedback that occurs as a result of cortisol, the PTSD cohort produced significantly lower ACTH than controls, but this did not lower the subsequent production of cortisol as would be expected (Duval et al., 2004).

Additionally, when given metyrapone, a drug that inhibits the final step of cortisol production, both the PTSD and control groups exhibit increased ACTH compared to baseline, however the increase was significantly larger in the PTSD group (Yehuda et al., 1996). This indicates there is normal pituitary responsiveness in the absence of cortisol, thus removing pituitary insufficiency as a potential cause for neuroendocrine alterations. Further, this result suggests alterations in the negative feedback mechanism within the HPA axis that are causing the altered concentrations of HPA axis hormones.

4.3. Cortisol

Cortisol findings in PTSD are not as clear cut as they may appear at first glance. As nicely reviewed in (Sbisa et al., 2023), which discussed 17 studies reporting cortisol findings, alterations in cortisol and HPA activity have been reported, but directionality of these alterations is not clear cut. 9 of these studies showed decreased cortisol in PTSD, 6 showed no significant difference, 1 showed elevated cortisol, and 1 showed mixed results when compared to controls (Sbisa et al., 2023). For example, one study showed decreased cortisol predicted PTSD symptom severity at 6 weeks and 6 months post trauma (Mouthaan et al., 2014). Conversely, Walsh and colleagues found elevated cortisol measured within 72 h of rape correlated with increased PTSD symptoms at a 6 week follow up, but only in those without a prior history of assault (Walsh et al., 2013). It is important to note that those with a prior history of assault had lower cortisol at the 72-h mark when compared to those without a history of prior assault (Walsh et al., 2013). Thus, many studies on cortisol in PTSD have conflicting results.

While the systematic review from (Sbisa et al., 2023) seems to indicate that decreased cortisol in PTSD is the trend, it is important to note, experimentally, that a statistically significant decrease in PTSD subject cortisol levels is only found in certain conditions and is dependent on other variables. These include method of measurement, other psychiatric comorbidities, time since the traumatic event, sex, type of trauma, and participation of trauma exposed control group with no reported PTSD ((Meewisse et al., 2007); (Sbisa et al., 2023); (Zoladz and Diamond, 2013)). Based on these data as well as an in depth review of the literature, this review will focus on cortisol being decreased in the salvia (von Majewski et al., 2023), urine (Pan et al., 2020), and serum (Schaffter et al., 2021) of PTSD patients when compared to controls.

4.4. Glucocorticoid receptors

PTSD patients have been shown to have increased numbers of highly sensitive GR in brain and lymphocytes (Yehuda et al., 1991). For example, one study showed the number of GR receptors prior to military deployment predicted the development of severe PTSD symptoms upon

return from deployment (van Zuiden et al., 2011). Furthermore, in a prospective longitudinal study, an increase in number of GR over time was correlated with number of traumatic events experienced during that time period (de Voogd et al., 2022). The size of this increase was additionally correlated to lower stress response cortisol in follow up appointments, indicating increased negative feedback within the HPA axis (de Voogd et al., 2022). The use of the dexamethasone suppression test (DST) is often used to measure response of the HPA axis to glucocorticoid; and, thus can be a measure the negative feedback within the HPA axis. Studies show increased cortisol suppression after the DST, indicating increased negative feedback in PTSD patients (Somvanshi et al., 2020). Overall, these data indicate there are increased GR numbers as

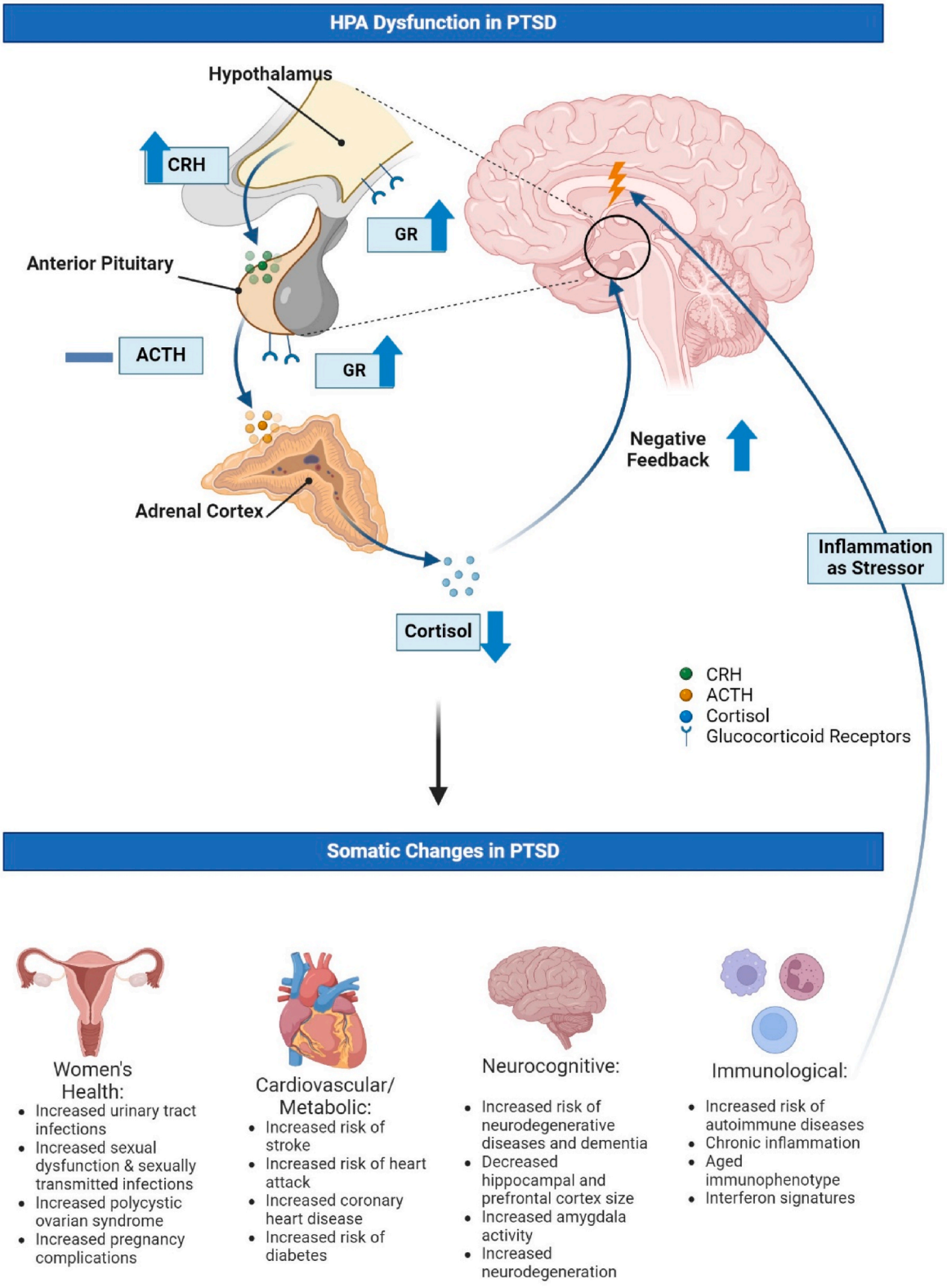

Fig. 1. HPA dysfunction in PTSD and associated somatic comorbidities.

well as sensitivity to glucocorticoid in PTSD patients when compared to controls.

4.5. Proposed mechanism of HPA dysfunction in PTSD

The current hypothesis is that there is enhanced negative feedback within the HPA axis of PTSD patients. Specifically, despite low concentrations of cortisol, these concentrations of cortisol are sufficient to interact with GR on the hypothalamus and pituitary and "turn off" the HPA axis response. This increase in inflammation can act as a stressor further exacerbating HPA axis dysfunction, resulting in chronic hypothalamic activation and thus further decreasing cortisol production. This is likely due to the increased number and sensitivity of GR in PTSD patients.

This hypothesis has yet to be proven and instead is based on a combination of previously produced data, as discussed earlier in this review. While an exact mechanism has yet to be elucidated, this hypothesis forms the foundation for PTSD/neuroendocrine research. A summary of the HPA axis and alterations associated with PTSD is shown in Fig. 1.

The remainder of this review will focus on how alterations and dysregulation of the HPA axis leads to immunological alterations and, subsequently, development of illnesses that disproportionately affect PTSD patients.

Fig. 1: A diagram is shown to depict alterations in the HPA axis negative feedback mechanism in PTSD patients. PTSD patients have increased serum CRH, no clear pattern of change in ACTH, and low cortisol when compared to controls. This low cortisol results in increased inflammation, which then acts as a stressor and exacerbates HPA Axis dysfunction (Chen et al., 2017). One potential mechanism of these changes is an increase in GR number and sensitivity. These alterations can alter the risk for somatic comorbidities in PTSD patients. Image created with BioRender.com.

GR, Glucocorticoid receptors; CRH, Corticotropin releasing hormone; ACTH, Adrenocorticotropin.

5. Immunological alterations as a result of HPA dysregulation

Besides neuroendocrine alterations, PTSD patients are thought to have chronic inflammation. Alterations in the HPA axis that are seen in PTSD patients (section 4) can influence various immunological mechanisms including cytokine production, immune cell populations, and immune cell activity to cause this chronic inflammatory state.

5.1. Cytokine production

Research has shown alterations in both inflammatory and anti-inflammatory cytokine profiles in PTSD patients. Specifically, pro-inflammatory cytokines such as IL-1β, TNFα, and IL-6 tend to be increased in the serum of PTSD patients when compared to controls ((Pace and Heim, 2011); (Ogłodek, 2022); (Guo et al., 2012); (Koirala et al., 2023); (Peruzzolo et al., 2022)). On the other hand, there are conflicting results on anti-inflammatory cytokine concentrations, including IL-10 and IL-4, with some studies showing increases in IL-10 concentrations with others finding lower IL-10 concentrations in PTSD groups ((Ogłodek, 2022); (Guo et al., 2012)).

The dysregulation of the HPA axis may influence the immune system to cause this inflammatory state. For example, peripheral CRH can be pro-inflammatory, however when produced through the HPA axis, CRH is considered to be anti-inflammatory because it leads to cortisol production, an anti-inflammatory mediator (Nezi et al., 2015). Interestingly, most plasma CRH is produced through non-hypothalamic sources, reducing the likelihood that excess HPA axis CRH is causative for inflammation in PTSD patients.

ACTH also has a pro-inflammatory ability in certain cell lines, however, is mostly considered to be anti-inflammatory. In an indirect mechanism, ACTH is anti-inflammatory because of its role in cortisol production. Directly, ACTH has been shown to have anti-inflammatory properties in gout mouse models, and has been used as a treatment for chronic inflammatory conditions for years ((Xu et al., 2022; Montero-Melendez, 2015)). Because of the lack of conclusive and reproducible alterations in ACTH in PTSD patients, is unlikely that ACTH is the main cause of increased inflammation in PTSD patients.

Cortisol, on the other hand, is widely considered to be anti-inflammatory. Specifically, cortisol suppresses inflammation via the production of anti-inflammatory cytokines (Hannibal and Bishop, 2014). As discussed throughout this paper, cortisol in PTSD patients is low, likely due to enhanced negative feedback. This decrease in cortisol and consequently its anti-inflammatory properties may lead to the chronic inflammation seen in PTSD patients.

5.2. Immune cell populations and activity

Besides cytokine alterations, there is also evidence of altered immune cell populations and function in PTSD patients. For example, PTSD patients have been found to have an aged immunophenotype (Aiello et al., 2016). Additionally, alterations in immune cell populations have been found including increased counts of total lymphocytes, total T cells, $CD4^+$ T cells (also known as helper T cells), and memory T cells ((Boscarino and Chang, 1999); (Katrinli and Smith, 2021)). Conversely, PTSD patients have decreased Tregs (T regulatory cells) (Sommershof et al., 2009).

These altered immune cell populations may be a result of HPA axis dysregulation seen in PTSD patients. For example, CRH can cause inflammation through mast cell activation (Nezi et al., 2000). Additionally, ACTH can effect immune cell activity due to the presence of melanocortin receptor 3 (MC3R) on most immune cells (Hasenmajer et al., 2021). Activation of MC3R can modulate T cell cytotoxicity as well as reduce inflammatory cytokine production (Hasenmajer et al., 2021). Lastly, cortisol may be able to stimulate cell immune cell proliferation, as shown in increased transcription of genes relating to proliferation using dexamethasone stimulation in human cell lines ((Shimba et al., 2021); (Franchimont et al., 2002)).

5.3. Gut microbiome alterations

Recently, studies of gut microbiome studies in PTSD have been published, specifically the microbiota-gut-brain axis. The microbiota-gut-brain axis is the idea that there is bidirectional communication between the gut microbiome, neuroendocrine and neurotransmitter systems, and immune signaling pathways (Ke et al., 2023). Additionally, alterations in this axis have been linked to several psychiatric conditions including schizophrenia, depression, and bipolar disorder (He et al., 2024). Further, dysregulation of the microbiota-gut-brain axis have been linked to physical comorbidities such as inflammatory bowel disease, cardiometabolic disorders, and diabetes (Ke et al., 2023). Alterations in the gut microbiome in PTSD patients have been identified; specifically *genus.Phascolarctobacterium* and *genus.RuminococcaceaeUCG004* were associated with increased risk of PTSD development (He et al., 2024). Some bacterial genera such as *Roseburia* and *Odoribacter* within the gut microbiome have anti-inflammatory properties (Ke et al., 2023). As a result, a clinical trial using *Lactobacillus rhamnosus* is underway as a treatment for PTSD associated inflammation (Petakh et al., 2024). While this field is still developing, it is important to consider the role of the gut microbiome in inflammation and neuroendocrine pathways and their relation to PTSD.

6. Somatic comorbidities

PTSD patients have been shown to have increased risk for cardiovascular events, autoimmune diseases, metabolic diseases, neurocognitive disorders, and women's health complications, each of which

will be discussed in detail below. It is proposed that this increased risk in physical health outcomes is due to the increases in inflammation associated with PTSD, potentially resulting from HPA Axis dysfunction.

6.1. Cardiovascular health and metabolic disorders

One of the most studied physical health outcomes associated with PTSD is the increased risk for cardiovascular diseases such as myocardial infarction and stroke. One systematic review of the subject determined that PTSD is associated with a 55% increase in coronary heart disease or cardiac-related mortality (Edmondson et al., 2013). Unfortunately, many cardiovascular risk factors overlap with behaviors that have been shown to be increased in PTSD patients, including smoking, substance abuse, and medication non-adherence ((Hapke et al., 2005); (McFarlane, 1998; Sullivan et al., 2009); (Kronish et al., 2012)). Additionally, a meta-analysis found a hazard ratio (HR) of 1.55 when looking at the relationship between PTSD and coronary heart disease. However, one twin study of Vietnam veterans showed that adjusting for these factors resulted in little effects on coronary heart disease risk imparted by PTSD (Vaccarino et al., 2013). Additionally, inflammatory cytokines that are risk factors for coronary heart disease, such as IL-6 and TNF-α, are also elevated in PTSD patients, creating a potential mechanism for the increased risk of cardiovascular events in PTSD patients ((Wirtz and von Känel, 2017); (Ryder et al., 2018)).

6.2. Immunological disorders

There is an increased risk for development of autoimmune diseases in PTSD patients including systemic lupus erythematosus (SLE) (HR = 1.4), multiple sclerosis (HR = 2.3), inflammatory bowel disease (HR = 1.6), and rheumatoid arthritis (HR = 1.6) ((Bookwalter et al., 2020); (Ryder et al., 2018; Song et al., 2018)). The increases in inflammatory cytokines coupled with decreases in anti-inflammatory and regulatory cytokines can lead to a state of chronic inflammation commonly seen in PTSD patients (Section 5). In fact, a 2016 study showed that anxiety and PTSD-like symptoms were reduced in rats with PTSD after treatment for chronic inflammation with the anti-inflammatory drug ibuprofen (Lee et al., 2016). Recent data suggest a potential role for chronic inflammation in the pathogenesis of autoimmune diseases, which potentially links PTSD and later development of autoimmune disorders (Duan et al., 2019). Additionally, gene expression studies show enrichment for immune related genes, including interferon related genes, both pre-deployment and after subsequent PTSD development in US Marines (Breen et al., 2015). That is, increased expression of interferon-regulated genes prior to trauma exposure was a risk factor for PTSD. Further, similar increased expression of interferon regulated genes is associated with some autoimmune diseases, including SLE (Postal et al., 2020). Thus, there may be factors, including genetics, that predispose individuals to both PTSD and autoimmune disease. This possibility is in contrast to the notion that changes in the immune system induced by PTSD then puts PTSD patients at risk for autoimmune disease.

6.3. Neurocognitive disorders

Recent data suggest altered neuroanatomy and function in PTSD, particularly in the prefrontal cortex, hippocampus, and amygdala (Pitman et al., 2012). The hippocampus is generally thought of as the memory center of the brain and is important for long term memory consolidation and retrieval, whereas the amygdala is important for emotional processing. The prefrontal cortex is important for regulating thoughts and emotions as well as higher-order thinking. PTSD is associated with reduced hippocampal and prefrontal cortex volumes; chronic activation of GR in these areas has been linked to dendritic atrophy and subsequent loss of signaling control ((Pitman et al., 2012); (McKlveen et al., 2013)). Functional neuroimaging also shows increased amygdala volumes and activation in patients ((Pitman et al., 2012); (Etkin and Wager, 2007)). In terms of PTSD, these alterations may play a role in the symptomology. Longitudinal studies suggest that PTSD may negatively affect neurocognition as shown by word association tests, digit-symbol pair recognition and recall, and visual memory recall tests (Jacob et al., 2019). Additionally, PTSD has been shown to be a risk factor for later development of dementias (OR: 2.3, $p < 0.001$) and other various neurological diseases such as Parkinson's disease (HR: 3.46) and multiple sclerosis (HR: 2.3) ((Qureshi et al., 2010; Chan et al., 2017); (Bookwalter et al., 2020)).

One hypothesis for the increased risk of dementia and Alzheimer's Disease (AD) in PTSD is neuroinflammation. Specifically, microglia, astrocyte, and mast cell activation may induce the production of inflammatory markers, subsequently contributing to neuroinflammation ((Kempuraj et al., 2017); (Li et al., 2023)). Current research indicates there may be a bidirectional relationship between neuroinflammation and PTSD, with a causal relationship not established (Li et al., 2023).

6.4. Women's health

PTSD diagnosis in the VA medical system has also been shown to have an association with women's health including increased rate of urinary tract infections (OR: 2.09, $p < 0.01$), sexually transmitted infections, polycystic ovarian syndrome (OR: 2.05,$p < 0.01$), sexual dysfunction (OR: 6.78, $p < 0.01$), endometriosis (OR: 2.35, $p < 0.01$), and cervical dysplasia (OR: 1.86, $p < 0.01$) (Cohen et al., 2012). Additional research shows increased risk of pregnancy complications, spontaneous pre-term births (OR: 1.26, $p = 0.006$), and gestational diabetes (RR = 1.4) in those with active PTSD ((Shaw et al., 2014; Shaw et al., 2017)). It is hypothesized that the increased risk of sexually transmitted infections may be due to increases in high-risk behavior associated with PTSD (Cohen et al., 2012). Cohen and colleagues also suggest the increased risk of sexual dysfunction may be due to PTSD associated apathy. Our review of this literature did not yield hypotheses for the increased risk of urinary tract infections, polycystic ovarian syndrome, endometriosis, and cervical dysplasia in PTSD patients. However, polycystic ovarian disease is associated with metabolic syndrome ((Alissa et al., 2023); (Kakoly et al., 2018); (Krentowska et al., 2021)) which is associated with PTSD (Section 6.1). Interestingly, the placenta is a major source of peripheral CRH, which acts as a prenatal clock (Yonkers et al., 2014). PTSD may prematurely increase peripheral CRH levels resulting in spontaneous preterm birth (Yonkers et al., 2014). Additionally, similar mechanisms that cause diabetes in PTSD patients may cause an increased risk of developing gestational diabetes in pregnant PTSD patients.

7. Conclusions

Physiological and psychological stressors can trigger a stress response that begins with the sympathetic adrenal medullar (SAM) axis and the hypothalamic pituitary adrenal (HPA) axis. While the initial immediate stress response is mediated by the SAM axis, a slower and longer response is mediated by the HPA axis. Specifically, after limbic system stimulation, the hypothalamus produces CRH, which acts at the pituitary to cause ACTH production. ACTH then acts at the adrenal gland to cause the release of cortisol, the main effector molecule of the HPA axis. Cortisol can then "turn off" the HPA axis response through negative feedback at both the hypothalamic and pituitary levels. This HPA axis can become dysregulated, likely through increased negative feedback sensitivity. Specifically, the low concentrations of cortisol found in PTSD patients are likely still sufficient to interact with increased glucocorticoid receptors at the hypothalamus and pituitary gland, further suppressing cortisol production. This likely occurs through increased numbers and sensitivity of glucocorticoid receptors found in chronic stress and PTSD patients.

The resulting neuroendocrine alterations can affect the immune system, resulting in a chronic inflammatory state, leading to changes in

physical health outcomes and can increase the prevalence of various cardiovascular, metabolic, immunological, neurocognitive, and women's health related diseases in PTSD patients. The overall poorer physical health outcomes in PTSD patients may be corrected by treating these neuroendocrine alterations or the resulting inflammatory state and improve physical health outcomes, and subsequently quality of life, in PTSD patients.

8. Future directions

Despite the distinct lack of prospective data, current research suggests there is a link between PTSD and somatic illness, and prospective studies can help elucidate this connection. For example, elaborating on Dr. Micheal Breen's prospective gene enrichment study (*Section 6.2*) would be of great interest. Dr. Breen and colleagues found increased interferon signatures both pre and post deployment in US Marines that developed PTSD post deployment. It would be beneficial to follow up with the patients that exhibited increased interferon related genes to determine if they later developed autoimmune diseases. Another potential study to further elaborate on the link between PTSD related HPA dysfunction and later development of somatic comorbidities would be to look at immune cell populations, specifically Tregs (T regulatory cells) both before and after deployment. Tregs have been shown to be decreased in PTSD patients, and Treg insufficiency is known to play a role in the development of several autoimmune diseases, due to their role in peripheral tolerance. While current research linking PTSD and HPA axis dysfunction is circumstantial, future prospective and longitudinal studies can develop this area of research.

CRediT authorship contribution statement

Stephanie Lawrence: Writing – original draft. **R. Hal Scofield:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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